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Total Synthesis of Caesalpinnone A

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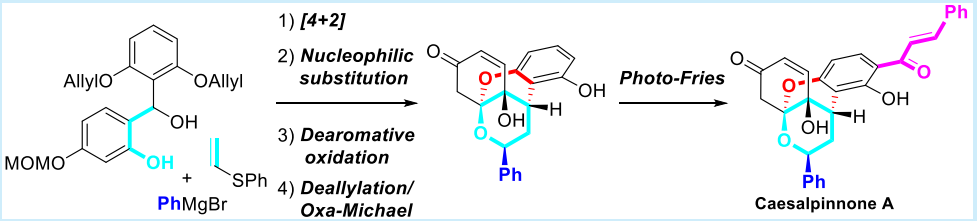
Supporting Information



ABSTRACT: Total synthesis of caesalpinnone A was achieved in 12 steps starting from resorcinol. Key features of the synthesis include BINOL-phosphoric acid catalyzed [4 + 2] cycloaddition, *trans*-selective nucleophilic substitution, deallylation/oxa-Michael addition cascade, and late-stage photo-Fries rearrangement.

Flavonoids are structurally and biologically important natural polyphenolic compounds, which have been reported on their various biological activities such as antioxidant, antithrombotic, antitumor, and anti-inflammatory, etc.[1] Caesalpinnone A (**1**, Figure 1) and caesalpinflavans A−C

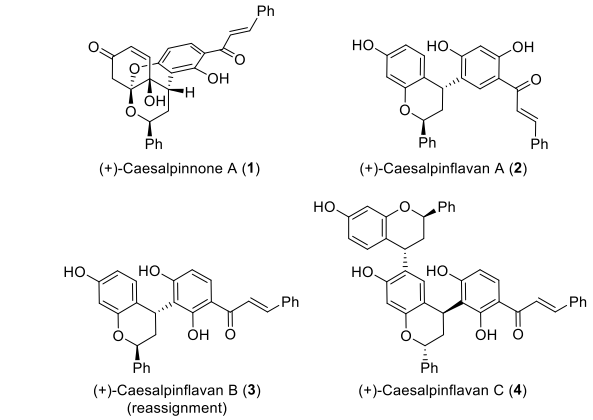
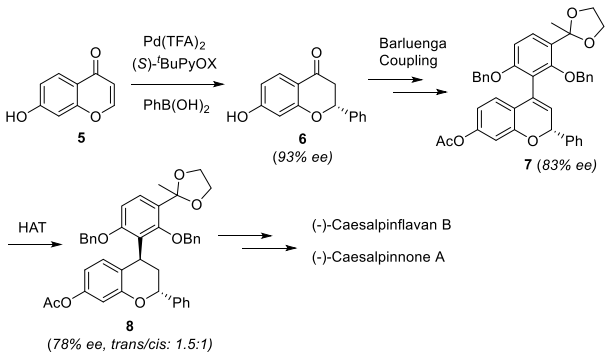


Figure 1. Four flavan−chalcone hybrids isolated from *Caesalpinia enneaphylla*.

(**2**−**4**) are flavan−chalcone hybrids isolated from the twigs and leaves of *Caesalpinnea enneaphylla* by Wang and co-workers in 2017.[2] These molecules exhibit cytotoxic activity against a number of cancer cell lines. The structural similarity and the same stereochemistry (except for caesalpinflavan C) reveal the close biogenetic relationship between these flavan−chalcone hybrids.

Very recently, the total syntheses of (−)-caesalpinnone A and (−)-caesalpinflavan B are accomplished by Wood and co-workers.[3] Their syntheses rely on a Pd-catalyzed conjugate addition to install the first stereocenter in compound **6** with high enantioselectivity, a Barluenga coupling between *N*-tosylhydrazone and aryl iodide, a Mn-catalyzed hydrogen atom transfer (HAT) hydrogenation, and a deallylation/oxa-Michael addition cascade (for caesalpinnone A) (Scheme 1).

Scheme 1. Wood's Asymmetric Strategy to (−)-Caesalpinflavan B and (−)-Caesalpinnone A



Despite the successful total synthesis of caesalpinnone A and caesalpinflavan B by Wood's group, we attempt to establish an alternative synthetic route, facilitating the construction of the 2,4-*trans*-diaryl flavonoid skeleton in high stereoselectivity as well as assembling the chalcone segment at a late stage of the total synthesis.

Our retrosynthetic analysis of caesalpinnone A is outlined in Scheme 2. The chalcone segment of **1** could be introduced by an acylation of phenol **9** and then a photo-Fries rearrangement. The bridged ketal substructure could be synthesized from a *p*-quinol via deallylation/oxa-Michael addition strategy, while the

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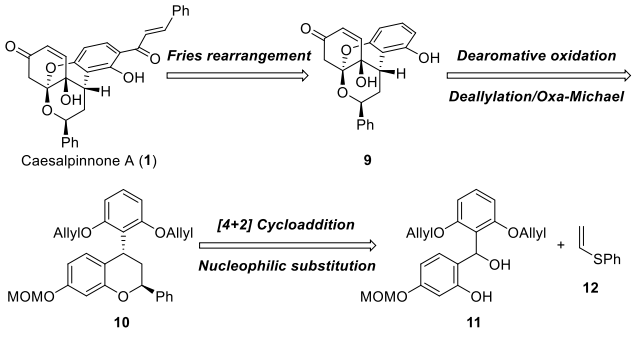
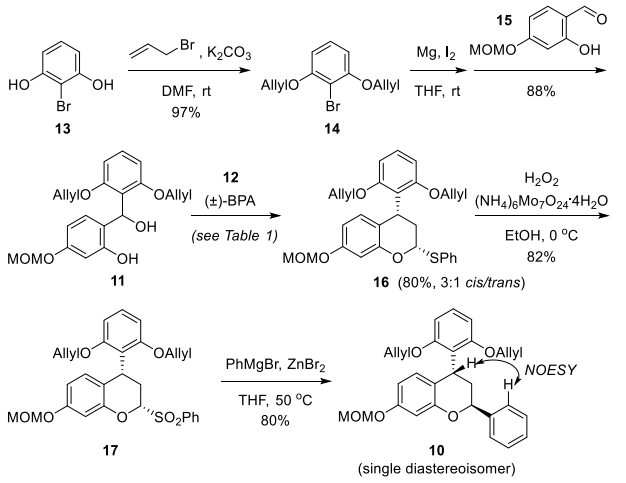
Scheme 2. Retrosynthetic Analysis of Caesalpinnone A



p-quinol intermediate could be derived from compound **10** through phenolic dearomative oxidation. In the preparation of compound **10**, we deploy an oxa-[4 + 2] cycloaddition between *o*-hydroxybenzyl alcohol **11** and phenyl vinyl sulfide **12** followed with a nucleophilic substitution of phenylsulfone to construct the *trans*-configuration, which effectively circumvents the issues of the diastereoselectivity and racemization of hydrogenation in Wood's synthetic route.

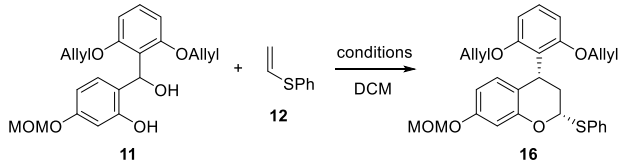
As shown in Scheme 3, our synthetic route started from the known compound **13**[4] which is commercially available or

Scheme 3. Synthesis of 2,4-*trans*-Diaryl Flavonoid 10

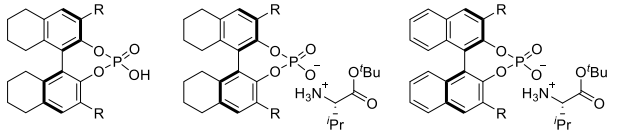


could be synthesized efficiently via a two-step reaction from resorcinol. Protecting of both phenol groups in **13** with allyl bromide afforded **14** in 97% yield. The corresponding Grignard reagent was prepared and reacted with the known salicylaldehyde **15**,[5] leading to the generation of diol **11**. With the resulting *o*-hydroxybenzyl alcohol **11** in hand, we next investigated the key oxa-[4 + 2] cycloaddition between **11** and an olefin to furnish 2,4-diaryl benzodihydopyran. Taking into account the atomic and step economy of cycloaddition, styrene would be the most suitable candidate. However, careful review of the existing literature informed us that such cycloaddition always yields the major *endo*-type products in *cis*-configuration.[6] The poor *trans*-selectivity promoted us to seek a more effective approach to establish the desired benzodihydopyran. Eventually, phenyl vinyl sulfide (**12**) was selected as the olefin for the oxa-[4 + 2] cycloaddition based on its high reactivity, the possibility for asymmetric synthesis, and feasibility for further transformation. Gratifyingly, by treating **11** and **12** with the racemic BINOL-phosphoric acid (BPA) in DCM at −15 °C, the cycloadduct **16** was obtained in 80% yield with a *cis*/*trans* ratio of 3:1. The diastereoselectivity here is inconsequential because a planned configuration reestablishment would be conducted in the next step. Subsequently, the asymmetric oxa-[4 + 2] cycloaddition under chiral BPAs was extensively explored (selected examples are shown in Table 1). Unlike the high asymmetric selection of the oxa-[4 +

Table 1. Studies on the Asymmetric [4 + 2] Cycloaddition



entry	catalyst	temp	yield (%)	*cis*/*trans*	ee (%)
1	(±)-BPA	−15 °C	80	3:1	0
2	**Cat-1**	rt	50	2.2:1	3
3	**Cat-2**	rt	75	4.6:1	31
4	**Cat-3**	rt	78	2.3:1	30
5	**Cat-4**	rt	70	2.3:1	−12
6	**Cat-5**	rt	49	3.8:1	30
7	**Cat-6**	rt	77	2.6:1	38



Cat-1: R = 9-phenanthryl
Cat-2: R = 2,4,6-(^{i}Pr)$_3$C$_6$H$_2$
Cat-3: R = 2,4,6-(^{i}Pr)$_3$C$_6$H$_2$ (Ag salt)
Cat-4: R = Br
Cat-5: R = 2,4,6-(^{i}Pr)$_3$C$_6$H$_2$
Cat-6: R = 2,4,6-(^{i}Pr)$_3$C$_6$H$_2$

2] cycloaddition reaction under the catalyst of **Cat-1** in Sun's report,[7] this catalyst exhibited nonenantioselectivity in our synthesis with a possible reason for steric hindrance of 2′,6′-diallyloxy substituents. After screening various substituted chiral BPAs and their silver or ammonia salts, it was found that only catalyst **Cat-6** gave the best result with 38% ee value.

We then moved forward to the construction of the 2,4-*trans*-diaryl flavonoid skeleton via the nucleophilic substitution strategy.[8] Oxidation of sulfide **16** to sulfone **17** was conducted smoothly under the condition of $(NH_4)_6Mo_7O_{24}\cdot 4H_2O/H_2O_2$.[9] Next, $ZnBr_2$-mediated *trans*-selective nucleophilic substitution of the resulting phenylsulfone **17** with PhMgBr successfully generated the expected 2,4-*trans*-diaryl benzodihydopyran **10** as a single diastereoisomer in 80% yield. The relative stereochemistry of **10** was further confirmed by the NOESY experiments.

With the successful synthesis of **10**, we turned our attention to the construction of the bridged ketal and the chalcone skeleton (see Scheme 4). After selective deprotection of MOM under MeOH and *p*TSA,[10] the resulting phenol **18** was ready for the dearomative oxidation. Numerous phenolic oxidation conditions were investigated,[11] and only $PhI(OAc)_2$ was effective to give the *p*-quinol **19** in 21% yield. The low yield was due to the formation of *o*-quinone (detected by NMR) and other unstable byproducts. Next, according to the Wood's method,[3] the deallylation/oxa-Michael sequence was conducted by treatment of **19** with $Pd(PPh_3)_4$ and 1,3-dimethyl barbituric acid, furnishing the expected oxa-Michael product **9** in moderate yield.[12] With this, completion of **1** only required a selective phenolic esterification and an ensuing photo-Fries

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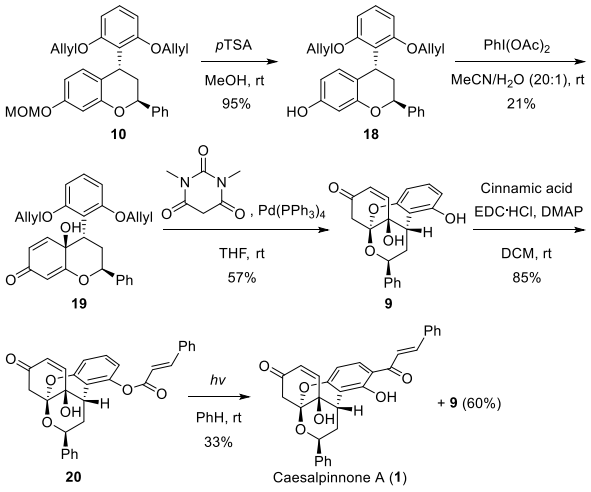
Scheme 4. Completion of the Synthesis of Caesalpinnone A



rearrangement process. Treating **9** with *trans*-cinnamic acid in the presence of EDC·HCl and DMAP resulted in the formation of ester **20**, which was irradiated under a 500 W mercury lamp in benzene for 15 h, giving caesalpinnone A (**1**) in 33% yield along with the deacylation product phenol **9** in 60% yield.[13] The NMR data of **1** were in full agreement with those of the natural product (see the Supporting Information).[2]

In summary, we have accomplished the total synthesis of caesalpinnone A through an oxa-[4 + 2] cycloaddition followed by a *trans*-selective nucleophilic substitution to construct the 2,4-*trans*-flavonoid core, a sequential dearomative oxidation/deallylation/oxa-Michael reaction to establish the characteristic bridged ketal, and a photo-Fries rearrangement to introduce the cinnamyl chain. Additionally, we have made an attempt to achieve the asymmetric oxa-[4 + 2] cycloaddition, although the ee value was not high (up to 38% ee). Improvement of the enantioselectivity of the oxa-[4 + 2] cycloaddition as well as evaluation of the biological activities of the synthesized compounds would be the focus of our future work.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge at https://pubs.acs.org/doi/10.1021/acs.orglett.9b04276.

Experimental procedures and physical properties of the compounds (PDF)

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Notes

The authors declare no competing financial interest.

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