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Synthesis of Chamaecypanone C Analogues from *in Situ*-Generated Cyclopentadienones and Their Biological Evaluation

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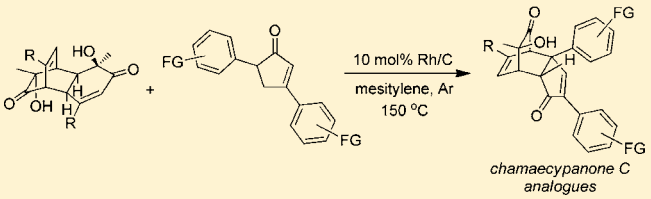
Supporting Information

ABSTRACT: A rhodium-catalyzed dehydrogenation protocol for the conversion of 3,5-diarylcyclopentenones to the corresponding 2,4-diarylcyclopentadienones has been developed. With this protocol, analogues of the cytotoxic agent chamaecypanone C have been synthesized *via* Diels–Alder cycloaddition between the cyclopentadienones and *in situ*-generated *o*-quinols. Biological evaluation of these analogues revealed a compound with higher activity as a microtubule inhibitor and cytotoxic agent in comparison with the parent structure.



INTRODUCTION

Cyclopentadienones are highly reactive and unstable species and in many cases are known to dimerize readily to release antiaromaticity.[1] As useful synthons, cyclopentadienone and derivatives have been utilized in both electrocyclic reactions[2] and pericyclic additions.[3] In these cases, "deantiaromatization" has been proposed to be a significant driving force. Moreover, cyclopentadienones have been used as key reagents to access biologically active natural products, including manzamenone A (**1**)[4] and chamaecypanone C (**2**)[5,6] (Figure 1).

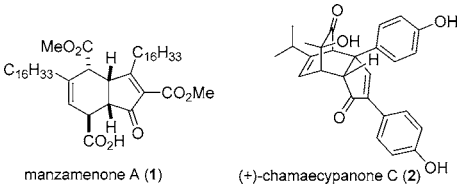
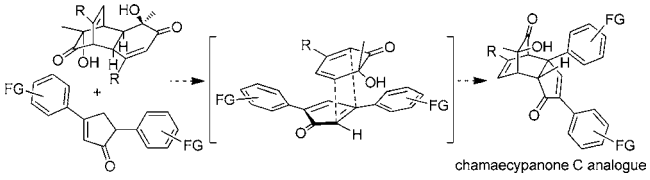


Figure 1. Cyclopentadienone-derived natural products.

We previously reported the synthesis of the bicyclo[2.2.2]-octenone-containing natural product (+)-chamaecypanone C (**2**) utilizing as the key step a retro-Diels–Alder/Diels–Alder cascade of a 6-alkyl-6-hydroxycyclohexa-2,4-dienone (*o*-quinol) dimer wherein an *in situ*-generated 2,4-diarylcyclopentadienone reacted with the *o*-quinol in a highly diastereoselective manner.[5a] The observed reactivity of the diarylcyclopentadienone reaction partner prompted further study of the key transformation. Furthermore, on the basis of the demonstrated tubulin inhibitory activity of chamaecypanone C,[5a,7] a general approach to analogues with modified structures was desirable for further biological studies, in particular for the evaluation of structure–activity relationships (SARs). With these considerations in mind, we focused on the synthesis of cycloadducts derived from 2,4-cyclopentadienones with variable aromatic substitution (Scheme 1).

Scheme 1. Approach to Chamaecypanone C Analogues



Herein we report our studies leading to the development of a general protocol for the preparation of 2,4-diarylcyclopentadienones *en route* to chamaecypanone C analogues as well as the biological evaluation of the target compounds as microtubule inhibitors.

RESULTS AND DISCUSSION

Syntheses of cyclopentadienones have been achieved using various protocols, including elimination of bromocyclopentenones[8] and hydroxycyclopentenones,[4a,9] condensations of propanones with α-diketones,[10] photochemical decarbonylation[11] and SO_2 extrusion,[12] and carbonylation of metallacyclopentadienes.[13] A recent elegant methodology developed by the Wender group involves rhodium(I)-catalyzed [3 + 2] cycloaddition of cyclopropenones and alkynes.[14] In most cases, tri- or tetrasubstituted cyclopentadienones are produced; mono- or disubstituted cyclopentadienones are less commonly reported, likely because of their instability or tendency to dimerize.[8c] In particular, to

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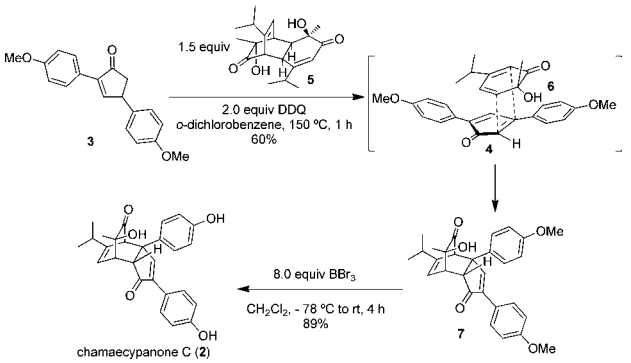
date there are very few reported examples of 2,4-disubstituted cyclopentadienones[15] and no reports of 2,4-diarylcyclopentadienones or derived dimers in the literature.

As a 2,4-diarylcyclopentadienone is a key precursor to chamaecypanone C, the preparation of analogues with similar substitution patterns requires a protocol to access the corresponding cyclopentadienones. In view of the abundance of the corresponding cyclopentenone precursors, it should be possible to dehydrogenate these compounds to obtain the target molecules. In our previous studies, 2,4-diarylcyclopentenone **3** was used as a substrate under 2,3-dichloro-5,6-dicyanobenzoquinone (DDQ)-mediated oxidation conditions (Scheme 2), which generated 2,4-diarylcyclopentadienone

Scheme 2. First-Generation Synthesis of Chamaecypanone C



4 *in situ*. In the same pot, the thermolytic retro-Diels–Alder reaction of dimer **5** afforded *o*-quinol **6**, which subsequently reacted with intermediate **4** to afford chamaecypanone C methyl ether (**7**) in a highly diastereoselective manner. Upon treatment with excess boron tribromide, cycloadduct **7** was demethylated to afford (+)-chamaecypanone C (**2**). This synthetic sequence also represents use of a dehydrogenative Diels–Alder cycloaddition in natural product synthesis.[16]

In our previous studies we were able to prepare di-*p*-methoxyphenyl-substituted cyclopentenone **3** from cyclopentene (**8**) using a sequence involving double Heck cross-coupling,[17] allylic hydroxylation, and 2-iodoxybenzoic acid (IBX) oxidation[5a] (Scheme 3a).[5a] However, we recognized that this route may not be optimal for the preparation of diarylcyclopentadienone precursors because of the potential limitation of aryl substitution and formation of isomerized alkene by-products in the double Heck reaction as well as the use of substoichiometric amounts of toxic selenium dioxide in the allylic oxidation step. Recently Xu, McLaughlin, and co-workers established a general and scalable method for the preparation of 3,5-diarylcyclopentenones with a broad scope (Scheme 3b).[18] We proposed that these cyclopentenones may react similarly to the corresponding 2,4-diaryl compounds in the dehydrogenative Diels–Alder event. Accordingly, our goal was to identify suitable reaction conditions to produce cyclopentadienones from the readily accessible 3,5-diarylcyclopentenones.

Investigation of Aerobic Dehydrogenation. Although dehydrogenation of ketones using IBX[19] or DDQ[20] is well-known, we first focused our attention on the evaluation of catalytic oxidative conditions to avoid the stoichiometric use of oxidants.[21] With 3,5-diphenylcyclopentenone (**9**)[18] as a model substrate, representative conditions for catalytic aerobic dehydrogenation, including $Pd(TFA)_2$/bipyridine/O_2[22] and TiO_2-supported gold nanoparticles (AuNP/TiO_2),[23] were investigated (Table 1, entries 1 and 2). Interestingly, instead of the desired

Scheme 3. Synthetic Routes to Diarylcyclopentenones

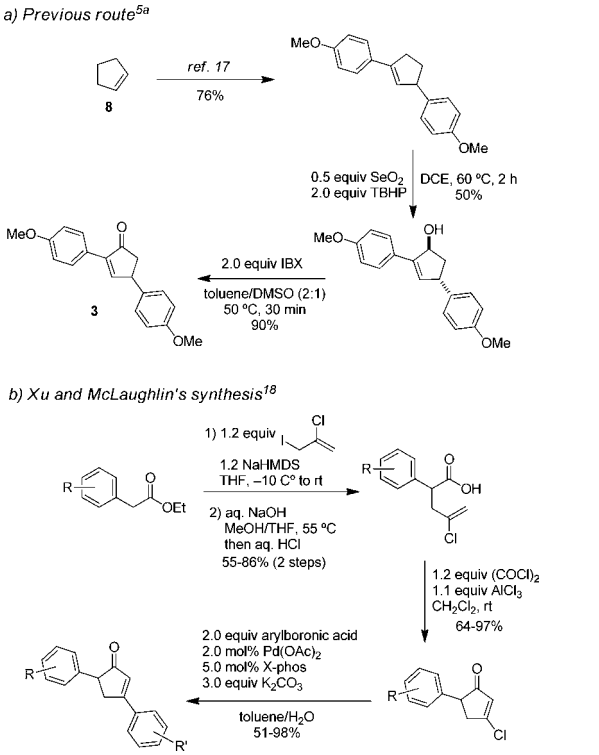
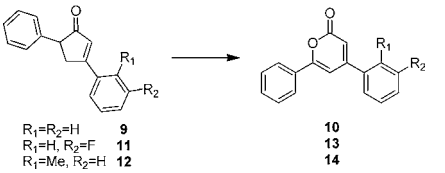


Table 1. Generation of α-Pyrones from Diarylcyclopentenones under Aerobic Dehydrogenation Conditions[a]



entry	cyclopentenone	catalyst[b]	time (h)	yield (%)[c]
1	**9**	$Pd(TFA)_2$/bipyridine	12	36
2	**9**	AuNP/TiO_2	12	80
3	**11**	AuNP/TiO_2	12	46
4	**12**	AuNP/TiO_2	12	50[d]

[a]Reaction conditions: 5 mol % catalyst, O_2, chlorobenzene, 100 °C. [b]$Pd(TFA)_2$ = palladium(II) trifluoroacetate; AuNP = gold nanoparticle. [c]Isolated yields after silica gel column chromatography. [d]The product was inseparable from the starting material, and the yield was based on ^{1}H NMR integration.

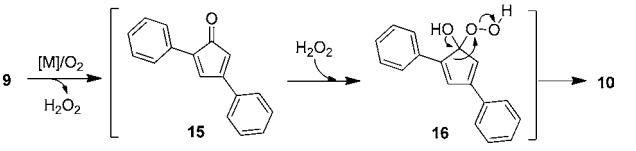
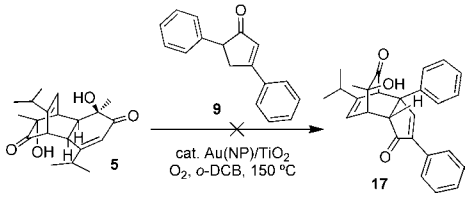


Figure 2. Possible mechanism leading to α-pyrones.

Scheme 4. *In Situ* Trapping Experiment



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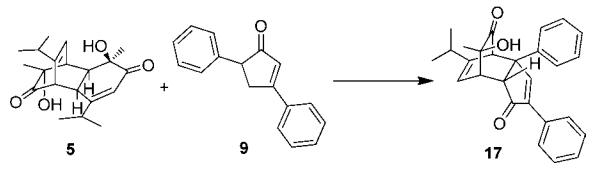
cyclopentadienone, 4,6-diphenyl-α-pyrone (**10**) was identified as the major product, and no diarylcyclopentadienone or derived products were produced under the reaction conditions. The ^{1}H and ^{13}C NMR spectra for **10** were identical to literature data,[24] and the structure was further confirmed by X-ray crystallography.[25]

Table 2. Reaction Optimization for the Dehydrogenation of Diarylcyclopentenones[a]



5 9 17

entry	catalyst or oxidant	time (h)	% conversion[b] to cycloadduct **17**
1	Pd/C	6	28
2	Pt/C	6	<5
3	Rh/Al_2O_3	6	<5
4	Rh/C	16	56
5[c]	Rh/C	18	>95 (81)[d]
6[e]	DDQ	2	33

[a]Reaction conditions: 3.0 equiv of **9** (1.5 equiv with respect to generated *o*-quinol monomer), 10 mol % catalyst (based on **9**), mesitylene, 150 °C, argon atmosphere. [b]Based on ^{1}H NMR integration of dimer **5** and product **17**. [c]5.0 equiv of **9** (2.5 equiv with respect to *o*-quinol monomer) was used in the reaction. [d]Isolated yield is given in parentheses. [e]5.0 equiv of **9**, 6.0 equiv of DDQ, *o*-DCB, 150 °C, argon atmosphere.

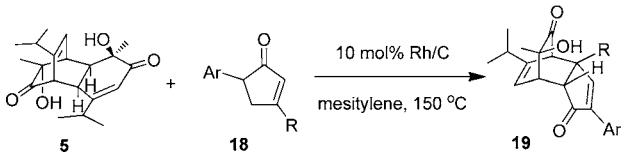
Two other cyclopentenones, **11** (entry 3) and **12** (entry 4), were also evaluated under the AuNP-catalyzed oxidation conditions and gave the corresponding 4,6-diaryl-α-pyrones **13** and **14** as the major products.

A plausible mechanism accounting for the generation of α-pyrone **10** is depicted in Figure 2. Under Pd- or AuNP-catalyzed conditions, aerobic dehydrogenation of **9** should afford cyclopentadienone **15** accompanied by the generation of hydrogen peroxide.[21,26] Because of the instability of **15**, the compound may subsequently react with H_2O_2 to afford intermediates such as hydroperoxide **16**, thereby releasing antiaromaticity.[1] Baeyer–Villiger-type rearrangement of **16** should then generate **10**.[27] A literature-reported example of aerobic oxidation of tetraphenylcyclopentadienone (tetracyclone) to an α-pyrone under thermolytic conditions[28] also supports the likely intermediacy of cyclopentadienone **15**.[29] Moreover, treatment of cyclopentenone **9** with 2.0 equiv of H_2O_2 (dioxane, 80 °C, 16 h) led to no reaction, indicating that cyclopentadienone formation may be required prior to Baeyer–Villiger reaction.[30]

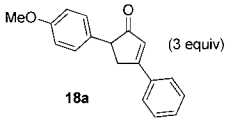
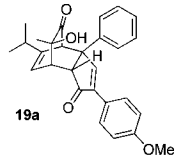
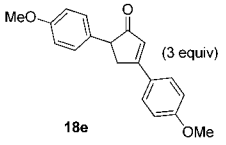
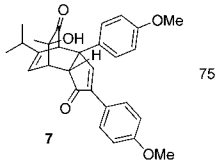
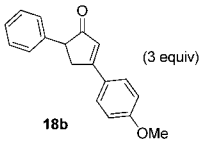
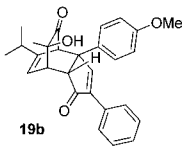
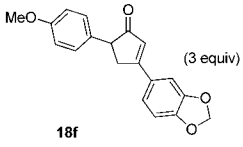
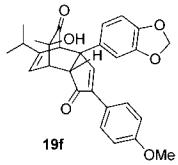
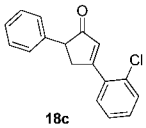
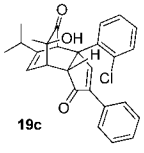
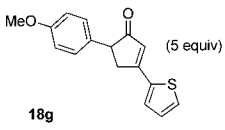
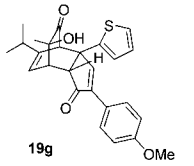
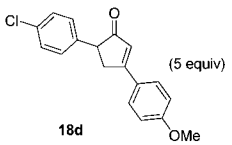
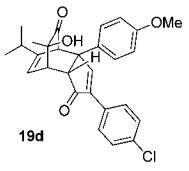
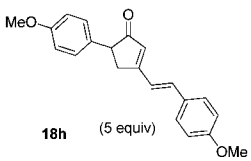
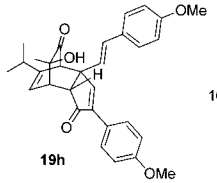
With the hope of intercepting the generated intermediate **15**, we also investigated a one-pot procedure in which a mixture of cyclopentenone **9** and the readily available dimer (±)-**5**[31] was heated in the presence of a AuNP/TiO_2 catalyst under an oxygen atmosphere. Unfortunately, the reaction afforded a complicated mixture, and no generation of the desired cycloadduct **17** was observed (Scheme 4).

Evaluation of Anaerobic Dehydrogenation Conditions. In view of the reactivity of 2,4-diarylcyclopentadienones to form byproducts, including α-pyrones under aerobic conditions,

Table 3. Diels–Alder Cycloadditions of *in Situ*-Generated *o*-Quinols and 2,4-Diarylcyclopentadienones[a]



5 18 19

entry	precursor (equiv)	time (h)	cycloadduct	yield[b] (%)	entry	precursor (equiv)	time (h)	cycloadduct	yield[b] (%)
1	 (3 equiv) **18a**	18	 **19a**	80	5	 (3 equiv) **18e**	12	 **7**	75
2	 (3 equiv) **18b**	18	 **19b**	59	6	 (3 equiv) **18f**	16	 **19f**	72
3	 (5 equiv) **18c**	18	 **19c**	22	7	 (5 equiv) **18g**	18	 **19g**	60
4	 (5 equiv) **18d**	18	 **19d**	66	8	 (5 equiv) **18h**	18	 **19h**	16[c]

[a]Reaction conditions: 10 mol % Rh/C (based on cyclopentenone), mesitylene, 150 °C, argon atmosphere. [b]Isolated yields after silica gel chromatography. [c]Full conversion based on cyclopentenone was observed.

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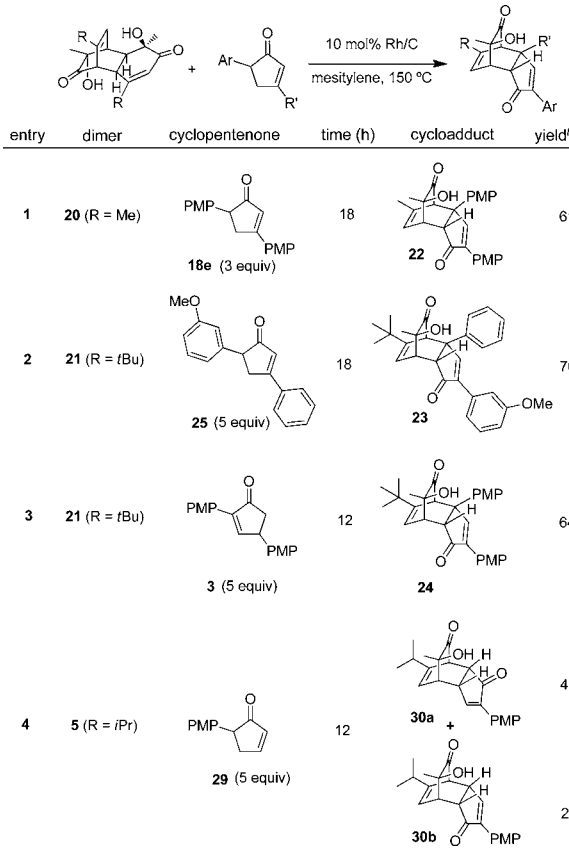
anaerobic dehydrogenation conditions were next investigated. Inspired by a reported dehydrogenation of arylcyclohexenones using palladium on carbon (Pd/C),[32] we evaluated several metal catalysts, including Pd(0), Pt(0), and Rh(0), for dehydrogenation of cyclopentenone **9** under an argon atmosphere at high temperatures. While in these cases no cyclopentadienone was observed or isolated, we discovered that in the presence of *o*-quinol dimer **5**, Pd/C successfully catalyzed the dehydrogenation of **9** to afford the corresponding dienone intermediate; this was reacted with an *in situ*-generated *o*-quinol leading to the formation of the desired cycloadduct **17** (Table 2, entry 1). Although **9** was completely consumed after the thermolysis in mesitylene for 6 h, a large amount of unreacted dimer **5** suggested the presence of other degradation pathways for **9**. When Pt/C or Rh/Al_2O_3 was used as the catalyst, a complex mixture of products was obtained, including the phenol 3-hydroxy-α,4-dimethylstyrene[33,34] (entry 2), or severe decomposition of the starting materials (entry 3) was observed. After extensive experimentation, reactions with Rh/C as the catalyst were found to afford the desired [4 + 2] cycloadduct **17** cleanly (entry 4). As the conversion of *o*-quinol dimer **5** was incomplete while all of the cyclopentenone was consumed, we decided to increase the amount of easily accessed reaction partner **9**. Accordingly, using 5.0 equiv of **9** (2.5 equiv with respect to *o*-quinol monomer) and extending the reaction time led to improved conversion (entry 5), affording product **17** in good yield (81%). The requirement of excess cyclopentenone may be due to the instability of the generated cyclopentadienone under the reaction conditions.

To evaluate further the efficiency of the Rh-catalyzed dehydrogenation relative to our previously developed protocol,[5a] DDQ (6.0 equiv) was slowly added to a mixture of dimer **5** and compound **9** (5.0 equiv) in *o*-dichlorobenzene (*o*-DCB) at 150 °C over a period of 1 h. Further reaction at the same temperature for an additional 1 h resulted in the generation of cycloadduct **17** with approximately 33% conversion (Table 2, entry 6) along with a significant amount of unreacted starting material. Attempts to improve the conversion by extending the reaction time led to severe decomposition. These results suggested that DDQ-mediated oxidation is less effective than the Rh-catalyzed protocol for substrate **9**.

Under the optimized conditions, 2,4-diarylcyclopentenone substrates **18a–h** were evaluated (Table 3). Substrates with electron-rich aryl substituents reacted smoothly to afford cycloadducts in moderate to good yields (entries 1, 2, and 4–6). In the case of 2-chlorophenyl-substituted compound **18c**, low conversion was observed because of its poor solubility, leading to a low isolated yield of the desired product **19c** (entry 3). Reaction with a substrate bearing a heterocyclic substituent also produced the [4 + 2] cycloadduct in moderate yield (entry 7). Styrenylcyclopentenone **18h** also underwent dehydrogenation under the Rh/C-catalyzed conditions (entry 8). However, only a small amount of product **19h** was isolated, presumably because of the multiple reaction sites for the generated cyclopentadienone intermediate. In all cases, reactions to form [4 + 2] adducts proceeded with high diastereoselectivity in accordance with previous observations in our synthesis of chamaecypanone C.[5a] Endo selectivity and facial selectivity align well with the observed reactivity of *o*-quinols,[35] wherein the bulky aromatic substituents are oriented away from the sterically demanding quaternary center.

To evaluate the scope and limitations of the methodology, selected *o*-quinol dimers[31,36] and masked *o*-benzoquinone (MOB) dimers[37] were explored as 2,4-cyclohexadienone precursors. A number of cyclopentenone and indanone substrates were also investigated as substrates for Rh/C-catalyzed dehydrogenation. Dimers (±)-**20** (Table 4, entry 1) and (±)-**21** (entries 2 and 3)

Table 4. Dehydrogenative Cycloadditions Using Alternative Dimers and Cyclopentenones[a]



[a]Reaction conditions: 10 mol % Rh/C (based on cyclopentenone), mesitylene, 150 °C. PMP = *p*-methoxyphenyl. [b]Isolated yields after silica gel chromatography.

were found to have similar reactivities in comparison to dimer **5**, and cycloadducts **22–24** were prepared in good yields from 3,5-diarylcyclopentenones **18e** and **25** and 2,4-diarylcyclopentenone **3**, respectively. In contrast, *o*-quinol dimers (±)-**26** (Figure 3) and **27** and MOB dimer **28** did not afford any of the corresponding desired cycloadducts. In the failed cases, dienone–phenol rearrangement of the 2,4-cyclohexadienone intermediate was typically observed.[38] The reaction using 5-arylcyclopentenone **29** and dimer **5** under the rhodium-catalyzed conditions (entry 4) generated a mixture of two [4 + 2] adducts, **30a** and **30b**, in good combined yield. The two products were separated and characterized as isomers derived from reactivity of the unsubstituted *cis*-alkene. This result correlates well with the previously observed higher reactivity of disubstituted *cis*-alkenes in cycloaddition reactions with *o*-quinols.[35] The lack of 4-aryl substitution on the cyclopentadienone appeared to diminish the steric differentiation resulting from the aryl group and the tertiary alcohol, thereby leading to the formation of isomeric cycloadducts.

When 3-arylcyclopentenone **31**[39] (Figure 3) was used as the cyclopentadienone precursor, no conversion of either starting material was observed, which suggests that 5-aryl substitution is required for successful dehydrogenation. This assumption was further confirmed by the fact that cyclopentenone **32** was also

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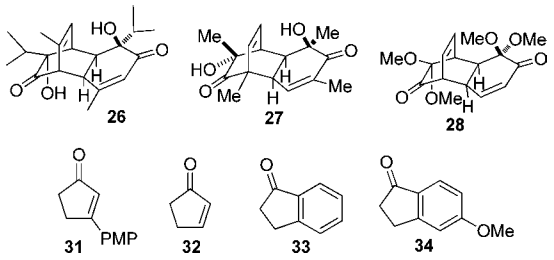

Figure 3. Methodology limitations.

inert under the rhodium-catalyzed dehydrogenation conditions. Additional attempted experiments using indanones **33** and **34** did not yield any of the desired cycloadducts, and no indenone formation was observed.

To prepare chamaecypanone C analogues with unprotected hydroxyl groups, previously prepared cycloadducts with methyl ethers were submitted to BBr_3-mediated demethylation conditions, and the corresponding hydroxyl products were isolated in moderate to good yields (Figure 4).

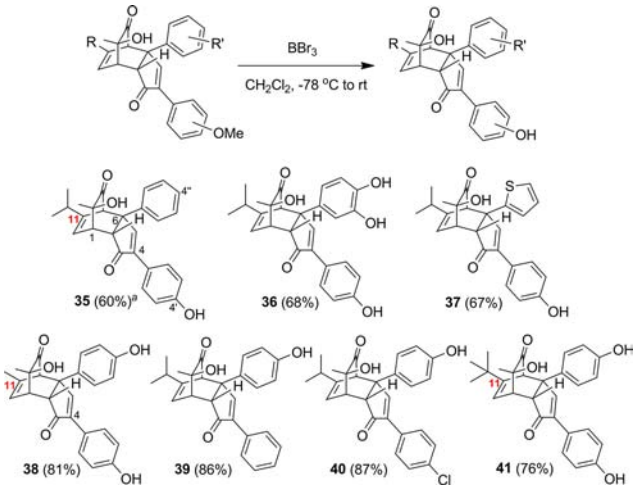

Figure 4. Preparation of chamaecypanone C analogues with unprotected phenols. Values in parentheses are isolated yields.

Biological Studies. We utilized the developed synthetic route to explore the structure–activity space of (+)-chamaecypanone C as a microtubule inhibitor and cytotoxic agent.[5a,7] Racemic chamaecypanone C analogues were first evaluated in a tubulin assembly assay. Diphenyl analogue **17**, chlorinated analogue **19c**, and all of the methyl-protected analogues were found to be inactive,[25] while structures **35**–**38** (Figure 4) showed good activity. Compounds **39** and **40** were also found to be inactive. Taking note of the previous finding that the (+)-enantiomer of chamaecypanone C is active while the (−)-enantiomer is not, we synthesized the enantiopure versions of active compounds (+)-**35** to (+)-**38** and tested them in both the tubulin assay and in the NCI-60 cell screen along with (+)-chamaecypanone C (**2**). As summarized in Table 5, these compounds were found to have activities comparable to that of the parent, with chemeacypanone C analogue (+)-**38** (entry 4) showing slightly greater activity as an inhibitor of tubulin assembly and as a cytotoxic agent in the NCI-60 screen (mean GI_{50} = 180 nM) relative to the natural product (+)-**2** (entry 5).

These results suggested that the 4-*p*-hydroxyphenyl group (Figure 4) is crucial for interactions with tubulin and showed

Table 5. Tubulin Assembly and Growth Inhibitory Activities of Enantiopure Chamaecypanone Analogues

entry	compound	inhibition of tubulin assembly IC_{50} ± SD (μM)	% inhibition of colchicine binding ± SD with 5 μM inhibitor	NCI-60 mean GI_{50} (μM)
1	(+)-**35**	2.8 ± 0.4	30 ± 0.8	0.55
2	(+)-**36**	3.2 ± 0.4	27 ± 0.8	0.56
3	(+)-**37**	2.4 ± 0.3	32 ± 0.5	0.91
4	(+)-**38**	1.5 ± 0.01	50 ± 2.0	0.18
5	(+)-**2**	2.2 ± 0.3	30 ± 4.0	0.28 (n = 2)

that reducing the isopropyl appendage [*cf.* (+)-**2**] to a methyl group [(+)-**38**] slightly improves the potency of both growth and tubulin assembly inhibition while a *t*-Bu group at C-11 (compound **41**) completely eliminates the activity.[25] While these differences are modest, it is clear that minor modifications of the parent structure are tolerated while larger changes are not. The 4′ phenolic group appears to be required as a hydrogen-bond donor, as the 4′-desoxy analogue **39** and the dimethoxy analogue **19e** were found to be inactive.[25] The 4″-OH group was found to be less critical, as both the thiophene analogue (+)-**37** (Table 5, entry 3) and the 4″-desoxy analogue (+)-**35** (entry 1) were active.

CONCLUSION

We have developed a rhodium-catalyzed anaerobic dehydrogenation protocol to convert 3,5-diarylcyclopentenones to the corresponding 2,4-diarylcyclopentadienones. A series of *in situ*-generated, highly reactive cyclopentadienones were successfully utilized to prepare a series of chamaecypanone C analogues via [4 + 2] cycloaddition with in situ-generated *o*-quinols. Our investigation also led to the discovery of a gold-nanoparticle-catalyzed transformation of 3,5-diarylcyclopentenones to diaryl-α-pyrones. Initial biological studies of chamaecypanone C analogues uncovered a chamaecypanone C derivative, (+)-**38**, with higher activity as a microtubule inhibitor and cytotoxic agent in comparison with the parent structure. Further biological studies of chamaecypanone C derivatives, as well as the chemistry of the chamaecypanone C core structure, are ongoing and will be reported in due course.

ASSOCIATED CONTENT

Supporting Information

Experimental procedures and characterization data for all new compounds, including X-ray structure analysis of compound **10**, X-ray crystallographic data (CIF), and detailed biological methods and results. This material is available free of charge via the Internet at http://pubs.acs.org.

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Notes

The authors declare no competing financial interest.

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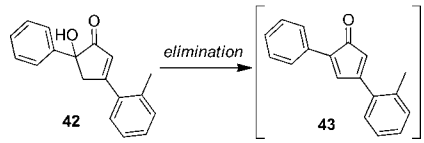

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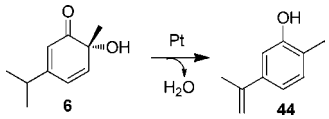

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