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Catalytic Hydroxycyclopropanol Ring-Opening Carbonylative Lactonization to Fused Bicyclic Lactones

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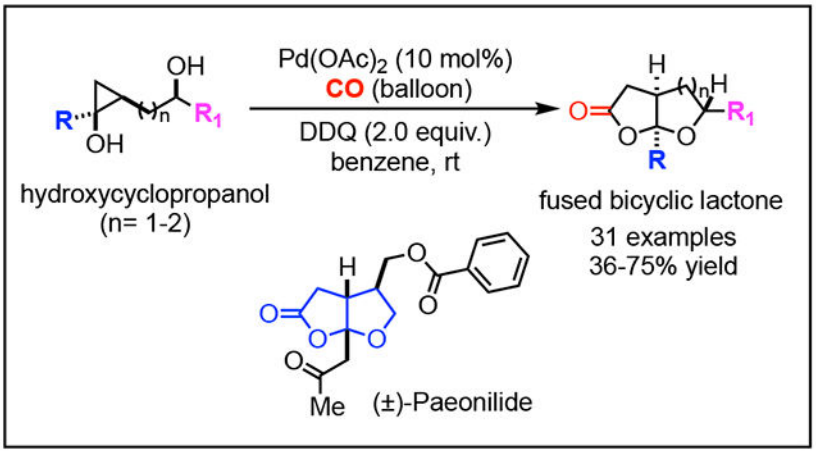
Abstract

A novel palladium-catalyzed ring opening carbonylative lactonization of readily available hydroxycyclopropanols was developed to efficiently synthesize tetrahydrofuran (THF) or tetrahydropyran (THP)-fused bicyclic γ-lactones, two privileged scaffolds often found in natural products. The reaction features mild reaction conditions, good functional group tolerability, and scalability. Its application was demonstrated in a short total synthesis of (±)-paeonilide. The fused bicyclic γ-lactone products can be easily diversified to other medicinally important scaffolds, which further broadens the application of this new carbonylation method.

Graphical Abstract



Nature has been constantly creating natural products with novel, diverse, and complex structures. Many of these natural products or their derivatives have been used as medicines to treat human diseases or are lead compounds for drug discovery.[1] While various biosynthetic pathways and different organisms are involved in natural product production,

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Supporting Information
The Supporting Information is available free of charge on the ACS Publications website.
Experimental procedures and spectra data (PDF file)
Cystallographic data for **16a** and **32** (cif file)

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privileged structural scaffolds shared by a large number of natural products can often be identified.[1c] *Cis*-2,8-dioxabicyclo[3.3.0]octan-3-one (a THF-fused bicyclic γ-lactone, also called cis-tetrahydro[2,3-*b*]furan-2(3*H*)-one) is one such privileged structural scaffold, which has been found in over 100 natural products from various origins (Figure 1).[2] In these molecules, the THF-fused γ-lactone forges diverse connections with the rest of the molecular structures. Part of them such as ginkgolide B (**1a**),[3] gracilin B (**1b**),[4] paracaseolide A (**1c**),[5] and darwinolide (**1d**),[6] have the bicyclic γ-lactone moiety embedded in a large polycyclic ring system. Another portion of them including norrisolide (**1e**)[7] and cheloviolene A (**1f**)[8] have the bicyclic γ-lactone connected with a second (poly)cyclic ring system via a C-C single bond. Why and how nature produces such fused bicyclic skeletons are yet to be understood. Natural products with such a bicyclic γ-lactone motif have demonstrated a wide range of biological activity and possess great potential in novel therapeutic development. For example, the ginkgolides can act as anti-platelet-activating factors; gracilins exhibit immunosuppressive and neuroprotective properties; paracaseolide A inhibits phosphatase CDC25B, an emerging and important target for anticancer drug discovery; the marine spongian diterpenoid norrisolide and its analogs demonstrated unique Golgi-modifying activity; darwinolide is a biofilm-penetrating anti-MRSA agent. Additionally, the related *cis*-2,9-dioxabicyclo[4.3.0]nonan-8-one (a THP-fused bicyclic γ-lactone, also called *cis*-tetrahydro-4H-furo[2,3-*b*]pyran-2(3*H*)-one) has been found in natural products,[9] including applanatumol B (**1h**),[9a] which showed activity against renal fibrosis.

Due to their unique and challenging chemical structures as well as their diverse biological applications, natural products with a THF/THP-fused bicyclic γ-lactone moiety have been popular targets in total synthesis practices.[10] Notably, the Overman group recently accomplished elegant total syntheses of several marine spongian diterpenoids including cheloviolene A (**1f**, Figure 1) with a THF-fused γ-lactone.[11] So far, most of these total syntheses utilized the hydroxy-acid-aldehyde (or their masked forms) condensation reactions to construct the desired THF/THP-fused γ-lactone moiety in the target molecules (eq. A-1, Figure 2A). In these processes, tedious functional group manipulations, protections, and deprotections are often involved, which added extra steps to the entire synthesis. Surprisingly, synthetic methodology development in this area is extremely barren.[12] Notably, Trost and Toste developed a Pd-catalyzed asymmetric nucleophilic substitution of 5-aceloxy-2-(5*H*)-furanone followed by reductive intramolecular Heck reaction to build THF-fused γ-lactones,[12a] but this method is limited to benzo-fused tricyclic systems (eq. A-2). Theodorakis[12b] and Reiser[12c] independently reported elegant activated cyclopropane rearrangements to THF-fused γ-lactones (eq. A-3). In the Reiser's case, the activated cyclopropanes were generated via Rh-catalyzed enantioselective cyclopropanation of furans. In general, these prior arts are limited to 5,5-fused γ-lactones and hydrogen atom substitution at the ring junction carbons. Thus, versatile, modular, and catalytic methods are highly desirable.

We recently developed a Pd-catalyzed hydroxycyclopropanol ring opening carbonylative lactonization to synthesize oxaspirolactones, another privileged scaffold frequently appears in natural products (**2→5**, Figure 2B).[13] This new synthetic capability significantly facilitated our total syntheses of C12 oxygenated diterpenes and *Stemona* alkaloids.[14] With

this success, we wondered the possibility of developing a catalytic carbonylation chemistry to prepare THF/THP-fused γ-lactones with various substitution patterns (Figure 2C). To achieve this goal, cyclopropanols such as **6** would be required. They can be convergently assembled from readily available ester **7** and homoallylic alcohol **8** using the cyclopropanol synthesis[15] protocol developed by Cha and co-workers.[16] We envisioned a process involving Pd-catalyzed β-carbon elimination to generate Pd-homoenolate **9**. Ideally, we hoped for an acetal formation followed by carbonylative lactonization to convert **9** to desired fused bicyclic γ-lactone **11**, presumably via an intermediate like **10**. In principle, several processes could compete with the desired one. For instance, β-hydride elimination would decompose **9** to an enone; the tethered secondary alcohol could attack the Pd center and a following C-O reductive elimination would give THF product **12**. Additionally, carbonylative lactonization with the same tethered alcohol would give δ-lac-tone **14** (**9→13→14**). At the planning stage, we didn't know which pathway would dominate, but it would be ideal to develop conditions to access **11**, **12**, or **14** at wish. We were particularly attracted by the conversion of hydroxycyclopropanol **6** to fused lactone **11**. The established modular assembly of **6** would enable the introduction of various substitutions in product **11**, especially at the ring junction carbon where the R group resides. Meanwhile, we were hoping that the use of bishomoallylic alcohols may eventually result in THP-fused γ-lactones. Given the prevalence of THF/THP-fused γ-lactones in biologically active natural products, this chemistry is expected to find broad application in facilitating the chemical syntheses of those natural products and their analogs. Herein, we report such a Pd-catalyzed hydroxycyclopropanol ring opening carbonylative lactonization to the aforementioned bicyclic γ-lactones and its application in a short total synthesis of (±)-paeonilide (**1g**) and other medicinally important bicyclic and polycyclic scaffolds.

Our investigation started with known hydroxycyclopropanol **15a** (Table 1).[16] When it was subjected to the carbonylative spirolactonization conditions we developed before with $([Pd(neoc)(OAc)]_2(OTf)_2$ as catalyst and 1,4-benzoquinone (BQ) as oxidant,[13] the formation of **16a** was not observed (entry 1). Switching $[Pd(neoc)(OAc)]_2(OTf)_2$ to palladium(II) trifluoroacetate ($Pd(TFA)_2$) was not fruitful either (entry 2). The break-through came by using $Cu(OTf)_2$ to replace BQ as the oxidant, which resulted in the formation of **16a** in 6% yield (entry 3). The structure of **16a** was unambiguously confirmed by X-ray crystallographic analysis.[17] The use of 2,3-dichloro-5,6-dicyano-1,4-benzoquinone (DDQ) as oxidant increased the yield to 18% (entry 4). Further investigation of palladium catalysts led to the identification of $Pd(OAc)_2$ as an optimal choice (entry 5-6). Other 1,4-benzoquinone derivatives including 2,5-DMBQ and 2,6-DMBQ were not effective (entry 8, 9). THF (entry 7), toluene (entry 10), and benzene (entry 14) were suitable solvents with benzene giving slightly better yield (also see **16e** and **16n**, Table 2). Elevating reaction temperature (40 °C, entry 11) or increasing the amount of DDQ (entry 12) led to reduced reaction yield. Finally, reducing the reaction concentration from 0.03 M to 0.01 M was beneficial and product **16a** was obtained in 74% yield (entry 14). The reaction is also scalable. Scaling up the reaction from 0.2 mmol to 2.92 mmol led to the formation of **16a** in 65% yield. Moreover, when enantioenriched homoallylic alcohol (1-phenylbut-3-en-1-ol, 92% ee) was used, **16a** was obtained in 92% ee (73% yield) after a sequence of cyclopropanol formation and carbonylative lactonization. Given the ready availability of

enantioenriched homoallylic alcohols, our method offers an efficient asymmetric alternative to THF-fused γ-lactones.

We then evaluated the scope and generality of this new Pd-catalyzed hydroxycyclopropanol ring opening carbonylative lactonization. The reaction proved to be very robust. A variety of hydroxycyclopropanol substrates could be transformed into the corresponding *cis*-fused bicyclic γ-lactones. THF-fused γ-lactone products with either an aryl or an alkyl group at the C5-position could be obtained. Notably, tosylate (**16e**), TBS-ether group (**16k**, **16l**, **16s**), and heteroaromatics including indole (**16g**), furan (**16h**), thiophene (**16i**), and pyrrole (**16j**) are all tolerated under the mild reaction conditions. Substrates containing sterically hindered secondary (**16m**) and tertiary alcohols (**16n**, **16o**, **16p**, **16q**) were effective as well. *Most of the previously reported methods are limited to have hydrogen atom at C6 of the ring junction*. In our case, the substituent at this position can be altered from a methyl group to a hydrogen (**16w**) or other bulkier alkyl groups including cyclohexyl and isopropyl groups (**16r**, **16s**, **16t**, **16u**, **16v**, **16x**, and **16y**). Variation of the stereochemistry of the secondary alcohol on the side chain was tolerated as well (cf. **16x** vs **16y**). Similar reaction yields were obtained, but the reaction of **16y** took longer time. Furthermore, THP-fused γ-lactones could be produced in modest to good yield (**16za**, **16zb**, **16zc**, and **16zd**). Additionally, slow addition of DDQ to the reaction mixture could be beneficial to improve the reaction yield (cf. **16c** and **16d**), but was not employed to all the substrates due to the operational inconvenience.

We also evaluated hydroxycyclopropanol **17**, which could undergo ring opening carbonylation to form either fused γ-lactone **21** or spirolactone **22** presumably via intermediate **19** or **20**, respectively (Scheme 1). Both **19** and **20** could be derived from the same palladium-homoenolate **18**. When **17** was subjected to the optimized carbonylative conditions (entry 14, Table 1), fused γ-lactone **21** was obtained in 47% yield without any spirolactone **22** formation. Interestingly, even when the carbonylative spirolactonization conditions were used ($[Pd(neoc)(OAc)]_2(OTf)_2$ and BQ),[13] fused lactone was still the dominant product, but in lower yield.

We next decided to test this new carbonylative lactonization method in natural product total synthesis and chose paeonilide (**1g**) as our initial target. Paeonilide is a monoterpenoid isolated from *Paeonia delavayi* by Liu and co-workers.[18] It selectively inhibits platelet aggregation induced by platelet activating factor and has been previously synthesized by the groups of Zhang (chiral pool synthesis starting from (*R*)-(-)-carvone, 14 LLS steps;[19a] racemic, 17 LLS steps[19b]), Du (racemic, 6 LLS steps),[19c] Reiser (enantioselective, 12 LLS steps),[19d] and Argade (racemic, 11 LLS steps)[19e] from commercially available starting materials. Our synthesis started with known compounds **23**[20] and **24**,[21] which were prepared in one and three steps, respectively, from commercially available starting materials. They were united via a Kulinkovich reaction to give desired hydroxycyclopropanol **25**, albeit in low yield due to the existence of the ketal, free alcohol, and primary TBS ether. When **25** was subjected to the carbonylative lactonization conditions, bicyclic γ-lactone **26** was produced in 42% yield (99% yield brsm). Removal of the TBS and ketal protecting groups under acidic conditions followed by benzoate formation completed the total synthesis (±)-

paeonilide in 4 LLS steps in 3.6% yield from known compounds **23** and **24** or 7 LLS steps from commercially available starting materials.

Additionally, the fused bicyclic lactone product can be diversified to other medicinally important structural scaffolds (Scheme 3). α-Methylene γ-butyrolactone is another privileged scaffold frequently found in natural products[22] Treatment of **16a** with the Bredereck's reagent followed by DIBAL-H reduction[23] could convert **16a** to α-methylene γ-butyrolactone containing bicyclic product **28** in high yield. The lactone moiety of **16a** could also be converted to a lactam (cf. **30**) via the treatment of MeNH2 followed by acid-promoted cyclization. Aldol reaction of **16a** with benzaldehyde gave a 3:1 mixture of diastereomers in 82% yield. The relative stereochemistry of the major product **31** was established by X-ray crystallographic analysis of its *p*-bromobenzoate derivative **32**.[17] Hexahydrofuro[2,3-*b*]furan is an important scaffold in protease inhibitors, including the FDA-approved anti-HIV drug Darunavir (**34**).[24] Bicyclic lactone **16a** could be readily converted to hexahydrofuro[2,3-*b*]furan-containing product **33** via a sequential DIBAL-H and triethylsilane reduction process. Furthermore, **16a** could also be elaborated to tricyclic products **36** and **37** via a series of standard functional group manipulations.[25] These two tricyclic scaffolds have been found in natural products such as gracilin B (**1b**) and potent protease inhibitors including GRL-0519A.[26] These diversification pathways demonstrate the potential broad application of the newly developed carbonylative lactonization method.

In summary, we have developed a novel Pd-catalyzed hydroxycyclopropanol ring opening carbonylative lactonization to synthesize THF/THP-fused bicyclic γ-lactones. This method features mild reaction conditions, good functional group tolerability, and scalability. Its application was demonstrated in a short total synthesis of racemic paeonilide. The bicyclic lactone products could be further elaborated to other valuable structures.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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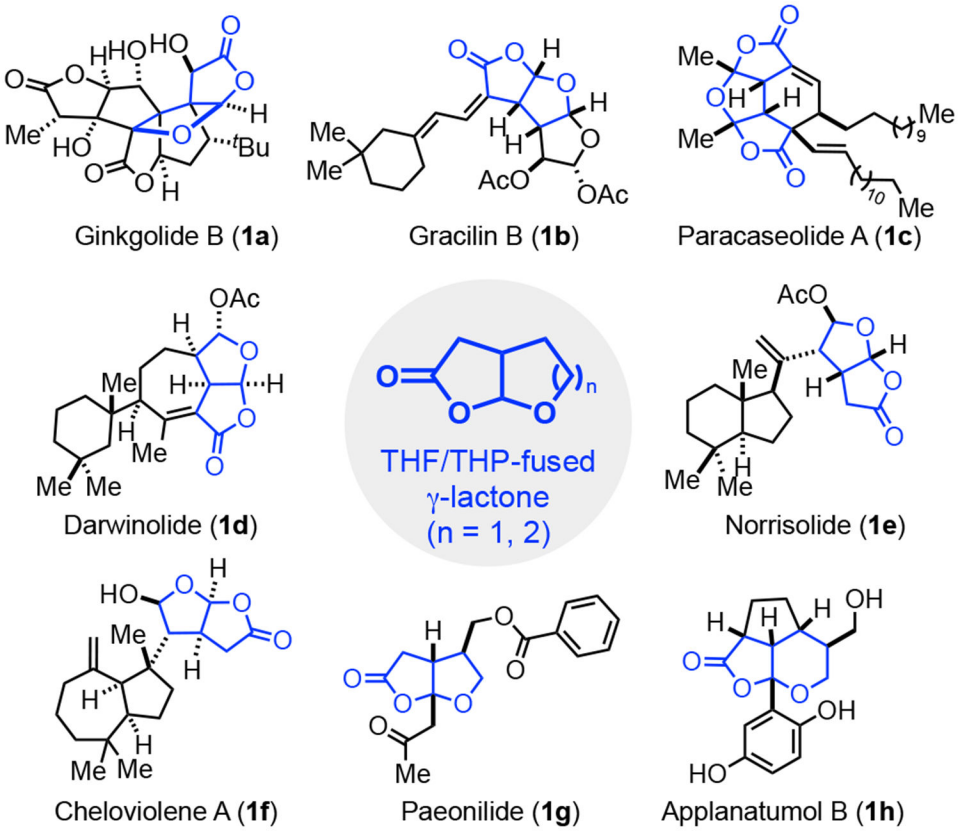


Figure 1.
Selected natural products with a THF/THP-fused bicyclic γ-lactone

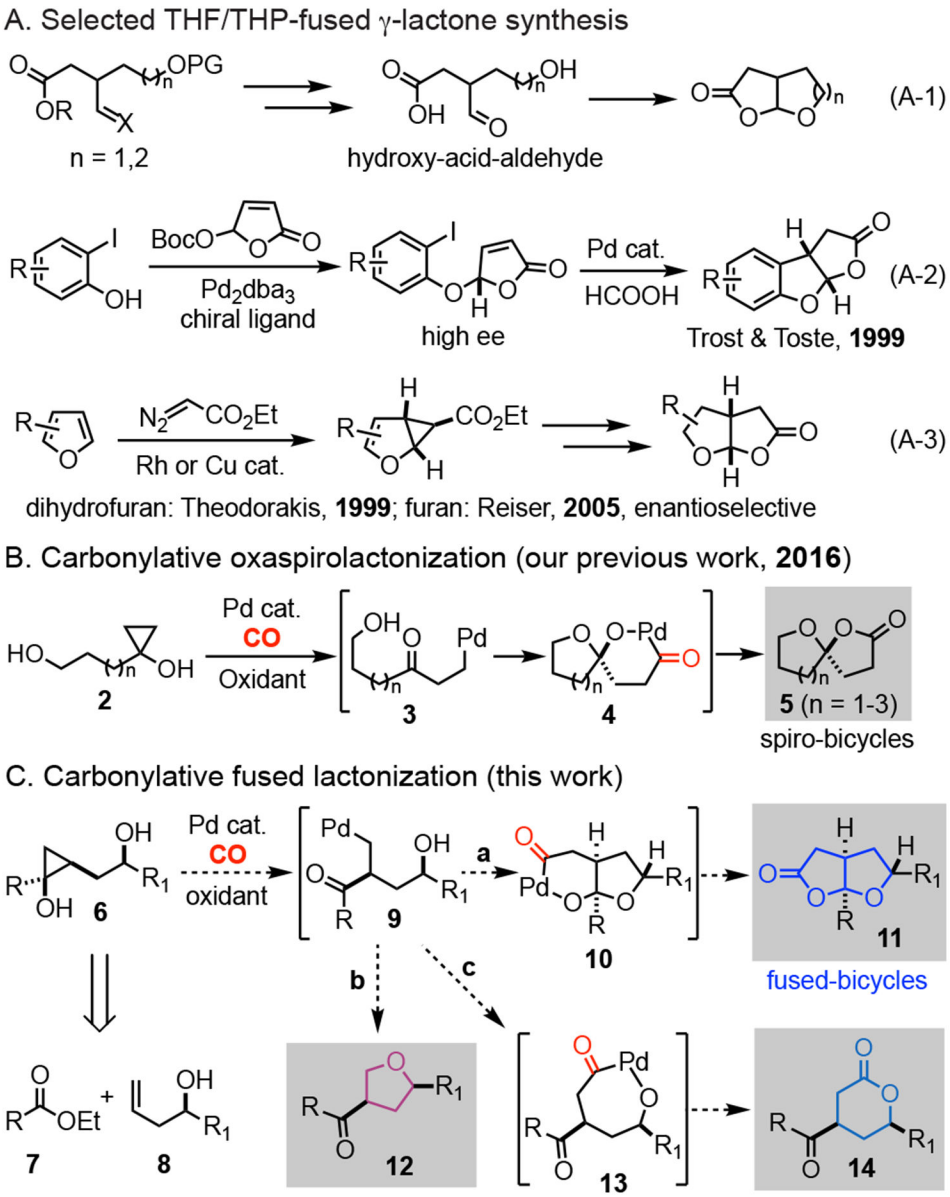
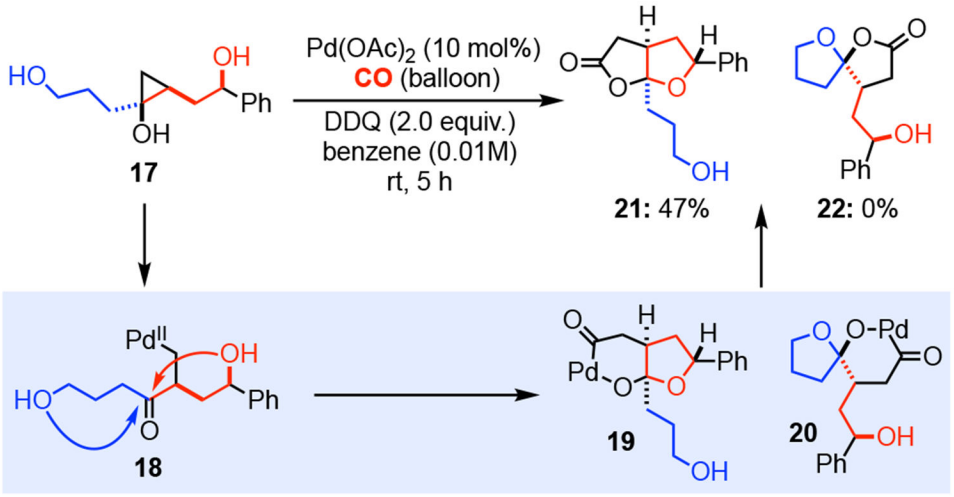
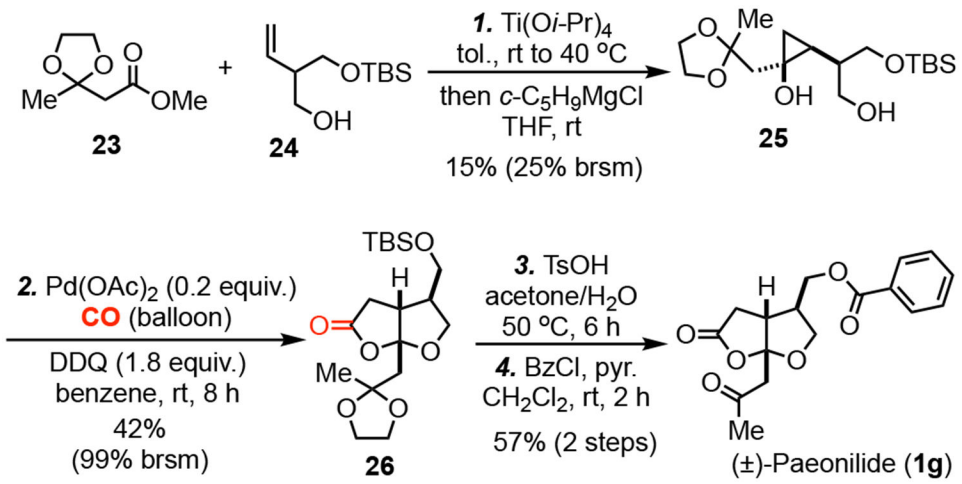


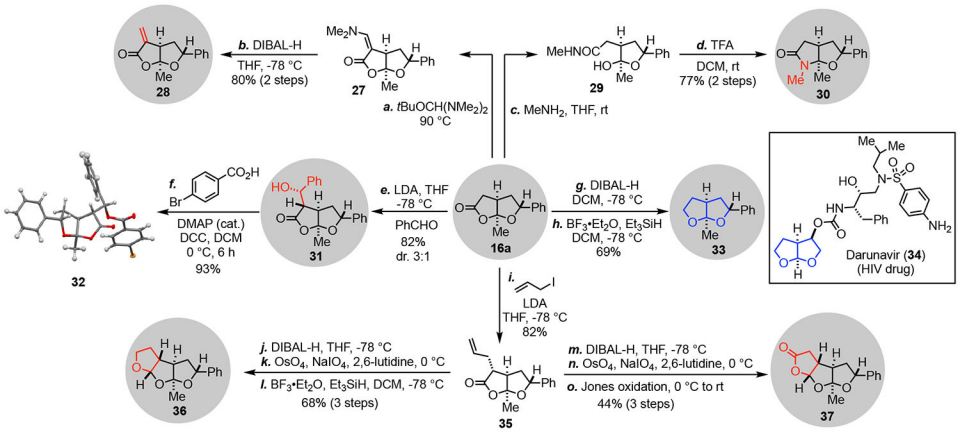
Figure 2.
Synthetic methodology design



Scheme 1.
A “competition” case



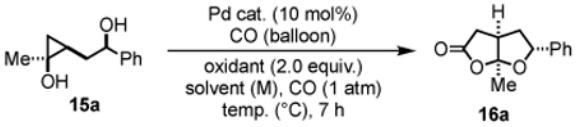
Scheme 2.
Total synthesis of (±)-paeonilide



Scheme 3.
Synthetic diversifications.

Table 1.

Reaction condition optimization[a]



entry	reaction conditions	yield[b]
1	$[Pd(neoc)(OAc)]_2(OTf)_2$, BQ, DCE (0.03), rt	0%
2	$Pd(TFA)_2$, BQ, DCE (0.03), rt	0%
3	$Pd(TFA)_2$, $Cu(OTf)_2$, DCE (0.03), rt	6%
4	$Pd(TFA)_2$, DDQ, DCE (0.03), rt	18%
5	$PdCl_2$, DDQ, DCE (0.03), rt	0%
6	$Pd(dppf)Cl_2$, DDQ, DCE (0.03), rt	trace
7	$Pd(OAc)_2$, DDQ, THF (0.03), rt	58%
8	$Pd(OAc)_2$, 2,5-DMBQ, THF (0.03), rt	trace
9	$Pd(OAc)_2$, 2,6-DMBQ, THF (0.03), rt	trace
10	$Pd(OAc)_2$, DDQ, toluene (0.03), rt	65%
11	$Pd(OAc)_2$, DDQ, toluene (0.03), 40 °C	51%
12	$Pd(OAc)_2$, DDQ (3.0 equiv.), toluene (0.03), rt	58%
13	$Pd(OAc)_2$, DDQ, toluene (0.01), rt	70%
14	$Pd(OAc)_2$, DDQ, benzene (0.01), rt	74%[c,d]

[a] General reaction conditions: To a stirred solution of **15a** (1.0 equiv., 0.2 mmol) and DDQ (2.0 equiv.) in benzene (0.01 M) under carbon monoxide (balloon) was added $Pd(OAc)_2$ (0.1 equiv.) in one portion. The resulting solution was stirred at room temperature until no more starting material left. The reaction process was monitored by thin-layer chromatography

[b] Isolated yield

[c] 65% for 0.56-gram scale (2.92 mmol)

[d] 73% yield and 92% ee when **15a** was prepared from the corresponding enantioenriched homoallylic alcohol with 92% ee; 2,5-DMBQ: 2,5-dimethylbenzoquinone; 2,6-DMBQ: 2,6-dimethylbenzoquinone.

Table 2.

Substrate scope