Chapter 3

Oxidative Transpositions Mediated by Selenium Dioxide[†]

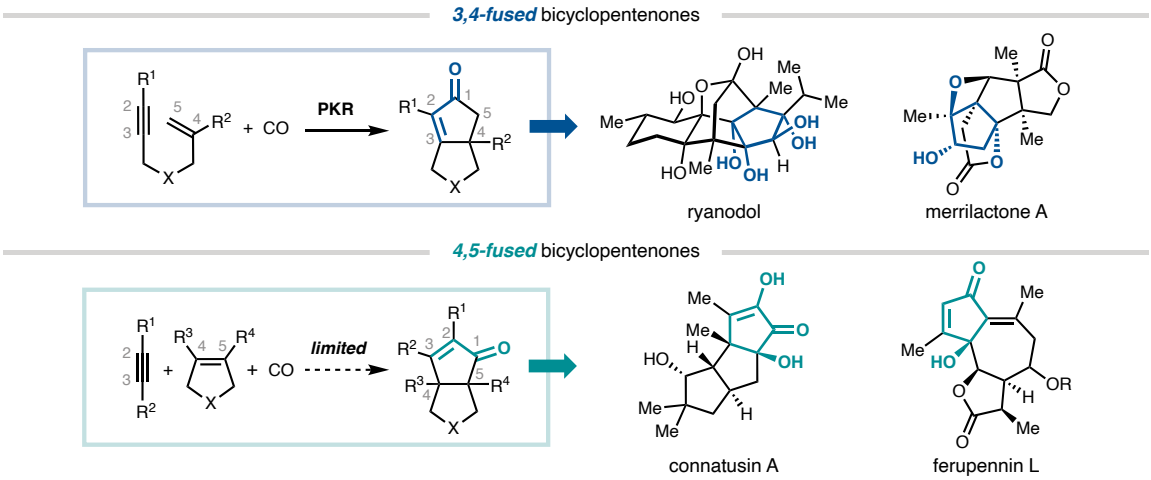
3.1 INTRODUCTION

The Pauson–Khand reaction (PKR) is a powerful method to prepare bicyclic cyclopentenones,[1,2] structural features found in many natural products. The intramolecular PKR is well-developed and affords 3,4-fused bicyclic systems from the corresponding tethered enynes (Figure 3.1).[3] The 3,4-fused bicyclic enone motif is commonly used as a precursor to highly oxidized five-membered carbocycles within complex structures, such as those of ryanodol and merrilactone A. The isomeric enones that are 4,5-fused can also serve as intermediates en route to these and other functionalized cyclopentanes. In addition, the 4,5-fused bicyclopentenones themselves constitute the cores of several natural products, including connatusin A and ferupennin L.

[†]Portions of this chapter were adapted from the following communication: Dibrell, S. E.;[‡] Maser, M. R.;[‡] Reisman, S. E. *J. Am. Chem. Soc.* **2020**, *142* (14), 6483–6487. The research presented in this chapter was completed in collaboration with Dr. Michael R. Maser, a former graduate student in the Reisman group.

Despite the utility and prevalence of 4,5-fused bicyclic enones within the context of natural product synthesis, there are few expedient methods to build these structures. Although intermolecular PKR could provide access to this oxidation pattern, limitations in scope hinder access to 4,5-fused bicycles that are highly functionalized (in contrast to the intramolecular variant).[4] Thus, a method to rapidly access 4,5-fused bicyclic enones with functional handles for further manipulation, which are inaccessible directly by PKR, would provide valuable synthetic building blocks.

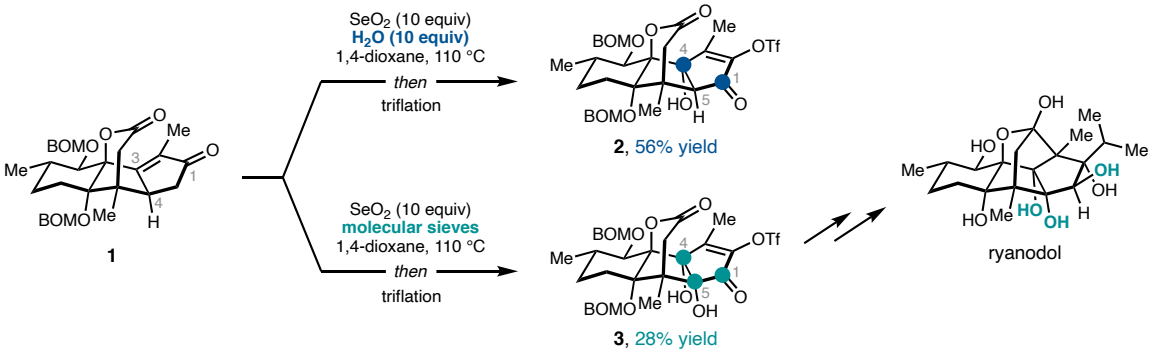
Figure 3.1 *Access to common bicyclopentenone motifs via PKR*



As part of the recent synthesis of the complex diterpene ryanodol, an unusual oxidative transformation mediated by selenium dioxide (SeO_2) was discovered (Figure 3.2).[5,6] Treatment of **1**, the product of intramolecular PKR, with SeO_2 under aqueous conditions led to α-oxidation relative to the starting enone in addition to installation of an additional oxygen atom at the β-position, furnishing dioxidation product **2**. Surprisingly, when water was omitted from the reaction, a third oxygen atom was incorporated at the γ-position of enone **1** to give trioxidation product **3**. Discovery of this transformation proved to be crucial to streamlining the synthesis, as it established the complete oxidation

pattern of the eastern 5-membered ring of the natural product in a single step.

Figure 3.2 *Discovery of SeO_2-mediated oxidative transpositions*



These di- and trioxidations were modest in yield, with no apparent explanation for the observed divergence in product distribution based on water content. However, the ability to construct oxidation patterns elusive via canonical PKRs sparked our interest in their wider application in synthesis. Specifically, we recognized the ability of these reactions to transpose the enone motif from the 3,4- to the 4,5-position of the fused ring system and questioned whether these transpositions could be general to other carbon scaffolds. We were thus inspired to investigate the scope and mechanism of SeO_2-mediated oxidative transpositions of 3,4-fused PKR products to prepare highly substituted bicyclopentenones of use in the synthesis of complex molecules.[7]

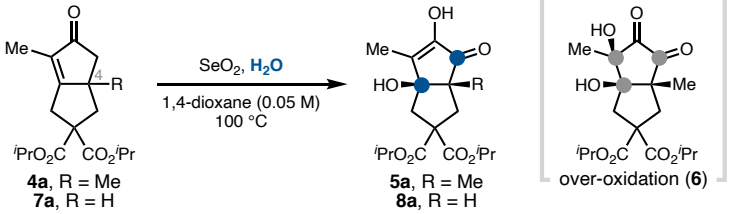
3.2 DEVELOPMENT OF DIOXIDATION REACTION

3.2.1 *Optimization of Reaction Conditions*

Our studies began with 3,4-fused bicyclopentenone **4a**, which is readily accessible via intramolecular PKR. The C4-γ-quaternary substitution of substrate **4a** (R = Me) prevents trioxidation, allowing analysis of the dioxidation process without competitive trioxidation. Under the previously reported conditions,[5] **4a** successfully underwent

dioxidation to generate 4,5-fused product **5a** (Table 3.1, entry 2); however, the yield was significantly lower than that observed in the ryanodane system. The primary mass balance was unreacted starting material (**4a**) and minor amounts of over-oxidation to tertiary alcohol **6**.

Table 3.1 *Optimization of dioxidation*



Entry	R	SeO_2 (equiv)	H_2O (equiv)	Time (h)	Dioxidation (% yield)
1	Me	10	0	3	11
2	Me	10	10	24	13
3	Me	10	100	38	71
4	Me	3	30	24	32
5	Me	3	100	48	62
6	Me	1.5	15	24	29
7	Me	1.5	100	120	42
8	H	10	100	4	64

Increasing the amount of water in the reaction led to a significant boost in conversion, providing dioxidized **5a** in 71% yield (Table 3.1, entry 3). In addition to enhancing the yield, the increased concentration of water also significantly improved the reaction profile. We hypothesize that excess water serves to inhibit formation of organic byproducts, such as **6**, by hydrolyzing organoselenium intermediates on undesired pathways or by destroying reactive selenium(II) electrophiles known to trap olefins.[8] Moreover, water-promoted reduction of selenium afforded the black allotrope, which

proved easier to remove from organic products than selenium red, a more soluble colloid.[8,9]

When the equivalents of SeO_2 were reduced, the effects of water on the reaction became more pronounced. Using 1.5 or 3 equiv SeO_2 while maintaining a 10:1 ratio of water to SeO_2, the yield of **5a** was approximately halved (Table 3.1, entries 4 and 6 versus 3). However, increasing the equivalents of water compared to SeO_2 led to an increase in yield, affording **5a** in 62% yield and 42% yield, respectively (entries 5 and 7). The recovery in yield was accompanied by significant retardation of the reaction rate; without excess SeO_2, reaction times extended upwards of several days.

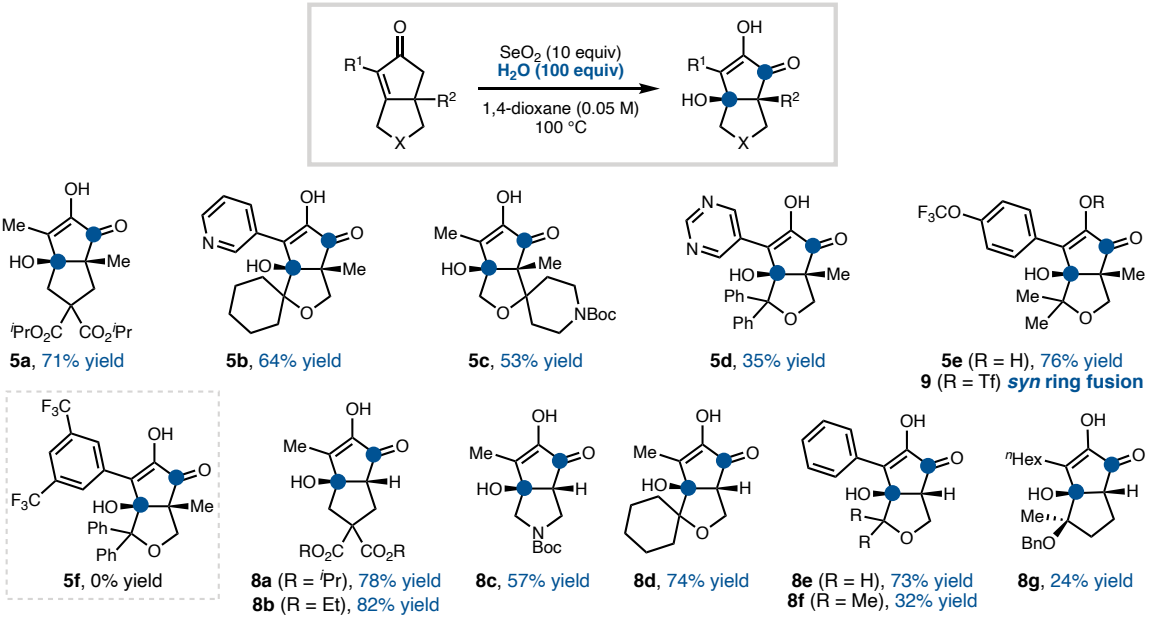
With reduced equivalents of SeO_2, acid and/or base additives failed to improve selective reactivity or reaction time. Instead, closely monitoring the reaction was most important for maximizing the yield, a known limitation of SeO_2-mediated oxidations.[8,10] If enone **4a** was allowed to be fully consumed, the yield of **5a** was lower than if the reaction was stopped with approximately 25% of **4a** remaining. Capping the reaction at three-fourths conversion of **5a** balanced maximum recovery of the enone with minimum over-oxidation and degradation of **5a**.

3.2.2 *Reaction Scope*

Having optimized conditions for model substrate **4a**, we turned our attention to the effect of substitution around the starting bicyclopentenone on the yield of the dioxidation product. When substrate **7a** (R = H), which lacks the C4-γ-quaternary center, was subjected to 10 equiv SeO_2 in the presence of excess water, dioxidation product **8a** was formed in comparable yield to that of **5a** (Table 3.1, entry 8). Bicyclopentenones

featuring various substituents at the α-position (R^1) were also tolerated under the conditions (Table 3.2), including alkyl chains (**8g**), arenes (**5e** and **8e**,**f**) and heterocycles (**5b** and **5d**). However, more electron-withdrawing aryl substitution hindered reactivity (e.g., **5f**). For substrates bearing saturated oxacycles (X = O), the reaction was tolerant of geminal disubstitution (**5b**–**e**, **8d**–**f**). Surprisingly, formation of the C6-γ-epimer of **8g** was not observed under the conditions employed. Lastly, substrates containing protected amines afforded dioxidation products in good yields (**5c** and **8c**).

Table 3.2 *Scope of dioxidation*



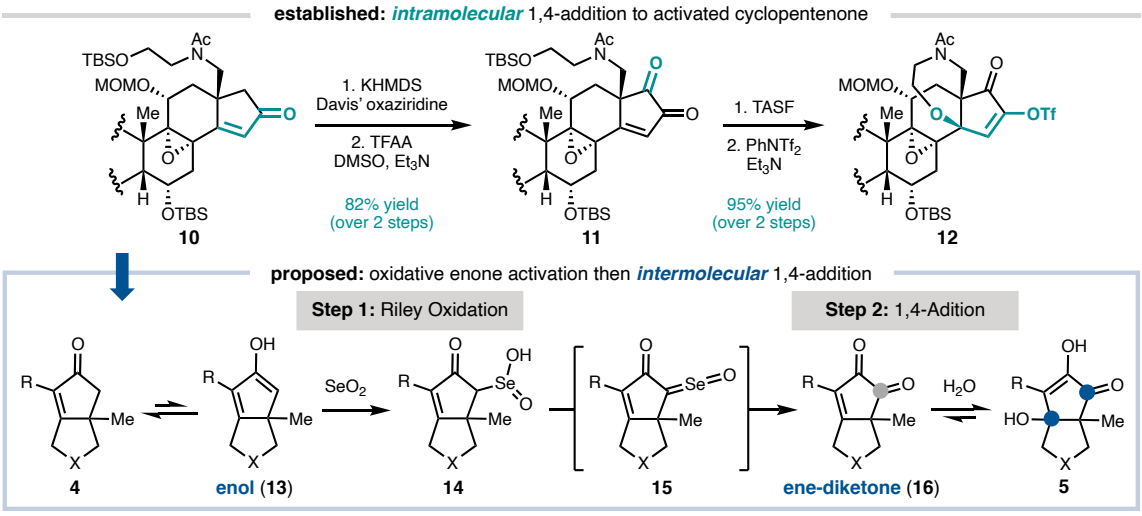
In addition to the moderate to good yields of the 4,5-fused bicyclic products, each was formed as a single diastereomer. Triflation of **5e** afforded the enol triflate (**9**) as a crystalline solid, and single crystal X-ray diffraction confirmed *syn* ring fusion (Table 3.2). By analogy, all oxidation products are assigned as *cis*-fused diastereomers.

3.3 MECHANISTIC INVESTIGATION OF DIOXIDATION

3.3.1 *Proposed Reaction Pathways*

The developed dioxidation reaction could proceed through a two-step pathway analogous to that suggested by studies of other complex cyclopentenone systems (Figure 3.2).[11,12] In synthetic efforts toward batrachotoxinin A, Kishi and coworkers targeted 4,5-fused cyclopentenone **12**, which features the same oxygenation pattern as dioxidation products (**5**). Starting from 3,4-fused **10**, intramolecular oxy-Michael addition required activation of the enone; a two-step oxidation sequence (α-hydroxylation and Swern oxidation) allowed access to ene-diketone **11** and enabled the desired 1,4-addition, with the adduct trapped as enol triflate **12**.[13] Formation of the ene-diketone (**11**) served three major purposes: activation of the enone for nucleophilic attack, stabilization of the resulting enolate, and installation of a functional handle to facilitate downstream chemistry.

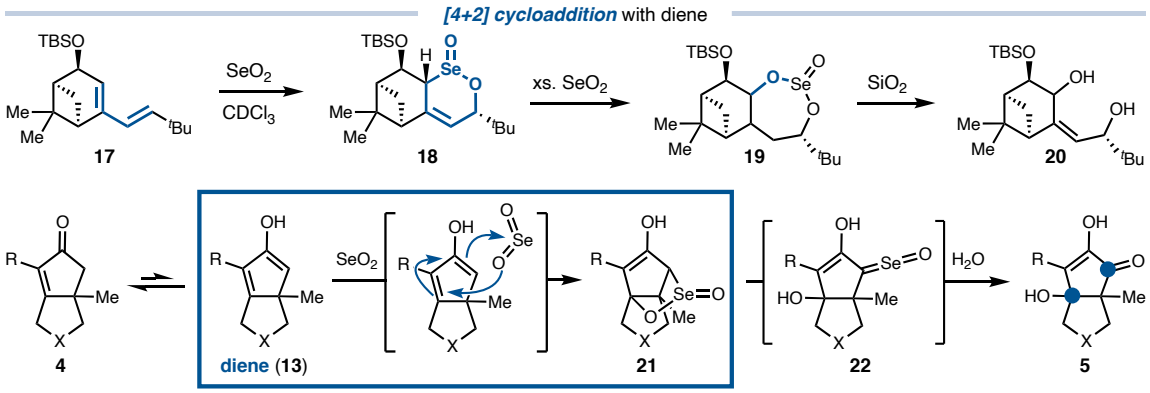
Figure 3.2 *Proposed dioxidation pathway: Riley oxidation then 1,4-addition*



The dioxidation reaction could proceed through a related stepwise pathway

(Figure 3.2). As a ketone, substrate **4** could undergo Riley oxidation in the presence of SeO_2 to form a carbon–oxygen double bond at the α-carbon, resulting in ene-diketone **16**.[14] Generally, Riley oxidation is thought to proceed via tautomerization followed by electrophilic attack of SeO_2, which results in a seleninic acid intermediate (**14**) primed for seleno-Pummerer rearrangement and dehydration to afford an unstable selenine (**15**). Rapid selenine hydrolysis can then release reduced selenium and the ene-diketone (**16**). Now an activated Michael acceptor, enone **16** could proceed to dioxidation product **5** upon intermolecular conjugate addition of water.

Figure 3.3 *Proposed dioxidation pathway: [4+2] cycloaddition*



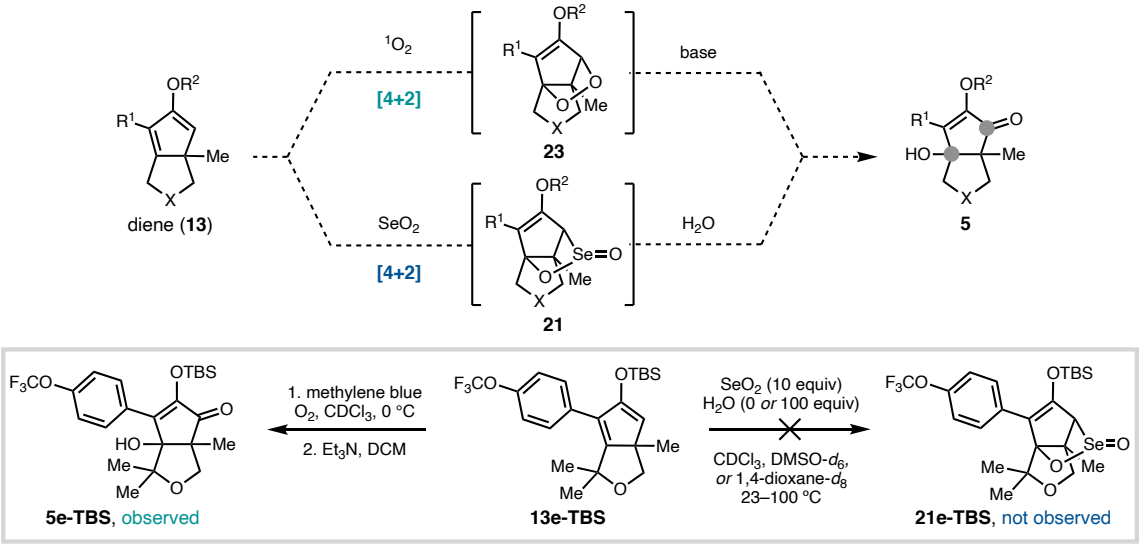
We also imagined an alternative pathway to dioxidation products, inspired by a report by Lee and coworkers (Figure 3.3).[15] In that case, selenino lactone **18** was spectroscopically observed to be the product of allylic ether **17** and anhydrous SeO_2. This surprising adduct (**18**) was proposed to arise from [4+2] cycloaddition of diene **17** and dienophile SeO_2. In the current system, cyclopentadiene **13**, the enol tautomer of **4**, could engage SeO_2 in a comparable manner to form cycloadduct **21**. Proton transfer could then open selenino lactone **21** to arrive at a selenine (**22**), from which hydrolysis would directly generate dioxidation product **5**. Whereas in the two-step pathway (see Figure 3.2)

SeO_2 engages the substrate as an enol (**13**),[16] the proposed cycloaddition requires **13** to behave as a diene.

3.3.2 *Investigation of Cycloaddition Pathway*

To distinguish between the proposed dioxidation pathways, we investigated the reactivity of common intermediate **13**. The ability of diene **13** to undergo cycloaddition was probed using singlet oxygen ($^1O_2$), which is known to perform [4+2] cycloadditions in the presence of cyclic dienes (Figure 3.4, teal).[17] To this end, cyclopentadiene **13e-TBS** was designed as a stable and isolable surrogate of enol tautomer **13e**. Isolation of products bearing the oxidation pattern of dioxidized **5** (i.e., **5e** or **5e-TBS**) provide evidence for the generation of cycloadduct **23**, which can undergo Kornblum–DeLaMare rearrangement upon addition of base. Indeed, rearranged product **5e-TBS** was observed.

Figure 3.4 *Proposed and experimental [4+2] cycloaddition reactivity*



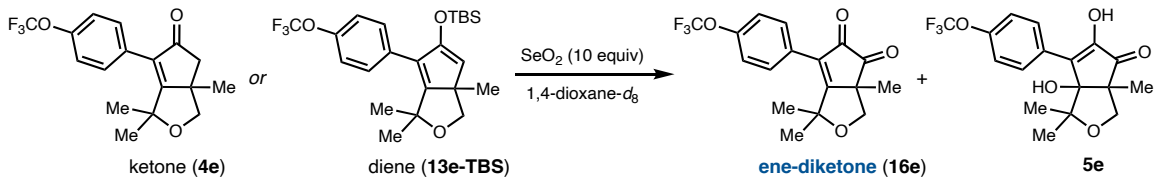
The successful cycloaddition of protected **13e-TBS** with $^1O_2$ suggests that this diene could likewise engage SeO_2 as dienophile, generating a seleno-cycloadduct

analogous to **23** (**21**, Figure 3.4, blue). In this case, the intermediacy of seleninic ester **21** could be spectroscopically observable.[15] However, under standard dioxidation conditions (i.e., aqueous SeO_2), no species en route to protected dioxidation product **5e-TBS** from **13e-TBS** could be observed by ^{1}H, ^{13}C, or ^{77}Se NMR. Excluding water also failed to yield evidence of intervening organoselenium species.

Instead, diene **13e-TBS** converted to a distinct species, which we spectroscopically characterized as ene-diketone **16e** (Table 3.3).[14,18] Monitoring the reaction over time by ^{1}H NMR revealed fast reversion of diene surrogate **13e-TBS** to the enone precursor (**4e**), likely promoted by adventitious water or H_2SeO_3 generated in situ (entry 1). Subjection of ketone **4e** to anhydrous SeO_2 also provided ene-diketone **16e**, (entry 2), and after extended reaction time, dioxidized **5e** was also observed (entry 3).

It is possible that SeO_2 is unable to engage the sterically hindered silyl protected enol (**13e-TBS**) but still undergoes cycloaddition with unprotected enol **13e**; however, the lability of the TBS ether under the conditions precludes conclusive attribution of ene-diketone formation to reaction of **13** as a diene. Nevertheless, this study implicates ene-diketone **16e** as a putative intermediate in dioxidation.

Table 3.3 *Discovery of ene-diketone*



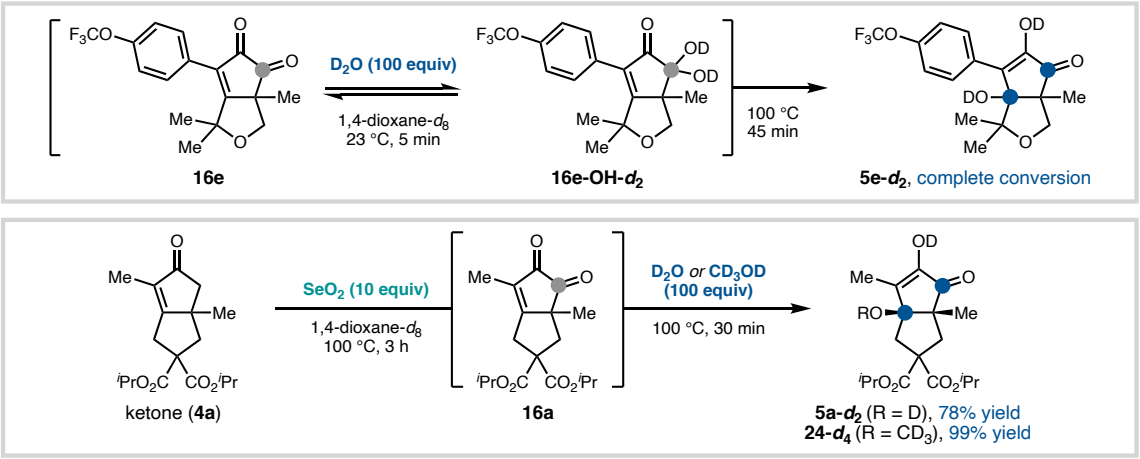
ketone (**4e**) diene (**13e-TBS**) **ene-diketone** (**16e**) **5e**

Entry	Substrate	Time	Result
1	diene (**13e-TBS**)	5 h	**4e** + **ene-diketone** (**16e**)
2	ketone (**4e**)	4 h	**4e** + **ene-diketone** (**16e**)
3	ketone (**4e**)	26 h	**16e** + dioxidation (**5e**)

3.3.3 *Investigation of Stepwise Pathway*

Given that an ene-diketone is a likely a product of Riley oxidation, generation of this species is indicative of the proposed two-step pathway to dioxidation products (see Figure 3.2). We investigated this pathway by quantitatively tracking the generation and conversion of such species by ^{1}H and ^{13}C NMR. At room temperature, addition of deuterated water to **16e**, generated in situ from ketone **4e**, rapidly established an equilibrium with deuterated hydrate **16e-OH-*d*$_2$**, which fully converted to deuterated dioxidation product **5e-*d*$_2$** upon heating (Figure 3.5). Using ketone **4a** instead, an analogous ene-diketone species (**16a**) was spectroscopically observed to form; addition of D_2O at 100 ºC then delivered deuterated dioxidation product **5a-*d*$_2$** in 78% yield. Under anhydrous conditions, adding deuterated methanol to **16a** provided **24-*d*$_4$** in excellent yield.[12,13] This result offers support for the hypothesis that oxidative activation of the enone (i.e., ene-diketone generation) and 1,4-addition are distinct and sequential steps.

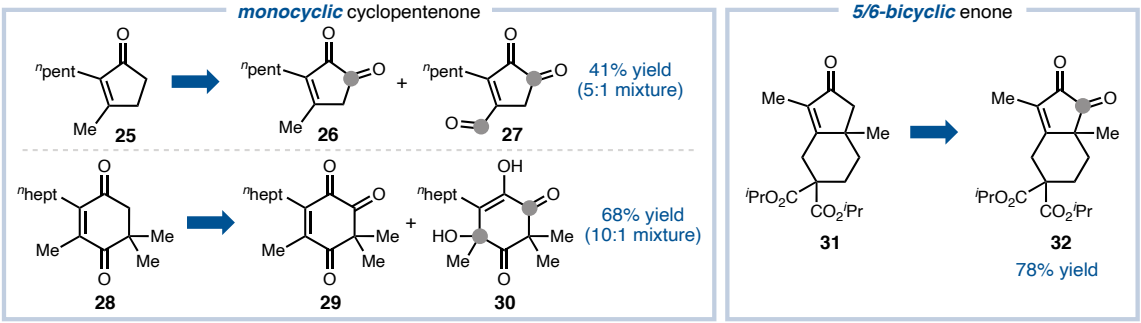
Figure 3.5 *Support for ene-diketone as dioxidation intermediate*



To further study the conjugate addition step, we subjected a set of substrates featuring ring systems alternative to 5/5-bicyclic enones to the standard dioxidation

conditions and monitored the product distribution by ^{1}H NMR (Figure 3.6). In the case of dihydrojasmone (**25**), a monocyclic cyclopentenone, initial Riley oxidation generated ene-diketone **26**; however, 1,4-addition of water was not spontaneous under these conditions. Instead, over-oxidation to aldehyde **27** preferentially occurred. Reaction of monocyclic cyclohexenone **28** similarly stopped after oxidation to α-carbonyl **29**, although the dioxidized 6-membered ring **30** was observed in trace amounts. In this case, product **30** could arise from oxy-Michael addition or via an alternative mechanism analogous to that producing byproduct **6** (see discussion of Fig. 3.9). Lastly, 5/6-bicyclic enone **31** afforded ene-diketone **32** in high yield but did not react further. Based on these results, we propose that the release of ring strain from the intermediate 5/5-bicyclic ene-diketones upon rehybridization serves as a driving force for oxy-Michael addition.

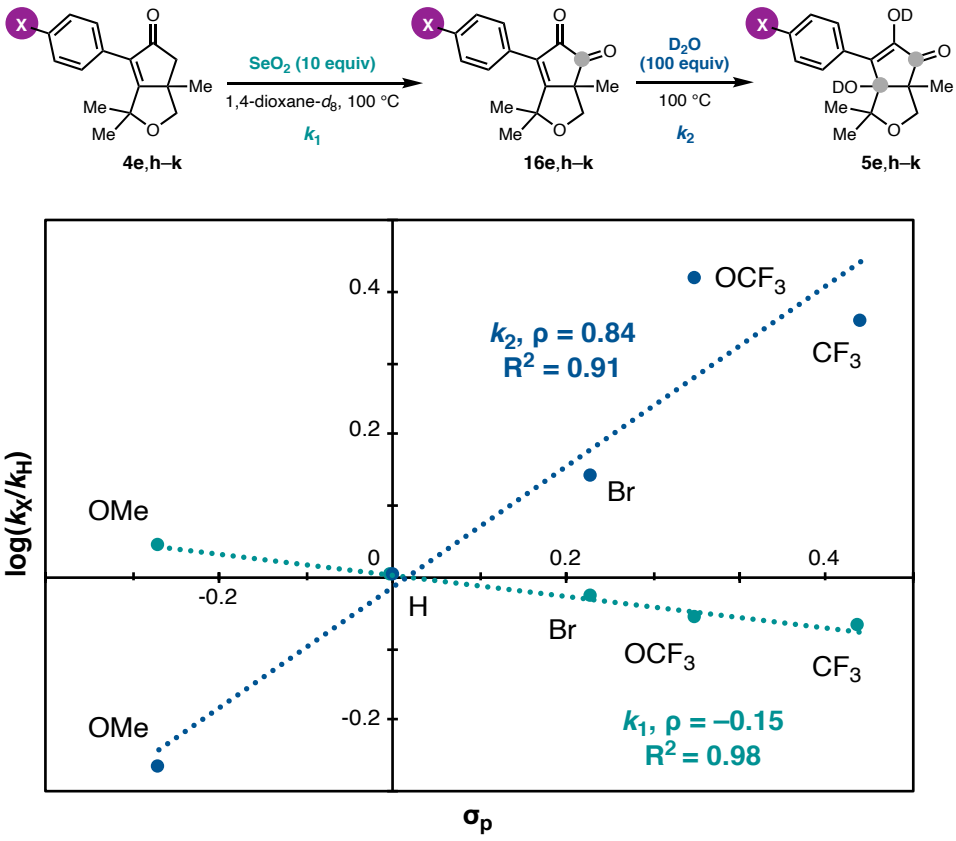
Figure 3.6 *Dioxidation of alternative ring systems*



We also studied the kinetics of the individual Riley oxidation and conjugate addition steps (Figure 3.7). Quantitative ^{1}H NMR was used to measure the rate of ene-diketone formation (**16**) from reaction of ketone **4** with anhydrous SeO_2 (k_1, teal), as well as the rate of consumption of hydrated ene-diketone **16** upon the addition of D_2O (k_2, blue). In general, Riley oxidation was slower than oxy-Michael addition by an order of magnitude. This observation suggests that extension of the overall reaction time in the

presence of excess water (observed during reaction development) is likely a result of depressed rates of the initial oxidation step (i.e., inefficient ene-diketone formation).

Figure 3.7 *Kinetic analysis of steps toward dioxidation*

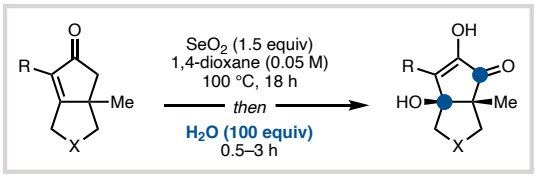


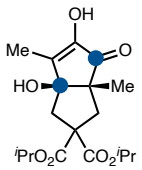
Preparation of substrate derivatives (**4e**,**h**–**k**) featuring various *para*-substituents on a pendant α-arene allowed investigation of electronic effects on dioxidation (Figure 3.7). Correlation of the reaction rates with Hammett parameters[19] revealed the rate of the conjugate addition (k_2) to be more dependent on substrate electronics than the rate of the Riley oxidation (k_1); the opposite signs of ρ for k_1 and k_2 indicate disparate charge buildup in both steps. Whereas 1,4-addition was much faster for electron-deficient systems, initial Riley oxidation was slightly faster for electron-rich substrates, consistent with proposed enol electrophilic attack (see Fig. 3.2). Together, these results account for

poor-performing substrates which are electron-poor (e.g., **5f**, Table 3.2): slow conversion to an ene-diketone intermediate due to deactivating electronics—and exaggerated by the presence of water—likely allows the starting enone to engage SeO_2 in undesired byproduct-forming pathways.

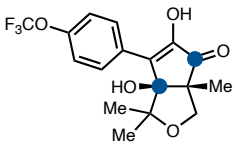
3.3.4 *Expansion of Dioxidation Scope*

Table 3.4 *Scope of improved dioxidation protocol*

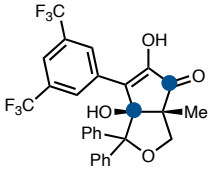




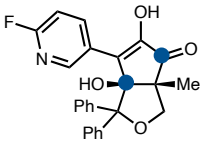
5a, 59% yield
(original: 71%)



5e, 63% yield
(original: 76%)



5f, 79% yield
(original: 0%)



5g, 54% yield
(original: 0%)

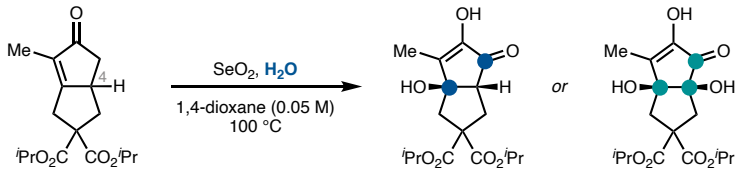
Based on our mechanistic studies, we hypothesized that a protocol separating the requisite steps for dioxidation (i.e., latent addition of water) would promote (1) faster access to dioxidation products with reduced equiv SeO_2, (2) cleaner reaction profiles, and (3) successful reaction of heretofore low-yielding substrates. To prevent excessive depression of Riley oxidation rates, the bicyclopentenone and 1.5 equiv SeO_2 were first reacted in the absence of water; then, addition of H_2O resulted in rapid product generation. For model substrates **4a** and **4e**, the corresponding dioxidation products were furnished via this protocol in yields comparable to those resulting from the standard aqueous conditions (Table 3.4). Notably, previously inaccessible electron-poor dioxidized **5f** and **5g** were afforded in 79% and 54% yield, respectively. This improved,

stepwise protocol has the potential to substantially broaden the scope of 3,4-fused bicyclopentenones in the dioxidation reaction.

3.4 DEVELOPMENT OF TRIOXIDATION REACTION

3.4.1 *Optimization of Reaction Conditions*

Table 3.5 *Optimization of trioxidation*



7a **8a** **33a**

Entry	SeO_2 (equiv)	H_2O (equiv)	Time (h)	Dioxidation (% yield)	Trioxidation (% yield)
1	10	100	4	64	0
2	10	100	46	0	14
3	10	10	1	0	15
4	10	0	2	0	21
5	3	0	3	0	10
6	3	100	14	7	15

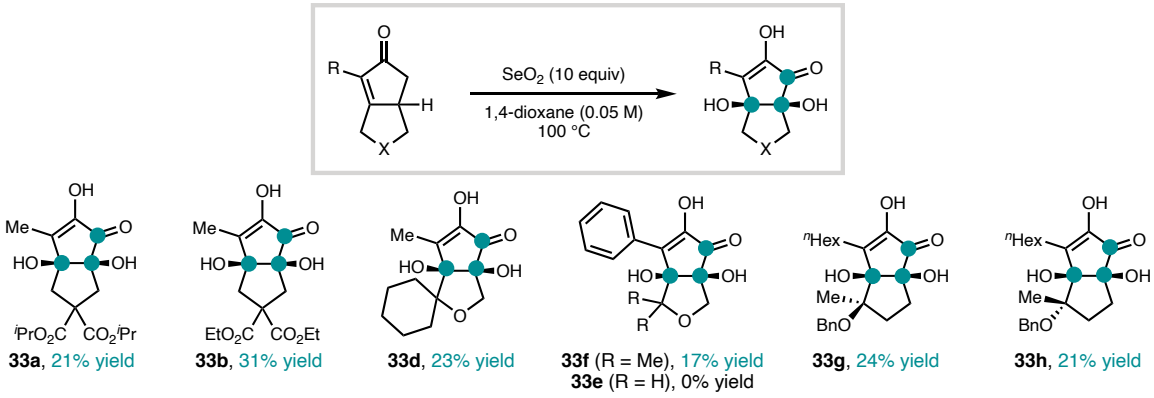
For bicyclopentenones lacking C4-γ-substitution (i.e., **7**), both dioxidation and trioxidation processes can occur in the presence of SeO_2. Under the optimized conditions for dioxidation of **7a**, use of excess water furnished dioxidized **8a** (Table 3.5, entry 1). Interestingly, subjection of **7a** to these same conditions for extended reaction times led to isolation of trioxidation product **33a** (entry 2), which had previously been observed only under rigorously anhydrous conditions.[5] Motivated by this observation, we investigated the selective formation of **33a**. Reducing the equivalents of water in the SeO_2-mediated

reaction provided trioxidized **33a** in faster rates with cleaner reaction profiles (entry 3). The complete exclusion of water provided **33a** in 21% yield with no trace of undesired **8a** (entry 4), and these conditions were selected as optimal for trioxidation.

Reducing the equivalents of SeO_2 served to decrease the yield of **33a** (Table 3.5, entry 5). Although addition of water to 3 equiv SeO_2 effected a minor increase in yield, this improvement came at the expense of selectivity between dioxidation and trioxidation products (**8a** and **33a**, respectively; entry 6). In all cases, the mass balance was an intractable mixture of byproducts arising from over-oxidation and/or decomposition.

3.4.2 *Reaction Scope*

Table 3.6 *Scope of trioxidation*



We next explored the scope of the trioxidation reaction (Table 3.6). While competitive decomposition of the trioxidation products (**33a**–**h**) generally resulted in diminished yields relative to those of dioxidations, the desired products could be isolated in approximately 20–30% yield. This range is similar to that observed in the trioxidation of **1**, which underscores the importance of installing three oxygens atoms in a single step regardless of moderate yield. Furthermore, each reaction was stereoselective, affording a

single diastereomer of product; trioxidized **33g** and **33h** were formed as single diastereomers from the corresponding diastereomeric bicyclopentenones.

It should be noted that substrates containing unsubstituted saturated heterocyclic rings, such as **33e**, mark a limitation of this method. In such cases, the observation of byproducts tentatively assigned as dienes suggests that the desired products may form but then rapidly eliminate water under the reaction conditions.

3.5 STEREOCHEMICAL ANALYSIS OF DI- AND TRIOXIDATIONS

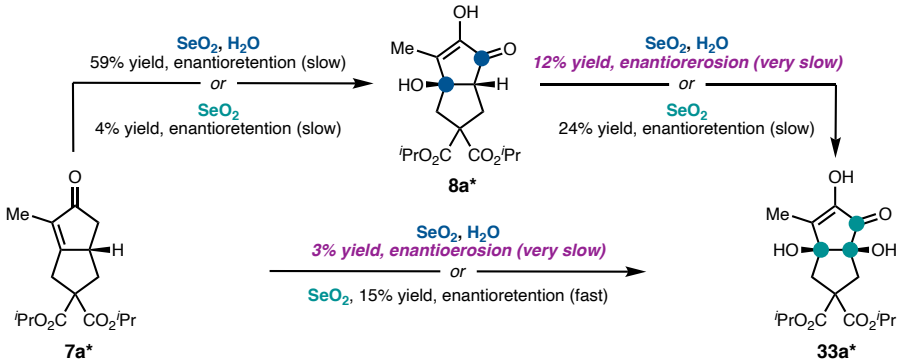
Having developed a mechanistic understanding of dioxidation reaction as well as conditions for selective trioxidation, we set out to explore the origins of selectivity between the dioxidation and trioxidation products. We anticipated that analyzing the stereochemical outcomes of standard di- and trioxidation reactions would facilitate interrogation of possible intermediates and pathways. To this end, we attempted to prepare the requisite enantioenriched bicyclopentenone (**7**) by asymmetric PKR, but these reactions proved to be inconsistent and not amenable to scale;[20] instead, separation of **7a** via chiral HPLC afforded this enone substrate as a single enantiomer (**7a***). Under standard aqueous and anhydrous reaction conditions, enantioenriched substrate **7a*** and products **8a*** and **33a*** were confirmed by control experiments to be configurationally stable.

3.5.1 *Investigation of Di- to Trioxidation Conversion*

As an initial study, we subjected enantiopure **7a*** to aqueous SeO_2, which delivered dioxidation product **8a*** with retention of enantiopurity, i.e., no loss of

enantiomeric excess compared to **7a*** (Table 3.7, entry 1). This result is consistent with both proposed dioxidation pathways (see section 3.3.1), given that either cycloaddition or 1,4-addition would be expected to be stereospecific and generate the *cis*-fused bicyclopentenone product that is likely significantly more stable than the *trans* isomer.

Table 3.7 *Stereochemical analysis of trioxidation via dioxidation*



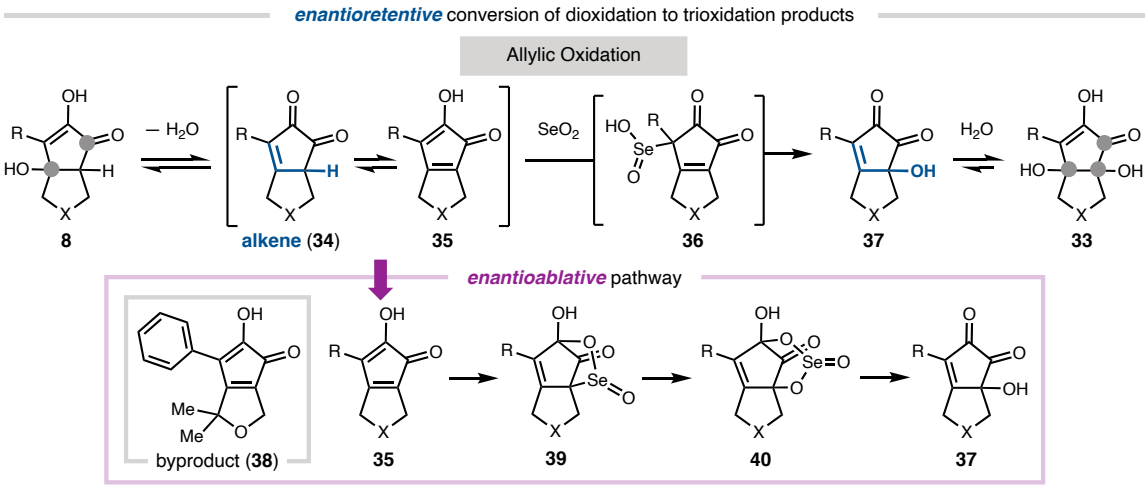
Entry	Reaction	Time (h)	ee (%)	Yield (%)
1	**7a*** → **8a***	24	>99 → >99	59
2	**7a*** → **33a***	24	>99 → 60	3
3	**8a*** → **33a***	12	>99 → 46	12
4	**7a*** → **8a***	1	>99 → >99	4
5	**8a*** → **33a***	1	>99 → >99	15
6	**7a*** → **33a***	2	>99 → >99	24

Under the same conditions, trace trioxidation product **33a*** was formed after extended reaction times (Table 3.7, entry 2); however, formation of **33a*** under these conditions proceeded with significant erosion of ee. Treatment of isolated dioxidation product **8a*** with H_2O/SeO_2 also resulted in the slow formation of **33a*** with substantial loss of ee (entry 3). The consistencies in reaction time and enantioerosion of the aqueous reaction of enone **7a*** and dioxidized **8a*** indicate that the dioxidation product could be

an intermediate toward trioxidation and provide mechanistic insight into this conversion.

One mechanistic possibility is that the dioxidation product (**8**) can dehydrate to reversibly generate an ene-diketone (**34**; Figure 3.8, blue); as an alkene, **34** could engage SeO_2 in standard allylic C–H oxidation,[16,21,22] likely proceeding through seleninic acid **36** followed by [2,3] sigmatropic rearrangement and loss of reduced selenium to access **37**. The resulting alcohol (**37**) would be sufficiently activated for oxy-Michael addition to afford trioxidized **33**. This process would likely be disfavored in the presence of water, given that the **8**/**34** equilibrium would lie to the left, which could account for the long reaction times required (e.g., several days) to access trioxidation products under aqueous conditions, i.e., selectivity for dioxidation when excess water is used.

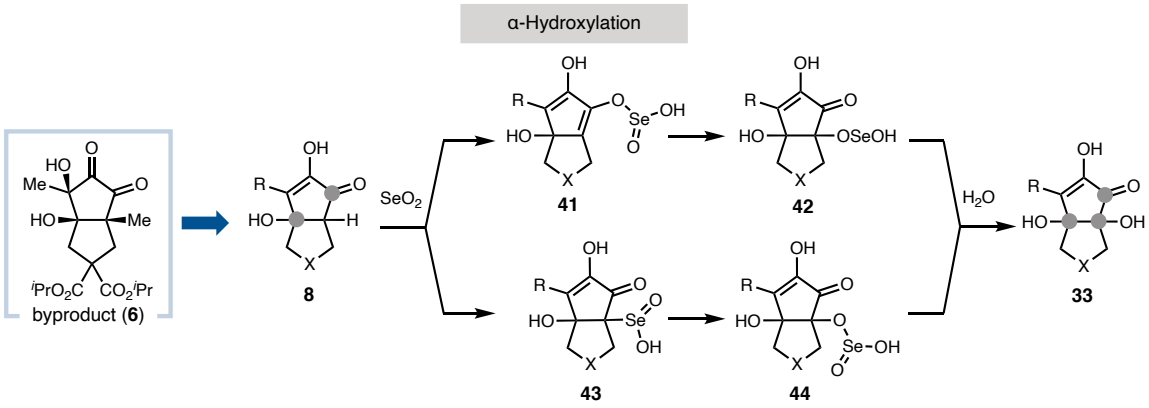
Figure 3.8 *Trioxidation via allylic oxidation or cycloaddition*



The stereospecific nature of SeO_2-mediated allylic oxidation suggests that this pathway would not result in erosion of starting enantiopurity (i.e., of **8***), which is not fully consistent with the data. However, the putative ene-diketone intermediate (**34**) can tautomerize to enol **35**, which is achiral.[23,24] Isolation of **38** from reaction of enone **7e** provides evidence for such an intermediate (Figure 3.8, purple). Due to the anti-aromatic

nature of cyclopentadienones, they rapidly oligomerize via Diels–Alder reactions if not stabilized by steric bulk or conjugated aryl substituents.[25] Thus, 2-hydroxycyclopentadienone **35**, highly reactive toward [4+2] cycloaddition, could be approached by dienophile SeO_2 to yield cycloadduct **39**. Conversion to **33** could occur via formal C–Se oxidation of seleninic ester **39** (see Fig. 3.3);[15] although atom-transfer from selenium is posited to be challenging,[26] C–Se oxidation of **39** would ultimately result in **37** following hydrolysis.[27,28] This hypothetical pathway should result in complete racemization of chiral substrate **8***, thus it is likely that multiple mechanisms are operative in the observed enantioerosive (but not enantioablative) conversion of dioxidized **8a*** to the trioxidation product (**33a***) in the presence of water.

Figure 3.9 *Trioxidation via α-hydroxylation*



In an additional plausible mechanistic scenario, dioxidation product **8** can undergo direct α-hydroxylation to afford trioxidized **33** (Figure 3.9). Isolation of byproduct **6** from reactions of the model substrate (**4a**) offers support for an α-hydroxylation pathway. Although C4-γ-substitution of **4a** blocks installation of oxygen adjacent to the newly formed carbonyl group, which would mimic conversion of **8** to **33**, an analogous process likely accounts for hydroxylation at C2 of enone **4a**. Such a process

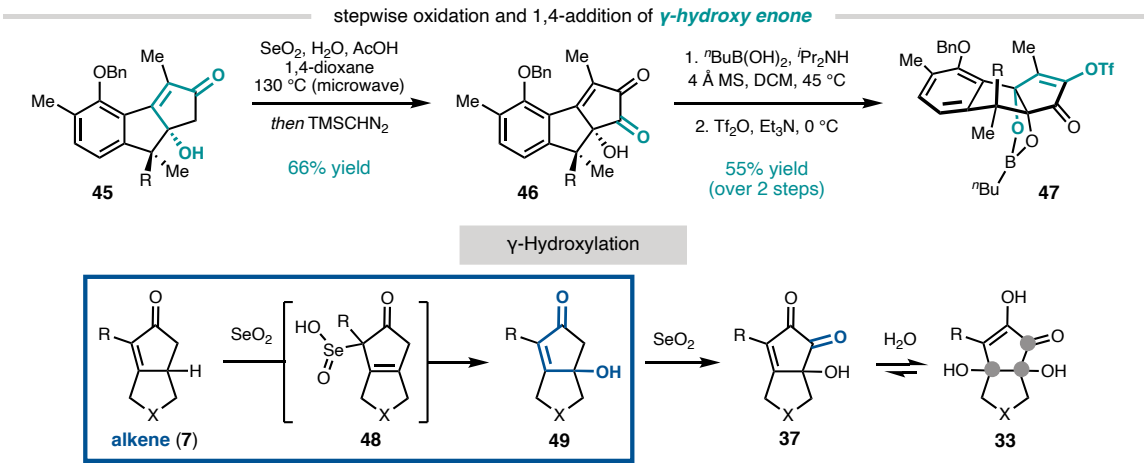
could proceed via electrophilic attack of **8** by selenous acid at oxygen, as proposed by Corey and Schaefer; from enol selenite **41**, subsequent [2,3] sigmatropic rearrangement could afford **42**.[29] Whereas secondary selenium(II) esters can oxidatively decompose, as would be the case for Riley oxidation, they are generally observed to rapidly hydrolyze.[18] Excess water would favor hydrolysis, and tertiary Se(II) ester **42** could thus convert to **33**. An alternative process could involve electrophilic attack of **8** at carbon to result in selenite **43**, which is primed for [1,2] shift or C–Se oxidation (*vide supra*) to afford the trioxidation product (**33**) via selenate monoester **44**.[15,18]

In either α-hydroxylation process, the requisite steps are stereospecific and would not be expected to result in erosion of substrate enantiopurity. Also, the dependence on hydrolysis of each process suggests that α-hydroxylation would likely be slow under anhydrous conditions. Considering these two points, α-hydroxylation could account for generation of the trioxidation product (**33**) from dioxidized **8** in the absence of water. Indeed, treatment of enone **7a*** with anhydrous SeO_2 slowly provided dioxidation product **8a*** with preservation of ee (Table 3.7, entry 4); subjection of isolated **8a*** to identical conditions resulted in slow conversion to trioxidized **33a*** with complete retention of ee (entry 5). The rate of these transformations, however, starkly contrasts with the standard anhydrous reaction of substrate **7a***, which rapidly provided trioxidation product **33a*** in a few hours, also without erosion of ee (entry 6). Thus, although dioxidized **8a*** may represent an intermediate en route to trioxidation in the absence of water, there is likely a more kinetically competent pathway.

3.5.2 *Investigation of Alternative Trioxidation Pathway*

We envisioned that the trioxidation product (**33**) could form without the intermediacy of the dioxidation product (**8**). Reisman and coworkers previously reported a sequence of steps that serve to transform alcohol **45** to 4,5-fused cyclopentenone **47**, which features the trioxidation pattern of **33** (Figure 3.10).[12] Interestingly, the SeO_2-mediated oxidation of **45** did not occur with concomitant addition of water; we hypothesize that enhanced stability of ene-diketone **46** due to arene conjugation outweighs ring strain-release that would otherwise drive oxy-Michael addition.

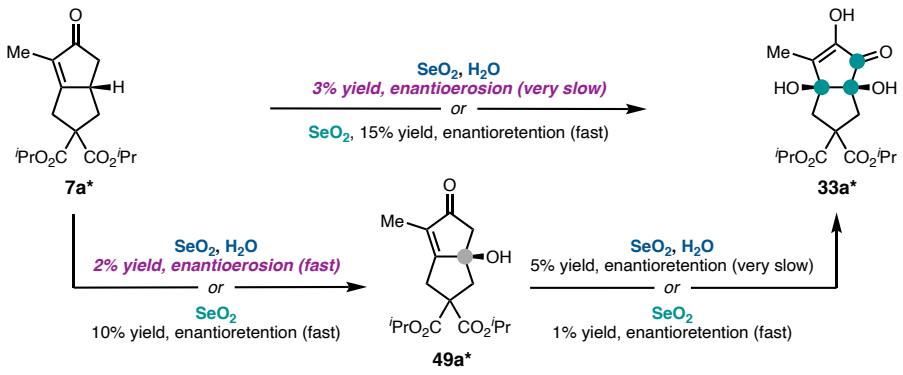
Figure 3.10 *Trioxidation via γ-hydroxylation*



Inspired by this report, we considered that a γ-hydroxy enone analogous to **45** could serve as an intermediate in the current system. If substrate **7** reacts with SeO_2 not as a ketone but as an alkene, then allylic oxidation would result in such a compound: alcohol **49** (Figure 3.10). Formation of the trioxidation product (**33**) through mono-oxidized **49** could occur via steps similar to those postulated for formation of **33** via the dioxidation product. In this case, selectivity for Riley oxidation of intermediate **49** (leading to trioxidized **33**) instead of substrate **7**, which provides dioxidized **8**, could arise from

increased α-proton acidity of **49**. Given that Corey and Schaefer have demonstrated the rate-limiting step of Riley oxidation to be tautomerization,[29] this step should be faster for γ-hydroxy enone **49**, the α-proton of which is predicted to be six pK_a units more acidic than that of **7**.[30] As in dioxidation, allylic oxidation (i.e., γ-hydroxylation) is stereospecific and should retain substrate enantiopurity.

Table 3.8 *Stereochemical analysis of alternative trioxidation pathway*



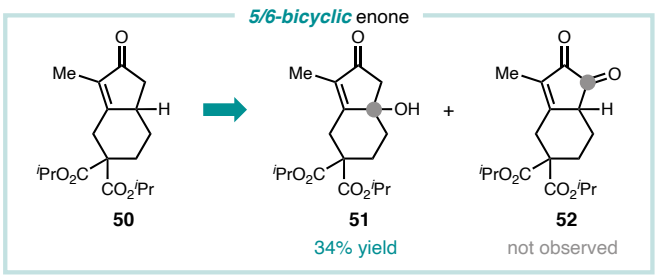
Entry	Reaction	Time (h)	ee (%)	Yield (%)
1	**7a*** → **49a***	1	>99 → 92	10
2	**49a*** → **33a***	3	92 → 92	1
3	**7a*** → **33a***	1	>99 → >99	15
4	**7a*** → **49a***	24	>99 → 36	2
5	**49a*** → **33a***	1	92 → 92	5
6	**7a*** → **33a***	24	>99 → 60	3

In support of hypothetical intermediate **49**, closely monitoring reactions of enantiopure enone **7a*** revealed the presence of several minor species in addition to di- and trioxidation products, each with a mass consistent with mono-oxidation. One such species was isolated and characterized as tertiary alcohol **49a***, which was formed with retention of ee in the absence of water (Table 3.8, entry 1). Subjection of **49a*** to

standard anhydrous conditions resulted in conversion to trioxidation product **33a*** with retention of enantiopurity (entry 2). Both transformations occurred in a timeframe similar to the overall reaction of substrate **7a*** to trioxidized **33a*** (entry 3). Taken together, these results demonstrate that γ-hydroxy enone **49a*** is a viable intermediate in the anhydrous formation of trioxidation product **33a***.

In contrast, mono-oxidation of **7a*** in the presence of water furnished putative intermediate **49a*** with significant erosion of ee (Table 3.8, entry 4). It is possible that enantioerosion occurs via dissociation of organoselenium intermediates during allylic oxidation which can generate planar species;[31] alternatively, reversible elimination of water from **49a*** would result in achiral alkene byproducts capable of unselective hydration to regenerate **49a***. Indeed, control experiments showed that **49a*** underwent slow loss of enantiopurity in the presence of both SeO_2 and H_2O. Subsequent treatment of isolated **49a*** with SeO_2/H_2O resulted in enantioretentive formation of trioxidized **33a*** (entry 5); altogether, kinetic and ee data are consistent with the intermediacy of **49a*** in the aqueous conversion of enone **7a*** to trioxidized **33a*** (entry 6). Furthermore, the several-day reaction time of this conversion may account for the apparent selectivity for dioxidation in the presence of water.

Figure 3.11 *Trioxidation of alternative ring system*



Given that the γ-hydroxylated intermediate (**49a***) was formed in low yields and

demonstrated poor conversion to **33a***, we searched for a mono-oxidized intermediate homologous to **49a*** arising from a more stable substrate. Although we were able to observe the mass of mono-oxidation products during reactions of several C4-γ-unsubstituted PKR products, isolation of these species remained evasive. Fortuitously, preliminary investigation of the trioxidation of additional ring systems uncovered alcohol **51** (Figure 3.11). Reaction of 5/6-fused bicyclopentenone **50** with anhydrous SeO_2 afforded γ-hydroxy enone **51** in 34% yield, a marked increase compared to **49a***. Our ability to cleanly isolate **51** without trace of the ene-diketone (**52**)—and the reluctance of **51** to advance to the corresponding trioxidation product—demonstrate that the 5/5-fused bicyclic system is unique in that disparate reactivities with SeO_2 are competitive processes.

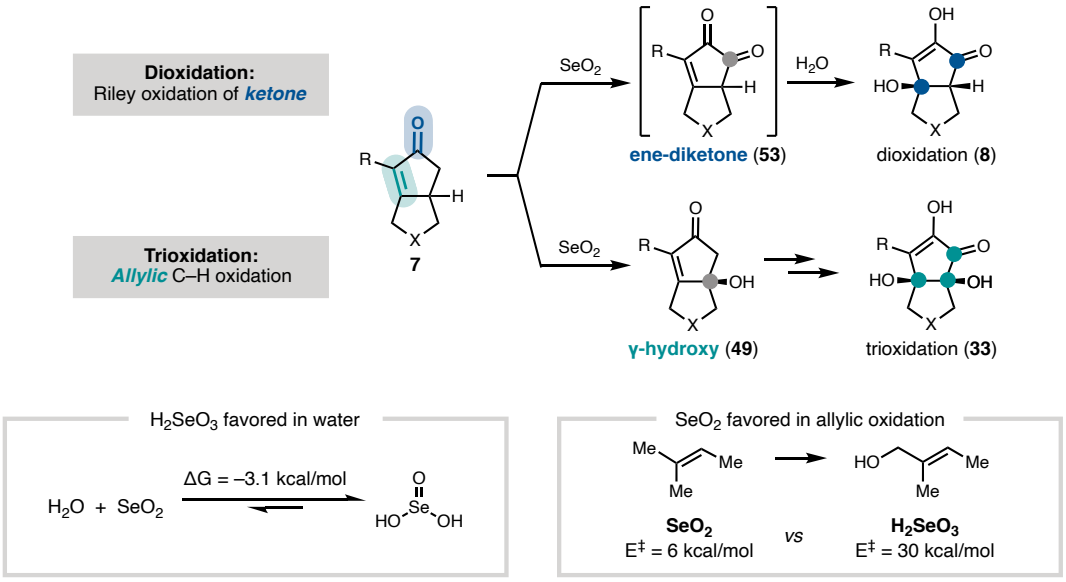
3.5.3 *Mechanistic Conclusion: Water-Dependent Product Distribution*

In conclusion, the distribution of dioxidized versus trioxidized products from the SeO_2-mediated reaction of a bicyclopentenone is based on partitioning between two dominant reactivities of SeO_2 (Figure 3.12). In the first, the enone substrate (**7**) behaves as a ketone and undergoes initial Riley oxidation by SeO_2 to generate a key intermediate ene-diketone (**53**), from which the dioxidation product (**8**) is selectively formed. In the second, SeO_2 preferentially performs allylic oxidation on the substrate alkene (**7**) to furnish a γ-hydroxy intermediate (**49**) that is then advanced to the trioxidation product (**33**). The product distribution is dependent on water because water influences how SeO_2 engages the substrate and thus which type of reactivity is more favorable.

When water is present, the equilibrium between SeO_2 and H_2SeO_3 lies toward

selenous acid;[32] however, kinetic isotope experiments have shown that SeO_2, as opposed to H_2SeO_3, is the energetically favored oxidizing species in the context of allylic oxidations.[33] Therefore, under aqueous conditions in which H_2SeO_3 is more abundant, allylic oxidation is less favored than Riley oxidation, and dioxidation is dominant. Conversely, the absence of water allows allylic oxidation by SeO_2 to be favored such that trioxidation occurs selectively.

Figure 3.12 *Effect of water on product distribution*

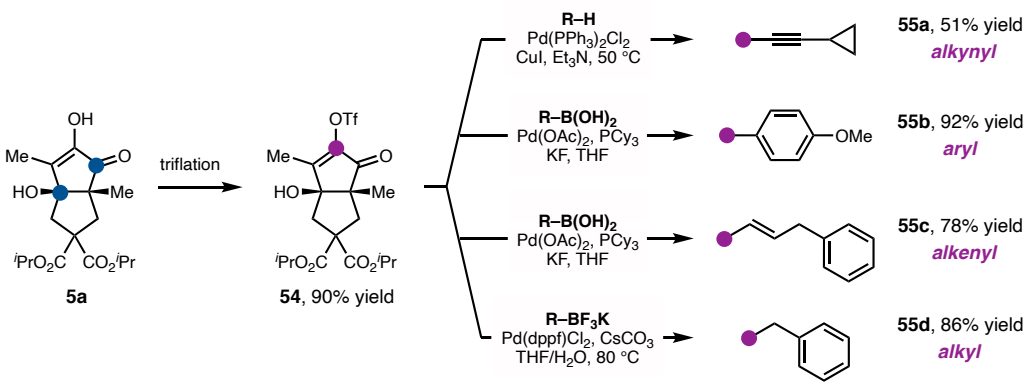


3.6 SYNTHETIC APPLICATIONS

A general advantage of using the developed SeO_2-mediated oxidative transpositions to access 4,5-fused bicyclopentenones is that the α-hydroxyenone functionality can be readily elaborated as a way to introduce additional complexity. As a representative example, Pd-catalyzed cross-coupling was used to demonstrate the synthetic utility of the dioxidation products. To this end, the enol triflate of **5a** was prepared in excellent yield (**54**, Figure 3.13). Although oxidative addition of α-hydroxy

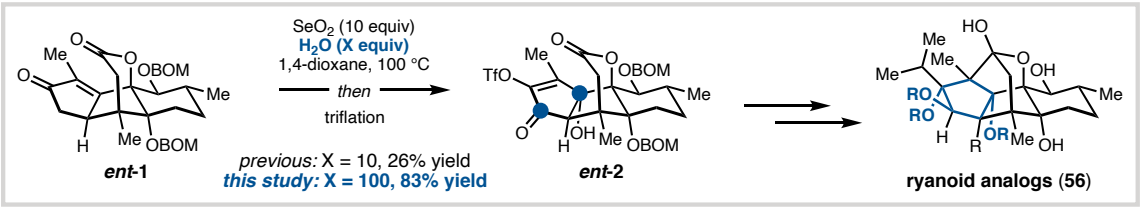
cyclopentenone triflates has previously been challenging for palladium catalysts,[34] subjection of **5a** to Sonogashira and Suzuki reactions with various coupling partners produced highly functionalized products **55a–d** in good to excellent yields.[34,35,36] Reaction with alkynyl, aryl, alkenyl, and alkyl partners demonstrates the ability to access fully substituted, diversely carbofunctionalized 4,5-fused bicyclopentenones.

Figure 3.13 *Functionalization of dioxidation product via cross-coupling*



Insight from the development of di- and trioxidation reactions on a general scaffold (e.g., 5/5-bicyclic **4a**) was found to be applicable to the ryanodane diterpene carbon skeleton (Figure 3.14). Whereas the previously reported conditions[5] provided moderate yields of dioxidized triflate ***ent*-2** from complex enone ***ent*-1**, use of the optimized aqueous reaction led to significant improvement in the yield of ***ent*-2** (83%). We thus expect our findings to facilitate preparation of ryanoid diterpenes analogs, as well as additional complex molecules featuring a 4,5-fused bicyclopentenone motif.

Figure 3.14 *Improved access to natural product analogs*



3.7 CONCLUDING REMARKS

In summary, we have developed SeO_2-mediated oxidative transpositions of the bicyclopentenone products of intramolecular PKRs. The highly oxidized 4,5-fused bicyclic enones accessed with this method would be otherwise challenging to prepare via canonical intermolecular PKRs. The 5/5-fused bicyclopentenone motif studied here also proved to be valuable as a unique platform for comparison of the various chemistries available to SeO_2. Kinetic and stereochemical analysis of the reactions, as well as investigation of potential intermediates, provided new insight into the disparate reactivity observed under aqueous or anhydrous conditions. Ultimately, mechanistic understanding enabled the development of an improved protocol that addressed limitations in the substrate scope. Notably, the di- and trioxidations enable the construction of transposed and highly functionalized PKR products that can be readily elaborated to complex intermediates pertinent to the synthesis of natural products.

3.8 EXPERIMENTAL SECTION

3.8.1 *Materials and Methods*

Unless otherwise stated, reactions were performed under a N_2 atmosphere with freshly dried solvents. Glassware was oven-dried at 120 °C for a minimum of four hours or flame-dried utilizing a Bunsen burner under high vacuum. Tetrahydrofuran (THF), methylene chloride (DCM), acetonitrile (MeCN), benzene (PhH), and toluene (PhMe) were dried by passing through activated alumina columns. Methanol (MeOH), HPLC grade, was purchased from Fisher Scientific. 1,4-dioxane, anhydrous ≥99.9%, was purchased from Millipore Sigma. Dichloroethane (DCE), triethylamine (Et_3N),

diisopropylamine ($^{i}Pr_2NH$), diisopropylethylamine (DIPEA), 2,6-lutidine, and *tert*-butanol ($^{t}BuOH$) were distilled from calcium hydride prior to use and stored under N_2. Unless otherwise stated, chemicals and reagents were used as received. Reactions were monitored by liquid chromatography mass spectroscopy (LCMS) or by thin layer chromatography (TLC) using EMD/Merck silica gel 60 F254 pre-coated plates (0.25 mm), visualized by UV (254 nm) and $KMnO_4$, *p*-anisaldehyde, iodine, or CAM staining. Flash column chromatography was performed using silica gel (SiliaFlash® P60, particle size 40-63 microns [230 to 400 mesh]) purchased from Silicycle. Optical rotations were measured on a Jasco P-2000 polarimeter using a 100 mm path-length cell at 589 nm. ^{1}H and ^{13}C NMR spectra were recorded on a Bruker Advance III HD with Prodigy Cryoprobe (at 400 MHz and 101 MHz, respectively) or Varian Inova 500 (at 500 MHz and 126 MHz, respectively) and are reported relative to internal $CDCl_3$ (^{1}H, δ = 7.26), CD_3OD (^{1}H, δ = 3.31), 1,4-dioxane-d_8 (^{1}H, δ = 3.53), $(CD_3)_2SO$ (^{1}H, δ = 2.50), or pyridine-d_4 (^{1}H, δ = 8.74) and $CDCl_3$ (^{13}C, δ = 77.16), CD_3OD (^{13}C, δ = 49.0), 1,4-dioxane-d_8 (^{13}C, δ = 66.66), $(CD_3)_2SO$ (^{13}C, δ = 39.51), or pyridine-d_4 (^{13}C, δ = 150.35). Data for ^{1}H NMR spectra are reported as follows: chemical shift (δ ppm) (multiplicity, coupling constant (Hz), integration). Multiplicity abbreviations are as follows: s = singlet, d = doublet, t = triplet, q = quartet, and m = multiplet. IR spectra were recorded on a Perkin Elmer Paragon 1000 spectrometer and are reported in frequency of absorption (cm^{-1}). Analytical chiral SFC was performed with a Mettler SFC supercritical CO_2 analytical chromatography system (CO_2 = 1450 psi, column temperature = 40 °C) with a Chiralcel OD–H column (4.6 mm x 25 cm). Preparative and analytical chiral HPLC was performed with an Agilent 1100 Series HPLC with a Chiralpak IH column (4.6 mm x 25

cm, Daicel Chemical Industries, Ltd.). HRMS were acquired using an Agilent 6200 Series TOF with an Agilent G1978A Multimode source in electrospray ionization (ESI) mode or obtained from the Caltech Mass Spectral Facility in fast-atom bombardment mode (FAB). Molecular formulas of the observed ion fragment of compounds are given (e.g., $[M + H]^+$). Optical rotations were measured on a Jasco P-2000 polarimeter using a 100 mm path-length cell at 589 nm.

3.8.2 *Substrate Preparation*

General Procedure A: To a round bottom flask with a stir bar was added NaH in a N_2-filled glovebox. The flask was sealed with a rubber septum, removed from the glovebox, and placed under an atmosphere of N_2. THF or DMF was then added and the mixture stirred at 0 °C. The substrate was then added dropwise, with a vent needle in place to ensure efficient release of hydrogen gas. The reaction was stirred at room temperature for 30 minutes then cooled to 0 °C where the alkyl bromide was added dropwise. The mixture was warmed to room temperature while stirring. Upon complete consumption of the substrate, the reaction was quenched by dropwise addition of sat. aq. NH_4Cl. The reaction was then diluted with water and Et_2O. The layers were separated and the aqueous layer extracted with Et_2O twice. Combined organics were washed with water and brine, dried over Na_2SO_4, filtered, and concentrated. The crude residue was purified by column chromatography to afford the desired product.

General Procedure B: To a round bottom flask with a stir bar was added $Pd(PPh_3)_2Cl_2$ and CuI in a N_2-filled glovebox. The flask was sealed with a rubber septum, removed from the glovebox, and placed under an atmosphere of N_2. The alkyne and aryl

halide were then added. The solids were taken up in amine and solvent and then stirred at the appropriate temperature. Upon complete consumption of the aryl halide, the reaction was warmed to room temperature and then diluted with EtOAc and water. The layers were separated and the aqueous layer extracted with EtOAc twice. Combined organics were washed with water and brine, dried over Na_2SO_4, filtered, and concentrated. The crude residue was purified by column chromatography to afford the desired product.

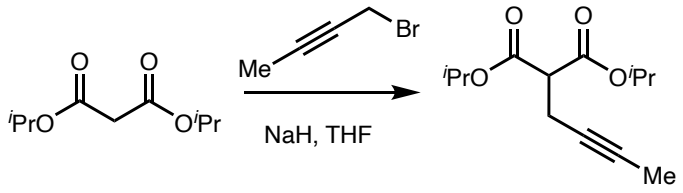
General Procedure C:[37] To a round bottom flask with a stir bar was added the enyne and placed under an atmosphere of N_2. Anhydrous solvent was added and the solution stirred at room temperature. $Co_2(CO)_8$ was added in one portion, and the reaction mixture was stirred for 1 h with a vent needle to allow efficient release of CO. **CAUTION:** all manipulations with CO should be performed in a well-ventilated fume hood. Upon complete consumption of the enyne as judged by TLC, anhydrous DMSO was added dropwise via syringe. The reaction mixture was then placed in a preheated oil bath and monitored by TLC. Upon complete consumption of the intermediate Co-alkyne complex, the reaction was allowed to reach room temperature and then diluted with EtOAc. Celite was added and the reaction mixture stirred overnight open to the air to sequester any Co species. The slurry was filtered over a pad of silica gel, washing with additional EtOAc. The filtrate was concentrated, and the crude residue was purified by column chromatography to afford the desired product. Note: initial elution with nonpolar solvent system is particularly important, as it washes away any remaining Co impurities that otherwise hamper purification.

General Procedure D:[38] To a round bottom flask with a stir bar was added $[Rh(CO)_2Cl]_2$ in a N_2-filled glovebox. The flask was sealed with a rubber septum,

removed from the glovebox, and placed under an atmosphere of N_2. The solid was taken up in *m*-xylene or PhMe and stirred, and the enyne was added via syringe. The solution was stirred at room temperature, sparged with dry N_2 and then dry CO successively for five minutes each, and was then kept under an atmosphere of CO via balloon. **CAUTION:** all manipulations with CO should be performed in a well-ventilated fume hood. At this time, the reaction was placed in a preheated oil bath at 120 °C and was stirred and monitored by TLC. Upon complete consumption of the enyne, the reaction was warmed to room temperature, and the CO was cautiously released into the fume hood. The reaction was concentrated, and the crude residue was purified by column chromatography to afford the desired product.

General Procedure E:[39] To a round bottom flask with a stir bar was added $Mo(CO)_3(DMF)_3$ in a glovebox. The flask was sealed with a rubber septum, removed from the glovebox, and placed under an atmosphere of N_2. The enyne was added as a solution in DCM, and the reaction was stirred at room temperature with a vent needle to allow efficient release of CO. Note: in the event of solvent evaporation, fresh DCM was added periodically. **CAUTION:** all manipulations with CO should be performed in a well-ventilated fume hood. Upon completion as judged by TLC, the reaction mixture was filtered over a pad of silica gel and celite, eluting with DCM. The filtrate was concentrated, and the crude residue was purified by column chromatography to afford the desired product.

diisopropyl 2-(but-2-yn-1-yl)malonate (57)



Prepared from diisopropyl malonate (11.4 mL, 60.0 mmol, 3.0 equiv), 1-bromobut-2-yne (1.75 mL, 20.0 mmol, 1.0 equiv), NaH (95%, 720 mg, 30.0 mmol, 1.5 equiv), and THF (60 mL, 0.33 M) following General Procedure A. The crude residue was purified by column chromatography (silica, 8 to 15% Et_2O/hexanes) to afford **57** (2.99 g, 63% yield) as a colorless oil.

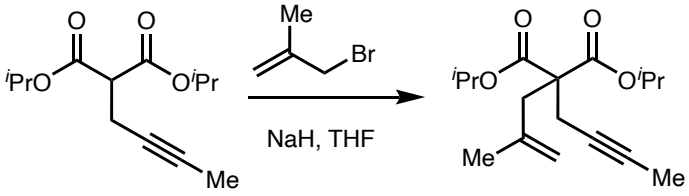
^{1}H NMR (500 MHz, CD_3Cl): δ 5.08 (hept, *J* = 6.2 Hz, 2H), 3.44 (t, *J* = 7.8 Hz, 1H), 2.69 (dq, *J* = 7.7, 2.5 Hz, 2H), 1.75 (t, *J* = 2.5 Hz, 3H), 1.26 (dd, *J* = 6.3, 4.3 Hz, 12H).

^{13}C NMR (126 MHz, $CDCl_3$): δ 167.98, 77.77, 74.96, 69.20, 52.15, 21.79, 21.69, 18.80, 3.60.

FTIR (NaCl, thin film, cm^{-1}): 3055, 2978, 2850, 1706, 1655, 1301, 1120, 1026, 907, 766, 696.

HRMS (TOF-ESI, *m/z*): $[M + H]^+$ calcd for $C_{13}H_{21}O_4$: 241.1434; found: 241.1439.

diisopropyl 2-(but-2-yn-1-yl)-2-(2-methylallyl)malonate (58)



Prepared from **57** (721 mg, 3.0 mmol, 1.0 equiv), methallyl bromide (0.34 mL, 3.3 mmol, 1.1 equiv), NaH (95%, 84.0 mg, 3.3 mmol, 1.1 equiv), and THF (6 mL, 0.50 M)

following General Procedure A. The crude, clear colorless oil of **58** was used without further purification (821 mg, 93% yield).

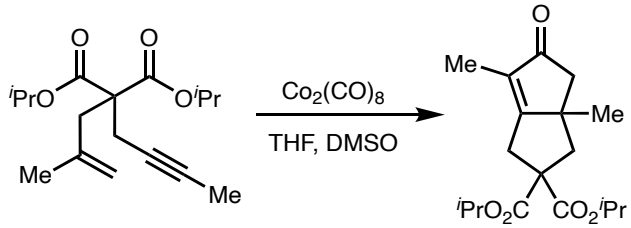
^{1}H NMR (500 MHz, $CDCl_3$): δ 5.05 (hept, *J* = 6.3 Hz, 2H), 4.88 (dt, *J* = 2.0, 1.5 Hz, 1H), 4.84 (dq, *J* = 1.8, 0.9 Hz, 1H), 2.79 (d, *J* = 0.9 Hz, 2H), 2.74 (q, *J* = 2.5 Hz, 2H), 1.78 – 1.72 (m, 3H), 1.69 (dd, *J* = 1.5, 0.8 Hz, 3H), 1.24 (dd, *J* = 6.3, 1.4 Hz, 12H).

^{13}C NMR (126 MHz, $CDCl_3$): δ 170.17, 140.58, 115.99, 78.87, 74.05, 69.06, 56.67, 39.39, 23.57, 23.03, 21.68, 3.59.

FTIR (NaCl, thin film, cm^{-1}): 3465, 3080, 2980, 2938, 1732, 1645, 1456, 1374, 1277.

HRMS (TOF-ESI, *m/z*): $[M + H]^+$ calcd for $C_{17}H_{27}O_4$: 295.1904; found: 295.1904.

diisopropyl 3a,6-dimethyl-5-oxo-3,3a,4,5-tetrahydropentalene-2,2(1H)-dicarboxylate (4a)



Prepared from **58** (2.95 g, 10.0 mmol, 1.0 equiv), $Co_2(CO)_8$ (3.77 g, 11.0 mmol, 1.1 equiv), DMSO (7.1 mL, 100.0 mmol, 10.0 equiv), and THF (100 mL, 0.10 M) following General Procedure C. The crude residue was purified by column chromatography (silica, 40 to 50% Et_2O/hexanes) to afford **4a** (3.06 g, 95% yield) as a white, glassy solid.

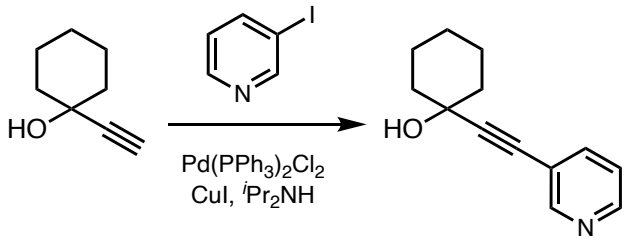
^{1}H NMR (500 MHz, $CDCl_3$): δ 5.10 (hept, *J* = 6.3 Hz, 1H), 5.00 (hept, *J* = 6.3 Hz, 1H), 3.34 (dq, *J* = 17.4, 1.9 Hz, 1H), 3.12 (d, *J* = 17.4 Hz, 1H), 2.55 (d, *J* = 13.6 Hz, 1H), 2.40 (d, *J* = 17.5 Hz, 1H), 2.34 (d, *J* = 17.5 Hz, 1H), 2.11 (d, *J* = 13.5 Hz, 1H), 1.70 (d, *J* = 1.7 Hz, 3H), 1.30 – 1.19 (m, 12H), 1.12 (s, 3H).

^{13}C NMR (126 MHz, $CDCl_3$): δ 209.55, 181.23, 171.41, 171.17, 131.63, 69.72, 69.68, 60.51, 51.23, 47.67, 44.74, 33.14, 26.76, 21.66, 21.64, 21.60, 21.57, 8.63.

FTIR (NaCl, thin film, cm^{-1}): 2981, 2934, 2874, 1727, 1714, 1677, 1375, 1262, 1183, 1104, 1064, 912.

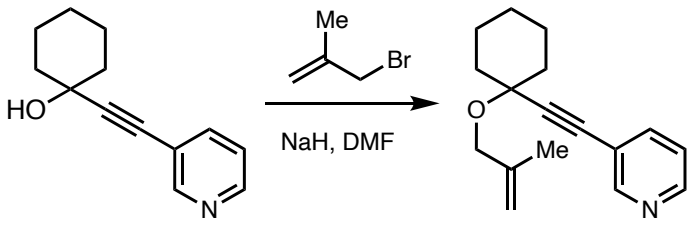
HRMS (TOF-ESI, *m/z*): $[M + H]^+$ calcd $C_{18}H_{27}O_5$: 323.1853; found: 323.1858.

3-((1-((2-methylallyl)oxy)cyclohexyl)ethynyl)pyridine (59)



Prepared from 1-ethynylcyclohexan-1-ol (1.49 g, 12.0 mmol, 1.2 equiv), 3-iodopyridine (2.05 g, 10.0 mmol, 1.0 equiv), $Pd(PPh_3)_2Cl_2$ (211 mg, 0.3 mmol, 0.03 equiv), CuI (58 mg, 0.30 mmol, 0.03 equiv), and $^{i}Pr_2NH$ (20 mL, 0.50 M) at 80 °C following General Procedure B. The crude residue was purified by column chromatography (silica, 55 to 65% EtOAc/hexanes) to afford **59** (2.00 g, >99% yield) as a tan, amorphous solid. Spectral data matched those reported in the literature.[40]

3-((1-((2-methylallyl)oxy)cyclohexyl)ethynyl)pyridine (60)



Prepared from **59** (1.01 g, 5.0 mmol, 1.0 equiv), methallyl bromide (0.56 mL, 5.5 mmol,

1.1 equiv), NaH (95%, 140 mg, 5.5 mmol, 1.1 equiv), and DMF (20 mL, 0.25 M) following General Procedure A. The crude, clear amber oil of **60** was used without further purification (1.23 g, 97% yield).

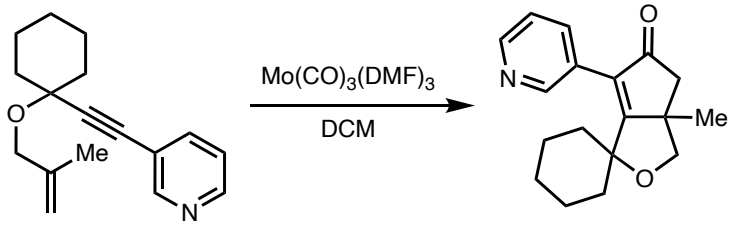
^{1}H NMR (400 MHz, $CDCl_3$): δ 8.61 (d, *J* = 55.6 Hz, 2H), 7.71 (dt, *J* = 7.9, 1.8 Hz, 1H), 7.24 (d, *J* = 7.9 Hz, 1H), 5.04 (dp, *J* = 1.9, 1.0 Hz, 1H), 4.88 (dp, *J* = 2.4, 1.1 Hz, 1H), 4.07 (d, *J* = 1.1 Hz, 2H), 2.00 (ddd, *J* = 12.0, 7.2, 4.5 Hz, 2H), 1.79 (t, *J* = 1.2 Hz, 3H), 1.72 (qt, *J* = 9.5, 2.5 Hz, 3H), 1.57 (dddt, *J* = 17.8, 11.5, 8.6, 3.5 Hz, 3H), 1.45 – 1.30 (m, 1H).

^{13}C NMR (101 MHz, $CDCl_3$): δ 152.51, 148.66, 143.07, 138.68, 123.11, 111.66, 94.60, 82.66, 74.23, 67.62, 37.28, 25.57, 22.96, 20.02.

FTIR (NaCl, thin film, cm^{-1}): 3077, 3029, 2935, 2857, 1656, 1560, 1475, 1448, 1406.

HRMS (TOF-ESI, *m/z*): $[M + H]^+$ calcd for $C_{17}H_{22}NO$: 256.1696; found: 256.1697.

3a'-methyl-6'-(pyridin-3-yl)-3a',4'-dihydrospiro[cyclohexane-1,1'-cyclopenta[*c*]furan]-5'(3'*H*)-one (4b)



Prepared from **60** (1.22 g, 4.8 mmol, 1.0 equiv) and $Mo(CO)_3(DMF)_3$ (2.10 g, 5.3 mmol, 1.1 equiv) following General Procedure E. The crude residue was purified by column chromatography (silica, 30 to 50% EtOAc/hexanes) to afford **4b** (241 mg, 18% yield) as a tan, amorphous solid.

^{1}H NMR (400 MHz, $CDCl_3$): δ 8.53 (dd, *J* = 4.9, 1.7 Hz, 1H), 8.45 (dd, *J* = 2.3, 0.9 Hz,

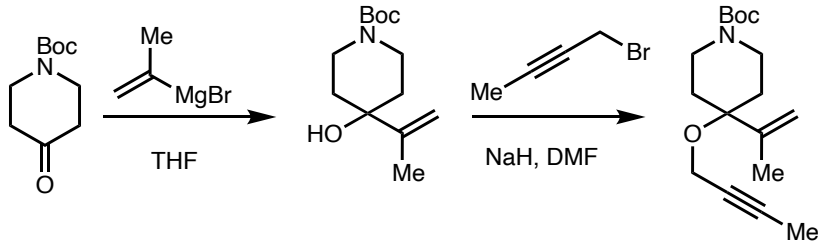
1H), 7.56 (dt, *J* = 7.8, 2.0 Hz, 1H), 7.28 (ddd, *J* = 7.8, 4.9, 0.9 Hz, 1H), 3.96 (d, *J* = 8.5 Hz, 1H), 3.48 (dd, *J* = 8.5, 0.9 Hz, 1H), 2.46 (d, *J* = 1.4 Hz, 2H), 2.17 (dp, *J* = 14.2, 2.7 Hz, 1H), 1.79 (td, *J* = 12.9, 4.8 Hz, 1H), 1.71 – 1.45 (m, 4H), 1.41 (s, 3H), 1.40 – 1.25 (m, 2H), 1.07 – 0.90 (m, 2H).

^{13}C NMR (101 MHz, $CDCl_3$): δ 207.28, 191.05, 149.86, 149.59, 136.91, 131.83, 127.70, 123.46, 81.04, 74.72, 50.50, 48.92, 38.56, 32.03, 26.20, 24.90, 22.02, 21.79.

FTIR (NaCl, thin film, cm^{-1}): 2934, 2855, 1710, 1652, 1447, 1411, 1117, 1015, 919, 734, 713.

HRMS (TOF-ESI, *m/z*): $[M + H]^+$ calcd for $C_{18}H_{22}NO_2$: 284.1645; found: 284.1642.

***tert*-butyl 4-(but-2-yn-1-yloxy)-4-(prop-1-en-2-yl)piperidine-1-carboxylate (61)**



Step 1: To a round bottom flask with a stir bar was added isopropenylmagnesium bromide (0.5 M in THF, 40.0 mL, 20.0 mmol, 2.0 equiv) and stirred at room temperature under an atmosphere of N_2. *N*-boc-piperidone (2.00 g, 10.0 mmol, 1.0 equiv) was then added as a solution in THF (27 mL, 0.15 M final), and the solution was stirred at room temperature and monitored by TLC. Upon complete consumption of the ketone, the reaction was quenched by slow dropwise addition of sat. aq. NH_4Cl, being careful not to cause vigorous propene gas evolution or exotherm. When propene evolution ceased, the reaction was diluted with water and EtOAc. The layers were separated and the aqueous

extracted twice with EtOAc. Combined organics were washed with water and brine, dried over Na_2SO_4, filtered, and concentrated.

Step 2: The crude oil (10.0 mmol, 1.0 equiv) was used directly in the next step, following General Procedure A with 1-bromobut-2-yne (1.1 mL, 12.5 mmol, 1.25 equiv), NaH (95%, 316 mg, 12.5 mmol, 1.25 equiv), and DMF (40 mL, 0.25 M). The crude oil was purified by column chromatography (silica, 15 to 25% Et_2O/hexanes) to afford **61** (1.64 g, 56% yield over 2 steps) as a colorless oil.

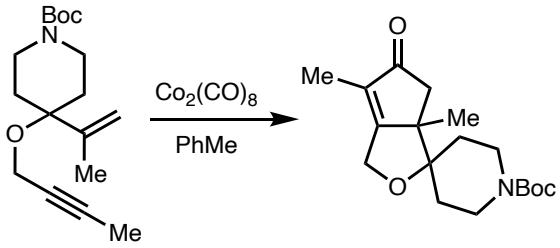
^{1}H NMR (500 MHz, $CDCl_3$): δ 5.04 (p, *J* = 1.4 Hz, 1H), 4.91 (t, *J* = 1.0 Hz, 1H), 3.99 – 3.72 (m, 4H), 3.18 (s, 2H), 1.93 – 1.84 (m, 2H), 1.84 (t, *J* = 2.4 Hz, 3H), 1.74 (dd, *J* = 1.4, 0.7 Hz, 3H), 1.63 – 1.53 (m, 2H), 1.45 (s, 9H).

^{13}C NMR (126 MHz, $CDCl_3$): δ 154.99, 146.69, 114.02, 81.64, 79.44, 77.03, 76.03, 50.94, 28.59, 18.23, 3.89.

FTIR (NaCl, thin film, cm^{-1}): 3495, 3364, 3091, 2927, 2318, 2241, 1958, 1822, 1689.

HRMS (TOF-ESI, *m/z*): $[M + H]^+$ calcd for $C_{17}H_{28}NO_3$: 294.2064; found: 294.2078.

***tert*-butyl 4,6a-dimethyl-5-oxo-3,5,6,6a-tetrahydrospiro[cyclopenta[*c*]furan-1,4'-piperidine]-1'-carboxylate (4c)**



Prepared from **61** (733 mg, 2.5 mmol, 1.0 equiv), $Co_2(CO)_8$ (941 mg, 2.75 mmol, 1.1 equiv), and PhMe (25 mL, 0.10 M) following modified General Procedure C without

addition of DMSO. Upon complete conversion of the enyne to the Co-alkyne complex, the reaction was placed in a preheated oil bath at 110 °C. Upon complete consumption of the Co-alkyne complex, the reaction was allowed to reach room temperature, filtered over a pad of SiO_2 and Celite, and the filtrate concentrated. The crude residue was purified by column chromatography (silica, 5 to 40% EtOAc/hexanes) to afford **4c** (494 mg, 62% yield) as an off-white, amorphous solid.

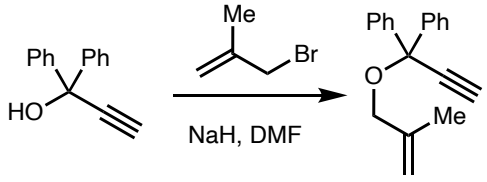
^{1}H NMR (400 MHz, $CDCl_3$): δ 4.64 (dq, *J* = 16.0, 1.7 Hz, 1H), 4.43 (d, *J* = 16.0 Hz, 1H), 4.14 – 3.82 (m, 2H), 3.01 (s, 2H), 2.34 (d, *J* = 17.7 Hz, 1H), 2.18 (d, *J* = 17.7 Hz, 1H), 1.85 – 1.74 (m, 1H), 1.70 (dd, *J* = 1.6, 1.0 Hz, 3H), 1.54 (td, *J* = 13.2, 5.3 Hz, 1H), 1.44 (s, 9H), 1.36 (dd, *J* = 12.7, 4.5 Hz, 1H), 1.29 – 1.19 (m, 1H), 1.18 (s, 3H).

^{13}C NMR (101 MHz, $CDCl_3$): δ 209.39, 180.68, 154.83, 130.62, 81.26, 79.66, 62.56, 52.62, 45.28, 31.68, 29.78, 28.56, 22.72, 8.74.

FTIR (NaCl, thin film, cm^{-1}): 3415, 2974, 2935, 1769, 1715, 1693, 1427, 1366, 1247, 1163, 1052, 737.

HRMS (TOF-ESI, *m/z*): $[M + H]^+$ calcd for $C_{18}H_{28}NO_4$: 322.2013; found: 322.2000.

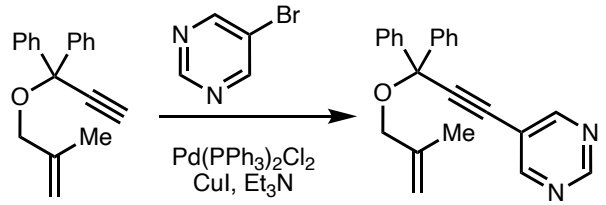
(1-((2-methylallyl)oxy)prop-2-yne-1,1-diyl)dibenzene (62)



Prepared from 1,1-diphenylprop-2-yn-1-ol (4.17 g, 20.0 mmol, 1.0 equiv), methallyl bromide (2.22 mL, 22.0 mmol, 1.1 equiv), NaH (95%, 556 mg, 22.0 mmol, 1.1 equiv), and DMF (80 mL, 0.25 M) following General Procedure A. The crude oil was purified by

column chromatography (silica, 1 to 3% Et_2O/hexanes) to afford **62** (4.69 g, 90% yield) as a yellow oil. Spectral data matched those reported in the literature.[41]

5-(3-((2-methylallyl)oxy)-3,3-diphenylprop-1-yn-1-yl)pyrimidine (63)



Prepared from **62** (374 mg, 1.42 mmol, 1.0 equiv), 5-bromopyrimidine (240 mg, 1.5 mmol, 1.05 equiv), $Pd(PPh_3)_2Cl_2$ (43 mg, 0.06 mmol, 0.04 equiv), CuI (11.5 mg, 0.06 mmol, 0.04 equiv), and Et_3N (6 mL, 0.25 M) at 50 °C following General Procedure B. The crude residue was purified by column chromatography (silica, 25 to 30% Et_2O/hexanes) to afford **63** (365 mg, 75% yield) as a yellow, amorphous solid.

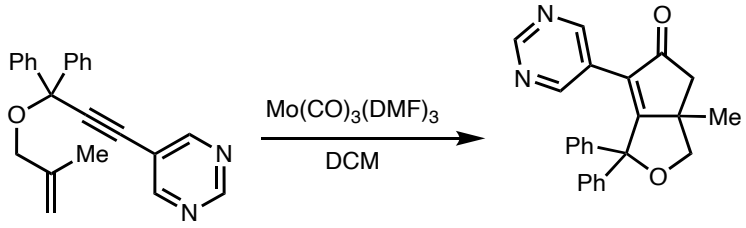
^{1}H NMR (400 MHz, $CDCl_3$): δ 9.17 (s, 1H), 8.85 (s, 2H), 7.64 – 7.56 (m, 4H), 7.40 – 7.32 (m, 4H), 7.34 – 7.25 (m, 2H), 5.12 (tp, *J* = 1.9, 0.9 Hz, 1H), 4.93 (dh, *J* = 2.6, 1.3 Hz, 1H), 3.97 (d, *J* = 1.5 Hz, 2H), 1.81 (dd, *J* = 1.5, 0.8 Hz, 3H).

^{13}C NMR (101 MHz, $CDCl_3$): δ 159.05, 157.30, 143.00, 142.24, 128.52, 128.13, 126.72, 119.29, 111.65, 96.49, 82.48, 80.69, 68.99, 20.13.

FTIR (NaCl, thin film, cm^{-1}): 3356, 3312, 2953, 2922, 2851, 2352, 2333, 1633, 1540, 1447, 1415, 1267.

HRMS (TOF-ESI, *m/z*): $[M + H]^+$ calcd for $C_{23}H_{21}N_2O$: 341.1648; found: 341.1653.

3a-methyl-1,1-diphenyl-6-(pyrimidin-5-yl)-3a,4-dihydro-1*H*-cyclopenta[*c*]furan-5(3*H*)-one (4d)



Prepared from **63** (340 mg, 1.0 mmol, 1.0 equiv) and $Mo(CO)_3(DMF)_3$ (401 mg, 1.0 mmol, 1.0 equiv) following General Procedure E. The crude residue was purified by column chromatography (silica, 30 to 60% EtOAc/hexanes) to afford **4d** (101 mg, 28% yield) as a light yellow, amorphous solid.

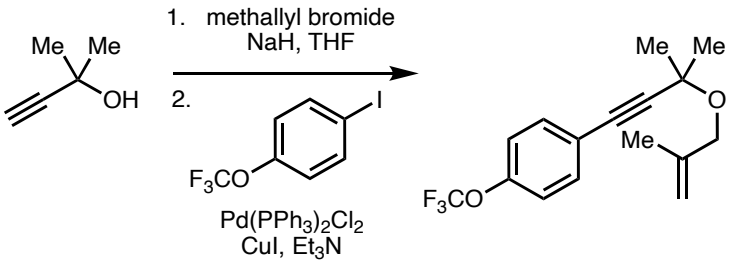
^{1}H NMR (400 MHz, $CDCl_3$): δ 8.92 (s, 1H), 8.22 (s, 2H), 7.50 – 7.37 (m, 5H), 7.07 – 6.93 (m, 3H), 6.84 – 6.76 (m, 2H), 4.39 (d, *J* = 8.2 Hz, 1H), 4.20 (dd, *J* = 8.1, 0.8 Hz, 1H), 2.81 (d, *J* = 17.7 Hz, 1H), 2.71 (d, *J* = 17.7 Hz, 1H), 1.31 (s, 3H).

^{13}C NMR (101 MHz, $CDCl_3$): δ 206.12, 187.62, 157.69, 156.30, 142.88, 141.70, 133.17, 128.77, 128.70, 128.27, 127.92, 127.76, 127.56, 124.55, 87.88, 78.83, 50.50, 49.64, 27.33.

FTIR (NaCl, thin film, cm^{-1}): 3055, 2969, 2926, 2858, 2362, 1715, 1548, 1447, 1413.

HRMS (TOF-ESI, *m/z*): $[M + H]^+$ calcd for $C_{24}H_{21}N_2O_2$: 369.1598; found: 369.1612.

1-(3-methyl-3-((2-methylallyl)oxy)but-1-yn-1-yl)-4-(trifluoromethoxy)benzene (64)



Step 1: Intermediate prepared from 2-methyl-3-butyn-2-ol (1.94 mL, 20.0 mmol, 1.0 equiv), methallyl bromide (2.22 mL, 22.0 mmol, 1.1 equiv), NaH (95%, 555 mg, 22.0 mmol, 1.1 equiv), and THF (80 mL, 0.25 M) following General Procedure A. The crude residue was purified by column chromatography (silica, 2 to 4% Et_2O/hexanes) to afford the desired intermediate as a clear colorless oil, which was left as a solution in hexanes to avoid product evaporation upon concentration.

Step 2: The intermediate (~690 mg in hexanes, ~5.0 mmol, 1.0 equiv) was then used directly in the next step, following General Procedure B with *p*-trifluoromethoxy-iodobenzene (0.79 mL, 5.0 mmol, 1.0 equiv), $Pd(PPh_3)_2Cl_2$ (141 mg, 0.2 mmol, 0.04 equiv), CuI (38.1 mg, 0.2 mmol, 0.04 equiv), and Et_3N (20 mL, 0.25 M). The crude oil was purified by column chromatography (silica, 2 to 3% Et_2O/hexanes) to afford **64** (799 mg, 54% yield over 2 steps) as a colorless oil.

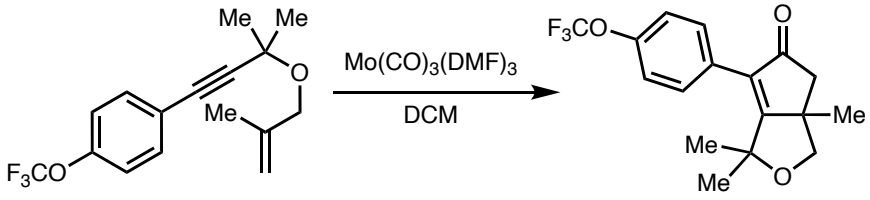
^{1}H NMR (400 MHz, $CDCl_3$): δ 7.48 – 7.40 (m, 2H), 7.15 (ddt, J = 7.7, 2.0, 1.0 Hz, 2H), 5.03 (dh, J = 2.2, 1.1 Hz, 1H), 4.88 (dqd, J = 2.4, 1.5, 0.8 Hz, 1H), 4.08 – 4.03 (m, 2H), 1.81 – 1.74 (m, 3H), 1.57 (s, 6H).

^{13}C NMR (101 MHz, $CDCl_3$): δ 148.98, 148.96, 143.00, 133.31, 120.50 (q, $^1J_{CF}$ = 160 Hz), 121.87, 120.96, 111.74, 92.63, 82.78, 70.90, 68.60, 28.96, 19.92.

FTIR (NaCl, thin film, cm^{-1}): 3437, 2984, 2935, 1726, 1608, 1507, 1264, 1219, 1162.

HRMS (TOF-ESI, *m/z*): $[M - C_4H_7O + H]^+$ calcd for $C_8H_5F_3O$: 227.0678; found: 227.0688.

1,1,3a-trimethyl-6-(4-(trifluoromethoxy)phenyl)-3a,4-dihydro-1*H*-cyclopenta[*c*]furan-5(3*H*)-one (4e)



Prepared from **64** (745 mg, 2.5 mmol, 1.0 equiv) and $Mo(CO)_3(DMF)_3$ (1.00 g, 2.5 mmol, 1.0 equiv) following General Procedure E. The crude residue was purified by column chromatography (silica, 30 to 35% EtOAc/hexanes). To remove residual [Mo] byproducts, the sample was taken up in 5 mL DCM, then 450 mg (0.2 mmol) TAAcONa capped silica gel (SiliCycle®) was added and the mixture stirred overnight. The mixture was then filtered and concentrated to afford **4e** (330 mg, 41% yield) as an off-white amorphous solid.

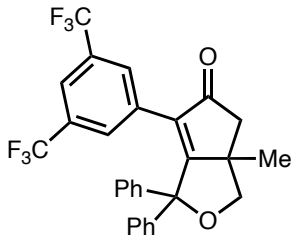
^{1}H NMR (400 MHz, $CDCl_3$): δ 7.31 – 7.23 (m, 2H), 7.23 – 7.15 (m, 2H), 3.95 (d, J = 8.4 Hz, 1H), 3.51 (dd, J = 8.5, 0.9 Hz, 1H), 2.48 (d, J = 1.0 Hz, 2H), 1.67 (s, 3H), 1.44 (s, 3H), 1.02 (s, 3H).

^{13}C NMR (101 MHz, $CDCl_3$): δ 207.17, 189.24, 149.40, 149.38, 149.36, 133.97, 130.81, 129.80, 120.54 (q, $^1J_{CF}$ = 258 Hz), 120.99, 79.23, 75.06, 50.63, 49.04, 29.60, 26.04, 25.13.

FTIR (NaCl, thin film, cm^{-1}): 2977, 2933, 2848, 1712, 1652, 1507, 1263, 1224, 1162.

HRMS (TOF-ESI, *m/z*): $[M + H]^+$ calcd for $C_{17}H_{18}F_3O_3$: 327.1203; found: 327.1203.

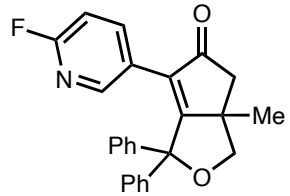
6-(3,5-bis(trifluoromethyl)phenyl)-3a-methyl-1,1-diphenyl-3a,4-dihydro-1*H*-cyclopenta[*c*]furan-5(3*H*)-one (4f)



^{1}H NMR (400 MHz, $CDCl_3$): δ 7.61 (tt, *J* = 1.6, 0.8 Hz, 1H), 7.50 – 7.37 (m, 5H), 7.30 (d, *J* = 1.8 Hz, 2H), 7.00 – 6.93 (m, 1H), 6.93 – 6.84 (m, 2H), 6.75 – 6.67 (m, 2H), 4.39 (d, *J* = 8.2 Hz, 1H), 4.23 – 4.16 (m, 1H), 2.81 (d, *J* = 17.6 Hz, 1H), 2.71 (d, *J* = 17.7 Hz, 1H), 1.32 (s, 3H).

^{13}C NMR (101 MHz, $CDCl_3$): δ 206.16, 186.80, 142.83, 141.75, 136.76, 132.24, 131.50, 131.17, 130.84, 129.29, 128.66, 128.08, 127.68, 127.60, 127.52, 124.44, 121.90, 121.72, 87.88, 78.76, 50.27, 49.67, 27.29.

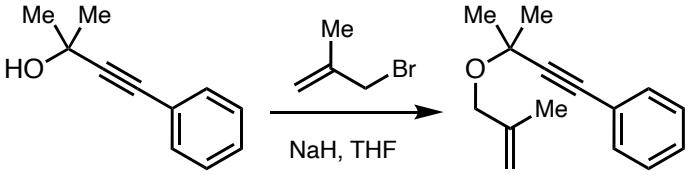
6-(6-fluoropyridin-3-yl)-3a-methyl-1,1-diphenyl-3a,4-dihydro-1*H*-cyclopenta[*c*]furan-5(3*H*)-one (4g)



^{1}H NMR (400 MHz, $CDCl_3$): δ 7.81 (dt, *J* = 2.5, 0.8 Hz, 1H), 7.46 – 7.35 (m, 5H), 7.17 (ddd, *J* = 8.5, 7.6, 2.5 Hz, 1H), 7.06 – 6.93 (m, 3H), 6.84 – 6.76 (m, 2H), 6.59 (ddd, *J* = 8.4, 3.0, 0.7 Hz, 1H), 4.37 (d, *J* = 8.1 Hz, 1H), 4.17 (dd, *J* = 8.2, 0.8 Hz, 1H), 2.77 (d, *J* = 17.7 Hz, 1H), 2.68 (d, *J* = 17.6 Hz, 1H), 1.31 (s, 3H).

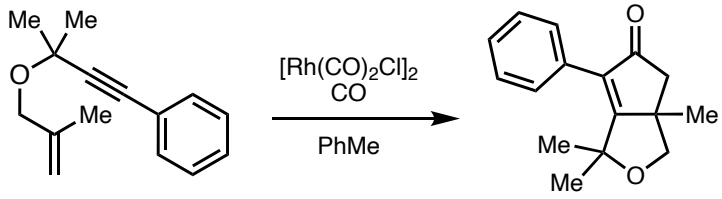
^{13}C NMR (101 MHz, $CDCl_3$): δ 206.84, 186.03, 164.27, 161.87, 147.82, 147.67, 143.10, 142.03, 141.57, 141.49, 135.07, 128.66, 128.57, 127.93, 127.80, 127.71, 127.68, 124.09, 124.04, 108.79, 108.42, 87.95, 78.79, 50.28, 49.55, 27.34.

(3-methyl-3-((2-methylallyl)oxy)but-1-yn-1-yl)benzene (65)



Prepared from 2-methyl-4-phenylbut-3yn-2-ol (270 mg, 1.7 mmol, 1.0 equiv), methallyl bromide (0.3 mL, 3.4 mmol, 2.0 equiv), NaH (95%, 53.2 mg, 2.1 mmol, 1.25 equiv), and THF (3.4 mL, 0.50 M) following General Procedure A. The crude residue was purified by column chromatography (silica, 0 to 10% EtOAc/hexanes) to afford **65** (127 mg, 35% yield) as a white powder. Spectral data matched those reported in the literature.[42]

1,1,3a-trimethyl-6-phenyl-3a,4-dihydro-1*H*-cyclopenta[*c*]furan-5(3*H*)-one (4h)



Prepared from **65** (60 mg, 0.28 mmol, 1.0 equiv), $[Rh(CO)_2Cl]_2$ (10.9 mg, 0.03 mmol, 0.1 equiv), and PhMe (1.4 mL, 0.20 M) following General Procedure D. The crude residue was purified by column chromatography (silica, 7% EtOAc/hexanes) to afford **4h** (21.7 mg, 32% yield) as a white powder.

^{1}H NMR (400 MHz, 1,4-dioxane-*d*$_8$): δ 7.23 – 7.00 (m, 5H), 3.66 (d, *J* = 8.3 Hz, 1H),

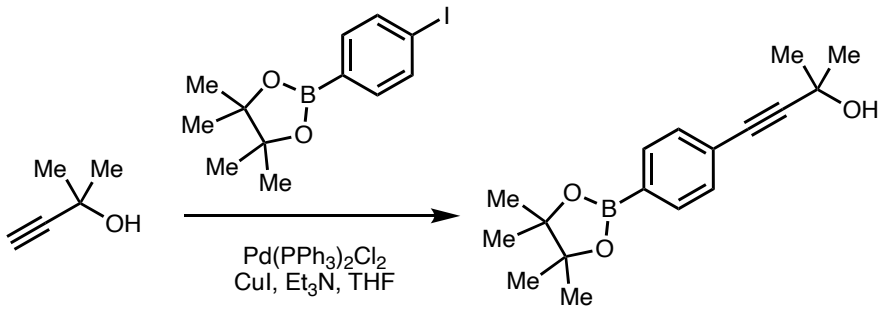
3.25 (d, *J* = 8.3 Hz, 1H), 2.23 (q, *J* = 16.9 Hz, 2H), 1.46 (s, 3H), 1.21 (s, 3H), 0.77 (s, 3H).

^{13}C NMR (101 MHz, 1,4-dioxane-*d*$_8$): δ 206.54, 188.15, 135.69, 132.59, 130.11, 129.02, 128.94, 79.53, 75.42, 50.96, 49.25, 29.93, 26.00, 25.20.

FTIR (NaCl, thin film, cm^{-1}): 2974, 2928, 2852, 1713, 1652, 1235, 1137, 1018, 699.

HRMS (TOF-ESI, *m/z*): $[M + H]^+$ calcd for $C_{16}H_{19}O_2$: 243.1380; found: 243.1385.

2-methyl-4-(4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl)but-3-yn-2-ol (66)



Prepared from 2-methylbut-3-yn-2-ol (0.12 mL, 1.2 mmol, 1.0 equiv), 4-iodophenylboronic acid pinacol ester (450 mg, 1.4 mmol, 1.1 equiv), $Pd(PPh_3)_2Cl_2$ (8.7 mg, 0.012 mmol, 0.01 equiv), CuI (4.7 mg, 0.025 mmol, 0.02 equiv), and Et_3N (0.52 mL, 3.7 mmol, 3.0 equiv), and THF (1.2 mL, 1.00 M) following General Procedure B. The crude residue was purified by column chromatography (silica, 0 to 20% Et_2O/hexanes) to afford **66** (355 mg, 73% yield) as a pale yellow powder.

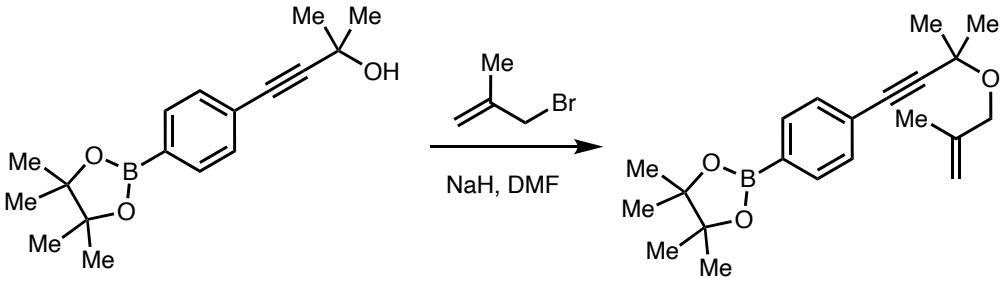
^{1}H NMR (400 MHz, $CDCl_3$): δ 7.77 – 7.70 (m, 2H), 7.44 – 7.37 (m, 2H), 1.62 (s, 6H), 1.34 (s, 12H).

^{13}C NMR (101 MHz, $CDCl_3$): δ 134.64, 130.96, 125.54, 114.80, 95.13, 84.11, 82.45, 65.81, 31.60, 25.03.

FTIR (NaCl, thin film, cm^{-1}): 3390, 2981, 2933, 1608, 1393, 1364, 1146, 1088, 963, 858, 658.

HRMS (TOF-ESI, *m/z*): $[M - H_2O + H]^+$ calcd for $C_{17}H_{22}BO_2$: 268.1744; found: 268.1743.

4,4,5,5-tetramethyl-2-(4-(3-methyl-3-((2-methylallyl)oxy)but-1-yn-1-yl)phenyl)-1,3,2-dioxaborolane (67)



Prepared **66** (242 mg, 0.7 mmol, 1.0 equiv), methallyl bromide (0.7 mL, 1.7 mmol, 2.5 equiv), NaH (95%, 32 mg, 1.3 mmol, 1.9 equiv), and DMF (3.4 mL, 0.20 M) following General Procedure A. The crude residue was purified by column chromatography (silica, 0 to 20% EtOAc/hexanes) to afford **67** (75 mg, 33% yield) as a yellow powder.

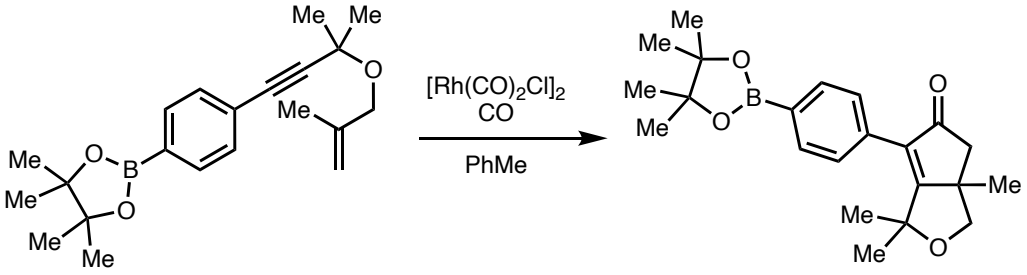
^{1}H NMR (400 MHz, $CDCl_3$): δ 7.77 – 7.70 (m, 2H), 7.44 – 7.37 (m, 2H), 5.05 – 5.00 (m, 1H), 4.90 – 4.84 (m, 1H), 4.07 (s, 2H), 1.81 – 1.76 (m, 3H), 1.57 (s, 6H), 1.34 (s, 12H).

^{13}C NMR (101 MHz, $CDCl_3$): δ 143.14, 134.65, 130.96, 125.77, 111.72, 93.02, 84.34, 84.10, 70.98, 68.61, 29.02, 25.02, 19.94.

FTIR (NaCl, thin film, cm^{-1}): 2981, 2931, 2856, 1608, 1398, 1360, 1323, 1144, 1089.

HRMS (TOF-ESI, *m/z*): $[M - C_4H_7O + H]^+$ calcd for $C_{17}H_{23}BO_2$: 268.1744; found: 268.1741.

1,1,3a-trimethyl-6-(4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl)-3a,4-dihydro-1*H*-cyclopenta[*c*]furan-5(3*H*)-one (68)



Prepared from **67** (75.4 mg, 0.22 mmol), $[Rh(CO)_2Cl]_2$ (8.6 mg, 0.022 mmol, 0.1 equiv), and PhMe (1.1 mL, 0.20 M), following General Procedure D. The crude residue was purified by column chromatography (silica, 7% EtOAc/hexanes) to yield **68** (25.1 mg, 31% yield) as an off-white powder.

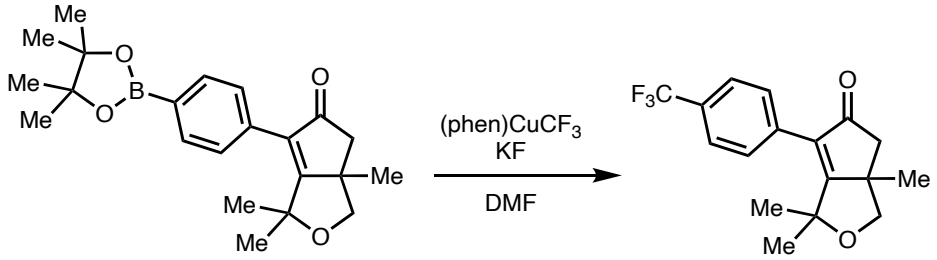
^{1}H NMR (400 MHz, $CDCl_3$): δ 7.83 – 7.77 (m, 2H), 7.28 – 7.22 (m, 2H), 3.97 (d, *J* = 8.4 Hz, 1H), 3.53 (d, *J* = 8.4 Hz, 1H), 2.50 (s, 2H), 1.69 (s, 3H), 1.46 (s, 3H), 1.32 (s, 12H), 1.01 (s, 3H).

^{13}C NMR (101 MHz, $CDCl_3$): δ 207.10, 188.65, 135.30, 134.74, 133.86, 128.44, 83.93, 79.26, 75.01, 50.40, 49.09, 29.47, 25.90, 24.99, 24.93, 24.88, 24.84, 14.22 (C_{Ar}–B not observed).

FTIR (NaCl, thin film, cm^{-1}): 2978, 2927, 2850, 1711, 1610, 1399, 1360, 1144, 1088.

HRMS (TOF-ESI, *m/z*): $[M + H]^+$ calcd for $C_{22}H_{30}BO_4$: 368.2268; found: 368.2278.

1,1,3a-trimethyl-6-(4-(trifluoromethyl)phenyl)-3a,4-dihydro-1*H*-cyclopenta[*c*]furan-5(3*H*)-one (4i)



Prepared from **68** (60.0 mg, 0.16 mmol, 1.0 equiv), (phen)$CuCF_3$ (61.1 mg, 0.2 mmol, 1.25 equiv), KF (9.46 mg, 0.16 mmol, 1.0 equiv), and DMF (1.63 mL, 0.10 M) at 100 °C following a literature procedure.[43] The crude residue was purified by column chromatography (silica, 0 to 20% EtOAc/hex) to yield **4i** (24.5 mg, 48% yield) as an off-white powder.

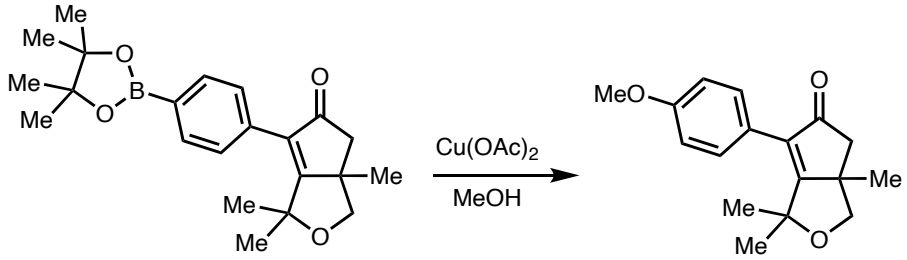
^{1}H NMR (400 MHz, 1,4-dioxane-*d*$_8$): δ 7.50 (d, *J* = 8.1 Hz, 2H), 7.24 (d, *J* = 8.1 Hz, 2H), 3.69 (d, *J* = 8.3 Hz, 1H), 3.28 (d, *J* = 8.4 Hz, 1H), 2.26 (q, *J* = 17.0 Hz, 2H), 1.47 (s, 3H), 1.22 (s, 3H), 0.78 (s, 3H).

^{13}C NMR (101 MHz, 1,4-dioxane-*d*$_8$): δ 206.01, 190.02, 136.45, 134.54, 130.69 (q, $^2J_{CF}$ = 32 Hz), 130.58, 126.05 (q, $^3J_{CF}$ = 4 Hz), 125.24 (q, $^1J_{CF}$ = 272 Hz), 79.53, 75.32, 51.30, 49.20, 29.75, 25.92, 25.36.

FTIR (NaCl, thin film, cm^{-1}): 2977, 2933, 2851, 1712, 1325, 1163, 1127, 1067, 1018.

HRMS (TOF-ESI, *m/z*): $[M + H]^+$ calcd for $C_{17}H_{19}F_3O_2$: 311.1253; found: 311.1258.

6-(4-methoxyphenyl)-1,1,3a-trimethyl-3a,4-dihydro-1*H*-cyclopenta[*c*]furan-5(3*H*)-one (4j)



Prepared from **68** (60 mg, 0.16 mmol, 1.0 equiv), $Cu(OAc)_2$ (3.0 mg, 0.016 mmol, 0.1 equiv), MeOH (0.8 mL, 0.20 M), and a balloon of O_2 following a literature procedure.[44] The crude residue was purified by column chromatography (silica, 0 to 20% EtOAc/hexanes) to yield **4j** (17 mg, 39% yield) as an off-white powder.

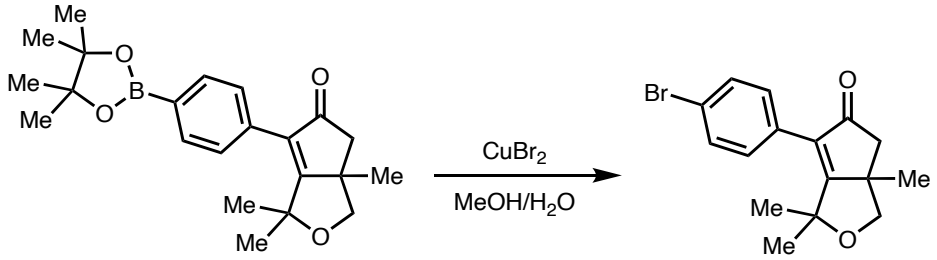
^{1}H NMR (400 MHz, 1,4-dioxane-*d*$_8$): δ 7.05 – 6.97 (m, 2H), 6.75 – 6.66 (m, 2H), 3.65 (d, *J* = 8.2 Hz, 1H), 3.23 (d, *J* = 8.1 Hz, 1H), 2.24 – 2.11 (m, 2H), 1.46 (s, 3H), 1.19 (s, 3H), 0.80 (s, 3H).

^{13}C NMR (101 MHz, 1,4-dioxane-*d*$_8$): δ 207.02, 186.72, 160.67, 135.20, 131.32, 124.68, 114.38, 79.53, 75.48, 55.34, 50.79, 49.16, 29.97, 26.03, 25.04.

FTIR (NaCl, thin film, cm^{-1}): 2974, 2934, 2852, 2342, 1706, 1512, 1249, 1018, 1031.

HRMS (TOF-ESI, *m/z*): $[M + H]^+$ calcd for $C_{17}H_{21}O_3$: 273.1485; found: 273.1498.

6-(4-bromophenyl)-1,1,3a-trimethyl-3a,4-dihydro-1*H*-cyclopenta[*c*]furan-5(3*H*)-one (4k)



Prepared from **68** (54 mg, 0.15 mmol, 1.0 equiv), $CuBr_2$ (32.7 mg, 0.15 mmol, 1.0 equiv), MeOH (1.8 mL, 0.04 M), and H_2O (1.8 mL, 0.04 M) at 100 °C following a literature procedure.[45] The crude residue was purified by column chromatography (silica, 0 to 20% EtOAc/hexanes) to yield **4k** (26.8 mg, 57% yield) as an off-white powder.

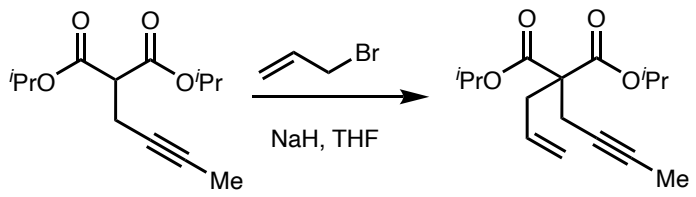
^{1}H NMR (400 MHz, 1,4-dioxane-*d*$_8$): δ 7.40 – 7.30 (m, 2H), 7.05 – 6.95 (m, 2H), 3.67 (d, *J* = 8.3 Hz, 1H), 3.25 (d, *J* = 8.3 Hz, 1H), 2.30 – 2.14 (m, 2H), 1.45 (s, 3H), 1.20 (s, 3H), 0.79 (s, 3H).

^{13}C NMR (101 MHz, 1,4-dioxane-*d*$_8$): δ 206.21, 188.84, 134.61, 132.28, 131.83, 131.52, 123.11, 79.52, 75.35, 51.12, 49.15, 29.82, 25.93, 25.22.

FTIR (NaCl, thin film, cm^{-1}): 2974, 2928, 2849, 1708, 1487, 1234, 1013.

HRMS (TOF-ESI, *m/z*): $[M + H]^+$ calcd for $C_{16}H_{18}BrO_2$: 321.0485; found: 321.0475.

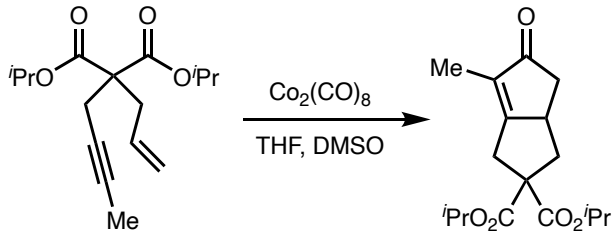
diisopropyl 2-allyl-2-(but-2-yn-1-yl)malonate (69)



Prepared from **57** (1.44 g, 6.0 mmol, 1.0 equiv), allyl bromide (0.55 mL, 6.3 mmol, 1.05

equiv), NaH (95%, 173 mg, 7.2 mmol, 1.2 equiv), and THF (15 mL, 0.40 M) following General Procedure A. The crude oil was purified by column chromatography (silica, 7 to 10% Et_2O/hexanes) to afford **69** (1.63 g, 97% yield) as a colorless oil. Spectral data matched those reported in the literature.[46]

diisopropyl 6-methyl-5-oxo-3,3a,4,5-tetrahydropentalene-2,2(1H)-dicarboxylate (7a)



Prepared from **69** (1.40 g, 5.0 mmol, 1.0 equiv), $Co_2(CO)_8$ (2.06 g, 6.0 mmol, 1.2 equiv), and THF (50 mL, 0.10 M) following General Procedure C. The crude residue was purified by column chromatography (silica, 10 to 60% Et_2O/hexanes) to afford **7a** (1.30 g, 85% yield) as a white powder.

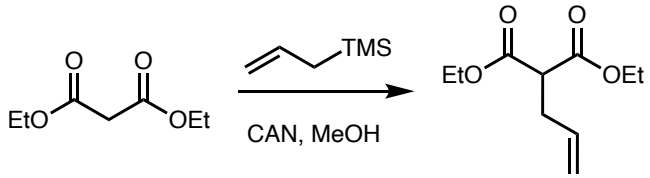
^{1}H NMR (400 MHz, CD_3OD): δ 5.04 (dhept, *J* = 20.8, 6.3 Hz, 2H), 3.19 (dt, *J* = 2.5, 1.5 Hz, 2H), 3.05 – 2.95 (m, 1H), 2.72 (dd, *J* = 12.7, 7.6 Hz, 1H), 2.61 (dd, *J* = 18.0, 6.2 Hz, 1H), 2.16 – 2.06 (m, 1H), 1.69 (dt, *J* = 2.5, 1.3 Hz, 3H), 1.64 (t, *J* = 12.5 Hz, 1H), 1.27 (d, *J* = 6.3 Hz, 6H), 1.24 (dd, *J* = 6.3, 3.7 Hz, 6H).

^{13}C NMR (101 MHz, $CDCl_3$): δ 209.80, 178.32, 171.41, 170.79, 133.14, 69.77, 69.68, 61.28, 42.90, 41.66, 39.32, 34.19, 21.77, 8.81.

FTIR (NaCl, thin film, cm^{-1}): 2981, 2924, 1728, 1714, 1678, 1455, 1375, 1271, 911.

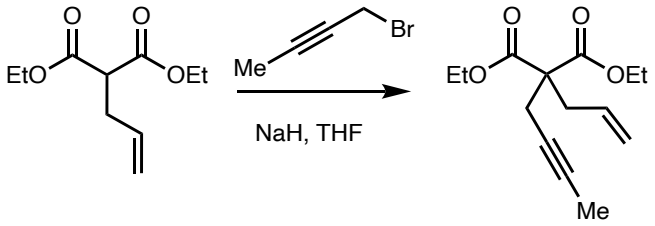
HRMS (TOF-ESI, *m/z*): $[M + H]^+$ calcd for $C_{17}H_{25}O_5$: 309.1697; found: 309.1684.

diethyl 2-allylmalonate (70)



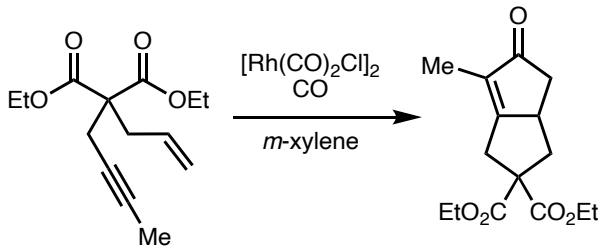
Prepared from diethylmalonate (2.29 mL, 15.0 mmol, 1.0 equiv) following a published procedure.[47] The crude oil was purified by column chromatography (silica, 15% Et_2O/hexanes) to afford **70** (1.70 g, 57% yield) as a colorless oil. Spectral data matched those reported in the literature.[47]

diethyl 2-allyl-2-(but-2-yn-1-yl)malonate (71)



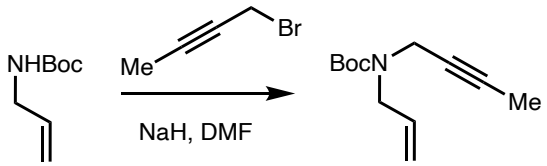
Prepared from **70** (1.00 g, 5.0 mmol, 1.0 equiv), 1-bromobut-2-yne (0.44 mL, 5.0 mmol, 1.0 equiv), NaH (60% in mineral oil, 240 mg, 6.0 mmol, 1.2 equiv), and THF (10 mL, 0.50 M) following General Procedure A. The crude residue was purified by column chromatography (12% Et_2O/hexanes) to afford **71** (1.12 g, 89% yield) as a colorless oil. Spectral data matched those reported in the literature.[48]

diethyl 6-methyl-5-oxo-3,3a,4,5-tetrahydropentalene-2,2(1*H*)-dicarboxylate (7b)



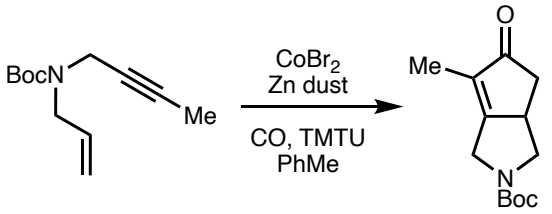
Prepared from **71** (504 mg, 2.0 mmol, 1.0 equiv), $[Rh(CO)_2Cl]_2$ (78.0 mg, 0.2 mmol, 0.1 equiv), and *m*-xylene (20 mL, 0.10 M) following General Procedure D. The crude residue was purified by column chromatography (silica, 30% EtOAc/hexanes) to afford **7b** (438 mg, 79% yield) as an off-white powder. Spectral data matched those reported in the literature.[49]

***tert*-butyl allyl(but-2-yn-1-yl)carbamate (72)**



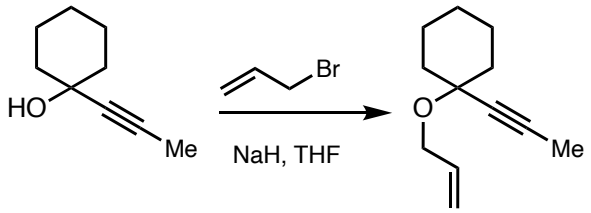
Prepared from *tert*-butyl allylcarbamate (786 mg, 5.0 mmol, 1.0 equiv), 1-bromobut-2-yne (0.44 mL, 5.0 mmol, 1.0 equiv), NaH (95%, 168 mg, 7.0 mmol, 1.4 equiv), and DMF (20 mL, 0.25 M) following General Procedure A. The crude residue of **72** was used in the next step without further purification (881 mg, 85% yield). Spectral data matched those reported in the literature.[50]

tert-butyl 6-methyl-5-oxo-3,3a,4,5-tetrahydrocyclopenta[*c*]pyrrole-2(1*H*)-carboxylate (7c)



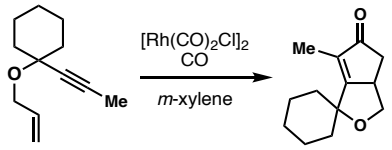
To a vial with a stir bar was added $CoBr_2$ (22 mg, 0.1 mmol, 0.1 equiv) in a glovebox. The flask was sealed with a rubber septum, removed from the glovebox, and placed under an atmosphere of dry CO via balloon. **CAUTION:** all manipulations with CO should be performed in a well-ventilated fume hood. Zinc dust (131 mg, 2.0 mmol, 2.0 equiv) and tetramethyltiourea (80 mg, 0.6 mmol, 0.6 equiv) were then added and the solids taken up in PhMe (20 mL, 0.50 M) and stirred. The solution was degassed with CO for 5 min and the reaction kept under an atmosphere of CO following addition of **72** (295 mg, 1.0 mmol, 1.0 equiv). The reaction was brought to 70 °C in a preheated oil bath and monitored by TLC. Upon complete consumption of the enyne (typically indicated by a color change from deep green to light turquoise green or colorless), the reaction mixture was filtered over a pad of silica gel and celite, eluting with EtOAc. The filtrate was concentrated, and the crude residue was purified by column chromatography (silica, 30 to 40% EtOAc/hexanes) to afford **7c** (165 mg, 70% yield) as an off-white, amorphous solid. Spectral data matched those reported in the literature.[50]

1-(allyloxy)-1-(prop-1-yn-1-yl)cyclohexane (73)



Prepared from 1-(prop-1-yn-1-yl)cyclohexan-1-ol (1.39 g, 10.0 mmol, 1.0 equiv), allyl bromide (1.73 mL, 20.0 mmol, 2.0 equiv), NaH (95%, 360 mg, 15.0 mmol, 1.5 equiv), and THF (20 mL, 0.50 M) following General Procedure A. The crude oil was purified by column chromatography (silica, 2 to 5% Et_2O/hexanes) to afford **73** (914 mg, 52% yield) as a colorless oil. Spectral data matched those reported in the literature.[51]

6'-methyl-3a',4'-dihydrospiro[cyclohexane-1,1'-cyclopenta[*c*]furan]-5'(3'*H*)-one (7d)



Prepared from **73** (446 mg, 2.5 mmol, 1.0 equiv), $[Rh(CO)_2Cl]_2$ (73 mg, 0.19 mmol, 0.75 equiv), and *m*-xylene (12.5 mL, 0.20 M) following General Procedure D. The crude oil was purified by column chromatography (silica, 20 to 30% EtOAc/hexanes) to afford **7d** (27 mg, 68% yield) as a clear yellow oil.

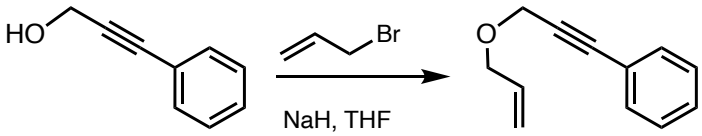
^{1}H NMR (500 MHz, $CDCl_3$): δ 4.29 – 4.17 (m, 1H), 3.28 – 3.17 (m, 3H), 2.58 (dd, *J* = 17.6, 5.9 Hz, 1H), 2.09 (dd, *J* = 17.5, 3.5 Hz, 1H), 1.79 (d, *J* = 2.2 Hz, 4H), 1.76 (ddt, *J* = 11.5, 6.5, 2.5 Hz, 2H), 1.72 – 1.59 (m, 6H), 1.33 – 1.19 (m, 1H).

^{13}C NMR (126 MHz, $CDCl_3$): δ 210.00, 182.70, 130.57, 79.72, 69.77, 44.10, 38.61, 35.28, 32.22, 25.40, 22.19, 21.58, 8.36.

FTIR (NaCl, thin film, cm^{-1}): 3412, 2924, 2856, 1698, 1682, 1446, 1269, 1058, 1024, 917, 840, 738, 665.

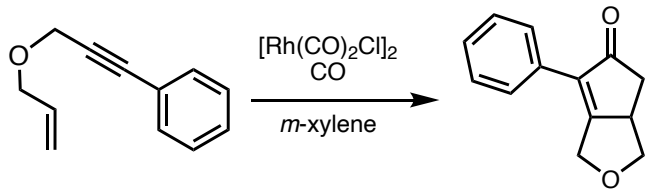
HRMS (TOF-ESI, *m/z*): $[M + H]^+$ calcd for $C_{13}H_{19}O_2$: 207.1380; found: 207.1376.

(3-(allyloxy)prop-1-yn-1-yl)benzene (74)



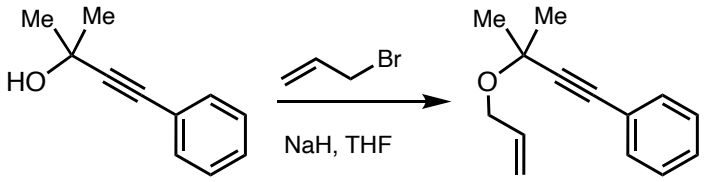
Prepared from 3-phenylprop-2-yn-1-ol (1.25 mL, 10.0 mmol, 1.0 equiv), allyl bromide (1.73 mL, 20.0 mmol, 2.0 equiv), NaH (95%, 300 mg, 12.5 mmol, 1.25 equiv), and THF (20 mL, 0.50 M) following General Procedure A. The resulting crude, colorless oil of **74** (1.68 g, 98% yield) was used without further purification. Spectral data matched those reported in the literature.[52]

6-phenyl-3a,4-dihydro-1*H*-cyclopenta[*c*]furan-5(3*H*)-one (7e)



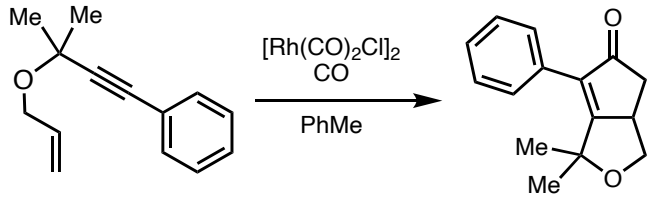
Prepared from **74** (345 mg, 2.0 mmol, 1.0 equiv), $[Rh(CO)_2Cl]_2$ (59 mg, 0.15 mmol, 0.75 equiv), and *m*-xylene (20 mL, 0.10 M) following General Procedure D. The crude residue was purified by column chromatography (silica, 30 to 40% EtOAc/hexanes) to afford **7e** (336 mg, 84% yield) as a white powder. Spectral data matched those reported in the literature.[50]

(3-(allyloxy)-3-methylbut-1-yn-1-yl)benzene (75)



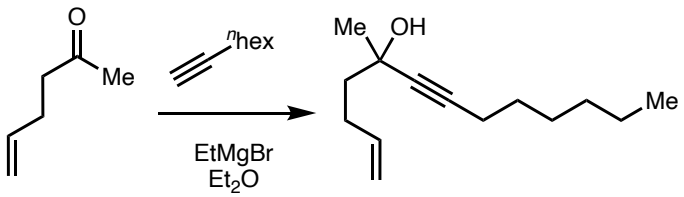
Prepared from 2-methyl-4-phenylbut-3-yn-2-ol (801 mg, 5.0 mmol, 1.0 equiv), allyl bromide (0.87 mL, 10.0 mmol, 2.0 equiv), NaH (95%, 158 mg, 6.25 mmol, 1.25 equiv), and THF (10 mL, 0.50 M) following General Procedure A. The resulting yellow oil of **74**5(283 mg, 48% yield) was used without further purification. Spectral data matched those reported in the literature.[53]

1,1-dimethyl-6-phenyl-3a,4-dihydro-1*H*-cyclopenta[*c*]furan-5(3*H*)-one (7f)



Prepared from **75** (20.0 mg, 0.1 mmol, 1.0 equiv), $[Rh(CO)_2Cl]_2$ (2.9 mg, 0.0075 mmol, 0.075 equiv), and PhMe (1 mL, 0.10 M) following General Procedure D. The crude residue was purified by column chromatography (silica, 15 to 25% EtOAc/hexanes) to yield **7f** (15.5 mg, 68% yield) as a white powder. Spectral data matched those reported in the literature.[53]

5-methyltridec-1-en-6-yn-5-ol (76)



To a round bottom flask with a stir bar was added oct-1-yne (8.9 mL, 60.0 mmol, 3.0 equiv) and Et_2O (100 mL, 0.1 M). 3 M EtMgBr in Et_2O (20.0 mL, 60.0 mmol, 3.0 equiv) was then added dropwise. The solution was then heated to 30 °C for 1 h then allowed to reach room temperature. To a separate round bottom flask with a stir bar was added hex-5-en-2-one (2.3 mL, 20.0 mmol, 1.0 equiv) and Et_2O (80 mL). This solution was added to the first solution slowly via canula. The reaction was allowed to stir at room temperature and monitored by TLC. Upon completion, the reaction was quenched by dropwise addition of sat. aq. NH_4Cl. The resulting mixture was diluted with Et_2O and water and the layers separated. The aqueous layer was extracted twice with Et_2O. Combined organics were washed with water and brine, dried over Na_2SO_4, filtered, and concentrated. The crude residue was purified by column chromatography (silica, 15 to 20% Et_2O/hexanes) to afford **76** (2.89 g, 70% yield) as a colorless oil.

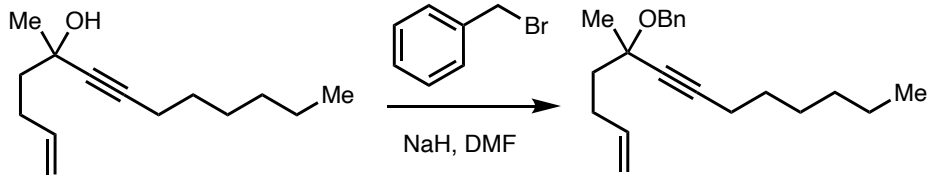
^{1}H NMR (500 MHz, $CDCl_3$): δ 5.88 (ddt, *J* = 16.9, 10.1, 6.6 Hz, 1H), 5.07 (dq, *J* = 17.1, 1.7 Hz, 1H), 4.98 (ddt, *J* = 10.2, 1.8, 1.3 Hz, 1H), 2.37 – 2.22 (m, 2H), 2.19 (t, *J* = 7.1 Hz, 2H), 1.96 – 1.91 (m, 1H), 1.80 – 1.66 (m, 2H), 1.55 – 1.48 (m, 2H), 1.47 (s, 3H), 1.43 – 1.35 (m, 2H), 1.35 – 1.24 (m, 3H), 0.90 (t, *J* = 7.0 Hz, 3H).

^{13}C NMR (126 MHz, $CDCl_3$): δ 138.74, 114.81, 84.41, 83.80, 68.39, 43.03, 31.44, 30.46, 29.53, 28.81, 28.64, 22.69, 18.73, 14.18.

FTIR (NaCl, thin film, cm^{-1}): 3364, 3078, 2930, 2859, 2239, 1642, 1455, 1371, 1127.

HRMS (TOF-ESI, *m/z*): $[M - H_2O + H]^+$ calcd for $C_{14}H_{23}$: 191.1800; found: 191.1794.

(((5-methyltridec-1-en-6-yn-5-yl)oxy)methyl)benzene (77)



Prepared from **76** (1.04 g, 5.0 mmol, 1.0 equiv), benzyl bromide (0.66 mL, 5.5 mmol, 1.1 equiv), NaH (95%, 139 mg, 5.5 mmol, 1.1 equiv), and DMF (20 mL, 0.25 M) following General Procedure A. The resulting crude residue of **77** was used in the next step without further purification (1.46 g, 98% yield).

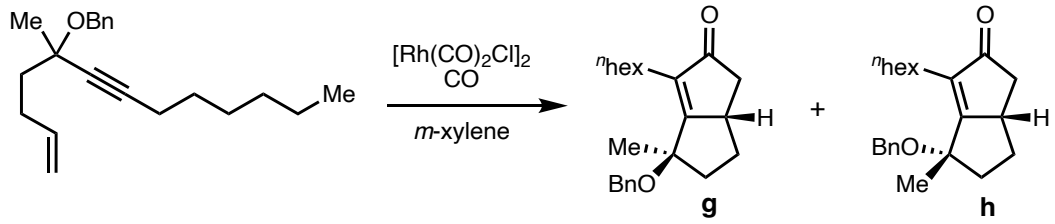
^{1}H NMR (400 MHz, $CDCl_3$): δ 7.40 – 7.33 (m, 3H), 7.35 – 7.21 (m, 2H), 5.87 (ddt, *J* = 16.8, 10.2, 6.5 Hz, 1H), 5.04 (dq, *J* = 17.2, 1.7 Hz, 1H), 4.95 (ddt, *J* = 10.2, 2.3, 1.3 Hz, 1H), 4.67 (d, *J* = 11.2 Hz, 1H), 4.57 (d, *J* = 11.2 Hz, 1H), 2.42 – 2.25 (m, 1H), 2.23 (t, *J* = 7.0 Hz, 2H), 1.92 – 1.71 (m, 2H), 1.60 – 1.48 (m, 2H), 1.48 (s, 3H), 1.45 – 1.35 (m, 2H), 1.29 (ddtt, *J* = 10.0, 7.1, 5.1, 2.5 Hz, 3H), 0.96 – 0.82 (m, 3H).

^{13}C NMR (101 MHz, $CDCl_3$): δ 139.64, 138.90, 128.37, 127.73, 127.32, 114.37, 86.46, 81.41, 73.80, 66.17, 41.38, 31.45, 29.08, 28.91, 28.64, 26.97, 22.71, 18.79, 14.19.

FTIR (NaCl, thin film, cm^{-1}): 2931, 2860, 2237, 1455, 1088, 1062, 911, 731, 697.

HRMS (TOF-ESI, *m/z*): $[M + H]^+$ calcd for $C_{21}H_{30}O$: 299.2369; found: 299.2378.

(4*R*,6a*S*)-4-(benzyloxy)-3-hexyl-4-methyl-4,5,6,6a-tetrahydropentalen-2(1*H*)-one (7g) and (4*S*,6a*S*)-4-(benzyloxy)-3-hexyl-4-methyl-4,5,6,6a-tetrahydropentalen-2(1*H*)-one (7h)



Prepared from **77** (1.19 g, 4.0 mmol, 1.0 equiv), $[Rh(CO)_2Cl]_2$ (77.7 mg, 0.2 mmol, 0.05 equiv), and *m*-xylene (40 mL, 0.10 M) following General Procedure D. The crude residue was purified by column chromatography (silica, 15 to 30% EtOAc/hexanes) to afford **7g** (693 mg, 53% yield) and **7h** (312 mg, 24% yield) as off-white oils.

(7g):

^{1}H NMR (500 MHz, $CDCl_3$): δ 7.37 – 7.25 (m, 5H), 4.45 (d, *J* = 10.8 Hz, 1H), 4.36 (d, *J* = 10.7 Hz, 1H), 3.11 (d, *J* = 8.8 Hz, 1H), 2.68 (dd, *J* = 17.9, 6.4 Hz, 1H), 2.42 – 2.26 (m, 3H), 2.22 (dtd, *J* = 12.3, 8.1, 2.8 Hz, 1H), 2.08 (dd, *J* = 17.9, 3.3 Hz, 1H), 1.99 (ddd, *J* = 13.6, 8.9, 2.8 Hz, 1H), 1.66 (s, 3H), 1.56 (d, *J* = 1.1 Hz, 1H), 1.58 – 1.15 (m, 9H), 0.92 – 0.85 (m, 3H).

^{13}C NMR (101 MHz, $CDCl_3$): δ 211.84, 179.39, 139.80, 139.20, 129.01, 128.16, 128.07, 81.63, 66.98, 43.78, 43.18, 42.03, 32.21, 30.37, 29.45, 28.99, 24.37, 23.20, 23.13, 14.68.

FTIR (NaCl, thin film, cm^{-1}): 2930, 1713, 1652, 1462, 1086, 736, 697.

HRMS (TOF-ESI, *m/z*): $[M + H]^+$ calcd for $C_{22}H_{31}O_2$: 327.2319; found: 327.2326.

(7h):

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.36 – 7.30 (m, 4H), 7.32 – 7.19 (m, 1H), 4.45 (d, *J* = 10.9 Hz, 1H), 4.26 (d, *J* = 11.2 Hz, 1H), 2.93 – 2.81 (m, 1H), 2.65 (dd, *J* = 17.9, 6.4 Hz,

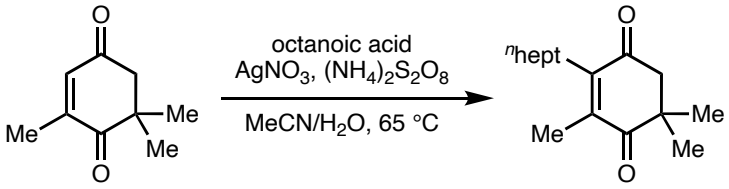
1H), 2.47 – 2.39 (m, 1H), 2.39 – 2.25 (m, 2H), 2.19 – 2.09 (m, 3H), 1.95 (ddd, J = 14.5, 12.0, 7.4 Hz, 1H), 1.62 (s, 3H), 1.49 – 1.13 (m, 12H), 0.89 – 0.80 (m, 3H).

^{13}C NMR (101 MHz, $CDCl_3$): δ 210.71, 181.73, 138.82, 138.11, 128.50, 127.55, 127.34, 81.23, 65.78, 42.91, 42.04, 38.46, 31.80, 31.20, 29.82, 28.79, 27.48, 23.53, 23.37, 22.74, 14.23.

FTIR (NaCl, thin film, cm^{-1}): 2928, 2858, 1698, 1660, 1455, 1062, 733, 696.

HRMS (TOF-ESI, *m/z*): $[M + H]^+$ calcd for $C_{22}H_{31}O_2$: 327.2319; found: 327.2314.

2-heptyl-3,5,5-trimethylcyclohex-2-ene-1,4-dione (28)



To a dry round-bottomed flask with a Teflon-coated stir bar was added ketoisophorone (0.74 mL, 5.0 mmol, 1.0 equiv), MeCN (15 mL), and H_2O (3 mL). Octanoic acid (1.98 mL, 12.5 mmol, 2.5 equiv) was added, and the mixture was stirred placed in a preheated oil bath at 65 °C. Silver nitrate (170 mg, 1.00 mmol, 0.20 equiv) was added in a single portion, and the flask was sealed with a rubber septum and flushed with N_2. Ammonium persulfate (1.49 g, 6.50 mmol, 1.3 equiv) was added as a solution in MeCN (15 mL) and H_2O (12 mL) (0.1 M final concentration) over 1.5 h via syringe pump. Upon complete consumption of the ketoisophorone as judged by TLC, the reaction was allowed to reach room temperature and concentrated to approximately ½ volume. The resulting liquid was extracted three times with EtOAc. Combined organics were washed with sat. aq. $NaHCO_3$ and brine, dried over Na_2SO_4, filtered, and concentrated. The crude residue was

purified by column chromatography (silica, 5 to 10% Et_2O/hexanes) to afford **28** (380 mg, 31% yield) as a clear oil.

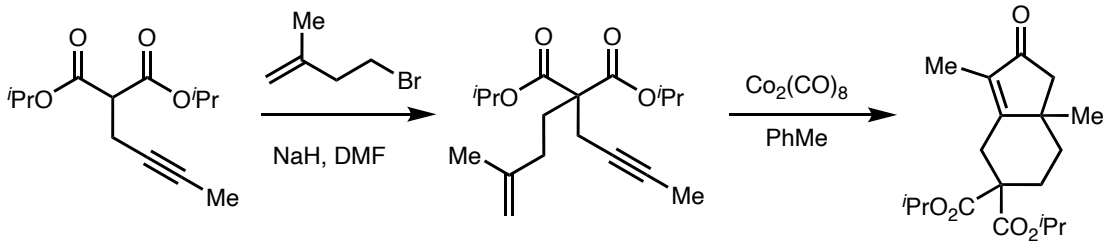
^{1}H NMR (400 MHz, $CDCl_3$): δ 2.70 (s, 2H), 2.41 (dd, *J* = 8.3, 6.4 Hz, 2H), 1.99 (s, 3H), 1.39 – 1.24 (m, 10H), 1.21 (s, 6H), 0.90 – 0.84 (m, 3H).

^{13}C NMR (101 MHz, $CDCl_3$): δ 203.74, 197.83, 149.20, 143.45, 77.48, 77.16, 76.84, 52.01, 45.23, 31.87, 30.01, 29.22, 28.46, 27.05, 26.38, 22.76, 14.22, 13.19.

FTIR (NaCl, thin film, cm^{-1}): 3340, 2957, 2923, 2856, 1682, 1614, 1469, 1378, 1276.

HRMS (GC-FAB+, *m/z*): $[M + H]^+$ calcd for $C_{16}H_{28}O_2$: 251.2011; found: 251.2001.

diisopropyl 3,7a-dimethyl-2-oxo-1,2,4,6,7,7a-hexahydro-5*H*-indene-5,5-dicarboxylate (31)



Step 1: Intermediate prepared from **57** (800 mg, 3.3 mmol, 1.0 equiv), 4-bromo-2-methylbut-1-ene (0.44 mL, 3.6 mmol, 1.1 equiv), NaH (95%, 151 mg, 6.0 mmol, 1.8 equiv), and DMF (4.15 mL, 0.80 M) following General Procedure A. The crude residue was purified by column chromatography (silica, 2% EtOAc/hexanes) to afford the crude intermediate (433 mg, 42% yield) as a colorless oil.

Step 2: The intermediate (308 mg, 1.0 mmol, 1.0 equiv) was then used directly in the next step with $Co_2(CO)_8$ (410 mg, 1.2 mmol, 1.2 equiv) and PhMe (10 mL, 0.10 M), following modified General Procedure C without addition of DMSO. Upon complete

conversion of the enyne to the Co-alkyne complex, the reaction was placed in a preheated oil bath at 110 °C. Upon complete consumption of the Co-alkyne complex, the reaction was allowed to reach room temperature, filtered over a pad of SiO_2 and Celite, and the filtrate concentrated. The crude residue was purified by column chromatography (silica, 10 to 20 to 35% EtOAc/hexanes) to afford **31** (134 mg, 40% yield) as a clear oil.

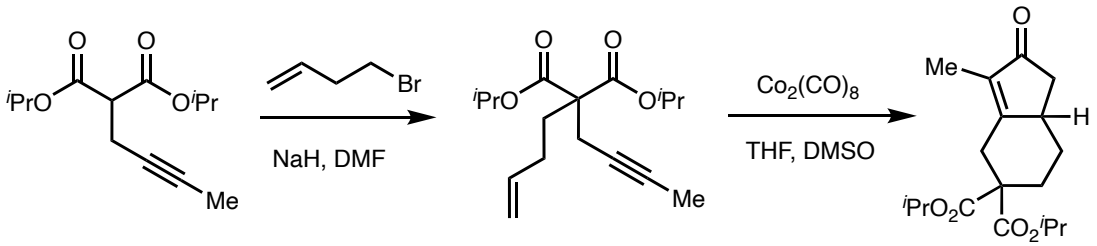
^{1}H NMR (400 MHz, $CDCl_3$): δ 5.03 (dp, *J* = 26.7, 6.3 Hz, 2H), 3.35 (dd, *J* = 14.0, 2.3 Hz, 1H), 2.67 (dd, *J* = 14.0, 1.7 Hz, 1H), 2.39 – 2.31 (m, 1H), 2.31 – 2.12 (m, 2H), 2.06 (td, *J* = 14.1, 4.0 Hz, 1H), 1.87 (ddd, *J* = 13.6, 3.9, 2.8 Hz, 1H), 1.72 (d, *J* = 1.4 Hz, 3H), 1.51 (td, *J* = 13.8, 4.0 Hz, 1H), 1.29 – 1.17 (m, 16H).

^{13}C NMR (101 MHz, $CDCl_3$): δ 207.88, 173.62, 170.97, 169.30, 135.44, 77.48, 77.16, 76.84, 69.63, 69.21, 56.86, 51.02, 40.64, 36.46, 29.74, 27.66, 24.56, 21.71, 21.68, 8.16.

FTIR (NaCl, thin film, cm^{-1}): 3456, 3394, 2980, 2924, 2870, 2049, 2021, 1731, 1704, 1659, 1456.

HRMS (GC-EI+, *m/z*): $[M]^+$ calcd for $C_{19}H_{28}O_5$: 336.1937; found: 336.1919.

diisopropyl 3-methyl-2-oxo-1,2,4,6,7,7a-hexahydro-5*H*-indene-5,5-dicarboxylate (50)



Step 1: Intermediate prepared from **57** (361 mg, 1.5 mmol, 1.0 equiv), homoallyl bromide (0.23 mL, 2.25 mmol, 1.5 equiv), NaH (95%, 57.0 mg, 2.25 mmol, 1.5 equiv), and DMF (3 mL, 0.50 M) following General Procedure A. The crude, clear colorless oil

of the intermediate was used without further purification (417 mg, 93% yield).

Step 2: The intermediate (368 mg, 1.25 mmol, 1.0 equiv) was then used directly in the next step with $Co_2(CO)_8$ (513 mg, 1.5 mmol, 1.2 equiv), DMSO (0.89 mL, 12.5 mmol, 10.0 equiv), and THF (12.5 mL, 0.10 M) following General Procedure C. The crude residue was purified by column chromatography (silica, 55 to 65% Et_2O/hexanes) to afford **50** (165 mg, 41% yield) as a white, amorphous solid.

^{1}H NMR (400 MHz, $CDCl_3$): δ 5.04 (dhept, *J* = 22.4, 6.3 Hz, 2H), 3.49 (dd, *J* = 14.0, 2.3 Hz, 1H), 2.64 – 2.42 (m, 4H), 2.12 (ddt, *J* = 13.5, 5.4, 3.4 Hz, 1H), 1.99 – 1.87 (m, 2H), 1.75 (t, *J* = 1.6 Hz, 3H), 1.29 – 1.17 (m, 13H).

^{13}C NMR (101 MHz, $CDCl_3$): δ 208.62, 170.97, 170.32, 169.41, 136.06, 77.48, 77.16, 76.84, 69.63, 69.18, 56.46, 41.00, 39.31, 33.25, 31.00, 30.70, 21.71, 21.70, 21.69, 21.67, 8.00.

FTIR (NaCl, thin film, cm^{-1}): 3446, 2980, 2932, 2873, 1723, 1714, 1696, 1453, 1373, 1254, 1107.

HRMS (GC-EI+, *m/z*): $[M]^+$ calcd for $C_{18}H_{26}O_5$: 322.1780; found: 322.1782.

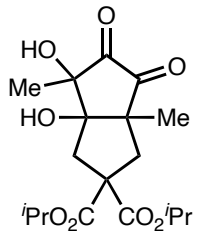
3.8.3 *Reaction Optimization*

General Procedure F: To a flame-dried vial with a Teflon-coated stir bar was added **6a** or **9a** (1.0 equiv), SeO_2, and 4 Å molecular sieves (activated by flame-drying under high vacuum for 10 minutes), if applicable. To this mixture was added 1,4-dioxane (0.05 M) and then H_2O, if applicable. The reaction was capped and sealed with Teflon tape, stirred, and brought to 100 °C in a preheated aluminum reaction block. The reaction was monitored by LCMS. When the reaction was judged to be complete, it was allowed

to reach room temperature and then concentrated. To the crude residue was added pyrazine as an internal standard, then the mixture was taken up in CD_3OD and filtered over a cotton plug into an NMR tube. Yield determined by ^1H NMR versus the internal standard.

Note: *The reactions were judged to be complete when the greatest amount of starting material had been consumed and the least amount of the desired product was degraded by further oxidation, as judged by LCMS. This is particularly important for the trioxidation; usually, after two-thirds of the starting material converted, rapid degradation of the desired product was observed.*

diisopropyl 3a,4-dihydroxy-4,6a-dimethyl-5,6-dioxohexahydropentalene-2,2(1*H*)-dicarboxylate (6)

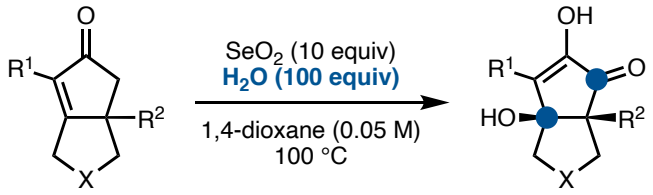


Observed to be a major byproduct during optimization of **4a** following General Procedure F, generally formed in 10–30% yield (by ^1H NMR versus an internal standard).

^1H NMR (400 MHz, CD_3OD): δ 5.08 (dp, *J* = 12.5, 6.2 Hz, 1H), 4.87 (p, *J* = 6.3 Hz, 1H), 3.01 (dd, *J* = 15.6, 1.2 Hz, 1H), 2.78 – 2.69 (m, 1H), 2.67 – 2.55 (m, 2H), 1.97 (s, 3H), 1.29 – 1.20 (m, 9H), 1.15 (dd, *J* = 7.2, 6.3 Hz, 5H).

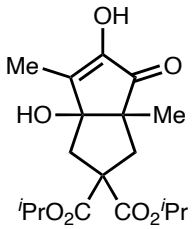
^{13}C NMR (101 MHz, $CDCl_3$): δ 202.54, 190.10, 173.51, 168.62, 102.83, 86.53, 77.36, 71.47, 69.94, 57.86, 55.94, 45.12, 42.98, 21.69, 21.53, 21.40, 18.75, 14.34.

3.8.4 *Dioxidation*



General Procedure G (Dioxidation): To a round bottom flask with a bar was added the enone (**4** or **7**) (1 equiv), SeO_2 (10 equiv), 1,4-dioxane (0.05 M), and water (100 equiv). The reaction was sealed with a rubber septum, stirred, and brought to 100 °C in a preheated oil bath. After the reaction was judged to be complete, typically 24–48 h (see note in General Procedure F), the reaction was cooled to room temperature and filtered over a pad of celite, washing with EtOAc. The filtrate was washed with sat. aq. $NaHCO_3$ twice then with water. Combined aqueous washings were extracted with EtOAc. Combined organics were dried over Na_2SO_4, filtered, and concentrated. The crude residue was purified by trituration or column chromatography to afford the desired product.

diisopropyl 5,6a-dihydroxy-3a,6-dimethyl-4-oxo-3,3a,4,6a-tetrahydropentalene-2,2(1*H*)-dicarboxylate (5a)



Prepared from **4a** (323 mg, 1.0 mmol) following General Procedure G. The crude residue was purified by column chromatography (silica, 30 to 35% EtOAc/hexanes) to yield **5a**

(251 mg, 71% yield) as an off-white powder.

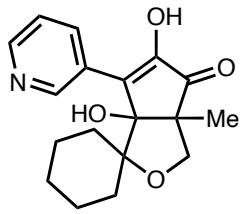
^{1}H NMR (400 MHz, CD_3OD): δ 5.08 (hept, *J* = 6.3 Hz, 1H), 4.97 (hept, *J* = 6.3 Hz, 1H), 3.36 (dq, *J* = 17.6, 1.9 Hz, 1H), 3.17 (d, *J* = 17.5 Hz, 1H), 2.55 (d, *J* = 13.6 Hz, 1H), 2.37 (s, 2H), 2.13 (d, *J* = 13.7 Hz, 1H), 1.67 (d, *J* = 1.7 Hz, 3H), 1.28 (dd, *J* = 6.2, 1.9 Hz, 6H), 1.21 (dd, *J* = 6.2, 2.9 Hz, 6H), 1.12 (s, 3H).

^{13}C NMR (126 MHz, $CDCl_3$): δ 203.71, 171.01, 169.52, 148.40, 141.75, 85.25, 69.93, 69.61, 58.23, 53.88, 42.74, 42.42, 21.61, 21.60, 21.57, 21.47, 19.31, 9.09.

FTIR (NaCl, thin film, cm^{-1}): 3444, 2981, 2937, 1731, 1455, 1372, 1266, 1106, 912, 823.

HRMS (TOF-ESI, *m/z*): $[M - H_2O + H]^+$ calcd for $C_{18}H_{25}O_6$: 337.1646; found: 337.1658.

5',6a'-dihydroxy-3a'-methyl-6'-(pyridin-3-yl)-3a',6a'-dihydrospiro[cyclohexane-1,1'-cyclopenta[*c*]furan]-4'(3'*H*)-one (5b)



Prepared from **4b** (14.4 mg, 0.05 mmol) following General Procedure G. The crude residue was purified by column chromatography (silica, 5% MeOH/DCM) to yield **5b** (10 mg, 64% yield) as an off-white powder.

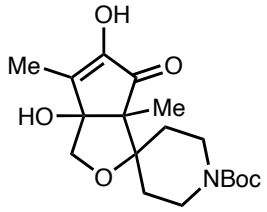
^{1}H NMR (400 MHz, pyridine-d_5): δ 10.25 (dd, *J* = 2.3, 0.9 Hz, 1H), 9.11 (dt, *J* = 8.1, 1.9 Hz, 1H), 8.70 (dd, *J* = 4.7, 1.7 Hz, 1H), 7.47 (s, 1H), 7.37 (ddd, *J* = 8.2, 4.7, 0.9 Hz, 1H), 3.76 (d, *J* = 9.4 Hz, 1H), 2.44 – 2.34 (m, 1H), 1.95 (td, *J* = 13.8, 4.1 Hz, 1H), 1.79 – 1.52 (m, 5H), 1.48 (s, 3H), 1.08 (qt, *J* = 13.1, 4.1 Hz, 1H).

^{13}C NMR (101 MHz, pyridine-d_5): δ 206.56, 153.09, 151.95, 150.63, 149.38, 137.32, 136.22, 135.72, 135.47, 133.14, 124.21, 123.72, 89.73, 86.24, 72.20, 58.90, 36.94, 29.16, 26.38, 23.93, 22.64, 17.80.

FTIR (NaCl, thin film, cm^{-1}): 3335, 2911, 2851, 2639, 2544, 2355, 2336, 2004, 1664, 1539.

HRMS (TOF-ESI, *m/z*): $[M + H]^+$ calcd for $C_{18}H_{22}NO_4$: 316.1543; found: 316.1552.

***tert*-butyl 3a,5-dihydroxy-4,6a-dimethyl-6-oxo-3,3a,6,6a-tetrahydrospiro[cyclopenta[*c*]furan-1,4'-piperidine]-1'-carboxylate (5c)**



Prepared from **4c** (161 mg, 0.5 mmol) following General Procedure G. The crude residue was purified by column chromatography (silica, 5 to 7% MeOH/DCM) to yield **5c** (94 mg, 53% yield) as off-white powder.

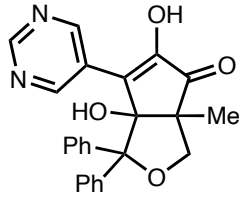
^{1}H NMR (400 MHz, $CDCl_3$): δ 3.95 (d, *J* = 10.0 Hz, 1H), 3.64 (d, *J* = 10.1 Hz, 1H), 2.94 (s, 2H), 1.99 (s, 3H), 1.92 – 1.74 (m, 2H), 1.74 – 1.58 (m, 2H), 1.45 (s, 10H), 1.38 – 1.27 (m, 1H), 1.02 (s, 3H).

^{13}C NMR (101 MHz, $CDCl_3$): δ 200.79, 153.90, 147.50, 139.31, 85.58, 85.35, 81.65, 78.73, 69.57, 58.29, 32.10, 28.84, 27.58, 27.15, 13.06, 8.20.

FTIR (NaCl, thin film, cm^{-1}): 3367, 2975, 2933, 2874, 1682, 1428, 1367, 1289, 1251.

HRMS (TOF-ESI, *m/z*): $[M + H]^+$ calcd for $C_{18}H_{28}NO_6$: 354.1911; found: 354.1926.

5,6a-dihydroxy-3a-methyl-1,1-diphenyl-6-(pyrimidin-5-yl)-1,3,3a,6a-tetrahydro-4*H*-cyclopenta[*c*]furan-4-one (5d)



Prepared from **4d** (18.4 mg, 0.05 mmol) following General Procedure G. The crude residue was purified by trituration from DCM and pentanes to yield **5d** (7 mg, 35% yield) as an off-white powder.

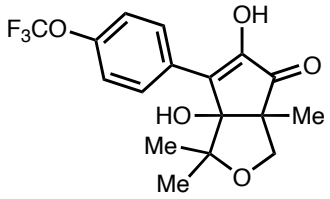
^{1}H NMR (400 MHz, pyridine-d_4): δ 9.12 (s, 1H), 8.54 (s, 2H), 7.78 (dd, J = 6.7, 3.0 Hz, 2H), 7.57 – 7.50 (m, 2H), 7.39 – 7.30 (m, 3H), 7.30 – 7.23 (m, 3H), 4.48 (d, J = 8.8 Hz, 1H), 3.87 (d, J = 8.8 Hz, 1H), 2.25 (s, 3H).

^{13}C NMR (101 MHz, pyridine-d_4): δ 202.69, 195.78, 186.85, 183.09, 182.92, 176.74, 176.47, 176.20, 169.54, 169.07, 162.36, 162.12, 161.87, 159.35, 157.26, 156.51, 155.15, 154.99, 154.86, 154.46, 154.26, 149.86, 121.19, 103.12, 83.26, 49.23, 26.56.

FTIR (NaCl, thin film, cm^{-1}): 3062, 2924, 2870, 2537, 2249, 1714, 1562, 1446, 1413, 1230, 1060.

HRMS (TOF-ESI, *m/z*): $[M + H]^+$ calcd for $C_{24}H_{20}N_2O_4$: 401.1496; found: 401.1503.

5,6a-dihydroxy-1,1,3a-trimethyl-6-(4-(trifluoromethoxy)phenyl)-1,3,3a,6a-tetrahydro-4*H*-cyclopenta[*c*]furan-4-one (5e)



Prepared from **4e** (164 mg, 0.5 mmol) following General Procedure G. The crude residue was purified by trituration from DCM and pentanes to yield **5e** (135 mg, 76% yield) as an off-white powder.

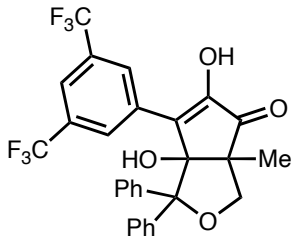
^{1}H NMR (500 MHz, $CDCl_3$): δ 7.27 (d, *J* = 9.2 Hz, 10H), 6.25 (dt, *J* = 8.1, 1.0 Hz, 2H), 5.53 (s, 1H), 3.06 (d, *J* = 9.7 Hz, 1H), 2.71 – 2.62 (m, 1H), 1.39 (s, 1H), 0.39 (s, 3H), 0.23 (s, 3H), 0.02 (s, 3H).

^{13}C NMR (126 MHz, $CDCl_3$): δ 204.08, 155.58, 149.35, 148.19, 135.62, 131.93, 131.67, 120.43, 89.18, 84.53, 71.45, 58.21, 26.87, 21.58, 16.51.

FTIR (NaCl, thin film, cm^{-1}): 3310, 2979, 2371, 2348, 1719, 1701, 1388, 1260, 1198.

HRMS (TOF-ESI, *m/z*): $[M + H]^+$ calcd for $C_{17}H_{17}F_3O_5$: 359.1101; found: 359.1114.

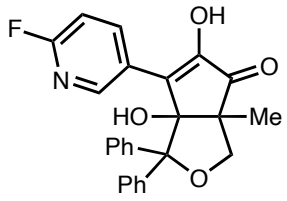
6-(3,5-bis(trifluoromethyl)phenyl)-5,6a-dihydroxy-3a-methyl-1,1-diphenyl-1,3,3a,6a-tetrahydro-4*H*-cyclopenta[*c*]furan-4-one (5f)



^{1}H NMR (400 MHz, $CDCl_3$) δ 7.31 (s, 1H), 7.27 (d, *J* = 4.5 Hz, 4H), 7.25 – 7.18 (m,

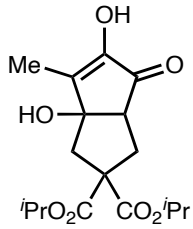
1H), 7.17 – 7.11 (m, 3H), 6.65 – 6.51 (m, 2H), 6.47 – 6.39 (m, 2H), 4.13 (d, *J* = 9.1 Hz, 1H), 3.77 (d, *J* = 9.1 Hz, 1H), 1.07 (s, 3H).

6-(6-fluoropyridin-3-yl)-5,6a-dihydroxy-3a-methyl-1,1-diphenyl-1,3,3a,6a-tetrahydro-4*H*-cyclopenta[*c*]furan-4-one (5g)



^{1}H NMR (400 MHz, $CDCl_3$): δ 7.97 – 7.92 (m, 1H), 7.58 – 7.50 (m, 4H), 7.52 – 7.45 (m, 1H), 7.40 – 7.32 (m, 1H), 7.03 – 6.87 (m, 3H), 6.81 – 6.74 (m, 2H), 6.61 (dd, *J* = 8.5, 3.0 Hz, 1H), 4.41 (d, *J* = 9.1 Hz, 1H), 4.05 (d, *J* = 9.1 Hz, 1H), 1.35 (s, 3H).

Diisopropyl 5,6a-dihydroxy-6-methyl-4-oxo-3,3a,4,6a-tetrahydropentalene-2,2(1*H*)-dicarboxylate (8a)



Prepared from **7a** (154.1 mg, 0.5 mmol) following General Procedure G. The crude residue was purified by column chromatography (silica, 60% EtOAc/hexanes) to yield **8a** (132 mg, 78% yield) as an off-white powder.

^{1}H NMR (400 MHz, CD_3OD): δ 4.98 (p, *J* = 6.3 Hz, 1H), 4.83 (dt, *J* = 12.6, 6.3 Hz, 1H), 2.72 (dd, *J* = 13.6, 1.6 Hz, 1H), 2.56 – 2.39 (m, 3H), 2.31 (d, *J* = 13.5 Hz, 1H), 1.88

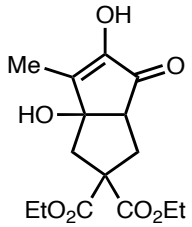
(d, J = 0.6 Hz, 3H), 1.27 – 1.11 (m, 12H).

^{13}C NMR (101 MHz, $CDCl_3$): δ 200.52, 171.93, 169.63, 147.90, 141.77, 85.26, 70.26, 69.70, 61.98, 55.66, 43.27, 34.53, 21.74, 21.73, 21.69, 21.63, 9.29.

FTIR (NaCl, thin film, cm^{-1}): 3431, 2988, 2936, 2742, 1732, 1455, 1377, 1168, 1022, 985, 901, 832, 758.

HRMS (TOF-ESI, *m/z*): $[M - H_2O + H]^+$ calcd for $C_{17}H_{23}O_6$: 323.1489; found: 323.1480.

diethyl 5,6a-dihydroxy-6-methyl-4-oxo-3,3a,4,6a-tetrahydropentalene-2,2(1*H*)-dicarboxylate (8b)



Prepared from **7b** (14.1 mg, 0.05 mmol) following General Procedure G. The crude residue was purified by column chromatography (silica, 60% EtOAc/hexanes) to yield **8b** (12.7 mg, 82% yield) as an off-white powder.

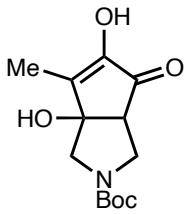
^{1}H NMR (500 MHz, CD_3OD): δ 5.73 (s, 1H), 4.25 (qd, J = 7.1, 2.6 Hz, 2H), 4.13 (q, J = 7.1 Hz, 2H), 2.98 (s, 1H), 2.79 (dd, J = 10.5, 5.3 Hz, 1H), 2.64 (ddd, J = 13.7, 10.4, 0.9 Hz, 1H), 2.61 – 2.50 (m, 2H), 2.43 (ddd, J = 13.8, 5.3, 0.8 Hz, 1H), 2.01 (d, J = 0.6 Hz, 3H), 1.30 (t, J = 7.1 Hz, 4H), 1.24 (t, J = 7.1 Hz, 3H).

^{13}C NMR (101 MHz, CD_3OD): δ 202.81, 171.92, 171.73, 151.49, 144.09, 84.55, 63.03, 62.97, 61.63, 55.97, 43.22, 35.59, 14.27, 14.22, 8.93.

FTIR (NaCl, thin film, cm^{-1}): 3381, 2984, 2940, 1727, 1714, 1672, 1437, 1405, 1370, 1262.

HRMS (TOF-ESI, *m/z*): $[M - H]^-$ calcd for $C_{15}H_{19}O_7$: 311.1136; found: 311.1122.

***tert*-butyl 5,6a-dihydroxy-6-methyl-4-oxo-3,3a,4,6a-tetrahydrocyclopenta[*c*]pyrrole-2(1*H*)-carboxylate (8c)**



Prepared from **7c** (24 mg, 0.1 mmol) following General Procedure G. The crude residue was purified by column chromatography (silica, 75% EtOAc/hexanes) to yield **8c** (15 mg, 57% yield) as an off-white powder.

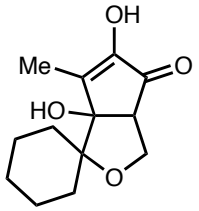
^{1}H NMR (400 MHz, CD_3OD): δ 3.81 (d, *J* = 11.9 Hz, 1H), 3.73 (dd, *J* = 11.7, 1.9 Hz, 1H), 3.49 (t, *J* = 10.2 Hz, 1H), 3.16 (d, *J* = 11.9 Hz, 1H), 2.55 (dd, *J* = 8.5, 1.9 Hz, 1H), 1.98 – 1.93 (m, 3H), 1.41 (s, 9H).

^{13}C NMR (101 MHz, CD_3OD, asterisk denotes minor rotamer): δ 201.58, 156.39, 151.57, 144.65*, 144.40*, 83.96*, 83.31*, 81.61, 56.88*, 56.22*, 55.31*, 54.75*, 47.87*, 47.42*, 28.65, 9.22*.

FTIR (NaCl, thin film, cm^{-1}): 3446, 2862, 2352, 1698, 1668, 1660, 1634, 1436, 1224.

HRMS (TOF-ESI, *m/z*): $[M + H]^+$ calcd for $C_{13}H_{20}O_5$: 270.1336; found: 270.1341.

5',6a'-dihydroxy-6'-methyl-3a',6a'-dihydrospiro[cyclohexane-1,1'-cyclopenta[*c*]furan]-4'(3'*H*)-one (8d)



Prepared from **7d** (104 mg, 0.5 mmol) following General Procedure G. The crude residue was purified by column chromatography (silica, 50% EtOAc/hexanes) to yield **8d** (87 mg, 74% yield) as an off-white powder.

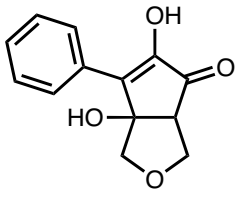
^{1}H NMR (400 MHz, $CDCl_3$): δ 4.00 (dd, *J* = 9.8, 8.6 Hz, 1H), 3.79 (dd, *J* = 9.8, 3.9 Hz, 1H), 2.89 – 2.81 (m, 1H), 2.07 – 1.94 (m, 4H), 1.73 – 1.60 (m, 2H), 1.60 – 1.38 (m, 4H), 1.34 – 1.09 (m, 3H).

^{13}C NMR (101 MHz, $CDCl_3$): δ 199.38, 148.53, 140.21, 87.16, 82.89, 62.25, 58.42, 31.52, 28.00, 24.58, 21.43, 20.97, 9.74.

FTIR (NaCl, thin film, cm^{-1}): 3342, 2928, 2858, 1713, 1698, 1668, 1402, 1361, 1133. 1060, 1022.

HRMS (TOF-ESI, *m/z*): $[M + H]^+$ calcd for $C_{13}H_{19}O_4$: 239.1278; found: 239.1282.

5,6a-dihydroxy-6-phenyl-1,3,3a,6a-tetrahydro-4*H*-cyclopenta[*c*]furan-4-one (8e)



Prepared from **7e** (500 mg, 2.5 mmol) following General Procedure G. The crude residue was purified by trituration from DCM and pentanes to yield **8e** (397.2 mg, 73% yield) as

an off-white powder.

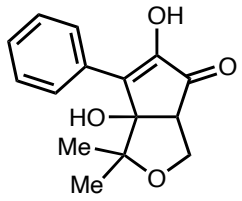
^{1}H NMR (400 MHz, CD_3OD): δ 8.18 – 8.11 (m, 2H), 7.46 – 7.38 (m, 2H), 7.38 – 7.30 (m, 1H), 4.12 (d, *J* = 9.2 Hz, 1H), 4.00 – 3.90 (m, 2H), 3.75 (d, *J* = 9.2 Hz, 1H), 2.74 (dd, *J* = 5.6, 3.5 Hz, 1H).

^{13}C NMR (101 MHz, CD_3OD): δ 202.00, 151.69, 139.33, 133.66, 130.60, 129.82, 129.29, 85.13, 76.95, 69.52, 58.97.

FTIR (NaCl, thin film, cm^{-1}): 3339, 2880, 2753, 1680, 1501, 1369, 1268, 1016, 698.

HRMS (TOF-ESI, *m/z*): $[M + H]^+$ calcd for $C_{13}H_{13}O_4$: 233.0808; found: 233.0802.

5,6a-dihydroxy-1,1-dimethyl-6-phenyl-1,3,3a,6a-tetrahydro-4*H*-cyclopenta[*c*]furan-4-one (8f)



Prepared from **7f** (22.8 mg, 0.11 mmol) following General Procedure G. The crude residue was purified by column chromatography (silica, 20% EtOAc/hexanes) to yield **8f**(8.0 mg, 32% yield) as an off-white powder.

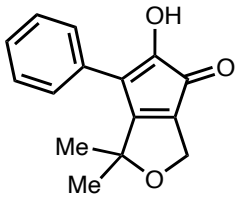
^{1}H NMR (400 MHz, CD_3OD): δ 8.27 – 8.19 (m, 2H), 7.45 – 7.35 (m, 2H), 4.17 – 4.08 (m, 1H), 3.82 (dd, *J* = 9.4, 3.6 Hz, 1H), 2.94 (dd, *J* = 8.2, 3.6 Hz, 1H), 1.40 (d, *J* = 4.0 Hz, 3H), 0.92 (s, 5H).

^{13}C NMR (101 MHz, CD_3OD): δ 202.61, 150.95, 139.36, 135.53, 130.86, 129.53, 128.92, 88.78, 85.74, 64.87, 61.51, 26.00, 22.64.

FTIR (NaCl, thin film, cm^{-1}): 3388, 2925, 2855, 1694, 1385, 1204, 1062.

HRMS (TOF-ESI, *m/z*): $[M + H]^+$ calcd for $C_{15}H_{17}O_4$: 261.1121; found: 261.1122.

5-hydroxy-1,1-dimethyl-6-phenyl-1,3-dihydro-4*H*-cyclopenta[*c*]furan-4-one (38)

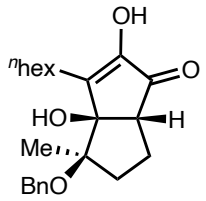


Prepared from **7f** (30.6 mg, 0.1 mmol) following General Procedure G. The crude residue was purified by column chromatography (silica, 30% EtOAc/hexanes) and then preparative thin layer chromatography (silica, 10% MeOH/DCM) to yield **38** (7.5 mg, 30% yield) as an off-white powder.

^{1}H NMR (400 MHz, $CDCl_3$): δ 8.03 – 7.86 (m, 2H), 7.60 (ddt, *J* = 7.9, 6.9, 1.3 Hz, 1H), 7.57 – 7.42 (m, 2H), 4.89 (s, 2H), 1.40 (s, 6H).

^{13}C NMR (101 MHz, $CDCl_3$): δ 193.41, 165.32, 157.15, 135.83, 134.29, 129.33, 128.91, 128.47, 91.27, 71.82, 29.86, 26.75.

(3a*R*,4*R*,6a*R*)-4-(benzyloxy)-3-hexyl-2,3a-dihydroxy-4-methyl-4,5,6,6a-tetrahydropentalen-1(3a*H*)-one (8g)



Prepared from **7g** (6.5 mg, 0.02 mmol) following General Procedure G. The crude residue was purified by preparative thin layer chromatography (silica, 40% EtOAc/hexanes) to yield **8g** (1.7 mg, 24% yield) as a white amorphous solid.

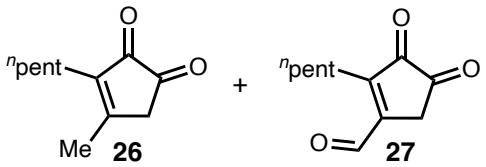
^{1}H NMR (400 MHz, $CDCl_3$): δ 7.44 – 7.28 (m, 5H), 5.63 (s, 1H), 4.56 (d, *J* = 10.9 Hz, 1H), 4.44 (d, *J* = 10.9 Hz, 1H), 4.23 (d, *J* = 0.8 Hz, 1H), 2.76 – 2.68 (m, 1H), 2.52 – 2.38 (m, 1H), 2.38 – 2.23 (m, 1H), 2.23 – 2.11 (m, 1H), 2.11 – 1.98 (m, 1H), 1.77 – 1.59 (m, 5H), 1.42 – 1.25 (m, 5H), 1.24 (s, 3H), 0.93 – 0.81 (m, 4H).

^{13}C NMR (101 MHz, $CDCl_3$): δ 202.81, 149.56, 145.27, 138.17, 128.69, 127.98, 127.70, 87.38, 84.14, 65.43, 56.15, 35.06, 31.73, 30.07, 27.66, 26.78, 22.75, 22.69, 19.59, 14.25.

FTIR (NaCl, thin film, cm^{-1}): 3388, 2925, 2855, 1694, 1385, 104, 1062.

HRMS (TOF-ESI, *m/z*): $[M + H]^+$ calcd for $C_{22}H_{31}O_4$: 359.2217; found: 359.2205.

4-methyl-3-pentylcyclopent-3-ene-1,2-dione (26) and 3,4-dioxo-2-pentylcyclopent-1-ene-1-carbaldehyde (27)



Prepared from dihydrojasmone **25** (41.6 mg, 0.25 mmol) following General Procedure G. The crude residue was purified by column chromatography (silica, 50% EtOAc/hexanes) to yield a 5:1 mixture of **26** and **27** (17.9 mg, 41% combined) as a pale yellow oil.

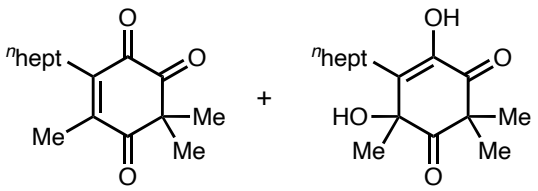
^{1}H NMR (400 MHz, $CDCl_3$) of 26: δ 2.94 (h, *J* = 1.2 Hz, 2H), 2.37 (t, *J* = 7.7 Hz, 2H), 2.23 (d, *J* = 1.2 Hz, 3H), 1.47 – 1.43 (m, 2H), 1.36 – 1.28 (m, 6H), 0.90 – 0.86 (m, 3H).

^{13}C NMR (101 MHz, $CDCl_3$) of 26: δ 198.55, 188.85, 166.73, 146.73, 77.48, 77.16, 76.84, 40.04, 31.84, 27.83, 23.45, 22.56, 17.82, 14.12.

FTIR (NaCl, thin film, cm^{-1}) of mixture: 3387, 2952, 2924, 2855, 1714, 1455, 1385, 1261, 1094.

HRMS (GC-EI+, *m/z*) of 26: $[M]^+$ calcd for $C_{11}H_{16}O_2$: 180.1150; found: 180.1141.

6-heptyl-3,3,5-trimethylcyclohex-5-ene-1,2,4-trione (29) and 5-heptyl-4,6-dihydroxy-2,2,6-trimethylcyclohex-4-ene-1,3-dione (30)



29 **30**

Prepared from **28** (47.3 mg, 0.20 mmol) following General Procedure G. The crude residue was purified by column chromatography (silica, 20% EtOAc/hexanes) to yield a 10:1 mixture of **29** and **30** (35.6 mg, 68% yield combined) as a pale yellow oil.

^{1}H NMR (400 MHz, $CDCl_3$) of 29: δ 2.62 – 2.55 (m, 2H), 2.15 (s, 3H), 1.42 (s, 6H), 1.30 (m, 10H), 0.90 – 0.85 (m, 3H).

^{13}C NMR (101 MHz, $CDCl_3$) of 29: δ 197.37, 194.47, 184.30, 150.74, 148.59, 77.48, 77.16, 76.84, 61.84, 31.79, 29.96, 29.11, 28.20, 26.91, 22.73, 21.88, 14.45, 14.20.

FTIR (NaCl, thin film, cm^{-1}) of mixture: 3442, 2953, 2924, 2854, 1728, 1667, 1463, 1380, 1312, 1156, 1034.

HRMS (GC-EI+, *m/z*) of 29: $[M]^+$ calcd for $C_{16}H_{24}O_3$: 264.1726; found: 264.1749.

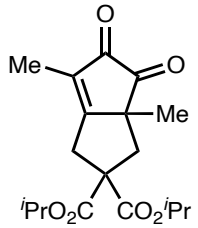
3.8.5 *Kinetic Analysis*

General Procedure K: All synthetic manipulations were performed in a glovebox. To a flame-dried vial with a stir bar was added the enone (**4e**,**h**–**k**) (0.1 mmol, 1.0 equiv), SeO_2 (111 mg, 1.0 mmol, 10.0 equiv), internal standard 1,2,4,5-tetrachloro-3-nitrobenzene (26 mg, 0.1 mmol, 1.0 equiv), and 1,4-dioxane-d_8 (0.8 mL, 0.125 M). The

reaction was capped and sealed with Teflon tape, stirred, and brought to 100 °C in a preheated aluminum reaction block. A t specified time points, the reaction was allowed to reach room temperature and an aliquot (0.1–0.2 mL) was removed and filtered over a cotton plug directly into a dry NMR tube, washing with additional 1,4-dioxane-d_8 (0.3–0.4 mL). The tube was sealed and analyzed by NMR. If applicable, D_2O (180 μL, 10.0 mmol, 100.0 equiv) or CD_3OD (406 μL, 10.0 mmol, 100.0 equiv) was added to the appropriate aliquot, which was then brought to 100 °C in a preheated oil bath (outside of the glovebox); at specified time points, the aliquots were allowed to reach room temperature, analyzed by NMR, then returned to the heat. Yield determined by ^{1}H NMR versus the internal standard.

Note: *Structural assignments of* ***16h–k*** *and* ***5h–k-d₂*** *made by analogy to ^{1}H and ^{13}C NMR spectra of* ***16e*** *and* ***5e-d₂****, respectively.*

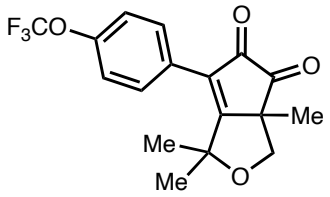
diisopropyl 3a,6-dimethyl-4,5-dioxo-3,3a,4,5-tetrahydropentalene-2,2(1*H*)-dicarboxylate (16a)



^{1}H NMR (400 MHz, 1,4-dioxane-d_8): δ 5.11 – 4.99 (m, 1H), 5.01 – 4.85 (m, 1H), 3.41 – 3.25 (m, 2H), 2.40 (d, J = 13.9 Hz, 1H), 2.26 (d, J = 16.2 Hz, 1H), 1.82 (d, J = 1.3 Hz, 3H), 1.28 – 1.21 (m, 12H), 1.18 (s, 3H).

^{13}C NMR (101 MHz, 1,4-dioxane-d_8): δ 199.87, 191.01, 177.25, 171.39, 170.72, 137.64, 70.37, 59.50, 51.49, 39.00, 34.09, 22.76, 21.70, 21.62, 21.59, 8.93.

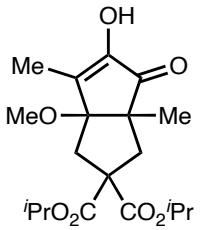
diisopropyl 5-hydroxy-6a-methoxy-3a,6-dimethyl-4-oxo-3,3a,4,6a-tetrahydropentalene-2,2(1*H*)-dicarboxylate (16e)



^{1}H NMR (400 MHz, 1,4-dioxane-*d*$_8$): δ 7.51 – 7.36 (m, 4H), 3.90 (d, *J* = 8.5 Hz, 1H), 3.66 (d, *J* = 8.5 Hz, 1H), 1.74 (s, 3H), 1.58 (s, 3H), 1.07 (s, 3H).

^{13}C NMR (101 MHz, 1,4-dioxane-*d*$_8$): δ 198.41, 189.55, 184.81, 150.43, 139.68, 133.93, 131.77, 131.50, 130.59, 122.69, 121.75, 121.61, 121.48, 80.73, 69.54, 55.28, 30.41, 30.11, 25.96, 23.02.

diisopropyl 5-hydroxy-6a-methoxy-3a,6-dimethyl-4-oxo-3,3a,4,6a-tetrahydropentalene-2,2(1*H*)-dicarboxylate (24)



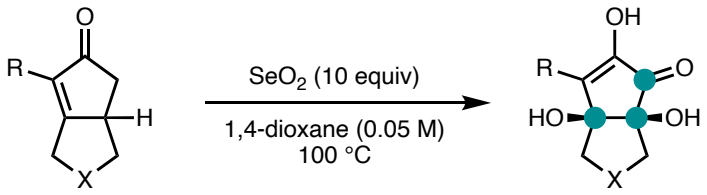
^{1}H NMR (400 MHz, CDCl$_3$): δ 4.98 (hept, *J* = 6.2 Hz, 1H), 4.85 (hept, *J* = 6.3 Hz, 1H), 3.15 (s, 3H), 2.78 (ddd, *J* = 13.8, 5.8, 2.2 Hz, 2H), 2.43 (d, *J* = 13.7 Hz, 1H), 1.97 (d, *J* = 13.9 Hz, 1H), 1.92 (s, 3H), 1.24 – 1.12 (m, 16H).

^{13}C NMR (101 MHz, CDCl$_3$): δ 203.53, 170.29, 169.71, 150.71, 138.57, 90.56, 77.36, 69.72, 69.64, 57.48, 53.05, 52.79, 44.42, 40.52, 29.86, 21.66, 21.64, 21.62, 21.53, 18.34, 10.29.

FTIR (NaCl, thin film, cm^{-1}): 3453, 2919, 2851, 1731, 1282, 1076.

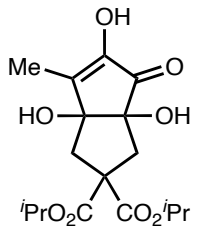
HRMS (TOF-ESI, *m/z*): $[M - CH_3OH + H]^+$ calcd for $C_{18}H_{25}O_6$: 337.1646; found: 337.1653.

3.8.6 *Trioxidation*



General Procedure H (Trioxidation): To a flame-dried vial with a stir bar was added the enone (**7**) (1 equiv), SeO_2 (10 equiv), and 1,4-dioxane (0.05 M). The reaction was capped and sealed with Teflon tape, stirred, and brought to 100 °C in a preheated aluminum reaction block. After the reaction was judged to be complete, typically 1–4 h (see note in General Procedure F), the reaction was cooled to room temperature then concentrated. The crude residue was purified by chromatography to afford the desired product.

diisopropyl 3a,5,6a-trihydroxy-6-methyl-4-oxo-3,3a,4,6a-tetrahydropentalene-2,2(1*H*)-dicarboxylate (33a)



Prepared from **7a** (7.0 mg, 0.02 mmol) following General Procedure H. The crude residue was purified by preparative thin layer chromatography (silica, 70%

EtOAc/hexanes) to yield **33a** (1.7 mg, 21% yield) as a white amorphous solid.

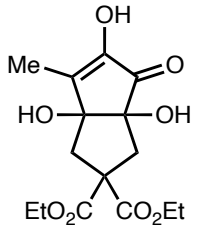
^{1}H NMR (400 MHz, CD_3OD): δ 4.97 (hept, *J* = 6.3 Hz, 1H), 4.87 – 4.78 (m, 1H), 2.86 (dd, *J* = 13.8, 1.9 Hz, 1H), 2.80 (dd, *J* = 13.3, 1.9 Hz, 1H), 2.33 (d, *J* = 13.4 Hz, 1H), 2.14 (d, *J* = 13.7 Hz, 1H), 1.86 (s, 3H), 1.30 – 1.11 (m, 12H).

^{13}C NMR (101 MHz, $CDCl_3$): δ 198.08, 172.12, 169.27, 147.56, 142.77, 83.23, 79.99, 70.64, 69.95, 59.43, 42.99, 42.03, 21.74, 21.68, 9.58.

FTIR (NaCl, thin film, cm^{-1}): 3438, 2984, 2931, 1727, 1714, 1660, 1263, 1100, 902.

HRMS (TOF-ESI, *m/z*): $[M + NH_4]^+$ calcd for $C_{17}H_{28}O_8N$: 374.1809; found: 374.1813.

diethyl 3a,5,6a-trihydroxy-6-methyl-4-oxo-3,3a,4,6a-tetrahydropentalene-2,2(1*H*)-dicarboxylate (33b)



Prepared from **7b** (14.1 mg, 0.05 mmol) following General Procedure H. The crude residue was purified by column chromatography (silica, 5% MeOH/DCM) to yield **33b** (5.1 mg, 31% yield) as a white amorphous solid.

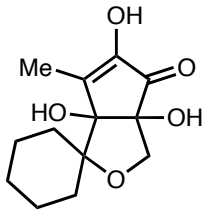
^{1}H NMR (400 MHz, CD_3OD): δ 4.15 (qd, *J* = 7.1, 1.3 Hz, 2H), 4.03 (qd, *J* = 7.2, 2.2 Hz, 2H), 2.86 (ddd, *J* = 20.9, 13.5, 2.0 Hz, 2H), 2.35 (d, *J* = 13.3 Hz, 1H), 2.17 (d, *J* = 13.7 Hz, 1H), 1.87 (s, 3H), 1.21 (dt, *J* = 8.2, 7.1 Hz, 6H).

^{13}C NMR (101 MHz, CD_3OD): δ 201.23, 171.88, 171.37, 152.07, 143.21, 82.47, 79.98, 63.17, 63.08, 57.10, 43.88, 41.87, 14.25, 14.22, 9.06.

FTIR (NaCl, thin film, cm^{-1}): 3402, 2984, 2940, 2852, 1728, 1667, 1404, 1366, 1252.

HRMS (TOF-ESI, *m/z*): $[M - NH_4]^-$ calcd for $C_{15}H_{19}O_8$: 327.1085; found: 327.1077.

3a',5',6a'-trihydroxy-6'-methyl-3a',6a'-dihydrospiro[cyclohexane-1,1'-cyclopenta[*c*]furan]-4'(3'*H*)-one (33d)



Prepared from **7d** (20.6 mg, 0.1 mmol) following General Procedure H. The crude residue was purified by column chromatography (silica, 40 to 50% EtOAc/hexanes) to yield **33d** (6.2 mg, 23% yield) as a white amorphous solid.

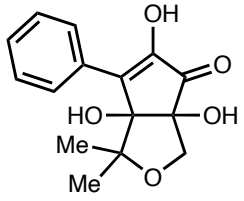
^{1}H NMR (400 MHz, CD_3OD): δ 5.49 (s, 1H), 3.89 (d, *J* = 10.0 Hz, 1H), 3.55 (d, *J* = 10.1 Hz, 1H), 1.97 (s, 3H), 1.77 – 1.35 (m, 8H), 1.35 – 1.12 (m, 2H).

^{13}C NMR (101 MHz, CD_3OD): δ 201.20, 152.33, 145.38, 85.90, 85.24, 81.39, 70.51, 54.81, 35.25, 30.76, 28.45, 26.69, 23.64, 22.39, 12.11.

FTIR (NaCl, thin film, cm^{-1}): 3394, 2925, 2855, 1714, 1650, 1460, 1361, 1109, 1072.

HRMS (TOF-ESI, *m/z*): $[M - H_2O + H]^+$ calcd for $C_{13}H_{17}O_4$: 237.1121; found: 237.1111.

3a,5,6a-trihydroxy-1,1-dimethyl-6-phenyl-1,3,3a,6a-tetrahydro-4*H*-cyclopenta[*c*]furan-4-one (33f)



Prepared from **7f** (15.0 mg, 0.07 mmol) following General Procedure H. The crude residue was purified by preparative thin layer chromatography (silica, 40 to 55% EtOAc/hexanes then 10% MeOH/DCM) to yield **33f** (3.0 mg, 17% yield) as a white amorphous solid.

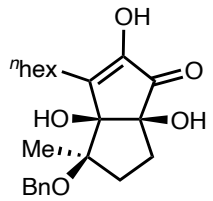
^{1}H NMR (400 MHz, CD_3OD): δ 8.24 – 8.17 (m, 2H), 7.43 – 7.28 (m, 3H), 3.98 (d, *J* = 10.1 Hz, 1H), 3.71 (d, *J* = 10.1 Hz, 1H), 1.35 (s, 3H), 0.90 (s, 3H).

^{13}C NMR (101 MHz, $(CD_3)_2SO$): δ 201.01, 150.42, 138.58, 135.22, 129.95, 128.81, 128.28, 84.91, 84.44, 80.63, 69.83, 27.14, 22.36.

FTIR (NaCl, thin film, cm^{-1}): 3341, 2920, 1694, 1463, 1393, 1049, 730.

HRMS (TOF-ESI, *m/z*): $[M - H_2O + H]^+$ calcd for $C_{15}H_{15}O_4$: 259.0965; found: 259.0963.

(3a*S*,4*R*,6a*S*)-4-(benzyloxy)-3-hexyl-2,3a,6a-trihydroxy-4-methyl-4,5,6,6a-tetrahydropentalen-1(3a*H*)-one (33g)



Prepared from **7g** (32.6 mg, 0.1 mmol) following General Procedure H. The crude

residue was purified by column chromatography (silica, 20% EtOAc/hexanes then 2% MeOH/DCM) to yield **33g** (9 mg, 24% yield) as a pale orange amorphous solid.

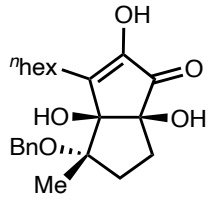
^{1}H NMR (400 MHz, $CDCl_3$): δ 7.43 – 7.30 (m, 5H), 4.55 – 4.43 (m, 2H), 4.41 (s, 1H), 3.32 (s, 1H), 2.51 (ddd, *J* = 13.9, 9.3, 6.7 Hz, 1H), 2.32 (ddd, *J* = 13.9, 9.1, 7.2 Hz, 1H), 2.13 – 2.02 (m, 2H), 1.94 – 1.80 (m, 1H), 1.77 – 1.60 (m, 1H), 1.39 (s, 3H), 1.37 – 1.18 (m, 6H), 0.92 – 0.83 (m, 3H).

^{13}C NMR (101 MHz, $CDCl_3$): δ 200.48, 150.53, 144.83, 137.59, 128.78, 128.14, 127.78, 85.29, 83.68, 79.42, 64.78, 31.69, 30.50, 30.26, 29.93, 27.83, 27.48, 22.73, 19.88, 14.23.

FTIR (NaCl, thin film, cm^{-1}): 3444, 2926, 2856, 1714, 1660, 1393, 1104, 1040, 738.

HRMS (TOF-ESI, *m/z*): $[M + H]^+$ calcd for $C_{22}H_{31}O_5$: 375.2166; found: 375.2174.

(3a*S*,4*S*,6a*S*)-4-(benzyloxy)-3-hexyl-2,3a,6a-trihydroxy-4-methyl-4,5,6,6a-tetrahydropentalen-1(3a*H*)-one (33h)



Prepared from **7h** (32.6 mg, 0.1 mmol) following General Procedure H. The crude residue was purified by column chromatography (silica, 20% EtOAc/hexanes) to yield **33h** (7.7 mg, 21% yield) as a pale orange amorphous solid.

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.42 – 7.17 (m, 5H), 5.44 (s, 1H), 4.50 (d, *J* = 11.4 Hz, 1H), 4.33 (d, *J* = 11.4 Hz, 1H), 3.21 (s, 1H), 2.98 (s, 1H), 2.54 (ddd, *J* = 14.3, 10.4, 5.8 Hz, 1H), 2.41 (ddd, *J* = 14.3, 10.4, 6.0 Hz, 2H), 2.08 – 1.90 (m, 2H), 1.83 (q, *J* = 6.4, 5.8 Hz, 1H), 1.77 – 1.67 (m, 1H), 1.68 – 1.51 (m, 1H), 1.49 (s, 3H), 1.37 – 1.11 (m, 6H), 0.84

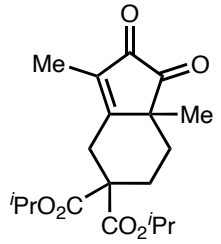
(t, *J* = 7.0 Hz, 3H).

^{13}C NMR (101 MHz, $CDCl_3$): δ δ 199.61, 149.37, 148.48, 138.98, 128.37, 127.31, 126.98, 86.24, 85.37, 80.20, 64.78, 33.08, 31.74, 31.59, 30.04, 27.67, 27.42, 22.75, 18.07, 14.24.

FTIR (NaCl, thin film, cm^{-1}): 3388, 2927, 2855, 1698, 1651, 1454, 1394, 1106, 1052, 734.

HRMS (TOF-ESI, *m/z*): $[M + H]^+$ calcd for $C_{22}H_{31}O_5$: 375.2166; found: 375.2164.

diisopropyl 3,7a-dimethyl-1,2-dioxo-1,2,4,6,7,7a-hexahydro-5*H*-indene-5,5-dicarboxylate (32)



Prepared from **31** (16.8 mg, 0.05 mmol) following General Procedure H with SeO_2 (27.7 mg, 0.25 mmol, 5.0 equiv). The crude residue was purified by column chromatography (silica, 25% EtOAc/hexanes) to yield **32** (12.6 mg, 72% yield) as a pale yellow oil.

^{1}H NMR (400 MHz, $CDCl_3$): δ 5.08 (hept, *J* = 6.3 Hz, 1H), 4.98 (hept, *J* = 6.3 Hz, 1H), 3.49 (dd, *J* = 14.1, 2.1 Hz, 1H), 2.74 (dq, *J* = 14.1, 1.4 Hz, 1H), 2.42 (ddt, *J* = 14.4, 4.1, 2.6 Hz, 1H), 2.15 (td, *J* = 14.2, 4.0 Hz, 1H), 1.95 (d, *J* = 1.3 Hz, 3H), 1.89 (ddd, *J* = 13.9, 4.0, 2.8 Hz, 1H), 1.51 (td, *J* = 13.9, 4.1 Hz, 1H), 1.31 (s, 3H), 1.26 (dd, *J* = 6.3, 3.5 Hz, 7H), 1.19 (dd, *J* = 6.3, 1.5 Hz, 6H).

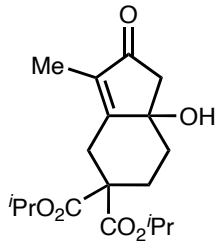
^{13}C NMR (101 MHz, $CDCl_3$): δ 202.05, 188.28, 172.37, 170.29, 168.81, 140.59, 77.48,

77.16, 76.84, 70.09, 69.70, 56.53, 43.83, 29.93, 29.27, 26.38, 21.68, 21.66, 19.94, 8.55.

FTIR (NaCl, thin film, cm^{-1}): 3505, 3408, 2980, 2939, 2872, 1732, 1633, 1456, 1386.

HRMS (TOF-ES+, *m/z*): $[M + H]^+$ calcd for $C_{19}H_{28}O_6$: 351.1808; found: 351.1784.

diisopropyl 7a-hydroxy-3-methyl-2-oxo-1,2,4,6,7,7a-hexahydro-5*H*-indene-5,5-dicarboxylate (51)



Prepared from **50** (16.1 mg, 0.05 mmol) following General Procedure H with SeO_2 (8.3 mg, 0.075 mmol, 1.5 equiv). The crude residue was purified by column chromatography (silica, 45% EtOAc/hexanes) to yield **51** (5.7 mg, 34% yield) as a pale yellow oil.

^{1}H NMR (400 MHz, $CDCl_3$): δ 5.03 (dp, *J* = 29.1, 6.3 Hz, 2H), 3.31 (dd, *J* = 13.9, 1.5 Hz, 1H), 2.89 (dq, *J* = 13.8, 1.6 Hz, 1H), 2.55 – 2.40 (m, 2H), 2.35 – 2.28 (m, 2H), 2.19 (dt, *J* = 14.3, 3.3 Hz, 1H), 1.75 (d, *J* = 1.5 Hz, 3H), 1.73 – 1.71 (m, 1H), 1.69 – 1.61 (m, 1H), 1.25 (dd, *J* = 6.3, 1.7 Hz, 7H), 1.20 (dd, *J* = 6.3, 4.0 Hz, 6H).

^{13}C NMR (101 MHz, $CDCl_3$): δ 205.34, 170.48, 169.23, 167.35, 137.18, 77.35, 77.03, 76.71, 73.98, 69.55, 69.16, 56.23, 49.77, 35.64, 29.27, 26.74, 21.58, 21.55, 7.90.

FTIR (NaCl, thin film, cm^{-1}): 3443, 2981, 2856, 1810, 1714, 1667, 1454, 1376, 1303, 1251, 1104.

HRMS (GC-FAB+, *m/z*): $[M + H]^+$ calcd for $C_{18}H_{28}O_6$: 339.1808; found: 339.1797.

3.8.7 *Stereochemical Analysis*

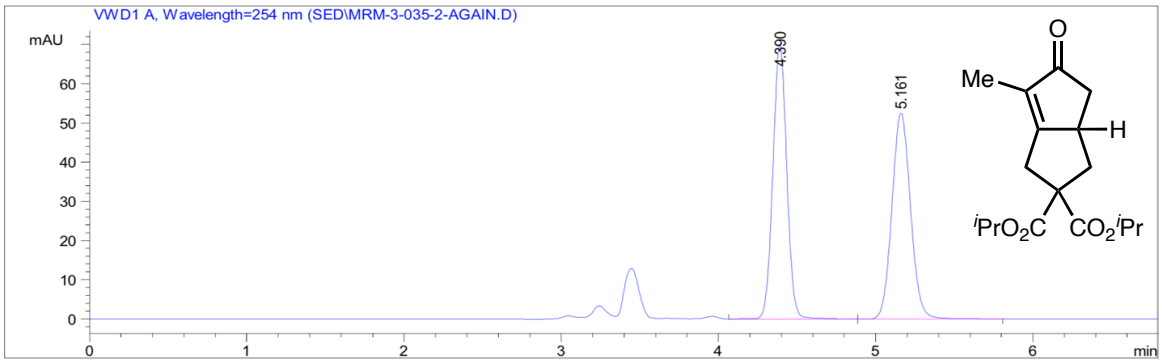
General Procedure I (Aqueous): To a flame-dried vial with a stir bar was added the substrate (1 equiv), SeO_2 (10 equiv), 1,4-dioxane (0.05 M), and water (100 equiv). The reaction was capped and sealed with Teflon tape, stirred, and brought to 100 °C in a preheated aluminum reaction block. At specified time points, the reaction was cooled to room temperature and an aliquot was removed and concentrated. To the residue was added an internal standard (pyrazine, ~1 equiv), then the mixture was taken up in CD_3OD and filtered over a cotton plug into an NMR tube. Yield determined by ^1H NMR versus the internal standard. Alternatively, isolated yields were determined by concentration of the entire reaction and purification of the crude residue by chromatography to afford the desired product. Enantiomeric excess determined by analytical chiral SFC or HPLC.

General Procedure J (Anhydrous): General Procedure I was followed except that the addition of water to the reaction was omitted.

diisopropyl 6-methyl-5-oxo-3,3a,4,5-tetrahydropentalene-2,2(1H)-dicarboxylate (7a)

Chiral HPLC: (IH, 1.0 mL/min, 10% IPA/hexanes, λ = 254 nm): t_R = 4.4 min, t_R = 5.2 min.

7a: racemic

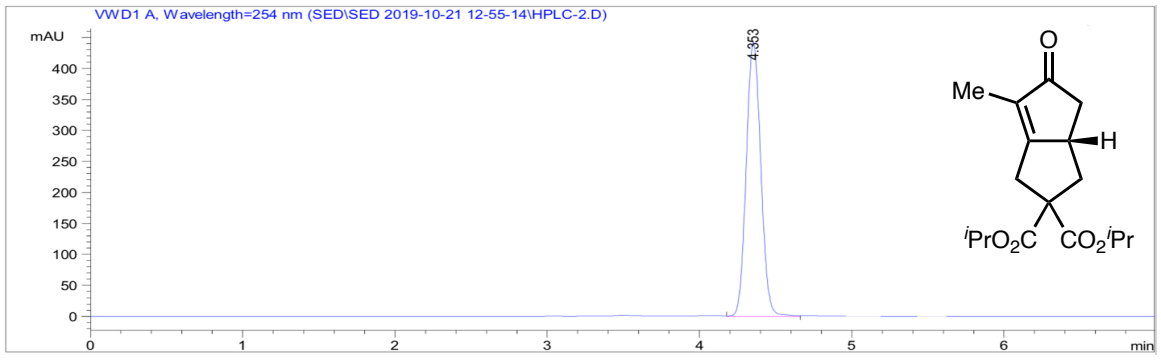


Peak #	RetTime [min]	Type	Width [min]	Area mAU *s	Height [mAU]	Area %
1	4.390	VV	0.0954	433.76349	70.21899	50.0120
2	5.161	VV	0.1281	433.55533	52.62845	49.9880

Prepared by purification of **7a** by chiral HPLC (IH, 1.0 mL/min, 10% IPA/hexanes, λ = 254 nm) to yield **(+)-7a*** as a single enantiomer.

$\boxed{[\alpha]_D^{22} =}$ +126 (c = 0.2, $CHCl_3$).

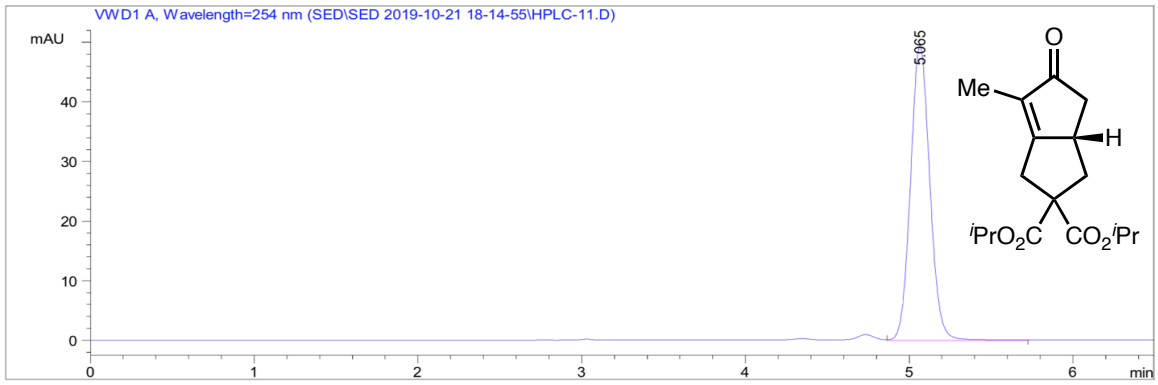
(+)-7a*: enantioenriched, >99% ee



Prepared by purification of **7a** by chiral HPLC (IH, 1.0 mL/min, 10% IPA/hexanes, λ = 254 nm) to yield **(–)-7a*** as a single enantiomer.

$\boxed{[\alpha]_D^{22} =}$ –95 (c = 0.3, $CHCl_3$).

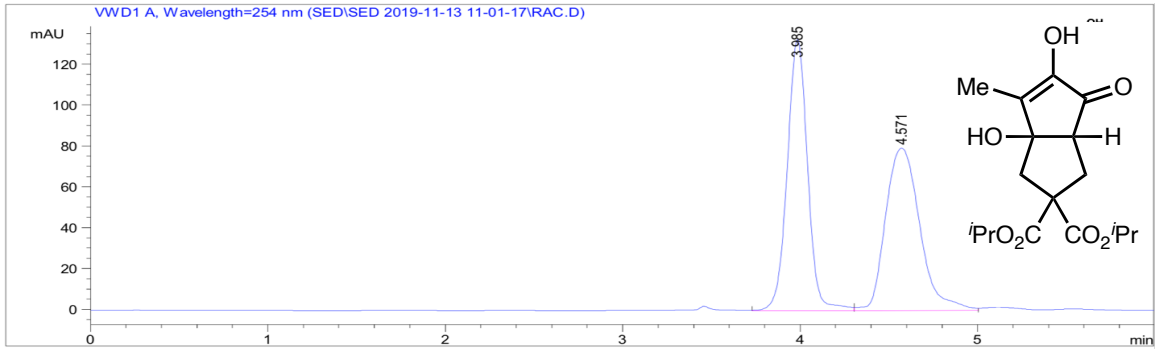
(–)-7a*: enantioenriched, >99% ee



diisopropyl 5,6a-dihydroxy-6-methyl-4-oxo-3,3a,4,6a-tetrahydropentalene-2,2(1*H*)-dicarboxylate (8a)

Chiral HPLC: (IH, 1.0 mL/min, 65% IPA/hexanes, λ = 254 nm): t_R = 3.9 min, t_R = 4.6 min.

8a: racemic

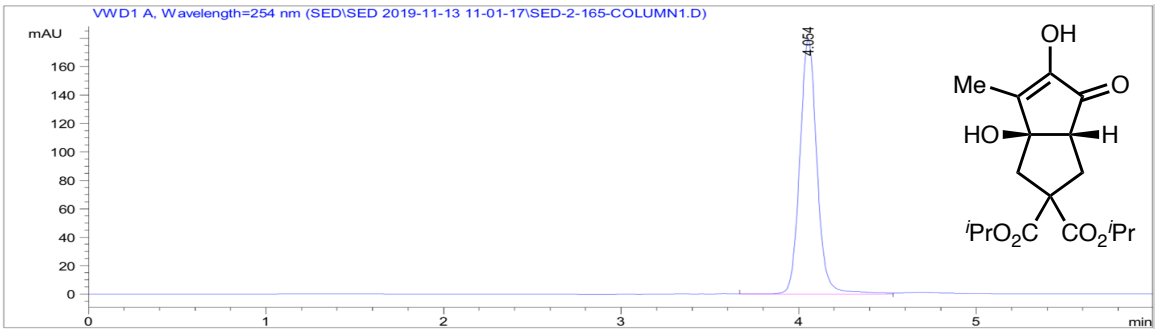


Peak #	RetTime [min]	Type	Width [min]	Area mAU *s	Height [mAU]	Area %
1	3.985	BV	0.1241	1063.69312	132.66316	49.8308
2	4.571	VV	0.2153	1070.91724	79.57430	50.1692

Prepared from **(–)-7a*** (176 mg, 0.57 mmol, >99% ee) following General Procedure I. The crude residue was purified by column chromatography (silica, 0 to 40% EtOAc/hexanes) to yield **(–)-8a*** (114 mg, 59% yield) in >99% ee.

$\boxed{[\alpha]_D^{22} =}$ –67 (c = 0.5, $CHCl_3$).

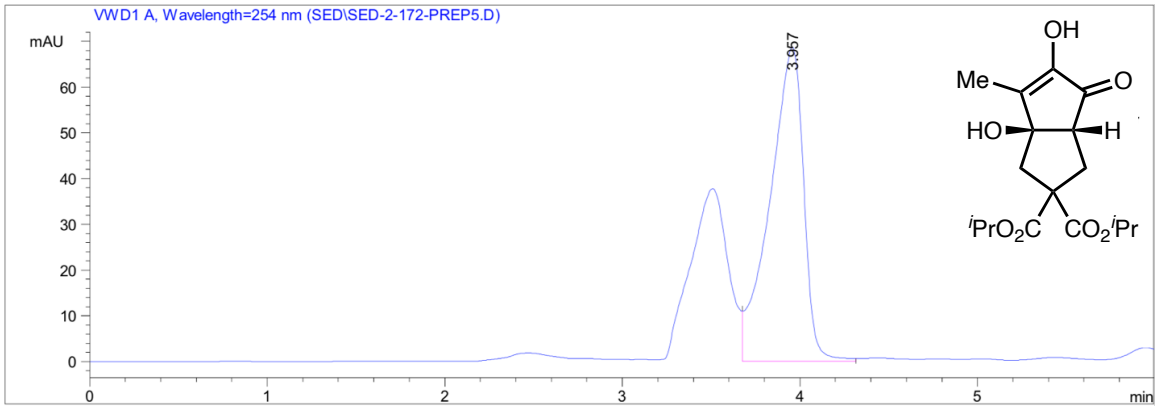
(–)-8a*: enantioenriched, >99% ee



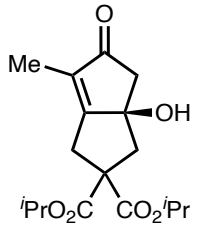
Prepared from **(–)-7a*** (22 mg, 0.07 mmol, >99% ee) following General Procedure J. The crude residue was purified by preparative thin layer chromatography (silica, 7% MeOH/DCM) to yield **(–)-8a*** (1.0 mg, 4% yield) in >99% ee.

$\boxed{[\alpha]_D^{22} =}$ –15 (c = 0.1, $CHCl_3$).

(–)-8a*: enantioenriched, >99% ee



diisopropyl 3a-hydroxy-6-methyl-5-oxo-3,3a,4,5-tetrahydropentalene-2,2(1*H*)-dicarboxylate (49a)



^{1}H NMR (500 MHz, $CDCl_3$): δ 5.09 (dp, *J* = 37.2, 6.2 Hz, 2H), 3.33 (dd, *J* = 18.5, 2.0 Hz, 1H), 3.26 (d, *J* = 18.5 Hz, 1H), 3.00 (s, 1H), 2.89 (d, *J* = 14.3 Hz, 1H), 2.63 (d, *J* = 17.9 Hz, 1H), 2.51 (d, *J* = 18.0 Hz, 1H), 2.11 (d, *J* = 14.4 Hz, 1H), 1.74 (dd, *J* = 1.9, 1.0 Hz, 3H), 1.37 – 1.14 (m, 12H).

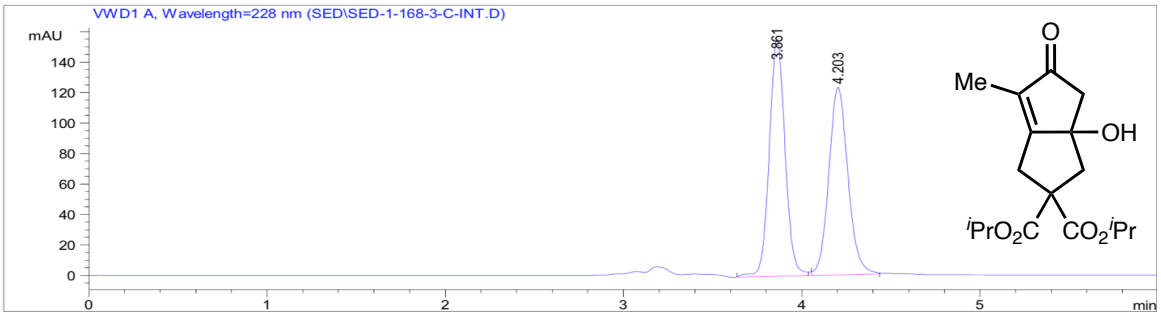
^{13}C NMR (101 MHz, $CDCl_3$): δ 207.52, 174.39, 173.24, 170.51, 134.39, 82.47, 70.68, 70.01, 61.00, 48.11, 45.22, 32.91, 21.74, 21.70, 8.78.

FTIR (NaCl, thin film, cm^{-1}): 3472, 2927, 2855, 1716, 1682, 1456, 1375, 1267, 1188, 1109, 1027, 913.

HRMS (TOF-ESI, m/z): calc'd for $C_{17}H_{24}O_6$: 307.1540 $[M–H_2O+H]^+$; found: 307.1549.

Chiral HPLC: (IH, 1.0 mL/min, 60% IPA/hexanes, λ = 228 nm): t_R = 3.9 min, t_R = 4.2 min.

49a: racemic

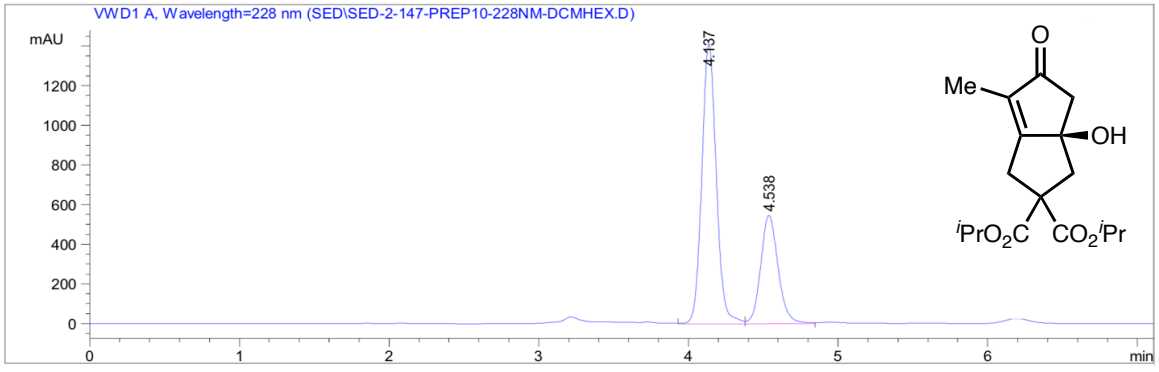


Peak #	RetTime [min]	Type	Width [min]	Area mAU *s	Height [mAU]	Area %
1	3.861	BB	0.0953	958.98309	155.45844	51.0419
2	4.203	BB	0.1149	919.83228	123.07118	48.9581

Prepared from **(+)-7a*** (200 mg, 0.65 mmol, >99% ee) following General Procedure I. The crude residue was purified by column chromatography (silica, 0 to 30% EtOAc/hexanes) followed by preparative thin layer chromatography (silica, 30 to 50% EtOAc/hexanes) to yield **(+)-49a*** (3.5 mg, 2% yield) in 36% ee.

$\boxed{[\alpha]_D^{22} =}$ +6 (c = 0.2, $CHCl_3$).

(+)-49a*: enantioenriched, 36% ee

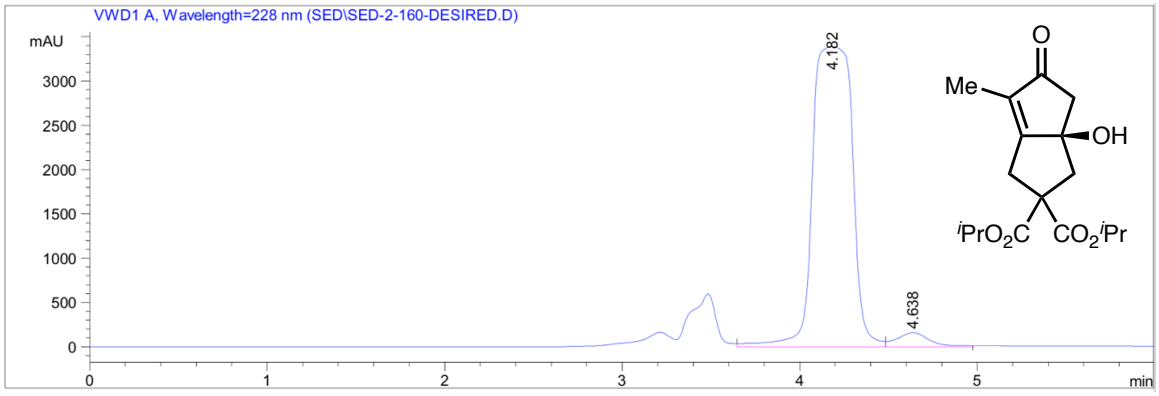


Peak #	RetTime [min]	Type	Width [min]	Area mAU *s	Height [mAU]	Area %
1	4.137	VV	0.1047	9508.88184	1414.22021	68.1725
2	4.538	VV	0.1250	4439.37842	548.41638	31.8275

Prepared from **(+)-7a*** (150 mg, 0.49 mmol) following General Procedure J. The crude residue was purified by column chromatography (silica, 0 to 30% EtOAc/hexanes). This procedure was repeated seven times, and the combined material yielded yield **(+)-49a*** (41 mg, 26% yield) in 92% ee.

$\boxed{[\alpha]_D^{22} =}$ +12 (c = 1.0, $CHCl_3$).

(+)-49a*: enantioenriched, 92% ee

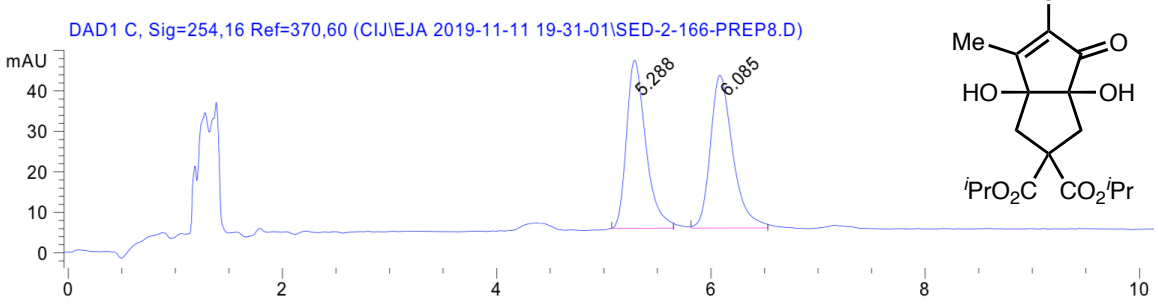


Peak #	RetTime [min]	Type	Width [min]	Area mAU *s	Height [mAU]	Area %
1	4.182	VV	0.2509	5.25926e4	3389.88306	96.1357
2	4.638	VV	0.1925	2114.04004	160.96941	3.8643

diisopropyl 3a,5,6a-trihydroxy-6-methyl-4-oxo-3,3a,4,6a-tetrahydropentalene-2,2(1*H*)-dicarboxylate (33a)

Chiral SFC: (OD-H, 1.0 mL/min, 15% IPA in CO_2, λ = 254 nm): t_R = 5.3 min, t_R = 6.0 min.

33a: racemic

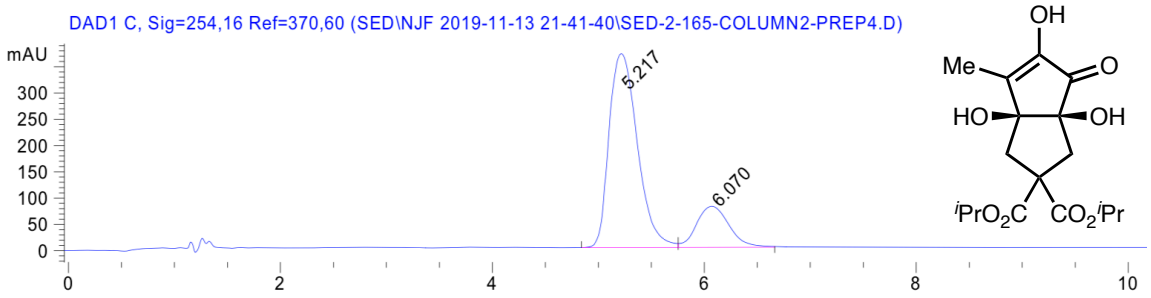


Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	5.288	BB	0.1903	519.55811	41.44424	48.6659
2	6.085	BB	0.2214	548.04315	37.73867	51.3341

Prepared from **(–)-7a*** (176 mg, 0.57 mmol, >99% ee) following General Procedure I. The crude residue was purified by column chromatography (silica, 0 to 40% EtOAc/hexanes) followed by preparative thin layer chromatography (7% MeOH/DCM) to yield **(–)-33a*** (6.9 mg, 3% yield) in 60% ee.

$\boxed{[\alpha]_D^{22} =}$ –49 (c = 0.5, $CHCl_3$).

(–)-33a*: enantioenriched, 60% ee

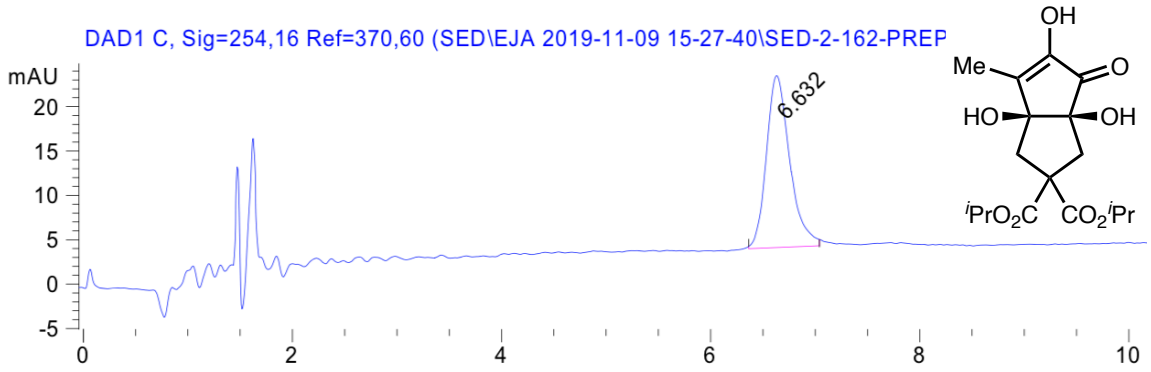


Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	5.217	BV	0.2970	6858.47607	368.79010	80.3824
2	6.070	VB	0.3388	1673.83008	77.87675	19.6176

Prepared from **(–)-7a*** (31 mg, 0.1 mmol, >99% ee) following General Procedure J. The crude residue was purified by preparative thin layer chromatography (silica, 70% EtOAc/hexanes then 7% MeOH/DCM) to yield **(–)-33a*** (5.2 mg, 15% yield) in >99% ee.

$\boxed{[\alpha]_D^{22} =}$ –59 (c = 0.3, $CHCl_3$).

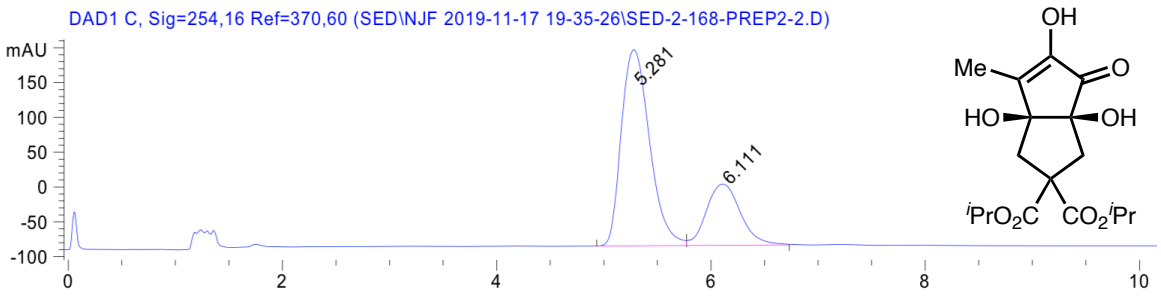
(–)-33a*: enantioenriched, >99% ee



Prepared from **(–)-8a*** (60 mg, 0.18 mmol, >99% ee) following General Procedure I. The crude residue was purified by preparative thin layer chromatography (silica, 10% MeOH/DCM) to yield **(–)-33a*** (7.5 mg, 12% yield) in 46% ee.

$\boxed{[\alpha]_D^{22} =}$ –29 (c = 0.3, $CHCl_3$).

(–)-33a*: enantioenriched, 46% ee

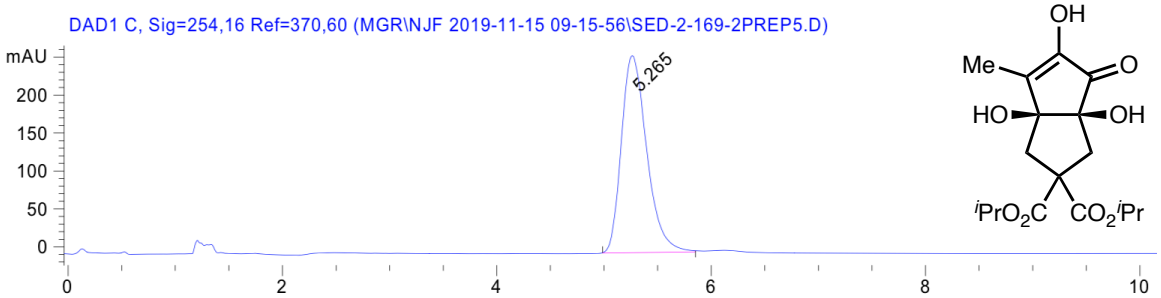


Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	5.281	BV	0.2901	5172.07080	281.81711	72.6377
2	6.111	VB	0.3501	1948.29785	88.05092	27.3623

Prepared from **(–)-8a*** (40 mg, 0.12 mmol, >99% ee) following General Procedure J. The crude residue was purified by preparative thin layer chromatography (silica, 10% MeOH/DCM) to yield **(–)-33a*** (10.1 mg, 24% yield) in >99% ee.

$\boxed{[\alpha]_D^{22} =}$ –90 (c = 0.7, $CHCl_3$).

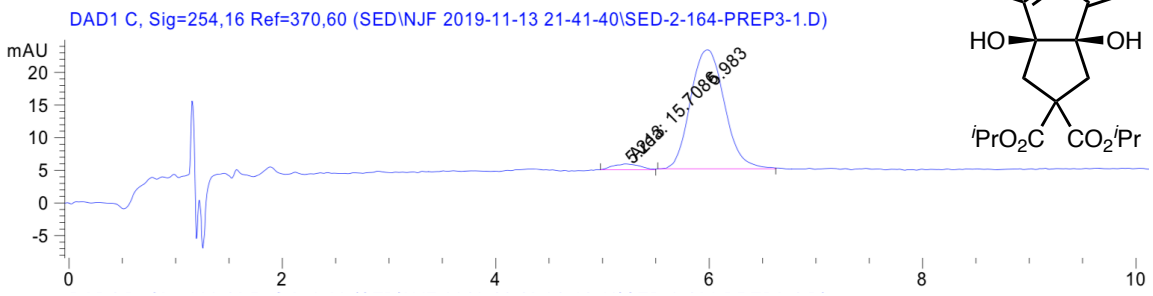
(–)-33a*: enantioenriched, >99% ee



Prepared from **(+)-49a*** (20 mg, 0.06 mmol, 92% ee) following General Procedure I. The crude residue was purified by column chromatography (silica, 7% MeOH/DCM) to yield **(+)-33a*** (1.1 mg, 5% yield) in 92% ee.

$\boxed{[\alpha]_D^{22} =}$ +14 (c = 0.1, $CHCl_3$).

(+)-33a*: enantioenriched, 92% ee

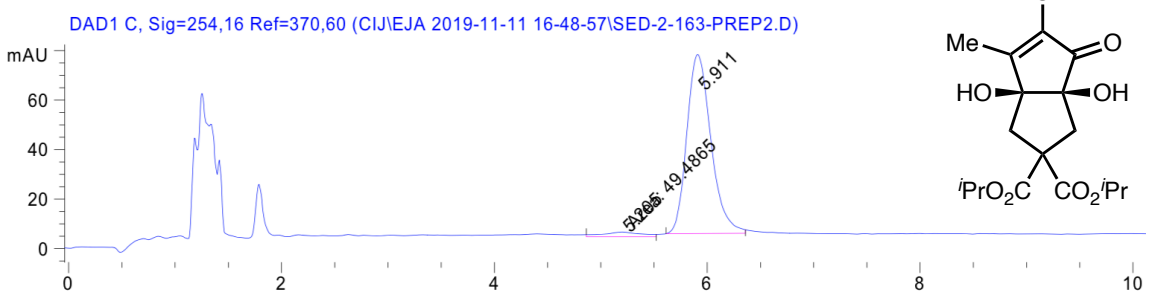


Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	5.213	MM	0.2931	15.70860	8.93133e-1	3.7445
2	5.983	BB	0.3545	403.80246	18.22254	96.2555

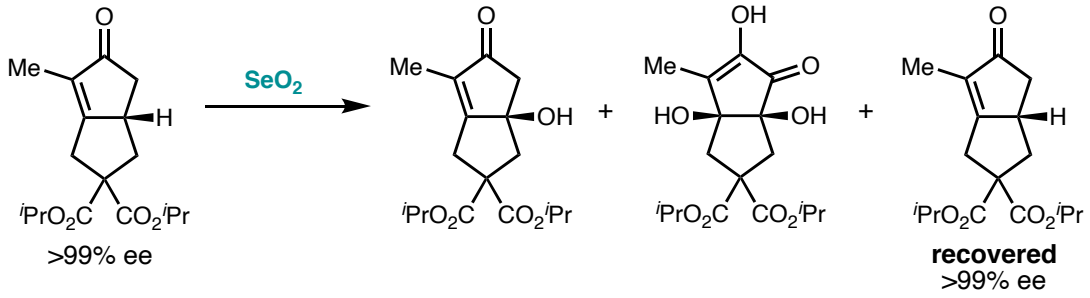
Prepared from **(+)-49a*** (20 mg, 0.06 mmol, 92% ee) following General Procedure J. The crude residue was purified by column chromatography (silica, 7% MeOH/DCM) to yield **(+)-33a*** (0.2 mg, 1% yield) in 92% ee.

$\boxed{[\alpha]_D^{22} =}$ +1 (c = 0.1, $CHCl_3$).

(+)-33a*: enantioenriched, 92% ee



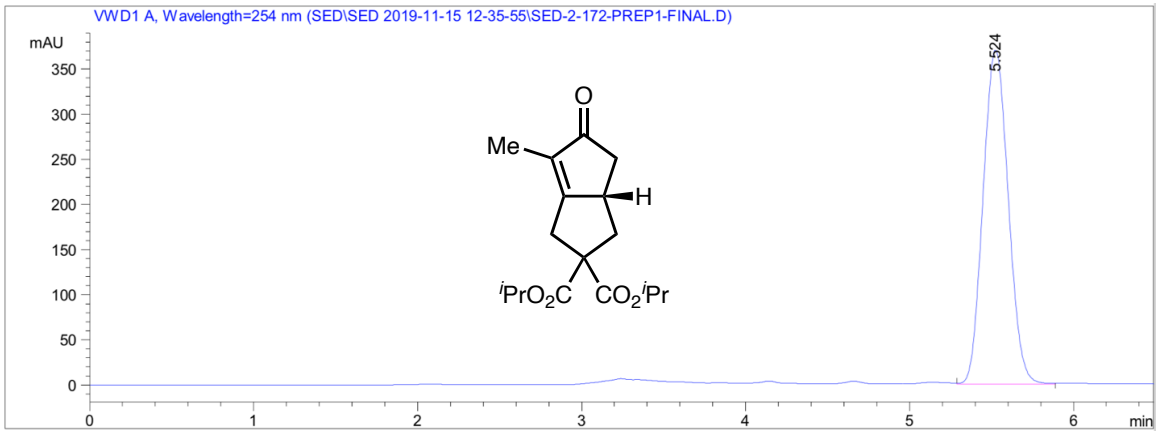
Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	5.205	MM	0.4254	49.48651	1.93883	4.1664
2	5.911	BB	0.2437	1138.27368	72.27718	95.8336

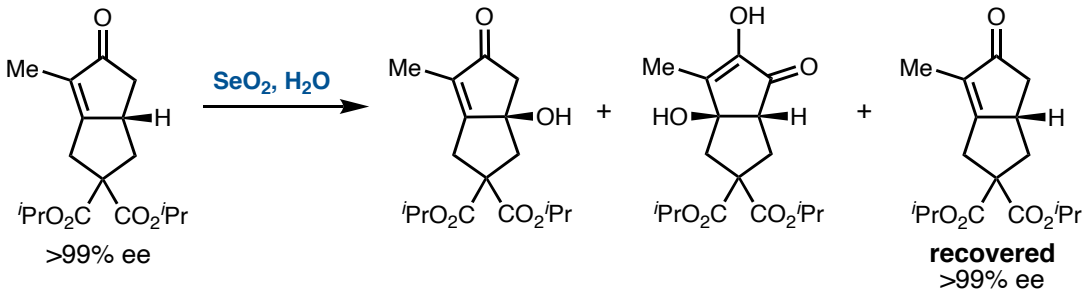


Recovered from **(–)-7a*** (22 mg, 0.07 mmol, >99% ee) following General Procedure J. The crude residue was purified by preparative thin layer chromatography (silica, 7% MeOH/DCM) to yield **(–)-7a*** (1 mg, 4% recovery) in >99% ee.

$\boxed{[\alpha]_D^{22} =}$ –94 (c = 0.7, $CHCl_3$).

(–)-7a*: enantioenriched, >99% ee

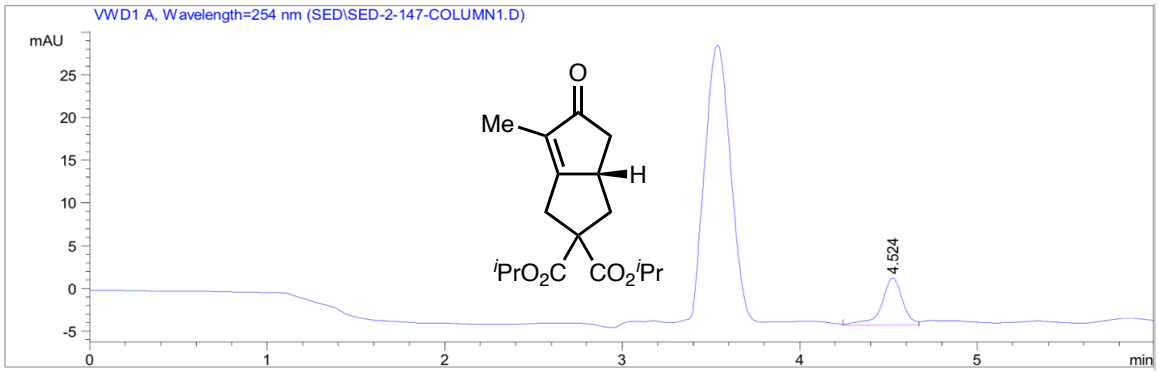


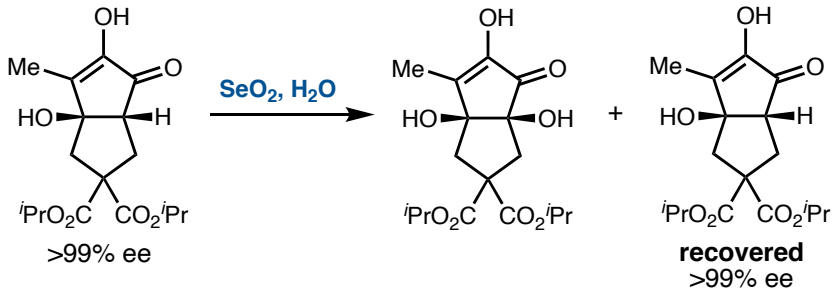


Recovered from **(+)-7a*** (200 mg, 0.65 mmol, >99% ee) following General Procedure I. The crude residue was purified by column chromatography (silica, 0 to 30% EtOAc/hexanes) to yield **(+)-7a*** (150 mg, 75% recovery) in >99% ee.

$\boxed{[\alpha]_D^{22} =}$ +126 (c = 0.2, $CHCl_3$).

(+)-7a*: enantioenriched, >99% ee

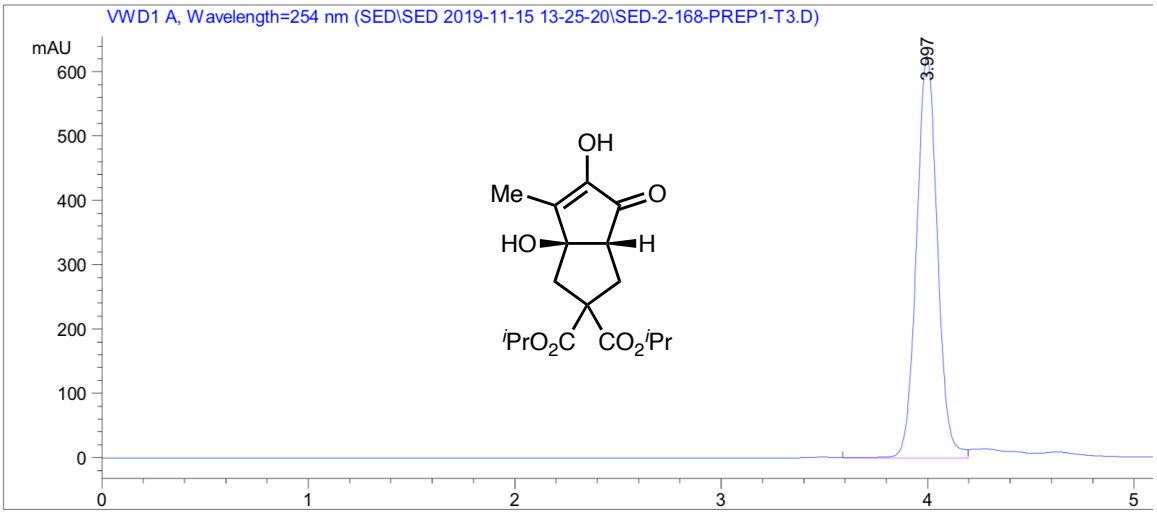


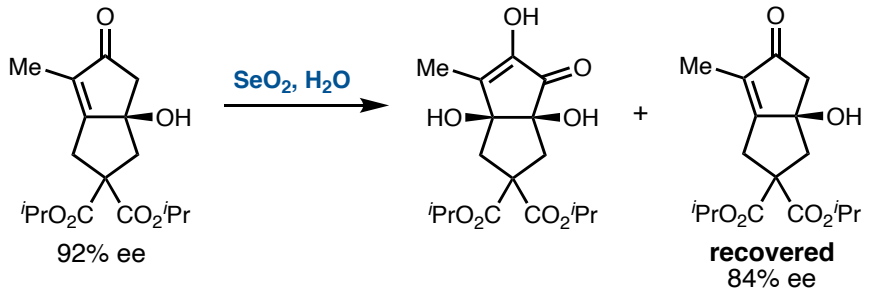


Recovered from **(–)-8a*** (60 mg, 0.18 mmol, >99% ee) following General Procedure I. The crude residue was purified by preparative thin layer chromatography (silica, 10% MeOH/DCM) to yield **(–)-8a*** (2.2 mg, 4% recovery) in >99% ee.

$\boxed{[\alpha]_D^{22} =}$ –36 (c = 0.1, $CHCl_3$).

(–)-8a*: enantioenriched, >99% ee

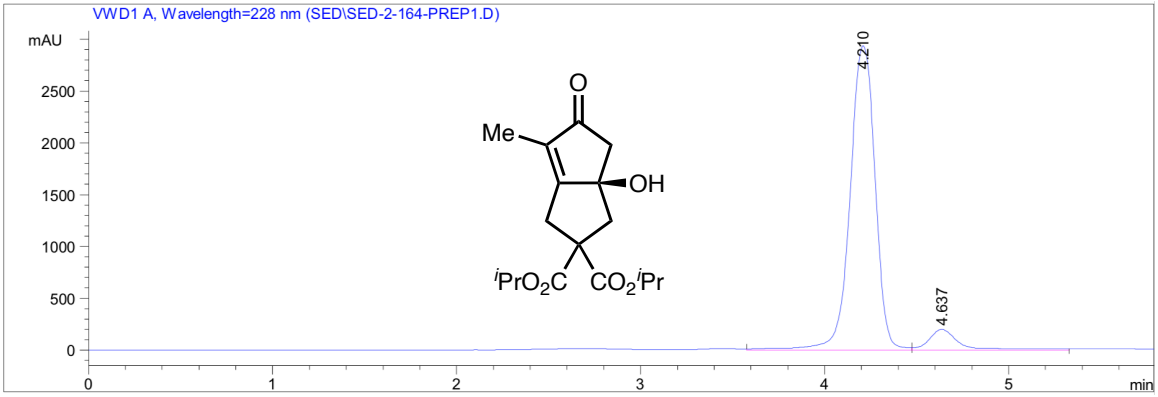




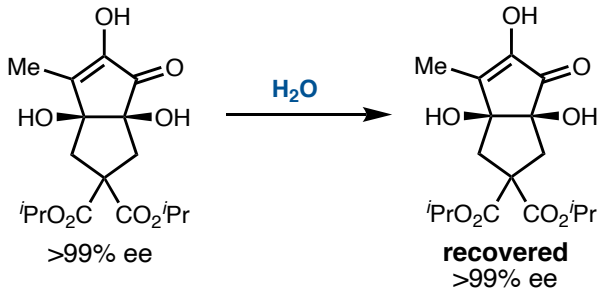
Recovered from **(+)-49a*** (20 mg, 0.65 mmol, 92% ee) following General Procedure I. The crude residue was purified by column chromatography (silica, 0 to 30% EtOAc/hexanes) followed by preparative thin layer chromatography (silica, 7% MeOH/DCM) to yield **(+)-49a*** (2.2 mg, 11% recovery) in 84% ee.

$\boxed{[\alpha]_D^{22} =}$ +30 (c = 0.1, $CHCl_3$).

(+)-49a*: enantioenriched, 84% ee



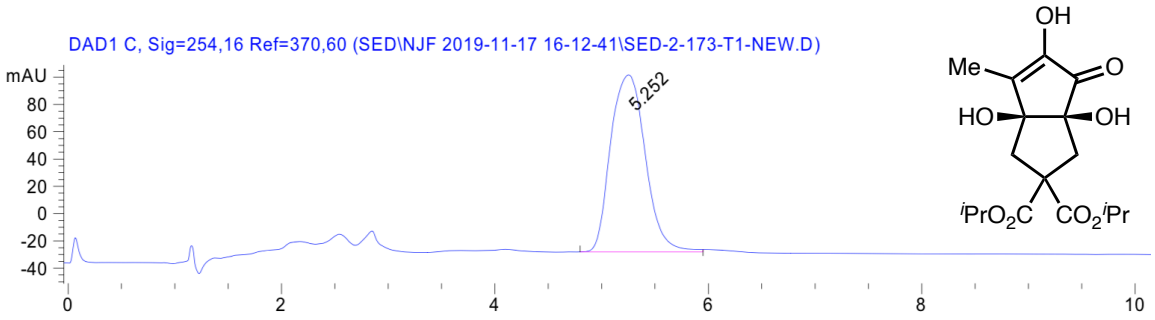
Peak #	RetTime [min]	Type	Width [min]	Area mAU *s	Height [mAU]	Area %
1	4.210	VV	0.1488	2.79395e4	2938.34180	92.1256
2	4.637	VB	0.1743	2388.11646	199.86485	7.8744



Recovered from **(–)-33a*** (10 mg, 0.03 mmol, >99% ee) following General Procedure I except that the addition of SeO_2 to the reaction mixture was omitted. The crude residue afforded **(–)-33a*** (10 mg, 99% recovery) in >99% ee.

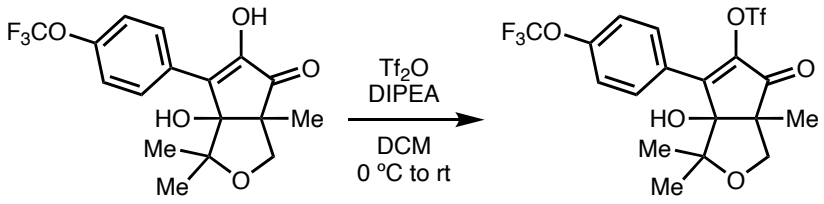
$\boxed{[\alpha]_D^{22} =}$ –90 (c = 0.7, $CHCl_3$).

(–)-33a*: enantioenriched, >99% ee



3.8.8 *Product Functionalization*

6a-hydroxy-1,1,3a-trimethyl-4-oxo-6-(4-(trifluoromethoxy)phenyl)-3,3a,4,6a-tetrahydro-1*H*-cyclopenta[*c*]furan-5-yl trifluoromethanesulfonate (9)



To a 1-dram vial with a stir bar was added **5e** (65 mg, 0.2 mmol, 1.0 equiv). The vial was sealed with a rubber septum and placed under an atmosphere of N_2. The solid was taken up in DCM (1 mL, 0.20 M) and stirred, $^{i}Pr_2NEt$ (53 μL, 0.3 mmol, 1.5 equiv) added, and the solution cooled to 0 °C in an ice water bath. Trifluoromethanesulfonic anhydride (34 μL, 0.2 mmol, 1.0 equiv) was then added dropwise via syringe, with a vent needle to release any triflic acid generated. The resulting mixture was allowed to reach room temperature and monitored by TLC. Upon completion, the reaction was quenched by dropwise addition of water then diluted with water and DCM. The layers were separated, and the aqueous layer was extracted twice with DCM. Combined organics were washed with water and brine, dried over Na_2SO_4, filtered, and concentrated. The crude residue was purified by trituration from DCM and pentanes (1:4) to yield **9** (88 mg, 0.20 mmol, 99% yield) as a white solid.

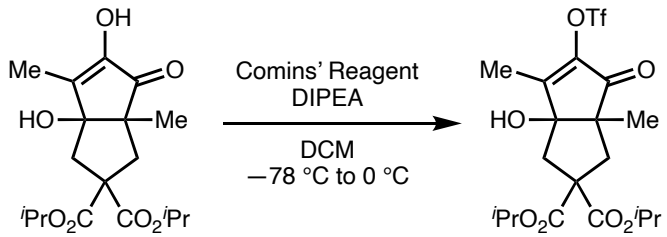
^{1}H NMR (400 MHz, $CDCl_3$): δ 8.00 – 7.92 (m, 2H), 7.32 (ddt, *J* = 8.0, 2.2, 1.1 Hz, 2H), 4.13 (d, *J* = 9.9 Hz, 1H), 3.68 (d, *J* = 9.9 Hz, 1H), 1.31 (d, *J* = 3.0 Hz, 6H), 0.96 (s, 3H).

^{13}C NMR (101 MHz, $CDCl_3$): δ 197.78, 154.23, 150.22, 142.15, 130.58, 127.74, 120.74, 119.77, 118.92, 118.16, 115.73, 87.96, 83.57, 70.39, 57.68, 28.85, 24.99, 20.77, 15.62.

FTIR (NaCl, thin film, cm^{-1}): 3446, 2994, 29256, 2854, 2355, 1738, 1732, 1715, 1632, 1506, 1434, 1212.

HRMS (TOF-ESI, *m/z*): $[M + H]^+$ calcd for $C_{18}H_{17}F_6O_7S$: 491.0594; found: 491.0603.

diisopropyl 6a-hydroxy-3a,6-dimethyl-4-oxo-5-(((trifluoromethyl)sulfonyl)oxy)-3,3a,4,6a-tetrahydropentalene-2,2(1*H*)-dicarboxylate (54)



To a round bottom flask with a stir bar was added **5a** (648 mg, 1.8 mmol, 1 equiv). The solid was taken up in DCM (37 mL, 0.05 M) and stirred, DIPEA (1.6 mL, 1.25 mmol, 5 equiv) added, and the solution cooled to –78 °C. Comins' Reagent (719 mg, 0.25 mmol, 1 equiv) was then added and the mixture cooled to 0 °C. Upon complete consumption of the substrate, the reaction was directly purified by column chromatography (silica, 20% EtOAc/hexanes) to afford **54** (797 mg, 90% yield) as an orange oil.

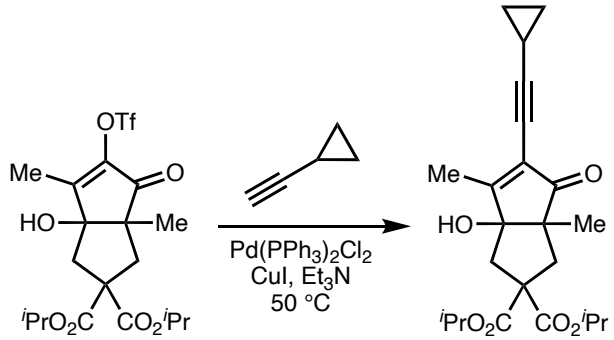
^{1}H NMR (400 MHz, $CDCl_3$): δ 5.06 (heptd, *J* = 6.3, 0.9 Hz, 1H), 4.93 (pd, *J* = 6.3, 0.8 Hz, 1H), 2.72 (d, *J* = 14.5 Hz, 1H), 2.52 (s, 2H), 2.24 (d, *J* = 14.5 Hz, 1H), 2.18 (s, 3H), 1.24 (dd, *J* = 6.3, 3.0 Hz, 6H), 1.21 – 1.09 (m, 9H).

^{13}C NMR (101 MHz, $CDCl_3$): δ 198.44, 171.95, 169.21, 162.78, 142.51, 120.15, 116.96, 85.09, 70.56, 70.02, 59.41, 55.72, 44.20, 41.99, 21.57, 21.55, 21.35, 19.30, 10.82.

FTIR (NaCl, thin film, cm^{-1}): 3477, 2982, 2939, 1738, 1732, 1715, 1428, 1219, 1099, 987, 896.

HRMS (TOF-ESI, *m/z*): $[M + NH_4]^+$ calcd for $C_{19}H_{29}F_3O_9SN$: 504.1510; found: 504.1521.

diisopropyl 5-(cyclopropylethynyl)-6a-hydroxy-3a,6-dimethyl-4-oxo-3,3a,4,6a-tetrahydropentalene-2,2(1*H*)-dicarboxylate (55a)



Prepared from **54** (24.4 mg, 0.05 mmol, 1.0 equiv), cyclopropyl acetylene (22 L, 0.25 mmol, 5.0 equiv), $Pd(PPh_3)_2Cl_2$ (3.5 mg, 0.005 mmol, 0.1 equiv), CuI (1.91 mg, 0.01 mmol, 0.2 equiv), Et_3N (0.20 mL, 0.25 M) at 50 °C following General Procedure B. The resulting crude residue was purified by column chromatography (silica, 30% EtOAc/hexanes) to afford **55a** (10.1 mg, 51% yield) as a brown oil.

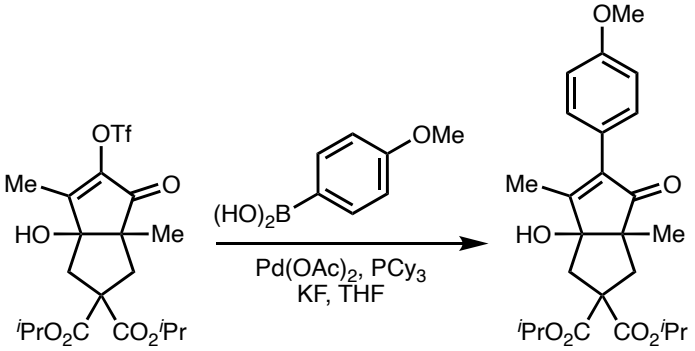
^{1}H NMR (400 MHz, $CDCl_3$): δ 5.02 (hept, *J* = 6.3 Hz, 1H), 4.89 (hept, *J* = 6.3 Hz, 1H), 2.73 (dd, *J* = 14.2, 1.3 Hz, 1H), 2.58 (dd, *J* = 13.9, 1.2 Hz, 1H), 2.56 (s, 1H), 2.44 (dd, *J* = 13.9, 0.8 Hz, 1H), 2.16 (s, 3H), 2.12 (dd, *J* = 14.1, 0.8 Hz, 1H), 1.44 (tt, *J* = 8.2, 5.0 Hz, 1H), 1.22 (dd, *J* = 6.3, 2.2 Hz, 6H), 1.18 (t, *J* = 6.0 Hz, 6H), 1.12 (s, 3H), 0.93 – 0.80 (m, 2H), 0.81 – 0.75 (m, 2H).

^{13}C NMR (101 MHz, $CDCl_3$): δ 206.20, 175.31, 171.87, 169.34, 125.41, 103.47, 87.80, 70.10, 69.76, 65.93, 59.21, 56.14, 44.03, 42.93, 30.10, 29.84, 22.84, 21.58, 21.57, 21.45, 19.47, 13.57, 9.21, 1.16.

FTIR (NaCl, thin film, cm^{-1}): 3480, 2927, 2870, 2231, 1716, 1627, 1456, 1386, 1259.

HRMS (TOF-ESI, *m/z*): $[M + H]^+$ calcd for $C_{23}H_{31}O_6$: 403.2155; found: 403.2135.

diisopropyl 6a-hydroxy-5-(4-methoxyphenyl)-3a,6-dimethyl-4-oxo-3,3a,4,6a-tetrahydropentalene-2,2(1*H*)-dicarboxylate (55b)



Prepared from **54** (43 mg, 0.09 mmol, 1.0 equiv), (*p*-methoxyphenyl boronic acid (41 mg, 0.27 mmol, 3.0 equiv), potassium fluoride (30.8 mg, 0.53 mmol, 6.0 equiv), THF (5 mL), and catalyst stock solution (0.9 mL, 0.10 M, 0.04 equiv [Pd], 0.05 equiv PCy_3), prepared from $Pd(OAc)_2$ (4.5 mg, 0.02 mmol) and tricyclohexyl phosphine (7.1 mg, 0.025 mmol), at 60 ºC following a literature procedure.[35] The crude residue was purified by column chromatography (silica, 30 to 40% EtOAc/hexanes) to afford **55b** (36.4 mg, 92% yield) as a white amorphous solid.

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.32 – 7.22 (m, 2H), 6.96 – 6.88 (m, 2H), 5.04 (hept, *J* = 6.3 Hz, 1H), 4.79 (hept, *J* = 6.3 Hz, 1H), 3.82 (s, 3H), 2.78 (ddd, *J* = 17.5, 13.9, 1.5 Hz, 2H), 2.48 (d, *J* = 12.4 Hz, 1H), 2.19 (d, *J* = 14.0 Hz, 1H), 2.18 (s, 3H), 1.22 (dd, *J* = 6.3, 1.2 Hz, 6H), 1.09 (d, *J* = 6.3 Hz, 3H), 0.99 (d, *J* = 6.3 Hz, 3H).

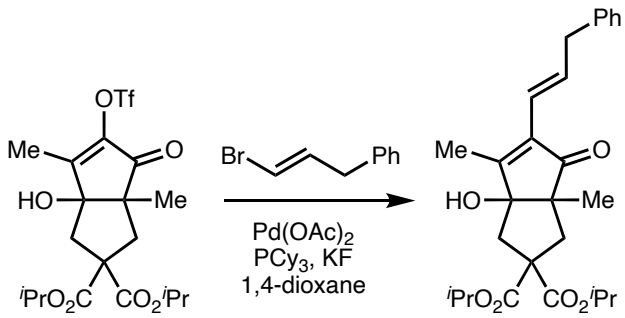
^{13}C NMR (101 MHz, $CDCl_3$): δ 207.85, 171.68, 169.63, 168.08, 159.46, 138.41, 130.55, 123.30, 113.76, 87.60, 69.99, 69.52, 58.88, 55.67, 55.39, 43.87, 43.14, 21.62, 21.53,

21.23, 19.59, 12.84.

FTIR (NaCl, thin film, cm^{-1}): 3471, 3047, 2843, 2549, 2248, 2056, 1713, 1454, 1249.

HRMS (TOF-ESI, *m/z*): $[M + H]^+$ calcd for $C_{25}H_{33}O_7$: 445.2221; found: 445.2242.

diisopropyl (*E*)-6a-hydroxy-3a,6-dimethyl-4-oxo-5-(3-phenylprop-1-en-1-yl)-3,3a,4,6a-tetrahydropentalene-2,2(1*H*)-dicarboxylate (55c)



Prepared from **54** (49 mg, 0.1 mmol, 1.0 equiv), (E)-(3-bromoallyl)benzene (49 mg, 0.3 mmol, 3.0 equiv), potassium fluoride (35 mg, 0.6 mmol, 6.0 equiv), 1,4-dioxane (1 mL), and catalyst stock solution (0.5 mL, 0.10 M, 0.04 equiv [Pd], 0.05 equiv PCy_3), prepared from $Pd(OAc)_2$ (1.8 mg, 0.008 mmol) and tricyclohexyl phosphine (2.8 mg, 0.01 mmol), at 60 ºC following a literature procedure.[35] The crude residue was purified by column chromatography (silica, 30% (Et_2O/EtOAc, 1:1)/hexanes) to afford **55c** (35.3 mg, 78% yield) as a white amorphous solid.

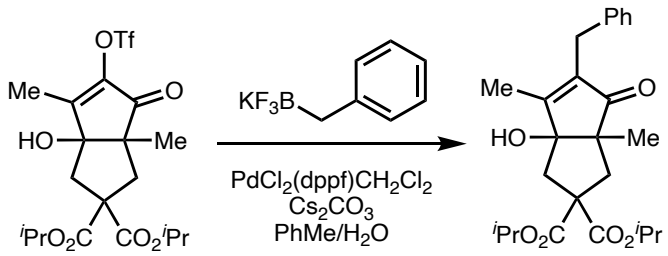
^{1}H NMR (400 MHz, $CDCl_3$): δ 7.33 – 7.23 (m, 2H), 7.19 (tt, *J* = 6.4, 1.2 Hz, 3H), 6.94 (dt, *J* = 15.8, 7.1 Hz, 1H), 6.03 (dt, *J* = 15.8, 1.6 Hz, 1H), 5.01 (hept, *J* = 6.2 Hz, 1H), 4.74 (pd, *J* = 6.3, 1.0 Hz, 1H), 3.51 – 3.44 (m, 2H), 2.74 (dd, *J* = 13.9, 1.4 Hz, 1H), 2.65 (dt, *J* = 13.7, 1.2 Hz, 1H), 2.40 (d, *J* = 13.7 Hz, 1H), 2.12 (d, *J* = 14.2 Hz, 1H), 2.10 (s, 3H), 1.21 (dd, *J* = 6.3, 1.5 Hz, 6H), 1.11 (t, *J* = 3.1 Hz, 6H), 1.05 (d, *J* = 6.3 Hz, 3H).

^{13}C NMR (101 MHz, $CDCl_3$): δ 13C NMR (101 MHz, CDCl3) δ 208.26, 171.72, 169.43, 167.36, 139.74, 136.99, 133.88, 128.78, 128.59, 126.29, 119.62, 87.37, 69.95, 69.56, 58.88, 55.87, 43.83, 43.07, 40.51, 21.59, 21.48, 21.37, 19.59, 12.03.

FTIR (NaCl, thin film, cm^{-1}): 3470, 2981, 2929, 1728, 1715, 1454, 1375, 1258, 1258.

HRMS (TOF-ESI, *m/z*): $[M - H_2O + H]^+$ calcd for $C_{27}H_{33}O_5$: 437.2323; found: 437.2320.

diisopropyl 5-benzyl-6a-hydroxy-3a,6-dimethyl-4-oxo-3,3a,4,6a-tetrahydropentalene-2,2(1*H*)-dicarboxylate (55d)



Prepared from **54** (36.8 mg, 0.08 mmol, 1.0 equiv), $BnBF_3K$ (41.9 mg, 0.23 mmol, 3.01 equiv), Cs_2CO_3 (70.7 mg, 0.22 mmol, 2.9 equiv), $PdCl_2(dppf)CH_2Cl_2$ (5.9 mg, 0.007 mmol, 0.1 equiv), and PhMe (0.43 mL) and water (0.14 mL, 0.125 M total ($PhMe/H_2O$, 3:1)) at 80 ºC following a literature procedure.[36] The crude residue was purified by column chromatography (silica, 10 to 20% EtOAc/hexanes) to afford **55d** (27.9 mg, 86% yield) as a yellow gel.

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.38 – 7.29 (m, 2H), 7.29 – 7.21 (m, 3H), 5.13 (hept, *J* = 6.2 Hz, 1H), 4.81 (heptd, *J* = 6.3, 1.3 Hz, 1H), 3.63 (d, *J* = 14.5 Hz, 1H), 3.47 (d, *J* = 14.5 Hz, 1H), 2.80 (dd, *J* = 14.2, 1.1 Hz, 1H), 2.68 (s, 1H), 2.65 (dd, *J* = 14.0, 1.1 Hz, 1H), 2.53 (d, *J* = 14.0 Hz, 1H), 2.26 (d, *J* = 14.1 Hz, 1H), 2.16 (s, 3H), 1.32 (dd, *J* = 6.3, 2.8 Hz, 6H), 1.23 (dd, *J* = 6.2, 1.5 Hz, 6H), 1.20 (s, 3H).

^{13}C NMR (101 MHz, $CDCl_3$): δ 208.88, 172.03, 169.47, 169.14, 138.67, 138.36, 128.67, 128.61, 126.25, 88.15, 70.00, 69.35, 59.31, 59.29, 55.95, 43.92, 42.41, 29.14, 21.58, 21.55, 21.45, 19.58, 12.18.

FTIR (NaCl, thin film, cm^{-1}): 3460, 2981, 2933, 1728, 1645, 1376, 1259, 1098.

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