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Formal Synthesis of (−)-Englerin A and Cytotoxicity Studies of Truncated Englerins

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Dedicated to Professor K. C. Nicolaou on the occasion of his 65th birthday

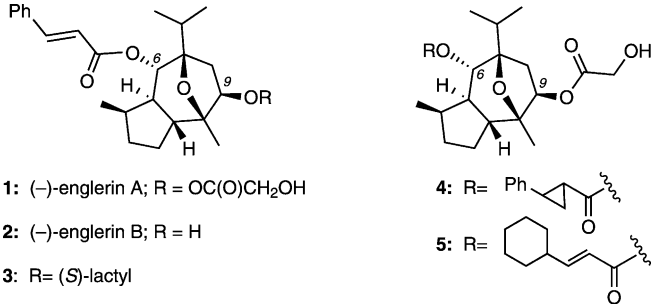
Abstract: An efficient formal synthesis of (−)-englerin A (**1**) is reported. The target molecule is a recently isolated guaiane sesquiterpene that possesses highly potent and selective activity against renal cancer cell-lines. Our enantioselective strategy involved the construction of the BC ring system of compound **1** through a Rh^{II}-catalyzed [4+3] cycloaddition reaction followed by subsequent attachment of the A ring through an intramolecular aldol condensation reaction. As such, this strategy allows the synthesis of truncated englerins. Evaluation of these analogues with the A498 renal cancer cell-line suggested that the A ring of englerin is crucial to its antiproliferative activity. Moreover, evaluation of these analogues led to the identification of potent growth-inhibitors of CEM cells with GI_{50} values in the range 1–3 μM.

Keywords: cancer · cycloaddition · leukemia · natural products · total synthesis

Introduction

The need to identify new chemical motifs as potential drug-leads has spurred the screening of plant extracts that are used in traditional African, Ayurvedic (Indian), and Chinese medicines.[1] In particular, South Africa has a remarkable botanical diversity with over 30000 flowering species, from which more than 3000 are used for medicinal purposes throughout the country.[2] Among them, plants of the genus *Phyllanthus* (Euphorbiaceae) are widely distributed and have long been used in African folk medicine to treat kidney and urinary tract infections.[3] With this in mind, the Beutler laboratory has been screening extracts of the Tanzanian plant *Plyllanthus engleri* against renal cell carcinoma (RCC) and has recently reported the isolation of two new bioactive sesquiterpenes, named englerin A (**1**) and englerin B (**2**; Scheme 1).[4]

Preliminary biological investigations[4] have shown that compound **1** possesses very potent growth-inhibitory activity (GI_{50} = 1–87 nM) against RCC with approximately 1000-fold tissue selectivity as compared to other carcinomas. These findings are of particular significance because RCC: 1) is among one of the ten leading cancer types in the US;[5] 2) is characterized by a lack of early warning signs, has diverse clinical manifestations, and shows resistance to radiation;[6] and 3) cannot be effectively treated with current chemotherapeutic agents, thus leaving surgical procedures as the only treatment option.[7]



1: (–)-englerin A; R = $OC(O)CH_2OH$

2: (–)-englerin B; R = H

3: R= (*S*)-lactyl

Scheme 1. Representative structures of natural and synthetic englerins.

Biogenetically, the englerins belong to a family of guaiane natural products in which a common bicyclic sesquiterpene skeleton has undergone a sequence of oxygenation and oxocyclization reactions.[8] Further decoration at the periphery of this core produces the structures of compounds **1** and **2**. Owing to the combination of uncommon structural architecture, potent and selective cytotoxicity against RCC, and promising pharmacology, the englerins have received the attention of the chemical community. Since their isolation in 2009, five total syntheses[9] and many strategies and studies[10] have been reported. These studies also led to the identification of synthetic englerin analogues, such as compounds **3**, **4**, and **5**, as products of various esterification reactions of the common tricyclic core. Several recent reviews have nicely summarized the current status of englerins.[11] Our continuous interest in exploring natural products from

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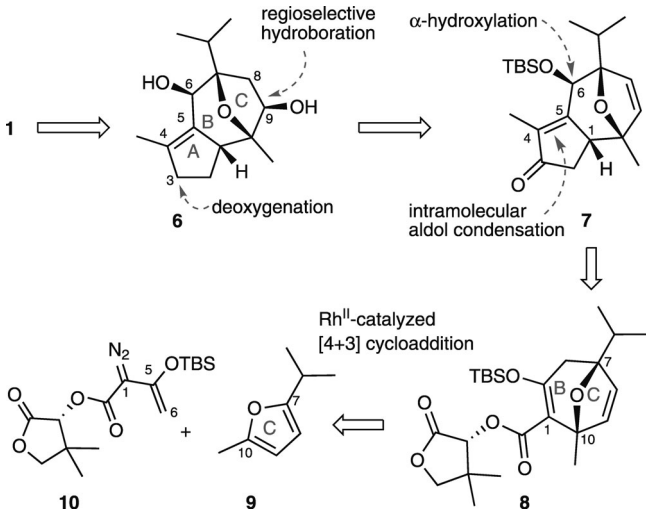
ethnomedicine as medicinal lead-compounds[12] has prompted us to design an enantioselective strategy toward the englerin family.[13] Herein, we describe in detail the results of our efforts and the biological evaluation of structurally simplified englerin analogues.

Results and Discussion

Retrosynthetic Analysis

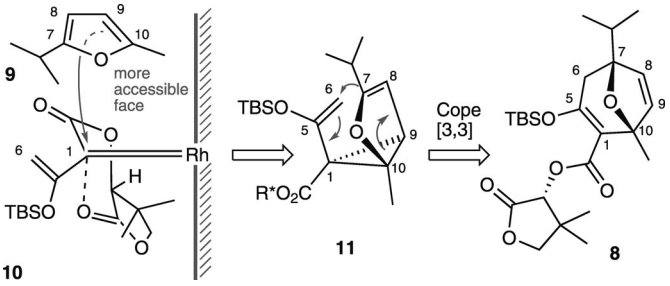
Our retrosynthetic analysis is shown in Scheme 2. We anticipated that a sequence of reactions, including inversion of the C6 stereocenter, hydrogenation of the C4–C5 alkene (englerin numbering), and selective esterifications at the C6 and C9 hydroxy groups would form englerin (**1**) from diol **6**. Compound **6** could be derived from enone **7** by C3 deoxygenation and a regioselective hydroboration of the C8–C9 double bond. We theorized that the cyclopentene moiety of compound **7** could be constructed from an intramolecular aldol condensation, whilst α-hydroxylation would produce the C6 hydroxy moiety. Disconnection along these lines led us to target the construction of bicyclic motif **8**, which possessed the BC ring scaffold of englerins. We hypothesized that compound **8** could be formed in its enantiomerically pure form by exploring a Rh^{II}-catalyzed [4+3] cycloaddition reaction between readily available furan **9**, which represented the C ring of compound **1**, and chiral pantolactone-derived diazoester **10**.



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

[4+3] Rhodium-Catalyzed Cycloaddition Reactions

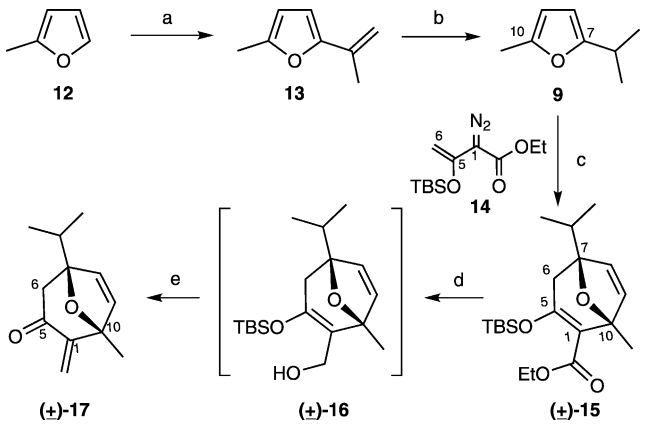
Rhodium-triggered cyclization reactions have been widely used in synthetic chemistry.[14] In 1996, Davies et al. reported an elegant enantioselective Rh^{II}-catalyzed [4+3] cycloaddition between furans and chiral diazoesters.[15] Selection of the appropriate pantolactone enantiomer as the chiral auxiliary allowed diastereocontrol of the oxy-bridged adduct. The transfer of chirality observed in this reaction can be rationalized by considering that the carbonyl moiety of pantolactone interacts with the Rh-carbenoid, as shown in Scheme 3. This interaction blocked one of the two faces of



Scheme 3. Rationale of the stereochemical consequences of the Davies Rh-catalyzed [4+3] cycloaddition reaction.

carbene **10**, thereby leading to a selective *si*-face attack by the 2-methyl-5-isopropyl-furan (**9**). The stereochemical outcome was consistent with a tandem cyclopropanation/Cope rearrangement (see intermediate [**11**]). Cyclopropanation of achiral furan **9** was expected to occur regioselectively at the less-substituted, and thus less-hindered, C9–C10 double bond. The potential of this cycloaddition to construct bicyclic structure **8** was of great interest to our strategy, as it provided efficient, rapid, and enantioselective access to the englerin core. Notably, both starting materials **9**[16] and **10**[15a,17] could be readily prepared on a more than 50 gram scale from commercially available materials in three steps.

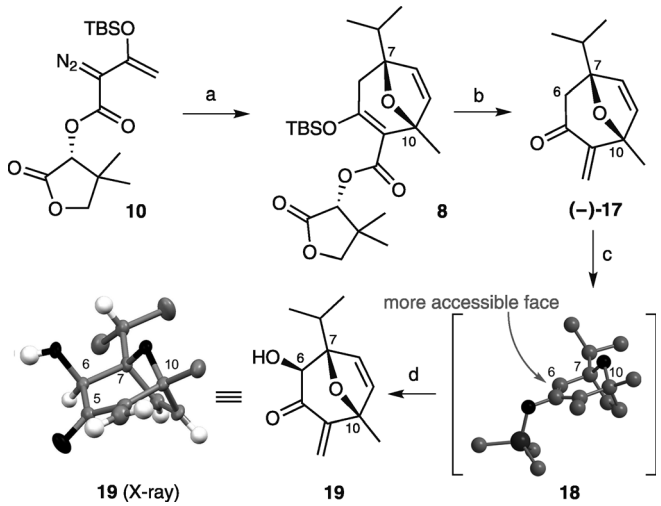
To the best of our knowledge, 2,5-disubstituted furans have not previously been evaluated as substrates in the Rh^{II}-catalyzed [4+3] cycloaddition. With this in mind, we initially evaluated the regioselectivity of this reaction by using achiral diazoester **14**[18] as a model system (Scheme 4). The synthesis of furan **9** is also shown in Scheme 4. Commercially available 2-methyl furan (**12**) was treated with *n*BuLi and acetone, followed by dehydration (Ac_2O/KOAc) to afford



Scheme 4. Reagents and conditions: a) *n*BuLi (0.94 equiv), Et_2O, −20 °C, reflux; then −20 °C, acetone (1.1 equiv), reflux; then Ac_2O (1.5 equiv), KOAc (0.63 equiv), 110 °C; b) Pd/C (catalytic), H_2 (1 bar), 1 h; c) [$Rh_2(Ooct)_4$] (2 mol %), hexanes, reflux, 95 %; d) DIBAL-H (2.5 equiv), CH_2Cl_2, −78 °C; e) BF_3·Et_2O (1.5 equiv), CH_2Cl_2, −30 °C, 81 %. DIBAL-H = diisobutylaluminum hydride.

alkene **13**. Regioselective hydrogenation of compound **13** proceeded smoothly by controlling the reaction time to 1 hour, and sequential distillation delivered the desired 2,5-disubstituted furan (**9**). Notably, this three-step preparation of compound **9** could be done on a more than 50 gram scale and only one distillation was needed for purification. Heating a mixture of compound **9** and diazoester **14** to reflux in *n*-hexane in the presence of catalytic amounts of rhodium(II) octanoate (2 mol%) afforded oxacyclic product (±)-**15** as the only regioisomer in excellent yield (95%). Cleavage of the ester auxiliary was more challenging than anticipated. In fact, the reported $LiAlH_4$ reductive cleavage only led to decomposition.[15a] However, treatment of ester **15** with DIBAL-H yielded labile β-hydroxy silyl enol ether **16** that, upon immediate treatment with stoichiometric amounts of $BF_3{\cdot}Et_2O$, underwent rearrangement[19] to afford exocyclic enone (±)-**17** in good yield (81%).

Encouraged by these results, we synthesized chiral diazoester **10** from (*R*)-pantolactone.[15a,17] The Rh^{II}-catalyzed [4+3] cycloaddition of diazoester **10** with compound **9** proceeded efficiently with $[Rh_2(Oct)_4]$ to yield compound **8** in good yield (90%), albeit in moderate diastereoselectivity (d.r. 3:1, calculated by using ^1H NMR spectroscopy; Scheme 5). Under the same conditions, the use of $[Rh_2(OAc)_2]$ only led to decomposition of the starting materials. Moreover, attempts to increase the d.r. by performing this reaction at lower temperatures or by using lower catalyst loading led to a significant decrease in the yield without any significant enhancement in the diastereoselectivity. Table 1 shows our efforts to optimize this cycloaddition reaction. The diastereomeric mixture of compound **8** was separated by column chromatography on silica gel. Our previously established reductive-cleavage conditions were applied to compound **8** to produce optically active enone (−)-**17**, although the yield was significantly lower (59%). This decrease in yield may have been due to the presence of the two reactive carbonyl moieties in compound **8** that required extended reaction times and excess DIBAL-H (7.5 equiv) compared to the reduction of compound (±)-**15** (2.5 equiv), thereby leading to partial decomposition of the sensitive silyl enol ether moiety.



Scheme 5. Reagents and conditions: a) compound **9** (2.0 equiv), $[Rh_2(Oct)_4]$ (2 mol%), hexanes, reflux, 95% for compound (±)-**16**, 90% for compound (−)-**16** (d.r. 3:1); b) DIBAL-H (7.5 equiv), CH_2Cl_2, −78°C, then $BF_3{\cdot}Et_2O$ (1.5 equiv), CH_2Cl_2, −30°C, 59%; c) LDA (4.6 equiv), TMSCl (4.6 equiv), −78°C to 0°C; d) *m*CPBA (1.1 equiv), $NaHCO_3$, CH_2Cl_2, 0°C, then $(COOH)_2$ (4.6 equiv), 36%; 87% brsm. brsm = based on recovered starting material.

Table 1. Optimization of the key [4+3] cycloaddition reaction between compounds **9** and **10**.[a]

Furan **9** [equiv]	Catalyst (mol%)	*T* [°C]	Yield [%] (d.r.)
10	$[Rh_2(Oct)_4]$ (2)	reflux	91 (3:1)
2	$[Rh_2(Oct)_4]$ (2)	reflux	90 (3:1)
2	$[Rh_2(Oct)_4]$ (1)	reflux	73 (3:1)
2	$[Rh_2(Oct)_4]$ (2)	−78	n.r.
2	$[Rh_2(Oct)_4]$ (2)	−40	n.r.
2	$[Rh_2(Oct)_4]$ (2)	0	n.r.
5	$[Rh_2(Oct)_4]$ (2)	30	31 (ND)
5	$[Rh_2(OAc)_4]$ (2)	reflux	n.r.

[a] n.r. = no reaction. ND = not determined.

Our attempts to install a hydroxy group onto the C6 carbon of compound (−)-**17** by using Davis oxaziridine reagents[20] were unsuccessful. However, Rubottom oxidation[21] provided the desired hydroxy enone **19** in good yield (36%; 87% brsm), although with inverse stereochemistry at the englerin C6 hydroxy moiety. The absolute stereochemistry of hydroxy enone **19** was established by single-crystal X-ray analysis,[22] which simultaneously confirmed the absolute stereochemistry of oxy-bridged ester **8**. We were pleased to observe that the Rubottom oxidation proceeded regioselectively at the more-electron-rich TMS enol ether without affecting any other alkenes in this molecule. The stereochemical outcome of this reaction was also satisfactory because it proceeded exclusively from the top face of the intermediate TMS-enolate [**18**], thus suggesting that this face was less hindered. We predicted that this selectivity would allow us to have complete substrate-control during the subsequent steps and invert the C6 stereochemistry at a later stage in our synthesis.

Formation of the A Ring Using Olefin Metathesis

The next stage of the synthesis involved constructing the tricyclic core of the englerin from compound **19**. We envisioned accomplishing this cyclization by the means of a Grubbs ring-closing metathesis (RCM)[23] of precursor **21** (Scheme 6), which, after oxidation of the C6 hydroxy group, would reveal a conjugate system for the 1,4-addition of a methyl nucleophile at the C4 site. To this end, a Lewis-acid-promoted conjugate allylation with allyltrimethylsilane afforded the corresponding ketone (**20**) in moderate yield (68%) as a single diastereomer. However, the subsequent olefination of the C5 position was unexpectedly challenging. After attempting many different methods, including the Wittig reaction, Peterson olefination,[24] Petasis,[25] and the Tebbe olefination,[26] only the $TiCl_4$-assisted Nysted olefination[27] gave low yields (15–36%) of trialkene **21**. Despite

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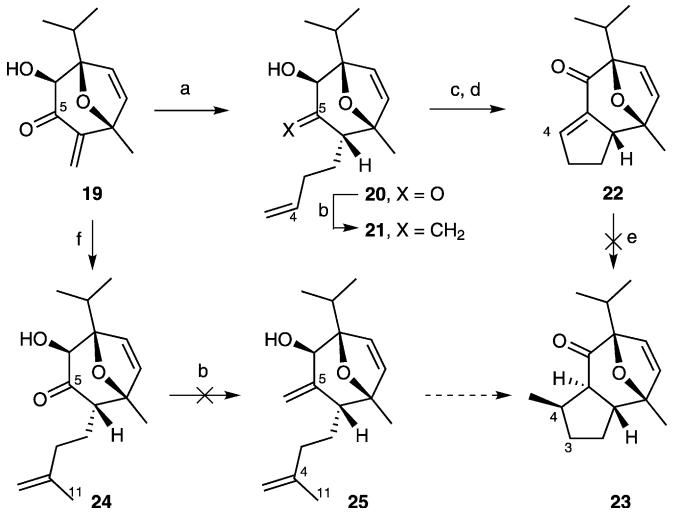
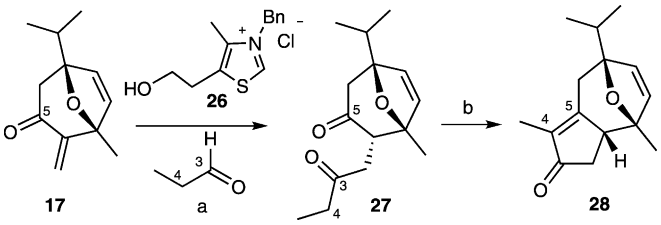


Scheme 6. Reagents and conditions: a) $TiCl_4$ (1.2 equiv), allyltrimethylsilane (3 equiv), CH_2Cl_2, −78 °C, 68 %; b) Nysted reagent (10 equiv), $TiCl_4$ (10 equiv), $NaHCO_3$ (7 equiv), −78 °C, 36 %; c) Grubbs second-generation catalyst (5 mol %), CH_2Cl_2, RT, 99 %; d) NMO (3 equiv), TPAP (0.1 equiv), CH_2Cl_2, RT, 72 %; e) various methyl cuprate reagents; f) $TiCl_4$ (1.1 equiv), trimethyl(2-methylallyl)silane (5 equiv), CH_2Cl_2, −78 °C, 71 %. NMO = *N*-methylmorpholine-*N*-oxide, TPAP = tetrapropylammonium perruthenate.



Scheme 7. Reagents and conditions: a) propanal (4 equiv), compound **26** (20 mol %), Et_3N (1.2 equiv), 80 °C, 75 %; b) KOH (5 equiv), EtOH, RT, 76 %.

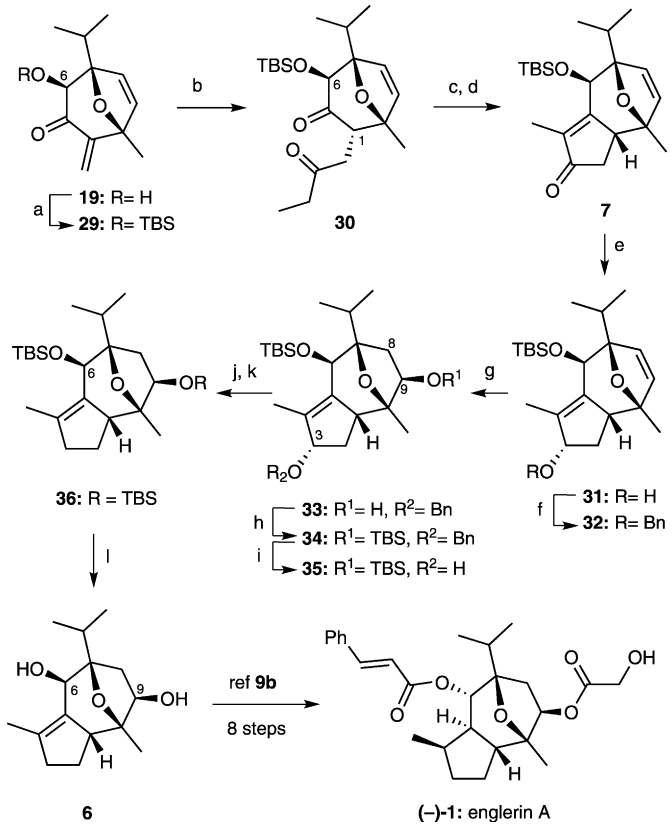
the inefficient formation of compound **21**, we attempted the RCM. We were pleased to see that this reaction proceeded smoothly in almost quantitative yield to give the allylic alcohol, which, after TPAP/NMO oxidation,[28] formed α,β-unsaturated ketone **22**. Unfortunately, all efforts to add methyl nucleophiles to compound **22** by conjugate addition were unsuccessful. To overcome this issue, we sought to perform the RCM on substrate **24**, which contained the challenging C11 methyl group. Consequently, we performed the allylation of compound **19** with methylallyltrimethyl silane. Whilst we were successful in producing compound **24**, olefination of this precursor at the C5 position gave irreproducible results, which prompted us to abandon this approach and seek an alternative strategy for the formation of the 5-membered ring from compound **19**.

Formation of the 5-Membered Ring (A Ring) from an Intramolecular Aldol Condensation Reaction and Completion of the Synthesis

Based on these results (see above), we pursued an alternative strategy for the construction of the tricyclic core of englerin that was based on an intramolecular aldol condensation reaction. Initially, we explored the feasibility of this reaction by using non-hydroxylated enone **17** as a model system. To this end, the treatment of propanal with thiazolium salt **26** and enone **17** under Stetter conditions[29] produced diketone **27** (Scheme 7). To our delight, the intramolecular aldol reaction of compound **27** proceeded under mild conditions (KOH/EtOH, RT, 24 h) to afford compound **28** in good yield (76 %).

Motivated by this result, we converted compound **19** into C6 silyl ether **29** and treated this product with propanal under the previously established Stetter conditions. This reaction proceeded efficiently under basic conditions to furnish diketone **30** as a single diastereomer in good yield (75 % over two steps). However, the application of the previously successful KOH condensation procedure only resulted in deprotection of the TBS ether, with no further reaction. This result prompted an extensive investigation on this intramolecular condensation reaction, with different C6 protecting groups (H, MOM, TES, etc.), various bases (*t*BuOK, KOH, NaOMe, LDA, etc.), and several reaction conditions tested. Many failed attempts at providing the tricyclic motif confirmed that this reaction was unexpectedly difficult. Eventually, the treatment of diketone **30** with NaHMDS afforded the corresponding aldol addition product, which underwent a sequential dehydration process (NaOMe/MeOH, heat) to produce the key tricyclic core (**7**) in acceptable yield (36 %; 43 % brsm). $NaBH_4$ reduction of enone **7** yielded allylic alcohol **31** (99 %) as a single diastereomer that, without further purification, was protected as a benzyl ether to furnish compound **32** in good yield (71 %). Treatment of compound **32** with BH_3·THF followed by oxidation with H_2O_2 afforded alcohol **33** (60 %) regio- and stereoselectively. Silylation of compound **33** followed by deprotection of the C3 benzyl ether yielded compound **35** via compound **34** in 99 % overall yield (Scheme 8). Our efforts to hydrogenate the tetrasubstituted alkene of compound **35** by using different catalysts and H_2 pressure were unsuccessful, presumably owing to the steric hindrance of the double bond (C4=C5). This result prompted us to deoxygenate the C3 hydroxy group under Barton–McCombie conditions[30] (40 % yield). In our efforts to improve this transformation, we discovered that the dehydration of compound **35** with Burgess reagent,[31] followed by standard hydrogenation, significantly improved the yield to 90 % over two steps. Deprotection of di-TBS ether **36** with TBAF gave poor results; however, we were pleased to find that a microwave-accelerated reaction under similar conditions (3 equiv TBAF, THF, 80 °C) made diol **6** in a quick and high-yielding conversion (45 min, 93 %).

To access the natural product from diol **6**, we would need to achieve stereoselective saturation of the tetrasubstituted bond, followed by esterification of the C9 hydroxy group, inversion of C6 stereocenter by oxidation/reduction sequence,

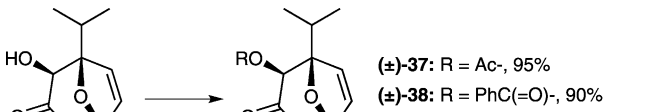


Scheme 8. Reagents and conditions: a) TBSOTf (2 equiv), NEt_3 (5 equiv), CH_2Cl_2, 0 °C to RT; b) propanal (4 equiv), compound **26** (20 mol %), Et_3N, 80 °C, 75% over 2 steps; c) NaHMDS (5 equiv), THF, 0 °C; d) NaOMe (1.3 equiv), MeOH, 65 °C, 36%; 43% brsm for 2 steps; e) $NaBH_4$ (5 equiv), MeOH, RT; f) NaH (4 equiv), BnBr (8 equiv), DMF, 60 °C, 71% for 2 steps; g) BH_3·THF (3 equiv), THF, RT then 3 M NaOH/30% H_2O_2, 60%; h) TBSOTf (2 equiv), Et_3N (4 equiv), CH_2Cl_2, RT, 97%; i) H_2 (1 atm), $Pd(OH)_2$ (catalytic), MeOH, RT, 99%; j) Burgess reagent (5 equiv), toluene, 80 °C, 90%; k) H_2 (1 atm), Pd/C (catalytic), MeOH, RT, 99%; l) TBAF (3 equiv), THF, 80 °C, microwave, 45 min, 93%. NaHMDS = sodium bis(trimethylsilyl)amide, Bn = benzyl, TBS = *tert*-butyldimethylsilyl, TBAF = tetrabutylammonium fluoride.

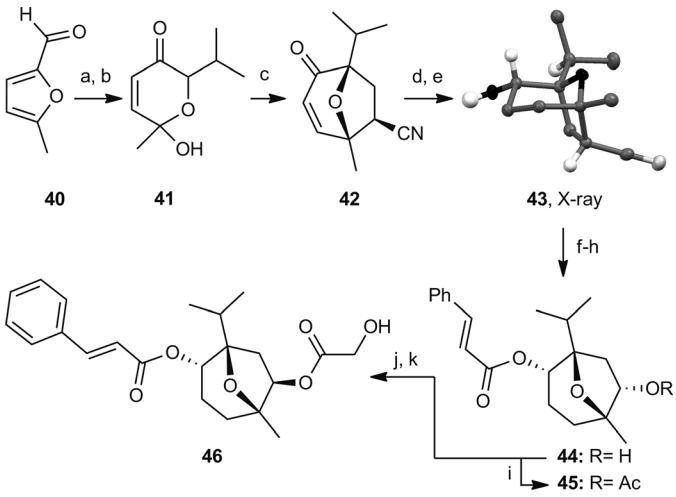
and finally esterification in the presence of cinnamic acid. An alternative synthesis of compound (+)-**6** was reported by Ma and co-workers.[9b] Our synthetic route to compound (+)-**6** provides another new and facile method for the construction of englerin A and related compounds. More significantly, the Rh-catalyzed [4+3]-annulation/intramolecular-aldol-condensation sequence presents a very useful, practical, and general method for the preparation of the guaiane sesquiterpene core that is present in englerin-related compounds.

Synthesis of Truncated Englerin Analogues

The intriguing bioactivity of englerin has prompted several groups to perform structure–activity relationship (SAR) studies[9f,10e] that have focused exclusively on modification of the C6 and C9 side-chains. An advantage of our strategy is that it can efficiently and stereoselectively produce compound **19**, which represents the BC ring system of englerins. In other words, this approach could provide information on the biological significance of the A ring of englerin. With this in mind, we synthesized truncated englerins **37**, **38**, and **39** (Scheme 9). To further expand such SAR studies, we designed a new approach towards compound **46**, which represented the nor-A-ring of englerin A. The synthesis of compound **46** (Scheme 10) was inspired by Wender's pioneering [5+2] cycloaddition reactions.[32] It is worth pointing out that this reaction has also been applied to the synthesis of englerin by the Nicolaou group.[9d] First, 2-methyl-5-furfural (**40**) was alkylated under Grignard conditions and the resulting alcohol was converted into hemiacetal **41** in 75% overall yield. Treatment of compound **41** with excess acrylonitrile



Scheme 9. Reagents and conditions: for compound **37**: Ac_2O (1.5 equiv), pyridine, 60 °C, 95%; for compound **38**: benzoic acid (2.0 equiv), 2,4,6-trichlorobenzoyl chloride (2.5 equiv), Et_3N (3.0 equiv), 4-DMAP (catalytic), toluene, 90%; for compound **39**: cinnamic acid (2.0 equiv), 2,4,6,-trichlorobenzoyl chloride (2.5 equiv), Et_3N (3.0 equiv), 4-DMAP (catalytic), toluene, 88%. 4-DMAP = 4-dimethylaminopyridine.



Scheme 10. Reagents and conditions: a) iPr_2MgCl (1.5 equiv), Et_2O, −10 °C; b) *m*CPBA (1.0 equiv), CH_2Cl_2, 75% over two steps; c) iPr_2NEt (1.2 equiv), MsCl (1.2 equiv), acrylonitrile (80 equiv), 100 °C, microwave, 45%; d) $NaBH_4$ (1.0 equiv), $CeCl_3$·H_2O (1 equiv), MeOH, 0 °C, 98%; e) H_2, Pd/C (catalytic), EtOH, 99%; f) LDA (2 equiv), THF, −78 °C, then O_2, then $SnCl_2$·HCl (30 equiv), 0 °C, 40%; g) cinnamic acid (2.0 equiv), 2,4,6,-trichlorobenzoyl chloride (2.5 equiv), Et_3N (3.0 equiv), 4-DMAP (catalytic), toluene, 95%; h) $NaBH_4$ (1.0 equiv), MeOH, 0 °C, 100%; i) Ac_2O (1.5 equiv), Et_3N (4.0 equiv), 4-DMAP (0.5 equiv), CH_2Cl_2, RT, 80%; j) LiHMDS (1.3 equiv), Im_2SO_2 (1.3 equiv), THF, 0 °C to RT, 99%; k) cesium hydroxy acetate (5 equiv), [18]crown-6 (5 equiv), toluene, 110 °C, 74%. *m*CPBA = *meta*-chloroperbenzoic acid, MsCl = methanesulfonyl chloride, LDA = lithium diisopropylamide.

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(iPr$_2$NEt/MsCl, 100 °C, 14 h) gave the desired bicyclic product (**42**) in 32 % yield. Moreover, this reaction was accelerated under microwave conditions to afford an improved yield (iPr$_2$NEt/MsCl, 150 °C, 4 h, 45 %). To the best of our knowledge, this is the first example of microwave acceleration of this type of [5+2] cycloaddition reaction. Luche reduction[33] followed by hydrogenation provided compound **43**[22] in almost quantitative yield. The transformation from compound **43** into compound **44** was accomplished in a three-step sequence that included: 1) oxidative cleavage of the cyanide group to the corresponding ketone; 2) esterification with cinnamic acid under Yamaguchi conditions;[34] and 3) hydride reduction of the C9 carbonyl moiety. The last two steps were performed according to a literature procedure[9b] to furnish compound **46**. Moreover, acetate analogue **45** was readily prepared from acetylation of compound **44**.

Cytotoxicity Studies of Truncated Englerins

The cytotoxicity of the truncated englerins was evaluated in both A498 renal cancer cells and CEM T-cell acute lymphoblastic leukemia (T-ALL) cells by using a ^{3}H-thymidine-incorporation assay. In our initial study, we compared the growth-inhibitory activity of englerin A to that of truncated englerins **44** and **46**. We found that englerin A inhibited the growth of A498 renal cancer cells with a GI_{50} of 45 nM, which is in agreement with previous results (Figure 1).[4, 9d, f, 10e] However, compounds **44** and **46** did not have any effect on the growth of A498 cells, even at concentrations of 100 nM or greater (Figure 1). These results suggest that the A ring is essential for the growth-inhibitory activity of englerin A in renal cancer cells.

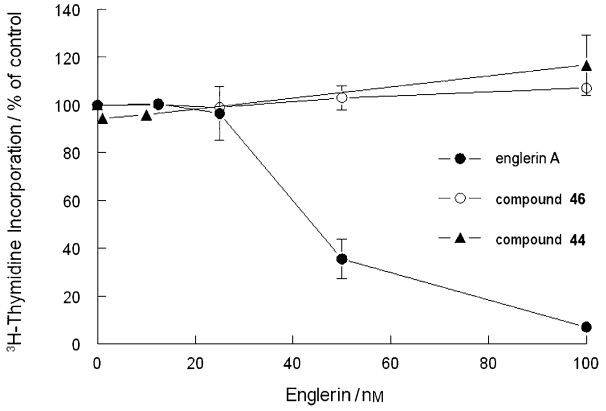

Figure 1. Effect of englerin A and analogues **44** and **46** on the proliferation of A498 renal cancer cells.

We then evaluated the antiproliferative activity of englerin analogues in CEM cells, a cell-line in which englerin A has little activity (GI_{50} = 20.4 μM).[4] Of all of the analogues tested, compounds **17**, (±)-**17**, and **19** had significant cytotoxicity, with GI_{50} values of 3.3, 1.8, and 2.4 μM, respectively (Figure 2, Table 2). It is likely that these cytotoxicities were due to the exocyclic enone moiety, which acted as a conjugate electrophile with bionucleophiles.[35] In contrast, englerin A and analogues that contained an additional ring, such as compound **7**, had little or no cytotoxicity at concentrations as high as 20 μM. These results suggested that the single-ring analogues can target leukemia cells effectively and the addition of structural complexity may result in a loss of cytotoxicity towards leukemia cells.

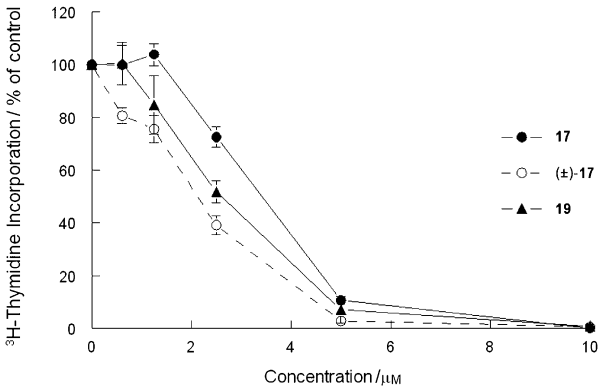

Figure 2. Dose-dependent inhibition of cell-proliferation by selected englerin analogues in T-ALL cells.

Table 2. Inhibition of cell-proliferation by (−)-englerin A and its analogues in T-ALL cells.[a]

Compound	% of Control at 20 μM	GI_{50} [μM]
(−)-englerin A	81.4(±2.5)	>20
44	74.6(±2.6)	>20
45	75.4(±4.5)	>20
46	88.7(±4.3)	>20
7	98.7(±4.0)	>20
17	0.2(±0)	3.3
(±)-**17**	ND	1.8
19	0.4(±0.1)	2.4
37	0.3(±0.3)	ND
38	0.2(±0.1)	ND
39	0.1(±0)	ND

[a] ND = not determined.

Conclusions

We have accomplished an efficient and enantioselective formal synthesis of englerin A (**1**), a potent and selective growth inhibitor of renal cancer cells. Our synthetic approach to intermediate **6** proceeded in 15 steps from readily available compounds **9** and **10** in 5 % overall yield. Key to our strategy was the enantioselective formation of the BC ring of compound **1** from a Rh^{II}-induced enantioselective [4+3] cycloaddition reaction, followed by the construction of the A ring from an intramolecular aldol condensation reaction. Inspired by this sequence, we also synthesized a small family of truncated englerins and evaluated their growth-inhibitory activities against certain renal cancer and leukemia cell-lines. These studies suggested that the A ring of englerin A plays an important role in its bioactivity and

tissue-selectivity. Interestingly, compounds (−)-**17**, (±)-**17**, and (−)-**19** have shown significant growth-inhibitory activity against CEM cell-lines at low micromolar concentrations (GI_{50} = 1–3 μM). Consequently, these compounds may represent new lead structures for the development of small-molecule therapeutics against leukemia.

Experimental Section

*(1R,5S)-(R)-4,4-Dimethyl-2-oxotetrahydrofuran-3-yl-3-[(tert-butyldimethylsilyl)oxy]-5-isopropyl-1-methyl-8-oxabicyclo[3.2.1]octa-2,6-diene-2-carboxylate (**8**)*

A solution of compound **10** (11.2 g, 31.6 mmol) in dry hexanes (750 mL) was added dropwise over 5.5 h to a refluxing solution of compound **9** (7.85 g, 8.8 mL, 63.2 mmol) and rhodium(II) octanoate dimer (492 mg, 0.63 mmol) in anhydrous hexanes (750 mL). The reaction mixture was stirred for an additional 30 min, after which TLC analysis showed no remaining starting material. The reaction mixture was allowed to cool to RT, filtered through a silica plug, and concentrated under vacuum. Column chromatography on silica gel (hexanes/EtOAc, 100:1 to 9:1 slow gradient) afforded 8.1 g of bicyclic ester **8** as a thick colorless oil (57%). $[\alpha]_D^{23} = +36.40$ ($c = 1.0$, $CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$): $\delta = 6.38$ (dd, $J = 5.7$, 0.5 Hz, 1H), 5.72 (d, $J = 5.7$ Hz, 1H), 5.40 (s, 1H), 4.04 (q, $J = 8.9$ Hz, 2H), 2.41 (d, $J = 17.4$ Hz, 1H), 1.95–1.83 (m, 2H), 1.62 (s, 3H), 1.24 (s, 3H), 1.17 (s, 3H), 1.00 (d, $J = 6.9$ Hz, 3H), 0.95 (d, $J = 6.8$ Hz, 3H), 0.92 (s, 9H), 0.19 (s, 3H), 0.18 ppm (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): $\delta = 172.4$, 164.2, 157.1, 141.6, 126.8, 117.9, 88.5, 82.8, 76.3, 75.0, 40.2, 37.1, 34.3, 25.8, 23.3, 21.5, 20.6, 18.4, 17.2, 17.1, −3.4, −3.5 ppm; HRMS (FAB): m/z calcd for $C_{24}H_{38}O_6SiNa$: 473.2330 $[M+Na]^+$; found: 473.2331.

*(1R,5S)-5-Isopropyl-1-methyl-2-methylene-8-oxabicyclo[3.2.1]oct-6-en-3-one (**17**)*

To a solution of compound **8** (20.7 g, 45.9 mmol) in dry CH_2Cl_2 (459 mL) was added DIBAL-H (344.3 mmol, 344.3 mL, 1.0 M in heptanes) dropwise quickly via an addition funnel at −78 °C. After the addition had been completed, the reaction was stirred for 15 min, after which TLC analysis showed no remaining starting material. The reaction mixture was quenched with saturated Rochelle salt solution (300 mL), allowed to warm to RT, and stirred for 1 h. The reaction mixture was filtered through Celite and washed with CH_2Cl_2 until TLC analysis showed no remaining crude product in the filter cake. The filtered mixture was separated, extracted with CH_2Cl_2 (2×150 mL), washed with brine (300 mL), dried over Na_2SO_4, filtered, and concentrated to 500 mL of CH_2Cl_2 under reduced pressure. The solution was flushed with argon and treated directly with $BF_3{\cdot}Et_2O$ (68.9 mmol, 8.7 mL) dropwise at −30 °C. After 5 min, TLC analysis showed no remaining starting material. The reaction mixture was further diluted with CH_2Cl_2 (250 mL), quenched with saturated $NaHCO_3$ solution (350 mL), and extracted with CH_2Cl_2 (2×200 mL). The combined organic layers were washed with brine (300 mL), dried over Na_2SO_4, filtered, and concentrated under vacuum. Purification by column chromatography on silica gel (hexanes/EtOAc, 100:1 to 9:1) afforded 5.2 g of ketone **17** as a yellow oil (59%). $[\alpha]_D^{23} = +103.01$ ($c = 1.0$, $CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$): $\delta = 6.05$ (d, $J = 5.8$ Hz, 1H), 5.96 (s, 1H), 5.92 (d, $J = 5.7$ Hz, 1H), 5.24 (s, 1H), 2.56 (d, $J = 17.7$ Hz, 1H), 2.46 (d, $J = 17.7$ Hz, 1H), 2.00–1.89 (m, 1H), 1.61 (s, 3H), 0.99 (d, $J = 4.9$ Hz, 3H), 0.98 ppm (d, $J = 4.7$ Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): $\delta =$ 197.8, 147.3, 136.3, 133.4, 115.3, 89.8, 84.9, 45.9, 33.7, 19.8, 17.3, 17.3 ppm; HRMS (FAB): m/z calcd for $C_{12}H_{16}O_2Na$: 215.1043 $[M+Na]^+$; found: 215.1045.

*(1S,2S,5R)-2-Hydroxy-1-isopropyl-5-methyl-4-methylene-8-oxabicyclo[3.2.1]oct-6-en-3-one (**19**)*

n-Butyllithium (77.6 mL, 124.2 mmol, 1.6 M in hexanes was added dropwise to a solution of dry diisopropylamine (19 mL, 135.0 mmol) in dry THF (800 mL) at −78 °C. The reaction mixture was stirred for 15 min, and then a solution of compound **17** (5.2 g, 27.0 mmol) in dry THF (500 mL) was quickly added dropwise to the reaction mixture. The temperature was raised from −78 °C to 0 °C over 45 min and stirred for 1 h at 0 °C. The reaction mixture was cooled to −78 °C and TMSCl (15.8 mL, 124.2 mmol) was added dropwise. The temperature was raised from −78 °C to 0 °C over 45 min and stirred for 1 h at 0 °C, at which time TLC analysis showed no remaining starting material. The reaction mixture was diluted with hexanes (650 mL), quenched with 5% $NaHCO_3$ solution (500 mL), washed with brine (300 mL), dried over Na_2SO_4, filtered, and concentrated under vacuum. To a solution of the crude enol-ether product in CH_2Cl_2 (250 mL) was added a solution of $NaHCO_3$ (250 mL, 10%) in a single portion at 0 °C. Then, a solution of *m*CPBA (5.2 g, 30.0 mmol) in CH_2Cl_2 (60 mL) was added slowly under vigorous stirring. The reaction was closely monitored by TLC. When trace amounts of enol ether (<5%) were observed, the reaction was further diluted in CH_2Cl_2 (200 mL), quenched with saturated $NaHSO_3$ solution (300 mL), allowed to warm to RT, extracted with CH_2Cl_2 (2×200 mL), washed with brine (300 mL), dried over Na_2SO_4, filtered, and concentrated under vacuum to approximately 250 mL. To this solution was added a solution of $(COOH)_2$ (15.6 g, 124.2 mmol) in MeOH (150 mL). After stirring for 30 min at RT, TLC analysis showed no remaining epoxide product. The reaction mixture was slowly quenched with saturated K_2CO_3 solution until neutral pH was achieved and then extracted with CH_2Cl_2 (2× 200 mL). The combined organic layers were washed with brine (300 mL), dried over Na_2SO_4, filtered, and concentrated under vacuum. Purification by column chromatography on silica gel (hexanes/EtOAc, 100:1 to 4:1) afforded compound **17** (2.7 g) and α-hydroxy ketone **19** as a crystalline solid (2.2 g, 36%; 87% brsm). Recrystallization from hexanes afforded crystals suitable for X-ray diffraction. $[\alpha]_D^{23} = +101.00$ ($c = 1.3$, $CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$): $\delta = 6.08$ (dd, $J = 5.8$, 0.9 Hz, 1H), 6.00 (d, $J = 5.9$ Hz, 1H), 5.97 (s, 1H), 5.28 (s, 1H), 3.81 (d, $J = 6.4$ Hz, 1H), 2.37–2.28 (m, 1H), 1.62 (s, 3H), 1.05 (d, $J = 6.9$ Hz, 3H), 0.94 ppm (d, $J = 6.8$ Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$): $\delta = 199.0$, 146.9, 140.2, 130.1, 116.5, 93.4, 85.5, 73.3, 28.4, 19.4, 17.7, 17.0 ppm; HRMS (ESI): m/z calcd for $C_{12}H_{16}O_3Na$: 231.0992 $[M+Na]^+$; found: 231.0993.

*(1S,2S,5R)-1-Isopropyl-5-methyl-4-methylene-3-oxo-8-oxabicyclo[3.2.1]oct-6-en-2-yl acetate (**37**)*

To a solution of compound **19** (5 mg, 0.024 mmol) in pyridine (0.25 mL) was added 4-DMAP (0.6 mg, 0.005 mmol) and Ac_2O (0.011 mL, 0.12 mmol). The mixture was heated at 60 °C for 3 h. The mixture was allowed to cool to RT, quenched with saturated $NaHCO_3$, and extracted three times with EtOAc. The combined organic layers were dried over $MgSO_4$, concentrated under vacuum, and the residue was purified by silica gel preparatory thin layer chromatography (hexanes/EtOAc, 20:1) to yield compound **37** as a white foam (5.7 mg, 95%). ^{1}H NMR (400 MHz, $CDCl_3$): $\delta = 6.16$ (d, $J = 5.9$ Hz, 1H), 6.02 (d, $J = 5.9$ Hz, 1H), 6.00 (s, 1H), 5.30 (s, 1H), 5.27 (s, 1H), 2.16 (s, 3H), 2.16 (m, 1H), 1.65 (s, 3H), 0.95 (d, $J = 6.9$ Hz, 3H), 0.92 ppm (d, $J = 6.9$ Hz, 3H); ^{13}C NMR (126 MHz, $CDCl_3$): $\delta = 194.1$, 170.0, 146.6, 141.2, 129.3, 116.9, 92.6, 85.7, 71.7, 29.9, 28.8, 19.5, 17.4, 17.1 ppm; HRMS (ESI): m/z calcd for $C_{14}H_{18}O_4Na$: 273.1097 $[M+Na]^+$; found: 273.1098.

*(1S,2S,5R)-1-Isopropyl-5-methyl-4-methylene-3-oxo-8-oxabicyclo[3.2.1]oct-6-en-2-yl benzoate (**38**)*

NEt_3 (15 μL, 0.11 mol) and 2,4,6-trichlorobenzoyl chloride (9 μL, 0.075 mol) were added successively to a stirring mixture of benzoic acid (7.3 mg, 0.06 mol) and compound **19** (6.5 mg, 0.026 mol) in dry toluene (0.55 mL). The reaction mixture was stirred for 10 min, then a catalytic amount of 4-DMAP (1 crystal) was added. After stirring for 16 h at RT, the mixture was diluted with EtOAc and the organic phase was washed successively with aqueous HCl solution (1 M), saturated sodium bicarbonate solution, and brine. The organic phase was dried over $MgSO_4$ and concentrated under vacuum after filtration. The residue was purified by column chromatography on silica gel (hexanes/EtOAc, 20:1) to afford benzoic keto-ester **38** (9.1 mg, 90%) as a colorless oil. ^{1}H NMR (400 MHz, $CDCl_3$): $\delta = 8.10$ (m, 2H), 7.57 (m, 1H), 7.24 (m, 2H), 6.21 (dd, $J = 5.8$, 0.9 Hz, 1H), 6.09 (d, $J = 5.8$ Hz, 1H), 6.02 (s, 1H), 5.51 (s,

1H), 5.32 (s, 1H), 2.25 (m, 1H), 1.69 (s, 3H), 0.96 (d, $J=6.9$ Hz, 3H), 0.93 ppm (d, $J=6.9$ Hz, 3H); ^{13}C NMR (126 MHz, $CDCl_3$): $\delta=193.8$, 165.5, 146.7, 141.1, 133.4, 130.1, 129.4, 128.4, 92.8, 85.6, 72.0, 28.9, 19.6, 17.4, 17.1 ppm; HRMS (ESI): *m/z* calcd for $C_{19}H_{20}O_4Na$: 335.1254 $[M+Na]^+$; found: 335.1256.

*(1S,2S,5R)-1-Isopropyl-5-methyl-4-methylene-3-oxo-8-oxabicyclo[3.2.1]oct-6-en-2-yl cinnamate (**39**)*

NEt_3 (11 μL, 0.08 mol) and 2,4,6-trichlorobenzoyl chloride (7 μL, 0.07 mol) were added successively to a stirring mixture of cinnamic acid (8 mg, 0.053 mol) and compound **19** (5.5 mg, 0.026 mol) in dry toluene (0.5 mL). The reaction mixture was stirred for 10 min, then a catalytic amount of 4-DMAP (1 crystal) was added. After stirring for 16 h at RT, the reaction was diluted with EtOAc and the organic phase was washed successively with aqueous HCl solution (1 M), saturated sodium bicarbonate solution, and brine. The organic phase was dried over $MgSO_4$ and concentrated under vacuum after filtration. The residue was purified by column chromatography on silica gel (hexanes/EtOAc, 20:1) to afford compound **39** (7.8 mg, 88%) as a colorless oil. ^{1}H NMR (500 MHz, $CDCl_3$): $\delta=7.70$ (d, $J=15.9$ Hz, 1H), 7.52 (m, 2H), 7.39 (m, 3H), 6.52 (d, $J=16.0$ Hz, 1H), 6.19 (d, $J=5.8$ Hz, 1H), 6.06 (d, $J=5.8$ Hz, 1H), 6.03 (s, 1H), 5.42 (s, 1H), 5.33 (s, 1H), 2.22 (m, 1H), 1.68 (s, 3H), 0.96 ppm (t, $J=6.9$ Hz, 6H); ^{13}C NMR (126 MHz, $CDCl_3$): $\delta=194.1$, 166.0, 146.5, 141.2, 134.3, 130.7, 129.4, 129.0, 128.4, 117.2, 116.9, 92.8, 85.7, 71.7, 28.8, 19.6, 17.5, 17.1 ppm; HRMS (ESI): *m/z* calcd for $C_{21}H_{22}O_4Na$: 361.1416 $[M+Na]^+$; found: 361.1417.

*(1R,5S,6S)-1-Isopropyl-5-methyl-2-oxo-8-oxabicyclo[3.2.1]oct-3-ene-6-carbonitrile (**42**)*

To a solution of compound **41** (1.6 g, 11.0 mmol) in acrylonitrile (60 mL) was added diisopropylethylamine (2.3 mL, 13 mmol), followed by methanesulfonyl chloride (1.0 mL, 13 mmol). The resulting solution was heated in a microwave at 150 °C for 4 h. After being allowed to cool to RT, the reaction mixture was filtered through a plug of Celite and the filtrate was concentrated in vacuo. Column chromatography on silica gel (EtOAc/hexanes, 20%) provided cycloadduct **42** (880 mg, 45%) as a colorless oil. ^{1}H NMR (500 MHz, $CDCl_3$): $\delta=6.93$ (d, $J=9.7$ Hz, 1H), 6.01 (d, $J=9.8$ Hz, 1H), 3.06 (dd, $J=9.2$, 2.9 Hz, 1H), 2.52 (dd, $J=14.3$, 2.9 Hz, 1H), 2.30 (p, $J=7.0$ Hz, 1H), 2.19 (dd, $J=14.3$, 9.3 Hz, 1H), 1.74 (s, 3H), 1.08 (d, $J=6.9$ Hz, 3H), 1.04 ppm (d, $J=6.9$ Hz, 3H); ^{13}C NMR (126 MHz, $CDCl_3$): $\delta=196.7$, 151.8, 128.1, 118.8, 100.0, 90.4, 37.4, 35.2, 30.0, 21.6, 17.6, 16.5 ppm; HRMS (ESI): *m/z* calcd for $C_{12}H_{15}NNaO_2$: 228.0995 $[M+Na]^+$; found: 228.0996.

^{3}H-Thymidine-Incorporation Assay

CEM cells were plated at $10–20\times10^3$ cells/well and A498 cells at 3500 cells/well in 96-well plates in Roswell Park Memorial Institute medium (RPMI) that was supplemented with 10% fetal bovine serum, 2 mM glutamine, and 100 u mL^{-1} penicillin/streptomycin (complete medium). Englerin A or its analogues were added to the cells at increasing concentrations and 0.1% DMSO was added to the control cells. The cells were incubated for 48 h and then pulsed with ^{3}H-thymidine for 6 h. The incorporation of ^{3}H-thymidine was determined by a scintillation counter (Beckman Coulter Inc., Fullerton, CA) after the cells had been washed and deposited onto glass microfiber filters using a cell-harvester M-24 (Brandel, Gaithersbur, MD).

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