Article

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Abstract Image
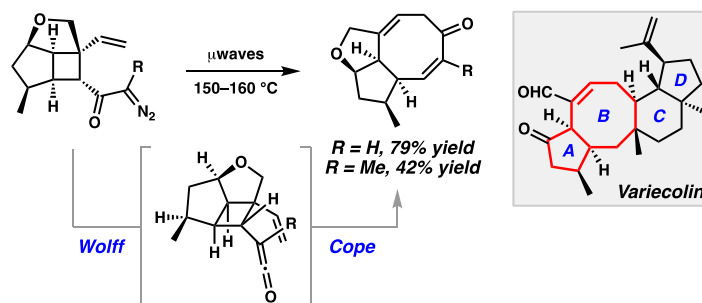
Abstract

A stereoselective synthesis of the AB ring of the complex sesterterpenoid variecolin is presented. Our strategy features the development of a tandem Wolff/Cope rearrangement of α-diazo cyclobutyl ketones for the construction of fused, eight-membered carbocycles. Preliminary studies revealed a facile Wolff rearrangement but a difficult vinyl ketene cyclobutane Cope rearrangement. We have leveraged an efficient microwave-promoted tandem rearrangement to prepare the desired functionalized cyclooctadienones that we envision as potential key intermediates in the convergent synthesis of variecolin.

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Introduction

The complex sesterterpenoid variecolin (**1**) was isolated in 1991 by Hensens and co-workers from the fungal fermentation extracts of *Aspergillus variecolor*.[1] The fascinating polycyclic structure of **1** was elucidated by NMR methods and later confirmed by X-ray crystallography,[2] with the natural antipode[3] represented in Figure 1. Preliminary biological evaluation has established an array of activities for variecolin. The original report identified **1** as a modest angiotensin II receptor binding inhibitor with potential application in the treatment of hypertension.[1] Subsequent studies demonstrated **1** to suppress the proliferation of induced mouse splenic lymphocytes.[3] Variecolin has also been shown to compete with macrophage inflammatory protein (MIP)-1α for binding to CCR5,[2] a key chemokine receptor involved in the uptake of HIV-1 into target cells. Other reports have identified general antifungal properties.[4] Several variecolin congeners have also been identified from other fungal species, with many exhibiting a similar biological profile (Figure 1).[2,3,4,5,6] The varied activity and intriguing molecular architecture of this family of sesterterpenes serves to stimulate new strategies targeting their chemical synthesis. Our interest in the pursuit of an effective synthetic strategy toward these bioactive natural products focused on variecolin given that it is the most widely studied and biologically relevant member.
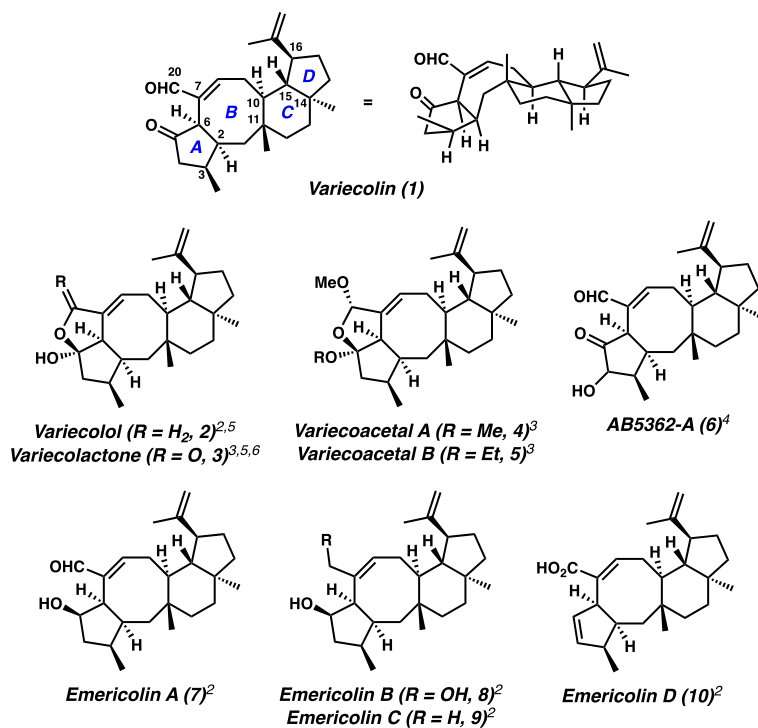
Figure 1. Variecolin family of sesterterpenes.

Synthesis Design

The 25-carbon tetracyclic core of variecolin (**1**) consists of a central eight-membered ring and possesses eight stereocenters, including two all-carbon quaternary stereocenters at C(11) and C(14) of the BC and CD ring fusions, respectively. Synthetic control of the relative and absolute stereochemistry of these trans-fused rings that form a stereopentad poses a notable design challenge for critical bond-forming reactions. We therefore envisioned that the assembly of these key features of variecolin in a convergent manner would provide opportunities to explore new reactivity. When considering key elements toward our synthetic design, we were drawn to the eight-membered B ring. Eight-membered rings are common structural motifs that occur in widely diverse terrestrial plants, insects, marine organisms, and fungi. The theoretical and synthetic intrigue of these medium-sized carbocyclic structures has stimulated the development of various strategies for their preparation, many of which have been applied toward the synthesis of complex molecular targets.[7] Inasmuch as we are restricted by the limitations of reaction scope in the state of the art, the selective preparation of eight-membered carbocycles remains a noteworthy and

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continuing challenge to modern chemical methods.[8] No total synthesis of variecolin or any family members has been reported to date, however, significant progress toward this end has been achieved by the Piers[9] and Molander[10] labs. Related general strategic advancements have also been reported.[11,12,13]

The formulation of our synthetic approach toward variecolin (**1**) focused on the construction of the central eight-membered ring, revealing a critical C ring disconnection that could simplify the target into two functional AB (**11**) and D ring (**12**) fragments (Scheme 1). The scalable synthesis of D ring fragment **13** has been advanced by our lab using an asymmetric alkylation/ring contraction technology.[14] Notably, this acylcyclopentene motif is amenable to selective functionalization. A suitable AB ring fragment could comprise functionalized cyclooctadienone **14** in order to facilitate selective bond forming reactions at the C(10) and C(11) positions. This structural unit is comparable to fused bicyclic cycloheptadienones that have been constructed using a powerful tandem Wolff/Cope rearrangement developed in our lab.[15] Extending this technology to eight-membered carbocycles, we anticipated that AB ring synthon **14** could be accessed through a Wolff/Cope rearrangement of highly functionalized α-diazo cyclobutyl ketone **15**, which may in turn be assembled via a cycloaddition of allylic alcohol **16** and an appropriate functionalized olefin component. The design of tandem reaction sequences for the rapid generation of molecular complexity is an area of constant investigation in our laboratory,[16] and therefore a primary objective of our synthetic endeavor toward variecolin (**1**) is the development of a tandem Wolff/Cope rearrangement to forge fused eight-membered carbocyclic systems. Application of this key transformation for the construction of the central B ring of **1** would expand the reaction scope, and furthermore, would create a new tool for the general preparation of natural and non-natural substances containing this eight-membered ring motif. Herein we report the asymmetric synthesis of the AB ring of variecolin employing a tandem Wolff/Cope rearrangement to forge the eight-membered carbocycle.

Scheme 1. Retrosynthetic analysis of variecolin (**1**)
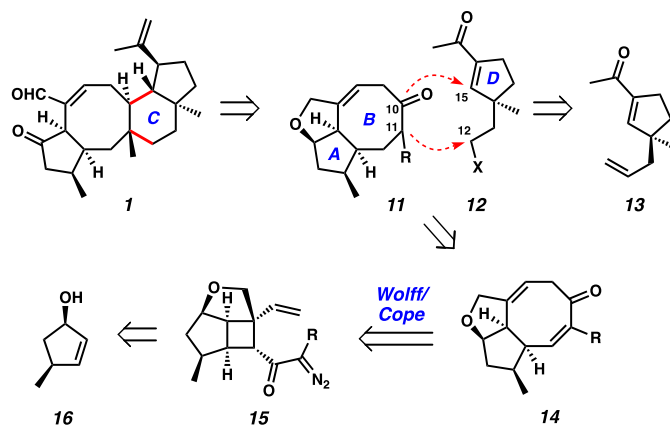
Results and Discussion

A. Synthesis of a Wolff/Cope Model Substrate. The development of a tandem Wolff/Cope rearrangement toward the fused bicyclic eight-membered AB ring fragment (**14**) required an expedient, regio and stereoselective synthesis of a highly substituted cyclobutane substrate (e.g., **15**). During the course of our efforts, we elected to employ an efficacious intramolecular cyclobutadiene–olefin cycloaddition for the rapid construction of this moiety.[17,18,19] Model studies pursued toward this goal provided insight into the identification and physical properties of reaction intermediates using a readily accessible cyclopentenol analogue.

Our investigations toward an AB ring model system began with the preparation of a suitable cyclopentenol that would engage cyclobutadiene via a tethered[20] cycloaddition. Convenient access to stereodefined 4-substituted cyclopentenols is possible using copper-catalyzed allylic substitution chemistry. Exposure of allylic monoacetate (±)-**17**[21] to a mixture of CuCN and *p*-tolylmagnesium bromide generated *anti*-cyclopentenol **18**[22] in excellent yield (Scheme 2). We then sought the alkylation of this alcohol with (cyclobutadiene)tricarbonyliron complexes that possess sufficient electrophilicity to react under mild conditions.[23] This was achieved by the zinc(II)-catalyzed alkylation[24] of cyclopentenol **18** with trichloroacetimidate **19** to prepare the requisite intramolecular cycloaddition substrate **20** in 76% yield. Oxidative liberation of cyclobutadiene promoted by ceric ammonium nitrate (CAN) and subsequent [4+2] cycloaddition rapidly assembled cyclobutene **21** as a single diastereomer in 76% yield.

Scheme 2. Tethered olefin-cyclobutadiene cycloaddition of alcohol (±)-**18**
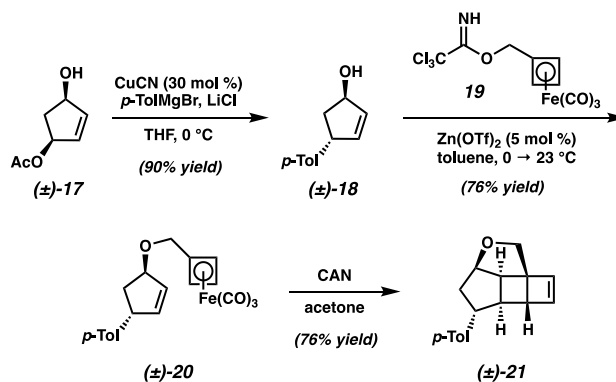
Advancement of cycloadduct **21** toward a Wolff/Cope substrate necessitated a regioselective olefin functionalization with our aim of generating a C(8) aldehyde and C(10) ester (i.e., **24**).[25] We were intrigued by Schreiber's method[26,27] for the ozonolytic cleavage of olefins to terminally differentiated products as it has been demonstrated as a powerful tool for the regioselective cleavage of advanced synthetic intermediates in complex molecule synthesis.[28] In the event, ozonolysis of cycloadduct **21** in CH_2Cl_2/MeOH followed by an acylation and base induced elimination provided a mixture of several of compounds, including undesired acetal **22** in 13% yield and an inseparable 9:1 mixture of acetal **23** and desired aldehyde **24** in 68% yield (Scheme 3). Direct Wittig methylenation of this mixture afforded pure acetal **23**[29] in addition to minor quantities of desired olefin **25**.

Scheme 3. Termini-differentiating ozonolysis of cyclobutene **21**
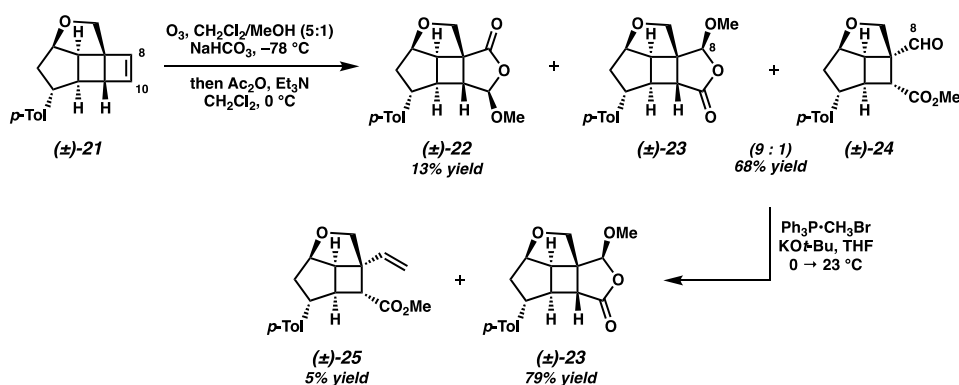
The production of acetals **22** and **23** from this unsymmetrical ozonolysis indicates diverging reaction pathways. Cycloaddition of ozone and cyclobutene **21** likely generates primary ozonide **26**, which could fragment in two possible ways (Scheme 4, paths *a* and *b*). Cleavage of the primary ozonide to **27** (path *a*) positions the carbonyl oxide on the fully substituted carbon. Subsequent addition of methanol to this intermediate and dehydration of **28** with Ac$_2$O/Et$_3$N generates acetal **22**. Conversely, primary ozonide cleavage in the opposite manner produces **29** (path *b*) with the carbonyl oxide positioned on the less-substituted carbon. This intermediate further reacts by another of two possible pathways: (1) addition of methanol from the reaction medium (path *c*) and dehydration of **30** to generate acetal **23**, or (2) methanol addition to the carbonyl oxide (path *d*) and dehydration of **31** to furnish aldehyde **24**. Although desired aldehyde **24** is a minor component of this reaction, the selectivity for the cleavage of primary ozonide **26** via the desired path *b* is favored in an approximate 5:1 ratio and is presumably the result of steric influences on the primary ozonide moiety.[30]

Scheme 4. Diverging pathways for the termini-differentiating ozonolysis of cycloadduct **21**
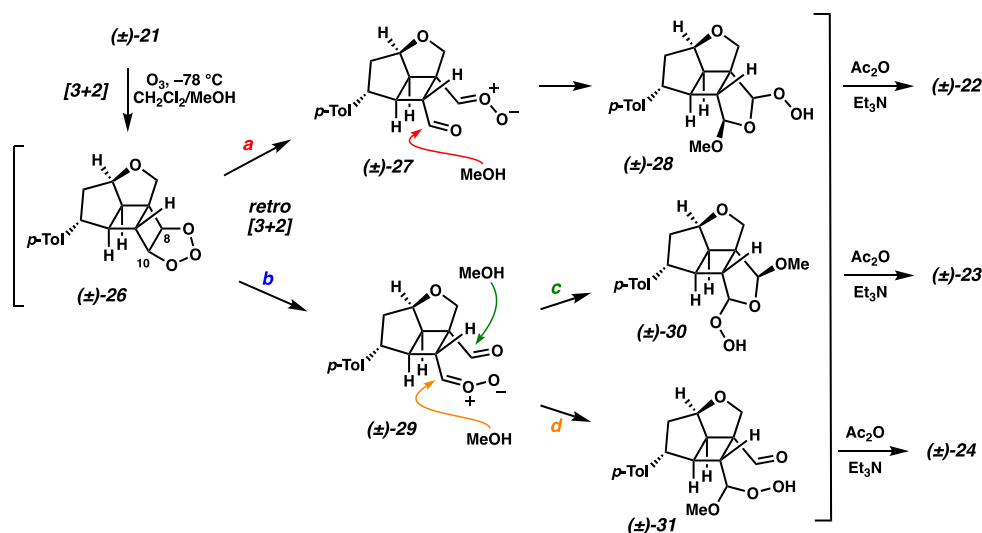
The identification of aldehyde **24** as a minor product from the unsymmetrical ozonolysis of cyclobutene **21** hindered progress toward a model Wolff/Cope substrate. Fortuitously, we recognized that acetal **23** and aldehyde **24** arise from the same fragmentation pathway (path *b*) and thus possess the same C(8) aldehyde oxidation state. Encouraged by this result, we explored potential equilibration conditions to determine the propensity for formation of aldehyde **24** from

the isomeric aldehyde/acetal mixture (Table 1). We were gratified to find that solvation of pure acetal **23** in methanol effected the equilibration in favor of aldehyde **24** and produced minor quantities of acetal diastereomer **32**[29] (entries 1 and 2). A survey of various Lewis acids identified the proficiency of divalent triflate salts in shifting the equilibrium to further favor **24** (entries 3–6).[31] Similarly, molecular sieves and combinations thereof with Lewis acids proved to be efficient for the conversion to **24** (entries 7–10) to reach the apparent equilibrium of ca. 3:1 aldehyde **24** to acetals **23** and **32**. We elected to proceed in our synthesis using 4 Å MS due to operational simplicity.

Table 1. Equilibration of acetal **23** to aldehyde **24**
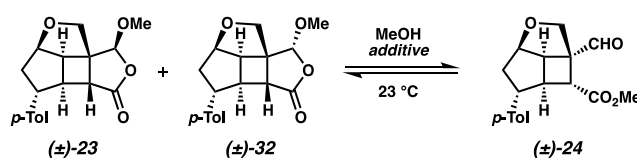
entry[a]	additive[b]	**23**/**32** : **24**[c]
1	—	66 : 34
2	—[d]	39 : 61
3	CuCl$_2$	75 : 25
4	ZnCl$_2$	41 : 59
5	Cu(OTf)$_2$	36 : 64
6	Zn(OTf)$_2$	30 : 70
7	3 Å MS	32 : 68
8	4 Å MS	29 : 71
9	4 Å MS/Zn(OTf)$_2$	27 : 73
10	4 Å MS/Cu(OTf)$_2$	28 : 72

[a] Each entry started from pure acetal **23**. [b] Lewis acids were used in 20 mol %; molecular sieves were used in 0.5 g/mmol. [c] Ratio determined by ^{1}H NMR analysis of crude reaction filtrate after 20–24 h. [d] At 50 °C.

The equilibration of acetal **23** to desired aldehyde **24** considerably improved the overall reaction sequence for the preparation of a Wolff/Cope α-diazo cyclobutyl ketone substrate. An optimized sequence involves the unsymmetrical ozonolysis of cyclobutene **21** followed by equilibration with 4 Å MS in methanol to afford ca.1:3 ratio of acetals **23**/**32** and aldehyde **24** (Scheme 5a). Wittig methylenation of this crude reaction mixture produced the desired olefin (**25**) in 40% yield over three steps and the recovery of acetal diastereomers **23** and **32** in 14% yield. The recovered acetal mixture enabled recycling of material to augment our quantity of olefin **25** (Scheme 5b). The model Wolff/Cope substrate synthesis was completed by the high-yielding

hydrolysis of ester **25** with KOTMS and conversion to α-diazoketone **34** by way of an acid chloride and diazomethane.

Scheme 5. a) Optimized synthesis of model α-diazo cyclobutyl ketone **34**; b) Recycling of acetal **23/32** to increase the production of olefin **25**
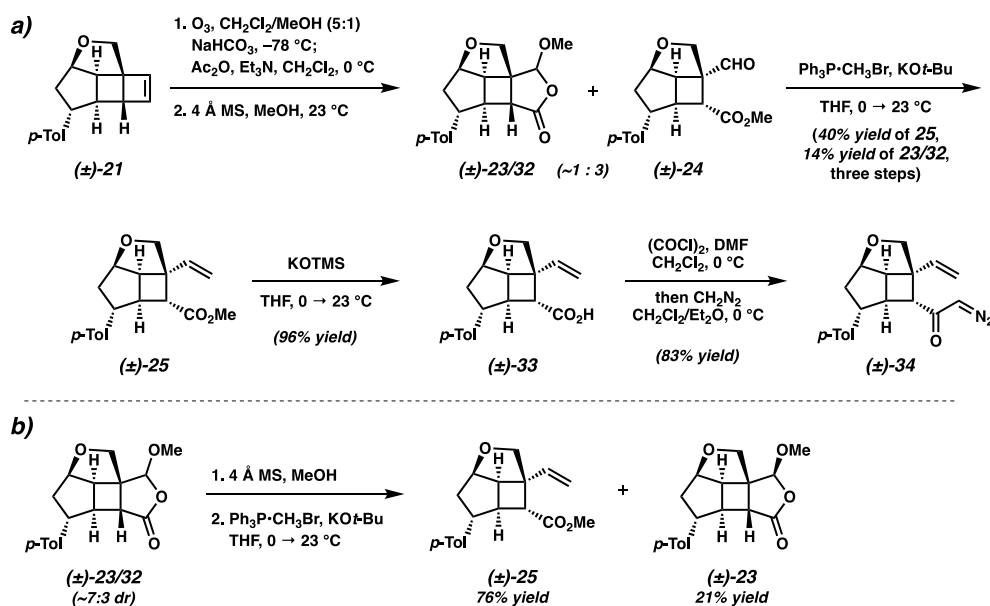
B. Wolff-Cope Examination. The synthesis of α-diazo cyclobutyl ketone **34** enabled the examination of our key Wolff/Cope rearrangement toward the eight-membered B ring of variecolin. A critical component to the success of our previously reported tandem Wolff/Cope rearrangement was the identification of photochemical or silver-catalyzed sonochemical conditions to allow direct access to a variety of [*n*–7] fused bicyclic systems in excellent yields.[15] Thorough investigations of this transformation using substrate **34** under various photochemical or silver(I)-catalyzed sonochemical conditions afforded only intractable mixtures and no evidence of the desired cyclooctadienone **35**. The lack of useful information acquired from these initial experiments required us to examine the tandem process in a stepwise manner. Accordingly, irradiation of α-diazo cyclobutyl ketone **34** in methanol at 350 nm induced the photochemical Wolff rearrangement to form homologated ester **37** as the sole product, confirming the intermediacy of ketene **36** (Scheme 6). This critical result indicated that we were likely accessing

a facile Wolff rearrangement, however, the ketene vinyl cyclobutane rearrangement does not readily occur under the conditions surveyed.

Scheme 6. Preliminary Wolff/Cope rearrangement studies of α-diazo cyclobutyl ketone **34**
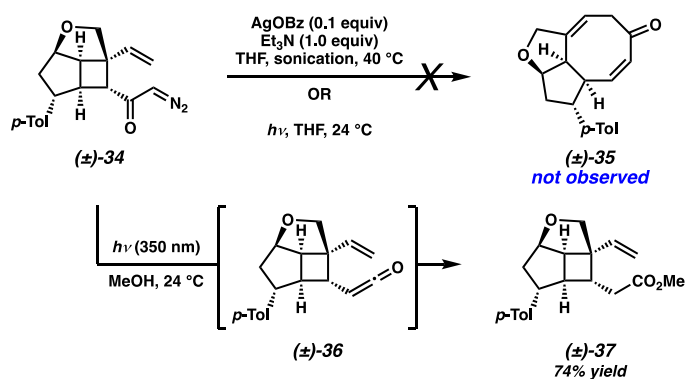
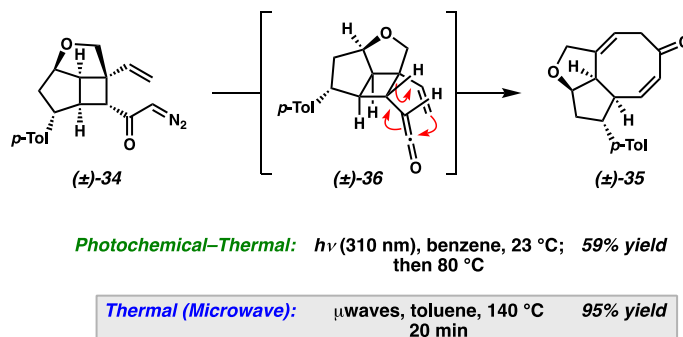In order to rationalize the difficulty of the *cis*-ketene vinyl cyclobutane rearrangement of **36** we considered the analogous *cis*-divinyl cyclobutane rearrangement.[32] A comparison of the experimental activation energy for a strain-releasing Cope rearrangement of *cis*-divinyl cyclobutane is approximately 4–5 kcal/mol higher than the barrier of the cyclopropane analogue,[33] and is consistent with the modestly elevated reaction temperatures known to be required for *cis*-divinyl cyclobutane rearrangements. This reactivity difference, when coupled with our observations that the ketene vinyl cyclopropane rearrangement to afford substituted cycloheptadienones occurs under mild conditions,[15] suggested that thermolysis of the intermediate ketene should facilitate the rearrangement. In the event, a photochemical Wolff rearrangement with subsequent thermolysis at 80 °C provided the desired cyclooctadienone **35** in 59% yield (Scheme 7). With the success of this tandem reaction, we recognized that the general instability of a ketene intermediate and the time between photolysis/thermolysis could account for the moderate yield of **35** and furthermore might hinder material throughput. Our search for alternative conditions was bolstered by reports harnessing microwave irradiation to promote Wolff rearrangements,[34] where we anticipated the surplus energy could facilitate a Cope rearrangement. Indeed, microwave irradiation of α-diazo cyclobutyl ketone **34** for 20 minutes at 140 °C in toluene afforded cyclooctadienone **35** in a remarkable 95% yield. The results of our model system explorations thereby confirm the Wolff/Cope strategy for the synthesis of the AB fragment of variecolin (**1**), and provide new tools for the construction of substituted eight-membered rings. Having

established a viable route toward the AB ring system of variecolin through model system studies, we then pursued an asymmetric synthesis of this desirable fragment.

Scheme 7. Optimal tandem Wolff/Cope rearrangement of α-diazo cyclobutyl ketone **34**

Photochemical–Thermal: $h\nu$ (310 nm), benzene, 23 °C; **59% yield**
then 80 °C

Thermal (Microwave): μwaves, toluene, 140 °C **95% yield**
20 min

C. Asymmetric Synthesis of the AB ring of Variecolin. The application of our proven intramolecular cycloaddition strategy for an asymmetric synthesis of the AB ring fragment (i.e., **14**) originated from a chiral cyclopentenol possessing *syn* stereochemistry. Allylic substitution of monoacetate (+)-**17**[35] using CuCN and methylmagnesium chloride afforded a 95:5 mixture of alcohols **38** and **39** in 91% yield (Scheme 8).[22] Mitsunobu inversion of this alcohol mixture[36] using benzoic acid and subsequent methanolysis of the resulting ester produced allylic alcohol **16** in 81% yield over two steps with the desired *syn* stereochemistry between C(3) and C(5). Lewis acid-catalyzed coupling[24] with trichloroacetimidate **19** gave the requisite intramolecular cycloaddition substrate **40** in good yield.

Scheme 8. Asymmetric synthesis of intramolecular cycloaddition substrate **40**
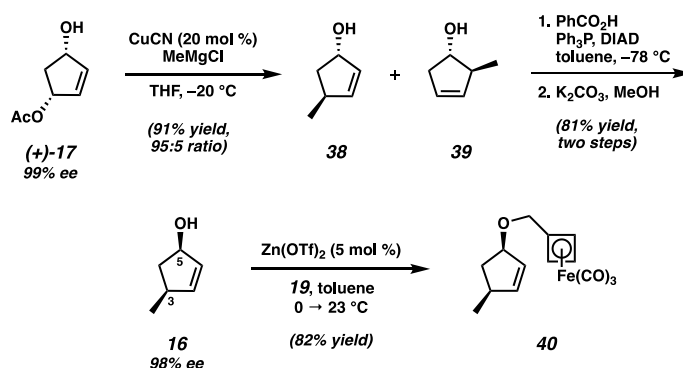
Initial efforts to implement the CAN-promoted intramolecular cyclobutadiene–olefin cycloaddition of **40** resulted in low yields and complex mixtures of products, presumably the result of competing intermolecular dimerization reactions. Snapper has demonstrated that the rapid oxidative decomplexation of (cyclobutadiene)tricarbonyliron complexes using CAN provides sufficient access to cycloadducts of substrates predisposed for the intramolecular cycloaddition.[37] This works well for *anti*-substrate **20**, however, *syn*-substrate **40** possesses a C(3) methyl group that sterically impedes cyclobutadiene access to the olefin. The alternative use of mild oxidants such as trimethylamine-*N*-oxide enact a slow release of highly reactive cyclobutadiene to facilitate access to cycloadducts of substrates with a lower propensity for the cycloaddition (e.g., **40**). Application of trimethylamine-*N*-oxide to facilitate the oxidative decomplexation of **40** in refluxing acetone smoothly generated cycloadduct **41** (Scheme 9).[29,38] Subsequent unsymmetrical ozonolysis of **41**, acetal equilibration promoted by 4 Å MS in refluxing methanol and Wittig methylenation afforded a 2.7:1 ratio of olefins **44** and **45**, in addition to acetals **42** and **43**.[29] This reaction sequence provided desired olefin **44** in 16% yield over four steps, together with 17% yield of recyclable acetal **42**.[39] Acetal **43** was sufficiently crystalline to enable X-ray analysis, providing further confirmation of the desired relative stereochemistry of this polycyclic fragment (Figure 2).[40] It is notable that the termini-differentiating ozonolysis of **41** provided ~ 3:1 ratio of products **44**:**45**, whereas this differentiation strategy with cyclobutene substrate **21** yielded ~ 5:1 ratio of products. The C(3) stereochemistry is the major structural difference between the two fused polycyclic substrates, and it is plausible that subtle changes of the fused ring conformation are impacting the primary ozonide fragmentation pathway (paths a and b, Scheme 4) in an unknown way.

Scheme 9. Cycloaddition, oxidative cleavage and olefination sequence toward an AB ring

Wolff/Cope substrate
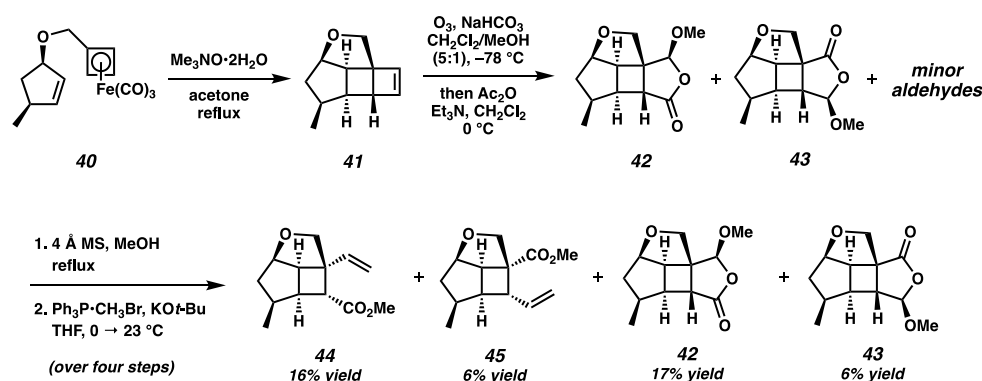
Figure 2. X-ray crystal structure of acetal **43**. The molecular structure is shown with 50%

probability ellipsoids.

We desired cyclooctadienone products in our synthesis of asymmetric AB ring fragment **14** where R = H, Me or alkyl. Model studies have demonstrated the tandem rearrangement where R = H (i.e., **34 → 35**). However, alkyl substitution had not yet been explored for the Wolff/Cope rearrangement and thus represented an unprecedented extension of this method. Advancing to the target α-diazoketones, hydrolysis of ester **44** to acid **46**, conversion to the acid chloride and treatment with either diazomethane (RCH$_2$N$_2$ where R = H) or diazoethane (R = Me) produced α-diazoketones **47** and **48**, respectively (Scheme 10). The efficiency of diazomethane in the acylation of the acid chloride of **46** was notable (91% yield), however, we were surprised by the capricious and lower-yielding results obtained using diazoethane.[41] Unfortunately, improvements in yield could not be realized despite efforts toward further optimization.[42] We were nonetheless delighted

to find that the microwave-promoted tandem Wolff/Cope rearrangement of both substrates resulted in the successful construction of their respective cyclooctadienones (**49** and **50**).

Scheme 10. AB ring α-diazo cyclobutyl ketone synthesis and Wolff/Cope rearrangement
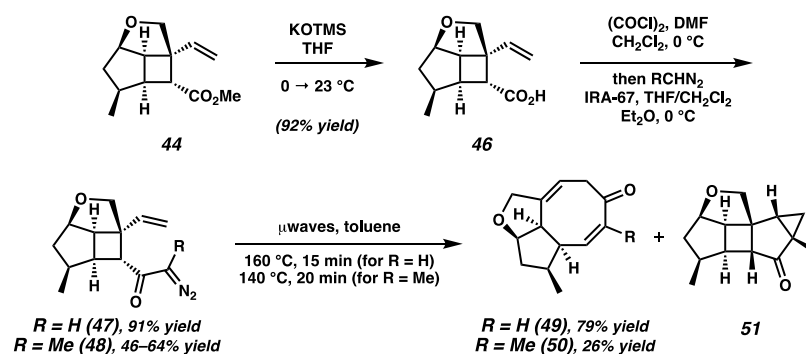
The low yield of α-substituted cyclooctadienone **50** (R = Me) using microwave irradiation is a result of the formation of numerous byproducts.[43] Inspection of these various compounds revealed that cyclopropane **51**[29] is a major side product (ca. 1:1 ratio of **50:51**) of this reaction, ostensibly formed through a carbene intermediate. Two mechanisms have been advanced for the Wolff rearrangement (Scheme 11), comprising a concerted group migration with nitrogen expulsion to a ketene (**53 → 56**) or the stepwise loss of nitrogen to generate an α carbonyl carbene intermediate (**54 → 57**).[42,44] The resulting carbene intermediate can then undergo the desired Wolff rearrangement to ketene **56**, or it can participate in other intra- or intermolecular reactions characteristic of carbenes, such as cyclopropanations, hydride shifts and C–H insertions. Substrate conformation has been demonstrated to be pivotal in the mechanistic outcome, with the *s-Z* conformation typically resulting in products consistent with the concerted pathway.[44,45] Moreover, the large barrier of rotation around the C–C bond imposes a balance between electrostatic attractions and steric repulsions that influence conformation. For example, substrates where R^2 = H exist mostly in the *s-Z* (**53**) conformation, whereas substrates where R^2 = Me exist predominately in the *s-E* conformation (**54**).[44,45]

Scheme 11. Mechanistic pathways for a Wolff rearrangement
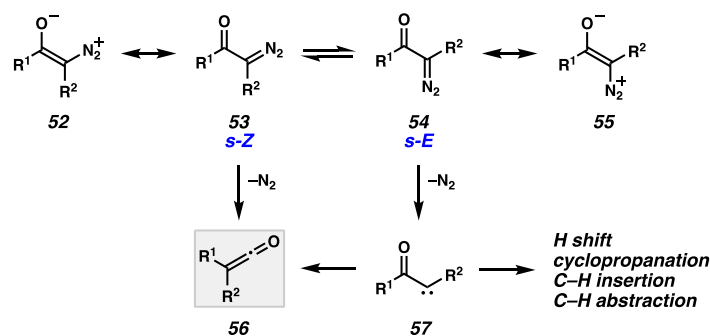
A complicating factor in our analysis of the rearrangement of **48** is that the two mechanisms often operate competitively with high substrate dependence. Given this insight and the interactions that affect conformation, we reasoned that solvent polarity was a plausible parameter to explore. We posited that non-polar solvents might enhance the electrostatic attraction in **52**, favoring the *s-Z* conformation and promoting the concerted rearrangement pathway to increase the production of our targeted cyclooctadienone **50** (Table 2).[46] We observed that the tandem rearrangement in higher dielectric solvents such as acetonitrile or 1,2-dichloroethane favored cyclopropane formation decidedly over the Wolff rearrangement (entries 1 and 2). The data suggests that polar solvents could stabilize the charge-separated conformation (**55**), leading to greater population of *s-E* and therefore increasing amounts of carbene-related products. Lower dielectric solvents, such as THF, ethyl acetate, and toluene, modulated the selectivity and improved the formation of desired product **50** (entries 3–6). Furthermore, the nonpolar solvents methylcyclohexane and heptane reversed the reaction selectivity to favor the desired **50** as a major product in a 3:1 ratio (entries 7 and 8). Although a trend in solvent dielectric roughly reflects product selectivity in which lower dielectric solvents seemingly favor the concerted Wolff rearrangement, the complex reaction profile and other unidentified reaction products make it difficult to conclusively correlate solvent polarity to the mechanistic pathway. Moreover, we do not know if the conformational interconversion is fast relative to decomposition of **48**. This is nonetheless an intriguing result that has broader implications for future applications of the Wolff/Cope method.

Table 2. Wolff/Cope solvent studies of substrate 48
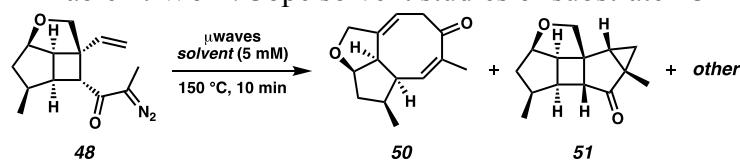
entry[a]	solvent	dielectric constant (ε)	50 : 51[b]
1	MeCN	37.5	1 : 4
2	DCE	10.4	1 : 2.8
3	THF	7.58	1 : 1.1
4	EtOAc	6.02	1 : 1.3
5	toluene	2.38	1.1 : 1
6	1,4-dioxane	2.21	1 : 1.7
7	methylcyclohexane	2.02	3 : 1
8	heptane	1.92	3 : 1

[a] α-Diazoketone **48** was consumed in all reactions. [b] Ratios determined by ^{1}H NMR analysis of crude reaction mixtures.

The application of solvent-optimized reaction conditions with heptane enabled the microwave-promoted rearrangement of **48** to produce α-methyl cyclooctadienone **50** in 42% isolated yield (Equation 1). The success of this rearrangement is significant as it represents the first example of the tandem Wolff/Cope rearrangement of a substrate possessing α-alkyl functionality. Moreover, the combined results from all α-diazo cyclobutyl ketone substrates in this study (i.e., **34**, **47** and **48**) highlight the utility of microwave irradiation to facilitate tandem rearrangements and expand the collection of eight-membered rings available by this method.

(1)
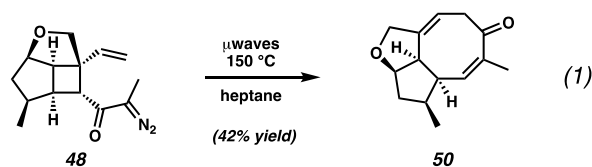
Conclusion

We have described our efforts to develop a Wolff/Cope strategy for the asymmetric synthesis of the AB ring of the complex sesterterpenoid variecolin. Our approach has employed an intramolecular cyclobutadiene–olefin cycloaddition to control product regio and stereoselectivity, as well as an advanced application of a termi-differentiating ozonolytic cleavage of a cyclobutene

intermediate toward α-diazo cyclobutyl ketone substrates. These investigations have demonstrated an efficient microwave-promoted tandem Wolff/Cope rearrangement to forge highly-substituted, fused cyclooctadienone structures. Efforts are underway in our laboratory to leverage Wolff/Cope products **49** and **50** in coupling reactions with suitable D ring fragments toward completion of variecolin and will be reported in due course.

Experimental Section

General Methods. *Reactions, reagents and solvents.* Unless otherwise stated, reactions were performed in flame-dried glassware under an argon or nitrogen atmosphere using dry, deoxygenated solvents. Solvents were dried by passage through an activated alumina column under argon. Water (18 MΩ) used as reaction medium was obtained from a Millipore MiliQ water purification system. All starting materials were purchased from commercial sources and used as received, unless otherwise stated. Liquids and solutions were transferred via syringe or positive-pressure cannulation. Triethylamine was distilled from CaH_2 prior to use. Oxalyl chloride was purified by distillation and stored in a Schlenk tube under nitrogen. Acetic acid was distilled from CrO_3. Solutions of *p*-TolMgBr, and MeMgCl were titrated[47] prior to use. Molecular sieves were dried and stored in a 115 °C oven. Diazomethane was freshly prepared from *N*-methyl-*N*-nitroso-*p*-toluenesulfonamide (Diazald) as a solution in Et_2O using a Diazald kit. Diazoethane was freshly prepared from *N*-ethyl-*N*-nitrosourea[48] as a solution in Et_2O using a Diazald kit. Diazoalkane solutions were dried over KOH pellets for ca. 30 min at or below 0 °C and cannula (Teflon) transferred under nitrogen to a dry Erlenmeyer flask prior to use.

Instruments, purification and analysis. Reaction temperatures were controlled by an IKAmag temperature modulator. Ozonolysis reactions were performed with an OzoneLab OL80 Desktop ozone generator. Photochemical irradiation was performed in septum sealed quartz tubes with a Luzchem Photochemical reactor or with a water-cooled Hanovia 450 W medium pressure mercury-vapor immersion lamp. Microwave reactions were performed with a Biotage Initiator Eight 400 W apparatus at 2.45 GHz and reaction temperatures were measured with an external surface sensor. Thin-layer chromatography was performed using E. Merck silica gel 60 F254 precoated plates (0.25 mm) and visualized by UV fluorescence quenching, *p*-anisaldehyde,

potassium permanganate, or ceric ammonium molybdate staining. SiliCycle SiliaFlash P60 Academic Silica Gel (particle size 40–63 μm; pore diameter 60 Å) was used for flash chromatography. Analytical chiral HPLC was performed with an Agilent 1100 Series HPLC utilizing a Chiralpak OD-H column (4.6 mm x 25 cm) obtained from Daicel Chemical Industries, Ltd. with 1 mL/min mobile phase and visualization at 254 nm. Analytical achiral GC was performed on an Agilent 6850 GC with FID detector using an Agilent DB-WAX (30.0 m x 0.25 mm) column at 1.0 mL/min He carrier gas flow. Chiral GC was performed on an Agilent 6850 GC with FID detector using a Chiraldex GTA column (30.0 m x 0.25 mm, purchased from Bodman Industries) at 1.0 mL/min He carrier gas flow. Optical rotations were measured with a Jasco P-1010 polarimeter at 589 nm using spectrophotometric grade solvents. ^{1}H and ^{13}C NMR spectra were recorded on a Varian Mercury 300 (at 300 MHz and 75 MHz respectively), Varian Inova 500 (at 500 MHz and 126 MHz, respectively) or Varian Inova 600 (at 600 MHz), and are reported relative to residual protio-solvent for ^{1}H (C_6D_5H at δ 7.16 ppm, $CHCl_3$ at δ 7.26 ppm) and solvent for ^{13}C (C_6D_6 at δ 128.06 ppm, $CDCl_3$ at δ 77.16 ppm). Data for ^{1}H NMR spectra are reported as follows: chemical shift (δ ppm) (multiplicity, coupling constant (Hz), integration). IR spectra were recorded on a Perkin Elmer Paragon 1000 spectrometer and are reported in wavenumbers (cm^{-1}). Melting points were acquired using a Buchi Melting Point B-545 instrument and the values are uncorrected. High-resolution mass spectra were acquired using an Agilent 6200 Series TOF with an Agilent G1978A Multimode source in ESI, APCI, or MM (ESI/APCI) ionization mode, in addition to the Caltech Mass Spectral Facility. Crystallographic data have been deposited at the CCDC, 12 Union Road, Cambridge CB2 1EZ, UK, and copies can be obtained on request, free of charge, by quoting the publication citation and the deposition number.

Trichloroacetimidate 19. To a round-bottom flask charged with hexanes-washed KH (41 mg, 1.0 mmol, 0.057 equiv) and Et_2O (43 mL) at 0 °C was added a solution of (hydroxymethyl cyclobutadiene)tricarbonyliron (**SI3**)[49] (3.86 g, 17.4 mmol, 1.0 equiv) in Et_2O (43 mL, 0.2 M total) by cannula transfer. After 10 min, trichloroacetonitrile (8.7 mL, 87 mmol, 5.0 equiv) was added dropwise by syringe to the light orange solution. The reaction turned dark brow over the course of the addition. After 15 min, the ice bath was removed and upon reaching ambient temperature the volatiles were removed in vacuo. The remaining dark brown oil was taken up in hexane (20 mL, anhydrous) with *vigorous* shaking, filtered through a pad of Celite, and the reaction flask was

washed with an additional portion of hexane (20 mL) and filtered. The combined filtrate was concentrated in vacuo to afford **19** (6.38 g, 17.4 mmol, 100% yield) as a clear, pale red oil. This oil was immediately used in the next step without further purification and it is not stable to prolonged storage. R_f = *unstable to SiO$_2$*; ^{1}H NMR (500 MHz, C$_6$D$_6$) δ 8.22 (br s, 1H), 4.25 (s, 2H), 3.49 (s, 2H), 3.30 (s, 1H); ^{13}C{^{1}H} NMR (126 MHz, C$_6$D$_6$) δ 214.5, 162.6, 92.0, 76.8, 65.7, 64.9, 64.5; IR (Neat Film NaCl) 3344, 2049, 1971, 1666, 1449, 1368, 1304, 1288 cm^{-1}; HRMS (FAB+) *m/z*: [M − CO]$^+$ calc'd for C$_9$H$_6$Cl$_3$FeNO$_3$ 336.8763, found 336.8769.

Model cycloaddition substrate 20. To a round-bottom flask charged with Zn(OTf)$_2$ (14.9 mg, 0.041 mmol, 0.05 equiv) and toluene (0.2 mL) at 0 °C was added aryl cyclopentenol **18**[22] (151.3 mg, 0.868 mmol, 1.0 equiv) by syringe. To this suspension was added a solution of **19** (370 mg, 1.01 mmol, 1.2 equiv) in toluene (0.2 mL) by cannula transfer, with further washing by additional toluene (0.2 mL). A yellow precipitate was observed at the beginning of the addition, and this turned into a thick slurry upon completion of the addition. The ice bath was allowed to expire over 1.5 h and the reaction was stirred for an additional 6 h. The crude reaction mixture was transferred directly onto a 5 g silica gel loading cartridge and purified by automated flash chromatography using a 40 g silica column (1:0 → 9:1 hexanes/EtOAc) to afford **20** (250.8 mg, 0.663 mmol, 76% yield) as a pale yellow oil. R_f = 0.56 (4:1 hexanes/EtOAc); ^{1}H NMR (300 MHz, C$_6$D$_6$) δ 6.97 (ABq, $\Delta\delta_{AB}$ = 0.06, J_{AB} = 7.8 Hz, 4H), 5.88–5.85 (m, 1H), 4.45–4.44 (m, 1H), 3.96–3.94 (m, 1H), 3.55 (ABq, $\Delta\delta_{AB}$ = 0.01, J_{AB} = 9.2 Hz, 2H), 3.46 (s, 2H), 3.33 (s, 1H), 2.28 (ddd, J = 13.8, 6.9, 5.4 Hz, 1H), 2.14 (s, 3H), 1.86 (ddd, J = 13.7, 6.9, 5.4 Hz, 1H); ^{13}C{^{1}H} NMR (126 MHz, C$_6$D$_6$) δ 215.0, 142.3, 140.1, 135.9, 131.6, 129.5, 127.4, 84.9, 82.5, 64.65, 64.64, 64.0, 62.3, 50.1, 41.2, 21.0; IR (Neat Film NaCl) 2863, 2044, 1959, 1513, 1075, 1048, 613 cm^{-1}; HRMS (FAB+) *m/z*: [M]$^+$ calc'd for C$_{20}$H$_{18}$O$_4$Fe 378.0554, found 378.0551.

Model cycloadduct 21.[29] To a vigorously stirring solution of cycloaddition substrate **20** (683 mg, 1.806 mmol, 1.0 equiv) in acetone (1.81 mL, 1 mM) was added CAN (1.98 g, 3.61 mmol, 2.0 equiv) under ambient atmosphere. After 15 min, a second portion of CAN (1.98 g, 3.61 mmol, 2.0 equiv) was added. After an additional 5 min, consumption of **20** by TLC (4:1 hexanes/Et$_2$O, developed twice) was observed and the reaction was quenched by addition of sat aq NaHCO$_3$ (50 mL). Stirring was ceased after 15 min, the solids were allowed to settle and the supernatant was

decanted into a flask (to prevent bumping) and concentrated in vacuo to ca. 50 mL. This slurry and the remnants of the flask were transferred to a separatory funnel with minimal acetone, diluted with brine (10 mL) and pentane (200 mL). The layers were separated, the organic phase was washed with water (2 x 100 mL), and the combined aq layers were extracted with 1:1 hexanes/Et$_2$O (200 mL). The combined organic layers were concentrated to ca. 25 mL, transferred to a sep funnel and diluted with CH$_2$Cl$_2$ (30 mL) and brine (25 mL). The layers were separated, the aq was extracted with CH$_2$Cl$_2$ (2 x 30 mL), the organics were dried over MgSO$_4$, filtered, and concentrated to a dark orange oil. The crude material was purified by flash chromatography on SiO$_2$ (2.5 x 21 cm, 15:1 → 9:1 hexanes/Et$_2$O, slow gradient) to afford **21** (326.2 mg, 1.37 mmol, 76% yield) as a colorless oil that solidified in a –20 °C freezer. R_f = 0.54 (4:1 hexanes/Et$_2$O, developed twice); ^{1}H NMR (500 MHz, CDCl$_3$) δ 7.01 (ABq, $\Delta\delta_{AB}$ = 0.03, J_{AB} = 8.2 Hz, 4H), 6.35 (d, J = 2.1 Hz, 1H), 6.31 (d, J = 2.3 Hz, 1H), 4.71–4.69 (m, 1H), 3.89 (ABq, $\Delta\delta_{AB}$ = 0.04, J_{AB} = 9.8 Hz, 2H), 3.27 (td, J = 7.8, 3.4 Hz, 1H), 3.06 (app t, J = 6.1 Hz, 1H), 2.94 (s, 1H), 2.46 (ddd, J = 13.8, 7.0, 2.4 Hz, 1H), 2.35 (app t, J = 4.8 Hz, 1H), 2.32 (s, 3H), 2.03 (ddd, J = 13.8, 8.9, 4.9 Hz, 1H); ^{13}C{^{1}H} NMR (126 MHz, CDCl$_3$) δ 142.9, 140.3, 138.4, 135.6, 129.3, 127.2, 84.1, 71.2, 59.6, 54.9, 52.6, 50.3, 46.5, 44.6, 21.1; IR (Neat Film NaCl) 3025, 2949, 1514, 1074, 1041, 1025, 811, 744 cm^{-1}; HRMS (FAB+) m/z: [M + H – H$_2$]$^+$ calc'd for C$_{17}$H$_{17}$O 237.1279, found 237.1271.

(±)-58
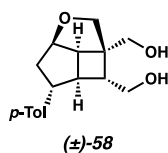
Diol 58. To a solution of cycloadduct **21** (18.0 mg, 75.5 μmol, 1.0 equiv) in a 2:1 mixture of CH$_2$Cl$_2$ (1.0 mL) and MeOH (0.5 mL) was added a solution of Sudan Red 7b (25 μL of a 0.05 wt % in MeOH) and cooled to –78 °C. The resulting pink solution was sparged with a gentle stream of oxygen for ca.1 min, then ozonolyzed until consumption of **21** by TLC (indicator typically turned colorless just prior to completion). The solution was sparged with oxygen for another 1 min, and NaBH$_4$ (28.8 mg, 0.76 mmol, 10 equiv) was added and the bath was removed. When the reaction reached room temperature, CH$_2$Cl$_2$ (2 mL) was added followed by quenching with 10% HCl (1 mL). The layers were separated, the aq extracted with CH$_2$Cl$_2$ (3 x 2 mL), the organics were dried over Na$_2$SO$_4$, filtered, and concentrated in vacuo. The crude material was purified by flash chromatography on SiO$_2$ to afford **58** (18.2 mg, 66.3 μmol, 88% yield) as a colorless oil. R_f

= 0.31 (3:1 hexanes/EtOAc); ^{1}H NMR (300 MHz, CDCl$_3$) δ 7.04 (ABq, $\Delta\delta_{AB}$ = 0.08, J_{AB} = 8.1 Hz, 4H), 4.60 (app t, J = 4.3 Hz, 1H), 4.23 (d, J = 11.5 Hz, 1H), 4.09 (d, J = 9.2 Hz, 1H), 3.87–3.74 (comp m, 2H), 3.69 (d, J = 9.2 Hz, 1H), 3.55 (d, J = 11.5 Hz, 1H), 3.42 (ddd, J = 10.5, 7.0, 3.7 Hz, 1H), 3.09 (br s, 2H), 2.82 (dd, J = 8.5, 5.3 Hz, 1H), 2.58 (dd, J = 14.0, 7.2 Hz, 1H), 2.36 (dd, J = 11.0, 5.4 Hz, 1H), 2.31 (s, 3H), 1.99 (app dt, J = 8.7, 4.4 Hz, 1H), 1.73 (ddd, J = 14.0, 10.5, 3.5 Hz, 1H); ^{13}C{^{1}H} NMR (75 MHz, CDCl$_3$) δ 143.1, 135.7, 129.3, 127.0, 86.2, 80.6, 63.5, 63.4, 51.4, 50.8, 50.7, 49.1, 44.8, 42.2, 21.1; IR (Neat Film NaCl) 3332 (br), 2922, 1514, 1436, 1100, 1037, 811 cm^{-1}; HRMS (FAB+) m/z: [M + H − H$_2$]$^+$ calc'd for C$_{17}$H$_{21}$O$_3$ 273.1491, found 273.1485.

Optimized preparation of model olefin 25. The following procedure represents a telescoped preparation of olefin **25**. Individual optimization procedures can be found in the supporting information. A solution of cyclobutene **21** (326.2 mg, 1.369 mmol, 1.0 equiv) in CH$_2$Cl$_2$/MeOH (5:1, 27.4 mL, 0.05 M) containing NaHCO$_3$ (34.5 mg, 0.411 mmol, 0.3 equiv) and Sudan Red 7b (150 μL of a 0.05 wt % solution in MeOH) at −78 °C was sparged with a stream of oxygen for ca. 1 min and ozonolyzed until consumption by TLC analysis (typically as indicator turned colorless). After sparging the solution with oxygen for an additional 3 min, the reaction was capped with a drying tube and warmed to room temperature. The solution was filtered through a cotton plug, washing with benzene (3 mL). The reaction was concentrated in vacuo to ca. 2 mL, and to this flask was added a stir bar, septum, and the flask was evacuated/purged briefly (3x). The crude was dissolved in CH$_2$Cl$_2$ (13.7 mL), cooled to 0 °C, and to this was added Ac$_2$O (387 μL, 4.11 mmol, 3.0 equiv) and Et$_3$N (286 μL, 2.05 mmol, 1.5 equiv). The bath was removed and the reaction was stirred at room temperature for 8 h, diluted with CH$_2$Cl$_2$ (25 mL), washed with 2% HCl (10 mL), then 10% NaOH (10 mL), dried over MgSO$_4$, filtered, and concentrated in vacuo to a pale yellow oil. The crude oil was purified by flash chromatography on SiO$_2$ (2.5 x 8 cm, 4:1 → 1:1 hexanes/Et$_2$O) to afford acetal **22** (61.5 g, 0.205 mmol, 15% yield) and a mixture of aldehyde **24** and acetals **23** and **32** (293.5 mg, 0.977 mmol, 71% yield).

The mixture of **23**, **24** and **32** (293.5 mg) was dissolved in MeOH (19.5 mL, 0.05 M) and to this was added oven-dried 4 Å MS (489 mg, 0.5 g/mmol). After 24 h at room temperature the reaction was diluted with EtOAc (20 mL), filtered through a plug of Celite, and concentrated to a

turbid yellow oil. This was dissolved in CH_2Cl_2 and passed through a small SiO_2 plug and concentrated in vacuo to afford a pale yellow oil (312.1 mg).

To a solution of $Ph_3P•CH_3Br$ (390 mg, 1.09 mmol, 1.05 equiv) in THF (3 mL) at 0 °C was added KOt-Bu (105 mg, 0.935 mmol, 0.9 equiv). The resulting bright yellow solution was stirred for 1 h, and a solution of aldehyde **24** and acetals **23** and **32** (312.1 mg) in THF (2 mL, 0.2 M total) was quantitatively transferred via cannulation. The bath was removed after 5 min and at 5 h the reaction was quenched with water (5 mL) and diluted with Et_2O (5 mL). The layers were separated, the aq was extracted with Et_2O (2 x 10 mL), the combined organics were dried over Na_2SO_4, filtered, and concentrated in vacuo to a pale yellow oil. The crude material was purified by flash chromatography on SiO_2 (2.5 x 15 cm, 9:1 → 1:1 hexanes/Et_2O) to afford olefin **25** (162.2 mg, 0.544 mmol, 40% yield over three steps) and ca. 7:3 mixture of acetals **23** and **32** (59.5 mg, 0.198 mmol, 14% yield over three steps).

Model acetal 22.[29] R_f = 0.52 (1:2 hexanes/Et_2O); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.13 (d, J = 7.8 Hz, 2H), 7.05 (d, J = 8.1 Hz, 2H), 5.37 (s, 1H), 4.77 (dd, J = 5.2, 4.0 Hz, 1H), 4.14 (d, J = 9.7 Hz, 1H), 4.03 (d, J = 9.7 Hz, 1H), 3.57 (app t, J = 6.4z Hz, 1H), 3.50 (s, 3H), 3.49 (ddd, J = 10.8, 6.8, 4.3, 1H), 2.57 (dd, J = 14.2, 7.0 Hz, 1H), 2.55–2.53 (comp m, 2H), 2.33 (s, 3H), 1.80 (ddd, J = 14.4, 10.8, 3.6 Hz, 1H); ^{13}C{^{1}H} NMR (126 MHz, $CDCl_3$) δ 175.5, 141.3, 136.3, 129.5, 127.2, 109.0, 85.9, 73.0, 56.8, 55.5, 51.9, 51.3, 51.2, 44.5, 44.2, 21.1; IR (Neat Film NaCl) 2927, 1773, 1515, 1353, 1182, 1143, 1118, 1018, 990, 930, 814 cm^{-1}; HRMS (FAB+) m/z: [M + H]$^+$ calc'd for $C_{18}H_{21}O_4$ 301.1440, found 301.1448.

Model desired acetal 23.[29] R_f = 0.33 (1:2 hexanes/Et_2O); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.08 (ABq, $\Delta\delta_{AB}$ = 0.04, J_{AB} = 8.0 Hz, 4H), 5.40 (s, 1H), 4.71 (dd, J = 5.4, 3.1 Hz, 1H), 4.08 (d, J = 10.5 Hz, 1H), 3.78 (d, J = 10.5 Hz, 1H), 3.55 (dt, J = 11.6, 6.1 Hz, 1H), 3.48 (s, 3H), 3.31 (dd, J = 7.4, 5.7 Hz, 1H), 2.89 (d, J = 2.4 Hz, 1H), 2.66 (ddd, J = 7.6, 5.2, 2.4 Hz, 1H), 2.53 (dd, J = 13.8, 6.7 Hz, 1H), 2.31 (s, 3H), 1.76 (ddd, J = 13.8, 11.7, 3.1 Hz, 1H); ^{13}C{^{1}H} NMR (126 MHz, $CDCl_3$) δ 177.7, 140.1, 136.1, 129.4, 127.1, 106.3, 85.7, 71.8, 56.8, 55.0, 51.1, 50.0, 47.9, 46.2, 43.9, 21.1; IR (Neat Film NaCl) 2925, 2847, 1772, 1516, 1352, 1207, 1168, 1144, 1108, 1042, 943, 814, 729, 705 cm^{-1}; HRMS (FAB+) m/z: [M + H]$^+$ calc'd for $C_{18}H_{21}O_4$ 301.1440, found 301.1444.

Model aldehyde 24. Aldehyde **24** was difficult to isolate as a pure compound, as it usually contained varying quantities of acetal **23**. It has the following spectral properties: ^{1}H NMR (300 MHz, $CDCl_3$) δ 9.76 (s, 1H), 7.07 (ABq, $\Delta\delta_{AB}$ = 0.05, J_{AB} = 8.3 Hz, 4H), 4.69 (dd, J = 4.6, 3.9 Hz,

1H), 4.10 (d, *J* = 9.6 Hz, 1H), 3.91 (d, *J* = 9.7 Hz, 1H), 3.70 (s, 3H), 3.59 (dd, *J* = 8.3, 5.3 Hz, 1H), 3.45 (ddd, *J* = 10.7, 7.1, 3.7 Hz, 1H), 3.06–2.97 (comp m, 2H), 2.63 (dd, *J* = 14.2, 7.2 Hz, 1H), 2.31 (s, 3H), 1.81 (ddd, *J* = 14.1, 10.7, 3.4 Hz, 1H).

Model olefin 25. R_f = 0.62 (2:1 hexanes/EtOAc); ^{1}H NMR (500 MHz, CDCl$_3$) δ 7.07 (ABq, $\Delta\delta_{AB}$ = 0.04, J_{AB} = 8.0 Hz, 4H), 5.94 (dd, *J* = 17.5, 10.8 Hz, 1H), 5.18 (dd, *J* = 10.8, 1.1 Hz, 1H), 5.14 (dd, *J* = 17.5, 1.1 Hz, 1H), 4.65–4.63 (m, 1H), 4.03 (d, *J* = 9.2 Hz, 1H), 3.62 (s, 3H), 3.57 (d, *J* = 9.2 Hz, 1H), 3.40 (ddd, *J* = 10.6, 7.1, 3.6 Hz, 1H), 3.26 (dd, *J* = 8.5, 5.2 Hz, 1H), 3.03 (ddd, *J* = 8.7, 5.2, 3.6 Hz, 1H), 2.98 (d, *J* = 5.5 Hz, 1H), 2.64 (dd, *J* = 14.1, 7.3 Hz, 1H), 2.31 (s, 3H), 1.78 (ddd, *J* = 14.0, 10.6, 3.4 Hz, 1H); ^{13}C{^{1}H} NMR (126 MHz, CDCl$_3$) δ 173.3, 142.6, 135.6, 134.7, 129.2, 127.1, 116.3, 86.5, 78.9, 55.2, 53.0, 51.6, 51.2, 51.1, 45.0, 40.8, 21.1; IR (Neat Film NaCl) 2952, 2922, 1733, 1515, 1435, 1210, 1158, 1055, 1037, 919, 812 cm^{-1}; HRMS (EI+) *m/z*: [M]$^+$ calc'd for C$_{19}$H$_{22}$O$_3$ 298.1569, found 298.1580.

Model desired acetal 32.[29] R_f = 0.19 (1:2 hexanes/Et$_2$O); ^{1}H NMR (500 MHz, CDCl$_3$) δ 7.08 (ABq, $\Delta\delta_{AB}$ = 0.04, J_{AB} = 8.0 Hz, 4H), 5.30 (s, 1H), 4.68 (dd, *J* = 5.6, 3.3 Hz, 1H), 4.07 (d, *J* = 9.5 Hz, 1H), 3.72 (dd, 7.2, 6.2 Hz, 1H), 3.69 (d, *J* = 9.5 Hz, 1H), 3.63 (s, 3H), 3.50 (dt, *J* = 11.4, 5.8 Hz, 1H), 2.85 (d, *J* = 2.7 Hz, 1H), 2.66 (ddd, *J* = 7.6, 4.9, 2.7 Hz, 1H), 2.54 (dd, *J* = 13.9, 6.8 Hz, 1H), 2.31 (s, 3H), 1.79 (ddd, *J* = 13.9, 11.4, 3.3 Hz, 1H); ^{13}C{^{1}H} NMR (126 MHz, CDCl$_3$) δ 175.8, 140.8, 136.1, 129.4, 127.1, 104.0, 86.0, 72.7, 58.7, 54.5, 50.23, 50.20, 47.7, 44.8, 44.0, 21.1; IR (Neat Film NaCl) 2922, 1770, 1515, 1450, 1386, 1209, 1170, 1106, 1041, 995, 942, 813 cm^{-1}; HRMS (MM: ESI/APCI) *m/z*: [M + H]$^+$ calc'd for C$_{18}$H$_{21}$O$_4$ 301.1434, found 301.1432.

(±)-59
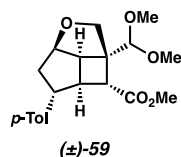
Model dimethyl acetal 59. To a solution of acetal **23** (1.0 equiv) in MeOH (25 mM) was added either La(OTf)$_3$ or Sm(OTf)$_3$ (0.20 equiv). The reaction was stirred until complete conversion by TLC, diluted with Et$_2$O, filtered through a plug of Celite, and concentrated in vacuo. The crude ^{1}H NMR showed **59** as the exclusive product. R_f = 0.36 (1:2 hexanes/Et$_2$O); ^{1}H NMR (600 MHz, CDCl$_3$) δ 7.06 (ABq, $\Delta\delta_{AB}$ = 0.04, J_{AB} = 7.9 Hz, 4H), 4.69 (s, 1H), 4.58 (dd, *J* = 4.8, 3.8 Hz, 1H), 3.87 (ABq, $\Delta\delta_{AB}$ = 0.01, J_{AB} = 9.2 Hz, 2H), 3.67 (s, 3H), 3.51 (s, 3H), 3.39 (s, 3H), 3.36 (ddd, *J* = 10.7, 7.4, 3.8 Hz, 1H), 3.23 (dd, *J* = 8.6, 5.3 Hz, 1H), 2.93 (ddd, *J* = 8.8, 5.4, 3.6 Hz, 1H), 2.82 (d,

J = 5.7 Hz, 1H), 2.60 (dd, J = 14.1, 7.4 Hz, 1H), 2.30 (s, 3H), 1.75 (ddd, J = 14.1, 10.4, 3.6 Hz, 1H); $^{13}C\{^1H\}$ NMR (126 MHz, CDCl$_3$) δ 174.1, 142.7, 135.6, 129.2, 127.1, 105.0, 85.8, 75.0, 58.3, 56.6, 54.5, 52.1, 51.7, 51.4, 49.4, 45.0, 42.4, 21.1; IR (Neat Film NaCl) 2952, 1727, 1515, 1435, 1362, 1210, 1069, 1042, 977, 813 cm^{-1}; HRMS (FAB+) *m/z*: [M + H − H$_2$]$^+$ calc'd for C$_{20}$H$_{25}$O$_5$ 345.1702, found 345.1701.

Model acid 33. To a solution of olefin **25** (162.2 mg, 0.544 mmol, 1.0 equiv) in THF (10.9 mL, 0.05 M) at 0 °C was added KOTMS (698 mg, 5.44 mmol, 10 equiv) in one portion. The cooling bath was removed and the reaction was stirred until consumption by TLC analysis (typically 5–6 h). The reaction was then cooled to 0 °C and slowly quenched with 1 N HCl (10 mL), diluted with EtOAc (20 mL) and brine (5 mL). The layers were separated, the aq was extracted with EtOAc (3 x 20 mL), the combined organics were dried over Na$_2$SO$_4$, filtered, and concentrated to a pale yellow semisolid. The crude material was purified by flash chromatography on SiO$_2$ (1:1 hexanes/EtOAc) to give **33** (148.7 mg, 0.523 mmol, 96% yield) as a white solid. R_f = 0.23 (2:1 hexanes/EtOAc); ^1H NMR (500 MHz, CDCl$_3$) δ 7.06 (ABq, Δδ$_{AB}$ = 0.04, J_{AB} = 8.0 Hz, 4H), 6.00 (dd, J = 17.5, 10.8 Hz, 1H), 5.21 (dd, J = 10.8, 1.1 Hz, 1H), 5.17 (dd, J = 17.6, 1.2 Hz, 1H), 4.64 (dd, J = 4.8, 3.6 Hz, 1H), 4.04 (d, J = 9.3 Hz, 1H), 3.57 (d, J = 9.3 Hz, 1H), 3.40 (ddd, J = 10.5, 7.2, 3.5 Hz, 1H), 3.26 (dd, J = 8.2, 5.2 Hz, 1H), 3.00–2.95 (comp m, 2H), 2.64 (d, J = 14.2, 7.3 Hz, 1H), 2.31 (s, 3H), 1.78 (ddd, J = 14.0, 10.6, 3.4 Hz, 1H); $^{13}C\{^1H\}$ NMR (126 MHz, CDCl$_3$) δ 177.7, 142.6, 135.7, 134.4, 139.3, 127.7, 116.6, 86.6, 79.0, 54.9, 53.2, 51.14, 51.10, 44.9, 40.8, 21.1; IR (Neat Film NaCl) 2923, 1729, 1700, 1515, 1418, 1223, 1053, 992, 918, 812 cm^{-1}; HRMS (FAB+) *m/z*: [M + H]$^+$ calc'd for C$_{18}$H$_{21}$O$_3$ 285.1491, found 285.1495.

Model α-diazo cyclobutyl ketone 34. To a solution of acid **33** (14.7 mg, 51.7 μmol, 1.0 equiv) in CH$_2$Cl$_2$ (2 mL, 0.025 M) at 0 °C was added a solution of oxalyl chloride (107 μL of a 1.45 M solution in CH$_2$Cl$_2$, 155 μmol, 3.0 equiv), followed by 1 drop of DMF. The reaction was stirred for 1 h, at which point the stir bar was removed and the volatiles were removed on a rotovap purged with argon. The septum and stir bar were replaced and the crude material was further dried under high vacuum for 10 min. The resulting crude semisolid was partially dissolved in CH$_2$Cl$_2$ (1 mL) and transferred quantitatively via Teflon cannula to a vigorously stirring solution of excess diazomethane (5–8 mL) at 0 °C. After 30 min the cooling bath was removed, and after a further

hour the diazomethane was pulled off via water aspirator. The pale yellow solution was filtered through a small SiO_2 plug (Et_2O) and concentrated in vacuo. The crude material was purified by flash chromatography on SiO_2 (9:1 → 3:1 hexanes/EtOAc) to afford **34** (13.2 mg, 42.8 μmol, 83% yield) as a bright yellow oil that solidified in a –20 °C freezer. R_f = 0.31 (2:1 hexanes/EtOAc); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.05 (ABq, $\Delta\delta_{AB}$ = 0.04, J_{AB} = 7.9 Hz, 4H), 6.01 (dd, 17.5, 10.8 Hz, 1H), 5.17 (d, J = 10.8 Hz, 1H), 5.11–5.06 (br m, 2H), 4.64 (app t, J = 4.0 Hz, 1H), 3.97 (br d, J = 9.1 Hz, 1H), 3.66 (br d, J = 8.6 Hz, 1H), 3.36 (ddd, J = 10.6, 7.7, 3.5 Hz, 1H), 3.19 (br s, 1H), 3.11 (br s, 1H), 2.92 (br s, 1H), 2.64 (dd, J = 14.1, 7.3 Hz, 1H), 2.30 (s, 3H), 1.78 (ddd, J = 13.7, 10.5, 3.0 Hz, 1H); ^{13}C{^{1}H} NMR (126 MHz, $CDCl_3$) δ 193.6, 142.5, 135.7, 134.9, 129.3, 127.1, 116.0, 86.5, 78.6, 60.8, 55.3, 53.6, 51.4, 44.9, 40.5, 30.4, 21.1; IR (Neat Film NaCl) 2955, 2921, 2100, 1633, 1514, 1370, 1352, 1048, 812 cm^{-1}; HRMS (FAB+) m/z: $[M + H]^+$ calc'd for $C_{19}H_{21}O_2N_2$ 309.1603, found 309.1619.

Model homologated ester 37. A solution of α-diazo cyclobutyl ketone **34** (3.2 mg, 104 μmol) in MeOH (5.2 mL, 2 mM) in a dried quartz tube was irradiated in a Luzchem rayonette (λ = 350 nm) for 1.5 h. The solution was concentrated in vacuo and revealed homologated ester **37** as the sole product by crude ^{1}H NMR. An analytical sample was obtained from purification by preparative TLC on SiO_2 (2:1 hexanes/EtOAc) to give **37** (2.4 mg, 7.7 μmol, 74% yield) as a colorless oil. R_f = 0.43 (2:1 hexanes/EtOAc); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.04 (ABq, $\Delta\delta_{AB}$ = 0.04, J_{AB} = 5 Hz, 4H), 5.89 (dd, J = 16.9, 10.2 Hz, 1H), 5.22 (d, J = 10.7 Hz, 1H), 5.13 (d, J = 17.5 Hz, 1H), 4.64 (app t, J = 3.9 Hz, 1H), 3.97 (d, J = 8.7 Hz, 1H), 3.51 (s, 3H), 3.50 (d, J = 8.7 Hz, 1H), 3.46–3.42 (m, 1H), 3.23 (dd, J = 7.9, 5.8 Hz, 1H), 2.61 (dd, J = 14.1, 7.3 Hz, 1H), 2.54–2.36 (comp m, 3H), 2.30 (s, 3H), 2.11 (app dt, J = 7.7, 3.8 Hz, 1H), 1.78 (ddd, J = 12.7, 10.4, 2.1 Hz, 1H); ^{13}C{^{1}H} NMR (126 MHz, $CDCl_3$) δ 173.1, 143.6, 135.5, 135.3, 129.2, 127.1, 116.4, 86.7, 79.2, 52.4, 51.9, 51.6, 50.1, 47.0, 46.9, 45.0, 37.2, 21.1; IR (Neat Film NaCl) 2951, 2922, 1736, 1514, 1435, 1207, 1163, 1041, 916, 808 cm^{-1}; HRMS (EI+) m/z: $[M]^+$ calc'd for $C_{20}H_{24}O_3$ 312.1726, found 312.1725.

Wolff/Cope rearrangement to cyclooctadienone 35. *Photochemical/Thermal:* A solution of α-diazo cyclobutyl ketone **34** (3.5 mg, 11.4 μmol) in benzene (5.7 mL, 2 mM) in a dried quartz tube was irradiated in a Luzchem photochemical reactor (λ = 310 nm) for 10 min, and then the

lamp was turned off and the quartz tube was placed in an 80 °C oil bath for 2 h. The reaction was concentrated in vacuo and purified by preparative TLC on SiO_2 (1:1 hexanes/Et_2O, developed twice) to give model cyclooctadienone **35** (1.9 mg, 6.8 μmol, 59% yield) as a colorless oil.

Microwave (thermal): A solution of α-diazo cyclobutyl ketone **34** (2.3 mg, 7.5 μmol) in toluene (1.5 mL, 5 mM) was prepared in a non-dried microwave vial containing a stir bar under ambient atmosphere. The vial was sealed and irradiated in a Biotage Initiator microwave reactor at 400 W until the temperature reached 140 °C, and the temperature was maintained for 20 min. The vial was cooled to room temperature, the seal was removed, and the contents were concentrated in vacuo. Reaction conversion was monitored by ^1H NMR analysis (C_6D_6). The crude material was purified by preparative TLC on SiO_2 (2:1 hexanes/EtOAc) to give **35** (2.0 mg, 7.1 μmol, 95% yield) as a colorless oil that solidified in a –20 °C freezer. R_f = 0.32 (3:1 hexanes/EtOAc); ^1H NMR (CDCl_3, 500 MHz) δ 7.15 (ABq, $\Delta\delta_{AB}$ = 0.02, J_{AB} = 8.3 Hz, 4H), 5.80–5.73 (comp m, 2H), 5.63–5.59 (m, 1H), 4.76 (app t, J = 5.2 Hz, 1H), 4.49 (dd, J = 13.1, 1.5 Hz, 1H), 4.40 (dd, J = 13.2, 1.0 Hz, 1H), 3.66 (td, J = 6.8, 4.0 Hz, 1H), 3.41 (dd, J = 14.7, 8.1 Hz, 1H), 3.23 (app t, J = 11.3 Hz, 1H), 3.13–3.05 (comp m, 2H), 2.34 (s, 3H), 2.30 (dd, J = 13.8, 5.9 Hz, 1H), 1.93 (ddd, J = 13.8, 12.1, 4.6 Hz, 1H); $^{13}C\{^1H\}$ NMR (126 MHz, CDCl_3) δ 203.3, 146.8, 139.7, 138.4, 136.9, 129.7, 129.2, 127.9, 144.2, 85.3, 72.2, 53.9, 50.6, 48.1, 45.4, 41.4, 21.2; ^1H NMR (500 MHz, C_6D_6) δ 6.99 (d, J = 7.7 Hz, 2H), 6.86 (d, J = 6.9 Hz, 2H), 5.77 (dt, J = 13.5, 1.3 Hz, 1H), 5.56 (d, J = 13.6 Hz, 1H), 5.11–5.08 (m, 1H), 4.35 (app t, J = 5.1 Hz, 1H), 4.24 (d, J = 13.1 Hz, 1H), 4.11 (d, J = 13.2 Hz, 1H), 3.04–2.89 (comp m, 4H), 2.70 (app t, J = 11.3 Hz, 1H), 2.20 (dd, J = 13.6, 5.9 Hz, 1H), 2.15 (s, 3H), 1.53–1.46 (m, 1H); $^{13}C\{^1H\}$ NMR (126 MHz, C_6D_6) δ 201.9, 147.2, 139.2, 138.6, 136.8, 130.1, 130.0, 128.7, 114.4, 85.5, 72.5, 53.8, 51.2, 48.3, 45.9, 41.9, 21.3; IR (Neat Film NaCl) 3015, 2922, 1693, 1661, 1516, 1435, 1318, 1208, 1062, 1030, 817 cm^{-1}; HRMS (MM: ESI/APCI) *m/z*: [M – H]$^-$ calc'd for $C_{19}H_{19}O_2$ 279.1391, found 279.1384.

Anti-cyclopentenol 38. A 2 L, 3-neck flask was charged with CuCN (2.01 g, 112.2 mmol. 0.2 equiv) and THF (280 mL), and the suspension was cooled to ca. –20 °C (internal) using a cryocool. To this was added a solution of MeMgCl (109 mL, 337 mmol of a 3.1 M solution in THF) and the internal temperature warmed to –14 °C. After 30 min at –20 °C, a solution of monoacetate (+)-**17**[35] (15.95 g, 112.2 mmol, 1.0 equiv) in THF (40 mL) was slowly transferred (quantitative) via cannulation at such a rate that the internal temperature does not rise above –10 °C (required ca. 1

h). After 30 min the reaction was slowly quenched with sat. aq NH$_4$Cl (100 mL), 50% sat. brine (100 mL), the cooling bath was removed and the viscous suspension was stirred vigorously for several hours. Additional water (200 mL) and 3% HCl (100 mL) was added and the layers were separated. The aq layer was extracted with Et$_2$O (3 x 200 mL), the combined organics were dried over MgSO$_4$, filtered, and concentrated carefully (water bath = 5 °C, down to 30 torr) to a pale yellow oil. The crude material was purified by short path distillation (bp = 88–92 °C, 40 torr) to afford a 95:5 mixture of **38** and **39** (8.847 g, 90.2 mmol, 80% yield). The early distillation fractions and Et$_2$O washings from the apparatus were combined and purified by flash chromatography on SiO$_2$ (2.5 x 27 cm, 6:1 → 1:1 pentane/Et$_2$O) to provide another 1.049 g of **38** and **39** (combined 9.996 g, 101.9 mmol, 91% yield). R_f (**38**) = 0.35 (1:1 hexanes/EtOAc); R_f (**39**) = 0.29 (1:1 hexanes/EtOAc); bp = 88–92 °C (40 torr). An analytical sample of **38** was obtained from the column conditions above. ^{1}H NMR (500 MHz, CDCl$_3$) δ 5.89 (dd, J = 5.5, 1.9 Hz, 1H), 5.79 (dt, J = 4.8, 2.3 Hz, 1H), 4.87 (dt, J = 4.8, 2.3 Hz, 1H), 2.95 (dqdt, J = 9.5, 7.2, 4.9, 2.3 Hz, 1H), 1.96 (ddd, J = 14.0, 7.5, 2.6 Hz, 1H), 1.71 (ddd, J = 14.0, 7.1, 5.2 Hz, 1H), 1.48 (br s, 1H), 1.03 (d, J = 7.1 Hz, 3H); ^{13}C{^{1}H} NMR (126 MHz, CDCl$_3$) δ 142.0, 132.1, 77.6, 42.7, 38.5, 21.0; IR (Neat Film NaCl) 3338 (br), 2956, 2870, 1354, 1088, 1017, 982, 742 cm^{-1}; HRMS (EI+) *m/z*: [M]$^+$ calc'd for C$_6$H$_{10}$O 98.07317, found 98.07171; [α]$_D^{21}$ –272.2 (*c* 0.39, CHCl$_3$, 99% ee). GC conditions: 45 °C isothermal, GTA column, t_R (min): major = 37.7, minor = 36.7.

Syn-cyclopentenol 16. To a suspension of Ph$_3$P (13.41 g, 51.12 mmol, 1.2 equiv) and benzoic acid (6.243 g, 51.12 mmol, 1.2 equiv) in toluene (237 mL) at –75 °C (internal) was added DIAD (10.1 mL, 51.12 mmol, 1.2 equiv) dropwise, neat over 15 min. The resulting yellow suspension was stirred vigorously for 30 min, at which point a solution of **38** and **39** (4.1806 g, 42.60 mmol, 1.0 equiv) in toluene (47 mL, 0.15 M total) was transferred via cannula quantitatively over 30 min (observed maximum temperature increase to –70 °C). When ca. 1/3 of this solution was added, the reaction mixture turned homogeneous. After complete addition of **38** and **39**, the reaction was stirred for an additional 30 min (white precipitate had formed) and quenched with sat. aq NaHCO$_3$ (100 mL) and water (100 mL) and the contents were warmed to room temperature. The layers were separated, the aq was extracted with Et$_2$O (2 x 50 mL), and the combined organics were shaken with 3% aq H$_2$O$_2$ until TLC showed disappearance of Ph$_3$P. The layers were separated, the aq was extracted with Et$_2$O (1 x 50 mL), and the combined organics were dried over MgSO$_4$, filtered, and

concentrated to a pale yellow solid. The crude material was purified by flash chromatography on SiO$_2$ (7 x 7.5 cm, 1:0 $\rightarrow$ 24:1 hexanes/Et$_2$O, dry loaded onto SiO$_2$) to give the expected *syn*-benzoate (**60**, 7.792 g, 38.53 mmol, 90% yield) as a pale yellow oil. R_f = 0.57 (3:1 hexanes/EtOAc); ^{1}H NMR (500 MHz, CDCl$_3$) δ 8.05-8.03 (m, 2H), 7.56–7.53 (m, 1H), 7.44–7.41 (m, 2H), 6.03 (dd, J = 4.4, 2.0 Hz, 1H), 5.90–5.86 (comp m, 2H), 2.80–2.73 (m, 1H), 2.65 (dt, J = 14.0, 7.8 Hz, 1H), 1.51 (dq, J = 12.5, 3.7 Hz, 1H), 1.16 (d, J = 7.0 Hz, 3H); ^{13}C{^{1}H} NMR (126 MHz, CDCl$_3$) δ 166.6, 142.9, 132.9, 130.8, 129.7, 128.6, 128.4, 80.9, 38.9, 38.7, 21.7; IR (Neat Film NaCl) 2961, 1716, 1451, 1340, 1315, 1272, 1110, 711 cm^{-1}; HRMS (EI+) *m/z*: [M]$^+$ calc'd for C$_{13}$H$_{14}$O$_2$ 202.0994, found 202.1019; [α]$_D^{25.7}$ +123.8 (*c* 1.175, CHCl$_3$, 98–99% ee).

60
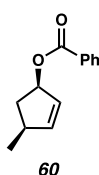
To a solution of *syn*-benzoate **60** (6.255g, 30.93 mmol, 1.0 equiv) in MeOH (62 mL, 0.5 M) was added K$_2$CO$_3$ (8.549 g, 61.85 mmol, 2.0 equiv) in one portion. After completion as judged by TLC analysis (3 h, 3:1 hexanes/EtOAc), the reaction was concentrated carefully in vacuo to a slurry (ca. 5–10 mL). The white slurry was diluted with brine (25 mL) and extracted with Et$_2$O (4 x 25 mL, follow by TLC), the organics were dried over MgSO$_4$, filtered, and concentrated carefully in vacuo. The crude material was purified by flash chromatography on SiO$_2$ (5 x 12 cm, 6:1 $\rightarrow$ 1:1 pentane/Et$_2$O) and concentrated down to 100 torr until ^{1}H NMR analysis revealed the absence of solvent to afford **16** (2.728 g, 27.79 mmol, 90% yield) as a colorless oil. R_f = 0.25 (3:1 hexanes/EtOAc); ^{1}H NMR (500 MHz, CDCl$_3$) δ 5.82 (dt, J = 5.5, 1.5 Hz, 1H), 5.73 (dt, J = 5.5, 2.0 Hz, 1H), 4.79 (br s, 1H), 2.66–2.59 (m, 1H), 2.52 (dt, J = 13.4, 7.6 Hz, 1H), 1.79 (br s, 1H), 1.17 (dt, 13.4, 5.4 Hz, 1H), 1.09 (d, J = 7.0 Hz, 3H); ^{13}C{^{1}H} NMR (126 MHz, CDCl$_3$) δ 140.4, 132.8, 77.8, 42.6, 39.0, 22.0; IR (Neat Film NaCl) 3338 (br), 3048, 2959, 2870, 1456, 1356, 1322, 1115, 1051, 755 cm^{-1}; HRMS (EI+) *m/z*: [M]$^+$ calc'd for C$_6$H$_{10}$O 98.07317, found 98.07135; [α]$_D^{27}$ –23.0 (*c* 0.475, CHCl$_3$, 98.2% ee). GC conditions: 50 °C isothermal, GTA column, t_R (min): major = 21.2, minor = 20.7.

Cycloaddition substrate 40. To a round-bottom flask containing Zn(OTf)$_2$ (271 mg, 0.745 mmol, 0.05 equiv) and toluene (3.7 mL) at 0 °C was added cyclopentenol **16** (1.45 g, 14.8 mmol,

1.0 equiv) by syringe. To this suspension was added a solution of cyclobutadiene trichloroacetimidate **19** (6.38 g, 17.4 mmol, 1.2 equiv) in toluene (2.0 mL) by cannula transfer, with further washing by toluene (1.7 mL). A yellow precipitate was observed at the beginning of the addition, and this turned into a viscous slurry upon completion of the addition. The ice bath was allowed to expire over 1.5 h and the reaction was stirred for an additional 0.5 h at ambient temperature. The crude reaction mixture was transferred directly onto a 25 g silica gel loading cartridge and purified by automated flash chromatography using a 125 g silica column (1:0 → 19:1 hexanes/EtOAc) to afford **40** (3.65 g, 12.2 mmol, 82% yield) as a pale yellow oil. R_f = 0.73 (4:1 hexanes/EtOAc); ^{1}H NMR (500 MHz, C$_6$D$_6$) δ 5.72 (app dt, J = 5.6, 1.9 Hz, 1H), 5.66 (app dt, J = 5.6, 1.6 Hz, 1H), 4.27–4.24 (m, 1H), 3.53 (ABq, $\Delta\delta_{AB}$ = 0.01, J_{AB} = 9.1 Hz, 2H), 3.48 (s, 2H), 3.32 (s, 1H), 2.43–2.39 (m, 1H), 2.15 (app dt, J = 13.3, 7.6 Hz, 1H), 1.26 (ddd, J = 17.0, 11.2, 6.9 Hz, 1H), 0.98 (d, J = 7.0 Hz, 3H); ^{13}C{^{1}H} NMR (126 MHz, C$_6$D$_6$) δ 215.0, 140.5, 130.5, 85.2, 82.6, 64.64, 64.58, 64.0, 62.2, 39.1, 38.9, 21.6; IR (Neat Film NaCl) 2961, 2871, 2046, 1965, 1359, 1076, 1055, 757 cm^{-1}; HRMS (FAB+) m/z: [M]$^+$calc'd for C$_{14}$H$_{14}$FeO$_4$ 302.0242, found 302.0244; $[\alpha]_D^{25}$ +22.7 (c 0.86, hexane, 98% ee).

Cycloadduct 41.[29] A solution of cycloaddition substrate **40** (2.3582 g, 7.806 mmol, 1.0 equiv) dissolved in acetone (780 mL, 10 mM) in a 1 L round-bottom flask fitted with a reflux condenser was warmed in a 70 °C oil bath. When the solution approached reflux, the condenser was momentarily removed and Me$_3$NO•2H$_2$O (8.77 g, 78.9 mmol, 10 equiv) was added in a single portion. The solution was allowed to reflux and within 10 min the reaction vessel was filled with a rust colored precipitate. After 4 h a second portion of Me$_3$NO•2H$_2$O (4.35 g, 45.9 mmol, 5.8 equiv) was added. The solution was heated at reflux for an additional 17 h after which the reaction was judged to be complete by TLC analysis (4:1 hexanes/EtOAc). The solution was cooled to room temperature and poured directly onto a SiO$_2$ column (25 x 5 cm) packed in pentane. The column was washed with 0 → 10% Et$_2$O in pentane, and all fractions containing cyclobutene **41** were combined and concentrated carefully to a volume of ca. 30 mL by atmospheric pressure distillation. This solution was purified by flash chromatography on SiO$_2$ (packed with pentane, eluted with 20:1 pentane/Et$_2$O). The fractions containing **41** were combined and concentrated to a volume of ca. 10 mL by atmospheric pressure distillation. This pale yellow cyclobutene solution in pentane was used directly in the following reaction. An analytical sample of cyclobutene **41**

could be prepared by further chromatography and exhaustive distillation of solvent. $R_f = 0.39$ (3:1 hexanes/Et$_2$O); ^{1}H NMR (500 MHz, CDCl$_3$) δ 6.27 (d, J = 2.2 Hz, 1H), 6.22 (s, 1H), 4.84 (app q, J = 7.2 Hz, 1H), 4.04 (d, J = 9.1 Hz, 1H), 3.94 (d, J = 8.6 Hz, 1H), 3.00 (s, 1H), 2.89 (app t, J = 5.8 Hz, 1H), 2.23 (tq, J = 12.7, 6.4 Hz, 1H), 2.10–2.05 (comp m, 2H), 1.37 (ddd, J = 13.0, 13.0, 7.0 Hz, 1H), 0.97 (d, J = 6.7 Hz, 3H); ^{13}C{^{1}H} NMR (126 MHz, CDCl$_3$) δ 140.2, 138.4, 84.7, 70.3, 57.9, 52.0, 47.8, 44.8, 39.0, 37.3, 14.3; IR (Neat Film NaCl) 2955, 2865, 1458, 1334, 1089, 1075, 1057, 1032, 931, 740 cm^{-1}; HRMS (EI+) m/z: [M]$^+$ calc'd for C$_{11}$H$_{14}$O 162.1045, found 162.1026; an optical rotation was not obtained due to the volatility of this compound. Cyclobutene **41** was found to possess an optical purity (ee) of 98% by chiral GC analysis; GC conditions: 110 °C isothermal, GTA column, t_R (min): major = 13.6, minor = 13.3.

Oxidative cleavage of 41, equilibration and olefination. In a 250 mL round-bottom flask, the cyclobutene **41** solution prepared above was diluted with CH$_2$Cl$_2$ (130 mL) and methanol (26 mL, 5:1, 0.05 M total). To this was added NaHCO$_3$ (205.2 mg, 2.44 mmol, 0.3 equiv) and a few drops of Sudan Red (0.05 wt % in MeOH) until the solution became a pale pink color (ca. 10 drops). The reaction vessel was cooled to –78 °C and the solution was sparged with O$_2$ gas (0.5 L/min) for 2 min. The reaction was then ozonolyzed (setting the ozone generator to "5" with an O$_2$ flow rate of 0.5 L/min) for 60 min, at which point the pink color of the solution had disappeared and the reaction was judged to be complete by TLC analysis. The ozone was sparged with O$_2$ gas (1 L/min) through the solution for 2 min, and the pale yellow solution was warmed to room temperature and filtered through a cotton plug to remove the solid NaHCO$_3$. The cotton plug was washed with benzene (10 mL) and the filtrate was concentrated to a small volume (ca. 3–4 mL). The resulting crude yellow oil was dissolved in CH$_2$Cl$_2$ (78 mL), cooled to 0 °C, and to this was added Et$_3$N (1.63 mL, 11.7 mmol, 1.5 equiv) and Ac$_2$O (2.21 mL, 23.4 mmol, 3.0 equiv) dropwise via syringe. After 6 h, the reaction was quenched by the addition of 2 M HCl (25 mL), the organic layer was separated and washed with 2 M NaOH (25 mL), and the combined aqueous layers were extracted with CH$_2$Cl$_2$ (5 x 25 mL). The organics were dried over MgSO$_4$, filtered, and concentrated to afford a pale brown oil which was passed through a SiO$_2$ plug eluting with EtOAc, and concentrated to afford a pale yellow oil (0.8504 g, 3.8 mmol, three steps, 48% crude yield) containing mostly acetals **42** and **43**.

The crude pale yellow oil prepared above was azeotroped from benzene (2 x 10 mL) in a 250 mL round-bottom flask and dissolved in MeOH (76 mL, 0.05 M). To this was added oven dried 4 Å MS (1.90 g, 0.5 g/mmol) and the flask was fitted with a reflux condenser and heated to reflux using an 80 °C oil bath. After 6 h, the reaction was judged complete by ^{1}H NMR analysis of a reaction aliquot and the reaction was cooled to room temperature. Most of the 4 Å MS were removed by filtration through Celite eluting with EtOAc. The filtrate was concentrated and the resultant turbid oil was further purified by filtration through a SiO_2 plug with EtOAc. This filtrate was concentrated to afford a yellow oil (0.8420 g) containing mostly aldehydes derived from **42** and **43** with the requisite acetals. This mixture was used directly in the following reaction.

A flask containing Ph$_3$P•CH$_3$Br (1.62 g, 4.54 mmol, 1.2 equiv) was partially dissolved with THF (15 mL) and cooled to 0 °C. To this was added KO*t*-Bu (423 mg, 3.77 mmol, 1.0 equiv) in one portion, and the solution immediately displayed a bright yellow color. The crude yellow oil of aldehydes/acetals (0.8420 g, ca. 3.7 mmol) prepared above was azeotroped from benzene (2 x 10 mL), dissolved in THF (7.5 mL), cooled to 0 °C, and transferred dropwise via positive pressure cannulation into the solution of phosphorane over ca. 10 min. The flask was then washed with a second portion of THF (7.5 mL) to ensure quantitative transfer. The reaction was gradually allowed to warm to room temperature. After 18 h the reaction was quenched by the addition of H$_2$O (25 mL) and extracted with Et$_2$O (4 x 20 mL) then EtOAc (2 x 20 mL). The combined organics were dried with MgSO$_4$, filtered and concentrated in vacuo. The crude yellow residue was purified flash chromatography on SiO$_2$ (15 x 2 cm, 20:1 → 4:1 hexanes/EtOAc) to afford olefins **44** and **45** (384.4 mg, 1.729 mmol, 2.7:1 ratio, 22.2% yield over four steps from cycloaddition substrate **40**) as a colorless oil and acetals **42** and **43** (400.5 mg, 1.786 mmol; 2.7:1 ratio, 22.9% yield over four steps from **40**) as pale yellow oil. Olefins **44** and **45** could be separated by further flash chromatography on SiO$_2$ (20:1 → 9:1 hexanes/EtOAc), and acetals **42** and **43** could be separated by further flash chromatography on SiO$_2$ (3:1 → 1:1 hexanes/EtOAc).

Olefin 44. R_f = 0.46 (9:1 hexanes/EtOAc, developed thrice); ^{1}H NMR (500 MHz, CDCl$_3$) δ 5.95 (dd, J = 17.5, 10.8 Hz, 1H), 5.15 (dd, J = 10.8, 1.2 Hz, 1H), 5.11 (dd, J = 17.5, 1.2 Hz, 1H), 4.59 (ddd, J = 6.3, 6.3, 1.5 Hz, 1H), 3.99 (d, J = 9.0 Hz, 1H), 3.64 (s, 3H), 3.54 (d, J = 9.0 Hz, 1H), 3.16 (d, J = 7.1 Hz, 1H), 3.02 (app t, 7.1 Hz, 1H), 2.95 (app q, J = 7.4 Hz, 1H). 2.39 (ddq, J = 14.0, 10.4, 7.0 Hz, 1H), 2.18 (ddd, J = 14.6, 10.4, 5.7 Hz, 1H), 1.71 (ddd, J = 14.6, 6.3, 1.7 Hz, 1H), 1.02 (d, J = 7.0 Hz, 3H); ^{13}C{^{1}H} NMR (126 MHz, CDCl$_3$) δ 173.6, 134.9, 115.9, 87.1, 78.7,

52.6, 51.6, 51.4, 44.8, 42.5, 38.9, 37.2, 17.2; IR (Neat Film NaCl) 2954, 1736, 1436, 1363, 1236, 1206, 1162, 1042, 920 cm^{-1}; HRMS (MM: ESI/APCI) m/z: [M + H]$^+$ calc'd for $C_{13}H_{19}O_3$ 223.13287, found 223.13255; [α]$_D^{16.8}$ −4.73 (c 1.18, CH_2Cl_2, 98% ee).

Olefin 45. R_f = 0.39 (9:1 hexanes/EtOAc, developed thrice); ^{1}H NMR (500 MHz, CDCl$_3$) δ 5.86 (ddd, J = 17.3, 10.3, 7.5 Hz, 1H), 5.05 (ddd, J = 17.1, 1.5, 1.5 Hz, 1H), 5.02 (ddd, J = 10.3, 1.4, 1.4 Hz, 1H), 4.67 (td, J = 6.6, 2.8 Hz, 1H), 4.02 (d, J = 9.4 Hz, 1H), 3.88 (d, J = 9.4 Hz, 1H), 3.68 (s, 3H), 3.30 (app t, J = 7.2 Hz, 1H), 3.00 (app t, J = 7.2 Hz, 1H), 2.54 (app q, 7.2 Hz, 1H), 2.35 (d sextets, J = 9.6, 7.2 Hz, 1H), 2.18 (ddd, J = 14.5, 9.7, 6.3 Hz, 1H), 1.67 (ddd, J = 14.5, 7.7, 2.8 Hz, 1H), 1.01 (d, J = 7.0 Hz, 3H); ^{13}C{^{1}H} NMR (126 MHz, CDCl$_3$) δ 172.3, 137.9, 115.9, 87.1, 76.0, 55.8, 51.7, 48.9, 44.9, 43.6, 41.8, 38.0, 16.2; IR (Neat Film NaCl) 2953, 5873, 1731, 1436, 1295, 1207, 1041, 917 cm^{-1}; HRMS (EI+) m/z: [M]$^+$ calc'd for $C_{13}H_{18}O_3$ 222.1256, found 222.1267; [α]$_D^{15.1}$ −0.49 (c 0.72, CH_2Cl_2, 98% ee).

Acetal 42.[29] R_f = 0.29 (2:1 hexanes/EtOAc); ^{1}H NMR (500 MHz, CDCl$_3$) δ 5.39 (s, 1H), 4.80 (ddd, J = 6.5, 6.5, 4.5 Hz, 1H), 3.99 (ABq, $\Delta\delta_{AB}$ = 0.01, J_{AB} = 10.5 Hz, 2H), 3.48 (s, 3H), 3.13 (app t, J = 6.7 Hz, 1H), 2.89 (d, J = 3.3 Hz, 1H), 2.61 (ddd, J = 6.9, 6.9, 3.3 Hz, 1H), 2.39–2.30 (m, 1H), 2.06 (ddd, J = 14.4, 8.4, 6.3 Hz, 1H), 1.60 (ddd, J = 13.3, 8.5, 4.5 Hz, 1H), 1.11 (d, J = 7.0 Hz, 3H); ^{13}C{^{1}H} NMR (126 MHz, CDCl$_3$) δ 179.0, 107.4, 86.7, 70.9, 56.8, 52.4, 51.5, 44.7, 40.8, 38.6, 37.2, 16.9; IR (Neat Film NaCl) 2961, 2877, 1772, 1353, 1150, 1128, 1100, 1062, 936, 710 cm^{-1}; HRMS (EI+) m/z: [M]$^+$ calc'd for $C_{12}H_{16}O_4$ 224.1049, found 224.1052; [α]$_D^{18.3}$ +73.0 (c 1.13, CH_2Cl_2, 98% ee).

Acetal 43.[29] R_f = 0.19 (2:1 hexanes/EtOAc); mp = 151.5–153 °C (Et$_2$O); ^{1}H NMR (600 MHz, CDCl$_3$) δ 5.30 (s, 1H), 4.89 (td, J = 7.2, 5.8 Hz, 1H), 4.19 (d, J = 9.6 Hz, 1H), 4.11 (d, J = 9.6 Hz, 1H), 3.49 (s, 3H), 3.33 (dd, J = 7.0, 6.3 Hz, 1H), 2.58 (d, J = 4.0 Hz, 1H), 2.40 (td, J = 6.0, 4.0, Hz, 1H), 2.26 (ddq, J = 13.7, 11.1, 6.8 Hz, 1H), 2.16 (dt, J = 14.1, 7.1 Hz, 1H), 1.55 (ddd, J = 14.0, 11.1, 5.7 Hz, 1H), 1.03 (d, J = 6.8 Hz, 3H); ^{13}C{^{1}H} NMR (126 MHz, CDCl$_3$) δ 177.2, 108.4, 86.6, 73.2, 56.5, 55.5, 50.1, 42.8, 41.2, 38.7, 38.2, 15.3; IR (Neat Film NaCl) 2934, 1766, 1460, 1359, 1199, 1171, 1143, 1130, 1115, 1063, 1045, 916, 904, 691 cm^{-1}; HRMS (EI+) m/z: [M]$^+$ calc'd for $C_{12}H_{16}O_4$ 224.1049, found 224.1044; [α]$_D^{17.9}$ −56.7 (c 0.62, CH_2Cl_2, 98% ee). Crystals suitable for X-ray analysis were obtained by slow evaporation from Et$_2$O.

Acid 46. To a solution of olefin **44** (41.0 mg, 0.184 mmol, 1.0 equiv) in THF (3.7 mL, 0.05 M) cooled to 0 °C was added KOTMS (236 mg, 1.84 mmol, 10 equiv) in one portion. After 5 min the reaction was warmed to room temperature. At 12 h the reaction was cooled to 0 °C and slowly quenched with 10% HCl (4 mL) and diluted with brine (4 mL) and EtOAc (10 mL). The layers were separated and the aq layer was extracted with EtOAc (3 x 10 mL), the combined organics were dried over Na_2SO_4, filtered, and concentrated to a pale yellow oil. The crude was purified by flash chromatography on SiO_2 (6:1 → 3:1 hexanes/EtOAc, CH_2Cl_2 load) to afford **46** (35.2 mg, 0.169 mmol, 92% yield) as a white solid. R_f = 0.21 (2:1 hexanes/EtOAc); ^{1}H NMR (600 MHz, CDCl₃) δ 6.04 (dd, J = 17.5, 10.8 Hz, 1H), 5.20 (dd, J = 10.8, 1.2 Hz, 1H), 5.17 (dd, J = 17.5, 1.2 Hz, 1H), 4.61 (td, J = 6.4, 1.6 Hz, 1H), 4.02 (d, J = 9.1 Hz, 1H), 3.54 (d, J = 9.1 Hz, 1H), 3.22 (d, J = 7.3 Hz, 1H), 3.05 (app t, J = 7.1 Hz, 1H), 2.91 (app q, J = 7.6 Hz, 1H), 2.40 (d sextets, J = 10.4, 7.0 Hz, 1H), 2.20 (ddd, J = 14.7, 10.4, 5.8 Hz, 1H), 1.73 (ddd, J = 14.7, 6.3, 1.7 Hz, 1H), 1.05 (d, J = 7.1 Hz, 3H); ^{13}C{^{1}H} NMR (126 MHz, CDCl₃) δ 178.6, 134.5, 116.2, 87.2, 78.8, 52.8, 51.2, 44.7, 42.5, 39.0, 37.2, 17.2; IR (Neat Film NaCl) 3085 (br), 2958, 2930, 1731, 1704, 1418, 1283, 1241, 1086, 1041, 996, 921 cm^{-1}; HRMS (EI+) m/z: [M]$^+$ calc'd for $C_{12}H_{16}O_3$ 208.1100, found 208.1094; $[\alpha]_D^{15.3}$ +28.3 (c 0.97, CH_2Cl_2, 98% ee).

α-Diazo cyclobutyl ketone 47. To a solution of acid **46** (62.5 mg, 0.300 mmol, 1.0 equiv) in CH_2Cl_2 (6.0 mL, 0.05 M) at 0 °C was added a solution of oxalyl chloride (353 μL of a 1.7 M solution in CH_2Cl_2, 0.600 mmol, 2.0 equiv), followed by 1 drop of DMF. The reaction was stirred for 45 min at 0 °C, at which point the stir bar was removed, toluene was added (6 mL), and the volatiles were removed on a rotovap purged with argon. The septum and stir bar were replaced and the crude material was further dried under high vacuum for 10 min. The resulting crude semisolid was partially dissolved in CH_2Cl_2 (2 mL) and THF (4 mL) and transferred quantitatively via Teflon cannula to a vigorously stirring solution of excess diazomethane (ca. 30 mL) containing IRA-67 (161 mg, ca. 0.9 mmol, 3.0 equiv) at 0 °C. The flask was further washed with CH_2Cl_2 (4 mL) and THF (2 mL) and quantitatively transferred. After 3.5 h the cooling bath was removed and the diazomethane was pulled off via water aspirator. The pale yellow solution was filtered through a small SiO_2 plug (Et₂O) and concentrated in vacuo. The crude material was purified by flash chromatography on SiO_2 (6:1 → 2:1 hexanes/Et₂O) to afford **47** (63.2 mg, 0.272 mmol, 91% yield) as a bright yellow oil that solidifies in a –20 °C freezer. R_f = 0.24 (3:1 hexanes/EtOAc); ^{1}H NMR

(500 MHz, CDCl$_3$) δ 6.01 (dd, *J* = 17.5, 10.8 Hz, 1H), 5.15 (dt, *J* = 10.9, 1.1 Hz, 1H), 5.10 (br s, 1H), 5.05 (d, *J* = 17.5 Hz, 1H), 4.59 (app t, *J* = 6.1 Hz, 1H), 3.92 (d, *J* = 9.0 Hz, 1H), 3.63 (d, *J* = 9.0 Hz, 1H), 3.11 (br d, *J* = 14.8, 2H), 2.96 (app t, *J* = 6.9 Hz, 1H), 2.44–2.35 (m, 1H), 2.20 (td, *J* = 12.6, 5.5 Hz, 1H), 1.70 (dd, *J* = 14.7, 6.3 Hz, 1H), 0.99 (d, *J* = 7.0 Hz, 3H); ^{13}C{^{1}H} NMR (126 MHz, CDCl$_3$) δ 193.7, 134.9, 115.7, 87.2, 78.3, 54.8, 53.3, 51.9, 50.4, 42.6, 38.3, 37.3, 17.2; IR (Neat Film NaCl) 3081, 2956, 2100, 1635, 1373, 1047, 919 cm^{-1}; HRMS (FAB+) *m/z*: [M + H]$^+$ calc'd for C$_{13}$H$_{17}$N$_2$O$_2$ 233.1290, found 233.1296; [α]$_D^{20.2}$ –66.3 (*c* 0.99, CH$_2$Cl$_2$, 98% ee).

α-Diazo cyclobutyl ketone 48. α-Diazoketone **48** was prepared by the same procedure as described for **47** using acid **46** (17.3 mg, 83.1 μmol, 1.0 equiv), but with freshly prepared and KOH-dried diazoethane (ca. 20 mL). After 4 h at 0 °C the excess diazoethane was removed via water aspirator. The pale orange solution was filtered through a small SiO$_2$ plug (Et$_2$O) and concentrated in vacuo. The crude material was purified by flash chromatography on SiO$_2$ (6:1 → 4:1 hexanes/Et$_2$O, CH$_2$Cl$_2$ load) to afford **48** (13.0 mg, 52.8 μmol, 64% yield) as a bright yellow oil. *R$_f$* = 0.38 (2:1 hexanes/Et$_2$O); ^{1}H NMR (500 MHz, CDCl$_3$) δ 5.95 (dd, *J* = 17.5, 10.9 Hz, 1H), 5.10 (d, *J* = 10.8 Hz, 1H), 5.05 (d, *J* = 17.6 Hz, 1H), 4.57 (app t, *J* = 5.7 Hz, 1H), 3.86 (d, *J* = 9.3 Hz, 1H), 3.66 (d, *J* = 9.3 Hz, 1H), 3.34 (d, *J* = 6.8 Hz, 1H), 3.28 (app q, *J* = 7.5 Hz, 1H), 2.93 (app t, *J* = 6.9 Hz, 1H), 2.45–2.36 (m, 1H), 2.16 (ddd, *J* = 14.9, 10.1, 5.2 Hz, 1H), 1.94 (s, 3H), 1.70 (dd, *J* = 14.5, 5.9 Hz, 1H), 0.98 (d, *J* = 7.1 Hz, 3H); ^{13}C{^{1}H} NMR (126 MHz, CDCl$_3$) δ 14.3, 134.8, 115.5, 87.0, 77.3, 53.0, 52.5, 47.7, 42.3, 36.7, 36.3, 17.3, 8.3; IR (Neat Film NaCl) 2957, 2926, 2064, 1631, 1286, 1050 cm^{-1}; HRMS (FAB+) *m/z*: [M + H]$^+$ calc'd for C$_{14}$H$_{19}$O$_2$N$_2$ 247.1447, found 247.1457; [α]$_D^{19.9}$ +71.6 (*c* 0.57, CH$_2$Cl$_2$, 98% ee).

Cyclooctadienone 49. A solution of α-diazo cyclobutyl ketone **47** (69.2 mg, 0.271 mmol) in toluene (54 mL, 5 mM) was partitioned equally into three non-dried 20 mL microwave reaction vessels containing a stir bar under ambient atmosphere. Each vial was sealed and irradiated in a Biotage Initiator microwave reactor at 400 W until the temperature reached 160 °C, and the temperature was maintained for 15 min. The vial was cooled to room temperature, the seal was removed, and the contents were concentrated in vacuo. Reaction conversion was monitored by crude ^{1}H NMR analysis (CDCl$_3$). The crude material was purified by flash chromatography on

SiO$_2$ (9:1 → 6:1 → 3:1 hexanes/EtOAc) to give **49** (43.9 mg, 0.215 mmol, 79% yield) as a colorless oil that solidifies in a –20 °C freezer. R_f = 0.35 (3:1 hexanes/EtOAc); ^{1}H NMR (500 MHz, CDCl$_3$) δ 6.08 (dd, J = 12.4, 6.5 Hz, 1H), 5.93 (app dt, J = 12.4, 1.9 Hz, 1H), 5.56–5.51 (m, 1H), 4.59 (dd, J = 14.1, 6.9 Hz, 1H), 4.38 (d, = 12.1 Hz, 1H), 4.32 (m, 1H), 3.44 (m, 1H), 3.28 (dd, J = 14.3, 9.8 Hz, 1H), 3.18–3.13 (m, 1H), 2.99 (ddd, J = 14.3, 6.2, 1.1 Hz, 1H), 2.36 (tq, J = 12.9, 6.5 Hz 1H), 2.18 (dtd, J = 13.2, 6.5, 1.1 Hz, 1H), 1.44 (td, J = 13.2, 5.9 Hz, 1H), 1.11 (d, J = 7.0 Hz, 3H); ^{13}C{^{1}H} NMR (126 MHz, CDCl$_3$) δ 204.4, 146.1, 139.2, 131.6, 114.2, 85.1, 74.6, 52.9, 47.8, 40.1, 38.9, 15.0; IR (Neat Film NaCl) 2958, 2874, 1691, 1666, 1116, 1064, 1032, 974, 867 cm^{-1}; HRMS (FAB+) m/z: [M + H]$^+$ calc'd for C$_{13}$H$_{17}$O$_2$ 205.1229, found 205.1223; [α]$_D^{20.4}$ –642 (c 1.38, CH$_2$Cl$_2$, 98% ee).

Wolff/Cope rearrangement of 48. A solution of α-diazo cyclobutyl ketone **48** (17.7 mg, 71.9 μmol) in heptane (14.4 mL, 5 mM) was prepared in a non-dried 20 mL microwave reaction vessel under ambient atmosphere and sealed. The contents were irradiated in a Biotage Initiator microwave reactor at 400 W until the temperature reached 150 °C, and the temperature was maintained for 10 min. The reaction was cooled to room temperature and TLC analysis showed consumption of **221**. The solution was concentrated in vacuo and purified by preparative TLC on SiO$_2$ (3:1 hexanes/EtOAc, develop twice) to afford α-methyl cyclooctadienone **50** (6.6 mg, 30.2 μmol, 42% yield) as a colorless oil and cyclopropane **51** as a single diastereomer.

Cyclooctadienone 50. R_f = 0.41 (3:1 hexanes/EtOAc); ^{1}H NMR (600 MHz, CDCl$_3$) δ 5.80 (app dq, J = 7.2, 1.3 Hz, 1H), 5.52–5.48 (m, 1H), 4.58 (td, J = 7.3, 6.2 Hz, 1H), 4.38 (d, J = 12.1 Hz, 1H), 4.31 (m, 1H), 3.36 (td, J = 8.2, 1.2 Hz, 1H), 3.24 (dd, J = 15.6, 9.5 Hz, 1H), 3.02–2.98 (comp m, 2H), 2.32 (td, J = 13.0, 6.2 Hz, 1H), 2.16 (ddd, J = 13.2, 7.1, 1.0 Hz, 1H), 1.84 (t, J = 1.5 Hz, 3H), 1.47 (td, J = 13.3, 5.9 Hz, 1H), 1.08 (d, J = 6.9 Hz, 3H). ^{13}C{^{1}H} NMR (126 MHz, CDCl$_3$) δ 207.6, 146.6, 137.2, 132.5, 113.7, 85.1, 74.5, 53.3, 47.0, 46.8, 40.3, 38.9, 20.8, 15.0; IR (Neat Film NaCl) 2956, 2923, 2874, 1693, 1667, 1452, 1375, 1076, 1045, 1020, 973, 873, 838 cm^{-1}; HRMS (MM: ESI/APCI) m/z: [M + H]$^+$calc'd for C$_{14}$H$_{19}$O$_2$ 219.1380, found 219.1379; [α]$_D^{25}$ –573 (c 0.35, CHCl$_3$, 98% ee)

Cyclopropane 51.[29] R_f = 0.36 (3:1 hexanes/EtOAc); ^{1}H NMR (500 MHz, CDCl$_3$) δ 4.80 (dt, J = 7.2, 6.0 Hz, 1H), 3.94 (d, J = 9.3 Hz, 1H), 3.84 (d, J = 9.3 Hz, 1H), 2.86 (d, J = 1.8 Hz, 1H),

2.84 (dd, J = 7.4, 5.8 Hz, 1H), 2.25 (d, J = 2.9 Hz, 1H), 2.16 (dddd, J = 10.5, 10.5, 8.6, 4.1 Hz, 1H), 2.12–2.07 (m, 1H), 2.04 (ddd, J = 8.7, 5.8, 2.8 Hz, 1H), 1.56–1.54 (comp m, 2H), 1.49 (dddd, J = 13.6, 10.2, 5.5, 4.1 Hz, 1H), 1.22 (s, 3H), 0.96 (d, J = 6.7 Hz, 3H); $^{13}C\{^1H\}$ NMR (126 MHz, CDCl$_3$) δ 198.7, 86.3, 74.3, 67.1, 57.9, 51.0, 49.7, 46.7, 43.1, 38.8, 37.4, 32.7, 15.2, 9.4; IR (Neat Film NaCl) 2953, 2923, 2868, 1776, 1449, 1073, 1015, 937 cm^{-1}; HRMS (MM: ESI/APCI) *m/z*: [M + H]$^+$ calc'd for $C_{14}H_{19}O_2$ 219.1380, found 219.1382; [α]$_D^{25}$ +46.1 (*c* 0.38, CHCl$_3$, 98% ee)

Acknowledgments

Supporting Information

Additional experimental procedures, X-ray data and new compound spectra (^1H, ^{13}C, IR and other NMR) are available in the Supporting Information.

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