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Total Synthesis

Total Synthesis of (±)-Englerin A and Its Tuncated Analogues

Colleen Reagan,[a] Graham Trevitt,[b] and Kirill Tchabanenko*[a]

Abstract: A convergent approach allowed total synthesis of (±)-Englerin A, and its truncated analogues, employing a thermal 1,3-dipolar cycloaddition of a highly substituted pyrylium ylide with vinyl acetate as the key step. The key intermediate, a 8-oxabicyclo[3,2,1]octane oxygenated at the C6 position, was directly converted into a truncated Englerin A analogue. Cu^{I} catalyzed conjugate addition of vinyl Grignard to an enone, ozonolysis, and epimerisation of the resulting aldehyde allowed stereoselective introduction of the side-chain leading to a total synthesis of the racemic natural product. The developed chemistry will allow synthesis of more complex analogues of the natural product based on the use of the key bicyclo[3,2,1]octane scaffold.

Introduction

Englerin A (**1**) is a naturally occurring sesquiterpene that was isolated from bark of *Phyllanthus engleri* by the NCI group under the supervision of Beutler in 2008.[1,2] It shows high potency and selectivity against a panel of renal cancers with no toxicity against normal renal cells. The remarkable properties and challenging structure have rendered Englerin A as a highly attractive synthetic target resulting in a number of elegant total syntheses and synthetic approaches.[3–18] Many of the authors have identified the oxygen-bridged seven-membered ring of the natural product as the key component and applied 1,3-dipolar cycloaddition strategies for its construction. [4+3] Cycloadditions of furans with oxy-allyl cation equivalents[9,10,12] and [5+2] cycloadditions of pyrylium ylides[5] and carbonyl ylides[15,16] have become reactions of choice for rapidly assembling this skeleton (Figure 1).

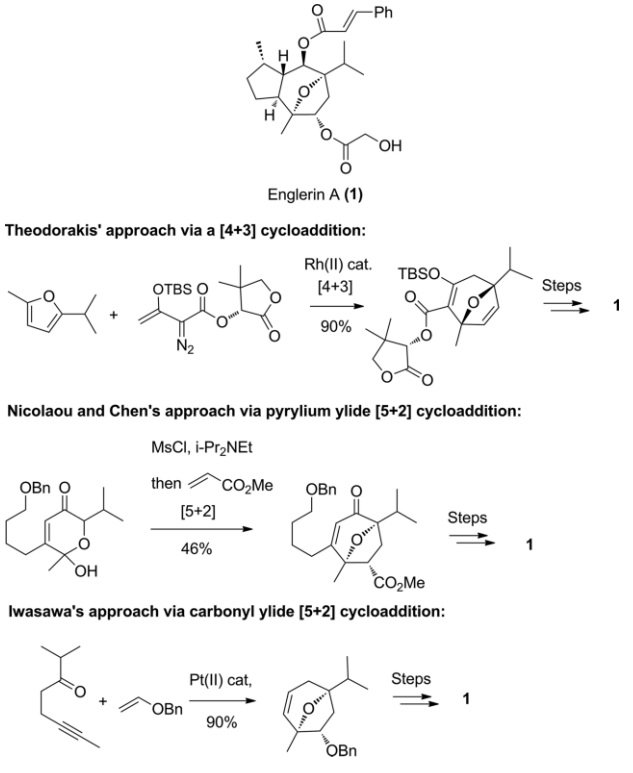


Figure 1. Dipolar cycloaddition strategies to **1**.

Our group has been involved in developing new applications for the 1,3-dipolar cycloaddition of pyrylium ylides over a number of years.[19,20] We also became interested in developing a novel rapid approach to Englerin A and a number of analogues using this versatile reaction.

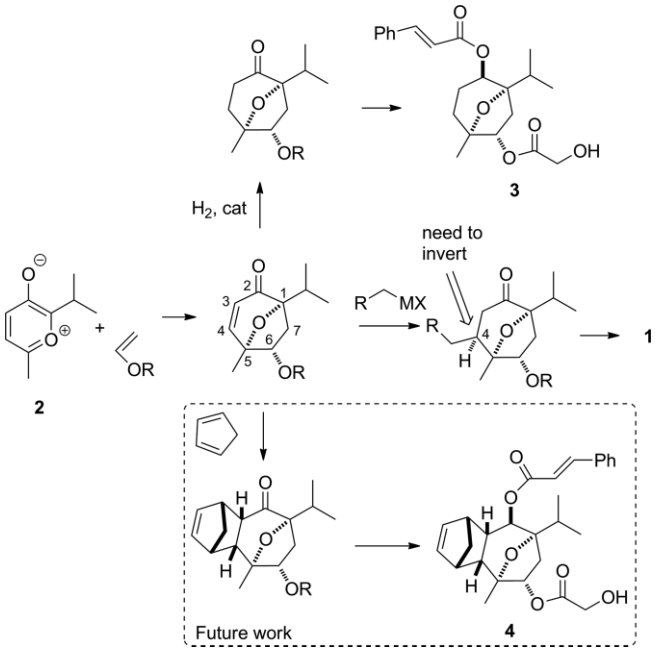
Results and Discussion

Synthetic Strategy

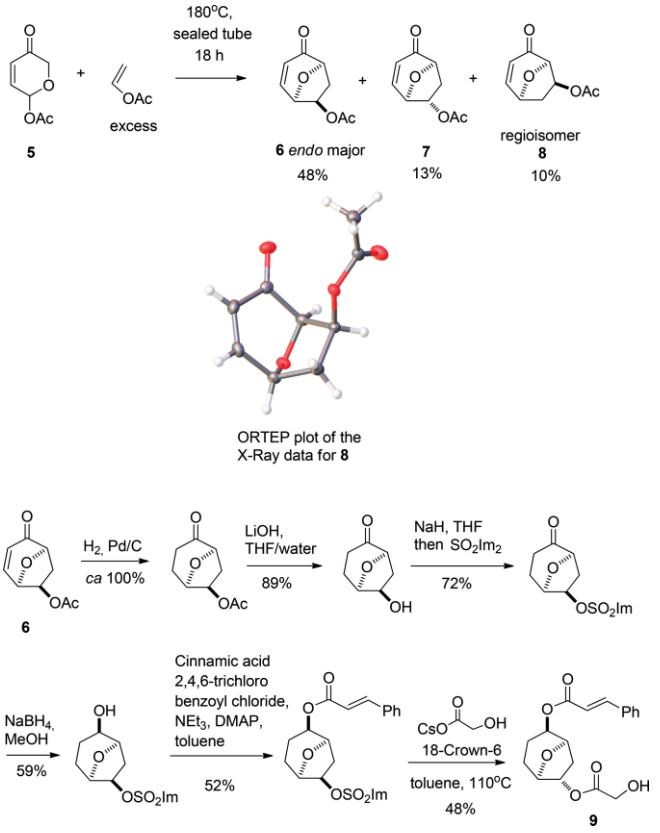
Early on we decided to develop a cycloaddition of a substituted pyrylium species **2** with an oxygen substituted dipolarophile (Scheme 1) that would enable direct synthesis of the hydroxyl function at the C-6 position of the seven-membered ring of the natural product. Next we decided to develop a convergent approach to a number of Englerin A analogues via a common cycloadduct. Thus reduction of the enone double bond followed by simple functional group conversion will lead to a truncated analogue **3**,[21] whilst a conjugate addition to the enone would require the correction of stereochemistry at C-4, and eventually lead to the required natural product. In addition, we envisaged the possibility to perform further cycloaddition reactions, for example the Diels-Alder reaction of the enone, shown in Scheme 1, thus allowing approach to more complex analogues like **4**.

[a] *School of Chemistry and Chemical Engineering, Queen's University Belfast David Keir Building, Belfast, BT9 5AG, United Kingdom*
E-mail: k.tchabanenko@qub.ac
[b] *Almac Discovery Ltd.*
Almac House, 20 Seagoe Industrial Estate, Craigavon, BT63 5QD United Kingdom

Supporting information and ORCID(s) from the author(s) for this article are available on the WWW under https://doi.org/10.1002/ejoc.201801544.



Scheme 1. Convergent strategy towards **1** and its analogues.



Scheme 2. Synthesis of a simple analogue **9**.

Synthesis of a Simple Analogue 9

Although the earlier SAR studies by Christmann and co-workers[4] showed the importance of the isopropyl group for the biological activity of Englerin A, we decided to start our investigation with the synthesis of a fully truncated analogue **9** (Scheme 2). We anticipated that the search for a suitable oxygenated dipolarophile and the optimization of the functional group transformations would be easier to carry out starting with a simple acetoxy pyrone **5**, a product of oxidation and acetylation of furfuryl alcohol.[22,23] With multigram quantities of the pyrone **5** in hand we quickly discovered that a thermal cycloaddition was possible with vinyl acetate[24] giving a mixture of diastereo-, and regioisomeric adducts **6**, **7** and **8** (Scheme 2). The reaction was best carried out using vinyl acetate as a solvent and the cycloadducts, **6**–**8**, were easily separated by column chromatography.

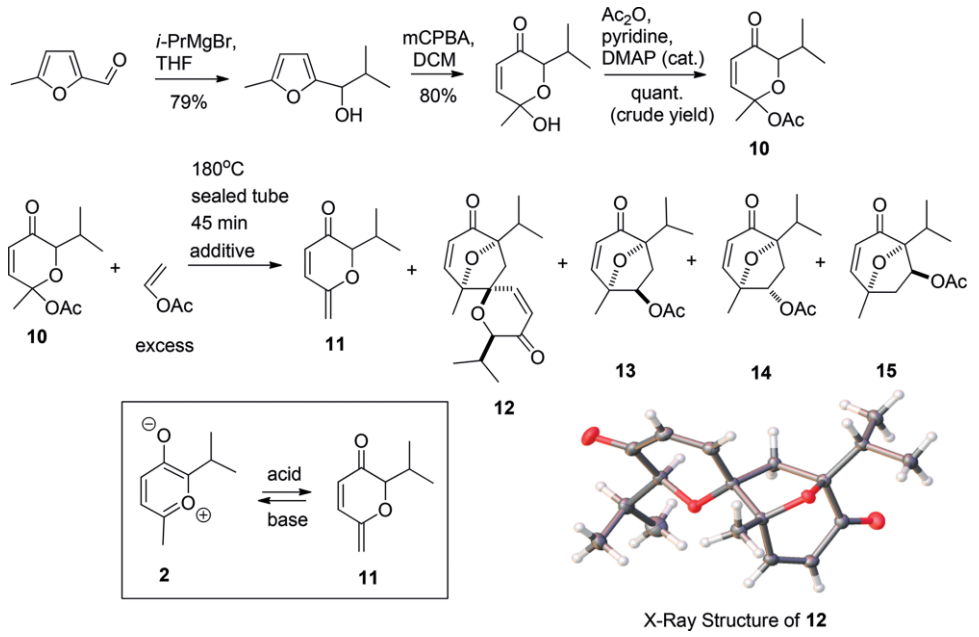
The reaction required 18 hours to achieve full consumption of the acetoxy pyrone starting material. The attempt to further heat the mixture of **6**, **7** and **8** expecting isomerization to the most stable adduct failed. We could not determine any equilibration of the products in the mixture, instead we only observed gradual decomposition of the products under the high temperature. The structure and stereochemistry of the regioisomeric cycloadduct **8** was confirmed by X-ray crystallography.[25]

Our next aim was to develop a straight-forward conversion of the major *endo* adduct **6** into **9** (Scheme 2) including an inversion of the C-6 hydroxyl stereochemistry. We planned to accomplish this in analogy to the chemistry described by Chain and co-workers in their remarkably short total synthesis of (–)-**1**.[11] The enone double bond in **6** was reduced over palladium on carbon and the acetate was then substituted for a sulfonylimidazole group required for the inversion step. We reasoned that an early protecting group exchange would avoid complications with chemoselective hydrolysis of an acetate in the presence of a cinnamate ester later in the synthesis. Sodium borohydride reduction of the ketone was followed by Yamaguchi esterification. Synthesis of **9** was accomplished by reaction with the cesium salt of glycolic acid introducing the glycolate ester with inversion of stereochemistry at the C-6.[11] The sequence allowed rapid synthesis of the fully truncated analogue **9**, which we were now ready to investigate for the adduct bearing the isopropyl and methyl groups.

Cycloaddition of a Substituted Pyrylium Ylide

The acetoxy pyrone precursor **10** was readily prepared from commercially available 5-methylfurfuryl aldehyde (Scheme 3).[10] Although we discovered that all our attempts to purify **10** led to hydrolysis of the acetate, it was possible to obtain a very pure product if the acetylation step was followed by a rapid aqueous workup and removal of the excess acetic anhydride under reduced pressure. The crude pyrone **10** was heated with vinyl acetate as previously discussed for the simple pyrone **5**. But this time the reaction noticeably became darker in color and was stopped after 45 minutes. NMR analysis showed that no starting pyrone remained, and a complex product mixture was obtained. Purification by flash chromatgrahy allowed separation of five new products **11**–**15** (Scheme 3 and Table 1).

Analysis of the product structures immediately identified the problem with the cycloaddition of **10** – formation of the alkene



Scheme 3. Cycloaddition of substituted pyrone **10**.

Table 1. Optimization of conditions.

Additive/Product yield	**11**[a]	**12**[b]	**13**[b]	**14**[b]	**15**[b]
No additive	25	16	10	6	5
10 mol-% AcOH	45	23	8	4	3
50 mol-% pyridine	trace	trace	16	9	7
1 equiv. 2,6-lutidine	5	2	28	15	14
1 equiv. 2,6-di*t*Bu-pyridine	trace	trace	30	16	15

[a] Yields from analysis of crude nmrs. [b] Isolated yields.

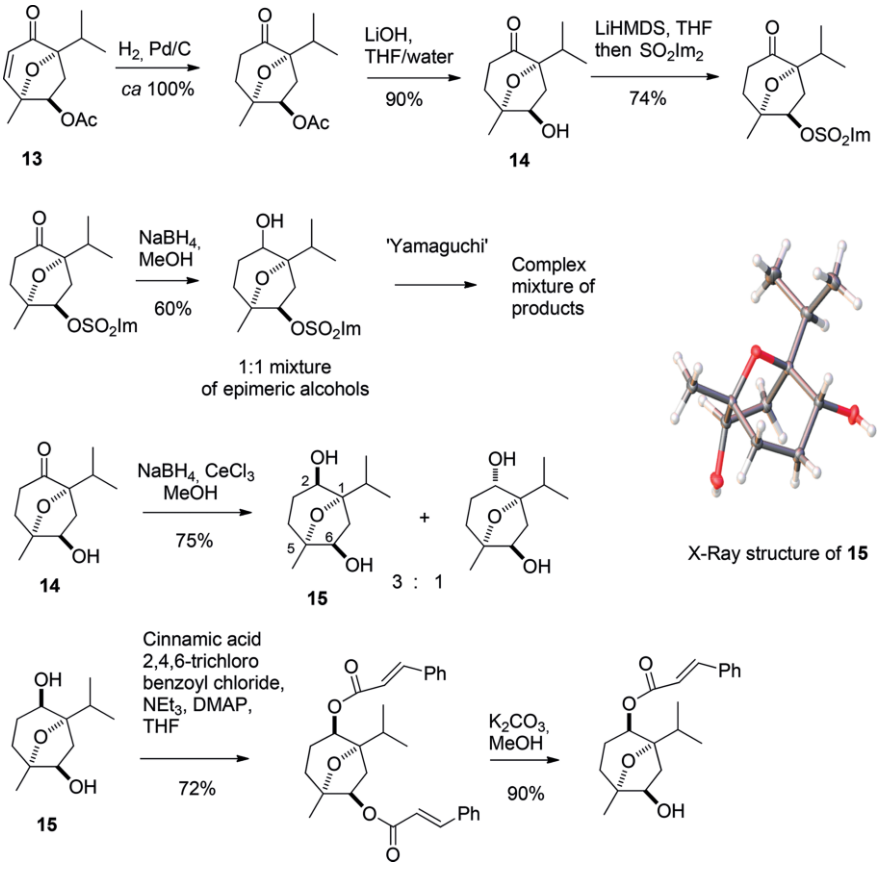
11 and its subsequent cycloaddition with pyrylium **2** to give the spirocyclic dimer **12**,[26] whose structure was confirmed by X-ray analysis.[27] The pyrylium species **2** and alkene **11** are isomers, and it was our aim to establish whether equilibration and overall formation of unwanted by-products could be overcome by controlling the reaction pH. Thus 10 mol-% of acetic acid was added to the reaction mixture. This increased the yields of the unwanted elimination product **11** and the dimer **12**, (Table 1 row 2). On the contrary, addition of pyridine eliminated the formation of these side products. (Table 1 row 3). Use of less nucleophilic 2,6-lutidine and 2,6-di-*tert*-butylpyridine led to further increase in the yield of the desired cycloadduct **13**. Once again, we were unable to achieve interconversion of the products **13**–**15** on attempted heating in toluene, showing that the cycloaddition with vinyl acetate is irreversible under neutral conditions. A threefold improvement in the reaction yield from the initial attempt allowed multigram synthesis of the required cycloadduct **13** from the readily available acetoxy pyrone **10**.

Synthesis of the Truncated Analogue 3

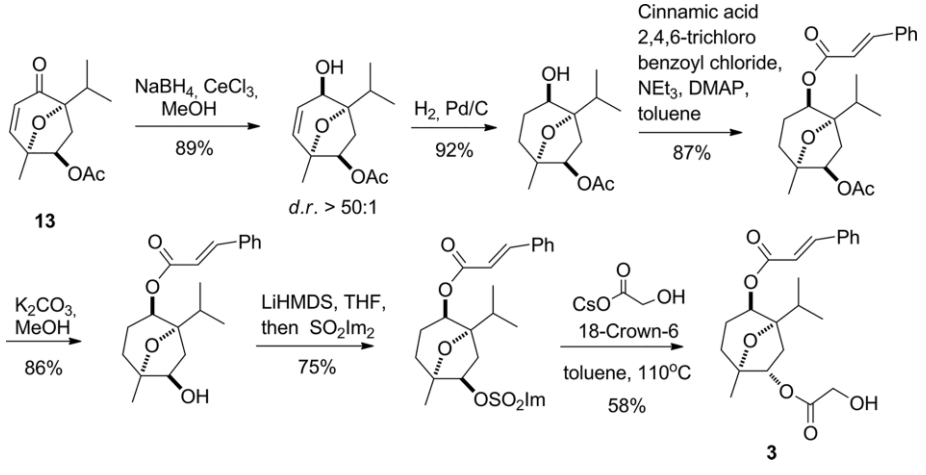
Initially we intended to carry out the same sequence of reactions which were successfully applied in the synthesis of the simple analogue **5** but this time on the cycloadduct **13** possessing an extra isopropyl and methyl groups (Scheme 4). Whereas the initial double bond reduction and exchange of the acetate for the sulfonyl imidazole group worked well, the sodium borohydride ketone reduction produced a 1:1 mixture of epimeric alcohols. The attempted Yamaguchi esterification of the mixture of both epimers resulted in the loss of the sulfonylimidazole group and formation of multiple products resulting from non-selective esterification of two diastereoisomeric diols. Thus showing that a different protecting strategy for the alcohol at C-6 was required. At this point in the synthesis we had a significant amount of alcohol **14** which we submitted to the Luche reduction conditions. Under these conditions the desired epimer of the diol **15** was obtained as a major product. It was isolated and its structure was confirmed by X-ray analysis.[28] Double Yamaguchi esterification was then attempted giving the bis-cinnamate ester **16**, which was subjected to mild ester hydrolysis conditions.[5] This resulted in selective hydrolysis of the ester at the C-6 position of the seven membered ring. The observed change in reactivity and selectivity is mostly due to the presence of the isopropyl group in the more substituted series. Whereas in the simple analogue case all reagents approached the bicyclic system from the face of the oxygen bridge giving remarkable selectivity, the presence of the isopropyl group in the latter case makes the face of the oxygen bridge more hindered, what leads to lower facial selectivity of the observed transformations. The isopropyl group also hinders the ester at C-2 making it unreactive towards mild nucleophiles.

With this in mind we attempted an approach to the truncated Englerin A analogue **3** keeping the acetate protecting group until the final steps of the synthesis (Scheme 5). Also we decided to perform the Luche reduction on the enone **13** prior to the hydrogenation of the enone double bond, similar to the strategy of Theodorakis and co-workers.[10]

Reduction of the ketone group in **13** proceeded with even higher stereoselectivity, giving only trace amounts of the un-



Scheme 4. Initial attempts to make **3**.

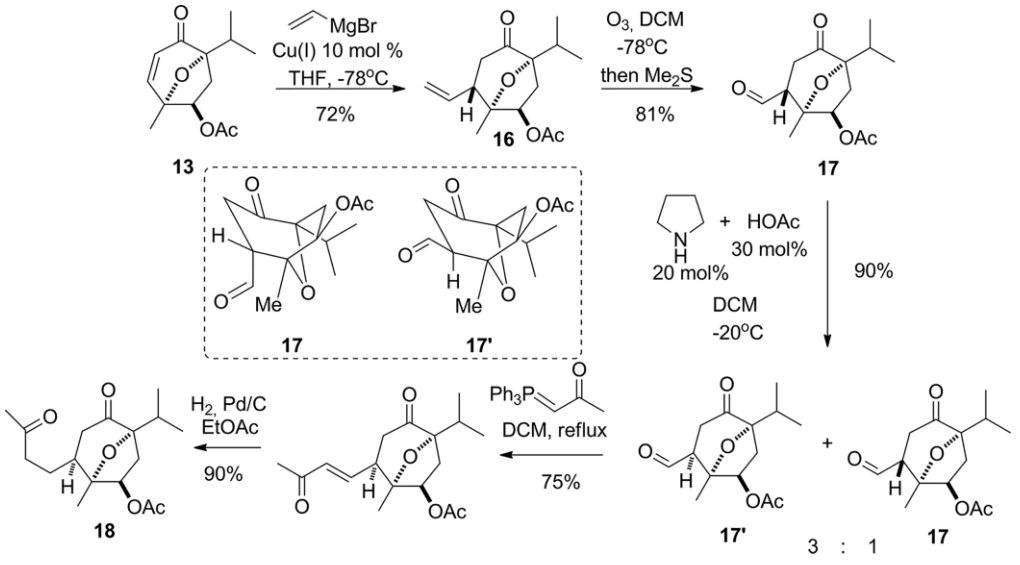


Scheme 5. Completion of the truncated analogue **3**.

wanted epimer at the C-2 position. This time we were able to use the acetate as protecting group for the C-6 alcohol and over a short number of steps (Scheme 5) completed the synthesis of truncated analogue **3**, which further streamlined our strategy for the synthesis of (±)-Englerin A (**1**).

Introduction of the Side Chain

From the outset we envisaged installation of an aldehyde moiety at the C4 of the oxygen bridged seven membered ring. This would allow epimerization if needed and further direct build-up of the side chain. We were able to incorporate the aldehyde via a Cu^{I} catalyzed conjugate addition of vinyl Grignard[29] and ozonolysis of the double bond (Scheme 6). The conjugate addition was stereoselective giving a single adduct **16** (Scheme 6) with the opposite stereochemistry of the newly formed C-C bond to the one required for the total synthesis. Thus the vinyl group was ozonolyzed to an aldehyde **17**. Epimerization of the aldehyde group in **17** was complicated by the possibility of the oxygen bridge elimination, and a mild procedure was required.



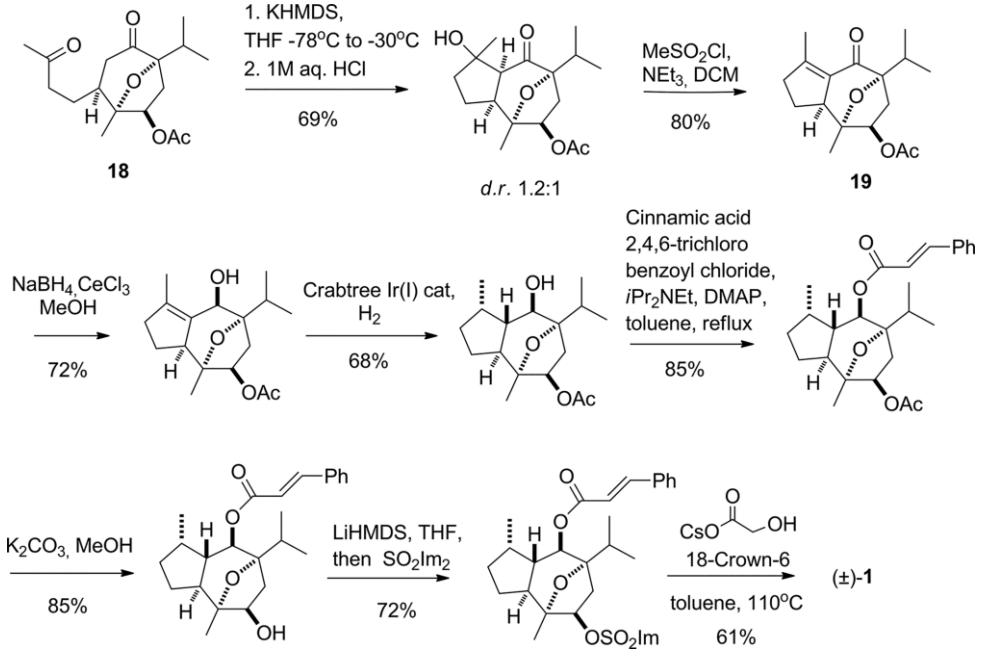
Scheme 6. Synthesis of the aldol precursor **19**.

The best result was obtained when we used pyrrolidine and acetic acid at low temperature.

Epimerization took over 2 days resulting in a 3:1 mixture of epimers favoring the isomer with relative stereochemistry required for the total synthesis of Englerin A. This fortunate outcome was probably due to the preference of the aldehyde group to adopt an equatorial position in **17′** as shown in Scheme 6. No further conversion of **17** into **17′** was possible on prolonged treatment under indicated conditions. Careful column chromatography allowed isolation of essentially pure aldehyde **17′**. Wittig olefination with 1-(triphenylphosphoranylidene)-2-propanone was carried out under literature conditions.[30] Standard hydrogenation afforded the intramolecular aldol precursor **18**.

Completion of the Synthesis

Next we performed the intramolecular aldol cyclisation to form the five-membered ring of the natural product. Although our advanced intermediate **19** was close in structure to the similar aldol precursor in Nicolaou and Chen's route,[5] we discovered that the acetoxy protecting group was incompatible with the highly basic conditions required for a direct conversion of **18**



Scheme 7. Completion of the total synthesis.

into the enone **19**. But treatment of the diketone **18** with one equivalent of base, allowing the aldol to go to completion and quenching with acid at low temperature allowed separation of two diastereomeric adducts in nearly 1:1 ratio (Scheme 7). The *syn* ring fusion was assigned for both products based on the same coupling constant between the ring junction hydrogens. Both adducts were submitted to mild elimination conditions giving the enone **19**. Luche reduction, Crabtree directed hydrogenation and Yamaguchi esterification were performed according to literature procedures.[5] As previously in the synthesis of the truncated analogue **3** we were able to selectively hydrolyse the acetate, leaving the cinnamate ester intact, and the final two steps were carried out according to Chain's methods[11] resulting in formation of racemic Englerin A (**1**).

Conclusions

In conclusion total synthesis of (±)-Englerin A based on a 1,3-dipolar cycloaddition of a substituted pyrylium ylide with vinyl acetate was achieved in 17 steps. New strategy allowed the synthesis of truncated analogues alongside with the natural product. Interesting stereochemical effects of the bridgehead substituents on the reactivity of the 8-oxabicyclo[3.2.1]octanes were uncovered. Synthesis of new analogues of the natural product, based, on the new methodology, is currently under way in our research laboratory.

Experimental Section

General Experimental: All reactions were carried out under atmosphere of argon unless stated otherwise. Reaction solvents (THF, diethyl ether) were freshly distilled from sodium/benzophenone under argon atmosphere prior to use. Dichloromethane and toluene were freshly distilled from calcium hydride under an argon atmosphere. All reagents were purchased from Sigma-Aldrich and were used as received unless specified. All NMR spectroscopic data was collected on a Bruker DRX-500, Bruker AV-400 or Bruker Av-300 spectrometers. All NMR experiments were run in $CDCl_3$ apart from the final sample of (±)-Englerin A, which was run in [D_6]DMSO for comparison with literature data. IR spectra were collected on a Perkin-Elmer Spectrum One FT-IR spectrometer and mass-spec data was collected on a Waters GCT-Premier Spectrometer with nanomate attachment.

(*rel*-1*R*,5*R*,6*R*)-2-Oxo-8-oxabicyclo[3.2.1]oct-3-en-6-yl Acetate (6): A solution of an unsubstituted acetoxy pyrone[22] (2 g, 12.8 mmol) in vinyl acetate (30 mL, excess) was placed in a sealed tube and heated in an oil bath at 180 °C for 18 h. The solvent was removed in vacuo and the residual oil was purified by flash column chromatography (3:1 petroleum ether/ethyl acetate eluent).

Cycloadduct 6: A colorless oil (1.11 g, 48 %); ν_{max}(thin film) 1737 (s), 1710 (s), 1693 (m), 1072 (m); ^{1}H (400 MHz, $CDCl_3$) 7.12 (1H, dd, *J* 10.0, 4.5 Hz), 6.20 (1H, d, *J* 10.0 Hz), 5.29 (1H, ddd, *J* 9.0, 5.5, 4.0 Hz), 5.02 (1H, dd, *J* 5.5, 4.5 Hz), 4.48 (1H, d, *J* 8.5 Hz), 2.85 (1H, ddd, *J* 13.5, 9.0, 4.5 Hz), 2.03 (3H, s), 1.70 (1H, dd, *J* 13.5, 4.0 Hz); ^{13}C (100 MHz, $CDCl_3$) 195.9, 170.6, 149.1, 128.4, 80.7, 74.5, 72.9, 31.7, 20.6; *m/z* (ES$^+$) found 183.0665 (MH$^+$) $C_9H_{11}O_4$ requires 183.0657.

Cycloadduct 7: A colorless oil (302 mg, 13 %); ν_{max}(thin film) 1738 (s), 1732 (s), 1072 (m); ^{1}H (400 MHz, $CDCl_3$) 7.22 (1H, dd, *J* 10.0, 5.0 Hz), 6.02 (1H, d, *J* 10 Hz), 5.16 (1H, dd, *J* 7.0, 2.5 Hz), 4.74 (1H, d, 5.0 Hz), 4.69 (1H, d, *J* 8.0 Hz), 2.35 (1H, ddd, *J* 14.0, 8.0, 2.5 Hz), 2.26 (1H, dd, *J* 14.0, 7.0 Hz); 2.10 (3H, s); ^{13}C (100 MHz, $CDCl_3$) 195.6, 170.9, 147.8, 127.4, 81.4, 78.6, 74.8, 32.7, 21.0; *m/z* (ES$^+$) found 183.0664 (MH$^+$) $C_9H_{11}O_4$ requires 183.0657.

Cycloadduct 8: White crystalline solid (111.0 mg, 10 %) m.p. 148 °C; ν_{max}(KBr) 1741 (s), 1712 (s), 1040 (m); ^{1}H (400 MHz, $CDCl_3$) 7.37 (1H, dd, *J* 10.0, 4.5 Hz), 6.10 (1H, d, *J* 10.0 Hz), 5.59 (1H, m), 4.77 (2H, m), 2.61 (1H, ddd, *J* 13.0, 9.0, 2.5 Hz), 1.95 (3H, s), 1.90 (1H, dd, *J* 13.0, 2.5 Hz); ^{13}C (100 MHz, $CDCl_3$) 193.2, 170.0, 152.6, 127.4, 82.3, 72.8, 71.1, 35.1, 20.6; *m/z* (ES$^+$) found 183.0644 (MH$^+$) $C_9H_{11}O_4$ requires 183.0657.

(*rel*-1*R*,5*R*,6*R*)-2-Oxo-8-oxabicyclo[3.2.1]octan-6-yl Acetate: To a solution of cycloadduct **6** (1.1 g, 6.1 mmol) in ethyl acetate (30 mL) was added palladium on carbon (5 wt.-%, 100 mg) and the resulting mixture was stirred under an atmosphere of hydrogen (atmospheric pressure) for 4 h. On completion the reaction was filtered through a pad of Celite and concentrated to give an essentially pure product as a colorless oil (1.109 g, quant), which was used further without extra purification. ν_{max}(thin film) 1731 (s), 1607 (s), 1275 (m), 1254 (m); ^{1}H (500 MHz, $CDCl_3$) 5.22 (1H, ddd, *J* 8.0, 6.0, 4.5 Hz), 4.57 (1H, app t, *J* 6.0 Hz), 4.16 (1H, d, *J* 8.0 Hz), 2.65 (1H, ddd, *J* 10.0, 9.0, 6.0 Hz), 2.51 (1H, dd, *J* 17.0, 9.0 Hz), 2.38 (1H, dd, *J* 17.0, 8.0 Hz), 2.13 (1H, m), 2.03 (3H, s), 1.92 (1H, ddd, *J* 14.0, 8.0, 6.0 Hz), 1.72 (1H, dd 14.0, 4.5 Hz); ^{13}C (125 MHz, $CDCl_3$) 207.0, 170.4, 80.8, 74.3, 73.1, 35.2, 32.50, 24.6, 20.8; *m/z* (EI$^+$) found 184.0705 (M$^+$) $C_9H_{12}O_4$ requires 184.0692.

(*rel*-1*R*,5*R*,6*R*)-6-Hydroxy-8-oxabicyclo[3.2.1]octan-2-one: To a solution of acetate ester starting material (500 mg, 2.75 mmol) in THF (10 mL) was added aqueous lithium hydroxide (1 M, 3 mL) dropwise over a period of 2 min and the resulting mixture was stirred for 2 h. Solvents were removed under reduced pressure and the residue was purified by filtration through a short pad of silica using ethyl acetate as eluent to give the product as a colorless oil (347 mg, 89 %); ν_{max}(thin film) 3661 (br s), 1727 (s), 1273 (s); ^{1}H (500 MHz, $CDCl_3$) 4.62 (1H, m), 4.36 (1H, app t, *J* 6.0 Hz), 4.10 (1H, d, *J* 8.5 Hz), 2.65 (1H, m), 2.57 (1H, ddd, *J* 12.5, 8.0, 6.5 Hz), 2.33 (1H, dd, *J* 17.0, 7.5 Hz), 2.23 (1H, m) 2.07 (1H, m), 1.61 (1H, dd, *J* 14.0, 2.0 Hz); ^{13}C (125 MHz, $CDCl_3$) 208.6, 81.2, 76.0, 71.2, 38.2, 32.7, 24.1; *m/z* (EI$^+$) found 142.0630 (M$^+$) $C_7H_{10}O_3$ requires 142.0631.

(*rel*-1*R*,5*R*,6*R*)-2-Oxo-8-oxabicyclo[3.2.1]octan-6-yl 1H-Imidazole-1-sulfonate: A stirred solution of free alcohol starting material (150 mg, 1.05 mmol) in THF (10 mL) was cooled to –40 °C and sodium hydride (60 % dispersion in mineral oil, 44 mg, 1.1 mmol) was added in one portion. The resulting mixture was stirred for 1 h at –40 °C and solid sulfonyldiimidazole (396 mg, 1.5 mmol) was added. The solution was warmed to room temperature and stirring was continued for 3 h. The reaction was diluted ethyl acetate (2 × 20 mL), and washed with brine (2 × 10 mL), dried ($MgSO_4$), and the solvent was evaporated to give the crude oil, which was purified by column chromatography (2:1 petroleum ether/ethyl acetate) to give the product as a pale yellow oil (205 mg, 72 %); ν_{max}(thin film) 1729 (s), 1350 (br s), 1273 (m), 1045 (s); ^{1}H (500 MHz, $CDCl_3$) 8.01 (1H, s), 7.34 (1H, s), 7.22 (1H, s), 5.13 (1H, ddd, *J* 10.5, 6.0, 3.0 Hz), 4.57 (1H, app t, *J* 6.0 Hz), 2.63 (1H, ddd, *J* 15.0, 10.0, 8.5 Hz), 2.51 (2H, m), 2.25 (1H, m), 2.11 (1H, m), 1.76 (1H, ddd, *J* 15.0, 3.0, 2.0 Hz); ^{13}C (125 MHz, $CDCl_3$) 205.0, 136.9, 131.9, 117.7, 82.0, 80.2, 73.9, 34.1, 31.8, 24.0; *m/z* (EI$^+$) found 272.0492 (M$^+$) $C_{10}H_{12}O_5N_2S$ requires 272.0467.

(*rel*-1*R*,2*R*,5*R*,6*R*)-2-Hydroxy-8-oxabicyclo[3.2.1]octan-6-yl 1H-Imidazole-1-sulfonate: To a stirred solution of ketone starting ma-

terial (150 mg, 0.55 mmol) in methanol (8 mL) at 0 °C was added sodiumborohydride (21 mg, 0.55 mmol) in one portion. The reaction was stirred for 30 min and was concentrated under reduced pressure. The residue was purified by column chromatography (1:1 petroleum ether/ethyl acetate as eluent). The product was isolated as a colorless oil (89 mg, 59 %); ν_{max}(thin film) 3501 (br s), 1345 (br s), 1262 (m), 1053 (s); ^{1}H (300 MHz, $CDCl_3$) 8.01 (1H, s), 7.36 (1H, s), 7.20 (1H, s), 5.00 (1H, ddd, *J* 10.0, 6.0, 4.0 Hz), 4.23 (1H, app t, *J* 6.0 Hz), 4.12 (1H, dd, *J* 7.5, 4.0 Hz), 3.94 (1H, ddd, *J* 10.0, 5.5, 4.0 Hz), 2.27 (1H, ddd, *J* 14.5, 10.0, 7.5 Hz), 2.01–1.68 (4H, m), 1.53 (1H, ddd, *J* 12.0, 10.0, 6.0 Hz); ^{13}C (100 MHz, $CDCl_3$) 137.1, 132.0, 118.0, 83.2, 78.8, 76.1, 67.5, 30.6, 29.7, 25.6; *m/z* (ES$^+$) found 275.0702 (MH$^+$) $C_{10}H_{15}O_5N_2S$ requires 275.0712.

(*rel*-1*R*,2*R*,5*R*,6*R*)-6-{[(1H-Imidazol-1-yl)sulfonyl]oxy}-8-oxa-bicyclo[3.2.1]octan-2-yl Cinnamate: To a stirred solution of alcohol starting material (45 mg, 0.17 mmol) in toluene (7 mL) were added cinnamic acid (50 mg, 0.34 mmol), triethylamine (50 μL, 0.36 mmol), 2,4,6-trichlorobenzoyl chloride (55 μL, 0.35 mmol) and DMAP (3 mg, 0.024 mmol) in succession and the mixture was stirred at room temperature for 16 h. The reaction was quenched with $NaHCO_3$ (sat. aq., 2 mL) and was extracted with ethyl acetate (2 × 10 mL). The combined organic layers were washed with brine (10 mL), dried ($MgSO_4$) and concentrated in vacuo. Flash column chromatography (3:1 petroleum ether ether/ethyl acetate) afforded a colorless oil (35.7 mg, 52 %); ν_{max}(thin film) 1692 (s), 1420 (m), 1387 (br s), 1372, (m), 1127 (m); ^{1}H (400 MHz, $CDCl_3$) 8.03 (1H, s), 7.64 (1H, d, *J* 16.5 Hz), 7.53 (2H, m), 7.39 (4H, m), 7.23 (1H, s), 6.37 (1H, d, *J* 16.5 Hz), 5.09 (1H, ddd, *J* 10.0, 5.5, 4.0 Hz), 4.96 (1H, ddd, *J* 10.0, 6.0, 4.0 Hz), 4.51 (1H, app t, *J* 6.0 Hz), 4.40 (1H, dd, *J* 8.0, 4.0 Hz), 2.21 (1H, ddd, *J* 15.0, 10.9, 6.5 Hz), 2.03 (1H, dd, *J* 15.0, 4.5 Hz), 1.89–1.75 (2H, m), 1.66 (2H, m); ^{13}C (100 MHz, $CDCl_3$) 165.8, 145.9, 137.0, 134.1, 131.6, 130.5, 128.9, 128.1, 117.9, 117.4, 82.9, 79.8, 76.2, 70.1, 30.2, 24.8, 22.5; *m/z* (ES$^+$) found 405.1120 (MH$^+$) $C_{19}H_{21}O_6N_2S$ requires 405.1120.

Cesium Glycolate: Glycolic acid (91.6 g, 20.3 mmol) and cesium carbonate (3 g, 9.23 mmol) were added to a steel reaction vessel containing a steel ball bearing. The reaction was carried out in a shaker mill at 25 MHz for 30 minutes. The solid product was dried in high vacuum of a Schlenk line (0.1 mm Hg) while heated at 40 °C in an oil bath for 16 h. This gave a white solid material (2.65 g, 63 %) which was used without any further purification.

(*rel*-1*R*,2*R*,5*R*,6*S*)-6-(2-Hydroxyacetoxy)-8-oxabicyclo[3.2.1]-octan-2-yl Cinnamate (9): Cesium glycolate (55.6 mg, 0.27 mmol) was added to the solution of monoester starting material (21.7 mg, 0.054 mmol) and 18-crown-6 (71 mg, 0.27 mmol) in toluene (3 mL). The resultant mixture was heated at reflux for 18 h. The solvent was removed in vacuo and the crude mixture was purified by silica gel column chromatography (2:1 petroleum ether ether/ethyl acetate) to give **9** as a colorless oil (8.6 mg, 48 %); ν_{max}(thin film) 3527 (br s), 1720 (s), 1638 (s), 1470 (m), 1273 (s); ^{1}H (500 MHz, $CDCl_3$) 7.67 (1H, d, *J* 16.0 Hz), 7.52 (2H, m), 7.39 (3H, m), 6.39 (1H, d, *J* 16.0 Hz), 5.24 (1H, dd, *J* 8.0, 3.0 Hz), 5.00 (1H, ddd, *J* 10.5, 5.5, 4.0 Hz), 4.26 (1H, m), 4.17 (2H, s), 2.59 (1H, dd, *J* 14.0, 7.5 Hz), 2.33 (1H, br s OH), 2.10 (1H, m), 1.99 (1H, ddd, *J* 13.5, 7.0, 2.5 Hz), 1.91–1.71 (2H, m), 1.46 (1H, m); ^{13}C (125 MHz, $CDCl_3$) 177.3, 165.9, 145.3, 134.2, 130.5, 128.9, 128.1, 117.7, 79.8, 78.4, 76.1, 68.8, 60.8, 33.7, 26.3, 22.6; *m/z* (ES$^+$) found 355.0696 (MNa$^+$) $C_{18}H_{20}O_6Na$ requires 355.0681.

(*rel*-1*S*,5*R*,6*R*)-1-Isopropyl-5-methyl-2-oxo-8-oxabicyclo[3.2.1]-oct-3-en-6-yl Acetate (13): To the solution of substituted hydroxylpyrone[10] (2.00 g, 11.76 mmol) in DCM (30 mL) at 0 °C were successively added acetic anhydride (20 mL), pyridine (10 mL) and DMAP (95 mg, 0.78 mmol). The reaction mixture was stirred for 4 h at 0^{O}C and was diluted with DCM (100 mL). The resulting solution was successively washed with $CuSO_4$ (10 % aqueous, 3 × 100 mL), deionised water (2 × 30 mL), $NaHCO_3$ (sat. aq. 2 × 50 mL) and brine (2 × 50 mL), dried (Na_2SO_4) and all volatiles were removed in vacuo[31] giving the crude acetoxy pyrone **10** (2.5 g, quant.). Which was mixed with vinyl acetate (30 mL) and 2,6-lutidine (1.36 mL, 11.76 mmol) and the resulting solution was transferred into a sealed tube which was immersed into an oil bath pre-heated at 180 °C. The reaction was continued for 45 min when the sealed tube was lifted from the oil bath and was cooled down to room temperature over a period of 1 h. Removal of volatiles was followed by silica gel column chromatography (5:1 petroleum ether/ethyl acetate) to give the reaction products.

Elimination Product 11 was never isolated in pure form due to its low polarity and volatility. The yield of **11** was assumed based on the relative integration of characteristic vinylic region peaks to those of the isolated adducts in the crude ^{1}H nmr. ^{1}H (300 MHz, $CDCl_3$) 6.99 (1H, d, *J* 10.0 Hz), 6.04 (1H, d, *J* 10.0 Hz), 4.93 (1H, s), 4.62 (1H, s), 4.22 (1H, d, *J* 5.0 Hz), 2.25 (1H, m), 1.02 (3H, d, *J* 6.5 Hz), 0.96 (3H, d, *J* 6.5 Hz).

Spirocycle 12: A white crystalline solid (35.8 mg, 2 %) m.p. 156 °C; ν_{max}(KBr) 1739 (s), 1768 (s), 1256 (m), 1140 (m); ^{1}H (400 MHz, $CDCl_3$) 6.99 (1H, d, *J* 9.0 Hz), 6.95 (1H, d, *J* 11.0 Hz), 6.11 (1H, d, *J* 11.0 Hz), 6.10 (1H, 9.0 Hz), 3.85 (1H, d, *J* 2.5 Hz), 2.41 (1H, m), 2.38 (1H, d, *J* 13.5 Hz), 2.25 (1H, m), 2.18 (1H, d, *J* 13.5), 1.41 (3H, s), 1.03 (6H, d, *J* 7.5 Hz), 0.94 (3H, d, *J* 7.0 Hz), 0.82 (3H, d, *J* 7.0 Hz); ^{13}C (100 MHz, $CDCl_3$) 197.4, 195.5, 154.1, 150.4, 126.6, 125.8, 88.3, 84.9, 81.4, 82.0, 38.7, 30.5, 28.3, 19.1, 18.8, 17.3, 16.3, 15.7; *m/z* (ES$^+$) found 305.1768 (MH$^+$) $C_{18}H_{25}O_4$ requires 305.1753.

Cycloadduct 13: A colorless oil (783 mg, 28 %); ν_{max}(thin film) 1738 (s), 1732 (s), 1072 (m); ^{1}H (400 MHz, $CDCl_3$) 6.93 (1H, d, 10.0 Hz), 6.10 (1H, d, *J* 10.0 Hz), 4.93 (1H, dd, *J* 9.0, 5.0 Hz), 2.75 (1H, dd *J* 14.0, 9.0 Hz), 2.19 (1H, sept, *J* 5.0 Hz), 2.03 (3H, s), 1.52 (1H, dd, *J* 14.0, 5.0 Hz), 1.52 (3H, s), 1.02 (3H, d, *J* 5.0 Hz), 1.00 (3H, d, *J* 5.0 Hz); ^{13}C (100 MHz, $CDCl_3$) 198.0, 170.4, 152.2, 128.3, 89.0, 79.7, 78.9, 36.2, 30.5, 21.7, 20.8, 17.3, 16.2; *m/z* (ES$^+$) found 239.1292 (MH$^+$) $C_{13}H_{19}O_4$ requires 239.1283.

Cycloadducts 14 & 15: Were isolated as a 1.1:1 mixture, a pale yellow oil (807.5 mg, 29 % combined yield); ^{1}H (400 MHz, $CDCl_3$) 7.06 (1H, d, *J* 9.5 Hz), 6.93 (1H, d, *J* 9.5 Hz), 6.02 (1H, d, *J* 9.5 Hz), 5.93 (1H, d, *J* 9.5 Hz), 5.52 (1H, dd, *J* 8.5, 2.0 Hz), 5.18 (1H, dd, *J* 7.0, 2.0 Hz), 2.37 (1H, sept,7.5 Hz), 2.24 (m, 3H), 2.12 (3H, s), 2.18–2.01 (2H, m), 1.93 (3H, s), 1.49 (3H,s), 1.42 (3H, s), 1.05 (6H, d, *J* 7.5 Hz),1.05 (3H, d, *J* 7.0 Hz), 0.98 (3H, d, *J* 7.0 Hz); ^{13}C (100 MHz, $CDCl_3$) 197.9, 195.3, 170.5, 170.1, 154.8, 151.8, 128.1, 127.5, 91.9, 89.5, 82.3, 78.7, 75.4, 73.8, 43.9, 37.2, 30.5, 29.4, 33.5, 20.9, 18.3, 17.6, 16.7, 16.1; *m/z* (ES$^+$) found 239.1275 (MH$^+$) $C_{13}H_{19}O_4$ requires 239.1283.

(*rel*-1*S*,5*R*,6*R*)-1-Isopropyl-5-methyl-2-oxo-8-oxabicyclo[3.2.1]-octan-6-yl Acetate: To a solution of adduct **13** (250 mg, 1.05 mmol) in ethyl acetate (8 mL) was added palladium on carbon (5 wt.-%, 15 mg) and the resulting mixture was stirred under an atmosphere of hydrogen (atmospheric pressure) for 4 h. On completion the reaction was filtered through a pad of Celite and concentrated to give an essentially pure reduction product as a colorless oil (250.5 mg, quant), which was used further without extra purification. ν_{max}(thin film) 1750 (s), 1705 (s), 1020 (m); ^{1}H (400 MHz, $CDCl_3$) 4.90 (1H, dd, *J* 10.0, 3.5 Hz), 2.57 (2H, m), 2.47 (1H, ddd, *J* 16.5,8.5, 4.5 Hz), 2.20 (1H, ddd, *J* 13.5, 10.0, 3.5 Hz), 2.12(1H, m), 2.10 (3H, s), 1.96 (1H, ddd, *J* 13.5, 8.5, 8.5 Hz), 1.65 (1H, dd, *J* 13.5, 3.5 Hz), 1.39 (3H, s), 0.94 (3H, d, *J* 6.5 Hz), 0.93 (3H, d, *J* 6.5 Hz); ^{13}C (100 MHz, $CDCl_3$) 209.6, 170.4, 88.8, 80.6, 78.40, 38.0, 34.3, 31.7, 30.4, 24.9, 20.9, 17.1, 16.7; *m/z* (ES$^+$) found 241.1455 (MH$^+$) $C_{13}H_{21}O_4$ requires 241.1440.

(*rel*-1*S*,2*R*,5*R*,6*R*)-1-Isopropyl-5-methyl-8-oxabicyclo[3.2.1]-octane-2,6-diol (15): To a stirred solution of the ketone (200 mg, 1.01 mmol) in methanol (7 mL) were added cerium trichloride heptahydrate (745 mg, 2 mmol) followed by sodiumborohydride (76 mg, 2 mmol) and the reaction mixture was stirred for 1 h. The reaction was quenched by addition of NH_4Cl (sat. aqueous, 0.5 mL) and extracted with ethyl acetate (2 × 50 mL). Combined organic extracts were dried ($MgSO_4$) and concentrated in vacuo. The residue was purified by flash column chromatography (SiO_2, petrol/ethyl acetate, 1:2) to give the ***syn*-diol 15** as a white crystalline solid (112.5 mg, 56 %); ν_{max}(KBr) 3691 (br, s), 1273 (m), 1019 (m); ^1H (400 MHz, $CDCl_3$) 3.84 (1H, dd, *J* 11.0, 5.5 Hz), 3.57 (1H, m), 2.33–2.04 (3H, m), 2.16 (1H, dd, *J* 12.5, 9.5 Hz), 1.66 (1H, dd, *J* 12.5, 6.5 Hz),1.64–1.48 (2H, m), 1.27 (1H, dd, *J* 13.5, 5.5 Hz), 1.14 (3H, s), 0.89 (3H, d, *J* 6.0 Hz), 0.76 (3H, d, *J* 6.0 Hz); ^{13}C (100 MHz, $CDCl_3$) 86.1, 81.4, 77.5, 67.0, 35.9, 28.9, 26.8, 26.3, 24.9, 17.4, 15.4; *m/z* (ES^+) found 201.1427 (MH^+) $C_{13}H_{21}O_3$ requires 201.1447.

***anti*-Diol** as a colorless oil (38.6 mg, 19 %); ν_{max}(thin film) 3685 (br, s), 3697 (br, s), 2983 (s), 1273 (s); ^1H (400 MHz, $CDCl_3$) 3.96 (1H, dd, *J* 10.0, 5.0 Hz), 3.88 (1H, dd, *J* 9.0, 5.0 Hz), 2.16 (1H, dd, *J* 13.5, 10.5 Hz), 1.95–1.82 (3H, m), 1.77 (1H, dd, *J* 13.5, 5.0 Hz), 1.74 (1H, m), 1.52 (1H, ddd, *J* 13.0, 6.5, 6.5), 1.25 (1H, m), 1.19 (3H, s), 1.00 (3H, d, *J* 7.0 Hz), 0.96 (3H, d, *J* 7.0 Hz); ^{13}C (100 MHz, $CDCl_3$) 84.5, 80.5, 78.5, 69.5, 36.7, 32.2, 31.4, 28.2, 24.4, 17.4, 16.6; *m/z* (ES^+) found 201.1429 (MH^+) $C_{13}H_{21}O_3$ requires 201.1447.

(*rel*-1*S*,2*R*,5*R*,6*R*)-1-Isopropyl-5-methyl-8-oxabicyclo[3.2.1]-octane-2,6-diyl Biscinnamate: To a stirred solution of cinnamic acid (207 mg, 1.4 mmol) and triethyl amine (190 μL, 1.4 mmol) in THF (5 mL) was added 2,4,6-trichlorobenzoyl chloride (361.5 mg, 1.5 mmol) and the reaction was stirred at room temperature for 30 min when a solution of diol **15** (112 mg, 0.56 mmol) in THF (3 mL) was added followed by DMAP (8.5 mg, 0.07 mmol), and the reaction was stirred for 18 h, was diluted with ethyl acetate (30 mL) and was washed with $NaHCO_3$ (sat. aq. 2 × 10 mL). Organic layer was separated, dried ($MgSO_4$) and concentrated in vacuo to give a crude oil, which was purified by flash column chromatography (silica gel, 3:1 petroleum ether ether/ethyl acetate as eluent) to give the diester as a colorless oil (185 mg, 72 %); ν_{max}(thin film) 1695 (s), 1690 (s), 1465 (m), 1442 (m), 1127 (m); ^1H (400 MHz, $CDCl_3$) 7.71 (1H, d, *J* 18.0 Hz), 7.63 (1H, d, 17.0 Hz), 7.52 (4H, m), 7.38 (6H, m), 6.48 (1H, d, *J* 18.0 Hz), 6.38 (1H, d, *J* 17.0 Hz), 5.16 (1H, dd, *J* 10.0, 6.0 Hz), 4.96 (1H, dd, *J* 11.5, 6.0 Hz), 2.55 (1H, dd, *J* 14.5, 10.0 Hz), 2.21 (1H, m), 2.07 (1H, dd, *J* 14.5, 6.0 Hz), 1.97 (1H, dd, *J* 14.5, 6.0 Hz), 1.92–1.82 (2H, m), 1.71 (1H, m), 1.30 (3H, s), 1.00 (3H, d, *J* 7.0 Hz), 0.96 (3H, d, *J* 7.0 Hz); ^{13}C (100 MHz, $CDCl_3$) 166.7, 165.9, 145.3, 145.0, 134.3, 134.2, 130.5, 130.3, 128.9, 128.9, 128.1, 128.1, 118.1, 117.8, 84.0, 80.5, 79.0, 71.3, 36.5, 33.2, 32.1, 24.7, 24.6, 17.5, 16.6; *m/z* (ES^+) found 461.2345 (MH^+) $C_{29}H_{33}O_5$ requires 461.2328.

(*rel*-1*S*,2*R*,5*R*,6*R*)-2-Hydroxy-1-isopropyl-5-methyl-8-oxabicyclo-[3.2.1]oct-3-en-6-yl Acetate: To a solution of enone **13** (500 mg, 2.1 mmol) in methanol (10 mL) was added cerium trichloride heptahydrate (1.56 g, 4.2 mmol) and the solution was stirred for 30 min and cooled to 0°C and sodium borohydride (160 mg, 4.2 mmol) was added in one portion. The reaction was stirred at 0°C for 1 h and was quenched by addition of ammonium chloride (sat. aq. 5 mL). To the resulting mixture was added ethyl acetate (50 mL), layers were separated and the organic layer was washed with brine (2 × 20 mL) and was concentrated to give the crude product. Flash column chromatography (silica gel, 3:1 petroleum ether ether/ethyl acetate eluent) gave the allylic alcohol as a colorless oil (448 mg, 89 %); ν_{max}(thin film) 3650 (br, s), 1739 (s), 1052 (m); ^1H (400 MHz, $CDCl_3$) 5.80 (1H, dd, *J* 9.0, 1.0 Hz), 5.62 (1H, dd, *J* 9.0, 1.5 Hz), 4.68 (1H, dd, *J* 9.5, 6.5 Hz), 4.63 (1H, m), 2.29 (1H, dd, *J* 14.0, 9.5 Hz), 2.04 (3H, s), 2.02 (1H, dd, *J* 14.0, 6.5 Hz), 1.91 (1H, sept, *J* 6.5 Hz), 1.30 (3H, s), 1.03 (3H, d, *J* 6.5 Hz), 1.00 (3H, d, *J* 6.5 Hz); ^{13}C (100 MHz, $CDCl_3$) 170.8, 133.7, 129.6, 84.8, 80.8, 78.0, 70.4, 34.3, 32.3, 21.3, 21.0, 17.2, 17.1; *m/z* (EI^+) found 240.1351 (MH^+) $C_{13}H_{21}O_4$ requires 240.1362.

(*rel*-1*S*,2*R*,5*R*,6*R*)-2-Hydroxy-1-isopropyl-5-methyl-8-oxabicyclo[3.2.1]octan-6-yl Acetate: To a solution of the allylic alcohol starting material (350 mg, 1.45 mmol) in ethyl acetate (8 mL) was added palladium on carbon (5 wt.-%, 15 mg) and the resulting mixture was stirred under an atmosphere of hydrogen (atmospheric pressure) for 8 h. On completion the reaction was filtered through a pad of Celite and concentrated. Flash column chromatography (silica gel, 4:1 petroleum ether ether/ethyl acetate eluent) gave the reduction product as a pale yellow oil (322 mg, 92 %); ν_{max}(thin film) 3645 (br s), 1725 (s), 1422 (m), 1156 (m); ^1H (400 MHz, $CDCl_3$) 4.75 (1H, dd, *J* 11.0, 5.0 Hz), 3.89 (1H, dd, *J* 10.5, 6.0 Hz), 2.31 (1H, dd, *J* 14.5, 11.0 Hz), 2.08 (3H,s), 1.95–1.50 (6H, m), 1.39 (1H, br s, OH) 1.21 (3H, s), 1.00 (3H, d, *J* 6.5 Hz), 0.99 (3H, d, *J* 6.5 Hz); ^{13}C (100 MHz, $CDCl_3$) 170.7, 84.9, 79.7, 79.0, 69.2, 34.6, 32.3, 27.9, 24.4, 21.0, 17.4, 16.6; *m/z* (EI^+) found 242.1535 (M^+) $C_{13}H_{21}O_4$ requires 242.1518.

(*rel*-1*S*,2*R*,5*R*,6*R*)-6-Acetoxy-1-isopropyl-5-methyl-8-oxa-bicyclo[3.2.1]octan-2-yl Cinnamate: To a stirred solution of cinnamic acid (296 mg, 2 mmol) and triethyl amine (272 μL, 2 mmol) in toluene (7 mL) was added 2,4,6-trichlorobenzoyl chloride (496 mg, 2.05 mmol) and the reaction was stirred at room temperature for 30 min when a solution of the alcohol starting material (250 mg, 1.03 mmol) in toluene (3 mL) was added followed by DMAP (10 mg, 0.08 mmol), and the reaction was stirred for 18 h, was diluted with ethyl acetate (50 mL) and was washed with $NaHCO_3$ (sat. aq. 2 × 20 mL). Organic layer was separated, dried ($MgSO_4$) and concentrated in vacuo to give a crude oil, which was purified by flash column chromatography (silica gel, 3:1 petroleum ether ether/ethyl acetate as eluent) to give the diester product as a colorless oil (332 mg, 87 %); ν_{max}(thin film) 1695 (s), 1690 (s), 1425 (m), 1370, (m), 1125 (m); ^1H (400 MHz, $CDCl_3$) 7.64 (1H, d, *J* 18.0 Hz), 7.52 (2H, m), 7.38 (3H, m); 6.38 (1H. d. *J* 18.0 Hz), 5.12 (1H, dd, *J* 10.0, 6.0 Hz), 4.80 (1H, dd, *J* 10.5, 5.0 Hz), 2.47 (1H, dd, *J* 14.0, 10.5 Hz), 2.16 (1H, m), 2.10 (3H, s), 1.96 (1H, dd, *J* 14.0, 5.0 Hz) 1.91–1.60 (4H, m), 1.25 (3H, s), 0.97 (3H, d, *J* 7.0 Hz), 0.93 (3H, d, *J* 7.0 Hz); ^{13}C (100 MHz, $CDCl_3$) 170.7, 165.9, 144.9, 134.3, 130.3, 128.9, 128.1, 118.1, 83.9, 80.2, 79.0, 71.3, 36.3, 33.1, 31.9, 24.6, 24.5, 21.1, 17.4, 16.6; *m/z* (ES^+) found 373.2032 (MH^+) $C_{22}H_{29}O_5$ requires 373.2015.

(*rel*-1*S*,2*R*,5*R*,6*R*)-6-Hydroxy-1-isopropyl-5-methyl-8-oxa-bicyclo[3.2.1]octan-2-yl Cinnamate: To a stirred solution of the diester starting material (250 mg, 0.67 mmol) in methanol (7 mL) was added potassium carbonate (276 mg, 2 mmol) and the resulting mixture was stirred for 1.5 h. The reaction was diluted with ethyl acetate (20 mL), washed with brine (2 × 10 mL), dried ($MgSO_4$) and evaporated to give the crude product, which was purified by flash column chromatography (silica gel, 2:1 petroleum ether ether/ethyl acetate eluent) to give the pure monoester as a colorless oil (190 mg, 86 %); ν_{max}(thin film) 3459 (br s), 1693 (s), 1430 (m), 1370, (m), 1122 (m); ^1H (400 MHz, $CDCl_3$) 7.64 (1H, d, *J* 16.0 Hz), 7.51 (2H, m), 7.37 (3H, m), 6.38 (1H, d, *J* 16.0 Hz), 5.12 (1H, dd, *J* 10.0, 6.5 Hz), 4.04 (1H, dd, *J* 10.5, 5.0 Hz), 2.31 (1H, dd, 13.0, 11.0 Hz), 2.13 (1H, m), 2.02–1.77 (4H, m), 1.60 (1H, m), 1.23 (3H, s), 0.96 (3H, d, *J* 7.0 Hz), 0.93 (3H, d, *J* 7.0 Hz); ^{13}C (100 MHz, $CDCl_3$) 166.0, 144.9, 134.4, 130.3, 128.9, 128.0, 118.3, 83.6, 81.1, 78.4, 71.7, 38.3, 33.1, 31.1, 24.8, 24.4, 17.5, 16.6; *m/z* (ES^+) found 331.1892 (MH^+) $C_{20}H_{27}O_4$ requires 331.1909.

(*rel*-1*S*,2*R*,5*R*,6*R*)-6-{[(1H-Imidazol-1-yl)sulfonyl]oxy}-1-isopropyl-5-methyl-8-oxabicyclo[3.2.1]octan-2-yl Cinnamate: To a stirred solution of the alcohol starting material (110 mg, 0.33 mmol) in THF (5 mL) at –78°C was added LiHMDS (1.06 M soln. in THF, 350 μL, 0.371 mmol) and after 30 min a solution of sulfonyldiimidazole (99 mg, 0.5 mmol) in THF (2 mL). Stirring was continued overnight allowing the dry ice/acetone bath to slowly warm to room temperature. The resulting mixture was quenched by addition of ammonium chloride (sat. aq. 2 mL) and extracted with ethyl acetate (20 mL). Organic extracts were washed with brine (2 × 10 mL), dried ($MgSO_4$) and the solvents evaporated in vacuo to give the crude product. Pure sulfonamide product was obtained after flash column chromatography (silica gel, 4:1 petroleum ether ether/ethyl acetate eluent) as a pale yellow oil (113 mg, 75 %); ν_{max}(thin film) 1705 (s), 1430 (m), 1379 (br s), 1350, (m), 1140 (m); ^{1}H (400 MHz, $CDCl_3$) 8.04 (1H, s), 7.64 (1H, d, *J* 16.0 Hz), 7.53 (2H, m), 7.39 (4H, m), 7.23 (1H, s), 6.36 (1H, d, *J* 16.0 Hz), 5.09 (1H, dd, *J* 9.5, 6.0 Hz), 4.51 (1H, dd, *J* 10.5, 5.0 Hz), 2.25 (1H, dd, *J* 14.5, 10.5 Hz), 2.18 (1H, m), 2.03 (1H, dd, *J* 14.5, 5.0 Hz), 1.90–1.57 (4H, m), 1.13 (3H, s), 0.91 (3H, d, *J* 6.0 Hz), 0.89 (3H, d, *J* 6.0 Hz); ^{13}C (100 MHz, $CDCl_3$) 165.7, 145.4, 137.1, 134.2, 131.7, 130.5, 128.9, 128.1, 117.8, 117.6, 88.7, 84.3, 80.2, 70.2, 34.6, 32.7, 31.4, 24.4, 23.6, 17.2, 16.4; *m/z* (ES$^+$) found 461.1752 (MH$^+$) $C_{23}H_{27}O_6N_2S$ requires 461.1746.

(*rel*-1*S*,2*R*,5*R*,6*S*)-6-(2-Hydroxyacetoxy)-1-isopropyl-5-methyl-8-oxabicyclo[3.2.1]octan-2-yl Cinnamate (3):[10] Cesium glycolate (166 mg, 0.8 mmol) was added to solution of the sulfonylimidazole derivative (76 mg, 0.16 mmol) and 18-crown-6 (211 mg, 0.8 mmol) in toluene (10 mL). The resultant mixture was heated at reflux for 18 h. The solvent was removed in vacuo and the crude mixture was purified by silica gel column chromatography (4:1 petroleum ether ether/ethyl acetate) to give **3** as a colorless oil (62 mg, 58 %); ν_{max}(thin film) 3540 (br s), 1718 (s), 1650 (s), 1468 (m); ^{1}H (400 MHz, $CDCl_3$) 7.65 (1H, d, *J* 16 Hz), 7.53 (2H, m), 7.39 (3H, m), 6.38 (1H, d, *J* 16.0 Hz), 5.25 (1H, dd, *J* 7.5, 2.5 Hz), 5.03 (1H, dd, *J* 10.0, 5.5 Hz), 4.20 (2H, s), 2.70 (1H, dd, *J* 14.0, 7.5 Hz), 2.38 (1H, br s, OH), 2.19 (1H, m), 1.90 (1H, m), 1.82 (1H, m), 1.75–1.64 (2H, m), 1.59 (1H, m), 1.47 (1H, m), 1.21 (3H, s), 0.99 (3H, d, *J* 7.0 Hz), 0.96 (3H, d, *J* 7.0 Hz); ^{13}C (100 MHz, $CDCl_3$) 172.9, 156.8, 145.2, 134.2, 130.4, 128.8, 128.1, 117.9, 85.2, 82.3, 79.6, 70.4, 60.6, 38.8, 34.2, 33.2, 24.4, 20.3, 17.9, 17.0; *m/z* (ES$^+$) found 411.1772 (MNa$^+$) $C_{22}H_{28}O_6Na$ requires 411.1784.

(*rel*-1S,4S,5R,6R)-1-Isopropyl-5-methyl-2-oxo-4-vinyl-8-oxa-bicyclo[3.2.1]octan-6-yl Acetate (16): To a pre-cooled (–78 °C) suspension of enone **13** (250 mg, 1.05 mmol) and Copper(I) iodide (19 mg, 0.1 mmol) in THF (10 mL) was added 1 M vinylmagnesium bromide solution in THF (1.2 mL, 1.2 mmol) dropwise over a period of 10 minutes. The mixture was stirred at –78 °C for an hour and was quenched at low temperature by addition of aqueous saturated ammonium chloride solution (3 mL). The reaction was warmed to room temperature and the organic compounds were extracted with ethyl acetate (2 × 10 mL portions). Combined organic extracts were dried ($MgSO_4$) filtered and evaporated, the residue was purified by column chromatography (silica gel, 10:1 petroleum ether ether/EtOAc) to give the conjugate addition product **16** as pale yellow oil (201.3 mg, 72 %). ν_{max}(thin film) 2971 (m), 1743 (s), 1680 (s), 1590 (m); ^{1}H (400 MHz, $CDCl_3$) 5.94 (1H, ddd, *J* 17.0, 10.0, 7.5 Hz), 5.12 (1H, dd *J* 10/0, 1.5 Hz). 5.05 (1H, dd, *J* 17.0, 1.5 Hz), 5.02 (1H, dd, *J* 10.5, 4.0 Hz), 2.93 (1H, dd, *J* 17.0, 7.0 Hz), 2.85–2/79 (1H, m), 2.58 (1H, dd, *J* 19.0, 10.5 Hz), 2.26 (1H, dd, *J* 15.0, 2.5 Hz), 2.13 (1H, sep, *J* 7/0 Hz), 2.12 (3H, s), 1.68 (1H, dd, *J* 15.0, 4.0 Hz), 1.29 (3H, s), 0.95 (6H, d, *J* 7.0 Hz); ^{13}C (100 MHz, $CDCl_3$) 208.4, 170.4, 138.0, 116.6, 98.2, 62.2, 79.8, 46.1, 41.2, 38.1, 30.1, 23.2, 21.0, 17.2, 16.5; *m/z* (ES$^+$) found 267.1605 (MH$^+$) $C_{15}H_{23}O_4$ requires 267.1596.

(*rel*-1*S*,4*R*,5*R*,6*R*)-4-Formyl-1-isopropyl-5-methyl-2-oxo-8-oxa-bicyclo[3.2.1]octan-6-yl Acetate (17): Through a pre-cooled colorless solution of alkene **16** (500 mg, 1.9 mmol) in DCM (20 mL) was passed a mixture of ozone and oxygen (Fisher ozone generator) until the solution became pale blue in colour. The ozone generator was turned off and oxygen was passed through the solution until the blue colour dissipated. To the resulting solution was added dimethylsulfide (3 mL, excess) and the resulting mixture was warmed to room temperature and was stirred overnight. The solution was concentrated and the crude product mixture was purified by column chromatography (petrol/EtOAc, 10:1) to give **17** as a colorless oil (408 mg, 81 %); ν_{max}(thin film) 1764 (s), 1749 (s), 1745 (s), 1373 (m), 1273 (m); ^{1}H (400 MHz, $CDCl_3$) 9.85 (1H, d, *J* 3.0 Hz), 4.93 (1H, dd, *J* 10.0, 4.0 Hz), 3.02 (1H, ddd, *J* 7.5, 5.0, 3.0 Hz), 2.78 (1H,dd, *J* 17.5, 5.0Hz), 2.68 (1H, dd, *J* 17.5, 7.5 Hz), 2.57 (1H, dd. *J* 14.0, 10.0 Hz), 2.12 (3H, s), 2.12 (1H, sept., *J* 7.0 Hz), 1.60 (1H, dd, *J* 14.0, 3.0 Hz),1.53 (3H, s), 0.96 (6H, d, *J* 7.0 Hz); ^{13}C (100 MHz, $CDCl_3$) 208.0, 200.7, 170.0, 90.7, 81.5, 80.0, 38.4, 34.5, 30.7, 22.8, 20.8, 16.0, 16.7; *m/z* (ES$^+$) found 269.1360 (MH$^+$) $C_{14}H_{21}O_5$ requires 269.1389.

(*rel*-1*S*,4*S*,5*R*,6*R*)-4-Formyl-1-isopropyl-5-methyl-2-oxo-8-oxa-bicyclo[3.2.1]octan-6-yl Acetate (17′): To a stirred pre-cooled (–20 °C) solution of aldehyde **17** (360 mg, 1.34 mmol) in DCM (10 mL) was added acetic acid (24 μL, 0.4 mmol) and pyrrolidine (22 μL, 0.26 mmol). The resulting mixture was stirred at –20 °C for 2 days and concentrated under reduced pressure. Column chromatography (silica gel, petrol/EtOAc, 20:1) allowed separation of epimeric aldehydes **17** (81 mg, 22.5 %) and essentially pure **17′** (243 mg, 67.5 %) as a colorless oil; ν_{max}(thin film) 3980 (m),1764 (s), 1750 (s), 1747 (s), 1380 (m), 1256 (m); ^{1}H (400 MHz, $CDCl_3$) 9.72(1H,s), 5.00 (1H, dd, *J* 10.5, 4.0 Hz), 3.08–2.98 (2H, m), 2.64–2.55 (2H, m), 2.19–2.12 (1H, m), 1.99 (3H, s), 1.74 (3H, s), 1.65 (1H, dd, *J* 15.0, 4.0 Hz), 0.96 (6H. d, *J* 7.0 Hz); ^{13}C (100 MHz, $CDCl_3$) 205.6, 198.2, 169.8, 89.2, 82.5, 78.4, 58.4, 37.8, 34.1, 30.0, 23.9, 20.5, 17.2, 16.5; *m/z* (ES$^+$) found 269.1360 (MH$^+$) $C_{14}H_{21}O_5$ requires 269.1389.

(*rel*-1*S*,4*R*,5*R*,6*R*)-1-Isopropyl-5-methyl-2-oxo-4-[(E)-3-oxobut-1-en-1-yl]-8-oxabicyclo[3.2.1]octan-6-yl Acetate: To a stirred solution of aldehyde **17′** (350 mg, 1.3 mmol) was added 1-(triphenylphosphoranylidene) propan-2-one (955 mg, 3.25 mmol) and the resulting solution was stirred at room temperature for 1 hour and then was heated at reflux for additional 5 hours, allowing complete consumption of the starting material. The resulting mixture was concentrated and purified by column chromatography (silica gel, petrol/EtOAc, 6:1) to give the product as a colorless oil (300.6 mg, 75 %); ν_{max}(thin film) 1730 (s), 1710 (s), 1690 (s), 1031 (m); ^{1}H (400 MHz, $CDCl_3$) 6.85 (1H,dd, *J* 16.0, 9.0 Hz), 6.07 (1H, d, *J* 16 Hz), 5.04 (1H, dd, *J* 10.0, 6.0 Hz), 3.04–2.97 (2H, m), 2.62 (1H, dd, *J* 15.0, 10.0 Hz), 2.30–2.23 (1H, m), 2.28 (3H, s), 2.17 (1H, sept., *J* 7.0 Hz), 2.14 (3H, s), 1.71 (1H, dd, *J* 15.0, 6.0 Hz), 1.28 (3H, s), 0.96 (6H, app dd, *J* 7.0, 2.0 Hz); ^{13}C (100 MHz, $CDCl_3$) 206.8, 198.2, 170.2, 146.1, 132.7, 89.6, 82.1, 79.8, 45.1, 40.2, 37.9, 30.0, 27.1, 23.4, 21.1, 17.3, 16.4; *m/z* (ES$^+$) found 309.1700 (MH$^+$) $C_{17}H_{25}O_5$ requires 309.1702.

(*rel*-1*S*,4*S*,5*R*,6*R*)-1-Isopropyl-5-methyl-2-oxo-4-(3-oxobutyl)-8-oxabicyclo[3.2.1]octan-6-yl Acetate (18): A mixture of the enone starting material (300 mg, 0.97 mmol) and palladium on activated carbon (5wt.-%, 3 mg) in ethyl acetate (8 mL) was placed under atmosphere of hydrogen and stirred for 8 hours at ambient temperature. The solids were removed via filtration through a short pad of Celite (approximately 0.5 g of filtration agent) and the volatiles were removed. The residue was purified by column chromatography (silica gel, petrol/EtOAc, 10:1) to give the reduction product **18** as a colorless oil (270.6 mg, 90 %); ν_{max}(thin film) 3920 (m), 1725 (multiple overlapping peaks s), 1051 (m), 1066 (m); ^{1}H (400 MHz, $CDCl_3$)

4.98 (1H, dd, *J* 10.0, 4.0 Hz), 2.77 (1H, dd, *J* 16.0, 8.0 Hz), 2.69 (1H, ddd, *J* 17.0, 10.0, 5.0 Hz), 2.59 (1H, dd, *J* 15.0, 10.0 Hz), 2.48 (1H, ddd, *J* 17.0, 10.0, 6.0 Hz), 2.32–2.04 (3H, m), 2.15 (3H, s), 2.09 (3H, s), 1.96- 1.88 (1H, m), 1.69–1.60 (2H, m), 1.39 (3H, s), 0.94 (6H, app dd, *J* 7.0, 0.5 Hz); ^{13}C (100 MHz, $CDCl_3$) 209.6, 208.2, 170.3, 89.3, 83.0, 80.5, 40.8, 40.1, 38.5, 30.3, 30.0, 24.4, 22.4, 21.1, 17.1, 16.6; *m/z* (ES^+) found 311.1841 (MH^+) $C_{17}H_{27}O_5$ requires 311.1858.

(*rel*-3a*S*,4*R*,5*R*,7*S*,8a*S*)-1-Hydroxy-7-isopropyl-1,4-dimethyl-8-oxodecahydro-4,7-epoxyazulen-5-yl Acetate: To a stirred solution of diketone **18** (360 mg, 1.16 mmol) in THF (6 mL) at –78 °C was added lithium hexamethyldisilazide (1.0 M soln. in THF, 1.1 mL) and the reaction was stirred at –78 °C for 30 minutes and the temperature in the cooling bath was allowed to increase to –30 °C and maintained at that temperature for an hour, when the reaction was quenched by addition of acetic acid (0.3 mL, 5 mmol). The mixture was warmed to room temperature and the volatiles were evaporated. Column chromatography of the residue (silica gel, petrol/EtOAc, 10:1) allowed separation of two diastereomeric products, which were assigned the structure as indicated above due to the same coupling constant exhibited by the hydrogens at the ring junction *J* 9.5 Hz common for *syn*-fused 5,6 ring systems.

Aldol-product I (135.5 mg, 37 %); ν_{max}(thin film) 3190 (br, s), 1751 (s), 1722 (s), 1373 (m), 1350 (m); ^{1}H (400 MHz, $CDCl_3$) 4.95 (1H, dd, *J* 9.0, 3.0 Hz), 3.05 (1H, br, s), 2.69 (1H, d, *J* 9.5 Hz), 2.59–2.45 (2H, m), 2.16 (1H, sept., *J* 6.5 Hz), 2.07 (3H. s), 2.06–1.97 (1H, m), 1.86–1.74 (2H, m), 1/61 (1H, dd, *J* 14.0, 3.0 Hz), 1.55–1.47 (1H, m), 1.47 (3H, s), 1.36 (3H, s), 0.99 (3H, d, *J* 6.5 Hz), 0.96 (3H, d, *J* 6.5 Hz); ^{13}C (100 MHz, $CDCl_3$) 212.2, 170.2, 89.9, 82.4, 81.9, 79.7, 57.2, 43.4, 40.4, 38.1, 30.4, 38.3, 26.4, 28.6, 21.1, 17.5, 17.3; *m/z* (ES^+) found 311.1869 (MH^+) $C_{17}H_{27}O_5$ requires 311.1858.

Aldol product II (111.5 mg, 31 %); ν_{max}(thin film) 3169 (br, s), 1750 (s), 1725 (s), 1350 (m), 1290 (m); ^{1}H (400 MHz, $CDCl_3$) 4.91 (1H, dd, *J* 10.0, 4.0 Hz), 2.87 (1H, d, *J* 10.0 Hz), 2.79–2.71 (1H, m), 2.52 (1H, dd, *J* 15.0, 10.0, Hz), 2.12 (1H, sept, *J* 6.0 Hz), 2.08 (3H, s), 1.86–1.71 (4H, m), 1.55 (1H, dd, *J* 15.0, 4.0 Hz), 1.34 (3H, s), 1.33 (3H, s), 0.99 (3H, d, *J* 6.5 Hz), 0.98 (3H, d, *J* 6.5 Hz); ^{13}C (100 MHz, $CDCl_3$) 211.5, 170.4, 89.6, 82.6, 82.2, 79.5, 58.1, 41.5, 40.0, 38.7, 30.9, 26.4, 26.0, 22.3, 21.1, 17.6, 17.3; *m/z* (ES^+) found 311.1855 (MH^+) $C_{17}H_{27}O_5$ requires 311.1858.

(*rel*-3a*S*,4*R*,5*R*,7*S*)-7-Isopropyl-1,4-dimethyl-8-oxo-2,3,3a,4,5,6,7,8-octahydro-4,7-epoxyazulen-5-yl Acetate (19): To a pre-cooled (0 °C) solution of aldol adducts (200 mg, 0.64 mmol) in DCM (6 mL) was added triethylamine (177 μL, 1.3 mmol) and methanesulfonyl chloride (51 μL, 0.66 mmol). The resulting mixture was stirred at 0 °C for an hour and was warmed to room temperature and stirred for additional 3 hours. To the reaction was added water (10 mL) and DCM (20 mL), the layers were separated and the organic layer was dried (Na_2SO_4) and the solvents evaporated. The residue was purified by column chromatography (silica gel, petrol/EtOAc, 6:1) to give the enone **19** as a colorless oil (149.5 mg, 80 %); ν_{max}(thin film) 1726 (s), 1695 (s), 1475 (m), 1376 (m); ^{1}H (400 MHz, $CDCl_3$) 4.72 (1H, dd, *J* 9.5, 7.0 Hz), 3.19–3.12 (1H, m), 2.60 (1H, dd, *J* 14.5, 9.5 Hz), 2.55–2.42 (1H, m), 2.33–2.16 (2H, m), 2.12 (3H, s), 2.07 (3H. s), 2.00–1.80 (2H, m), 1.58–1.52 (2H, m), 1.32 (3H, s), 1.01 (3H, d, *J* 6.5 Hz), 0.94 (3H, d, *J* 6.5 Hz); ^{13}C (100 MHz, $CDCl_3$) 200.0, 170.4, 156.4, 133.1, 88.7, 80.5, 79.0, 44.8, 36.5, 35.8, 30.7, 30.2, 21.0, 20.5, 17.5, 16.2, 16.1; *m/z* (ES^+) found 293.1775 (MH^+) $C_{17}H_{25}O_4$ requires 293.1753.

(*rel*-3a*S*,4*R*,5*R*,7*S*,8*R*)-8-Hydroxy-7-isopropyl-1,4-dimethyl-2,3,3a,4,5,6,7,8-octahydro-4,7-epoxyazulen-5-yl Acetate: To a solution of enone **19** (110 mg, 0.37 mmol) in methanol (10 mL) at 0°C was added $CeCl_37H_2O$ (275 mg, 0.74 mmol) and the mixture was stirred for 10 min and $NaBH_4$ (28 mg, 0.74 mmol) was added. The resulting mixture was stirred for 1 h and was quenched with ammonium chloride (sat. aq., 2 mL). To the resulting mixture was added ethyl acetate (30 mL) and the layers were separated. The aqueous layer was extracted with ethyl acetate (20 mL) and the combined organic layers were washed with brine (2 × 20 mL). dried ($MgSO_4$) and concentrated in vacuo. Purification by flash column chromatography (silica gel, 5:1 petroleum ether ether/ethyl acetate eluent) gave alcohol product as a colorless oil (78 mg, 72 %); ν_{max}(thin film) 3520 (br s), 1735 (s), 1380 (m), 1255 (m), 1110 (m); ^{1}H (400 MHz, $CDCl_3$) 4.77 (1H, dd, *J* 7.5, 3.0 Hz), 4.34 (1H, s), 2.85 (1H, dd, *J* 15.0, 9.0 Hz), 2.41–2.26 (2H, m), 2.04 (3H, s),1.90–1.80 (1H, m), 1.76 (3H, s), 1.73–1.60 (2H, m), 1/42–1.37 (1H, m), 1.32 (3H. s), 1.07 (6H. d, *J* 7.0 Hz); ^{13}C (100 MHz, $CDCl_3$) 169.8, 132.1, 129.2, 88.6, 86.5, 72.4, 61.9, 46.9, 44.7, 36.3, 34.6, 30.1, 24.9, 21.2, 19.0, 18.4, 15.5; *m/z* (ES^+) found 317.1705 (MNa^+) $C_{17}H_{26}O_4Na$ requires 317.1729.

(*rel*-1*S*,3a*S*,4*R*,5*R*,7*S*,8*R*,8a*S*)-8-Hydroxy-7-isopropyl-1,4-dimethyldecahydro-4,7-epoxyazulen-5-yl Acetate: To a solution of allylic alcohol (75 mg, 0.25 mmol) in DCM (5 mL) was added (1,5-Cyclooctadiene)(pyridine)(tricyclohexylphosphine)-iridium(I) hexa fluorophosphate (56 mg, 0.07 mmol) and the resulting mixture was stirred under H_2 (1 atm.) for 18 h before it was concentrated in vacuo. Flash column chromatography (silica gel, 5:1 petroleum ether ether/ethyl acetate) gave the saturated product **24** (51.5 mg, 68 %) as a colorless oil; ν_{max}(thin film) 3510 (br s), 1735 (s), 1369 (m), 1190 (m); ^{1}H (400 MHz, $CDCl_3$) 5.02 (1H, dd, *J* 7.5 Hz, 3.0 Hz), 3.65 (1H, d, *J* 10.0 Hz), 2.44 (1H, dd, *J* 14.0, 7.5 Hz), 2.35–2.29 (1H, m), 2.06 (3H, s), 2.03–1.97 (2H, m), 1.70–1.64 (3H, m), 1.35–1.29 (2H, m), 1.22–1.20 (1H, m), 1.17 (3H, s), 1.06 (6H, d *J* 7.0 Hz), 0.89 (3H, d, *J* 5.5 Hz); ^{13}C (100 MHz, $CDCl_3$) 170.7, 85.8, 84.3, 75.1, 70.7, 48.0, 47.9, 38.7, 32.3, 31.2, 30.5, 25.5, 21.1, 18.9, 18.3, 17.4, 16.8; *m/z* (ES^+) found 319.1907 (MNa^+) $C_{17}H_{28}O_4Na$ requires 319.1885.

(*rel*-1*S*,3a*S*,4*R*,5*R*,7*S*,8*R*,8a*S*)-5-Acetoxy-7-isopropyl-1,4-dimethyldecahydro-4,7-epoxyazulen-8-yl Cinnamate: To a stirred solution of cinnamic acid (50 mg, 0.34 mmol) in toluene (5 mL) was added triethyl amine (100 μL, 0.7 mmol) and 2,4,6-trichlorobenzoyl chloride (97 mg, 0.4 mmol) and the resulting mixture was stirred for 1 h before a solution of alcohol (50 mg, 0.17 mmol) in toluene (3 mL) followed by DMAP (61 mg, 0.5 mmol). The resulting mixture was heated at 80°C for 4 h, when it was cooled to room temperature and quenched by addition of $NaHCO_3$ (sat. aq. 2 mL). Layers were separated and the aqueous layer was extracted with ethyl acetate (2 × 10 mL). Combined organic extracts were washed with brine (2 × 10 mL), dried ($MgSO_4$) and the solvents evaporated in vacuo. Flash column chromatography (silica gel, 10:1 petroleum ether ether/ethyl acetate) to give the cinnamic ester (61.5 mg, 85 %) as a colorless oil;(%); ν_{max}(thin film) 1716 (s), 1714 (s), 1649 (m), 1450 (m), 1245 (m), 1040 (m); ^{1}H (400 MHz, $CDCl_3$) 7.65 (1H, d, *J* 15.5 Hz), 7.54–7.51 (2H, m), 7.40–7.31 (3H, m), 6.40 (1H, d, *J* 15.5 Hz); 5.13 (1H, d, *J* 10.0 Hz), 5.09 (1H, dd, *J* 7.5, 3.0 Hz), 2.65 (1H, dd, *J* 14.0, 8.0 Hz), 2.16–2.10 (1H, m), 2.09 (3H, s), 1,97–1.86 (2H, m), 1.73–1.67 (3H, m), 1.55–1.53 (1H, m), 1.28–1.23 (2H, m), 1.21 (3H,s), 1.02 (3H, d, *J* 5.5 Hz), 0.93 (3H, d, *J* 7.0 Hz), 0.34 (3H. d, *J* 7.0 Hz); ^{13}C (100 MHz, $CDCl_3$) 170.8, 165.6, 144.9, 134.3, 130.3, 129.0, 128.1, 118.1, 85.5, 84.4, 75.0, 71.4, 47.5, 46.9, 40.2, 33.2, 31.3, 30.9, 24.6, 21.1, 19.0, 18.3, 17.5, 16.9; *m/z* (ES^+) found 427.2509 (MH^+) $C_{26}H_{35}O_5$ requires 427.2484.

(*rel*-1*S*,3a*S*,4*R*,5*R*,7*S*,8*R*,8a*S*)-5-Hydroxy-7-isopropyl-1,4-dimethyldecahydro-4,7-epoxyazulen-8-yl Cinnamate: To a stirred solution of diester starting material (60 mg, 0.14 mmol) in methanol (5 mL) was added potassium carbonate (58 mg, 0.42 mmol) and

the mixture was stirred for 1 h when it was diluted with ethyl acetate (20 mL) and washed with brine (2 × 10 mL), dried ($MgSO_4$) and concentrated in vacuo. Flash column chromatography (silica gel, 5:1 petroleum ether ether/ethyl acetate) gave the pure hydroxyl ester (31.2 mg, 85 %) as a colorless oil; ν_{max}(thin film) 3440 (br s), 1720 (s), 1640 (m), 1460 (m), 1200 (m); ^{1}H (400 MHz, $CDCl_3$) 7.67 (1H, d, *J* 16.5 Hz), 7.52 (2H, m), 7.38 (3H, m), 6.39 (1H, d, *J* 16.5 Hz), 5.22 (1H, d, *J* 10.5 Hz), 4.19 (1H, dd, *J* 10.5, 5.0 Hz), 2.37 (1H, m), 2.30 (1H, dd, *J* 14.5, 10.5 Hz), 2.12 (1H, m), 2.04 (1H, dd, *J* 14.5, 5.0 Hz), 1.98–1.65 (6H, m), 1.32 (3H, s), 1.20 (1H, m), 0.93 (3H, d, *J* 6.0 Hz), 0.89 (3H, d, *J* 6.0 Hz), 0.88 (3H, d, *J* 9.0 Hz); ^{13}C (100 MHz, $CDCl_3$) 166.5, 134.2, 134.7, 130.4, 129.1, 128.3, 118.6, 84.7, 81.5, 81.2, 72.8, 49.4, 46.4, 39.5, 33.1, 31.7, 31.4, 24.6, 23.5, 17.9, 17.3, 17.1; *m/z* (ES^+) found 407.2173 (MNa^+) $C_{24}H_{32}O_4Na$ requires 407.2198.

(*rel*-1*S*,3a*S*,4*R*,5*R*,7*S*,8*R*,8a*S*)-5-{[(1H-Imidazol-1-yl)sulfonyl]oxy}-7-isopropyl-1,4-dimethyldecahydro-4,7-epoxyazulen-8-yl Cinnamate:[11] To a stirred solution of alcohol starting material (30 mg, 0.078 mmol) in THF (3 mL) at –78°C was added LiHMDS (1.06 M soln. in THF, 0.36 mL, 0.39 mmol mmol) and after 30 min a solution of sulfonyldiimidazole (77.2 mg, 0.39 mmol) in THF (2 mL), and the resulting mixture was warmed to room temperature over a period of 16 h. To the reaction were added DCM (10 mL) and $NaHCO_3$ (sat. aq., 3 mL) and layers were separated. Aqueous layer was extracted with DCM (2 × 10 mL), organic extracts were combined, washed with brine (2 × 10 mL), dried (Na_2SO_4) and the solvents evaporated in vacuo. Flash column chromatography (silica gel, 6:1 petroleum ether ether/ethyl acetate) of the residue gave the protected alcohol (40.1 mg, 72 %) as a colorless oil; ν_{max}(thin film) 2960 (m), 1715 (s), 1650 (m), 1380 (br s), 1140 (m); ^{1}H (400 MHz, $CDCl_3$) 8.03 (1H, s), 7.65 (1H, d, *J* 16.0 Hz), 7.53 (m, 2H), 7.40 [m, 4H, 7.24 (s, 1H), 6.38 (1H, d, *J* 16.0 Hz), 5.20 (1H, d, *J* 10.0 Hz), 4.59 (1H, dd, *J* 10.5, 5.0 Hz), 2.23 (1H, dd, *J* 14.0, 6.5 Hz), 2.19–2.09 (2H, m), 2.08–1.99 (2H, m), 1.90 (1H, m), 1.81–1.62 (3H, m), 1.22–1.18 (1H, m), 1.19 93H, s], 0.95–0.88 (9H, m); ^{13}C (100 MHz, $CDCl_3$) 165.8, 145.6, 137.4, 134.4, 131.8, 129.2, 128.4, 118.2, 118.9, 90.7, 85.4, 81.3, 71.3, 49.0, 46.4, 35.8, 32.7, 31.4, 31.3, 24.1, 22.6, 17.6, 17.0, 17.0; *m/z* (ES^+) found 515.2198 (MH^+) $C_{27}H_{35}N_2O_6$ requires 515.2216.

(±)-Englerin A (1):[11] To a stirred solution of the activated alcohol (15 mg, 0.029 mmol) in toluene (3 mL) was added cesium glycolate (6 mg, 0.145 mmol) and 18-crown-6 (38.3 mg, 0.145 mmol) and the resulting mixture was heated at reflux for 18 h, then was cooled and diluted with DCM (5 mL) and water (5 mL). The layers were separated and the aqueous layer was extracted with DCM (2 × 5 mL), combined organic extracts were dried (Na_2SO_4) and concentrated in vacuo. Flash column chromatography (silica gel, 6:1 petroleum ether ether/ethyl acetate) gave (±)-**1** (7.8 mg, 61 %) as a colorless oil; ν_{max}(thin film) 3460 (br s), 1715 (s), 1640 (m), 1205; 1165 (m); ^{1}H (400 MHz, [D_6]DMSO) 7.73–7.70 (2H, m), 7.68 (1H, d, *J* 16.0 Hz), 7.45–7.40 (3H, m), 6.59 (1H, d, *J* 16.0 Hz), 5.15 (1H, dd, *J* 9.0, 2.0 Hz), 4.96 (1H, d, *J* 10.0 Hz), 4.04 (2H, s), 2.64 (1H, dd, *J* 14.5, 8.0 Hz), 2.07–2.00 (1H, m), 1.97–1.89 (1H, m), 1.78 (1H, sept, *J* 7.0 Hz), 1.73 (1H, dd, *J* 14.5, 2.0 Hz), 1.69–1.60 (3H, m), 1.27–1.10 (2H, m), 1.10 (3H, s), 0.94 (3H, d, *J* 7.0 Hz), 0.88 (3H, d, *J* 7.0 Hz), 0.84 (3H, d, *J* 7.0 Hz); ^{13}C (100 MHz, [D_6]DMSO) 172.5, 165.2, 145.3, 133.9, 130.6, 129.0, 128.4, 117.8, 84.6, 84.3, 74.5, 70.5, 59.7, 47.1, 46.0, 32.8, 30.7, 30.5, 24.1, 18.7, 18.1, 17.4, 16.7 (one ^{13}C resonance is missing due to overlap with solvent peaks); *m/z* (ES^+) found 465.2229 (MNa^+) $C_{26}H_{34}O_6Na$ requires 465.2253.

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Keywords: Total synthesis · Englerin A · Truncated analogue · 1,3-Dipolar cycloaddition · Synthetic strategy

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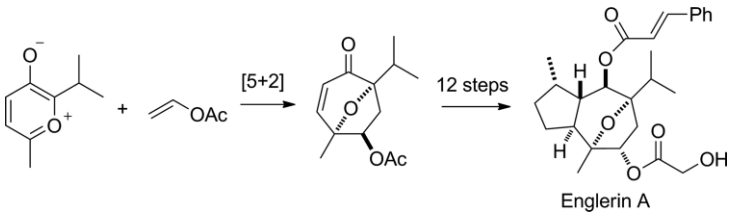
Total Synthesis



Total synthesis of (±)-Englerin A and a number of truncated analogues was developed based on a 1,3-dipolar cycloaddition of a substituted pyrylium ylide. The bicyclic enone scaffold was further converted into a truncated analogue and the natural product. Interesting stereochemical effects of the bridgehead substituents on the reactivity of the 8-oxabicyclo[3.2.1]octanes were uncovered.

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