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Total Synthesis of Englerin A

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Abstract: Total synthesis of englerin A, a recently reported sesquiterpenoid exhibiting potent and selective growth inhibition against renal cancer cell lines, has been accomplished. The successful strategy featured a [5 + 2] cycloaddition reaction to cast the seven-membered oxabicyclic key intermediate in both racemic and optically active forms. Synthetic (±)-englerin A, (±)-englerin B, (±)-englerin B acetate, a hydroxy acetate, a *tert*-butyldimethylsilyl ether, and hydrogenated (±)-englerin A (**31**) were tested for their cytotoxicity against a selected panel of cancer cell lines, and the results are path-pointing to more focused structure−activity relationship studies.

Introduction

Englerin A (**1**, Figure 1) is a newly discovered guaiane sesquiterpene from the stem bark of *Phyllanthus engleri* collected in Tanzania.[1] Its importance derives from its potent and selective growth inhibitory (GI) activities against renal cancer cells (i.e., 786-O, A498, ACHN, RXF-393, VO-31, $GI_{50} < 20$ nM, ca. 1000-fold selectivity as compared to most other cancer cell lines of the NCI-60 panel tested).[1] Its unique structure includes a tricyclic motif carrying two esters, one to a cinnamic acid (C_6, englerin A numbering) and the other to a glycolic acid (C_9) residue. The latter is apparently crucial for its potency and selectivity, since englerin B (**2**, Figure 1) and englerin B acetate (**3**, Figure 1) showed significant loss of potency and selectivity toward renal cancer cells.[1] Intrigued by the structure and biological properties of englerin A (**1**) as a lead compound for drug discovery, we initiated a program directed at its total synthesis. Herein we report the total synthesis of englerin A [(±)-**1**], englerin B [(±)-**2**], and englerin B acetate [(±)-**3**] from simple starting materials. In addition, a formal asymmetric synthesis of these compounds has also been accomplished by reaching a late-stage key intermediate in its optically active form.[2]

Results and Discussion

Retrosynthetic Analysis. Scheme 1 shows, in retrosynthetic format, the key carbon−carbon bond disconnections employed to devise the synthetic strategy toward englerin A (**1**) [and therefore englerin B (**2**) and englerin B acetate (**3**)], in which a [5 + 2] cycloaddition reaction played the key role in the formation of the bicyclo[3.2.1] ring framework of the molecule. The envisioned [5 + 2] cycloaddition reaction between oxopyrilium species **5** and ethyl acrylate (**6**) was expected to lead to oxabicyclic enone **4** in its racemic form, whereas an asymmetric synthesis of either enantiomer of the natural product could, in principle, arise through the use of this venerable reaction engaging chiral sulfonamide acrylate derivative **7** or its enantiomer.

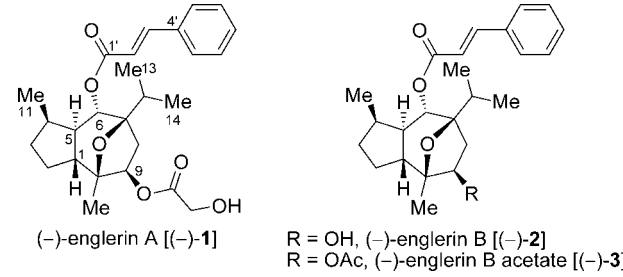


Figure 1. Structures of (−)-englerin A [(−)-**1**], (−)-englerin B [(−)-**2**], and (−)-englerin B acetate [(−)-**3**].

Construction of Oxabicyclic Hydroxy Ketoester 16. The synthesis of hydroxy ketoester **16** commenced from the readily available propargylic alcohol **8**,[3] whose regioselective iodination (Red-Al, I_2) led to vinyl iodide **9** (87% yield) (Scheme 2). Coupling of the latter intermediate with trimethylsilyl (TMS) acetylene [$Pd(PPh_3)_4$ cat.] furnished enyne **10**, from which the TMS group was removed (K_2CO_3, MeOH) to afford hydroxy enyne **11** (89% yield for the two steps). Gold-catalyzed ring closure of **11** (Ph_3PAuCl, AgOTf)[4] then generated furan system **12** in 91% yield. Formylation of the latter compound ($POCl_3$, DMF)[5] led to aldehyde **13** (88% yield), which reacted with *i*-PrMgCl to afford hydroxy furan **14**. The latter intermediate

(1) (a) Ratnayake, R.; Covell, D.; Ransom, T. T.; Gustafson, K. R.; Beutler, J. A. *Org. Lett.* **2009**, *11*, 57–60. (b) Beutler, J. A.; Ratnayake, R.; Covell, D.; Johnson, T. R. WO2009/088854, 2009.

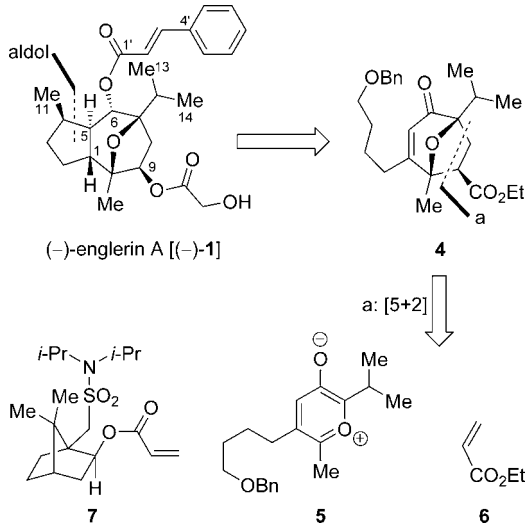
(2) A recent synthesis of *ent*-englerin A [(+)-**1**] from the natural product *cis*,*trans*-nepetalactone has recently been reported; it proved the absolute configuration of englerin to be that depicted by structure (−)-**1**: (a) Willot, M.; Radtke, L.; Könning, D.; Fröhlich, R.; Gessner, V. H.; Strohmann, C.; Christmann, M. *Angew. Chem., Int. Ed.* **2009**, *48*, 9105–9108. For total synthesis of (−)-**1**, see: (b) Zhou, Q.; Chen, X.; Ma, D. *Angew. Chem., Int. Ed.* **2010**, *49*, 3513–3516. (c) Molawi, K.; Delpont, N.; Echavarren, A. M. *Angew. Chem., Int. Ed.* **2010**, *49*, 3517–3519.

(3) Nicolaou, K. C.; Veale, C. A.; Webber, S. E.; Katerinopoulos, H. *J. Am. Chem. Soc.* **1985**, *107*, 7515–7518.

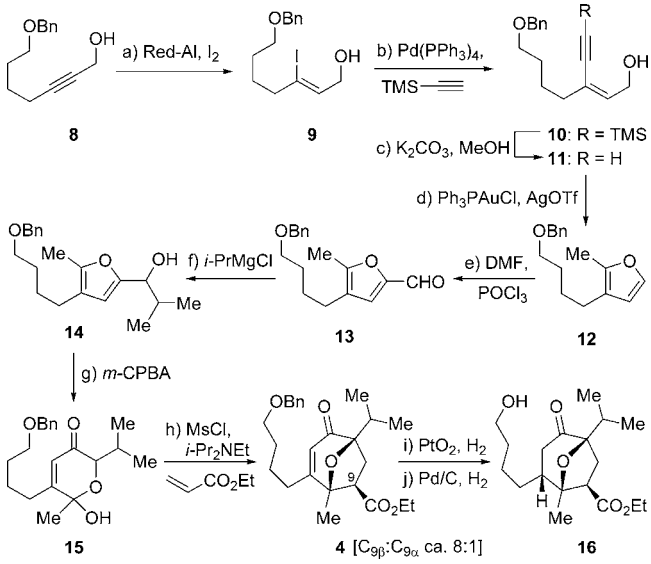
(4) Du, X.; Song, F.; Lu, Y.; Chen, H.; Liu, Y. *Tetrahedron* **2009**, *65*, 1839–1845.

(5) Jones, G.; Stanforth, S. P. *Org. React.* **1997**, *49*, 1–330.

Scheme 1. Retrosynthetic Disconnection of Englerin A (**1**) Leading to Oxabicyclic Enone **4**, Oxopyrilium Species **5**, Ethyl Acrylate (**6**), and Chiral Sulfonamide Acrylate Derivative **7**



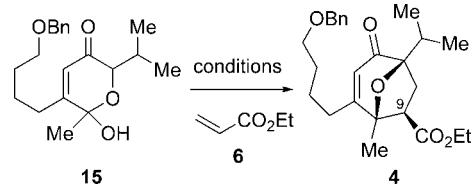
Scheme 2. Synthesis of Oxabicyclic Hydroxy Ketoester **16**[a]



[a] Reagents and conditions: (a) Red-Al (70% in toluene, 1.6 equiv), THF, −15 → 0 °C, 24 h; then EtOAc (1.6 equiv), I_2 (1.6 equiv), −78 → 23 °C, 1 h, 87%; (b) trimethylsilyl acetylene (1.5 equiv), $Pd(PPh_3)_4$ (0.05 equiv), CuI (0.2 equiv), Et_3N/*i*-Pr_2NEt (2:1), 23 °C, 30 min, 92%; (c) K_2CO_3 (3.0 equiv), MeOH, 23 °C, 30 min, 97%; (d) Ph_3PAuCl (0.02 equiv), AgOTf (0.02 equiv), THF, 23 °C, 1 h, 91%; (e) $POCl_3$ (1.5 equiv), DMF, 0 → 23 °C, 1 h, 88%; (f) *i*-PrMgCl (2.0 M in THF, 1.2 equiv), THF, −20 °C, 30 min, 83%; (g) *m*-CPBA (77% wt/wt, 1.2 equiv), CH_2Cl_2, 0 °C, 0.5 h, 84%; (h) MsCl (1.2 equiv), *i*-Pr_2NEt (0.9 equiv), ethyl acrylate (20 equiv), toluene, 85 °C, 3 h (8:1 mixture of diastereoisomers by ^1H NMR), 46%; (i) Pt_2O (0.2 equiv), H_2 (1 atm), benzene, 24 h, 88%; (j) Pd/C (10% wt/wt, 0.2 equiv), H_2 (1 atm), MeOH, 2 h, 91%. Abbreviations: Red-Al, sodium bis(2-methoxyethoxy)aluminum hydride; EtOAc, ethyl acetate; DMF, *N*,*N*′-dimethylformamide; OTf, trifluoromethanesulfonate; *m*-CPBA, *m*-chloroperoxybenzoic acid; Ms, methanesulfonyl.

underwent Achmatowicz rearrangement[6] upon exposure to *m*-CPBA to give ring-expanded lactol **15** (84% yield). With the stage set for the crucial [5 + 2] cycloaddition reaction, generation of oxopyrilium species **5** (see Scheme 1) from **15** (MsCl, *i*-Pr_2NEt) and its reaction with ethyl acrylate (**6**) were investi-

Table 1. [5 + 2] Cycloaddition Reaction between Lactol **15** and Ethyl Acrylate (**6**) Leading to Oxabicyclic Enone **4**[a]



entry	conditions	yield (%)[e]	$C_{9\beta}$:$C_{9\alpha}$[f]
1	*i*-Pr_2NEt (1.2 equiv), toluene (0.15 M), 3 h	47	5:1
2	*i*-Pr_2NEt (1.2 equiv), THF (0.15 M), 3 h	UM[g]	
3	*i*-Pr_2NEt (1.2 equiv), CH_3CN (0.15 M), 3 h	50	1.5:1
4	*i*-Pr_2NEt (1.2 equiv), $ClCH_2CH_2Cl$ (0.15 M), 3 h	UM[g]	
5[b]	*i*-Pr_2NEt (1.2 equiv), additive (1.0 equiv), toluene (0.15 M), 3 h	UM[g]	
6	*i*-Pr_2NEt (1.2 equiv), LiCl (1.0 equiv), toluene (0.15 M), 3 h	25	3.3:1
7[c]	*i*-Pr_2NEt (1.5 equiv), toluene (0.13 M), 3 h	26	5:1
8[c]	*i*-Pr_2NEt (1.5 equiv), CH_2Cl_2 (0.13 M), 3 h	19	3:1
9[c,d]	*i*-Pr_2NEt (1.2 equiv), toluene (0.13 M), 3 h	49	5:1
10[c,d]	*i*-Pr_2NEt (0.9 equiv), toluene (0.04 M), 3 h	46	8:1

[a] **15** (1.0 equiv), **6** (10.0 equiv), MsCl (1.2 equiv), 23 °C → reflux. [b] $Yb(OTf)_3$, $TiCl_4$, AgOTf, CuCl, and $ZnBr_2$ were used as additives. [c] A solution of **15** (1.0 M) was added to the reaction mixture at reflux via syringe pump over 1 h, giving a final concentration of 0.13 M (entries 7−9) or 0.04 M (entry 10). [d] 20 equiv of **6** was used. [e] Yields refer to chromatographically and spectroscopically homogeneous materials. [f] Determined by ^1H NMR analysis of the crude reaction mixture. [g] Unidentified mixture.

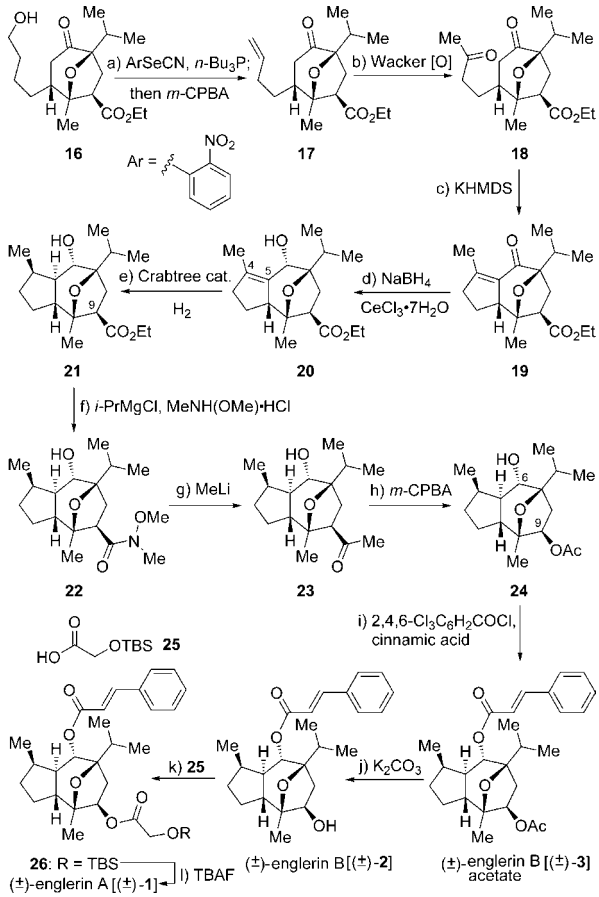
gated, and the results are shown in Table 1. Of the solvents examined (Table 1, entries 1−4), only toluene (Table 1, entry 1) and CH_3CN (Table 1, entry 3) were productive for this process, giving oxabicyclic enone **4** together with its 9α isomer (englerin A numbering, separable) in comparable yields (47% and 50%, respectively) but notably different diastereoselectivity ($C_{9\beta}$:$C_{9\alpha}$ ca. 5:1 and ca. 1.5:1, respectively). Lewis acidic additives (Table 1, entry 5) generally led to an unidentifiable mixture of byproducts, apart from LiCl (Table 1, entry 6), which led to oxabicyclic system **4** and its 9α isomer ($C_{9\beta}$:$C_{9\alpha}$ ca. 3.3:1) in 25% yield. A reverse addition protocol [slow addition of a solution of lactol **15** to a refluxing solution of MsCl, *i*-Pr_2NEt, and ethyl acrylate (**6**)] was examined next (Table 1, entries 7−10). Ultimately, the optimized conditions (Table 1, entry 10) were established by employing substoichiometric amounts of *i*-Pr_2NEt (0.9 equiv) under high dilution (0.04 M) to furnish bicycle **4** together with its 9α isomer ($C_{9\beta}$:$C_{9\alpha}$ ca. 8:1) in 46% yield. Sequential exposure of pure **4** to catalytic hydrogenation conditions (PtO_2, H_2; Pd/C, H_2) resulted in reduction of the olefinic bond and cleavage of the benzyl ether to afford, stereoselectively, hydroxy ketoester **16** in 80% overall yield.

Completion of the Total Synthesis of (±)-Englerin A [(±)-1], (±)-Englerin B [(±)-2], and (±)-Englerin B Acetate [(±)-3]. Compound **16** was converted to (±)-englerin B acetate [(±)-**3**], (±)-englerin B [(±)-**2**], and (±)-englerin A [(±)-**1**], as shown in Scheme 3. Thus, dehydration of **16** through its selenide derivative (ArSeCN, *n*-Bu_3P; then *m*-CPBA, 84% yield), followed by subjecting the resulting terminal olefin **17** to Wacker oxidation[7] conditions (O_2, $PdCl_2$ cat., CuCl cat., 86% yield), afforded diketone **18**. Treatment of diketone **18** with KHMDS at −10 °C, followed by warming the reaction mixture

(6) Achmatowicz, O.; Bielski, R. *Carbohydr. Res.* **1977**, *55*, 165–176.

(7) Clement, W. H.; Selwitz, C. M. *J. Org. Chem.* **1964**, *29*, 241–243.

Scheme 3. Completion of the Total Synthesis of (±)-Englerin A [(±)-**1**], (±)-Englerin B [(±)-**2**], and (±)-Englerin B Acetate [(±)-**3**][a]



[a] Reagents and conditions: (a) 2-nitrophenyl selenocyanate (1.4 equiv), PBu_3 (2.0 equiv), THF, 23 °C, 0.5 h; then *m*-CPBA (77% wt/wt, 2.0 equiv), CH_2Cl_2, 0 °C, 0.5 h; DBU (2.0 equiv), toluene, 80 °C, 8 h, 84%; (b) $PdCl_2$ (0.05 equiv), CuCl (0.2 equiv), O_2 (1 atm), DMF/H_2O (9:1), 23 °C, 6 h, 86%; (c) KHMDS (0.6 M in toluene, 2.2 equiv), THF, −10 → 0 °C, 2 h, 77%; (d) $CeCl_3 \cdot 7H_2O$ (2.0 equiv), $NaBH_4$ (2.0 equiv), MeOH, 0 °C, 0.5 h, 95%; (e) Crabtree catalyst (0.3 equiv), H_2 (1 atm), CH_2Cl_2, 12 h, 91%; (f) MeNHOMe·HCl (4.0 equiv), *i*-PrMgCl (2.0 M in THF, 10.0 equiv), THF, −15 → 0 °C, 3 h, 90%; (g) MeLi (4.0 equiv), THF/Et_2O (1:1), −78 → −60 °C, 1.5 h, 73%; (h) *m*-CPBA (77% wt/wt, 4.0 equiv), 1,2-dichloroethane, 80 °C, 48 h, 65%; (i) cinnamic acid (2.0 equiv), 2,4,6-trichlorobenzoyl chloride (2.2 equiv), Et_3N (4.0 equiv), 4-DMAP (2.6 equiv), toluene, 80 °C, 2 h, 86%; (j) K_2CO_3 (3.0 equiv), MeOH, 23 °C, 1 h, 92%; (k) **25** (2.0 equiv), 2,4,6-trichlorobenzoyl chloride (2.2 equiv), Et_3N (4.0 equiv), 4-DMAP (2.6 equiv), toluene, 80 °C, 1 h, 86%; (l) TBAF (2.0 equiv), THF, 0 °C, 10 min, 89%. Abbreviations: KHMDS, potassium hexamethyldisilazane; TBS, *tert*-butyldimethylsilyl; 4-DMAP, *N*,*N*′-(dimethylamino)pyridine.

to 0 °C, led, through an intramolecular aldol/dehydration sequence, to enone **19** in 77% yield. Stereoselective reduction of ketone **19** under Luche[8] conditions furnished allylic alcohol **20**, which underwent stereoselective hydrogenation (C_4-C_5 olefinic bond) in the presence of Crabtree's catalyst[9] to afford tricyclic system **21** in 91% yield and as a single diastereoisomer. The directing effect of the neighboring hydroxyl group within **20** was crucial in the Crabtree hydrogenation, as confirmed by the fact that enone **19** underwent hydrogenation (Pd/C, H_2) from the opposite face of the C_4-C_5 olefinic bond. The desired oxygenation at C_9 was achieved through a Baeyer−Villiger[10] oxidation of methyl ketone **23** (*m*-CPBA, 65% yield), obtained through Weinreb amide[11] **22** (MeLi, 73% yield), which in turn was formed from ethyl ester **21** by reaction with *i*-PrMgCl−MeNH(OMe)·HCl (90% yield). Ketone **23** (mp =161−162 °C, hexane/CH_2Cl_2) yielded to X-ray crystallographic analysis, confirming its structural assignment as shown in Figure 2.[12] All that separated hydroxy acetate **24** from englerin A (**1**) was attachment of the proper ester side chains on its cyclic framework. To this end, **24** was first coupled with cinnamic acid through the Yamaguchi protocol[13] to afford (±)-englerin B acetate [(±)-**3**] (86% yield), from which the acetate group was removed (K_2CO_3) to give (±)-englerin B [(±)-**2**] (92% yield). Installment of the desired glycolic acid residue on the latter compound proceeded smoothly under Yamaguchi conditions (86% yield) to afford, upon desilylation (TBAF, 89% yield), (±)-englerin A [(±)-**1**] through intermediate **26**. The physical data of synthetic (±)-**3**, (±)-**2**, and (±)-**1** matched

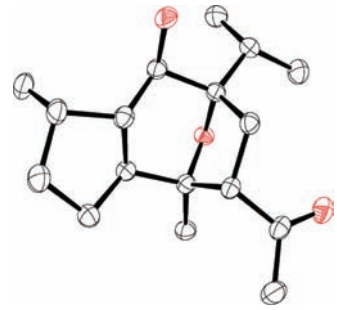
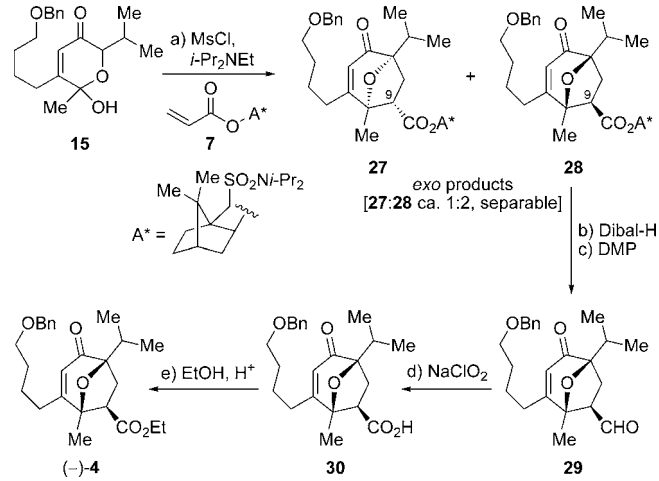


Figure 2. X-ray-derived ORTEP of hydroxy ketone **23** with thermal ellipsoids shown at the 50% probability level.[12]

Scheme 4. Asymmetric Synthesis of Oxabicyclic Enone **4**[a]



[a] Reagents and conditions: (a) MsCl (1.2 equiv), *i*-Pr_2NEt (1.2 equiv), **7** (2.0 equiv), toluene, 85 °C, 3 h (2:1 mixture of diastereoisomers by ^1H NMR), 30%; (b) Dibal-H (1.0 M in CH_2Cl_2, 4.5 equiv), CH_2Cl_2, −78 °C, 30 min; (c) DMP (1.2 equiv), $NaHCO_3$ (5.0 equiv), CH_2Cl_2, 23 °C, 30 min, 88% over the two steps; (d) $NaClO_2$ (2.0 equiv), 2-methyl-2-butene (10.0 equiv), *t*-BuOH/pH 7 phosphate buffer (1:1), 23 °C, 1 h; (e) H_2SO_4 (0.1 M in EtOH, 0.1 equiv), EtOH/toluene (1:1), 23 → 80 °C, 6 h, 75% over the two steps. Abbreviations: Dibal-H, diisobutylaluminum hydride; DMP, Dess−Martin periodinane.

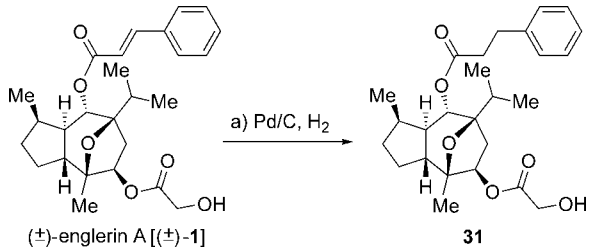
(8) (a) Molander, G. A. *Chem. Rev.* **1992**, *92*, 29–68. (b) Luche, J. L. *J. Am. Chem. Soc.* **1978**, *100*, 2226–2227.
(9) Crabtree, R. H.; Davis, M. W. *J. Org. Chem.* **1986**, *51*, 2655–2661.
(10) Baeyer, A.; Villiger, V. *Ber. Dtsch. Chem. Ges.* **1899**, *32*, 3625–3633.
(11) Nahm, S.; Weinreb, S. M. *Tetrahedron Lett.* **1981**, *22*, 3815–3818.
(12) CCDC-771308 contains the supplementary crystallographic data for compound **20**. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif.
(13) Inanaga, J.; Hirata, K.; Saeki, H.; Katsuki, T.; Yamaguchi, M. *Bull. Chem. Soc. Jpn.* **1979**, *52*, 1989–1993.

Table 2. Cytotoxicity of (±)-Englerin A [(±)-**1**], (±)-Englerin B [(±)-**2**], (±)-Englerin B Acetate [(±)-**3**], Hydroxy Acetate **24**, TBS Ether **26**, and Hydrogenated (±)-Englerin A (**31**) against Selected Cancer Cell Lines (GI_{50} values in μM)[a]

		cell line				
entry	compound	MCF-7[b]	NCI-H460[b]	ACHN[b]	A498[b]	UO31[b]
1	doxorubicin	0.066 ± 0.004	0.010 ± 0.000	0.072 ± 0.006	0.243 ± 0.062	0.693 ± 0.221
2	Taxol	0.007 ± 0.001	0.006 ± 0.001	0.076 ± 0.008	0.078 ± 0.006	0.721 ± 0.146
3	(±)-**1**	>10	>10	0.113 ± 0.071	0.045 ± 0.004	0.037 ± 0.005
4	(±)-**2**	>10	>10	>10	>10	>10
5	(±)-**3**	>10	>10	>10	6.341 ± 0.229	9.275 ± 0.013
6	**24**	>10	>10	>10	>10	>10
7	**26**	>10	>10	>10	>10	>10
8	**31**	>10	>10	0.745 ± 0.166	0.287 ± 0.139	0.359 ± 0.006

[a] Antiproliferative effects of tested compounds against human tumor cell lines in a 48 h growth inhibition assay using the sulforhodamine B staining method. Human cancer cell lines: breast (MCF-7), lung (NCI-H460), and renal (ACHN, A498, and UO31). Growth inhibition of 50% (GI_{50}) is calculated as the drug concentration which caused a 50% reduction in the net protein increase in control cells during drug incubation. GI_{50} values for each compound are given in μM and represent the mean of 2−5 independent experiments ± standard error of the mean. [b] These cell lines were provided by the National Cancer Institute (NCI), Division of Cancer Treatment and Diagnosis (DCTD).

Scheme 5. Synthesis of Hydrogenated (±)-Englerin A (**31**)[a]



[a] Reagents and conditions: (a) Pd/C (10% wt/wt, 0.5 equiv), H_2 (1 atm), MeOH, 3 h, 100%.

(except for optical rotations) those reported for the naturally derived materials.[1]

Asymmetric Synthesis of Oxabicyclic Enone 4. Having secured a racemic entry to (±)-englerin A [(±)-**1**] [together with (±)-englerin B [(±)-**2**] and (±)-englerin B acetate [(±)-**3**]], as outlined in our retrosynthetic blueprint (Scheme 1), an asymmetric synthesis of oxabicyclic enone **4** through the [5 + 2] cycloaddition reaction between oxopyrilium species **5** and chiral sulfonamide acrylate derivative **7**[14] was pursued, as shown in Scheme 4. Thus, generation of oxopyrilium species **5** (see Scheme 1) from **15** (MsCl, *i*-Pr_2NEt) in the presence of chiral sulfonamide acrylate derivative **7** delivered oxabicyclic enones **27** and **28** (30% yield, unoptimized) as a chromatographically separable mixture (**27**:**28** ca. 1:2). Although ultimately proven unwarranted, caution was exercised at this stage for possible epimerization at C_9 under basic saponification conditions for **28**. Therefore, enone ester **28** was subjected to a two-step reduction/oxidation (Dibal-H; then DMP) sequence to afford aldehyde **29** in 88% yield overall yield. Oxidation of aldehyde **29** to acid **30** ($NaClO_2$), followed by esterification of the latter under acidic conditions (H_2SO_4, EtOH, 75% yield over the two steps), proceeded smoothly to furnish optically active enone ethyl ester (−)-**4** [$[\alpha]_D^{25} = -95$ ($CHCl_3$, $c = 0.18$)]. The ^1H and ^{13}C NMR data of (−)-**4** were in full agreement with those of racemic **4** (Scheme 2). The arrival at optically active **4**, therefore, constitutes a formal asymmetric synthesis of (−)-englerin A [(−)-**1**], (−)-englerin B [(−)-**2**], and (−)-englerin B acetate [(−)-**3**].

Biological Studies. (±)-Englerin A [(±)-**1**], (±)-englerin B [(±)-**2**], (±)-englerin B acetate [(±)-**3**], hydroxy acetate **24**, TBS ether **26**, and hydrogenated (±)-englerin A (**31**, see Scheme 5) were tested against a panel of cancer cells, including breast (MCF-7), lung (NCI-H460), and renal (ACHN, A498, and UO31), using doxorubicin and Taxol as standards. The results are summarized in Table 2. (±)-Englerin A [(±)-**1**] demonstrated high potency and selectivity toward renal cancer cell lines (Table 2, entry 3). Compounds (±)-**2**, (±)-**3**, **24**, and **26** (Table 2, entries 4−7) failed to demonstrate any significant level of biological activities [except for (±)-**3**, see entry 5], evidence which further supports the importance of the glycolic acid residue.[1] The most noteworthy finding was that hydrogenated (±)-englerin A (**31**, Table 2, entry 8) also demonstrated excellent selectivity toward renal cancer cells with moderate activities, suggesting structural tolerance of the saturated cinnamate ester domain. Future work in this area should serve to uncover more insightful structure−activity relationship information, particularly concerning the cinnamate and glycolic ester side chains.

Conclusion

The described chemistry provides a ready access to englerins A and B and englerin B acetate (**1**−**3**). A formal asymmetric total synthesis of these compounds has also been demonstrated through the synthesis of optically active advanced key intermediate bicyclic enone **4**. The synthetic strategy employed features a [5 + 2] cycloaddition reaction of an oxopyrilium species **5** with appropriate acrylate esters, stereoselective Luche and Crabtree reductions, and a Baeyer−Villiger oxidation to secure the tricyclic core onto which the two ester side chains were attached through Yamaguchi esterifications. Biological evaluations of selected synthesized compounds provided valuable structure−activity relationships for future investigations toward drug discovery and development in cancer chemotherapy.

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Supporting Information Available: Experimental procedures and compound characterization. This material is available free of charge via Internet at http://pubs.acs.org.

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