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Total Synthesis of Caesalpinnone A and Caesalpinflavan B: Evolution of a Concise Strategy

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Supporting Information Placeholder

ABSTRACT: The total syntheses of caesalpinnone A (**1**) and its putative biosynthetic precursor caesalpinflavan B (**3**) are described. Herein, we describe the evolution of a synthetic strategy toward **1** and **3**, which entails a convergent Barluenga coupling that quickly delivers a heavily-functionalized benzopyran containing the core carbon framework and exploration of two distinct synthetic routes for forging the flavanoid C-ring by reducing a sterically-encumbered embedded alkene: one via a stepwise approach and a second, more direct and atom-economical, enabled by a Shenvi-HAT hydrogenation. The latter strategy allowed access to caesalpinflavan B in 6 steps after Pd-mediated deallylation. A late-stage dearomative phenolic oxidation and deallylation/oxa-Michael cascade was implemented to access caesalpinnone A (**1**) in 7 steps. We also describe an enantioselective total synthesis and stereochemical revision of (–)-caesalpinflavan B as well as a formal enantioselective synthesis of (–)-caesalpinnone A, by implementing an enantioselective Pd-catalyzed conjugate addition chemistry developed by Stoltz.

Introduction

Caesalpinnone A ((+)-**1**) is a hybrid flavan-chalcone natural product recently isolated from the twigs and leaves of *caesalpinnea enneaphylla* obtained from the Yannan province in China.[1] Accompanying (+)-**1** were 3 other flavan-chalcone hybrids, the caesalpinflavans (A–C, (+)-**2**–**4**), all of which possess a *trans*-2,4-diaryl substitution pattern on the flavanoid C ring (Figure 1). However, the *trans*-2,4-diaryl substituted C ring in **1** (Figure 1, highlighted in red), is embedded within a unique dioxotricyclo[5.3.3.0^{1,6}]tridecane core structure. Interestingly, as illustrated, the assigned absolute stereochemistry was not consistent across the four congeners. From a biological perspective, caesalpinnone A and the caesalpinflavans A–C were all shown to exhibit cytotoxic activity against a number of cancer cell lines, the most potent of which (**1**) has IC_{50} values in the sub-micromolar range (0.54–0.87 μM).

Given the relatively potent biological activity of the caesalpinnone congeners and the fascinating core architecture of **1**, we sought to develop a synthesis that would pass through caesalpinflavan B (**3**, Figure 1, inset) as well as several structurally related intermediates, thereby providing numerous interesting compounds for future biological assays. From a biosynthetic perspective, **3** appeared to be the logical precursor to **1**, however, based on the opposite absolute stereochemistry assigned to C-2" and -4", this supposition was unclear. Thus, this approach, employing **3** as a precursor to **1**, would also potentially address this apparent stereochemical anomaly. Herein, we describe the realization of this goal by developing concise syntheses of (±)-**1**, (±)-**3**, and (–)-**3**. The latter of which enabled the stereochemical reassignment of (+)-**3** and clarified the potential biosynthetic origin of (+)-**1**.

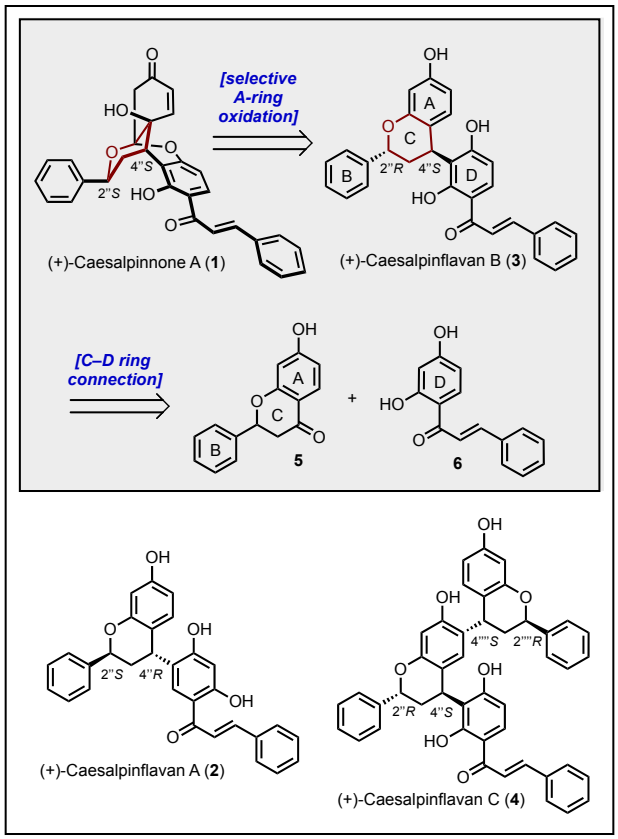
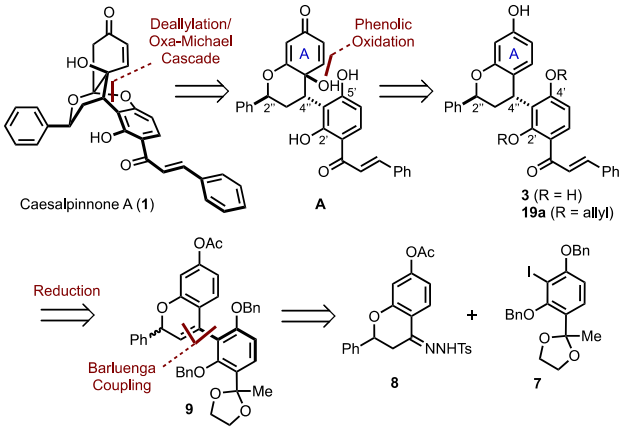


Figure 1. Isolates from *caesalpinnea enneaphylla* and proposed preparation of 1 from 3.

Results and Discussion

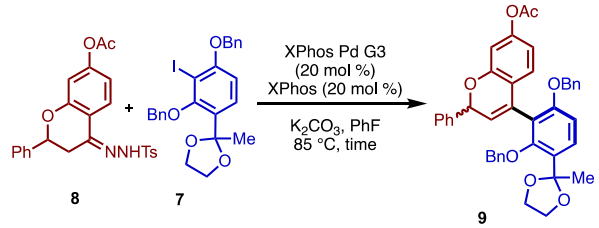
Retrosynthetic Analysis. As illustrated retrosynthetically in Scheme 1, in developing our synthetic strategy we envisioned that **1** would arise from dearomative oxidation of the flavanoid A ring in **3**, followed by capture of the resulting *p*-quinol (**A**, Scheme 1) by the most nucleophilic and least sterically encumbered D ring C4' phenol.[2] In further consideration of biosynthetic origins, we recognized **3** as a pseudo-dimer of the structurally-related natural products 7-hydroxyflavanone (**5**)[3] and 2',4'-dihydroxychalcone (**6**, Figure 1, inset),[4] thus suggesting the eventual disconnection at the C,D-ring juncture.[5] To this end, **3** was seen as arising from reduction of functionalized benzopyran **9**, setting the necessary *trans*- relationship between the 2" and 4" arenes (caesalpinnone A numbering). Formal construction of the C,D-ring union would occur in the production of **9** wherein the congested olefin would be produced via a Pd-catalyzed coupling of *N*-tosylhydrazone **8** with aryl iodide **7** (i.e., the Barluenga coupling).[6] The latter was particularly appealing given its demonstrated success in coupling sterically-demanding arenes to form 1,1'-diarylalkenes.[7]

Scheme 1. Overall Retrosynthetic Analysis of 3 and 1.



Development of a Barluenga Cross Coupling. Our synthetic approach began with the synthesis of benzopyran **9** via Barluenga Coupling. The requisite *N*-tosylhydrazone component (**8**) and aryl iodide (**7**) were each prepared in one step from known materials.[8] With **7** and **8** in hand, we began exploring conditions for the planned Barluenga coupling. To this end, we found that heating a fluorobenzene solution containing **7** (1 equiv), **8** (1.2 equiv), and excess K_2CO_3 in the presence of a catalytic amount of both XPhos Pd G3 and XPhos resulted in full consumption of **7** and provided benzopyran **9** in 37% yield as a 1:1.8 mixture of inconsequential atropisomers (Table 1, entry 1). Selection of these initial coupling conditions were influenced by preliminary attempts to prepare **1** via intermediates derived from a similar Barluenga coupling (see Supporting Information). Unfortunately, increasing the equivalents of *N*-tosylhydrazone **8** showed little improvement in the yield of **9** (Table 1, entry 2); however, while monitoring this reaction by mass spectrometry, we observed significant formation of side-product, presumably derived from **8**.[9] In efforts to mitigate these side-products, we first chose to increase the equivalents of **7** (Table 1, entries 3 and 4), which, gratifyingly, led to isolation of **9** in up to 68% yield on multi-gram scale. In further attempts to improve the reaction efficiency, we eventually found that slow addition of **8** to the reaction mixture provided **9** in up to 91% yield (Table 1, entry 5). Having developed an efficient method for accessing benzopyran **9**, the stage was set for the key reduction of the C3''– C4'' bond.

Table 1. Selected optimization trials for the Barluenga coupling between 7 and 8.



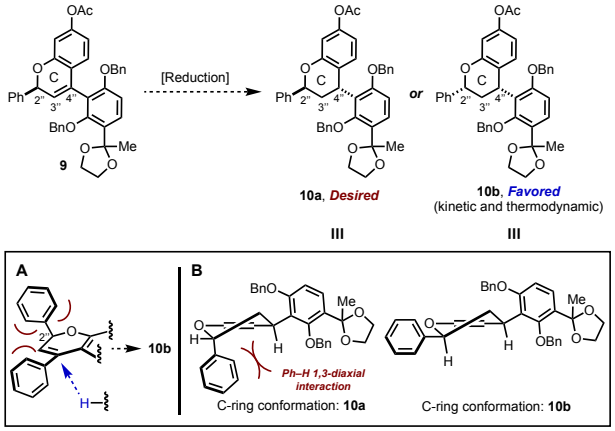
	entry	Equiv 8 (addition time)	Equiv 7	Equiv K_2CO_3	time (h)	yield[a]
excess **8**	1	1.2 (n/a)	1.0	2.8	4	37
	2	2.5 (n/a)	1.0	4.0	12	41–44
excess **7**	3	1.0 (n/a)	2.0	3.0	12	41–67
	4	1.0 (n/a)	2.5	3.0	22	68
slow addition (**8**)	5[b,c]	2.5 (10 h)	1.0	5.0	16	82–91

[a]Isolated yield.[b]Total reaction time: 10 h slow addition, followed by 6 hours additional reaction time. [c]1:2.2 v/v PhF–1,4-dioxane.

C-Ring Reduction: Conformational Analysis and Preliminary Studies. Perhaps the most challenging aspect of our planned approach to **1** was the development of conditions for the chemo- and *trans*-stereo-selective reduction of **9**, as the literature suggested that the requisite *trans* relationship of the C2'' and C4'' arenes in the desired product (**10a**) would likely be disfavored both thermodynamically and kinetically (Figure 2).[10,11] As illustrated, the kinetically favored path for reduction of **9** would likely involve hydrogen delivery *anti*- to the 2" phenyl group, which would provide the undesired *cis*-diastereomer **10b** (Figure 2, inset A). Additionally, a *cis*-substitution pattern between the 2" and 4" arenes would also likely be favored thermodynamically as this allows both arenes to be positioned pseudo-equatorially about the C-ring (Figure 2, inset B). Moreover, no examples were found describing the direct reduction of 2*H*-chromenes, such as **9**, to synthetically useful amounts of a corresponding *trans*-2",4"-diaryl product.[12] In practice, hydrogenation of the C3"–C4" double bond in **9** was found to be slow under a variety of both hetero- and

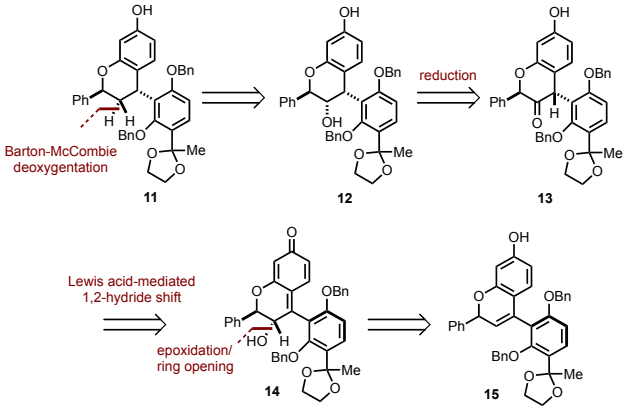
homogeneous conditions and typically accompanied by more facile benzyl aryl ether hydrogenolysis. Further, attempts at thermodynamic reduction of **9** by exposure to a myriad of Birch reduction conditions only led to deprotection and fragmentation. These initial undesired outcomes led us to develop a stepwise approach to reduce the benzopyran double bond and imbed the crucial 2",4"-*trans*- stereochemistry of the flavanoid C-ring (*vide infra*).

Figure 2. The 2",4"-*cis*- stereoisomer 10b is favored both kinetically (inset A) and thermodynamically (inset B) in the reduction of 9.



C-Ring Reduction: A Stepwise Approach. As illustrated retrosynthetically in Scheme 2, to circumvent the issues observed in the direct reduction, we envisioned the key dihydrobenzopyran intermediate **11** arising from a Barton-McCombie deoxygenation sequence applied to alcohol **12**, which would be derived from the reduction of ketone **13**. Ketone **13** would originate from β-hydroxy *p*-quinone methide **14** by way of a Lewis acid-mediated *syn*-facial 1,2-hydride shift and rearomatization. Alcohol **14** would be accessed from benzopyran **15** via epoxidation followed by ring-opening to the *p*-quinone methide.

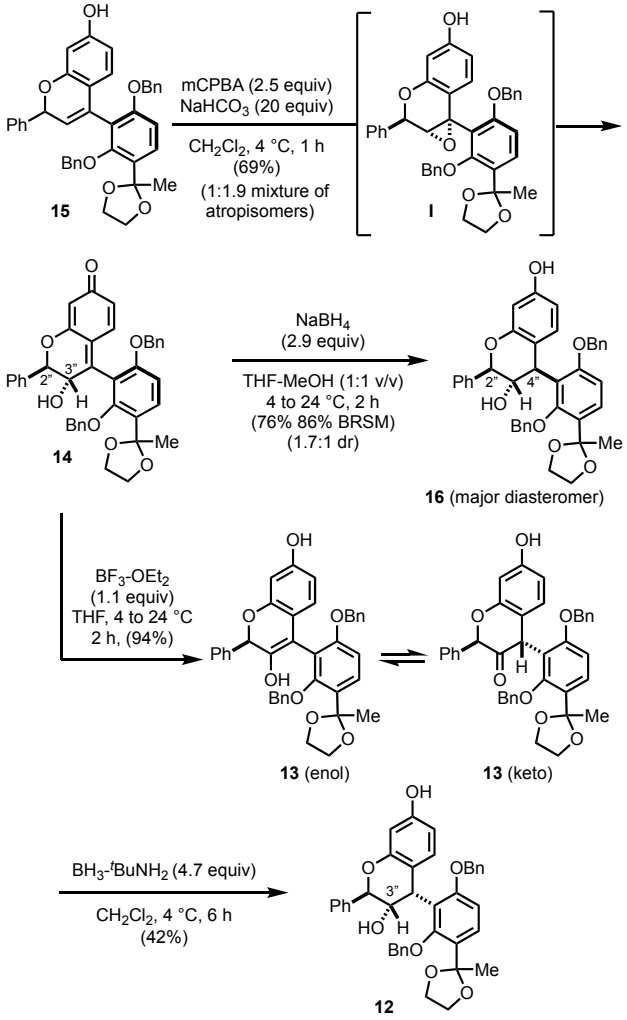
Scheme 2. Retrosynthetic Analysis of phenol 11 from the formal reduction of benzopyran 15.



This approach commenced with formation of the necessary hydroxy *p*-quinone methide (**14**). In the event, **15** was exposed to *m*-CPBA and sodium bicarbonate to furnish **14** in 69% yield as a 1:1.9 mixture of inconsequential of atropisomers,[13] presumably through the intermediacy of epoxide **I**, wherein oxygen has been delivered to the less hindered alkene face (Scheme 3). Direct reduction of **14** by sodium borohydride afforded alcohol **16** in 76% yield, but disappointingly, with the incorrect 2",4"-*cis* C-ring stereochemistry, later verified by single crystal X-Ray analysis of a downstream intermediate from a previous synthetic approach to **1** (see Supporting Information).

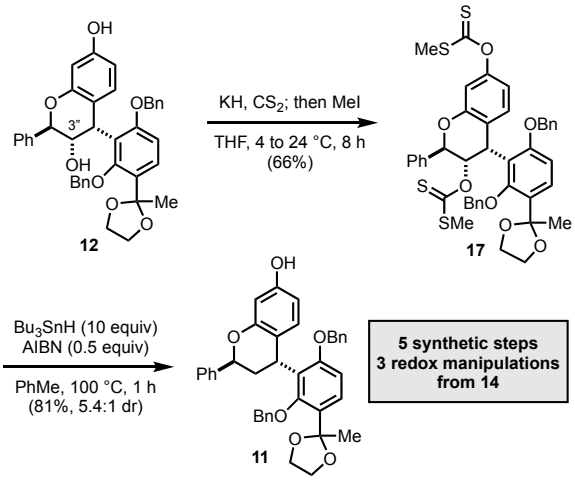
Given the undesired outcome of the direct reduction of **14**, we sought to instead leverage the *trans*-relationship between the 2" phenyl group and 3" hydroxyl group in *p*-quinone methide **14** by promoting a Lewis acid-mediated *syn*-facial-1,2-hydride shift to form ketone **13** (Scheme 3). After some experimentation, we found that treatment of **14** with BF_3-OEt_2 effected the desired 1,2-hydride shift, but isolation led to the corresponding enol (**13**-enol). Undeterred, semi-empirical calculations suggested that a *trans*- relationship between the 2" and 4" arenes in ketone **13** would be favored, and thus, we proceeded to reduce **13** with BH_3-^{t}BuNH$_2$, which furnished **12** possessing the desired 2",4"-*trans* diastereomer shown in Scheme 3.[14]

Scheme 3. Elaboration of benzopyran 15 to phenol 12.



With **12** in hand, deoxygenation of the unnecessary 3" hydroxy group was undertaken. Treatment of **12** with KH and CS_2, followed by methylation, furnished bis-xanthate **17** (Scheme 4). While a number of conditions were investigated for xanthylation of the sterically-hindered 3" alcohol, those illustrated in Scheme 4 were by far the most efficacious. Exposure of **17** to standard Barton-McCombie conditions furnished phenol **11** in good yield and as a 5.4:1 mixture of *trans*- and *cis*- isomers.[15] While the overall sequence from benzopyran **14** to dihydrobenzopyran **11** afforded our desired C-ring stereochemistry with good overall stereoselectivity, it was unacceptably inefficient, requiring five-steps and three redox manipulations for the formal *trans*-hydrogenation of **15**. In light of this inefficiency, we turned toward identifying a more direct method for accessing **11.**

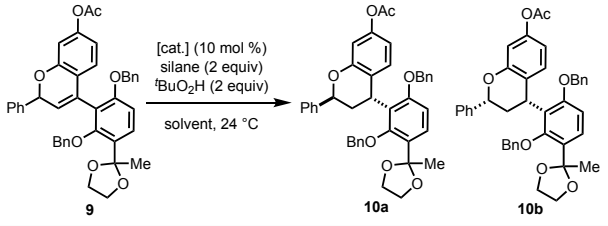
Scheme 4. Barton-McCombie deoxygenation of 12.



Direct C-Ring Reduction via Hydrogen Atom Transfer. In seeking a more direct method for reducing the C3"–C4" double bond in benzopyran **9**, we eventually turned to Shenvi's recently developed hydrogen atom transfer (HAT) chemistry.[16] As this method generally provides a thermodynamic mixture, it was likely to deliver useful quantities of the *trans*- isomer in a single synthetic transformation. In an initial experiment, a solution of **9** in CH_2Cl_2/^{i}PrOH (1:1 v/v) was treated with a catalytic amount of $Mn(dpm)_3$, ^{t}butyl hydroperoxide, and phenylsilane and found to undergo effective reduction of the C3''–C4'' double bond, affording a separable 1:2.2 mixture of *trans* and *cis*-isomers (**10a** and **10b**) in good yield (Table 2, entry 1); we were able to unambiguously assign the relative stereochemistry of **10a** by single crystal X-ray diffraction (Table 2, inset). However, given the undesirable product ratio, considerable effort was expended to increase selectivity in the HAT hydrogenation of **9** (Table 2, entries 2–15). Interestingly, employing Shenvi's more active reductant ^{i}PrO(Ph)SiH_2 led to incomplete conversion of **9**, and slightly less desirable 1:2.5 ratio of **10a**:**10b**.[17b] Subsequently, a variety of other HAT catalysts (entries 3–5) were also assessed and led to no conversion of **9**, even at extended reaction times. We then turned to evaluating the effect of solvent on the HAT hydrogenation. While chlorinated co-solvents (entries 1–6) afforded an undesirable ratio of **10a**:**10b**, and ethereal co-solvents led to no reaction (entry 7), we found that utilization of aromatic solvents led to higher selectivity for the desired diastereomer **10a** (Table 2, entries 8–15). In an initial finding, we found that HAT hydrogenation of **9** in the presence of a 1:1 mixture of PhH and ^{i}PrOH led to a 1.1:1 ratio of **10a** and **10b**, favoring, for the first time, **10a**, albeit with incomplete conversion (entry 8).[17] Using toluene as the co-solvent sluggishly led to a 1.5:1 ratio of **10a**:**10b**, but with reduced yield relative to chlorinated solvents. Further solvent screening identified fluorinated aromatic hydrocarbons as being particularly enabling for this transformation (entries 9–15) with trifluorotoluene ($PhCF_3$) leading to a 1.5:1 ratio of

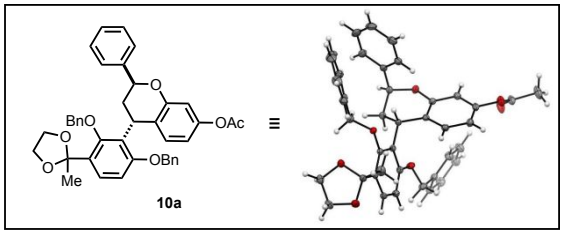
10a:**10b** in just 2.5 hours (Table 2, entry 12). Increasing the ratio of $PhCF_3$ in the solvent system led to increased reaction rates and concomitant increase in chemical yield while maintaining a 1.5:1 dr of **10a**/**10b** (entry 13). Using this solvent mixture, we also found that performing the reaction at –25 ºC led to no change in the product ratio (entry 14), and likewise, substitution of 2-propanol with hexafluoroisopropanol (HFIP) led to no reaction (entry 15). In addition, a number of protecting groups were investigated for the A-ring phenol (Piv, MOM, 2-Ns), but none had a positive effect in increasing selectivity for **10a**. Although we attempted to advance **10a** and **10b** to **1** and C2"-*epi*-**1**, respectively, only the former proved amenable to delivering the caesalpinnone ring-system (*vide infra*).

Table 2. Selected optimization trials for the HAT hydrogenation of 9.



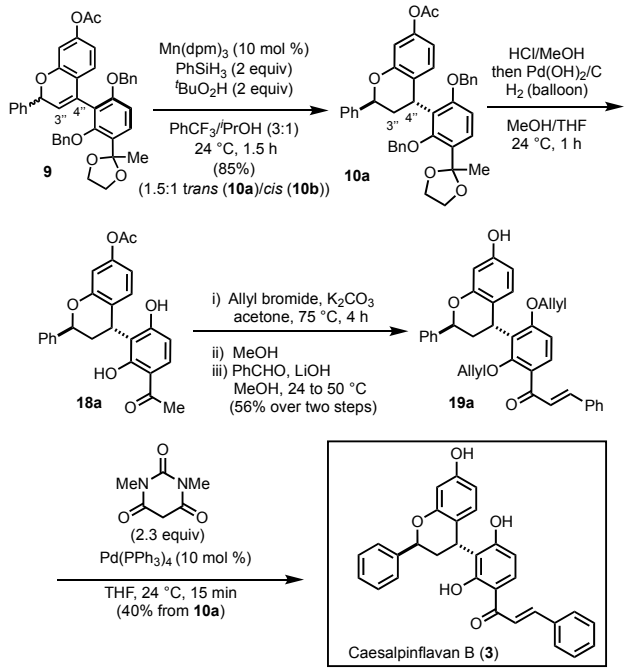
entry	[cat.]	silane	solvent	yield[a]	time (h)	10a:10b[b]
1	$Mn(dpm)_3$	$PhSiH_3$	CH_2Cl_2/^{i}PrOH (1:1)	84	2	1:2.2
2	$Mn(dpm)_3$	^{i}PrO(Ph)SiH_2	CH_2Cl_2/^{i}PrOH (1:1)	(68)	4	1:2.5
3	$Fe(acac)_3$	$PhSiH_3$	CH_2Cl_2/^{i}PrOH (1:1)	≤5	18	–
4	(*R*,*R*)-Mn(Salen$^{t\text{-Bu},t\text{-Bu}}$)Cl	$PhSiH_3$	CH_2Cl_2/^{i}PrOH (1:1)	≤5	18	–
5	(*R*,*R*)-Co(Salen$^{t\text{-Bu},t\text{-Bu}}$)	$PhSiH_3$	CH_2Cl_2/^{i}PrOH (1:1)	≤5	18	–
6[c]	$Mn(dpm)_3$	$PhSiH_3$	DCE/^{i}PrOH (1:1)	(45)	8	1:2.2
7	$Mn(dpm)_3$	$PhSiH_3$	THF/^{i}PrOH (1:1)	≤5	24	–
8	$Mn(dpm)_3$	$PhSiH_3$	PhH/^{i}PrOH (1:1)	(74)	22	1:1.1
9	$Mn(dpm)_3$	$PhSiH_3$	PhMe/^{i}PrOH (1:1)	67	5	1:5:1
10	$Mn(dpm)_3$	$PhSiH_3$	PhF/^{i}PrOH (1:1)	82	4	1.3:1
11	$Mn(dpm)_3$	$PhSiH_3$	C_6F_6/^{i}PrOH (1:1)	62	4.5	1:1.1
12	$Mn(dpm)_3$	$PhSiH_3$	$PhCF_3$/^{i}PrOH (1:1)	75	2.5	1.5:1
13	***$Mn(dpm)_3$***	***$PhSiH_3$***	***$PhCF_3$/^{i}PrOH (3:1)***	***85***	***1.5***	***1.5:1***
14[d]	$Mn(dpm)_3$	$PhSiH_3$	$PhCF_3$/^{i}PrOH (1:1)	66	16	1.5:1
15	$Mn(dpm)_3$	$PhSiH_3$	$PhCF_3$/HFIP (1:1)	≤5	24	–

[a]Isolated yields. Yields in parentheses refer to conversion as judged by ^{1}H NMR. [b]Ratios were obtained by ^{1}H NMR analysis. [c]Reaction run at 60 °C. [d]Reaction conducted at –25 °C.



Having established reliable access to the *trans* stereochemistry of the flavanoid C-ring, we turned our attention to accessing caesalpinflavan B (**3**) en route to completing the synthesis of **1**. At this juncture, all that remained to complete **3** was global deprotection of **10a** and installation of the enone moiety. To be completed effectively, this conversion required three steps[18] beginning with concomitant acetal hydrolysis (MeOH/HCl) and benzyl ether hydrogenolysis with Pearlman's catalyst to furnish bisphenol **18a**.[19] Allylation of **18a** followed by methanolysis and Claisen-Schmidt condensation with benzaldehyde furnished **19a**,[20,21] which upon deallylation[22] delivered caesalpinflavan B (**3**) in 40% yield over the three steps.

Scheme 5. HAT hydrogenation of the C3"–C4" bond and completion of caesalpinflavan B (3).



Completion of Caesalpinnone A (1) and Unexpected formation of Tricycle 21. With **3** in hand, we attempted to access **1** by way of phenolic oxidation of the more electron-rich A-ring, and subsequent oxa-Michael addition of the C4' D-ring phenol onto the vinylogous ester moiety of the resulting *p*-quinol (Figure 3). Unfortunately, all attempts to access **1** through this sequence proved futile.[23]

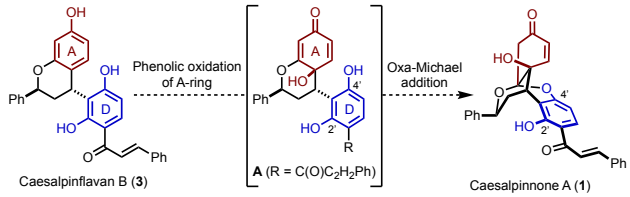
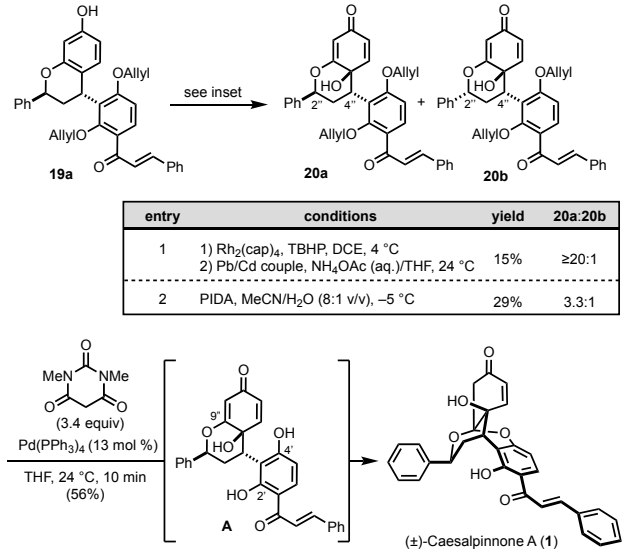


Figure 3. Attempted direct conversion of 3 to 1

Undeterred, we decided to attempt phenolic oxidation prior to allyl deprotection of the D-ring phenols. Previous investigations in our laboratories revealed Doyle's dearomative phenolic oxidation method as effective for the dearomative phenolic oxidation of sterically-encumbered substrates.[24,25] Given this, we treated **19a** with catalytic $Rh_2(cap)_4$ in the presence of TBHP and, after reductive cleavage of the internal peroxide with Pb/Cd couple, received 15% yield of the desired *p*-quinol

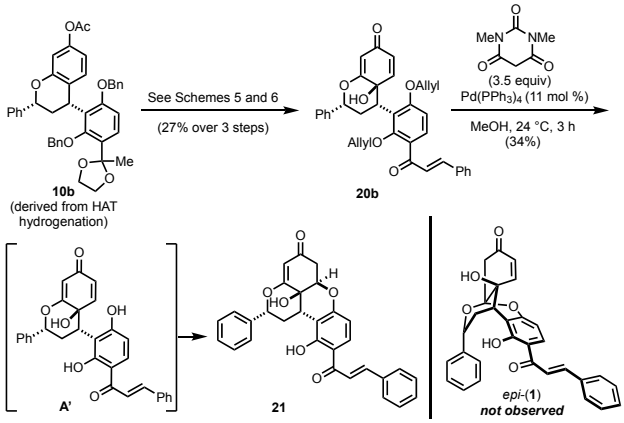
20a (Scheme 6, inset). Efforts to develop more efficient conditions for this conversion ultimately led to the treatment of **19a** with phenyliodide(III) diaceate (PIDA) in a mixture of acetonitrile and water (8:1 MeCN–H_2O v/v) at –5 ºC. Under these conditions we obtained a 3.3:1 mixture of *p*-quinols **20a** and **20b** in 29% yield. (Scheme 6, inset).[26,27]

Scheme 6. Phenolic oxidation of 12a and completion of the total synthesis of caesalpinnone A (1).



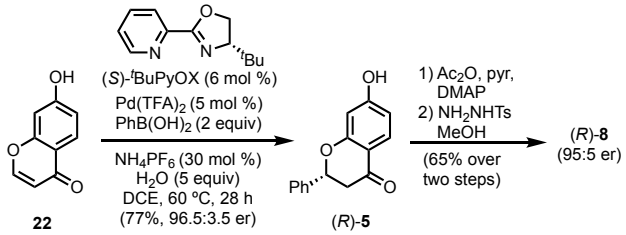
Having implemented the phenolic oxidation, we turned toward allyl deprotection and completion of the synthesis. To this end, exposure of the mixture of **20a** and **20b** to catalytic $Pd(PPh_3)_4$ and 3.4 equivalents of 1,3-dimethylbarbituric acid resulted in rapid consumption of both with the former producing (**±**)-**1** in 56% yield, likely through the intermediacy of **A** (Scheme 3). Monitoring of this reaction by UPLC/MS revealed the presence of a minor isomeric product, presumably derived from **20b**. To further explore this latter event, a sample of pure **20b** was prepared and subjected to the deallylation conditions. Interestingly, this reaction was found to produce the regiomeric tricycle **21** as the only isolable product (34% yield) and not *epi*-**1** as initially expected (Scheme 7).

Scheme 7. Synthesis of 20b and surprising formation of tricycle 21.



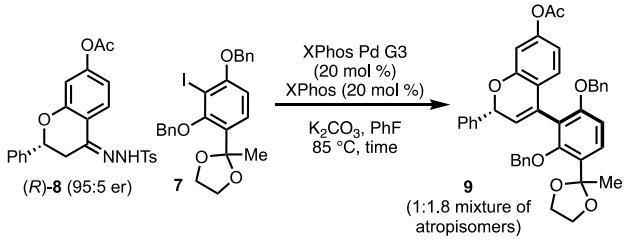
Enantioselective Total Synthesis of (–)-3 and Formal Total Synthesis of (–)-1. Having completed syntheses of **1** and **3** in racemic form, we began exploring means to render the synthesis enantioselective. To this end we opted to pursue the unnatural enantiomer of caesalpinnone A, (–)-**1**, and thus began exploring methods for accessing *N*-tosylhydrazone **8** enantioselectively. To this end, we turned to a palladium-catalyzed conjugate addition method developed by Stoltz and co-workers,[28] which had been used to generate (*R*)-**5** in one step from 7-chromenone (**22**, Scheme 8). Subsequent conversion of (*R*)-**5** to (*R*)-**8** would then set the stage for Barluenga coupling. As illustrated in Scheme 8, this method was found to work exactly as reported and allowed for preparation of (*R*)-**5** in 77% yield and in 96.5:3.5 er, which was further manipulated to (*R*)-**8** in 95:5 er (Scheme 8) in the same manner as the racemic material.[29]

Scheme 8. Enantioselective conjugate addition of 22 and elaboration to (*R*)-8



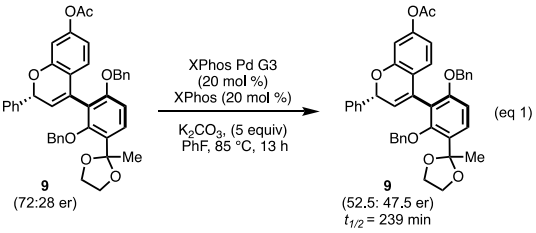
With (*R*)-**8** in hand, the stage was set for the synthesis of enantioenriched benzopyran **9**. Employing the optimized conditions for the synthesis of racemic **9** (Table 3, entry 1) afforded optically enriched **9** in 91% yield, but with significant erosion of enantiopurity (72:28 er). To probe the cause of this unexpected racemization, we subjected **9** (72:28 er) to the reaction conditions (equation 1) and observed nearly complete racemization after 13 hours ($t_{1/2}$ = 238 min).

Table 3. Optimization trials of (*R*)-8 and 7 to produce enantioenriched 9.



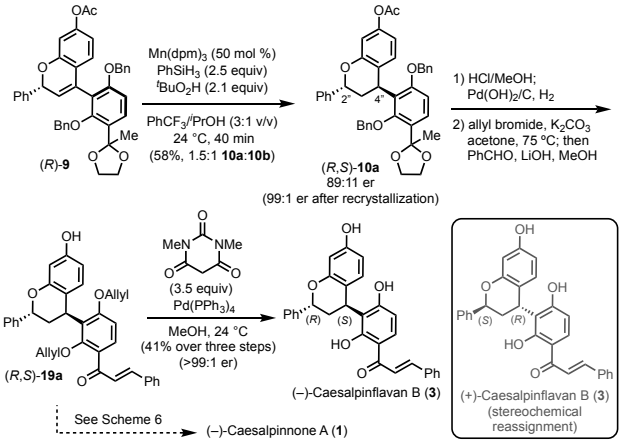
entry	Equiv 8 (addition time)	Equiv 7	Equiv K_2CO_3	time (h)	yield[a]	er
1[b,c]	2.5 (10 h)	1.0	5.0	15	91	72:28
2[c]	1.0	2.5	6.0	0.5	35	91:9
3[d]	1.0	4.0	6.0	1	58	91.5:8.5
4[d]	1.0	4.0	6.0	1.5	59	89.5:10.5

[a]Isolated yield. [b]1:2.2 v/v PhF–1,4-dioxane. [c]Reaction concentration: 55 mM. [d]110 mM.



Given this outcome, we set out to further optimize the Barluenga coupling between (*R*)-**8** and **7** to limit racemization of **9**. To this end, we reasoned that slow addition of (*R*)-**8** to the reaction mixture was detrimental as it required long reaction times. Indeed, a Barluenga coupling employing (*R*)-**8** and 2.5 equivalents **7** afforded **9** in a modest 35% yield after 30 minutes, albeit with minimal loss of stereochemistry (Table 3, entry 2). We envisaged that the racemization of **9** may be occurring through reversible Pd-π-allyl formation/intramolecular phenoxide addition of **9** and decided to change reaction conditions to increase the rate of our desired, intermolecular coupling process.[30] To accomplish this, we found that increasing the concentration of the reaction, as well as increasing the equivalents of **7**, led to higher conversion without significant racemization, affording **9** in 58% yield and 91.5:8.5 er after 60 minutes (Table 3, entry 3). We subsequently found that heating this reaction mixture for longer time periods (Table 3, entry 4) failed to significantly increase the chemical yield and only led to lower enantiomeric ratios of **9**.

Having optimized the Barluenga coupling for the enantioenriched substrate we next turned our attention to the HAT hydrogenation of enantioenriched **9**. While seemingly innocuous, the reduction of the C–C double bond in **9** required a HAT reaction in the presence of an exceedingly weak benzylic, allylic ether C–H bond. In practice, applying our previous optimized HAT reduction procedure (Table 2, entry 13) to enantioenriched **9** led to isolation of **10a** with significant erosion of enantiopurity (84.5:15.5 er). To circumvent this, we found that increasing the loading of $Mn(dpm)_3$ to 50 mol % and lowering the equivalents of TBHP allowed for isolation of **10a** with only small amounts of epimerization (89:11 er, Scheme 9). Gratifyingly, the enantiopurity of **10a** could easily be upgraded to 99:1 er with a single recrystallization from hexanes/^{i}PrOH.



Scheme 9. Conversion of (*R*)-9 to (–)-3 and formal enantioselective synthesis of (–)-1.

Establishing the viability of (+)-3 as the biosynthetic precursor to (+)-1: Stereochemical Revision of (+)-3. The absolute stereochemistry of natural (+)-**1** was unambiguously assigned during its initial isolation by high quality single crystal X-ray diffraction. In contrast, the absolute stereochemistry of natural (+)-**3** was assigned only by analysis of its CD spectrum.[1] Based on analyses of these data, Wang and co-workers assigned the carbon atoms at C2" and C4" in natural (+)-**1** and (+)-**3** as being opposite in absolute configuration. Given potential biosynthetic considerations, this was puzzling and, if indeed correct, anticipates that (C2"*R*, C4"*S*)-**10a** (Scheme 9) would produce the natural enantiomer of caesalpinflavan B (i.e., (+)-**3**). However, as illustrated in Scheme 9, elaboration of (C2"*R*, C4"*S*)-**10a** was found to furnish (–)-**3**, wherein the optical rotation is opposite in sign to natural (+)-**3**. Based on this analysis, natural (+)-**3** was determined to possess the same absolute configuration at C2" and C4" as naturally occurring (+)-**1**, thus arguing strongly for their biosynthetic relationship. In addition to the synthesis of unnatural (–)-**3**, the enantioselective synthesis of (*R*,*S*)-**19a** constitutes a formal total synthesis of unnatural (–)-**1**.

Conclusions

In conclusion, we have developed the first total syntheses of caesalpinflavan B (**3**) and caesalpinnone A (**1**), in 6 and 7 steps, respectively. In addition to providing expedient access to these bioactive natural products and several structural analogs, our synthetic efforts have further expanded the scope of the venerable Barluenga coupling reaction by highlighting its utility for sterically-demanding couplings and, to our

knowledge, providing the first example of its use in the context of a natural product total synthesis.[31] Additionally, these efforts have further demonstrated the utility of Shenvi's HAT hydrogenation protocol, which in the current context, provided stereo-divergent access to two distinct molecular scaffolds. We have likewise described the enantioselective total synthesis of (–)-**3**, the stereochemical reassignment of naturally-derived **3**, and a formal enantioselective total synthesis of (–)-**1**, which were all enabled by the use of enantioselective palladium-catalyzed conjugate addition to provide (*R*)-**5**. We anticipate the synthetic strategy described in this article will serve as inspiration for the stereoselective synthesis other structurally-related flavan-chalcone hybrids, along with related flavanoid natural products.

Future efforts will be directed towards biological investigation of **1**, with particular regard to applications as a selective cytotoxic agent and mode-of-action studies. Furthermore, owing to both the brevity and potential modularity of this synthetic sequence, analogs of **1** and **21**, along with synthetic intermediates, will likewise be investigated and the results of these investigations reported in due course.

ASSOCIATED CONTENT

The Supporting Information is available free of charge on the ACS Publications website.

Experimental procedures, analytical data for new compounds (^{1}H and ^{13}C NMR, HRMS, IR), optimization tables, and HPLC traces for enantioenriched materials (PDF)

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8. See Supporting Information for the synthesis of **7** and **8**.

9. Mass spectroscopic analysis of the Barluenga coupling between **7** and **8** suggested significant formation of diazine-derived side-products. However, we were unable to isolate and unambiguously characterize these side-products.

10. For examples of catalytic hydrogenation of 2-substituted-(2H)-chromes giving predominantly *cis*-2,4-substituted dihydrobenzopyrans, see: Pawar, G. G.; Tiwari, V. K.; Jena, H. S.; Kapur, M. Hetereoatom-Guided, Palladium-Catalyzed, Site-Selective C–H Arylation of 4*H*-Chromenes: Diastereoselective Assembly of the Core Structure of Myristinin B through Dual C–H Functionalization. *Chem. Eur. J*. **2015**, *21*, 9905. b) Rueping, M.; Uria, U.; Lin, M-.Y.; Atodiresei, I. Chiral Organic Contact Ion Pairs in Metal-Free Catalytic Asymmetric Allylic Substitutions. *J. Am. Chem. Soc*. **2011**, *133*, 3732.

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12. For alternative approaches to *trans*-2",4"-diaryl flavanoids, see: a) Maloney, D. J.; Deng, J-.; Z.; Stark, S. R.; Gao, Z.; Hecht, S. M. (+)-Myristinin A, a Naturally Occurring DNA Polymerase Inhibitor and Potent DNA-Damaging Agent. *J. Am. Chem. Soc*. **2005**, *127*, 4140. b) Li, K.; Vanka, K.; Thompson, W. H.; Tunge, J. A. Stereochemical Control in the Reduction of 2-Chromanols. *Org. Lett*. **2006**, *8*, 4711.

13. The atropisomers of **14** were separable by preparative HPLC. Analysis of the isolated compounds indicated that both possessed the same C2", C3" stereochemistry. The axial chirality was not assigned and thus illustrations here reflect an arbitrary atropisomeric choice. See Supporting Information for more details.

14. We also attempted to deoxygenate ketone **13** directly using classical Wolff-Kishner conditions, which only led to decomposition.

15. Hecht and co-workers also saw small amounts of epimerization of the 2" stereocenter during a deoxygenation step in their synthesis of myristinin A. For more information, see reference 12a.

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17. We found it imperative that **9** be completely consumed in the HAT hydrogenation due to our inability to efficiently separate **9** and **10a**/**b** on silica gel chromatography.

18. We define a chemical step as the conversion of one material to another in a single reaction flask, without isolation or removal from the flask, and regardless of the number of reagent additions or manipulations. This step count convention is based on the definition given by Baran, see: Kawamura, S.; Chu, H.; Felding, J. Baran P. S. Nineteen-step total synthesis of (+)-phorbol. *Nature*, **2016**, *532*, 90.

19. The benzyl groups were replaced with allyl groups at this point for two reasons: 1) We found that installation of the chalcone moiety needed to be performed with the D-ring phenols protected and 2) hydrogenolysis of the benzyl ethers in the presence of the chalcone moiety would likely prove troublesome.

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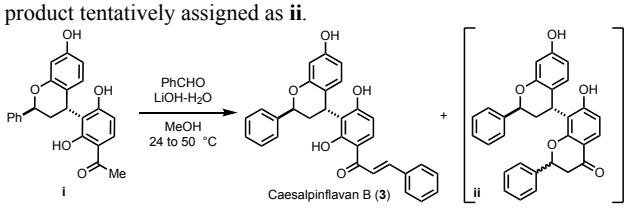
21. Initially, we attempted the Claisen-Schmidt on an unprotected substrate (i.e., **i**). However, we were unable to isolate appreciable amounts of **3**. Instead, this reaction delivered an inseparable mixture containing **3** accompanied by at least one other cyclized flavanone product tentatively assigned as **ii**.



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23. Treatment of **3** with hypervalent iodine reagents in the presence of water led to complex mixtures of oxidized products as evidenced by UPLC/MS analysis.

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26. Monitoring this conversion by ESI-MS putatively identified formation of a *o*-quinone containing compound, which was formed in similar yield to **20a**/**20b**. Additionally, **20a** underwent partial oxidation during purification by silica gel chromatography, contributing further to the modest yield. See supporting information for more details.

27. It is not currently understood how **20b** is formed in the PIDA-mediated dearomative oxidation of **19a** but, as suggested by one reviewer, a possible manifold is benzylic deprotonation/re-protonation, which is driven by the thermodynamic stability of the *cis*-configuration in **20b**.

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29. The slight enantioerosion from (*R*)-**5** to (*R*)-**8** occurred during the *N*-tosylhydrazone forming step.

30. Heating a solution of enantioenriched **9** in PhF and K_2CO_3 at 85 ºC for 18 hours led to no detectible racemization. As such, alternative reaction pathways, such as retro 6-π photoracemization of 2H-chromenes, were discounted; for a seminal reference in this area, see: Wipf, P.; Weiner, W. S. Enantioselective Synthesis and Photoracemization Studies of (+)-2-Cyclopropyl-7,8-dimethoxy-2H-chromene-5-carboxylic Acid Methyl Ester, an Advanced Intermediate of a Dihydrofolate Reductase Inhibitor *J. Org. Chem*. **1999**, *64*, 5321.

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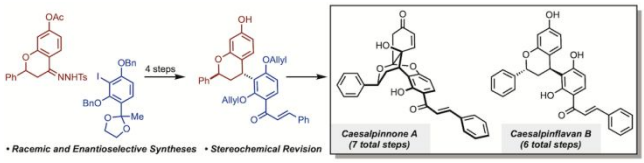

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