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Synthesis of Chamaecypanone C Analogues from *in situ*-Generated Cyclopentadienones and their Biological Evaluation

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Abstract

A rhodium-catalyzed dehydrogenation protocol has been developed for conversion of 3,5-diarylcyclopentenones to the corresponding 2,4-diarylcyclopentadienones. Using this protocol, analogues of the cytotoxic agent chamaecypanone C have been synthesized *via* Diels-Alder cycloaddition between the cyclopentadienones and *in situ*-generated *ortho*-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 readily dimerize to release antiaromaticity.¹ As useful synthons, cyclopentadienone and derivatives have been utilized in both electrocyclic reactions² 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**, Figure 1)⁴ and chamaecypanone C (**2**).^{5,6}

We have previously reported the synthesis of the bicyclo[2.2.2]octenone-containing natural product (+)-chamaecypanone C (**2**) utilizing a retro-Diels-Alder/Diels-Alder cascade of a 6-alkyl-6-hydroxycyclohexa-2,4-dienone (*ortho*-quinol) dimer as the key step wherein an *in situ*-generated 2,4-diarylcyclopentadienone was reacted with an *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 evaluation of structure-activity relationships (SAR). With these considerations in mind, we focused on the synthesis of cycloadducts derived from 2,4-cyclopentadienones with

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Supporting Information Available 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 (PDF). This material is available free of charge *via* the Internet at <http://pubs.acs.org>.

variable aromatic substitution (Scheme 1). Herein, we report our studies on development of a general protocol for 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 bromocyclopentenones⁸ and hydroxycyclopentenones,^{4a, 9} condensations of propanones with α -diketones,¹⁰ photochemical decarbonylation¹¹ and SO₂ extrusion,¹² and carbonylation of metallacyclopentadienes.¹³ A recent elegant methodology developed by the Wender group involved rhodium(I)-catalyzed [3+2] cycloaddition of cyclopropanones and alkynes.¹⁴ In most cases, trisubstituted or tetrasubstituted cyclopentadienones are produced. Mono- or disubstituted cyclopentadienones are less commonly reported, likely due to their instability or tendency towards dimerization.^{8c} In particular, there are very few examples of 2,4-disubstituted cyclopentadienones reported in the literature,¹⁵ and no reports of 2,4-diarylcyclopentadienones or derived dimers to date.

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. Considering the abundance of the corresponding cyclopentenone precursors, it should be possible to dehydrogenate these compounds to the target molecules. In our previous studies, 2,4-diarylcyclopentenone **3** was used as a substrate (Scheme 2) under DDQ-mediated oxidation conditions which generated 2,4-diarylcyclopentadienone **4** *in situ*. In the same pot, thermolytic retro-Diels-Alder reaction of dimer **5** afforded *ortho*-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 usage of a dehydrogenative Diels-Alder cycloaddition in natural product synthesis.¹⁶

While we were able to prepare di-*para*-methoxyphenyl substituted cyclopentenone **3** from cyclopentene (**8**) using a double-Heck cross-coupling (Scheme 3a),¹⁷ allylic hydroxylation, and IBX oxidation sequence,^{5a} we recognized that this route may not be optimal to prepare diarylcyclopentadienone precursors due to the potential limitation of aryl substitution and formation of isomerized alkene byproducts in the double Heck reactions, as well as usage of substoichiometric amounts of toxic selenium dioxide in the allylic oxidation step.

Recently Xu, McLaughlin, and coworkers established a general and scalable method for preparation of 3,5-diarylcyclopentenones with a broad scope (Scheme 3, b).¹⁸ We proposed that these cyclopentenones may react similarly as the 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 the installation of α,β -unsaturation to a ketone substrate using IBX¹⁹ or DDQ²⁰ is well known, we first focused our attention on the evaluation of catalytic, oxidative conditions to avoid stoichiometric use of oxidants.²¹ Utilizing 3,5-diphenylcyclopentenone (**9**, Table 1)¹⁸ as a model substrate, representative conditions for catalytic, aerobic dehydrogenation including Pd(TFA)₂/bipyridine/O₂²² and Au(NP)/TiO₂,²³ were investigated (Table 1, entries 1–2). Interestingly, instead of the desired cyclopentadienone, 4,6-diphenyl- α -pyrone **10** was identified as the major product with no

diarylcyclopentadienone or derived product produced under the reaction conditions. ^1H and ^{13}C -NMR spectra of α -pyrone **10** were identical to literature data²⁴ and the structure was further confirmed by X-ray crystallography.²⁵ Two other cyclopentenones **11** (entry 3) and **12** (entry 4) were further evaluated under the gold nanoparticle-catalyzed oxidation conditions in which case the corresponding 4,6-diaryl- α -pyrones **13** and **14** were observed as major products.

A plausible mechanism accounting for the generation of α -pyrone **10** is depicted in Figure 2. Under palladium or gold nanoparticle-catalyzed conditions, aerobic dehydrogenation of cyclopentenone **9** should afford cyclopentadienone **15** which is accompanied by the generation of hydrogen peroxide.^{21,26} Due to the instability of diarylcyclopentadienone **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 α -pyrone **10**.²⁷ A literature reported example of aerobic oxidation of tetraphenylcyclopentadienone (tetracyclone) under thermolytic conditions to an α -pyrone²⁸ 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 which indicates that cyclopentadienone formation may be required prior to Baeyer-Villiger reaction.³⁰

With the hope of intercepting the generated intermediate **15**, a one-pot procedure was also investigated by heating a mixture of cyclopentenone **9** and the readily available dimer ($\pm$)-**5**³¹ in the presence of a Au(NP)/TiO₂ 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

Taking into account the reactivity of 2,4-diarylcyclopentadienone to form byproducts, including α -pyrones under aerobic conditions, anaerobic dehydrogenation conditions were next investigated. Inspired by a reported dehydrogenation of arylcyclohexenones using palladium on carbon,³² several metal catalysts, including palladium(0), platinum(0), and rhodium(0), were evaluated for dehydrogenation of cyclopentenone **9** under an argon atmosphere at high temperatures. While in these cases no cyclopentadienones were observed or isolated, we discovered that in the presence of *o*-quinol dimer **5**, Pd/C successfully catalyzed dehydrogenation of cyclopentenone substrates to afford the corresponding dienone intermediates which were reacted with an *in situ* generated *o*-quinol leading to the formation of the desired cycloadduct **17** (Table 2, entry 1). Although cyclopentenone **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/Al₂O₃ were used as catalysts, production of a complex mixture of products including the phenol 3-hydroxy- α ,4-dimethyl styrene^{33,34} (entry 2) or severe decomposition of starting materials (entry 3) was observed. After extensive experimentation, reactions with Rh/C as catalyst were found to cleanly afford the desired [4+2] cycloadduct **17** (entry 4). As the conversion of *o*-quinol dimer **5** was incomplete, whilst all cyclopentenone was consumed, we decided to increase the amount of easily accessed reaction partner **9**. Accordingly, use of 5.0 equiv cyclopentenone **9** (2.5 equiv in respective to 1.0 equiv *o*-quinol monomer) and extending the reaction time led to improved conversion (entry 5) to afford product **17** in good yield (81%). The requirement for excess cyclopentenone may be due to the instability of generated cyclopentadienone under the reaction conditions.

To further evaluate the efficiency of the Rh-catalyzed dehydrogenation in comparison to our previously developed protocol,^{5a} to a mixture of dimer **5** and compound **9** (5.0 equiv) in *o*-

dichlorobenzene was slowly added DDQ (6.0 equiv) at 150 °C over a period of one hour. Further reaction at the same temperature for an additional hour resulted in the generation of cycloadduct **17** in approximately 33% conversion (Table 2, entry 6) along with a significant amount of unreacted starting materials. Attempts to improve the conversion by extending the reaction time led to severe decomposition. These results suggested that DDQ-mediated oxidation was less effective in comparison to the Rh-catalyzed protocol for substrate **9**.

Utilizing the optimized conditions, a number of 2,4-diarylcyclopentadienone substrates were evaluated (Table 3). Substrates with electron rich aryl substituents reacted smoothly to afford cycloadducts in moderate to good yields (entries 1,2,4–6). In the case of 2-chlorophenyl-substituted compound **18c**, a low conversion was observed due to 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 Rh/C-catalyzed conditions. However, only a small amount of product **19h** was isolated (entry 8), presumably due to the multiple reaction sites for the generated cyclopentadienone intermediate. In all cases, reactions to form [4+2] adducts proceeded in high diastereoselectivity which was in accordance with previous observations in our synthesis of chamaecyanone 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, select *o*-quinol dimers^{32, 36} and masked-*o*-benzoquinone (MOB) dimers³⁷ 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 ($\pm$)-**20** (Table 4, entry 1) and ($\pm$)-**21** (entries 2–3) 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**, **25**, and 2,4-diarylcyclopentenone **3**, respectively. In contrast, *o*-quinol dimers ($\pm$)-**26** (Figure 3) and **27** and MOB dimer **28** did not afford any 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** (Table 4, entry 4) and dimer **5** under the rhodium-catalyzed conditions 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 cyclopentadienone appears to have diminished the steric differentiation resulted 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 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 inert to the rhodium-catalyzed dehydrogenation conditions. Further attempted experiments using indanones **33** and **34** did not yield any desired cycloadducts and no indenone formation was observed.

To prepare chamaecyanone C analogues with unprotected hydroxyl groups, previously prepared cycloadducts with methyl ethers were submitted to BBr₃-mediated demethylation conditions and the corresponding hydroxyl products were isolated in moderate to good yields (Figure 4).

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. The diphenyl analogue **17**, chlorinated analogues **19c**, and all methyl protected analogues were found to be inactive,²⁵ while structures **35** to **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 (–)-enantiomer is not, we therefore 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 showed comparable activity to that of the parent with the chamaecypanone C analogue (+)-**38** (entry 4) which was found to have a slightly greater activity as an inhibitor of tubulin assembly and as a cytotoxic agent in the NCI-60 (mean GI₅₀=180 nM) relative to the natural product (+)-**2** (entry 5).

These results suggested that the 4-*para*-hydroxyphenyl group (Figure 4) is crucial for interactions with tubulin and showed that reducing the isopropyl appendage (*cf.* (+)-**2**) to a methyl group ((+)-**38**) slightly improved potency in both growth and tubulin assembly inhibition, while a *tert*-Bu group at C-11 (compound **41**) completely eliminated 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 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 *ortho*-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.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

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References

1. Ogliaruso MA, Romanelli MG, Becker EI. *Chem Rev.* 1965; 65:261.
2. Harmata M, Zheng P, Schreiner PR, Navarro-Vázquez A. *Angew Chem, Int Ed.* 2006; 45:1966.
3. Harmata M, Gomes MG. *Eur J Org Chem.* 2006:2273.
4. Al-Busafi S, Doncaster JR, Drew MGB, Regan AC, Whitehead RC. *J Chem Soc, Perkin Trans 1.* 2002:476. Isolation, see: Tsukamoto S, Takeuchi S, Ishibashi M, Kobayashi J. *J Org Chem.* 1992; 57:5255.
5. Dong S, Hamel E, Bai R, Covell DG, Beutler JA, Porco JA Jr. *Angew Chem, Int Ed.* 2009; 48:1494. For isolation of chamaecyanone C, see: Chien SC, Chang JY, Kuo CC, Hsieh CC, Yang NS, Kuo YH. *Tetrahedron Lett.* 2007; 48:1567.
6. For other representative examples of utilizing cyclopentadienones as building blocks in natural product synthesis, see: Baraldi PG, Barco A, Benetti S, Pollini GP, Polo E, Simoni D. *J Chem Soc, Chem Commun.* 1984:1049. Schuda PF, Phillips JL, Morgan TM. *J Org Chem.* 1986; 51:2742. Takano S, Sato T, Inomata K, Ogasawara K. *J Chem Soc, Chem Commun.* 1991:462.
7. Hsieh C, Kuo Y, Kuo C, Chen L, Cheung CA, Chao T, Lin C, Pan W, Chien S, Chen T, Lung C, Chang J. *Biochem Pharmacol.* 2010; 79:1261. [PubMed: 20034474]
8. DePuy CH, Lyons CF. *Chem Ind.* 1961:429. DePuy CH, Isaks M, Eilers KL, Morris GF. *J Org Chem.* 1964; 29:3503. For a recent report, see: Harmata M, Barnes CL, Brackley J, Bohnert G, Kirchhoefer P, Kürti L, Rashatasakhon P. *J Org Chem.* 2001; 66:5232. [PubMed: 11463277]
9. Fuchs B, Pasternak M, Pazhenchevsky B. *J Org Chem.* 1981; 46:2017.
10. (a) Allen CFH, VanAllan JA. *J Am Chem Soc.* 1950; 72:5165. (b) Van Ornum SG, Li J, Kubiak GG, Cook JM. *J Chem Soc, Perkin Trans 1.* 1997:3471. (c) Walsh CJ, Mandal BK. *J Org Chem.* 1999; 64:6102. (d) Moore JE, York M, Harrity JPA. *Synlett.* 2005:860.
11. DeSelms RC, Schleigh WR. *Synthesis.* 1973:614.
12. Ried W, Bopp DCH. *Angew Chem, Int Ed.* 1977; 16:653.
13. For a review of reactions of metallacyclobutadienes with leading references, see: Müller E. *Synthesis.* 1974:761–774.
14. Wender PA, Paxton TJ, Williams TJ. *J Am Chem Soc.* 2006; 128:14814. [PubMed: 17105285]
15. Bandyopadhyay C, Sur KR, Patra R. *J Chem Res-S.* 2002:414–415.
16. For a recent report of dehydrogenative Diels-Alder cycloadditions, see: Stang EM, White MC. *J Am Chem Soc.* 2011; 133:14892. [PubMed: 21842902]
17. Prashad M, Tomesch JC, Wareing JR, Smith HC, Cheon SH. *Tetrahedron Lett.* 1989; 30:2877.
18. Xu Y, McLaughling M, Chen C, Reamer RA, Dormer PG, Davies IW. *J Org Chem.* 2009; 74:5100. [PubMed: 19485346]
19. Nicolaou KC, Zhong Y, Baran PS. *J Am Chem Soc.* 2000; 122:7596.
20. (a) Walker D, Hiebert JD. *Chem Rev.* 1967; 67:153. [PubMed: 4859921] (b) Buckle, DR. *Encyclopedia of Reagents for Organic Synthesis.* 3. Paquette, LA., editor. John Wiley & Sons; Chichester, UK: 1995. p. 1699
21. For recent examples of Pd-catalyzed α,β -dehydrogenation of carbonyl compounds, see: Diao T, Stahl SS. *J Am Chem Soc.* 2011; 133:14566. [PubMed: 21851123] Diao T, Wadzinski TJ, Stahl SS. *Chem Sci.* 2012; 3:887. [PubMed: 22690316]
22. Tokunaga M, Harada S, Iwasawa T, Obora Y, Tsuji Y. *Tetrahedron Lett.* 2007; 48:6860.
23. Sun H, Su F, Ni J, Cao Y, He H, Fan K. *Angew Chem, Int Ed.* 2009; 48:4390.
24. Li GQ, Dai LX, You SL. *Org Lett.* 2009; 11:1623. [PubMed: 19271747]
25. See Supporting Information for detailed experimental data.
26. For gold nanoparticle-catalyzed aerobic oxidation involving hydrogen peroxide formation, see: Miyamura H, Shiramizu M, Matsubara R, Kobayashi S. *Chem Lett.* 2008; 37:360.
27. For a recent example of heterogeneous catalytic Baeyer-Villiger oxidation of ketones, see: Jeong EY, Ansari MB, Park SE. *ACS Catal.* 2011; 1:855.

28. Thiemann T, Iniesta J, Walton DJ. *J Chem Res.* 2008;173. For Baeyer Villiger-type rearrangement of tetracyclone to an α -pyrone with bis(trimethylsilyl) monoperoxysulfate, see: Adam W, Rodriguez WA. *J Org Chem.* 1979; 44:4969.
29. For Au(NP)-catalyzed oxidation of cyclopentenone **12**, hydroxycyclopentenone **42** was isolated as an intermediate. Dehydration of this compound should lead to cyclopentadienone **43** (*cf.* refs 5 and 9a).

30. For a recent report of Sn (IV)-mediated Baeyer-Villiger reactions using H₂O₂ as oxidant at elevated temperature, see: Corma A, Iborra S, Mifsud M, Renz M, Susarte M. *Adv Synth Catal.* 2004; 346:257.
31. Dong S, Zhu J, Porco JA Jr. *J Am Chem Soc.* 2008; 130:2738. [PubMed: 18266375]
32. Horning EC, Horning MG. *J Am Chem Soc.* 1947; 69:1359.
33. Patwardhan SA, Gupta AS. *Phytochemistry.* 1983; 22:2080.
34. Phenol byproduct **44** was presumably derived from *o*-quinol intermediate **6** through an elimination process:

35. Dong S, Cahill KJ, Kang MI, Colburn NH, Henrich CJ, Wilson JA, Beutler JA, Johnson RP, Porco JA Jr. *J Org Chem.* 2011; 76:8944. [PubMed: 21942286]
36. Gagnepain J, Castet F, Quideau S. *Angew Chem, Int Ed.* 2007; 46:1533.
37. Liao CC, Peddinti RK. *Acc Chem Res.* 2002; 35:856. and references therein. [PubMed: 12379138]
38. For a recent review on the dienone-phenol rearrangement, see: Whiting DA, Trost BM, Fleming I. *Comp Org Synth.* Pergamon Press Oxford 1991; 3:803–821.
39. Li JH, Wang DP, Xie YX. *Synthesis.* 2005:2193.

Figure 1.
Cyclopentadienone-derived natural products.

Figure 2.
Possible mechanism leading to α -pyrones.

Figure 3.
Methodology limitations

Figure 4.

Preparation of chamaecyparone C analogues with unprotected phenols. ^a Isolated yield in parenthesis.

Scheme 1.
Approach to chamaecypanone C analogues

Scheme 2.
First generation synthesis of chamaecypanone C

a) Previous route^{5a} b) Xu and McLaughlin's synthesis¹⁸

Scheme 3.
Synthetic routes to diarylcyclopentenones

Scheme 4.
In situ trapping experiment

Table 1Generation of α -pyrones from diarylcyclopentenones under aerobic dehydrogenation conditions.^a

entry	cyclopentenone	Catalyst	time (h)	yield ^b (%)
1	9	Pd(TFA) ₂ /bipyridine	12	36
2	9	Au(NP)/TiO ₂	12	80
3	11	Au(NP)/TiO ₂	12	46
4	12	Au(NP)/TiO ₂	12	50 ^c

^a Reaction conditions: 5 mol% catalyst, O₂, chlorobenzene, 100 °C;^b isolated yield after silica gel column chromatography;^c product inseparable from starting material, yield based on ¹H-NMR integration.Pd(TFA)₂ = palladium(II) trifluoroacetate; Au(NP) = gold nanoparticles.

Table 2Reaction optimization for dehydrogenation of diarylcyclopentenones^a

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

^a Reaction conditions: 3.0 equiv cyclopentadienone **9** (1.5 equiv in respect to 1.0 equiv of *o*-quinol monomer generated), 10 mol% catalyst (based on cyclopentenone), mesitylene, 150 °C, argon atmosphere;

^b Conversion based on ¹H-NMR integration of dimer **5** and product **17**.

^c 5.0 equiv of **9** (2.5 equiv with respect to 1.0 equiv of *o*-quinol monomer) used in the reaction.

^d Isolated yield in parenthesis.

^e 5.0 equiv of **9**, 6.0 equiv of DDQ, *o*-dichlorobenzene, 150 °C, argon atmosphere.

Table 3Diels-Alder cycloadditions of *in situ* generated *o*-quinols and 2,4-diarylcyclopentadienones

entry	precursor(equiv)	time(h)	cycloadduct	yield ^a (%)
1	 18a	18	 19a	80
2	 18b	18	 19b	59
3	 18c	18	 19c	22
4	 18d	18	 19d	66
5	 18e	12	 7	75

entry	precursor(equiv)	time(h)	cycloadduct	yield ^a (%)
6	<p>18f</p>	16	<p>19f</p>	72
7	<p>18g</p>	18	<p>19g</p>	60
8	<p>18h</p>	18	<p>19h</p>	16 ^b

Reaction conditions: 10 mol% Rh/C (based on cyclopentenones), mesitylene, 150 °C, argon atmosphere.

^a Isolated yield after silica gel chromatography.

^b Full conversion observed based on cyclopentenone.

Table 4

Dehydrogenative cycloadditions using alternative dimers and cyclopentenones

entry	dimer	cyclopentenone	time (h)	yield ^a (%)
1	20 (R = Me)	18e (3 equiv)	18	61
2	21 (R = <i>n</i> Bu)	25 (5 equiv)	18	70
3	21 (R = <i>n</i> Bu)	3 (5 equiv)	12	64

entry	dimer	cyclopentenone	time (h)	cycloadduct	yield ^a (%)
4	5 (R = <i>i</i> Pr)	12 29 (5 equiv)		30a 30b	45 29

Reaction conditions: 10 mol% Rh/C (based on cyclopentenones), mesitylene, 150 °C.

^a Isolated yield after silica gel chromatography.

PMP = *para*-Methoxyphenyl.

Table 5

Tubulin and Growth Inhibitory Activity of Enantiopure Chamaecypanone Analogues

Entry	Compound	Inhibition of Tubulin Assembly IC ₅₀ ±SD (μM)	% Inhibition of Colchicine Binding ± SD 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)