



Published in final edited form as:

*J Org Chem.* 2017 December 15; 82(24): 13051–13067. doi:10.1021/acs.joc.7b02030.

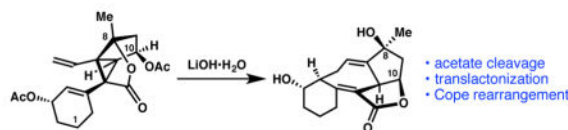
## Model Studies to Access the [6,7,5,5]-Core of Ineleganolide Using Tandem Translactonization-Cope or Cyclopropanation-Cope Rearrangements as Key Steps

Jennifer L. Roizen, Amanda C. Jones, Russell C. Smith, Scott C. Virgil, and Brian M. Stoltz\*  
Warren and Katharine Schlinger Laboratory for Chemistry and Chemical Engineering, Division of Chemistry and Chemical Engineering, California Institute of Technology, 1200 E. California Boulevard, MC 101–20, Pasadena, CA 91125 (USA)

### Abstract

Recently, we reported a convergent cyclopropanation-Cope approach to the core of ineleganolide, which was the first disclosed synthesis of the core of the norditerpene natural product ineleganolide. In this complementary work, a model system for the core of ineleganolide has been prepared through a series of tandem cyclopropanation-Cope and translactonization-Cope rearrangements. Work with this model system has enriched our understanding of the cyclopropanation-Cope rearrangement sequence. Additionally, research into this model system has driven the development of tandem translactonization-Cope rearrangements.

### Graphical Abstract



### Introduction

In 1999, Duh and co-workers isolated a norditerpene from the soft coral *Sinularia<sup>1</sup> inelegans* and named it ineleganolide (**1**, Figure 1).<sup>2,3</sup> Ineleganolide demonstrates *in vitro* cytotoxicity against murine lymphocytic leukemia P388 cell lines ( $ED_{50} = 3.82 \mu\text{g/mL}$ ),<sup>2</sup> yet does not demonstrate activity against human oral epidermoid (KB) and liver (Hepa59T/VGH) carcinoma cells ( $ED_{50} > 20 \mu\text{g/mL}$ ).<sup>3</sup> The structure of ineleganolide (**1**) was elucidated by single crystal X-ray diffraction,<sup>2</sup> revealing the relative configuration of nine stereocenters, six of which lined a central cycloheptanone core. The absolute configuration was established by Pattenden's biomimetic semi-synthesis from 5-*epi*-sinuleptolide (**3**), which furnished the only disclosed laboratory preparation of ineleganolide.<sup>4</sup> Owing to the novel structures and

\*Corresponding Author: stoltz@caltech.edu.

#### Notes

The authors declare no competing financial interest.

#### Supporting Information

Spectra (<sup>1</sup>H NMR, <sup>13</sup>C NMR, and IR). This material is available free of charge via the Internet at <http://pubs.acs.org>.

bioactivity of ineleganolide (**1**), Nicolaou, Moeller, Vanderwal, Frontier, Romo and co-workers have disclosed inventive and formidable approaches to its synthesis,<sup>5</sup> none of which have provided access to its central [6,7,5,5]-core. We have accessed this core through a cyclopropanation-Cope cascade.<sup>6</sup> Herein, we disclose model studies for that critical cyclopropanation-Cope sequence, as well as three complementary tandem transformations: transactonization-Cope, cyclopropanation-Cope-epoxidation and cyclopropanation-Cope-enolization cascades. Each transformation furnishes the [6,7,5,5]-core of ineleganolide.

## Results and Discussion

From the outset, we sought to overcome the challenges of the enantioselective installation of the C(8) tertiary ether and construction of the seven-membered ring core of ineleganolide (Scheme 1). To evaluate strategies, we targeted the simpler model, des-isopropenyl-ent-ineleganolide (**5**). Initial retrosynthetic simplification of the C(8)–C(5) ether and other oxidation state manipulations revealed cycloheptadienone **6**. Access to model compound **6** would proceed through a strain-release Cope rearrangement of diene **7**.<sup>7</sup> The cyclopropane in diene **7** would arise from vinylcyclopropane **8**. In turn, vinylcyclopropane **8** would be directly available from vinyldiazoester **9**, which itself would be the coupling product of carboxylic acid **10** and alcohol **11**. Embedded within alcohol **11** was a tertiary stereocenter at C(8), which we targeted through an enantioselective allylation strategy.<sup>8</sup>

In the forward direction, the first critical challenge was installation of the C(8) stereocenter. To this end, we found inspiration in work within our laboratory to establish quaternary stereogenic centers through the enantioselective decarboxylative allylation of cyclic enolates.<sup>9</sup> If this method could be employed with a substrate bearing  $\alpha$ -oxygenation,<sup>8b</sup> we would be able to access the C(8) center embedded within alcohol **11** (Scheme 2).<sup>8a</sup> At the time, there was limited evidence that  $\alpha$ -heteroatoms might be tolerated in the reaction.<sup>10</sup> Coincident with early model system investigations, we developed a general enantioselective alkylation of dioxanone-derived enol ethers,<sup>8a</sup> which could be used to prepare alcohol **11**<sup>8b</sup> by way of chloroallyl dioxanone **15**. Treatment of triethylsilylether **12** with Pd(dmdba)<sub>2</sub> (5 mol%), tris(CF<sub>3</sub>)-(S)-*t*-BuPHOX (**14**, 5.5 mol%),<sup>11</sup> and chloroallyl me-sylate (**13**, 1.05 equiv) with an equivalent of TBAT in PhMe at 25 °C, yielded the desired tetrasubstituted ether **15** with good enantioselectivity (91% ee). Chloroolefin **15** was converted in a fickle two-step oxidative bromination/Wittig olefination sequence to volatile cyclopentenone **16**.<sup>8a</sup> In turn, facile diastereoselective reduction furnished cyclopentenol **11**, which contains both C(8) and C(10) stereogenic centers.

Having prepared enantioenriched cyclopentenol **11**, we sought access to its coupling partner, carboxylic acid **10** (Scheme 3). Conversion of cyclohexenone (**17**) proceeded by an efficient CeCl<sub>3</sub>-mediated 1,2-addition of the lithium enolate of EtOAc.<sup>12</sup> Oxidative rearrangement with allylic transposition<sup>13</sup> and saponification generated carboxylic acid **10** in 67% overall yield. Notably, TEMPO<sup>+</sup>BF<sub>4</sub><sup>-</sup> could be employed as an environmentally benign alternative to affect an oxidative rearrangement, albeit in slightly lower 54% overall yield.<sup>14</sup> To prepare for the key cyclopropanation, we coupled alcohol **11** and carboxylic acid **10** with DCC. Subsequently, diazo transfer was accomplished upon treatment with *p*-ABSA (**20**) to provide the targeted cyclopropanation precursor (**9**) in excellent yield.

Under standard cyclopropanation conditions, diazoester **9** did not give way to desired cyclopropane **8**. Rather, a thermal rearrangement occurred to furnish pyrazole **21** in 59% yield (Scheme 4). This type of reaction had been previously reported,<sup>15</sup> and Padwa had proposed that pyrazole formation proceeds through a 1,5-cyclization followed by a proton shift.<sup>15f</sup> Indeed, pyrazole **21** was generated cleanly when diazoester **9** was heated in benzene at reflux, in the absence of copper. The structure of pyrazole **21** was characterized by X-ray crystallographic diffraction, and this structure confirmed the *syn*-arrangement of C(8) and C(10) oxygenation.

At lower temperatures, neither cyclopropane **8** nor pyrazole **21** formed. One potential explanation for this lack of reactivity was that diazoester **9** did not generate the requisite metal carbenoid. To interrogate this hypothesis, we exposed diazoester **9** to Rh<sub>2</sub>(oct)<sub>4</sub> and ambient air at 0 °C, anticipating that oxygen or water could intercept a formed metal carbenoid, ultimately furnishing oxidation products. Indeed, under these conditions, oxidized **22** formed along with its acetonide-cleaved analogue (**23**) suggesting that a carbenoid was generated upon exposure of diazoester **8** to Rh<sub>2</sub>(oct)<sub>4</sub>, but that this carbenoid failed to undergo cyclopropanation. Close examination of diazoester **9** and cyclopropane **8** revealed a 1,3-diaxial interaction between methyl groups at C(8) and on the acetonide that would likely disfavor cyclopropanation, as this 1,3-diaxial interaction was necessarily enhanced in cyclopropane **8**, relative to diazoester **9**.

To avoid this strain, we converted ester **19** to an alternative cyclopropanation precursor (Scheme 5). To this end, we turned to De Waard's catalytic conditions for ketal cleavage,<sup>16</sup> which enabled cleavage of acetonide **19** without olefin isomerization.<sup>16</sup> Silylation provided ready access to an ether, which reacted with TsN<sub>3</sub> to generate diazoester **24**. We were pleased to find that copper *tert*-butyl salicylaldehyde (Cu(tbs)<sub>2</sub>) affected cyclopropanation in 74% yield.

With the cyclopropane successfully installed, we sought to advance silyl ether **25a** to the requisite divinylcyclopropane Cope precursor (Scheme 6). Desilylation of cyclopropane **25a** occurred readily; however, an array of products formed under a variety of oxidation conditions. At least one problematic side reaction was documented. Upon oxidation with Dess-Martin periodinane, ether **26** was observed as the major product (Scheme 6). Presumably, this product arises through conjugate addition of the primary alcohol into the enone functionality.

Having struggled with oxidation to provide the targeted Cope precursor (e.g., silyl ether **25a** → divinyl cyclopropane **7**, Scheme 1), we chose to mask the problematic C(8) tertiary alcohol and the C(3) ketone in cyclopropane **25a**. Initially, we targeted formation of C(8) benzyl ether and acetyl ester (e.g., **25b** and **25c**, R=Bn and Ac respectively; Scheme 7). By standard analytical measurements (e.g., <sup>1</sup>H- and <sup>13</sup>C-NMR and IR spectroscopy, and HRMS), the formed products matched expectations for the C(8)-ester and C(8)-ether (e.g., **25b** and **25c**, R=Bn or Ac); however, careful analysis of gradient-heteronuclear multiple bond correlation (gHMBC) spectroscopy revealed that all efforts to alkylate the C(8) alcohol result in translactonization<sup>17</sup> to furnish instead a C(8) lactone (e.g., **25a** → **27**). Specifically, benzylation of the C(10) alcohol was achieved on treatment of C(8) alcohol **25a** with BnBr,

KI, and Ag<sub>2</sub>O at room temperature forming benzylated ether **27a**, while base-mediated acetylation (Ac<sub>2</sub>O, pyridine, DMAP) yielded the translactonized product **27b** containing a C(8) lactone and a C(10) acetyl ester.<sup>18</sup>

While these products were not originally targeted, we anticipated that acetyl-masked **27b** could still be converted to the core of ineleganolide (i.e., **6**) by way of a divinylcyclopropane (Scheme 8). Having previously recognized the problematic reactivity of the C(3) ketone (see Scheme 6), divinylcyclopropane **29** was targeted as a suitable precursor for this tandem transformation. We found that Luche reduction of ketone **27b** furnished a 1:1.5 ratio of diastereomeric alcohols **28a** and **b**. These diastereomers were separated and carried through subsequent reactions in parallel. Secondary alcohol **28b** was masked as an acetyl ester, then the silyl ether was desilylated. The resultant alcohol was oxidized to an aldehyde, and subjected to methylenation to provide divinylcyclopropane **29b** in 76% yield over four steps.

We suspected that bisacetyl-masked divinyl cyclopropane **29b** could still be converted to the central [6,7,5,5]-fused system within ineleganolide through an acetate-cleavage/translactonization/Cope rearrangement (Scheme 9). We expected that both translactonization and Cope rearrangement would be thermodynamically governed transformations (Scheme 9). Consequently, when acetyl ester cleavage revealed alcohol **29c**, it would enable the reaction to funnel to the lowest energy product, namely less-strained cycloheptadiene **32b** via initial translactonization to lactone **31b** and subsequent Cope rearrangement. A hypothetical and disfavored direct Cope rearrangement of the C(8) lactone would form highly-strained **30b**, possessing two anti-Bredt, bridgehead alkenes.<sup>19</sup> Were hypothetical intermediate **30b** to form, it would presumably undergo translactonization to cycloheptadiene **32b**. In the event, lithium hydroxide-mediated acetate cleavage of bis-acetyl ester **29b** promoted a translactonization–Cope rearrangement cascade to deliver cycloheptadiene **32b** in 55% yield, producing the carbocyclic core framework of ineleganolide for the first time. To our knowledge, this is also the first example of a translactonization-triggered Cope rearrangement.

An alternative translactonization–Cope approach was pursued concurrently, and also furnished the central [6,7,5,5]-fused system within ineleganolide (Scheme 10). Efforts to mask the C(3) ketone through ketalization proved fruitless under many standard conditions, as ketones **25a** and **27b** either decomposed, or formed complex product mixtures. Moreover, these ketones were unreactive toward mild conditions designed to prevent alkene isomerization (TMSOTf, (TMSOCH<sub>2</sub>)<sub>2</sub>, CH<sub>2</sub>Cl<sub>2</sub>, –78 °C). At a higher temperature (0 °C), ketalization proceeded, albeit with undesired alkene isomerization. Subsequent desilylation and oxidation of the primary alcohol to an aldehyde followed by Wittig olefination delivers divinyl-cyclopropane **33**, an appropriate Cope precursor.

Although this olefin isomer was not originally designed into our synthetic approach to ineleganolide, we expected that ketal **33** would be an appropriate precursor for a tandem translactonization–Cope rearrangement. Acetyl ester **33** reacted with nucleophilic superhydride to form desired cycloheptadiene **35**, presumably by a translactonization–Cope process (i.e., **33** → **34** → **35**). Importantly, this translactonization–Cope rearrangement

again provided access to the [6,7,5,5]-fused core of ineleganolide, albeit with modified substitution on the cyclohexyl ring.

Having established a route to the carbon scaffold of ineleganolide (i.e., cycloheptadiene **35**), we attended to C(6) oxygenation and reduction of the C(12)–C(13) tetrasubstituted alkene (Scheme 11). To our delight, the tertiary C(8) alcohol could direct vanadium-mediated diastereoselective epoxidation of the C(6)–C(7) alkene to generate epoxide **36**. For subsequent functionalization, we anticipated that olefin reduction could prove useful. Expecting direct reduction of the C(12)–C(13) alkene to be challenging, we chose to pursue deketalization of cycloheptene **36**, which could potentially induce alkene isomerization to furnish enone **37**. We envisioned that the carbonyl in enone **37** could facilitate olefin reduction. Regrettably, selective deketalization of ketal **36** was not accomplished under a broad range of conditions.

As a result of the aforementioned challenges, we continued concurrent pursuit of a tandem cyclopropanation-Cope approach to form the [6,7,5,5]-fused core of ineleganolide. The tandem cyclopropanation-Cope<sup>20,21</sup> rearrangement was developed by Davies and co-workers for application in diastereoselective intramolecular reactions.<sup>22,23,24,25</sup> To investigate this reaction, we targeted diazoester **39** as the precursor to this key tandem cyclopropanation-Cope rearrangement (Scheme 12). Unfortunately, we were unable to directly convert acetonide **19** to diazoester **39** due to an inability to affect the requisite olefination. We speculated that deprotonation of the acidic  $\gamma$ -proton of the  $\alpha,\beta$ -unsaturated ketone/ $\delta$ -ester system interfered with the attempted Wittig methylenation. To access diazoester **39**, we carried out the methylenation on the cyclopentene fragment prior to coupling it with the cyclohexenone carboxylic acid (Scheme 13). Thus, cyclopentenone **16** was converted to allylic benzoyl ester **40**. Reduction and benzoylation furnished benzoyl ester **40** in 98% yield over two-steps. Benzoyl ester **40** was treated with acid to cleave the ketal, oxidized with Dess-Martin periodinane and olefinated to deliver diene **41**. Alkoxide-mediated debenzoylation furnished alcohol **42**, which was coupled with carboxylic acid **10**. Subsequent diazotization provided targeted diazoester **39**.

This diazoester was poised for a tandem cyclopropanation-Cope cascade to generate cycloheptadiene **6** directly (Scheme 14). To our surprise, treatment of diazoester **39** with Cu(tbs)<sub>2</sub> under N<sub>2</sub>-atmosphere in a glovebox resulted in the formation of a compound possessing three olefins, instead of two as in desired product **6**. After careful analysis, we identified cycloheptatriene **44** as the major product of this reaction. Introduction of DBU into the reaction resulted in conversion of minor products, which were presumably olefin positional isomers of cycloheptatriene **44** to triene **44**. Cycloheptatriene **44** likely arose from air-accelerated oxidation during work-up of cycloheptadiene **43**. <sup>1</sup>H NMR spectroscopic analysis of the crude reaction mixture prior to exposure to air revealed the presence of double-bond isomerized enone **43**, instead of expected Cope product **6**. Presumably, the undesired oxidation and isomerization reactions are facilitated by the acidic  $\beta$ - and  $\delta$ -protons of the C(3) ketone.

With cycloheptatriene **44** in hand, we suspected that appropriate orbital overlap could render C(5) as the reactive electrophile in a conjugated acceptor, a property we would hope to use

in a total synthesis of ineleganolide. Nucleophilic epoxidation of cycloheptatriene **44** with the lithium salt of *tert*-butyl hydroperoxide yielded epoxide **45**, in a selective process that provided proof-of-concept for the anticipated reactivity of the C(4)–C(5) olefin.

Concurrently, alternative routes to the [6,7,5,5]-system were evaluated, with a focus on approaches that would avoid over-oxidation to the triene (Scheme 15). Formation of the triene could be avoided by employing lower Cu(*t*bs)<sub>2</sub>-loadings, and intercepting the intermediate cycloheptadiene **43** prior to exposure to air. For example, diastereoselective epoxidation of the C(6)–C(7) olefin of intermediate diene **43** with VO(acac)<sub>2</sub> and TBHP afforded epoxide **46** in 32% yield in a formal cyclopropanation, Cope rearrangement, epoxidation sequence. Alternatively, acetylation of the intermediate C(3) ketone furnished enol ester **47** in 44% yield in a formal cyclopropanation, Cope rearrangement, enolate trapping sequence. In turn, triene **47** could undergo selective oxidation of the C(6)–C(7) olefin either by epoxidation catalyzed by VO(acac)<sub>2</sub> and TBHP to generate epoxide **48** diastereoselectively, or by oxidative rearrangement with pyridinium chlorochromate (PCC) to install C(6) ketone **49**, albeit with elimination of the critical C(8) alcohol. These additional transformations brought us tantalizingly close to a full synthesis of the des-isopropyl model system of ineleganolide (i.e., **5**). Full details of the ensuing challenges have been described in a series of manuscripts detailing a related model system.<sup>6</sup>

## Conclusion

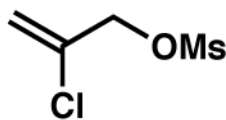
The construction of the ring system of ineleganolide (**1**) has been demonstrated in a strategy that merges the asymmetric ketone alkylation and tandem translactonization-Cope rearrangements or formal cyclopropanation-Cope-epoxidation or cyclopropanation-Cope-enolate trapping sequences. This effort prompted the development of the previously unknown palladium-catalyzed asymmetric alkylation of dioxanones,<sup>8b</sup> and a mild oxidative bromination, Wittig olefination and reduction sequence<sup>8a</sup> to advance the resultant chloroalkene to enantioenriched cyclopentenol **11**. This alcohol can be coupled with cyclohexenone acid **10**, and the resultant vinylogous β-ketoesters can be advanced to rigid cyclopropanes. By necessity, we have created a rich body of chemistry exploring translactonizations in *cis*-substituted cyclopentane diols, including a translactonization-Cope cascade and a formal cyclopropanation-Cope-epoxidation sequence. This research complements a recently disclosed route to access the carbon framework of ineleganolide via a formal cyclopropanation–Cope sequence.<sup>6</sup> All of these cascade sequences provide access to the rigid [6,7,5,5]-fused scaffold of ineleganolide (**1**).

## EXPERIMENTAL SECTION

### General Methods

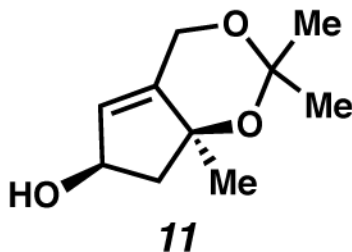
Unless otherwise stated, reactions were performed in flame-dried glassware under an argon atmosphere using dry, deoxygenated solvents. Solvents were dried by passage through an activated alumina column under argon. Tetrabutylammonium triphenyldifluorosilicate (TBAT) was purchased from Sigma-Aldrich Chemical Company and azeotropically dried five times from acetonitrile prior to use. Trimethylsilyl chloride (TMSCl), pyridine, and triethylamine (NEt<sub>3</sub>) were distilled from sodium hydride immediately prior to use. Sodium

iodide was dried by heating at 90 °C (2 torr) for 12 h. TEMPO<sup>+</sup>BF<sub>4</sub><sup>-</sup>,<sup>14</sup> *p*-acetamidobenzenesulfonyl azide (*p*ABSA), TsN<sub>3</sub>,<sup>26</sup> bis(*N*-*tert*-butylsalicylaldehydiminato) copper (II, Cu(tbs)<sub>2</sub>),<sup>27</sup> Dess-Martin periodinane (DMP),<sup>28</sup> diazomethane,<sup>29</sup> and Amberlyst A26 (S<sub>2</sub>O<sub>3</sub><sup>2-</sup>)<sup>30</sup> were prepared by known methods. Other reagents were used without further purification. Molecular sieves were purchased from Sigma Aldrich Chemical Company as activated 5 μm powder and stored in a 120 °C drying oven until immediately prior to use unless otherwise noted. Rhodium octanoate was purchased from Strem. *N*-(3-dimethylaminopropyl)-*N'*-ethylcarbodiimide hydrochloride (EDC·HCl) and 4-(dimethylamino)pyridine (DMAP) and *N,N'*-dicyclohexylcarbodiimide (DCC) were purchased from Sigma Aldrich Chemical Company. Reaction temperatures were controlled by an IKAmag temperature modulator. Thin-layer chromatography (TLC) was performed using E. Merck silica gel 60 F254 pre-coated plates (0.25 mm) and visualized by UV fluorescence quenching, anisaldehyde, or CAM staining. Florisil® (100–200 mesh) and ICN Silica gel (particle size 0.032–0.063 mm) were used for flash chromatography. Chiral HPLC analysis was performed with an Agilent 1100 Series HPLC utilizing chiralpak AD or chi-racel OD-H columns (4.6 mm × 25 cm) obtained from Daicel Chemical Industries, Ltd. with visualization at 254 nm or 220 nm. Chiral GC analysis was performed with an Agilent 6850 GC utilizing a G-TA (30 m × 0.25 cm) column (1.0 mL/min carrier gas flow). Optical rotations were measured with a Jasco P-1010 polarimeter at 589 nm. <sup>1</sup>H and <sup>13</sup>C NMR spectra were recorded on a Varian Mercury 300, 500, or 600 NMR spectrometer (at 300, 500, or 600 MHz, and 75, or 125 MHz, respectively), and are reported relative to Me<sub>4</sub>Si (δ 0.0). Data for <sup>1</sup>H NMR spectra are reported as follows: chemical shift (δ ppm) (multiplicity, coupling constant (Hz), integration). Data for <sup>13</sup>C NMR spectra are reported in terms of chemical shift relative to Me<sub>4</sub>Si (δ 0.0). If carbons were not recorded in a particular spectrum, then the missing carbons were noted by italicizing the absent carbon in a partial formula at the beginning of the spectrum. IR spectra were recorded on a Perkin Elmer Paragon 1000 spectrometer and are reported in wavenumbers (cm<sup>-1</sup>). High resolution mass spectra were obtained from the Caltech Mass Spectral Facility, or acquired using an Agilent 6200 Series TOF with an Agilent G1978A Multimode source in electrospray ionization (ESI), atmospheric pressure chemical ionization (APCI), or mixed (MM) ionization mode.

**13**

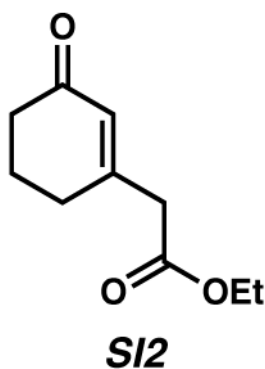
**2-Chloroallyl mesylate (13)**—A flask was charged with 2-chloroallyl alcohol (1.0 g, 10.8 mmol, 1 equiv), THF (20 mL, 0.54 M), and NEt<sub>3</sub> (3.0 mL, 21.5 mmol, 2 equiv) at 0 °C (ice water bath). The solution was treated dropwise with mesyl chloride (1.26 mL, 16.2 mmol, 1.5 equiv). After 2 h at 0 °C, the reaction was quenched by addition of NaHCO<sub>3</sub>, and the mixture was extracted with Et<sub>2</sub>O. The organic layer was washed successively with 1N HCl (20 mL), aq NaHCO<sub>3</sub> (20 mL), and brine (20 mL), dried over MgSO<sub>4</sub>, filtered, and concentrated under reduced pressure. The residue was purified by column chromatography

(SiO<sub>2</sub> (ca. 50 g) with 1:4 EtOAc:hexanes as the eluent) to provide a colorless oil (1.716 g, 93% yield). *R<sub>f</sub>* 0.34 (1:2 EtOAc:hexanes); <sup>1</sup>H NMR (300 MHz, CDCl<sub>3</sub>) δ 5.65 (d, 1H, *J* = 0.5 Hz), 5.55 (d, 1H, *J* = 0.5 Hz), 4.77 (s, 2H), 3.10 (s, 3H); <sup>13</sup>C NMR (75 MHz, CDCl<sub>3</sub>) δ 134.1, 117.7, 70.9, 38.4; IR (thin film/NaCl) 3033, 2943, 1639, 1360, 1175, 1010 cm<sup>-1</sup>; HRMS (EI) *m/z*: [M+]<sup>+</sup> Calcd for C<sub>4</sub>H<sub>7</sub>O<sub>3</sub>SCl 169.9804; Found 169.9811.



**(6*R*,7*αS*)-2,2,7*α*-Trimethyl-4,6,7,7*α*-tetrahydrocyclopenta[*d*][1,3]dioxin-6-ol (**11**)**

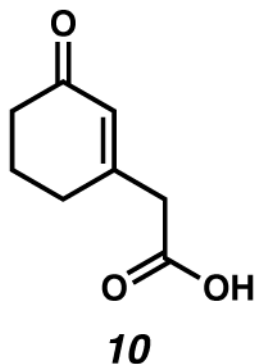
—A flask was charged with a colorless solution of ketone **16** (0.110 g, 0.60 mmol, 1 equiv), MeOH (7.4 mL, 0.082 M) and CeCl<sub>3</sub>·7H<sub>2</sub>O (0.292 g, 0.78 mmol, 1.3 equiv). The solution was cooled to 0 °C (ice water bath), and treated with NaBH<sub>4</sub> (55 mg). Bubbles evolved. The solution was treated with a 1.5 M NaOH solution, extracted with EtOAc (to 150 mL), dried over Na<sub>2</sub>SO<sub>4</sub>, filtered, and concentrated under reduced pressure, and immediately diluted with CH<sub>2</sub>Cl<sub>2</sub>. Alcohol **11** was purified by silica gel chromatography (SiO<sub>2</sub> (ca. 16 mL)) with 1:1 pentane:Et<sub>2</sub>O as the eluent to give pure alcohol **11** as a colorless oil (75 mg, 67% yield). The alcohol was immediately diluted in Et<sub>2</sub>O. *R<sub>f</sub>* 0.11 (50% Et<sub>2</sub>O in hexanes; visualized with anisaldehyde); <sup>1</sup>H NMR (300 MHz, CDCl<sub>3</sub>) δ 5.57 (q, *J* = 1.7, 1H), 4.77–4.70 (m, 1H), 4.70–4.61 (m, 2H), 2.57 (dd, *J* = 12.4, 6.5, 1H), 1.82 (ddd, *J* = 12.5, 6.8, 1.1, 1H), 1.63 (dt, *J* = 6.8, 3.3, 1H), 1.48 (s, 3H), 1.41 (s, 6H); <sup>13</sup>C NMR (126 MHz, CDCl<sub>3</sub>) δ 144.7, 125.7, 105.0, 100.2, 81.1, 74.0, 60.4, 53.5, 30.0, 28.3, 26.0; IR (NaCl) 3400 (b), 1197, 1156, 1107, 1088, 1061, 1037, 847; HRMS (EI) *m/z*: [M–Me]<sup>+</sup> Calcd for C<sub>9</sub>H<sub>13</sub>O<sub>3</sub> 169.0865; Found 169.0858; [α]<sub>D</sub><sup>21.6</sup> –2.7° (*c* 0.235, CHCl<sub>3</sub>, 91% ee).



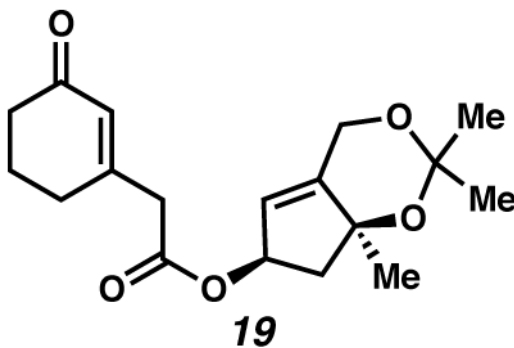
**Ethyl 2-(3-oxocyclohex-1-enyl)acetate (S12)**<sup>12</sup>—To a 0.17 M acetonitrile solution of known allylic alcohol **50**<sup>12</sup> (1.14 g, 6.19 mmol) at ambient temperature was added TEMPO<sup>+</sup>BF<sub>4</sub><sup>-</sup> (1.49 g, 6.15 mmol). After stirring for 1 hour, the orange solution was poured



onto H<sub>2</sub>O (30 mL) and Et<sub>2</sub>O (100 mL). The organic and aqueous phases were separated and the aqueous layer further extracted with Et<sub>2</sub>O (2 × 100 mL). The combined organic layers were dried with Na<sub>2</sub>SO<sub>4</sub>, filtered and concentrated under reduced pressure. The crude material was purified by flash chromatography (1:10→1:4→1:1 EtOAc:hexanes) to yield known<sup>12</sup> cyclohexenone **51** (0.77 g, 69% yield) as a colorless liquid. <sup>1</sup>H NMR of this compound was as reported in the literature.<sup>12</sup>

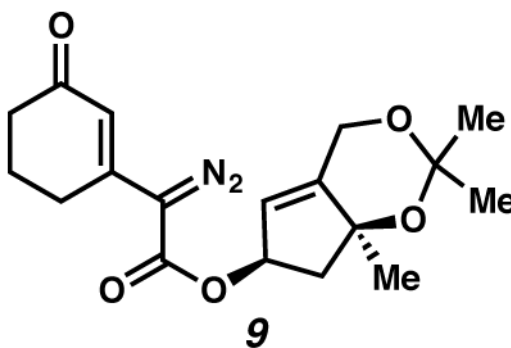


**2-(3-Oxocyclohex-1-enyl)acetic acid (10)**—To a 1:1 EtOH/H<sub>2</sub>O solution (0.14 M) of ester **51**<sup>12</sup> (0.76 g, 4.2 mmol) cooled in an ice water bath was added NaOH (aq) (1.8 mL, 3.04 M, 5.47 mmol) dropwise. The bright yellow solution was allowed to warm to room temperature and stirred for 5 hours. The solution was quenched with 10% HCl (aq) (15 mL) and extracted with EtOAc (5 × 100 mL). The combined organic layers were dried over Na<sub>2</sub>SO<sub>4</sub>, filtered, and concentrated under reduced pressure. The crude oil was purified by flash chromatography (3:1→1:1→0:1 hexanes/EtOAc eluent) to yield carboxylic acid **10** (0.57 g, 89% yield) as a yellow oil. <sup>1</sup>H NMR (500 MHz, CDCl<sub>3</sub>) δ 6.02–6.00 (m, 1H), 3.28 (d, J = 0.7, 2H), 2.43–2.39 (m, 4H), 2.06–2.00 (m, 2H); <sup>13</sup>C NMR (125 MHz, CDCl<sub>3</sub>) δ 200.1, 174.5, 157.1, 129.1, 43.1, 37.0, 29.8, 22.6; IR (thin film/NaCl) 3445, 1722, 1652, 1260 cm<sup>-1</sup>; HRMS (ESI-APCI) *m/z*: [M+H]<sup>+</sup> Calcd for C<sub>8</sub>H<sub>10</sub>O<sub>3</sub> 155.0703; Found 155.0704.

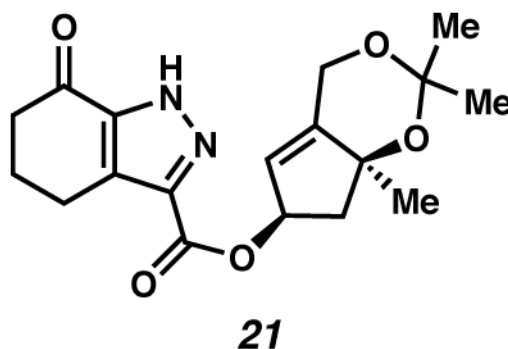


**Ester 19**—A concentration flask was charged with a yellow mixture of acid **10** (1.303 g, 8.4 mmol, 3 equiv), alcohol **11** (from 2.95 mmol ketone **16**, 1 equiv) and EDC-HCl (1.131g,

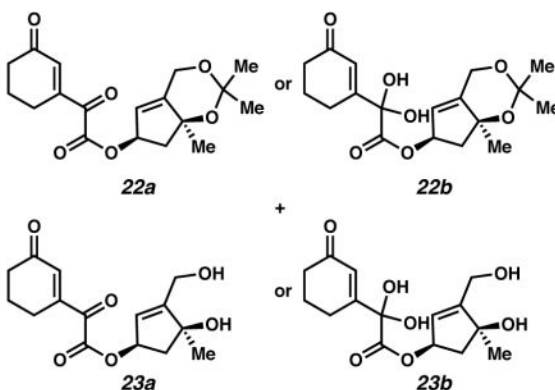
5.9 mmol, 2 equiv) in  $\text{CH}_2\text{Cl}_2$  (29.5 mL, 0.1 M). The suspension was cooled to 0 °C (ice water bath) and treated with DMAP (72 mg, 0.59 mmol, 0.2 equiv). The suspension was allowed to gradually warm to room temperature (ca. 25 °C) as the ice bath melted. After 3.5 hours, the reaction was treated with additional EDC·HCl (1.131 g, 5.9 mmol, 2 equiv). After 1.5 hours, the solution was cooled to 0 °C (ice water bath) and treated with 0.1 N HCl (6 mL). The layers were separated, and the organics were further rinsed with 0.1 N HCl (6 mL), 5%  $\text{K}_2\text{CO}_3$  (aq, 6 mL  $\times$  2), and brine (6 mL) in succession. Each aqueous layer was further extracted with EtOAc (12 mL  $\times$  10). The organic extracts were dried over  $\text{MgSO}_4$ , filtered and concentrated under reduced pressure to give ester **19** as a yellow oil (0.923 g, 98% yield).  $R_f$  0.72 (EtOAc; UV active; visualized with anisaldehyde stain);  $^1\text{H}$  NMR (300 MHz,  $\text{CDCl}_3$ )  $\delta$  5.93 (d,  $J$  = 0.7, 1H), 5.59–5.56 (m, 1H), 5.54–5.53 (m, 1H), 4.67–4.63 (m, 2H), 3.24 (s, 2H), 2.58 (ddd,  $J$  = 12.9, 6.7, 1.2, 1H), 2.40–2.32 (m, 4H), 2.03 (dt,  $J$  = 12.7, 6.5, 2H), 1.94 (dd,  $J$  = 12.8, 6.6, 1H), 1.46 (s, 3H), 1.44 (s, 3H), 1.41 (s, 3H);  $^{13}\text{C}$  NMR (125 MHz,  $\text{CDCl}_3$ )  $\delta$  199.5, 169.4, 157.1, 147.2, 129.1, 121.3, 100.4, 81.0, 77.0, 60.4, 49.3, 43.6, 37.3, 30.1, 29.8, 28.6, 25.8, 22.8; IR (thin film/ $\text{NaCl}$ ) 1732, 1667, 1169, 1127, 974  $\text{cm}^{-1}$ ; HRMS (EI)  $m/z$ :  $[\text{M}]^+$  Calcd for  $\text{C}_{18}\text{H}_{24}\text{O}_5$  320.1624; Found 320.1613;  $[\alpha]_D^{24.1}$  28.4° ( $c$  0.11,  $\text{CHCl}_3$ , derived from ketone **16** with 91% ee).



**Diazoester 9**—A vial beneath  $\text{N}_2(\text{g})$  was charged with ester **19** (32 mg, 0.1 mmol, 1 equiv),  $\text{CH}_3\text{CN}$  (0.5 mL, 0.2 M) and *p*ABSA (31 mg, 0.13 mmol, 3 equiv).<sup>31</sup> The solution turned deep yellow upon dropwise addition of  $\text{NEt}_3$  (0.04 mL, 0.3 mmol, 3 equiv). After six hours, the yellow mixture was treated with  $\text{Et}_2\text{O}$  and filtered through a plug of  $\text{SiO}_2$  (ca. 1 mL) with copious elution. The yellow solution was concentrated under reduced pressure. The residue was diluted with EtOAc and purified by flash chromatography ( $\text{SiO}_2$  (ca. 14 mL), 1:3  $\rightarrow$  1:2 EtOAc:hexanes eluent) to give diazoester **9** as a yellow oil (37 mg, >99% yield).  $R_f$  0.38 (1:1 EtOAc:hexanes; visualized with UV);  $^1\text{H}$  NMR (500 MHz,  $\text{CDCl}_3$ )  $\delta$  6.37 (s, 1H), 5.67 (dddd,  $J$  = 8.5, 6.7, 3.4, 1.9, 1H), 5.54 (dd,  $J$  = 3.5, 1.5, 1H), 4.69–4.65 (m, 1H), 4.65–4.61 (m, 1H), 2.58 (dd,  $J$  = 12.8, 6.9, 1H), 2.54–2.49 (m, 2H), 2.41–2.36 (m, 2H), 2.06 (dt,  $J$  = 12.7, 6.3, 2H), 1.97 (dd,  $J$  = 12.9, 6.5, 1H), 1.43 (s, 3H), 1.43 (s, 3H), 1.39 (s, 3H);  $^{13}\text{C}$  NMR (125 MHz,  $\text{CDCl}_3$ ,  $-\text{C}=\text{N}_2$  or  $-\text{C}(\text{CH}_3)_2$ )  $\delta$  197.4, 162.7, 147.5, 147.2, 121.3, 120.9, 100.5, 81.0, 77.5, 60.4, 49.4, 37.0, 30.0, 28.6, 26.8, 25.9, 22.5; IR ( $\text{CH}_2\text{Cl}_2$ ) 2101, 1708, 1580, 1191, 1137, 1110, 1064, 994  $\text{cm}^{-1}$ ; HRMS (EI)  $m/z$ :  $[\text{M}]^+$  Calcd for  $\text{C}_{18}\text{H}_{22}\text{O}_5\text{N}_2$  346.1529; Found 346.1524;  $[\alpha]_D^{24.4}$  47.9° ( $c$  0.11,  $\text{CHCl}_3$ , derived from ketone **16** with 91% ee).



**Pyrazole 21**—A flask fitted with a reflux condenser was charged with diazoester **9** (20 mg, 0.054 mmol, 1 equiv) and PhMe (8 mL, 0.00675 M). The yellow solution was treated with a warm (previously refluxing) solution of copper(II) acetylacetonate (2.8 mg, 0.011 mmol, 0.2 equiv) in PhMe (2 mL, with 10 mL wash, 0.054 M in diazoester **9**). The solution was heated in an oil bath at 110 °C. After 40 minutes, the solution was removed from heat and concentrated under reduced pressure. The residue was diluted with 1:1 EtOAc:hexanes and purified by flash chromatography (SiO<sub>2</sub> ~ 8 mL; 1:1 EtOAc:hexanes eluent) to give pyrazole **21** as a white solid (10 mg, 59% yield). Colorless crystals could be obtained by slow diffusion of PhH into a solution of pyrazole **21** in CHCl<sub>3</sub>. Melting point analysis resulted in crystals yellowing at 149–150 °C and then converting to a red liquid as gas evolved at 170–172 °C. R<sub>f</sub> 0.26 (1:1 EtOAc:hexanes; visualized with UV or anisaldehyde stain); <sup>1</sup>H NMR (500 MHz, CDCl<sub>3</sub>) δ 11.40 (s, 1H), 5.83 (ddtd, J = 6.8, 5.0, 3.4, 1.9, 1H), 5.70 (dt, J = 3.0, 1.5, 1H), 4.73 (ddd, J = 15.7, 3.3, 2.4, 1H), 4.70–4.68 (m, 1H), 3.04 (t, J = 6.1, 2H), 2.71 (dd, J = 12.7, 6.8, 1H), 2.63 (dd, J = 7.3, 5.6, 2H), 2.23–2.13 (m, 3H), 1.66 (s, 2H), 1.49 (s, 3H), 1.48 (s, 3H), 1.40 (s, 3H); <sup>13</sup>C NMR (125 MHz, CDCl<sub>3</sub>, –C=O, –CC(O)OR) δ 147.2, 131.8, 121.4, 110.2, 100.4, 81.0, 77.2, 60.4, 49.5, 38.7, 30.1, 29.9, 28.6, 25.9, 24.6, 21.5; IR (thin film/NaCl) 3286, 1716, 1689, 1188, 1172, 1094, 1042, 994 cm<sup>-1</sup>; HRMS (EI) *m/z*: [M + H]<sup>+</sup> Calcd for C<sub>18</sub>H<sub>23</sub>O<sub>5</sub>N<sub>2</sub> 347.1607; Found 347.1596; [α]<sub>D</sub><sup>27.4</sup> +45.6° (*c* 0.59, acetone, derived from ketone **16** with 91% ee).

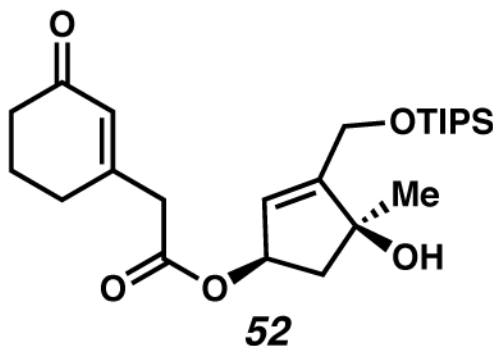


**Oxidized 22a, or 22b, and 23a, or 23b<sup>17a</sup>**—As a note of clarification, one set of data has been acquired for compound **22**, and another for compound **23**. <sup>13</sup>C and IR spectra

support their assignment as ketones **22a** and **23a**, respectively, while HRMS data supports their assignment as hydrates **22b** and **23b**, respectively. It is likely that these hydrates form under the conditions used to obtain HRMS data.

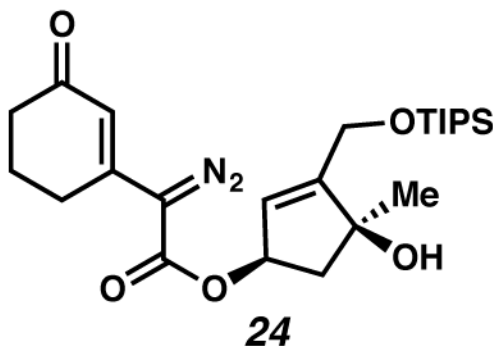
A vial was charged with rhodium octanoate dimer ( $\text{Rh}_2(\text{oct})_4$ , 0.6 mg, 0.0007 mmol, 0.01 equiv) and  $\text{CH}_2\text{Cl}_2$  (0.2 mL, 0.375 M relative to diazoester **9**). The pale green solution was cooled to 0 °C (ice water bath). To it was added dropwise diazoester **9** (28 mg, 0.075 mmol, 1 equiv) in  $\text{CH}_2\text{Cl}_2$  (0.22 mL, 0.341 M). After 25 minutes, the yellow solution was treated with additional  $\text{Rh}_2(\text{oct})_4$  (0.4 mg, 0.0005 mmol, 0.007 equiv). After an additional 18 hours, the yellow solution was treated with a third portion of  $\text{Rh}_2(\text{oct})_4$  (0.4 mg, 0.0005 mmol, 0.007 equiv). After an additional two hours, the reaction was diluted with EtOAc (10 mL), filtered through a plug of celite and concentrated under reduced pressure. The residue was diluted with EtOAc (10 mL), filtered and concentrated. This residue was purified by flash chromatography ( $\text{SiO}_2 \sim 16 \text{ mL}$ ; 1:40  $\rightarrow$  1:20  $\rightarrow$  1:5  $\rightarrow$  1:0 EtOAc: $\text{CH}_2\text{Cl}_2$  then 1:20 MeOH:EtOAc elution) to give oxidized **22a** (9.8 mg, 41% yield).  $R_f$  0.61 (1:5 EtOAc: $\text{CH}_2\text{Cl}_2$ ; UV/Vis);  $^1\text{H}$  NMR (500 MHz,  $\text{CDCl}_3$ )  $\delta$  6.62 (t,  $J = 1.7$ , 1H), 5.75–5.70 (m, 1H), 5.58 (dd,  $J = 3.7$ , 1.7, 1H), 4.70–4.62 (m, 2H), 2.64 (dd,  $J = 12.9$ , 6.9, 1H), 2.54 (td,  $J = 6.1$ , 1.8, 2H), 2.52–2.47 (m, 2H), 2.11–2.02 (m, 3H), 1.45 (d,  $J = 0.5$ , 3H), 1.42 (s, 3H), 1.38 (s, 3H);  $^{13}\text{C}$  NMR (125 MHz,  $\text{CDCl}_3$ )  $\delta$  200.0, 188.7, 162.7, 150.0, 148.6, 137.0, 120.2, 100.6, 81.0, 79.0, 60.3, 49.0, 38.2, 30.1, 28.7, 25.7, 23.0, 21.9; IR (thin film/NaCl) 3384, 2934, 2871, 1732, 1682, 1455, 1429, 1416, 1373, 1350, 1317, 1257, 1195, 1148, 1110, 1065, 1030, 978, 949, 902, 849, 735  $\text{cm}^{-1}$ ; HRMS (ES)  $m/z$ :  $[\text{M}+\text{H}]^+$  Calcd for **22**  $\text{C}_{18}\text{H}_{24}\text{O}_7$  353.1600; Found 353.1631;  $[\alpha]_D^{26.6} +30.4^\circ$  ( $c$  0.15,  $\text{CHCl}_3$ , derived from ketone **16** with 91% ee).

Chromatography also furnished slightly impure acetonide-cleaved **23a** or **23b**. Acetonide-cleaved **23a** or **23b** was purified by flash chromatography ( $\text{SiO}_2 \sim 2 \text{ mL}$ ; 4:1 EtOAc:hexanes elution) to give acetonide-cleaved **23a** (4.8 mg, 23% yield).  $R_f$  0.40 (EtOAc; UV active, visualized with anisaldehyde stain);  $^1\text{H}$  NMR (300 MHz,  $\text{CDCl}_3$ )  $\delta$  6.65 (t,  $J = 1.7$ , 1H), 5.84 (q,  $J = 1.7$ , 1H), 5.70–5.64 (m, 1H), 4.45–4.35 (m, 2H), 2.60 (dd,  $J = 14.7$ , 7.2, 2H), 2.54 (ddd,  $J = 6.0$ , 6.0, 1.8, 2H), 2.51–2.43 (m, 2H), 2.44 (s, 1H), 2.16 (dd,  $J = 14.6$ , 3.3, 1H), 2.13–2.03 (m, 3H), 1.44 (s, 3H);  $^{13}\text{C}$  NMR (125 MHz,  $\text{CDCl}_3$ )  $\delta$  200.2, 188.6, 162.6, 155.2, 150.1, 137.1, 124.4, 81.4, 78.8, 59.2, 47.9, 38.2, 26.6, 23.0, 21.9; IR (thin film/NaCl) 3382, 2968, 2935, 1732, 1682, 1193, 1110, 1092, 1065, 1030,  $\text{cm}^{-1}$ ; HRMS (ES+)  $m/z$  Calcd for **23**  $\text{C}_{15}\text{H}_{18}\text{O}_6$   $[\text{M}+\text{H}]^+$ : 295.1182; Found 295.1195; HRMS (ES)  $m/z$ :  $[\text{M}+\text{H}]^+$  Calcd for **23**  $\text{C}_{15}\text{H}_{20}\text{O}_7$  313.1287; Found 313.1286;  $[\alpha]_D^{24.9} +48.8^\circ$  ( $c$  0.09,  $\text{CHCl}_3$ , derived from ketone **16** with 91% ee).

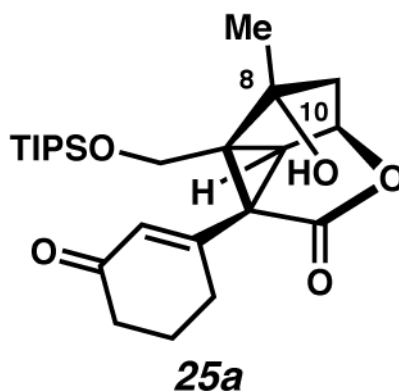


**Silyl ether 52**—A flask was charged with acetonide **19** (0.451 g, 1.41 mmol, 1 equiv) in MeOH (30 mL, 0.047 M), and the solution was cooled to 0 °C (ice water bath). The solution was treated dropwise with a solution of fumaric acid (59 mg, 0.50 mmol, 0.36 equiv) in MeOH (10 mL, 0.14 M total relative to acetonide). After 3 days, the reaction was quenched by addition of a 1:1 solution of H<sub>2</sub>O and saturated aq NaHCO<sub>3</sub> (40 mL each), and extracted with EtOAc (300 mL, and then 200 mL × 5). The organic extracts were dried over Na<sub>2</sub>SO<sub>4</sub>, filtered and concentrated under reduced pressure to give a golden/orange oil.

The resultant oil was dissolved in CH<sub>2</sub>Cl<sub>2</sub> (35 mL, 0.040 M), placed beneath an Ar(g) atmosphere, and cooled to 0 °C (ice water bath). The solution was treated dropwise with imidazole (0.303 g, 4.46 mmol, 3.16 equiv) in CH<sub>2</sub>Cl<sub>2</sub>, followed by TIPSCl (0.91 mL, 4.25 mmol, 3.01 equiv) and DMAP (20 mg, 0.16 mmol, 0.11 equiv) in CH<sub>2</sub>Cl<sub>2</sub>. After 17 hours, the solution was quenched with saturated aq NH<sub>4</sub>Cl (50 mL), and extracted with EtOAc (150 mL × 3). The organic extracts were dried over Na<sub>2</sub>SO<sub>4</sub>, filtered and concentrated under reduced pressure. The reaction was purified by flash chromatography (1:19 → 1:9 EtOAc:CH<sub>2</sub>Cl<sub>2</sub> eluent) to give silyl ether **52** (0.371 g, 59% yield over two steps) as a yellow oil. R<sub>f</sub> 0.76 (EtOAc, UV/Vis, visualized with anisaldehyde stain); <sup>1</sup>H NMR (500 MHz, CDCl<sub>3</sub>) δ 5.95 (t, J = 1.0, 1H), 5.73 (dd, J = 3.5, 1.7, 1H), 5.51 (dtd, J = 7.2, 3.6, 1.8, 1H), 4.59–4.38 (m, 2H), 3.24 (s, 2H), 2.82 (s, 1H), 2.52 (dd, J = 14.4, 7.3, 1H), 2.42–2.35 (m, 4H), 2.11–1.91 (m, 3H), 1.41 (s, 3H), 1.21–1.10 (m, 3H), 1.09–1.05 (m, 18H); <sup>13</sup>C NMR (125 MHz, CDCl<sub>3</sub>) δ 199.6, 169.5, 157.3, 153.6, 129.1, 124.5, 81.1, 76.9, 60.4, 48.0, 43.7, 37.4, 29.8, 26.8, 22.8, 18.2, 12.0; IR (thin film/NaCl) 3440, 1733, 1668, 1192, 1165, 1127, 1107, 1055, cm<sup>-1</sup>; HRMS (mixed EIC) *m/z*: [M+Na]<sup>+</sup> Calcd for C<sub>24</sub>H<sub>40</sub>O<sub>5</sub>Si 459.2537; Found 459.2539; [α]<sub>D</sub><sup>18.9</sup> +44.8° (c 0.93, CHCl<sub>3</sub>, derived from ketone **16** with 91% ee).

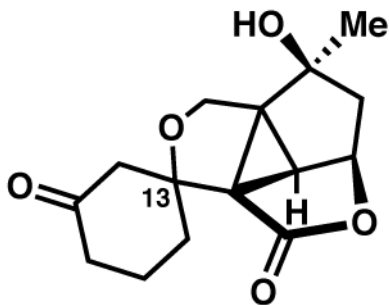


**Diazoester 24**—A flask was charged with a pale yellow solution of ester **52** (53 mg, 0.121 mmol, 1 equiv) in CH<sub>3</sub>CN (4.7 mL, 0.026 M) with TsN<sub>3</sub> (0.600 g, 0.535 mmol, 4.4 equiv), and cooled to 0 °C (ice water bath). CAUTION!!! TsN<sub>3</sub> is SHOCK SENSITIVE AND POTENTIALLY EXPLOSIVE. The solution was treated with Et<sub>3</sub>N (0.03 mL, 0.22 mmol, 1.8 equiv) dropwise, and immediately turned deeper yellow in color. After 24 hours, the reaction was concentrated under reduced pressure. The crude yellow mixture was purified by flash chromatography (SiO<sub>2</sub> ~ 16 mL; 1:5 EtOAc:PhH eluent) to give diazoester **24** (48.9 mg, 87% yield) as a yellow oil. R<sub>f</sub> 0.48 (1:2 EtOAc:PhH; visualized with UV); <sup>1</sup>H NMR (500 MHz, CDCl<sub>3</sub>) δ 6.37 (s, 1H), 5.71 (dd, J = 3.3, 1.6, 1H), 5.59 (ddd, J = 7.3, 3.7, 1.9, 1H), 2.82 (s, 1H), 2.58–2.49 (m, 3H), 2.41–2.35 (m, 2H), 2.10–2.00 (m, 3H), 1.40 (s, 3H), 1.13 (tt, J = 12.2, 6.9, 3H), 1.08–1.03 (m, 21H); <sup>13</sup>C NMR (125 MHz, CDCl<sub>3</sub>, –C=N<sub>2</sub>) δ 197.5, 162.7, 153.7, 147.5, 124.4, 120.6, 81.0, 77.4, 60.4, 48.2, 37.0, 27.0, 26.8, 22.5, 18.2, 12.0; IR (thin film/NaCl) 3407, 2101, 1709, 1645, 1191, 1138, 1106, 1061, 993 cm<sup>-1</sup>; HRMS (ES) *m/z*: [M+H]<sup>+</sup> Calcd for C<sub>24</sub>H<sub>39</sub>N<sub>2</sub>O<sub>5</sub>Si 463.2628; Found 463.2640; [α]<sub>D</sub><sup>23.4</sup> +48.5° (c 0.175, CHCl<sub>3</sub>, derived from ketone **16** with 91% ee).



**Cyclopropane 25a**—In the glovebox, a flask was charged with Cu(tbs)<sub>2</sub> (92.2 mg, 0.22 mmol, 1.1 equiv) and CH<sub>2</sub>Cl<sub>2</sub> (20 mL, 0.01 M). This solution was treated with diazoester **24** (93.2 mg, 0.20 mmol, 1 equiv) in CH<sub>2</sub>Cl<sub>2</sub> (8 mL, 0.025 M). After 7 days, the reaction was removed from the glovebox and concentrated under reduced pressure to yield a brown residue, which was purified by flash chromatography (SiO<sub>2</sub> ~ 16 mL; 1:1 EtOAc:hexanes

eluent) to give cyclopropane **25a** as a yellow oil (62.8 mg, 74% yield).  $R_f$  0.18 (1:1 EtOAc:hexanes; UV active; visualized with anisaldehyde stain);  $^1\text{H}$  NMR (500 MHz,  $\text{CDCl}_3$ )  $\delta$  5.87 (s, 1H), 4.87 (td,  $J = 6.2, 2.9, 1\text{H}$ ), 4.07 (d,  $J = 11.5, 1\text{H}$ ), 3.49 (d,  $J = 11.5, 1\text{H}$ ), 2.68–2.60 (m, 1H), 2.59 (d,  $J = 5.9, 1\text{H}$ ), 2.45–2.23 (m, 2H), 2.17–1.97 (m, 3H), 1.93–1.83 (m, 1H), 1.74 (s, 1H), 1.49 (s, 3H), 1.11–0.76 (m, 21H);  $^{13}\text{C}$  NMR (125 MHz,  $\text{CDCl}_3$ )  $\delta$  199.7, 173.1, 156.4, 130.0, 93.8, 70.6, 59.9, 59.6, 53.8, 48.0, 42.8, 37.6, 29.5, 22.8, 19.1, 18.2, 12.1; IR (thin film/ $\text{NaCl}$ ) 3427, 1759, 1668, 1626, 1192, 1175, 1122, 1085, 1065  $\text{cm}^{-1}$ ; HRMS (FAB)  $m/z$ :  $[\text{M}+\text{H}]^+$  Calcd for  $\text{C}_{24}\text{H}_{39}\text{O}_5\text{Si}$  435.2567; Found 435.2586;  $[\alpha]_D^{21.2} -12.6^\circ$  ( $c$  0.125,  $\text{CHCl}_3$ , derived from ketone **16** with 91% ee).

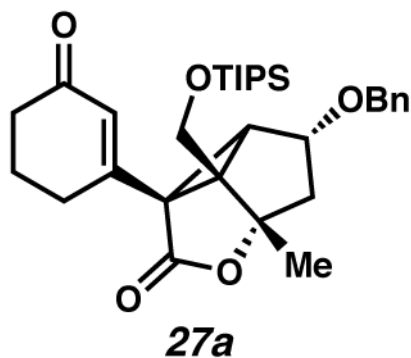


**26**  
mixture of C(13)  
diastereomers

**Dihydropyran 26**—A flask was charged with a colorless solution of silyl ether **25a** (1 equiv) in THF (0.00825 M) at 0 °C (ice water bath). The solution was treated with TBAF (1M in THF, 1.2 equiv), and the solution turned yellow in color. After 30 min, the reaction was filtered through  $\text{SiO}_2$  (ca. 1 mL; EtOAc elution), and concentrated under reduced pressure to give a crude white paste, assigned as crude diol **53**.  $R_f$  0.14 (EtOAc; UV/Vis active);  $^1\text{H}$  NMR (500 MHz,  $\text{CDCl}_3$ )  $\delta$  5.93 (s, 1H), 4.93 (t,  $J = 6.3, 1\text{H}$ ), 3.94 (d,  $J = 11.9, 1\text{H}$ ), 3.66 (d,  $J = 12.0, 1\text{H}$ ), 2.74–2.65 (m, 2H), 2.69 (d,  $J = 6.0, 1\text{H}$ ), 2.47–2.34 (m, 3H), 2.31–2.23 (m, 2H), 2.19 (dd,  $J = 14.0, 7.0, 1\text{H}$ ), 2.13 (d,  $J = 13.5, 1\text{H}$ ), 2.11–2.01 (m, 2H), 1.99–1.89 (m, 2H), 1.69 (s, 3H); HRMS (EI)  $m/z$ :  $[\text{M}^+]^+$  Calcd for  $\text{C}_{15}\text{H}_{18}\text{O}_5$  278.1154; Found 278.1143.

A flask was charged with a solution of crude diol **53**,  $\text{CH}_2\text{Cl}_2$  (1.1 mL, 0.012 M) and pyridine (0.02 mL, 0.159 mmol, 12 equiv) at 0 °C (ice water bath), which was subsequently treated with DMP (7.9 mg, 0.018 mmol, 1.4 equiv). CAUTION! DMP is a HEAT- and SHOCK-SENSITIVE COMPOUND, showing exotherms when heated (>130 °C). ALL OPERATIONS SHOULD BE CONDUCTED BEHIND A BLAST SHIELD. After 2 days at this temperature, the mixture was diluted with EtOAc (ca. 10 mL), and concentrated under reduced pressure. The resultant semi-solid was treated with  $\text{CH}_2\text{Cl}_2$  (ca. 1 mL) and Amberlyst A26 ( $\text{S}_2\text{O}_3^{2-}$ ) (19.6 mg). After 6.5 h, the mixture was treated with JandaJel (2.3 mmol/g, 17.2 mg, 0.0396 mmol, 3.0 equiv). After an additional 17.5 h, the mixture was

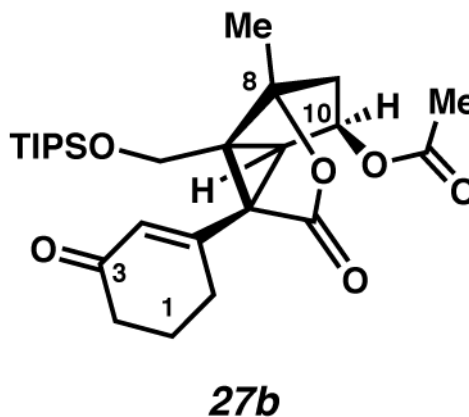
filtered through SiO<sub>2</sub> (ca. 0.2 mL; EtOAc elution), and concentrated under reduced pressure. The diastereomeric mixture was purified by thin layer chromatography on a 250 μm silica gel plate (10 cm wide, 20 cm tall; Et<sub>2</sub>O × 2 elution). The desired diastereomeric mixture was removed from the plate at R<sub>f</sub> 0.10. The diastereomeric mixture of dihydropyrans (**26**) was further purified by thin layer chromatography on a 250 μm silica gel plate (10 cm wide, 20 cm tall; 1:1 EtOAc:PhH elution). The diastereomeric mixture was removed from the plate at R<sub>f</sub> 0.27, as a white solid (<20% yield). Major diastereomer: <sup>1</sup>H NMR (500 MHz, CDCl<sub>3</sub>) δ 4.94 (app. q, J = 3.7, 1H), 4.02 (d, J = 9.4, 1H), 3.90 (d, J = 9.4, 1H), 3.18 (d, J = 4.8, 1H), 2.77 (ddd, J = 14.2, 11.6, 5.1, 1H), 2.71 (d, J = 14.1, 1H), 2.43–2.28 (m, 2H), 2.27 (dt, J = 14.1, 2.3, 1H), 2.18 (dd, J = 14.3, 2.0, 1H), 2.08–2.03 (m, 1H), 2.04–1.86 (m, 3H), 1.76–1.70 (m, 1H), 1.52 (s, 3H); <sup>13</sup>C NMR (125 MHz, CDCl<sub>3</sub>) δ 208.5, 172.9, 84.7, 80.5, 78.0, 64.7, 55.7, 53.0, 46.2, 45.9, 43.7, 40.9, 31.5, 27.8, 20.2. Minor dia-steromer: <sup>1</sup>H NMR (500 MHz, CDCl<sub>3</sub>) δ 4.94 (app. q, J = 3.7, 1H), 4.11 (d, J = 9.6, 1H), 3.88 (d, J = 9.6, 1H), 3.61 (d, J = 15.1, 1H), 3.18 (d, J = 4.8, 1H), 2.77 (ddd, J = 14.2, 11.6, 5.1, 1H), 2.59 (d, J = 15.1, 1H), 2.43–2.28 (m, 2H), 2.18 (dd, J = 14.3, 2.0, 1H), 2.08–2.03 (m, 1H), 2.04–1.86 (m, 3H), 1.76–1.70 (m, 1H), 1.51 (s, 3H); <sup>13</sup>C NMR (125 MHz, CDCl<sub>3</sub>) δ 209.7, 173.0, 84.7, 80.5, 78.1, 64.7, 56.6, 52.8, 48.5, 45.6, 43.9, 40.6, 31.2, 27.8, 21.5. Diastereomeric Mixture: IR (thin film/NaCl) 3460, 1756, 1712, 1172, 1109, 1073, 1047, 1012 cm<sup>-1</sup>; HRMS (ESI-APCI) *m/z*: [M+Na]<sup>+</sup> Calcd for C<sub>15</sub>H<sub>18</sub>O<sub>5</sub> 301.1046; Found 301.1067.



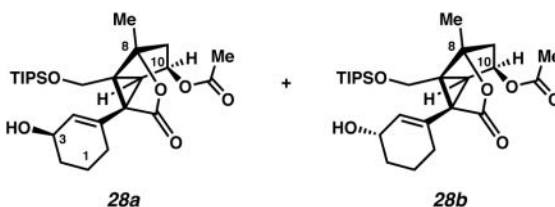
**Benzyl ether 27a**<sup>32</sup>—A flask was charged with a solution of silyl ether **25a** (1.1 mg, 0.0026 mmol, 1 equiv) in PhMe (0.2 mL, 0.013 M) beneath an Ar(g) atmosphere at room temperature (22.5 °C). The solution was treated with KI (0.9 mg, 0.0054 mmol, 2.1 equiv) and Ag<sub>2</sub>O (0.9 mg, 0.0039 mmol, 1.5 equiv), followed by BnBr (10 μL, 0.084 mmol, 32 equiv). After 2 days, the yellow mixture was heated in an oil bath at 40 °C for 22 hours, at which point additional BnBr (10 μL, 0.084 mmol, 32 equiv) was added to the reaction. After 24 h, the suspension was treated with Ag<sub>2</sub>O (3.0 mg, 0.013 mmol, 5 equiv) and KI (4.6 mg, 0.028 mmol, 10.6 equiv). After an additional 27 h, additional BnBr (10 μL, 0.084 mmol, 32 equiv) was added to the reaction. After an additional 27 h, the reaction was diluted with EtOAc (10 mL), filtered through SiO<sub>2</sub>, and concentrated under reduced pressure. The mixture was purified by thin layer chromatography on a 250 μm silica gel plate (10 cm wide, 20 cm tall; 1:10 acetone:CH<sub>2</sub>Cl<sub>2</sub> elution) to give benzoyl ester **27a** (0.5 mg, 37% yield, R<sub>f</sub> 0.69). R<sub>f</sub> 0.22 (1:1 Et<sub>2</sub>O:heptanes, UV/Vis, visualized with anisaldehyde stain); <sup>1</sup>H NMR (600 MHz, CDCl<sub>3</sub>) δ 7.36–7.32 (m, 4H), 7.29–7.26 (m, 1H), 5.93 (t, J = 1.4, 1H), 4.63 (d, J



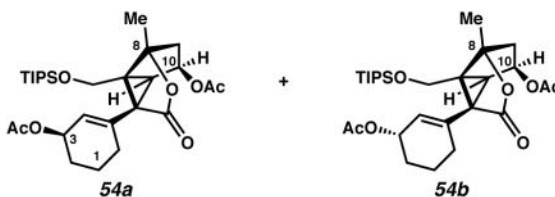
= 11.7, 1H), 4.53 (dd,  $J = 7.5, 5.6$ , 1H), 4.38 (d,  $J = 11.6$ , 1H), 4.17 (d,  $J = 11.5$ , 1H), 3.57 (d,  $J = 11.5$ , 1H), 2.79–2.72 (m, 1H), 2.61 (d,  $J = 5.6$ , 1H), 2.47 (ddd,  $J = 16.6, 9.2, 4.7$ , 1H), 2.39 (ddd,  $J = 12.1, 7.9, 4.7$ , 1H), 2.29 (d,  $J = 13.9$ , 1H), 2.21–2.08 (m, 2H), 2.14 (dd,  $J = 13.9, 7.6$ , 1H), 1.95 (tdd,  $J = 13.8, 9.3, 4.6$ , 1H), 1.70 (s, 3H), 1.12–0.90 (m, 21H);  $^{13}\text{C}$  NMR (125 MHz,  $\text{C}_6\text{D}_6$ )  $\delta$  199.2, 172.5, 156.2, 137.5, 129.7, 128.7, 128.2, 128.0, 93.1, 76.9, 71.4, 59.9, 59.4, 52.1, 48.1, 40.3, 37.6, 29.5, 22.9, 19.0, 18.2, 12.1; IR (thin film/NaCl) 1760, 1674, 1190, 1177, 1125, 1086, 1039  $\text{cm}^{-1}$ ; HRMS-MM (ESI-APCI)  $m/z$ :  $[\text{M}+\text{H}]^+$  Calcd for  $\text{C}_{31}\text{H}_{44}\text{O}_5\text{Si}$  525.3031; Found 525.3023;  $[\alpha]_{\text{D}}^{22.9} +5.9^\circ$  ( $c$  0.20,  $\text{CHCl}_3$ , derived from ketone **16** with 91% ee).



**Secondary acetate 27b**—A flask charged with  $\text{CH}_2\text{Cl}_2$  (0.96 mL, 0.027 M), tertiary alcohol **25a** (11.2 mg, 0.0258 mmol, 1 equiv),  $\text{Ac}_2\text{O}$  (0.03 mL, 0.33 mmol, 13 equiv) and pyridine (0.03 mL, 0.38 mmol, 15 equiv) at room temperature (23 °C) was treated with DMAP (0.4 mg, 0.003 mmol, 0.13 equiv). After 1 h 10 m, the solution was extracted with EtOAc (10 mL  $\times$  4), and rinsed successively with 1N HCl (3 mL) and brine (3 mL  $\times$  2). The organic extracts were dried over  $\text{MgSO}_4$ , filtered, and concentrated under reduced pressure to yield a secondary acetate **27b** (11.7 mg, 87.3% yield) as a pale yellow oil.  $R_f$  0.64 (1:1 EtOAc:hexanes, UV/Vis, visualized with anisaldehyde stain);  $^1\text{H}$  NMR (500 MHz,  $\text{C}_6\text{D}_6$ )  $\delta$  6.17 (t,  $J = 1.5$ , 1H), 5.11 (dd,  $J = 7.7, 5.9$ , 1H), 3.77 (d,  $J = 11.6$ , 1H), 3.40 (d,  $J = 11.6$ , 1H), 2.62 (d,  $J = 5.9$ , 1H), 2.46 (dddd,  $J = 9.4, 7.3, 5.0, 1.7$ , 1H), 2.11–1.96 (m, 4H), 1.80–1.72 (m, 4H), 1.58–1.44 (m, 2H), 1.42 (s, 3H), 0.93 (d,  $J = 1.9$ , 18H), 0.95–0.87 (m, 3H);  $^1\text{H}$  NMR (500 MHz,  $\text{CDCl}_3$ )  $\delta$  5.89 (t,  $J = 1.5$ , 1H), 5.40 (td,  $J = 6.0, 2.1$ , 1H), 4.18 (d,  $J = 11.4$ , 1H), 3.52 (d,  $J = 11.5$ , 1H), 2.80 (d,  $J = 5.9$ , 1H), 2.54 (dddd,  $J = 18.1, 7.3, 4.9, 1.5$  1H), 2.45–2.29 (m, 2H), 2.23 (d,  $J = 0.9$ , 1H), 2.23 (d,  $J = 5.0$ , 1H), 2.21–2.13 (m, 1H), 2.09–2.01 (m, 1H), 2.00 (s, 3H), 1.99–1.89 (m, 1H), 1.69 (s, 3H), 1.10–0.92 (m, 3H), 1.01 (d,  $J = 3.8$ , 18H);  $^{13}\text{C}$  NMR (125 MHz,  $\text{C}_6\text{D}_6$ )  $\delta$  196.5, 171.2, 170.1, 153.9, 130.1, 91.8, 73.1, 59.7, 57.9, 50.2, 47.6, 41.3, 37.1, 28.8, 22.5, 19.9, 18.5, 17.7, 11.8; IR (film) 1769, 1740, 1675, 1191, 1173, 1127, 1082, 1064  $\text{cm}^{-1}$ ; HRMS (ESI-APCI)  $m/z$ :  $[\text{M}+\text{H}]^+$  Calcd for  $\text{C}_{26}\text{H}_{40}\text{O}_6\text{Si}$  477.2667; Found 477.2667;  $[\alpha]_{\text{D}}^{17.9} -11.6^\circ$  ( $c$  0.35,  $\text{CH}_3\text{CN}$ , derived from ketone **16** with 91% ee).

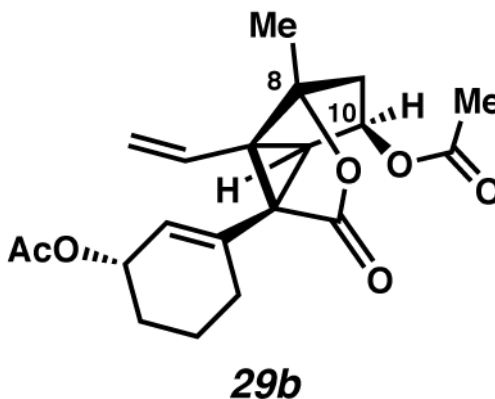


**Alcohols 28**—Alcohol **25a** (57.2 mg, 0.131 mmol, 1 equiv) was converted to acetate **27b**, as described above. The crude **27b** as a pale yellow oil was dissolved in MeOH (12.0 mL, 0.011 M), cooled to 0 °C (ice water bath) and treated with NaBH<sub>4</sub> (18.6 mg, 0.491 mmol, 3.75 equiv). After 24 m, the yellow solution was treated with a saturated aq solution of NH<sub>4</sub>Cl (0.70 mL). The mixture was diluted with EtOAc (125 mL), filtered through SiO<sub>2</sub> (ca. 2 mL) and concentrated under reduced pressure to an off-white solid. The solid was purified by preparative thin layer chromatography on a 250 μm analytical plate (2:1 CH<sub>2</sub>Cl<sub>2</sub>:EtOAc × 2 elution) to give alcohol **28a** (21.4 mg, 34% yield) as a colorless oil and alcohol **28b** (32.2 mg, 51% yield) as a colorless oil. Alcohol **28a**: R<sub>f</sub> 0.65 (1:1 EtOAc:hexanes, visualized by UV/Vis, or with anisaldehyde stain); <sup>1</sup>H NMR (500 MHz, CDCl<sub>3</sub>) δ 5.73 (app dt, J = 3.1, 1.7, 1H), 5.41 (dt, J = 5.9, 4.1, 1H), 4.27 (d, J = 11.4, 2H), 3.45 (dd, J = 11.4, 8.7, 1H), 2.79 (d, J = 5.9, 1H), 2.26–2.21 (m, 2H), 2.19–2.11 (m, 1H), 2.00 (s, 3H), 1.91 (tdd, J = 7.8, 4.8, 3.1, 1H), 1.79–1.74 (m, 1H), 1.73 (ddd, J = 7.6, 4.3, 2.2, 1H), 1.70 (s, 3H), 1.68–1.61 (m, 1H), 1.50 (dddd, J = 12.5, 9.4, 6.5, 3.2, 1H), 1.44 (s, 1H), 1.14–0.94 (m, 21H); <sup>13</sup>C NMR (125 MHz, CDCl<sub>3</sub>) δ 174.2, 171.3, 133.7, 133.0, 93.0, 73.8, 65.9, 60.0, 57.5, 51.0, 48.3, 41.9, 31.6, 28.1, 20.9, 19.3, 18.9, 18.2, 12.1; IR (film) 3482, 2941, 2866, 1760, 1740, 1462, 1374, 1242, 1080, 1065, 882, 683 cm<sup>-1</sup>; HRMS (ESI–APCI) *m/z*: [M+NH<sub>4</sub>]<sup>+</sup> Calcd for C<sub>26</sub>H<sub>42</sub>O<sub>6</sub>Si 496.3089; Found 496.3071; [α]<sub>D</sub><sup>27.2</sup> +8.7° (*c* 1.52, CHCl<sub>3</sub>, derived from ketone **16** with 91% ee). Alcohol **28b**: R<sub>f</sub> 0.61 (1:1 EtOAc:hexanes, UV/Vis, visualized with anisaldehyde stain); <sup>1</sup>H NMR (500 MHz, CDCl<sub>3</sub>) δ 5.74 (dt, J = 3.3, 1.6, 1H), 5.42 (dt, J = 5.9, 4.1, 1H), 4.26 (d, J = 11.4, 1H), 4.17 (app d, 1H), 3.43 (d, J = 11.4, 1H), 2.77 (d, J = 5.9, 1H), 2.23 (d, J = 4.1, 1H), 2.19–2.14 (m, 2H), 2.02 (s, 3H), 1.82–1.72 (m, 3H), 1.69 (s, 3H), 1.66–1.51 (m, 2H), 1.11–0.95 (m, 21H); <sup>13</sup>C NMR (125 MHz, CDCl<sub>3</sub>) δ 174.1, 171.2, 133.9, 132.6, 93.0, 73.7, 65.8, 59.9, 57.2, 51.0, 48.3, 41.7, 31.7, 28.1, 20.9, 19.3, 18.9, 18.2, 12.1; IR (thin film/NaCl) 3447, 1763, 1740, 882 cm<sup>-1</sup>; HRMS (EI) *m/z*: [M+NH<sub>4</sub>]<sup>+</sup> Calcd for C<sub>26</sub>H<sub>42</sub>O<sub>6</sub>Si 496.3089; Found 496.3099; [α]<sub>D</sub><sup>26.8</sup> +33.1° (*c* 1.01, CHCl<sub>3</sub>, derived from ketone **16** with 91% ee).



**Bisacetates 54**—For representative acetylation and reduction procedures, see acetylation of tertiary alcohol **25a** to **27c**, and reduction of **27c** to **28**. Alcohols **28** can be acetylated without attempting their purification or separation. Bisacetates **54** can be separated by preparative thin layer chromatography on a 250 μm analytical plate (eluent: 20:1

CH<sub>2</sub>Cl<sub>2</sub>:EtOAc × 2) to give bisacetate **54b** as a colorless oil (6.3 mg, 51% yield over three steps) and bisacetate **54a** as a white solid (2.6 mg, 21% yield over three steps). Alternatively, bisacetates **54** can be formed by acylation in parallel. Alcohol **28b** (20.0 mg, 0.042 mmol, 1 equiv) furnished bisacetate **54b** (21.7 mg, 99% yield), while alcohol **28a** (13.9 mg, 0.029 mmol, 1 equiv) provided bisacetate **54a** (12.1 mg, 80% yield). In this case, bisacetates were carried on without further purification. Bisacetate **54a**: R<sub>f</sub> 0.41 (1:20 EtOAc:CH<sub>2</sub>Cl<sub>2</sub> × 2, visualized with anisaldehyde stain); <sup>1</sup>H NMR (500 MHz, CDCl<sub>3</sub>) δ 5.68 (app dt, J = 3.5, 1.6, 1H), 5.43 (dd, J = 10.0, 4.1, 1H), 5.34–5.29 (m, 1H), 4.27 (d, J = 11.4, 1H), 3.45 (d, J = 11.4, 1H), 2.81 (d, J = 6.0, 1H), 2.28–2.21 (m, 3H), 2.02 (d, J = 5.7, 6H), 1.93–1.86 (m, 1H), 1.80–1.70 (m, 1H), 1.69 (s, 3H), 1.69–1.65 (m, 2H), 1.65–1.60 (m, 1H), 1.12–0.94 (m, 21H); <sup>13</sup>C NMR (125 MHz, CDCl<sub>3</sub>) δ 173.8, 171.3, 170.6, 135.9, 128.3, 93.0, 73.7, 68.0, 59.8, 57.6, 51.1, 48.4, 41.5, 28.1 (2C), 21.5, 20.9, 19.1, 18.9, 18.2, 12.1; IR (thin film/NaCl) 2944, 2867, 1770, 1738, 1732, 1667, 1463, 1433, 1373, 1321, 1297, 1241, 1200, 1172, 1129, 1100, 1080, 1065, 1045, 1025, 965, 947, 918, 901, 883, 792, 748, 730 cm<sup>-1</sup>; HRMS (ESI–APCI) *m/z*: [M–OAc]<sup>+</sup> Calcd for C<sub>28</sub>H<sub>44</sub>O<sub>7</sub>Si 461.2718; Found 461.2740; [α]<sub>D</sub><sup>25.8</sup> +72.4° (*c* 0.19, CHCl<sub>3</sub>, derived from ketone **16** with 91% ee). Bisacetate **54b**: R<sub>f</sub> 0.56 (1:20 EtOAc:CH<sub>2</sub>Cl<sub>2</sub> × 2, visualized with anisaldehyde stain); <sup>1</sup>H NMR (500 MHz, CDCl<sub>3</sub>) δ 5.62 (app dt, J = 3.5, 1.8, 1H), 5.43 (ddd, J = 5.9, 4.9, 3.4, 1H), 5.23–5.18 (m, 1H), 4.26 (d, J = 11.4, 1H), 3.46 (d, J = 11.4, 1H), 2.71 (d, J = 6.0, 1H), 2.28–2.21 (m, 3H), 2.04 (s, 3H), 2.03 (s, 3H), 1.86–1.76 (m, 3H), 1.73–1.63 (m, 1H), 1.69 (s, 3H), 1.63–1.55 (m, 1H), 1.14–0.82 (m, 21H); <sup>13</sup>C NMR (125 MHz, CDCl<sub>3</sub>) δ 173.8, 171.2, 171.0, 136.1, 128.1, 92.9, 73.7, 68.1, 60.1, 57.3, 51.1, 48.1, 41.6, 28.1, 27.9, 21.5, 20.9, 19.4, 18.9, 18.2, 12.1; IR (film) 1770, 1738, 883 cm<sup>-1</sup>; HRMS (ESI–APCI) *m/z*: [M–OAc]<sup>+</sup> Calcd for C<sub>28</sub>H<sub>44</sub>O<sub>7</sub>Si 461.2718; Found 461.2732; [α]<sub>D</sub><sup>26.0</sup> –28.5° (*c* 0.16, CHCl<sub>3</sub>, derived from ketone **16** with 91% ee).



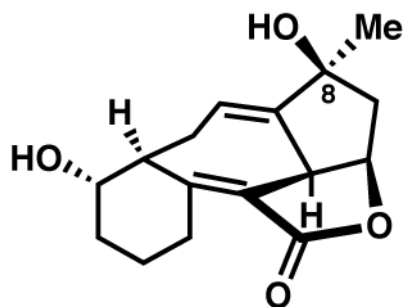
### Divinylcyclopropane **29b**

**Desilylation:** A flask charged with THF (4.8 mL, 0.012 M) and bisacetate **54b** (30.0 mg, 0.0576 mmol, 1 equiv) was cooled to 0 °C (ice-water bath) and treated dropwise with TBAF (1 M in THF, 0.09 mL, 0.09 mmol, 1.56 equiv). After 30 m, the yellow solution was diluted with EtOAc (to 25 mL), filtered through SiO<sub>2</sub> (ca. 0.3 mL) and concentrated under reduced

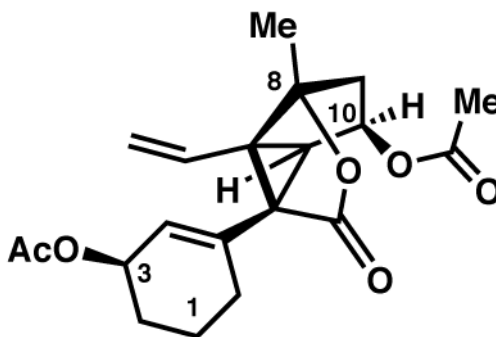
pressure to give desilylated compound as an oil ( $R_f$  0.11 (1:1 EtOAc:hexanes, visualized with anisaldehyde stain)).

**Oxidation:** The crude oil was taken up in  $\text{CH}_2\text{Cl}_2$  (30 mL), cooled to  $-20\text{ }^\circ\text{C}$  (cryocool) beneath an Ar atmosphere, and treated with crushed Me-IBX (34 mg, 0.12 mmol, 2.0 equiv). After 10 m, the mixture was allowed to gradually warm to  $4\text{ }^\circ\text{C}$  (cold room). Two additional portions of crushed Me-IBX (34.6 and 29.5 mg, 0.12 and 0.10 mmol, 2.0 and 1.7 equiv) were added to the mixture ca. 6 and ca. 9 hours after the initial addition. On completion of the reaction (ca. 21 h), the mixture was diluted with EtOAc (to 100 mL) and filtered through  $\text{SiO}_2$  (ca. 2 mL). The organics were concentrated under reduced pressure to give aldehyde as a cream-colored solid ( $R_f$  0.31 (1:1 EtOAc:hexanes, visualized with anisaldehyde stain)). The solid was placed under an argon atmosphere and quickly dissolved in THF (0.5 mL).

**Wittig olefination:** A room temperature (ca.  $24\text{ }^\circ\text{C}$ ) flask charged with a mixture of  $\text{MePPh}_3\text{Br}$  (0.230 g, 0.643 mmol, 11.1 equiv) and THF (30 mL, 0.0019 M) beneath an Ar atmosphere was treated dropwise with *n*-BuLi (2.5 M in hexanes, 0.40 mL, 1 mmol, 17 equiv). The yellow solution was stirred for 30 min, and then cooled to  $-65\text{ }^\circ\text{C}$  (*i*-PrOH/dry ice bath). The yellow solution was treated dropwise with aldehyde in THF (0.5 mL  $\times$  2). The solution was allowed to warm to  $-10\text{ }^\circ\text{C}$  over ca. 1 h, at which point it was quenched by addition of acetone (1 mL). The white mixture was rinsed with 1:1  $\text{H}_2\text{O}$ : brine (ca. 5 mL) and extracted with EtOAc (to 75 mL). The extracts were dried over  $\text{MgSO}_4$ , filtered, and concentrated under reduced pressure. The resulting solid was dissolved in EtOAc (10 mL), filtered through  $\text{SiO}_2$  (ca. 0.3 mL), and concentrated under reduced pressure. The semi-solid was purified by preparatory thin layer chromatography on a  $250\text{ }\mu\text{m}$  plate (1:15 EtOAc: $\text{CH}_2\text{Cl}_2 \times 2$  eluent) to give divinylcyclopropane **29b** as a colorless oil (16.0 mg, 77% yield).  $R_f$  0.17 (1:15 EtOAc: $\text{CH}_2\text{Cl}_2$ , visualized with anisaldehyde stain);  $^1\text{H}$  NMR (500 MHz,  $\text{CDCl}_3$ )  $\delta$  6.09 (dd,  $J = 17.0, 10.6$ , 1H), 5.67–5.62 (m, 1H), 5.44 (t,  $J = 6.6$ , 1H), 5.30–5.23 (m, 1H), 5.17 (dd,  $J = 10.5, 1.2$ , 1H), 5.01 (dd,  $J = 17.0, 1.2$ , 1H), 3.03 (d,  $J = 5.9$ , 1H), 2.23 (d,  $J = 14.1$ , 2H), 2.17 (dd,  $J = 14.4, 7.5$ , 2H), 2.06 (s, 3H), 2.04 (s, 3H), 1.83–1.62 (m, 4H), 1.59 (s, 3H);  $^{13}\text{C}$  NMR (125 MHz,  $\text{CDCl}_3$ )  $\delta$  173.4, 171.2, 171.1, 135.4, 128.7, 127.0, 118.7, 92.6, 73.2, 68.2, 58.3, 50.8, 49.8, 40.0, 28.1, 27.7, 21.6, 20.9, 20.0, 19.4; IR (film) 2937, 1760, 1738, 1733, 915  $\text{cm}^{-1}$ ; HRMS (ESI–APCI)  $m/z$ .  $[\text{M}-\text{H}]^-$  Calcd for  $\text{C}_{20}\text{H}_{24}\text{O}_6$  359.1500; Found 359.1513;  $[\alpha]_D^{22.8} -48.0^\circ$  ( $c$  0.13,  $\text{CHCl}_3$ , derived from ketone **16** with 91% ee).

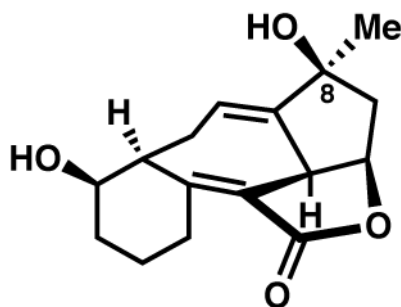
**32b****Cycloheptadiene 32b**

A flask charged with bisacetate **29b** (7.3 mg, 0.020 mmol, 1 equiv) in THF (5.2 mL, 0.0039 M) at 0 °C (ice water bath) was treated dropwise with a solution of LiOH·H<sub>2</sub>O (9.1 mg, 0.22 mmol, 10.8 equiv) in H<sub>2</sub>O (0.91 mL, 0.022 M). After 9 h, the solution was diluted with EtOAc (to 40 mL), filtered through SiO<sub>2</sub> (ca. 0.4 mL) and concentrated under reduced pressure. The semi-solid was purified by preparatory thin layer chromatography on a 250 μm plate (1:3 acetone:CH<sub>2</sub>Cl<sub>2</sub> elution) to give cycloheptadiene **32b** (3.1 mg, 55% yield, R<sub>f</sub> 0.14) as a white solid. R<sub>f</sub> 0.45 (EtOAc, UV/Vis, stained blue in anisaldehyde); <sup>1</sup>H NMR (600 MHz, CD<sub>2</sub>Cl<sub>2</sub>) δ 5.71 (app td, J = 5.2, 2.7, 1H), 4.82 (dt, J = 9.2, 7.5, 1H), 4.23 (d, J = 9.0, 1H), 3.69 (ddd, J = 8.5, 7.0, 1H), 3.13–3.05 (m, 1H), 2.84–2.75 (m, 1H), 2.66 (t, J = 8.0, 1H), 2.57–2.50 (m, 1H), 2.44 (dd, J = 12.8, 7.1, 1H), 2.32 (dddd, J = 16.3, 9.2, 4.9, 2.2, 1H), 1.91 (dtd, J = 12.8, 5.4, 3.6, 1H), 1.84–1.76 (m, 1H), 1.74 (dd, J = 12.8, 7.9, 1H), 1.60–1.52 (m, 3H), 1.51–1.44 (m, 1H), 1.25 (s, 3H); <sup>13</sup>C NMR (125 MHz, CD<sub>2</sub>Cl<sub>2</sub>, –lactone carbon, –disubstituted carbon of trisubstituted olefin) δ 158.4, 123.3, 118.9, 78.8, 76.1, 72.0, 49.0, 48.7, 43.7, 32.6, 28.7, 27.1, 26.1, 21.0; IR (film) 3393, 2929, 1719, 1653, 966 cm<sup>-1</sup>; HRMS (ESI–APCI) *m/z*: [M+H]<sup>+</sup> Calcd for C<sub>16</sub>H<sub>20</sub>O<sub>4</sub> 277.1434; Found 277.1427; [α]<sub>D</sub><sup>28.1</sup> +33.5° (*c* 0.17, CH<sub>2</sub>Cl<sub>2</sub>, derived from ketone **16** with 91% ee).

**29a**

### Divinylcyclopropane 29a

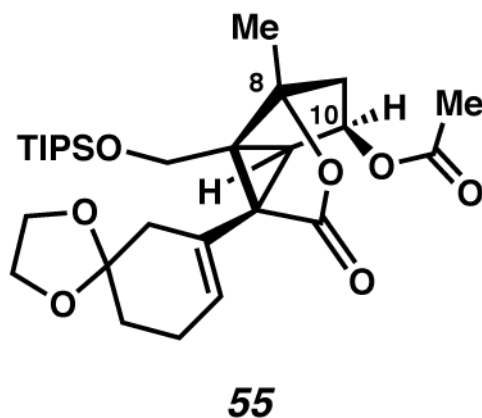
For a representative procedure, see silyl ether **54b** → divinylcyclopropane **29b**. 59% yield over three steps.  $R_f$  0.35 (1:20 acetone:CH<sub>2</sub>Cl<sub>2</sub>, visualized with anisaldehyde stain); <sup>1</sup>H NMR (500 MHz, CDCl<sub>3</sub>) δ 6.13 (dd, *J* = 17.1, 10.5, 1H), 5.67 (dt, *J* = 3.5, 1.7, 1H), 5.42 (dd, *J* = 7.1, 6.1, 1H), 5.31 (dddd, *J* = 7.3, 5.5, 3.7, 1.8, 1H), 5.19 (dd, *J* = 10.5, 1.1, 1H), 5.02 (dd, *J* = 17.1, 1.1, 1H), 3.06 (d, *J* = 5.9, 1H), 2.24 (d, *J* = 14.1, 1H), 2.18 (dd, *J* = 14.4, 7.5, 1H), 2.14–2.08 (m, 1H), 2.04 (s, 3H), 2.03 (s, 3H), 1.89 (ddd, *J* = 17.8, 9.6, 5.6, 1H), 1.81–1.74 (m, 1H), 1.65 (dt, *J* = 12.4, 6.2, 2H), 1.60 (s, 3H), 1.57–1.50 (m, 1H); <sup>13</sup>C NMR (125 MHz, CDCl<sub>3</sub>) δ 173.4, 171.2, 170.7, 135.3, 129.3, 127.1, 118.5, 92.6, 73.3, 68.4, 58.5, 50.8, 49.7, 40.6, 28.0, 27.7, 21.5, 20.9, 20.0, 19.2; IR (film) 2937, 1759, 1738, 1733, 915 cm<sup>-1</sup>; HRMS (ESI-APCI) *m/z*: [M - H]<sup>-</sup> Calcd for C<sub>20</sub>H<sub>24</sub>O<sub>6</sub> 359.1500; Found 359.1488; [α]<sub>D</sub><sup>23.7</sup> +30.4° (*c* 0.18, CHCl<sub>3</sub>, derived from ketone **16** with 91% ee).



**32a**

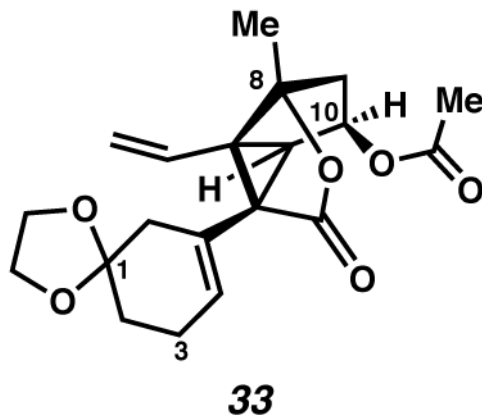
### Cycloheptadiene 32a (white solid)

For a representative procedure see, divinylcyclopropane **29b** → cycloheptadiene **32b**. 51% yield.  $R_f$  0.44 (EtOAc, visualized by UV/Vis or with anisaldehyde stain); <sup>1</sup>H NMR (500 MHz, C<sub>6</sub>D<sub>6</sub>) δ 5.55 (s, 1H), 4.22 (dd, *J* = 16.1, 7.8, 1H), 3.50 (dd, *J* = 12.2, 6.7, 1H), 3.43 (d, *J* = 7.7, 1H), 3.32–3.09 (m, 1H), 2.91 (app s, 1H), 2.56 (dd, *J* = 10.0, 4.6, 1H), 2.44 (ddd, *J* = 17.3, 8.6, 4.2, 1H), 1.99 (dd, *J* = 12.6, 7.3, 1H), 1.76–1.63 (m, 1H), 1.56 (dq, *J* = 19.2, 6.4, 1H), 1.46–1.11 (m, 6H), 0.93 (s, 3H).; <sup>13</sup>C NMR (125 MHz, C<sub>6</sub>D<sub>6</sub>) δ 168.7, 157.1, 148.5, 125.4, 119.4, 78.6, 75.7, 71.6, 48.9, 44.8, 43.3, 30.7, 28.3, 25.2, 24.4, 21.6; IR (film) 3369, 2929, 1724, 1654 cm<sup>-1</sup>; HRMS (ESI-APCI) *m/z* [M+H]<sup>+</sup> Calcd for C<sub>16</sub>H<sub>20</sub>O<sub>4</sub> 277.1434; Found 277.1445; [α]<sub>D</sub><sup>26.6</sup> +100.0° (*c* 0.16, acetone, derived from ketone **16** with 91% ee).



### Ketal **55**

A flask was charged with a colorless solution of ketone (7.0 mg, 0.015 mmol, 1 equiv), CH<sub>2</sub>Cl<sub>2</sub> (2 mL, 0.0073 M), and 1,2-bis(trimethylsilyloxy)ethane (0.10 mL, 0.41 mmol, 28 equiv). The solution was cooled to 0 °C (ice water bath), and treated dropwise with a 1% v/v solution of TMSOTf in CH<sub>2</sub>Cl<sub>2</sub> (150 μL, 0.000008 mmol, 0.0005 equiv). After two days, the solution was treated sequentially with CH<sub>2</sub>Cl<sub>2</sub> (0.5 mL, 0.0294 M), 1,2-bis(trimethylsilyloxy)ethane (0.10 mL, 0.41 mmol, 28 equiv) and TMSOTf (150 μL of a solution containing TMSOTf (10 μL) in CH<sub>2</sub>Cl<sub>2</sub> (1 mL), 0.000008 mmol, 0.0005 equiv). After an additional 12 h, the reaction was quenched through addition of pyridine (0.3 mL, 0.0037 mmol, 0.25 equiv), and then concentrated under reduced pressure. The resultant yellow oil was purified by thin layer chromatography on a 250 μm plate (12 cm × 20 cm; 1:1 Et<sub>2</sub>O:hexanes, then 2:1 Et<sub>2</sub>O:pentane elution) to furnish ketal **55** (5.1 mg, 67% yield) as a colorless oil. *R*<sub>f</sub> 0.64 (1:2 EtOAc:PhH, visualized with anisaldehyde stain); <sup>1</sup>H NMR (600 MHz, CDCl<sub>3</sub>) δ 5.71 (tt, *J* = 3.5, 1.6, 1H), 5.42 (ddd, *J* = 5.6, 5.6, 2.8, 1H), 4.33 (d, *J* = 11.4, 1H), 3.99–3.88 (m, 3H), 3.88–3.82 (m, 1H), 3.39 (d, *J* = 11.5, 1H), 2.81 (d, *J* = 6.0, 1H), 2.49 (d, *J* = 16.8, 1H), 2.36–2.26 (m, 1H), 2.26–2.18 (m, 3H), 2.02 (s, 3H), 1.77 (dddd, *J* = 16.8, 9.2, 4.8, 1.2, 2H), 1.70–1.60 (m, 4H), 1.56–1.51 (m, 3H), 1.10–0.98 (m, 21H); <sup>13</sup>C NMR (125 MHz, CDCl<sub>3</sub>) δ 174.1, 171.4, 129.5, 127.9, 107.9, 92.8, 73.9, 64.7, 64.5, 59.6, 57.2, 51.2, 48.5, 42.2, 38.4, 30.6, 24.6, 21.0, 18.9, 18.2, 18.2, 12.1; IR (thin film/NaCl) 2943, 2892, 1763, 1739, 903, 852 cm<sup>-1</sup>; HRMS (ESI-APCI) *m/z*: [M+H]<sup>+</sup> Calcd for C<sub>28</sub>H<sub>44</sub>O<sub>7</sub>Si 521.2925; Found 521.2929; [α]<sub>D</sub><sup>21.0</sup> +16.8° (*c* 0.37, CHCl<sub>3</sub>, derived from ketone **16** with 91% ee).



### Divinylcyclopropane 33

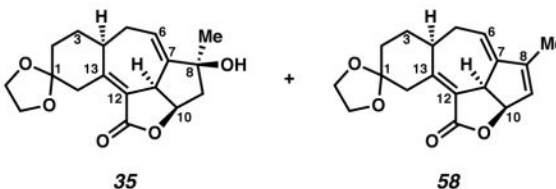
A flask was charged with silyl ether **55** (15.0 mg, 0.027 mmol, 1 equiv) in THF (2.3 mL, 0.012 M) at 0 °C (ice water bath). The colorless solution was treated dropwise with TBAF (1M in THF, 40  $\mu$ L, 0.040 mmol, 1.5 equiv), generating a yellow solution. After 1.5 h, the solution was diluted with EtOAc (to 40 mL), filtered through SiO<sub>2</sub> (ca. 0.1 mL) and concentrated under reduced pressure to give primary alcohol **56** as a yellow oil. This yellow oil had already been characterized analytically as a byproduct in the ketalization reaction. *R<sub>f</sub>* 0.07 (1:1 EtOAc:hexanes, visualized with anisaldehyde stain); <sup>1</sup>H NMR (500 MHz, CDCl<sub>3</sub>)  $\delta$  5.67 (dd, *J* = 5.9, 3.3, 1H), 5.40 (td, *J* = 6.7, 1.6, 1H), 4.02 (dd, *J* = 6.1, 2.2, 1H), 4.01 (d, *J* = 6.1, 1H), 3.94 (d, *J* = 6.1, 1H), 3.92 (dd, *J* = 6.1, 1.3, 1H), 3.85 (d, *J* = 12.9, 1H), 3.82 (d, *J* = 13.0, 1H), 2.95 (d, *J* = 6.0, 1H), 2.75–2.68 (m, 1H), 2.40–2.32 (m, 1H), 2.27–2.18 (m, 3H), 2.02 (s, 3H), 1.97 (app d, *J* = 16.7, 1H), 1.78 (dd, *J* = 9.3, 6.6, 1H), 1.83–1.73 (m, 2H), 1.69 (s, 3H); <sup>13</sup>C NMR (125 MHz, CDCl<sub>3</sub>)  $\delta$  173.9, 171.3, 128.1, 127.1, 108.3, 92.7, 73.5, 64.8, 64.6, 58.6, 57.8, 50.9, 47.8, 41.0, 38.8, 30.0, 24.6, 20.9, 18.7; IR (thin film/NaCl) 2932, 1738 cm<sup>-1</sup>; HRMS (ESI–APCI) *m/z*: [M+H]<sup>+</sup> Calcd for C<sub>19</sub>H<sub>24</sub>O<sub>7</sub> 365.1595; Found 365.1598; [ $\alpha$ ]<sub>D</sub><sup>22.5</sup> +36.7° (*c* 0.13, CHCl<sub>3</sub>, derived from ketone **16** with 91% ee).

The crude alcohol **56** was thrice concentrated from PhH (0.15 mL each), and backfilled with Ar(g). The diol **56** was diluted with CH<sub>2</sub>Cl<sub>2</sub> (16 mL, 0.0017 M), cooled to –15 °C (cryocool temperature), and treated with crushed Me-IBX (15 mg, 0.051 mmol, 1.9 equiv). After 5 min, the solution was allowed to warm gradually to 4 °C (cold room temperature). After 18, 24, 30, 45, and 55 h, additional portions were added of crushed Me-IBX (67.4 mg total, 0.23 mmol, 8.5 equiv). After 65 h, the reaction was diluted with EtOAc (to ca. 25 mL), filtered through SiO<sub>2</sub> (ca. 0.2 mL), and concentrated under reduced pressure to give crude aldehyde **57**.

A flask was charged with a mixture of Ph<sub>3</sub>PMeBr (0.129 g, 0.36 mmol, 13 equiv) in THF (9 mL, 0.003 M) at room temperature (ca. 24 °C). The mixture was treated dropwise with *n*-BuLi (2.5 M in hexanes, 0.13 mL, 0.325 mmol, 12.0 equiv), generating an orange solution. After 55 min, the orange solution had been cooled to –78 °C (acetone/dry ice) and was treated dropwise with crude aldehyde **57** in THF (0.3 mL  $\times$  2). The solution was allowed to gradually warm to –10 °C (over 1.33 h), at which point it was treated with acetone (0.3 mL).



The reaction was rinsed with 1:1 brine:H<sub>2</sub>O (ca. 1 mL), and extracted with EtOAc (to ca. 50 mL). Extracts were dried over MgSO<sub>4</sub>, filtered and concentrated under reduced pressure. The mixture was purified by thin layer chromatography on 250 μm plates (10 cm × 20 cm; EtOAc × 2 elution) to furnish the desired divinyl-cyclopropane (**33**, R<sub>f</sub> 0.79, 7.9 mg including ca. 5% other, 91% yield of slightly impure material) as an oil. <sup>1</sup>H NMR (500 MHz, CDCl<sub>3</sub>) δ 6.09 (ddd, J = 17.1, 10.5, 0.5, 1H), 5.74 (tt, J = 3.5, 1.7, 1H), 5.40 (dd, J = 6.9, 5.9, 1H), 5.17 (dd, J = 10.5, 1.1, 1H), 5.03 (dd, J = 17.1, 1.1, 1H), 4.02–3.91 (m, 4H), 3.04 (d, J = 5.9, 1H), 2.38–2.30 (m, 2H), 2.24 (app dd, J = 14.3, 0.6, 1H), 2.26–2.19 (m, 1H), 2.17 (dd, J = 14.4, 7.6, 1H), 2.03 (s, 3H), 1.95–1.90 (m, 1H), 1.75 (ddd, J = 14.0, 6.9, 3.9, 1H), 1.64–1.59 (m, 1H), 1.59 (s, 3H); <sup>13</sup>C NMR (125 MHz, CDCl<sub>3</sub>, –CO<sub>2</sub>R) δ 171.4, 130.1, 127.8, 127.0, 118.5, 107.9, 92.4, 73.4, 64.6, 64.5, 58.1, 50.6, 49.8, 41.0, 37.6, 30.7, 24.5, 21.0, 20.0; IR (thin film/NaCl) 2932, 1759, 1738, 958, 851 cm<sup>-1</sup>; HRMS (ESI–APCI) *m/z*: [M+Na]<sup>+</sup> Calcd for C<sub>20</sub>H<sub>24</sub>O<sub>6</sub> 383.1465; Found 383.1466; [α]<sub>D</sub><sup>20.4</sup> –11.2° (c 0.17, CHCl<sub>3</sub>, derived from ketone **16** with 91% ee).

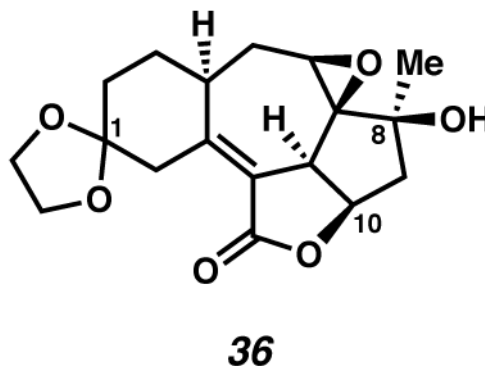


### Cycloheptadiene **35**

A flask was charged with acetate **33** (2.0 mg, 0.0055 mmol, 1 equiv) in THF (2.0 mL, 0.0028 M) at –78 °C (acetone, dry ice bath). The colorless solution was treated dropwise with LiEt<sub>3</sub>BH (0.5 M solution in THF, 24 μL, 2.2 equiv). After 10 min, the solution was allowed to warm to –20 °C (cryocool temperature). After an additional 6 h, the reaction was treated with H<sub>2</sub>O (0.02 mL), allowed to warm to room temperature (ca. 24 °C), diluted with EtOAc (to 10 mL), filtered through SiO<sub>2</sub> (ca. 0.2 mL), and concentrated under reduced pressure. The product was combined with product from two equivalent reactions that had been run with acetate **33** (0.4 and 1.0 mg, respectively). The reactions were purified by thin layer chromatography on a 250 μm plate (10 cm × 20 cm; EtOAc elution) to furnish the desired cycloheptadiene (**35**, R<sub>f</sub> 0.34, slightly impure material). The material was further purified by thin layer chromatography on a 250 μm plate (10 cm × 20 cm; 1:5 acetone:CH<sub>2</sub>Cl<sub>2</sub> elution) to furnish the desired cycloheptadiene (**35**, R<sub>f</sub> 0.29, 1.8 mg, 68% yield). R<sub>f</sub> 0.56 (EtOAc, UV/Vis, visualized with anisaldehyde stain); <sup>1</sup>H NMR (600 MHz, C<sub>6</sub>D<sub>6</sub>) δ 5.37 (ddd, J = 2.8, 5.0, 5.0 Hz, 1H), 4.17 (ddd, J = 7.1, 8.0, 9.2 Hz, 1H), 3.71 (ddd, J = 6.2, 6.8, 6.8 Hz, 1H), 3.68 (ddd, J = 5.1, 6.9, 6.9 Hz, 1H), 3.57 (br d, J = 15 Hz, 1H), 3.52 (ddd, J = 4.8, 6.9, 6.9 Hz, 1H), 3.48 (ddd, J = 5.9, 6.9, 6.9 Hz, 1H), 3.32 (br d, J = 9 Hz, 1H), 2.21 (dddd, J = 4.5, 4.5, 8.9, 8.9 Hz, 1H), 1.96 (dd, J = 7.1, 12.8 Hz, 1H), 1.93 (dddd, J = 3.6, 3.6, 5.4, 16.7 Hz, 1H), 1.89 (dddd, J = 1.0, 4.3, 6.0, 13.7 Hz, 1H), 1.73 (ddd, J = 4.9, 10.8, 13.9 Hz, 1H), 1.67 (dddd, J = 2.4, 4.8, 9.5, 16.7, 1H), 1.43 (dddd, J = 5.4, 5.4, 5.4, 13.6 Hz, 1H), 1.37 (dddd, J = 4.2, 9.0, 10.6, 13.5 Hz, 1H), 1.34 (dd, J = 7.9, 12.8 Hz, 1H), 0.89 (d, J = 0.9 Hz, 1H); <sup>13</sup>C NMR (125 MHz, CDCl<sub>3</sub>) δ 169.6, 156.0, 149.9, 124.5, 119.1, 109.8, 78.8, 76.3, 65.0, 64.8, 48.9, 43.6, 39.6, 35.6, 34.3, 30.8, 28.5, 28.5; IR (thin film/NaCl) 3446, 2927, 1738, 1647, 955 cm<sup>-1</sup>; HRMS (ESI–APCI) *m/z*: [M+H]<sup>+</sup> Calcd for

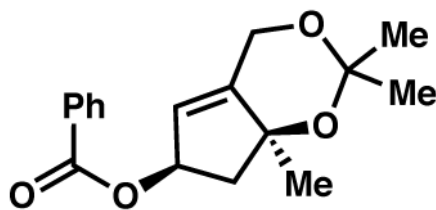
$C_{18}H_{22}O_5$  319.1540; Found 319.1530;  $[\alpha]_D^{23.8} +23.3^\circ$  ( $c$  0.18,  $CH_2Cl_2$ , derived from ketone **16** with 91% ee).

Dehydration product **58**.  $R_f$  0.68 (1:5 acetone:PhH; visualized with anisaldehyde stain);  $^1H$  NMR (600 MHz,  $CD_2Cl_2$ )  $\delta$  5.88 (s, 1H), 5.58 (dt,  $J = 2.2, 6.0$ , 1H), 5.36–5.33 (m, 1H), 4.32–4.30 (m, 1H) 3.96–3.91 (m, 2H), 3.90–3.83 (m, 2H), 2.87 (ddd,  $J = 16.1, 5.0, 5.0$ , 1H), 2.68 (m, 1H), 2.47–2.42 (m, 1H), 2.17 (dddd,  $J = 15.9, 6.5, 6.5, 1.1$ , 1H), 1.85–1.73 (m, 6H), 1.63–1.71 (m, 1H);  $^{13}C$  NMR (125 MHz,  $CDCl_3$ )  $\delta$  170.1, 154.0, 150.8, 145.7, 130.0, 123.1, 117.0, 109.3, 81.6, 64.6, 64.3, 43.6, 40.1, 36.0, 34.8, 30.8, 29.1, 12.1; IR (thin film/NaCl) 3456 (br), 2934, 1738, 1733, 1645  $cm^{-1}$ ; HRMS (ESI-APCI)  $m/z$   $[M+H]^+$  Calcd for  $C_{18}H_{20}O_4$  301.1434; Found 301.1439;  $[\alpha]_D^{25.8} -25.5^\circ$  ( $c$  0.22,  $CH_2Cl_2$ , derived from ketone **16** with 91% ee).

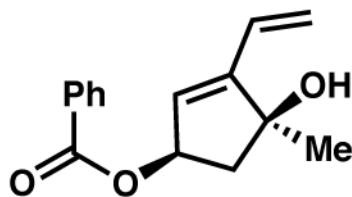


### Epoxide **36**

A flask was charged with cycloheptadiene **35** (0.9 mg, 0.0028 mmol, 1 equiv) and  $VO(acac)_2$  (0.2 mg, 0.00075 mmol, 0.27 equiv) in PhH (0.4 mL). The pale green solution was treated with TBHP, 5.5 M in decane (ca. 10  $\mu$ L, 1 drop), and then turned burgundy in color. After 12 minutes, the solution was treated with saturated aq  $Na_2SO_3$  (0.04 mL), diluted with EtOAc (to 10 mL), filtered through  $SiO_2$  (ca. 0.2 mL), and concentrated under reduced pressure. This compound was combined with the crude product from an analogous reaction carried out with cycloheptadiene **35** (1.8 mg, 0.0056 mmol). The reactions were purified by thin layer chromatography on a 250  $\mu$ m plate (10 cm  $\times$  20 cm; 1:5 acetone: $CH_2Cl_2$  elution) to furnish epoxide **36** (1.6 mg, 56% yield,  $R_f$  0.34) as a colorless oil.  $R_f$  0.40 (EtOAc, visualized by UV/Vis, or with anisaldehyde stain);  $^1H$  NMR (500 MHz,  $CD_2Cl_2$ )  $\delta$  4.83 (ddd,  $J = 8.7, 7.5, 6.6$ , 1H), 4.03–3.85 (m, 5H), 3.34 (t,  $J = 3.0$ , 1H), 3.28 (d,  $J = 15.0$ , 1H), 3.07 (d,  $J = 15.1$ , 1H), 2.70–2.62 (m, 1H), 2.52 (dd,  $J = 13.5, 7.5$ , 1H), 2.27 (s, 1H), 2.07–2.03 (m, 1H), 2.05 (d,  $J = 2.6$ , 1H), 1.90–1.77 (m, 3H), 1.73–1.67 (m, 2H), 1.29 (s, 3H);  $^{13}C$  NMR (125 MHz,  $CDCl_3$ )  $\delta$  169.3, 156.4, 120.0, 109.5, 75.8, 74.8, 68.7, 65.1, 64.8, 55.9, 47.6, 42.8, 39.4, 35.3, 34.0, 29.2, 29.1, 23.7; IR (thin film/NaCl) 3473, 1739, 1662, 1268, 1120  $cm^{-1}$ ; HRMS (ESI-APCI)  $m/z$   $[M+H]^+$  Calcd for  $C_{18}H_{22}O_6$  335.1489; Found 335.1483;  $[\alpha]_D^{22.1} +28.6^\circ$  ( $c$  0.16,  $CH_2Cl_2$ , derived from ketone **16** with 91% ee).

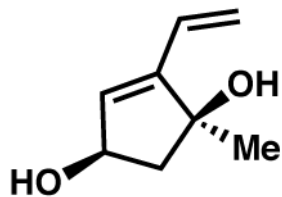
**40****Benzoyl ester 40**

A dilute solution of enone **16** in Et<sub>2</sub>O was concentrated at 150 torr to 0.645 g of a 30% (w/w) solution as determined by <sup>1</sup>H NMR (0.19 g enone, 1.04 mmol) and dissolved in THF (8 mL, 0.13 M). [The volatility of the starting enone precluded preparation of fully concentrated samples without significant loss of material.] The solution was cooled in a dry ice/acetone bath and to it was added DIBALH (2.3 mL, 1 M toluene, 2.3 mmol). The starting material was consumed within 10 minutes according to TLC. The solution was warmed to room temperature and quenched with saturated aq sodium potassium tartrate (20 mL) and saturated aq NH<sub>4</sub>Cl (20 mL) and stirred vigorously for 2 h. The solution was extracted with Et<sub>2</sub>O (6 × 50 mL) and the combined organic phases dried with Na<sub>2</sub>SO<sub>4</sub>, filtered and concentrated at 150 torr. The crude material was purified by flash chromatography (1:1 pentane:Et<sub>2</sub>O), concentrated at 150 torr and dissolved immediately in CH<sub>2</sub>Cl<sub>2</sub> (17 mL, 0.06 M) for use in the next step. The CH<sub>2</sub>Cl<sub>2</sub> solution of allylic alcohol was cooled in an ice water bath and to it was added DMAP (0.27 g, 2.2 mmol) and Et<sub>3</sub>N (1.3 mL, 9.38 mmol) followed by benzoic anhydride (0.472 g, 2.1 mmol). The solution was stirred for 4 hr with warming to ambient temperature, then quenched with saturated aq NH<sub>4</sub>Cl (20 mL) and extracted with EtOAc (3 × 75 mL). The combined organic phases were dried with Na<sub>2</sub>SO<sub>4</sub>, filtered and concentrated under reduced pressure. The crude material was purified by flash chromatography (2:1 hexanes:CH<sub>2</sub>Cl<sub>2</sub> with 2% Et<sub>3</sub>N) to yield benzoate ester **40** (0.294 g, 98% yield, 2 steps) as a colorless oil. *R<sub>f</sub>* 0.66 (1:1 EtOAc:hexanes, visualized by UV/Vis, or with anisaldehyde stain); <sup>1</sup>H NMR (300 MHz, CDCl<sub>3</sub>) δ 8.08–8.03 (m, 2H), 7.60–7.53 (m, 1H), 7.48–7.41 (m, 2H), 5.83–5.75 (m, 1H), 5.69–5.66 (m, 1H), 4.77–4.64 (m, 2H), 2.69 (dd, *J* = 6.9, 12.8, 1H), 2.13 (dd, *J* = 6.9, 12.9, 1H), 1.50 (s, 3H), 1.50 (s, 3H), 1.42 (s, 3H); <sup>13</sup>C NMR (75 MHz, CDCl<sub>3</sub>) δ 166.6, 146.5, 133.2, 130.4, 129.8, 128.5, 122.0, 100.3, 81.0, 76.6, 60.4, 49.4, 30.0, 28.6, 25.9; IR (thin film/NaCl) 2990, 1715, 1602, 1268, 1158 cm<sup>-1</sup>; HRMS (EI) *m/z*: [M+H]<sup>+</sup> Calcd for C<sub>17</sub>H<sub>20</sub>O<sub>4</sub> 288.1362; Found 288.1366; [α]<sub>D</sub><sup>24.7</sup> +74.2° (*c* 1.0, CHCl<sub>3</sub>, derived from ketone with 91% ee).

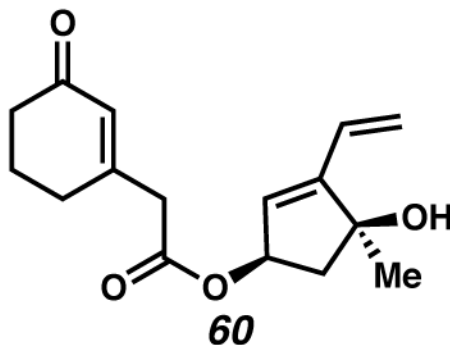
**41****Allylic benzoyl ester 41**

To a MeOH (3 mL, 0.037 M) solution of acetonide **40** (0.031 g, 0.11 mmol), cooled in an ice water bath, was added trimethyl orthoformate (0.16 mL, 0.96 mmol) followed by a MeOH (1.5 mL) solution of fumaric acid (0.032 g, 0.28 mmol). The solution was allowed to gradually warm to ambient temperature and stirred an additional 10 hr. The solution was quenched with saturated aq NaHCO<sub>3</sub> (10 mL) and extracted with EtOAc (3×20 mL). The combined organic phases were dried with MgSO<sub>4</sub>, filtered and concentrated in vacuo to yield crude diol **59** (0.028 g, >99% yield) as a colorless oil, which was used immediately.

Crude diol **59** (0.028, 0.11 mmol) was dissolved in CH<sub>2</sub>Cl<sub>2</sub> (2 mL, 0.055 M) and cooled in an ice water bath. To the solution was added DMP (0.11 g, 0.27 mmol). CAUTION! DMP is a HEAT- and SHOCK-SENSITIVE COMPOUND, showing exotherms when heated (>130 °C). All operations should be carried out behind a blast shield. The solution was stirred for an additional two hr (with warming to ambient temperature) and quenched with saturated aq NaHCO<sub>3</sub> (3 mL) and saturated aq Na<sub>2</sub>S<sub>2</sub>O<sub>3</sub> (6 ml). The two phases were stirred vigorously for 5 min and then extracted with EtOAc (6 × 25 mL). The combined organic phases were dried with MgSO<sub>4</sub>, filtered and concentrated in vacuo. The crude aldehyde was used immediately as is. A solution of methylenetriphenylphosphorane was prepared in THF (8 mL, 0.06 M) from triphenylphosphonium bromide (0.17 g, 0.48 mmol) and potassium *t*-butoxide (0.053 g, 0.47 mmol). The yellow solution was cooled in an ice water bath after stirring for 30 min at ambient temperature, and to it added crude aldehyde dropwise as a solution in THF (4 mL). The reaction was complete within 10 min according to TLC. The brown solution was quenched with H<sub>2</sub>O (20 mL) and extracted with CH<sub>2</sub>Cl<sub>2</sub> (3 × 30 mL). The combined organic phases were dried with Na<sub>2</sub>SO<sub>4</sub>, filtered and concentrated in vacuo. The crude material was purified by flash chromatography (1:20 EtOAc:hexanes elution) to yield allylic benzoyl ester **41** as a pale yellow oil (0.019 g, 69% yield, 3 steps). *R*<sub>f</sub> 0.62 (1:2 EtOAc:hexanes, visualized with anisaldehyde stain); <sup>1</sup>H NMR (300 MHz, CDCl<sub>3</sub>) δ 8.03 (dt, *J* = 8.4, 1.5, 2H), 7.56 (app t, *J* = 7.4, 1H), 7.44 (app t, *J* = 7.7, 2H), 6.36 (dd, *J* = 17.9, 11.3, 1H), 5.94 (d, *J* = 2.2, 1H), 5.84–5.77 (m, 1H), 5.75 (ddd, *J* = 7.0, 4.7, 2.0, 1H), 5.34 (dd, *J* = 11.3, 1.6, 1H), 2.75 (dd, *J* = 14.1, 7.3, 1H), 2.16 (dd, *J* = 14.1, 4.7, 1H), 1.91 (s, 1H), 1.50 (s, 3H); <sup>13</sup>C NMR (75 MHz, CDCl<sub>3</sub>, –CO<sub>2</sub>Ph) δ 151.3, 133.2, 130.4, 129.8, 129.2, 128.6, 127.2, 119.4, 81.3, 76.1, 49.5, 27.0; IR (thin film/NaCl) 3436 (br), 3063, 2974, 2931, 2865, 1715, 1602, 924, 859, 713 cm<sup>-1</sup>; HRMS (EI) *m/z* [M<sup>+</sup>]<sup>+</sup> Calcd for C<sub>15</sub>H<sub>16</sub>O<sub>3</sub> 244.1100; Found 244.1101; [α]<sub>D</sub><sup>27.3</sup> +150.0° (*c* 0.13, CHCl<sub>3</sub>, derived from ketone **16** with 91% ee).

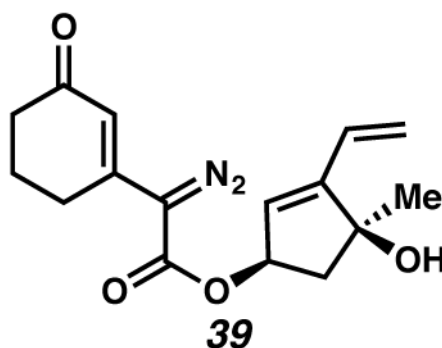
**42****Alcohol 42**

To a MeOH (5 mL, 0.05 M) solution of allylic benzoyl ester **41** (0.062 g, 0.25 mmol) was added a MeOH solution of sodium hydroxide (0.85 mL, 0.64 M, 0.54 mmol) dropwise. The solution was stirred at ambient temperature for 3 hours, quenched with H<sub>2</sub>O (10 mL) and extracted with EtOAc (6 × 25 mL). The combined organic phases were dried with Na<sub>2</sub>SO<sub>4</sub>, filtered and concentrated in vacuo. The crude material was purified by flash chromatography (4:1 CH<sub>2</sub>Cl<sub>2</sub>:EtOAc → 1:1 hexanes/EtOAc elution) to yield alcohol **42** as a white solid (0.030 g, 84% yield). *R<sub>f</sub>* 0.13 (1:5 EtOAc:CH<sub>2</sub>Cl<sub>2</sub>, visualized with anisaldehyde stain); <sup>1</sup>H NMR (300 MHz, CDCl<sub>3</sub>) δ 6.33 (ddt, *J* = 17.7, 11.2, 0.7, 1H), 5.82 (d, *J* = 2.1, 1H), 5.75 (dd, *J* = 17.9, 1.7, 1H), 5.29 (dd, *J* = 11.2, 1.7, 1H), 4.68 (dd, *J* = 11.5, 5.1, 1H), 2.57 (dd, *J* = 13.6, 6.8, 1H), 1.88 (app dd, *J* = 13.6, 4.8, 2H), 1.71 (d, *J* = 6.6, 1H), 1.43 (s, 3H); <sup>13</sup>C NMR (75 MHz, CDCl<sub>3</sub>) δ 149.5, 131.3, 129.5, 118.6, 81.3, 73.0, 53.1, 26.8; IR (thin film/NaCl) 3287, 3252, 2968, 2930, 2873, 926 cm<sup>-1</sup>; HRMS (EI) *m/z*. [M+]<sup>+</sup> Calcd for C<sub>8</sub>H<sub>12</sub>O<sub>2</sub>, 140.0837; Found 140.0859; [α]<sub>D</sub><sup>24.2</sup> +100.0° (*c* 0.085, MeOH, derived from ketone **16** with 91% ee).

**60****Ester 60**

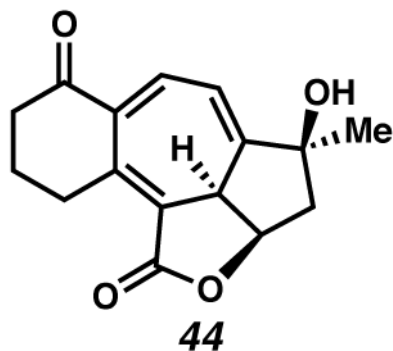
A CH<sub>2</sub>Cl<sub>2</sub> (15 mL, 0.026 M) solution of alcohol **42** (0.054 g, 0.39 mmol) with carboxylic acid **10** (0.16 g, 1.1 mmol) was cooled in an ice water bath. EDC·HCl (0.21 g, 1.1 mmol) was added followed by DMAP (0.011 g, 0.09 mmol). The deep yellow solution was allowed to warm to ambient temperature and stirred an additional 1 hour. The solution was quenched with aq HCl (20 mL, 0.12 M) and extracted with EtOAc (2 × 50 mL). The combined organic phases were washed with aq HCl (20 mL, 0.12 M), aq K<sub>2</sub>CO<sub>3</sub> (2 × 20 mL 5 % w/v), brine

(20 mL), and saturated aq  $\text{NH}_4\text{Cl}$  (20 mL). The organic phase was dried with  $\text{Na}_2\text{SO}_4$ , filtered and concentrated to provide crude ester **60** (0.125 g, 117% crude yield) as an orange oil. The crude ester was used without further purification. An analytical sample was obtained at another point, upon purification by preparatory thin layer chromatography with  $\text{Et}_2\text{O} \times 2$  as the eluent.  $R_f$  0.21 (1:5 EtOAc: $\text{CH}_2\text{Cl}_2$ , visualized with anisaldehyde stain);  $^1\text{H}$  NMR (300 MHz,  $\text{CDCl}_3$ )  $\delta$  6.30 (dd,  $J = 17.9, 11.3$ , 1H), 5.94–5.91 (m, 1H), 5.80 (d,  $J = 2.2$ , 1H), 5.83–5.75 (m, 1H), 5.53–5.47 (m, 1H), 5.36 (dq,  $J = 1.6, 0.5$ , 1H), 5.32 (dq,  $J = 1.7, 0.6$ , 1H), 3.23 (s, 2H), 2.64 (dd,  $J = 14.1, 7.3$ , 1H), 2.42–2.38 (m, 4H), 2.06–1.93 (m, 3H), 1.84 (s, 1H), 1.46 (s, 3H);  $^{13}\text{C}$  NMR (75 MHz,  $\text{CDCl}_3$ )  $\delta$  199.6, 169.4, 157.2, 151.7, 129.1, 129.0, 126.5, 119.7, 81.1, 76.5, 49.2, 43.7, 37.3, 29.8, 27.0, 22.7; IR (thin film/ $\text{NaCl}$ ) 3417, 2925, 2853, 1732, 1661, 959, 887  $\text{cm}^{-1}$ ; HRMS (EI)  $m/z$ :  $[\text{M}]^+$  Calcd for  $\text{C}_{16}\text{H}_{20}\text{O}_4$  276.1362; Found 276.1363;  $[\alpha]_{\text{D}}^{23.2} +45.6^\circ$  ( $c$  0.20,  $\text{CHCl}_3$ , derived from ketone **16** with 91% ee).



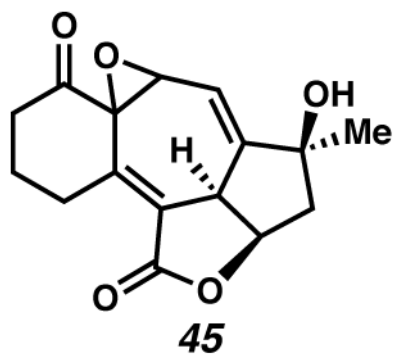
### Diazoester **39**

To a  $\text{CH}_3\text{CN}$  (42 mL, 0.01 M) solution of ester **60** (0.125 g, 0.385 mmol) was added  $\text{TsN}_3$  (0.670 g, 3.4 mmol) dropwise using a flame-dulled pipette. CAUTION!!!  $\text{TsN}_3$  is SHOCK SENSITIVE AND POTENTIALLY EXPLOSIVE. The flask was equipped with an argon balloon and cooled in an ice water bath.  $\text{Et}_3\text{N}$  (0.8 mL, 5.8 mmol) was added dropwise causing the solution to become deep orange in color. The solution was allowed to warm to ambient temperature and stirred an additional 11 hr. The solution was concentrated in vacuo and purified using flash chromatography (4:1  $\text{CH}_2\text{Cl}_2$ :EtOAc) to yield diazoester **39** (0.746 g, 64% yield, 2 steps) as a bright yellow oil.  $R_f$  0.18 (1:5 EtOAc: $\text{CH}_2\text{Cl}_2$ , UV/Vis, visualized with anisaldehyde stain);  $^1\text{H}$  NMR (500 MHz,  $\text{C}_6\text{D}_6$ ) 6.75 (t,  $J = 1.3$ , 1H), 6.15 (dd,  $J = 17.8, 11.3$ , 1H), 5.72 (dd,  $J = 17.8, 1.8$ , 1H), 5.60 (d,  $J = 2.0$ , 1H), 5.46–5.24 (m, 1H), 5.11 (dd,  $J = 11.3, 1.8$ , 1H), 2.32 (dd,  $J = 13.7, 7.3$ , 1H), 2.16–2.07 (m, 2H), 1.82 (dd,  $J = 13.7, 5.2$ , 1H), 1.64 (m, 2H), 1.39 (dt,  $J = 12.4, 6.2$ , 2H), 1.37–1.20 (m, 1H), 1.17 (s, 3H);  $^{13}\text{C}$  NMR (125 MHz,  $\text{C}_6\text{D}_6$ ,  $-\text{CN}_2$ )  $\delta$  195.0, 162.4, 151.7, 144.6, 129.3, 126.2, 121.6, 119.0, 80.3, 76.7, 49.2, 36.8, 26.9, 26.0, 22.1; IR (thin film/ $\text{NaCl}$ ) 3407, 2930, 2103, 1707, 1644, 992  $\text{cm}^{-1}$ ; HRMS (EI)  $m/z$ :  $[\text{M}+\text{H}]^+$  Calcd for  $\text{C}_{16}\text{H}_{18}\text{N}_2\text{O}_4$  303.1345; Found 303.1339;  $[\alpha]_{\text{D}}^{20.4} +67.0^\circ$  ( $c$  0.24,  $\text{CHCl}_3$ , derived from ketone **16** with 91% ee).



### Cycloheptatriene **44**

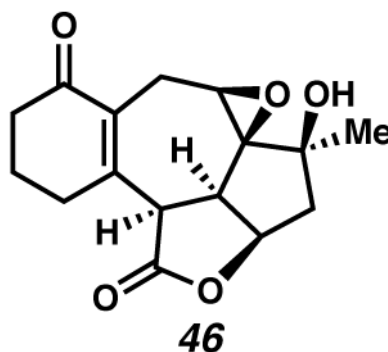
To a  $\text{CH}_2\text{Cl}_2$  (2.4 mL) solution of  $\text{Cu}(\text{tbs})_2$  (0.035 g, 0.084 mmol, 3.2 eq.) in a moisture-free, oxygen-free glovebox was added diazoester **39** (0.008 g, 0.026 mmol) as a solution in  $\text{CH}_2\text{Cl}_2$  (5.6 mL). The deep maroon solution was stirred for 5 days at 29 °C and removed from the glove box. DBN (0.01 mL, 0.08 mmol) was added and the solution stirred for 2 hr. The solution was diluted with EtOAc, filtered over a sort silica plug, concentrated in vacuo and purified by preparatory thin layer chromatography (2:1 EtOAc/benzene) to yield cycloheptatriene **44** (0.0022 g, 31% yield) as a pale yellow solid.  $R_f$  0.50 (1:2 EtOAc:PhH, UV/Vis, visualized with anisaldehyde stain);  $^1\text{H}$  NMR (500 MHz,  $\text{CDCl}_3$ )  $\delta$  7.72 (d,  $J = 6.4$ , 1H), 6.54 (dd,  $J = 6.4, 2.2$ , 1H), 5.17 (ddd,  $J = 7.9, 6.6, 4.5$ , 1H), 3.59 (m, 1H), 3.21 (d,  $J = 7.9$ , 1H), 2.94 (dt,  $J = 17.5, 5.7$ , 1H), 2.61 (m, 2H), 2.52 (dd,  $J = 14.5, 6.6$ , 1H), 2.27 (dd,  $J = 14.5, 4.4$ , 1H), 2.03–1.92 (m, 2H), 1.77 (s, 1H), 1.54 (s, 3H);  $^{13}\text{C}$  NMR (125 MHz,  $\text{CDCl}_3$ )  $\delta$  199.9, 168.4, 156.3, 144.8, 139.8, 139.2, 117.3, 115.3, 79.2, 78.2, 48.3, 46.4, 39.6, 28.1, 26.5, 20.9; IR (thin film/NaCl) 3416 (br), 2956, 2925, 2853, 1739, 1734, 802  $\text{cm}^{-1}$ ; HRMS (TOF)  $m/z$ :  $[\text{M}+\text{H}]^+$  Calcd for  $\text{C}_{16}\text{H}_{17}\text{O}_4$  273.1121; Found 273.1131;  $[\alpha]_D^{25} -86.9$  ( $c$  0.43,  $\text{CH}_2\text{Cl}_2$ , derived from ketone **16** with 91% ee).



### Epoxide **45**

In a flame-dried, argon purged RBF was added THF (4 mL) and *t*-BuOOH (0.07 mL, 5–6 M/decane, 0.35–0.42 mmol). The solution was cooled in a dry ice/acetone bath and to it added *n*-BuLi (0.1 mL, 2.3 M/hexanes, 0.25 mmol). The solution was allowed to warm to room temperature. A separate RBF was prepared with triene **44** (2.1 mg, 0.0077 mmol) in

THF (0.8 mL) and cooled in a dry ice/acetone bath. The *t*-BuOOLi/THF solution (0.25 mL, 0.058 M, 0.015 mmol) was added dropwise. The reaction was allowed to warm to room temperature, then quenched with Na<sub>2</sub>S<sub>2</sub>O<sub>3</sub> (aq) and stirred vigorously for 10 min. The solution was extracted with EtOAc (3 × 5 mL), dried with Na<sub>2</sub>SO<sub>4</sub> and filtered. Purification by thin-layer chromatography with 2:1 EtOAc:PhH eluent yielded the epoxide (1.4 mg, 64% yield). <sup>1</sup>H NMR (500 MHz, CDCl<sub>3</sub>): δ 5.95 (dd, *J* = 4.3, 2.6 Hz, 1H), 4.99 (ddd, *J* = 8.6, 6.5, 5.7 Hz, 1H), 4.59 (dd, *J* = 8.6, 2.5 Hz, 1H), 3.90 (dd, *J* = 4.2, 0.5 Hz, 1H), 3.62 (dm, *J* = 17.2, 1H), 3.14 (dm, *J* = 17.2 Hz, 1H), 2.73 (dt, *J* = 17.8, 6.6 Hz, 1H), 2.64 (dt, *J* = 17.8, 6.6 Hz, 1H), 2.40 (dd, *J* = 13.9, 6.5 Hz, 1H), 2.06–1.97 (m, 2H), 1.99 (dd, *J* = 13.9, 5.7 Hz, 1H), 1.68 (s, 1H), 1.41 (s, 3H); <sup>13</sup>C NMR (125 MHz, CDCl<sub>3</sub>) δ 202.9, 169.0, 155.2, 146.9, 122.4, 113.5, 79.3, 78.1, 62.7, 62.5, 47.3, 43.2, 40.6, 28.5, 28.4, 20.0; IR (Neat film, NaCl) 3446 (br), 2965, 2928, 2872, 1732, 1738, 1262, 806, 735 cm<sup>-1</sup>; HRMS (TOF) *m/z*: [M+H]<sup>+</sup> Calcd for C<sub>16</sub>H<sub>17</sub>O<sub>5</sub> 289.1071; Found 289.1085; [α]<sub>D</sub><sup>25</sup> = +35.1 (*c* 0.14, CH<sub>2</sub>Cl<sub>2</sub>)

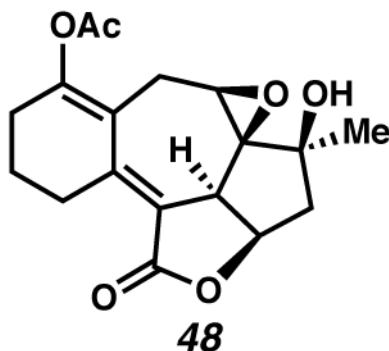


### Epoxide 46

To a CH<sub>2</sub>Cl<sub>2</sub> (2 mL) solution of Cu(*t*bs)<sub>2</sub> (0.0062 g, 0.015 mmol, 0.4 equiv) in a moisture-free, oxygen-free glove box was added diazoester **39** (0.0108 g, 0.036 mmol) as a solution in CH<sub>2</sub>Cl<sub>2</sub> (2.5 mL). The deep maroon solution was stirred for 5 days at 30–31 °C and then concentrated in vacuo (predominantly diene, R<sub>f</sub> 0.36 in 2:1 EtOAc:benzene, visualized by UV/Vis, or with anisaldehyde stain). PhH (3 mL) was added and the solution removed from the glovebox. VO(acac)<sub>2</sub> (0.010 g, 0.038 mmol) followed by *t*-BuOOH (0.05 mL, 5.5 M decane, 0.275 mmol). Upon addition of *t*-BuOOH the solution turns an even deeper maroon and over the course of 20 minutes, after which time starting material has been consumed by TLC, the solution gradually becomes a light tan color. The solution was diluted with EtOAc, filtered over a short silica plug, concentrated in vacuo and purified by preparatory TLC (2:1 EtOAc:PhH) to yield epoxide **46** (3.3 mg, 32% yield) as an off-white solid. R<sub>f</sub> 0.23 (1:2 EtOAc:PhH, UV/Vis, visualized with KMnO<sub>4</sub> stain); <sup>1</sup>H NMR (600 MHz, CDCl<sub>3</sub>) δ 4.84 (ddd, *J* = 6.0, 4.6, 1.6, 1H), 3.82 (dd, *J* = 18.4, 6.1, 1H), 3.52 (d, *J* = 6, 1H), 3.41 (dd, *J* = 6.3, 4.6, 1H), 3.38 (d, *J* = 6.4, 1H), 3.26–3.18 (m, 1H), 2.54 (ddd, *J* = 16.9, 7.5, 4.8, 1H), 2.52 (s, 1H), 2.46–2.36 (m, 3H), 2.24–2.14 (m, 1H), 2.12–2.04 (m, 1H), 1.97–1.90 (m, 1H), 1.37 (s, 3H); <sup>13</sup>C NMR (125 MHz, CDCl<sub>3</sub>) δ 198.7, 172.2, 150.0, 129.9, 80.0, 75.0, 70.3, 54.3, 51.0, 46.1, 43.7, 37.9, 32.7, 26.9, 22.0, 21.8; IR (thin film/NaCl) 3472 (br), 2960, 2933, 2857, 1766, 1661, 1266, 919, 785 cm<sup>-1</sup>; HRMS (ESI-APCI) *m/z*: [M+H]<sup>+</sup> Calcd for C<sub>16</sub>H<sub>18</sub>O<sub>5</sub>

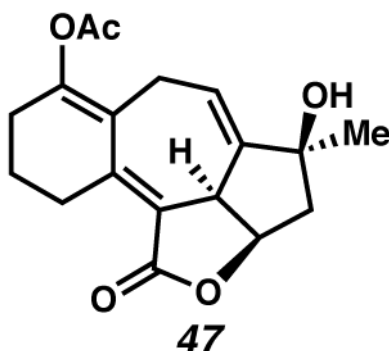


291.1227; Found 291.1228;  $[M-H]^-$ : Calcd for  $C_{16}H_{18}O_5$  289.1081; Found 289.1086;  $[\alpha]_D^{25.4} +86.2$  ( $c$  0.16,  $CH_2Cl_2$ , derived from ketone **16** with 91% ee).



### Epoxide **48**

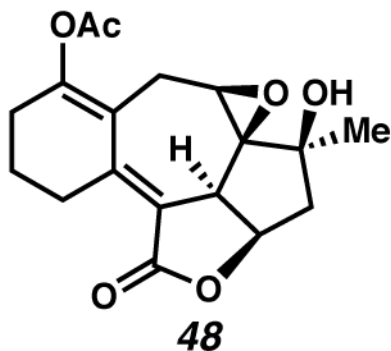
To  $CH_2Cl_2$  (0.6 mL) solution of epoxide **46** (2.9 mg, 0.01 mmol) was added DMAP (3.3 mg, 0.027 mmol) followed by  $Ac_2O$  (0.005 mL, 0.053 mmol), added in two equal batches. The solution was purified directly by thin-layer chromatography (EtOAc) to yield epoxide **48** (1.5 mg, 45% yield) as a white solid.  $^1H$  NMR (500 MHz,  $CDCl_3$ )  $\delta$  4.83 (ddd,  $J = 9.4, 7.6$  Hz, 1H), 3.84 (d,  $J = 9.4$  Hz, 1H), 3.51–3.45 (m, 1H), 3.47 (d,  $J = 6.1$  Hz, 1H), 3.29 (dd,  $J = 16.5, 6.3$  Hz, 1H), 2.94–2.87 (m, 1H), 2.60 (dd,  $J = 13.0, 7.1$  Hz, 1H), 2.49 (dt,  $J = 16.5, 2.8$  Hz, 1H), 2.40–2.37 (m, 2H), 2.34 (s, OH), 2.25 (s, 3H), 1.95 (dd,  $J = 13.0, 7.9$  Hz, 1H), 1.89–1.82 (m, 1H), 1.78–1.71 (m, 1H), 1.31 (s, 3H);  $^{13}C$  NMR (125 MHz,  $CDCl_3$ )  $\delta$  170.4, 168.2, 156.7, 152.5, 122.6, 115.0, 74.0, 73.3, 70.9, 53.1, 48.6, 42.2, 29.3, 25.7, 23.8, 23.6, 21.3, 21.1; IR (neat film, NaCl) 3491 (br), 2972, 2935, 1757, 1732, 1274, 934, 788  $cm^{-1}$ ; HRMS (TOF)  $m/z$ :  $[M+H]^+$  Calcd for  $C_{18}H_{21}O_6$  333.1333; Found 333.1333;  $[\alpha]_D^{25} = +265.6$  ( $c$  0.15,  $CH_2Cl_2$ ).



### Cycloheptadiene **47**

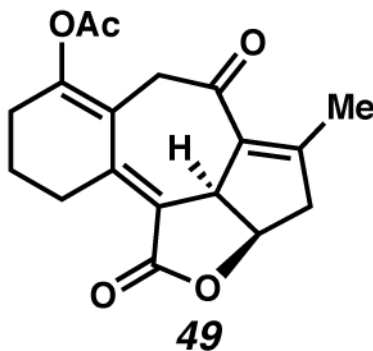
To a  $CH_2Cl_2$  (1 mL) solution of  $Cu(tbs)_2$  (0.0055 g, 0.013 mmol) in a moisture-free, oxygen-free glove box was added diazoester **39** (0.0087 g, 0.029 mmol) as a solution in  $CH_2Cl_2$  (1.9 mL). The deep maroon solution was stirred for 2 days at 35–36 °C. The solution was then removed from the glove box and to it added acetic anhydride (0.02 mL,

0.21 mmol) followed by DMAP (0.0056 g, 0.046 mmol) as a solution in 0.4 mL. The solution turned to a light green solution and was loaded directly onto a single analytical TLC plate and purified using 2:1 EtOAc:PhH eluent to provide enol acetate **47** (0.004 g, 0.013 mmol, 44% yield) as a yellow oil.  $^1\text{H NMR}$  (500 MHz,  $\text{CDCl}_3$ )  $\delta$  5.82 (ddd,  $J = 8, 6, 2.7$  Hz, 1H), 4.85 (ddd,  $J = 8.5, 6.7, 1\text{H}$ ), 4.35 (d,  $J = 9$  Hz, 1H), 3.18 (dd,  $J = 14.8, 8$  Hz, 1H), 3.15–3.04 (m, 2H), 2.94 (ddt,  $J = 14.6, 3.3$  Hz, 1H), 2.44 (dd,  $J = 13.1, 6.8$  Hz, 1H), 2.40–2.30 (m, 1H), 2.24 (s, 3H), 2.11 (s, 1H), 1.97 (dd,  $J = 12.8, 8$  Hz, 1H), 1.82–1.76 (m, 2H), 1.33 (s, 3H);  $^{13}\text{C NMR}$  (125 MHz,  $\text{CDCl}_3$ )  $\delta$  170.4, 168.6, 155.2, 154.1, 149.9, 121.4, 119.0, 117.3, 77.4, 75.5, 49.3, 46.2, 29.1, 28.5, 26.0, 25.9, 21.5, 21.1; IR (Neat film, NaCl) 3444 (br), 2970, 2933, 2868, 1738, 1626  $\text{cm}^{-1}$ ; HRMS (TOF)  $m/z$ :  $[\text{M}+\text{H}]^+$  Calcd for  $\text{C}_{18}\text{H}_{21}\text{O}_5$  317.1384; Found 317.1388;  $[\alpha]_{\text{D}}^{25.4} = +65.6$  ( $c$  0.38,  $\text{CH}_2\text{Cl}_2$ ).



### Epoxide 48

Enol acetate **47** (4 mg, 0.013 mmol) was dissolved in benzene (2 mL) and to it added excess *t*-BuOOH followed by  $\text{VO}(\text{acac})_2$  (3.4 mg, 0.013 mmol). The deep maroon solution was purified directly by thin-layer chromatography (EtOAc) to yield epoxide (3.3 mg, 76% yield) as a white solid.



### Ketone 49

To a  $\text{CH}_2\text{Cl}_2$  (1.8 mL) solution of allylic alcohol **47** (0.0028 g, 0.0089 mmol) was added PCC (0.031 g, 0.15 mmol). The solution was stirred for 45 minutes, diluted with ethyl acetate and filtered through a plug of silica. The crude reaction mixture was purified by

preparatory thin-layer chromatography with 2:1 EtOAc/PhH eluent to provide the rearranged enone (0.001 g, 0.0032 mmol, 36% yield) as a colorless oil. <sup>1</sup>H NMR (500 Mhz, CDCl<sub>3</sub>) δ 5.13 (ddd, *J* = 8.3, 8.3, 3.2 Hz, 1H), 4.64 (d, *J* = 8.3, 1H), 3.57 (dt, *J* = 13.7, 2.4 Hz, 1H), 3.52 (d, *J* = 13.7 Hz, 1H), 3.36–3.28 (m, 1H), 3.07 (dd, *J* = 20.1, 8.3 Hz, 1H), 3.01–2.92 (m, 1H), 2.76 (d, *J* = 20.1 Hz, 1H), 2.43–2.39 (m, 2H), 2.26 (s, 3H), 2.15 (app q, *J* = 1.1 Hz, 3H), 1.86–1.76 (m, 2H); <sup>13</sup>C NMR (125 MHz, CDCl<sub>3</sub>) δ 193.8, 170.5, 168.2, 156.8, 152.6, 148.2, 133.9, 120.6, 119.6, 75.8, 51.6, 47.6, 43.6, 29.3, 25.6, 21.3, 21.1, 16.1; IR (neat film, NaCl) 2931, 1762, 1737, 1687 cm<sup>-1</sup>; HRMS (TOF) *m/z*. [M+H]<sup>+</sup> Calcd for C<sub>18</sub>H<sub>19</sub>O<sub>5</sub> 315.1227; Found 315.1233; [α]<sub>D</sub><sup>25</sup> = +122.56 (*c* 0.16, CH<sub>2</sub>Cl<sub>2</sub>).

## Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

## Acknowledgments

The authors wish to thank the NIH-NIGMS (R01GM080269), Amgen, the Gordon and Betty Moore Foundation, and Caltech for financial support. Additionally, the authors gratefully acknowledge Larry Henling and the late Dr. Michael Day (Caltech) for X-ray crystallographic structural determination, Dr. Mona Shahgholi and Naseem Torian (Caltech) for mass spectrometric analysis, Dr. David VanderVelde (Caltech) for NMR experimental assistance and helpful discussions, Dr. Masaki Seto, Dr. N. Sherden, and Dr. D. E. White for helpful discussions, and Dr. R. A. Craig, II for editorial suggestions. J.L.R. thanks the California Tobacco-Related Disease Research Program of the University of California, Grant Number 14DT-0004 for a predoctoral fellowship. A.C.J. thanks the NIH (F32GM082000) for a postdoctoral fellowship.

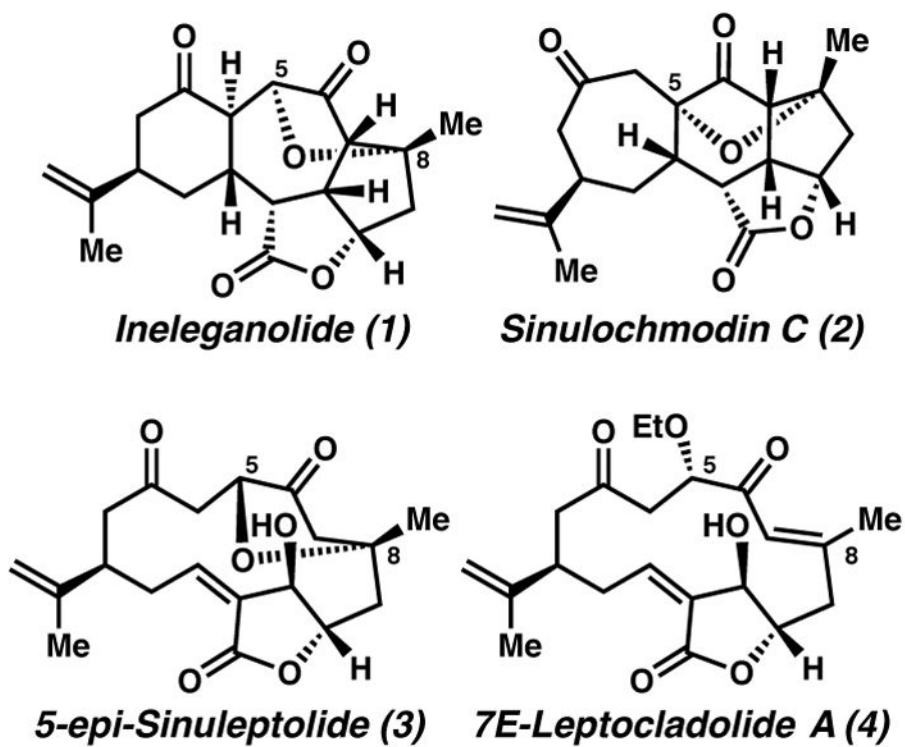
## References

1. For a review on the terpenoids that have been isolated from *Sinularia*, see Kamel HN, Slattery M. *Pharmaceutical Biology*. 2005; 43:253.. The taxonomy of *Sinularia* has been well reviewed in Coll JC. *Chem Rev*. 1992; 92:613.
2. Duh CY, Wang SK, Chia MC, Chiang MY. *Tetrahedron Lett*. 1999; 40:6033.
3. (a) Sheu JH, Ahmed AF, Shiue RT, Dai CF, Kuo YH. *J Nat Prod*. 2002; 65:1904. [PubMed: 12502336] (b) Ahmed AF, Shiue RT, Wang GH, Dai CF, Kuo YH, Sheu JH. *Tetrahedron*. 2003; 59:7337. (c) Tseng YJ, Ahmed AF, Hsu CH, Su JH, Dai CF, Sheu JH. *J Chinese Chem Soc*. 2007; 54:1041. (d) Cheng SY, Chuang CT, Wen ZH, Wang SK, Chiou SF, Hsu CH, Dai CF, Duh CY. *Bioorg Med Chem*. 2010; 18:3379. [PubMed: 20430633] (e) Thao NP, Nam NH, Cuong NX, Quang TH, Tung PT, Dat LD, Chae D, Kim S, Koh YS, Kiem PV, Minh CV, Kim YH. *Bioorg Med Chem Lett*. 2013; 23:228. [PubMed: 23200246] (f) Lillsunde KE, Festa C, Adel H, De Marino S, Lombardi V, Tilvi S, Nawrot DA, Zampella A, D'Souza L, D'Auria MV, Tammela P. *Mar Drugs*. 2014; 12:4045. [PubMed: 25056629]
4. (a) Li Y, Pattenden G. *Tetrahedron*. 2011; 67:10045. (b) Li Y, Pattenden G. *Nat Prod Rep*. 2011; 28:1269. [PubMed: 21637894] (c) Li Y, Pattenden G. *Nat Prod Rep*. 2011; 28:429. [PubMed: 21212904]
5. (a) O'Connell, C. PhD dissertation. Queen's University of Belfast; Belfast, Northern Ireland, U.K: 2006. O'Connell, CE., *Frontier, AJ. Abstracts of Papers, 32nd Northeast Regional Meeting of the American Chemical Society; Rochester, NY. Oct 31–Nov 3, 2004; American Chemical Society; 2004. GEN-088(c) Pratt, BA. PhD dissertation. Scripps Research Institute; La Jolla, California: 2008. (d) Liu, G. PhD dissertation. Texas A&M University; College Station, Texas: 2011. Liu, G., Romo, D. *Abstracts of Papers, 237th American Chemical Society National Meeting; Salt Lake City, UT. Mar 22–26, 2009; American Chemical Society; 2009. ORGN-083(f) Tang, F. PhD dissertation. Washington University in St. Louis; St. Louis, Missouri: 2009. (g) Tang F, Moeller KD. *Tetrahedron*. 2009; 65:10863. (h) Tang F, Moeller KD. *J Am Chem Soc*. 2007; 129:12414. [PubMed: 17894501] (i) Horn EJ, Silverston JS, Vanderwal CD. *J Org Chem*. 2016; 81:1819. [PubMed: 26863401] (j) Horn, EJ. PhD dissertation. University of California at Irvine; Irvine, CA: 2014.**

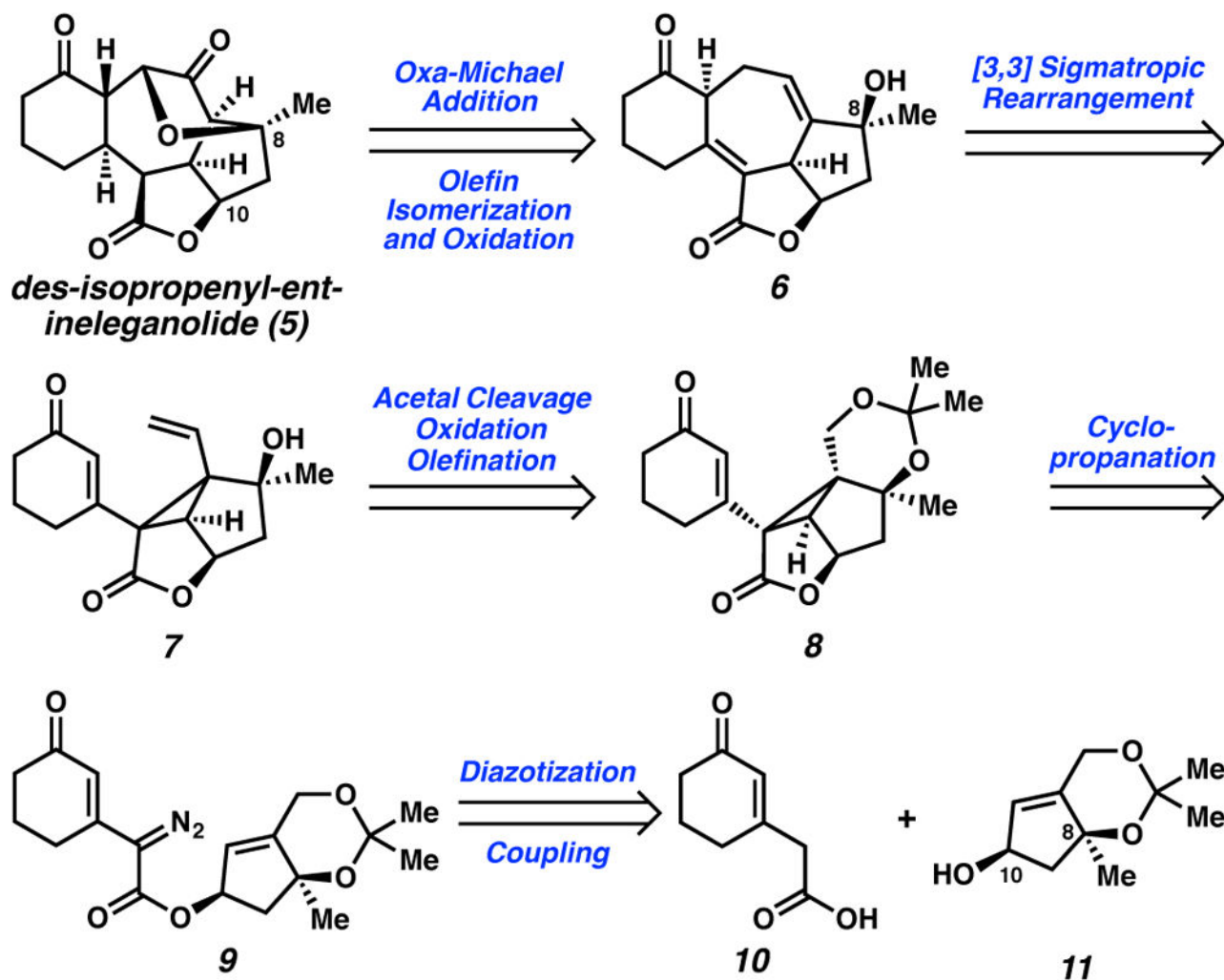
6. Craig RA II, Roizen JL, Smith RC, Jones AC, Virgil SC, Stoltz BM. *Chem Sci.* 2017; 8:507. [PubMed: 28239443]
7. (a) Krüger S, Gaich T. *Beilstein J Org Chem.* 2014; 10:183.(b) Davies HML, Stafford DG, Doan BD, Houser JH. *J Am Chem Soc.* 1998; 120:3326.(c) Davies HML. *Tetrahedron.* 1993; 49:5203.(d) Vogel E. *Angew Chem, Int Ed.* 1963; 2:1.
8. (a) Craig RA II, Roizen JL, Smith RC, Jones AC, Stoltz BM. *Org Lett.* 2012; 14:5716. [PubMed: 23101616] (b) Seto M, Roizen JL, Stoltz BM. *Angew Chem Int Ed.* 2008; 47:6873.
9. (a) Behenna DC, Mohr JT, Sherden NH, Marinescu SC, Harned AM, Tani K, Seto M, Ma S, Novák Z, Krout MR, McFadden RM, Roizen JL, Enquist JA Jr, White DE, Levine SR, Petrova KV, Iwashita A, Virgil SC, Stoltz BM. *Chem – Eur J.* 2011; 17:14199. [PubMed: 22083969] (b) Mohr JT, Stoltz BM. *Chem–Asian J.* 2007; 2:1476. [PubMed: 17935094] (c) Mohr JT, Behenna DC, Harned AM, Stoltz BM. *Angew Chem Int Ed.* 2005; 44:6924.(d) Behenna DC, Stoltz BM. *J Am Chem Soc.* 2004; 126:15044. [PubMed: 15547998]
10. Trost BM, Xu J, Reichle M. *J Am Chem Soc.* 2007; 129:282. [PubMed: 17212401]
11. (a) Tani K, Behenna DC, McFadden RM, Stoltz BM. *Org Lett.* 2007; 9:2529. [PubMed: 17536810] (b) Krout MR, Mohr JT, Stoltz BM. *Org Synth.* 2009; 86:181. [PubMed: 20072718] (c) Helmchen G, Pfaltz A. *Acc Chem Res.* 2000; 33:336. [PubMed: 10891051] (d) Williams JMJ. *Synlett.* 1996:705. and references therein.
12. Liu HJ, Zhu BY. *Can J Chem.* 1991; 69:2008.
13. Herscovici J, Egron M-J, Antonakis K. *J Chem Soc, Perkin Trans 1.* 1982:1967.
14. For similar transformations, see: Shibuya M, Tomizawa M, Iwabuchi Y. *J Org Chem.* 2008; 73:4750. [PubMed: 18500838]
15. Pyrazole formation has been previously reported in thermolysis of vinyl diazo compounds: Doyle MP, Yan M, Gao HM, Blossey EC. *Org Lett.* 2003; 5:561. [PubMed: 12583769] Doyle MP, Yan M. *J Org Chem.* 2002; 67:602. [PubMed: 11798339] Hutchinson IS, Matlin SA, Mete A. *Tetrahedron Lett.* 2001; 42:1773. Pellicciari R, Natalini B, Sadeghpour BM, Marinuzzi M, Snyder JP, Williamson BL, Kuethe JT, Padwa A. *J Am Chem Soc.* 1993; 118:1. Davies HML, Huby NJS, Cantrell WR Jr, Olive JL. *J Am Chem Soc.* 1993; 115:9468. Padwa A, Kulkarni YS, Zhang Z. *J Org Chem.* 1990; 55:4144. Bailey RJ, Card PJ, Shechter H. *J Am Chem Soc.* 1983; 105:6096. Hurd CD, Lui SC. *J Am Chem Soc.* 1935; 57:2656.
16. De Leeuw JW, De Waard ER, Beetz T, Huisman HO. *Recl Trav Chim Pays-Bas.* 1973; 92:1047.
17. For related examples involving intramolecular transactonization of  $\gamma$ -lactones, see: Raffaelli B, Pohjoispää M, Hase T, Cardin CJ, Gan Y, Wähälä K. *Org Biomol Chem.* 2008; 6:2619. [PubMed: 18600283] Mulzer J, Giester G, Gilbert M. *Helv Chim Acta.* 2005; 88:1560. Duret P, Figadère B, Hocquemiller R, Cavé A. *Tetrahedron Lett.* 1997; 38:8849. Clardy J, Springer JP, Buechi G, Matsuo K, Wightman R. *J Am Chem Soc.* 1975; 97:663. [PubMed: 1133368]
18. The immediate product of acetylation does not demonstrate the necessary gHMBC correlations; however, ketone reduction generates two diastereomers, one of which exhibits diagnostic gHMBC correlations.
19. Bredt J. *Justus Liebigs Annalen der Chemie.* 1924; 437:1.
20. (a) Tei T, Sugimura T, Katagiri T, Tai A, Okuyama T. *Tetrahedron: Asymmetry.* 2001; 12:2727.(b) Davies HML, Calvo RL, Townsend RJ, Ren P, Churchill RM. *J Org Chem.* 2000; 65:4261. [PubMed: 10891124] (c) Davies HML. *Tetrahedron.* 1993; 49:5203.(d) Davies HML, Clark TJ, Smith HD. *J Org Chem.* 1991; 56:3817.(e) Cantrell WR Jr, Davies HML. *J Org Chem.* 1991; 56:723.(f) Davies HML, Clark DM, Smith TK. *Tetrahedron Lett.* 1985; 26:5659.
21. Davies HML, Smith HD, Korkor O. *Tetrahedron Lett.* 1987; 28:1853.
22. (a) Davies HML, McAfee MJ, Oldenburg CEM. *J Org Chem.* 1989; 54:930.(b) Davies HML, Oldenburg CEM, McAfee MJ, Nordahl JG, Henretta JP, Romines KR. *Tetrahedron Lett.* 1988; 29:975.
23. For intermolecular cascades, see: Davies HML, Stafford DG, Doan BD, Houser JH. *J Am Chem Soc.* 1998; 120:3326. Davies HML, Peng ZQ, Houser JH. *Tetrahedron Lett.* 1994; 35:8939.
24. Davies HML, Doan BD. *J Org Chem.* 1999; 64:8501.
25. For asymmetric intramolecular cascades, see: Davies HML, Ahmed G, Churchill MR. *J Am Chem Soc.* 1996; 118:10774. For related uses of chiral auxiliaries in cyclopropanation/Cope reactions,

see: Davies HML, Matasi JJ, Hodges LM, Huby NJS, Thornley C, Kong N, Houser JH. *J Org Chem.* 1997; 62:1095.

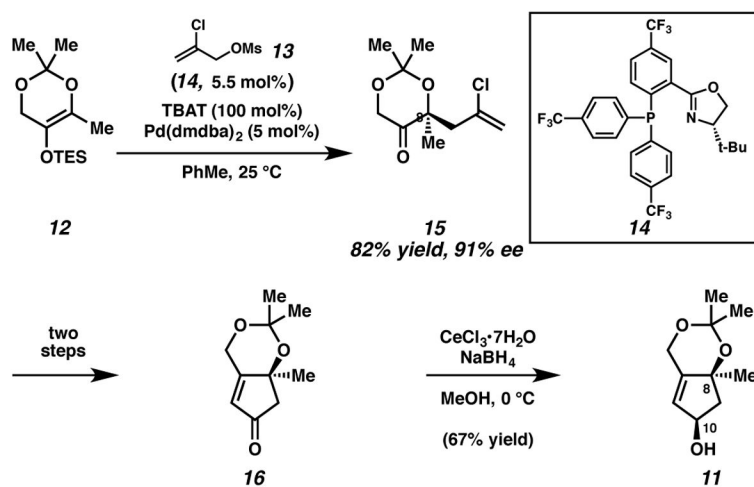
26. Danheiser RL, Miller RF, Brisbois RG, Park SZ. *J Org Chem.* 1990; 55:1959.
27. Nozaki H, Takaya H, Moriuti S, Noyori R. *Tetrahedron.* 1968; 24:3655.
28. (a) Frigerio M, Santagostino M, Sputore S. *J Org Chem.* 1999; 64:4537.(b) Boeckman RK Jr, Shao P, Mullins JJ. *Org Syn.* 2000; 77:141.
29. de Boer Th J, Backer HJ. *Org Syn.* 1963Coll. 4:250–253.
30. Parlow JJ, Case BL, South MS. *Tetrahedron.* 1999; 55:6785.
31. Baum JS, Shook DA, Davies HML, Smith HD. *Synth Comm.* 1987; 17:1709.
32. This procedure has been influenced by: Bouzide A, Sauvé G. *Tetrahedron Lett.* 1997; 38:5945.



**Figure 1.**  
A subset of metabolites (1–4) isolated from plants of the genus *Sinularia*.

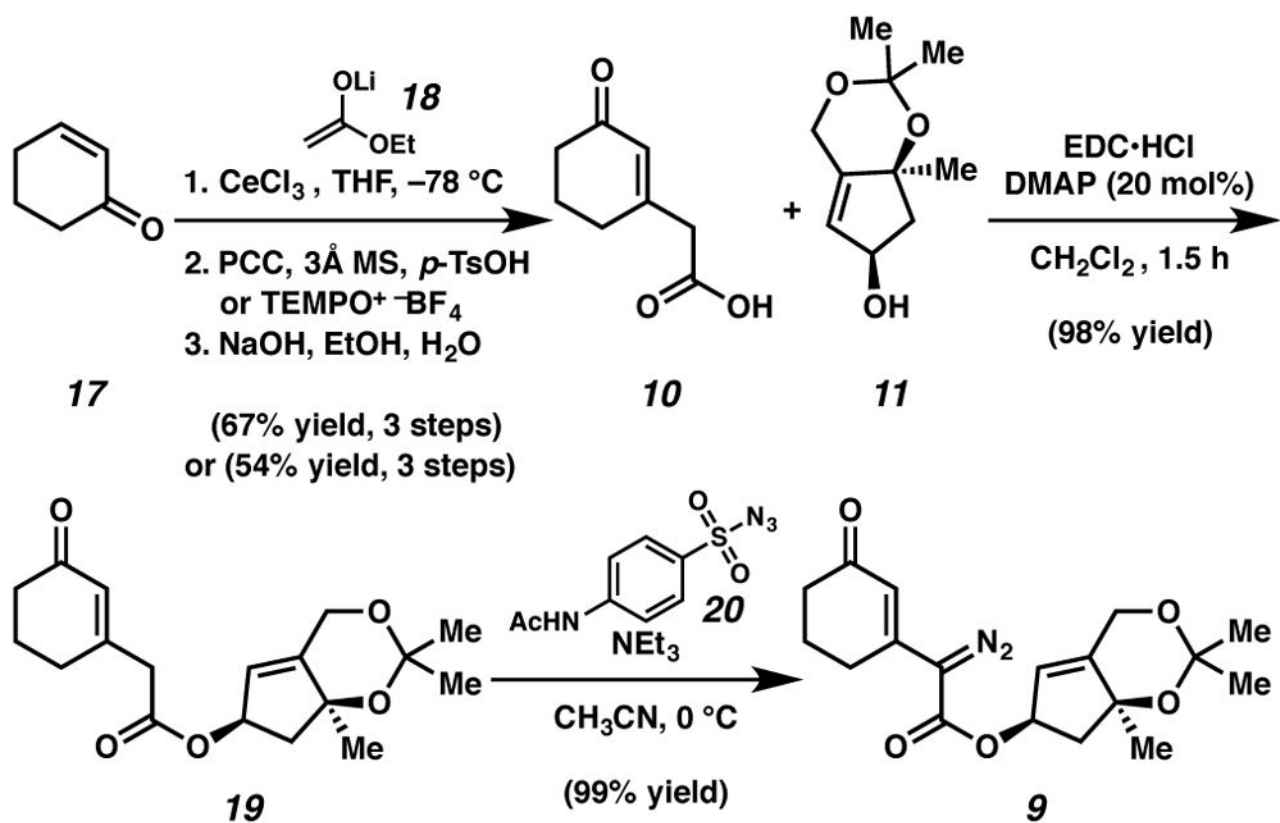


Scheme 1.  
Initial retrosynthetic analysis of *des-isopropenyl-ent-ineleganolide (5)*

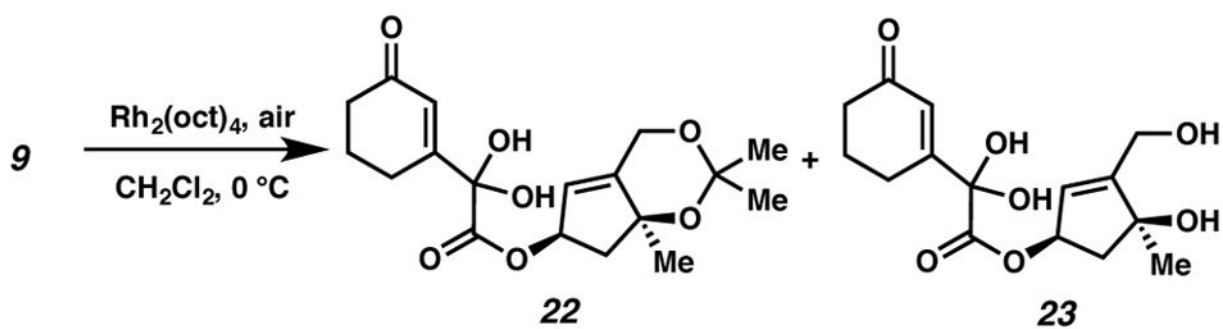
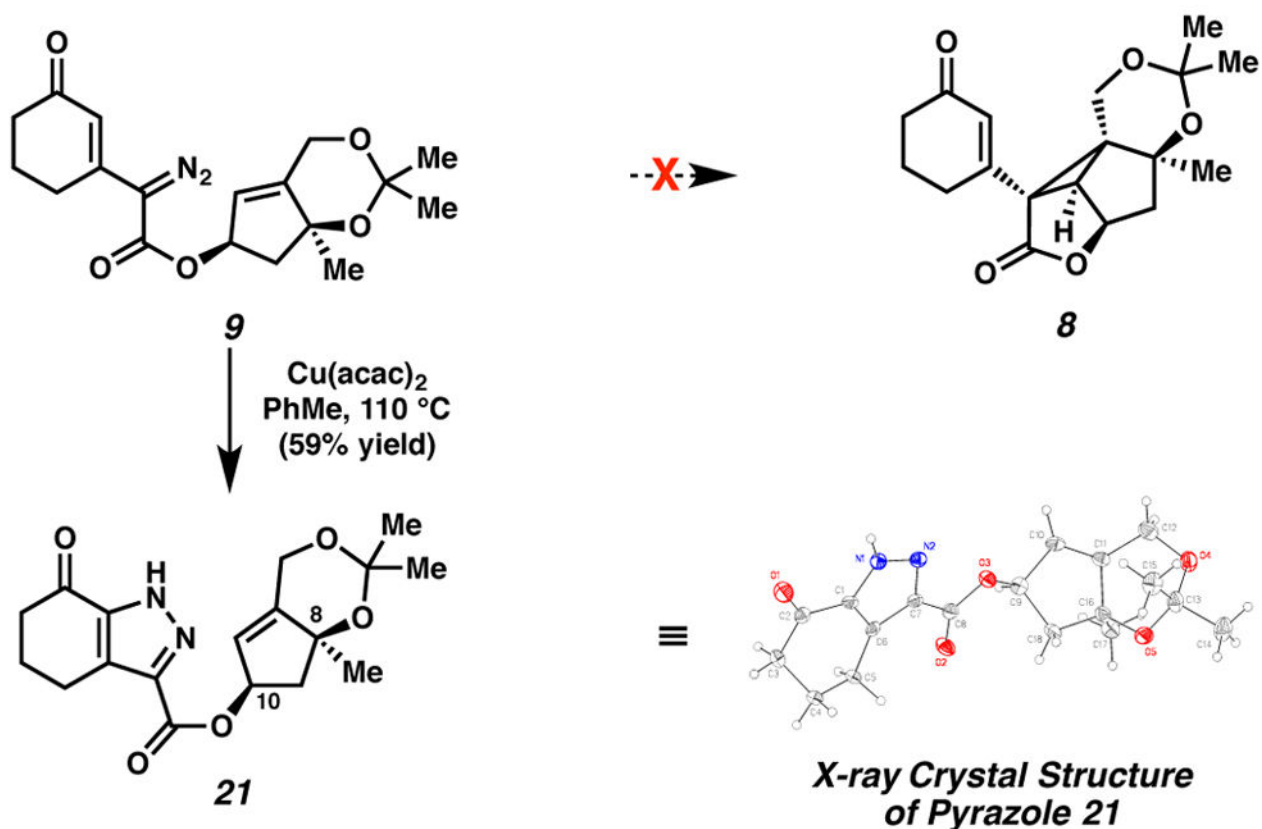


**Scheme 2.**  
Synthesis of cyclopentenol 11

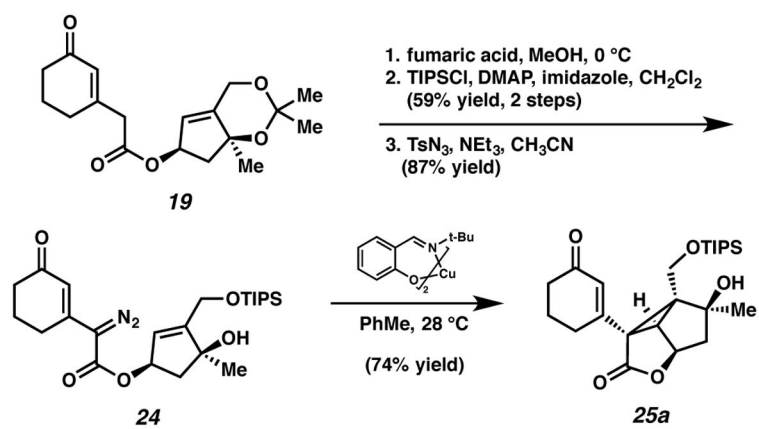




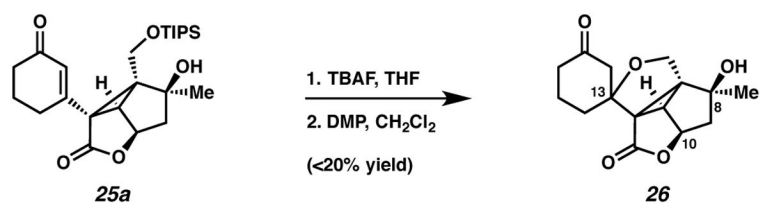
**Scheme 3.**  
Toward the cyclopropanation substrate



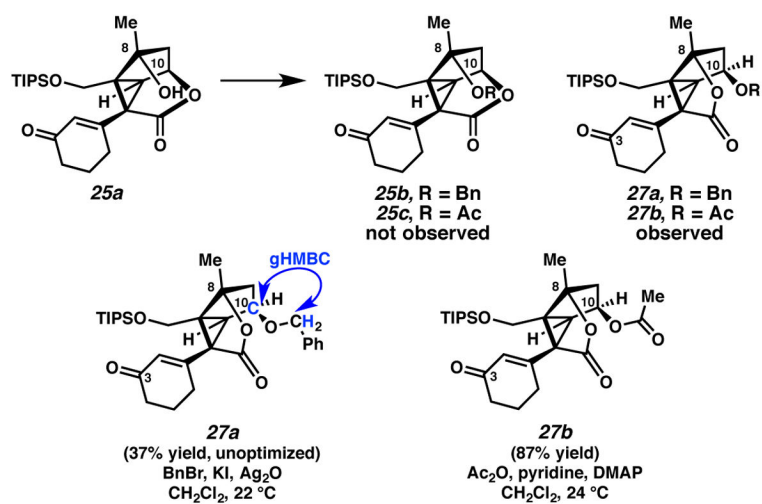
**Scheme 4.**  
Pyrazole formation and oxidation plague initial cyclopropanation approach



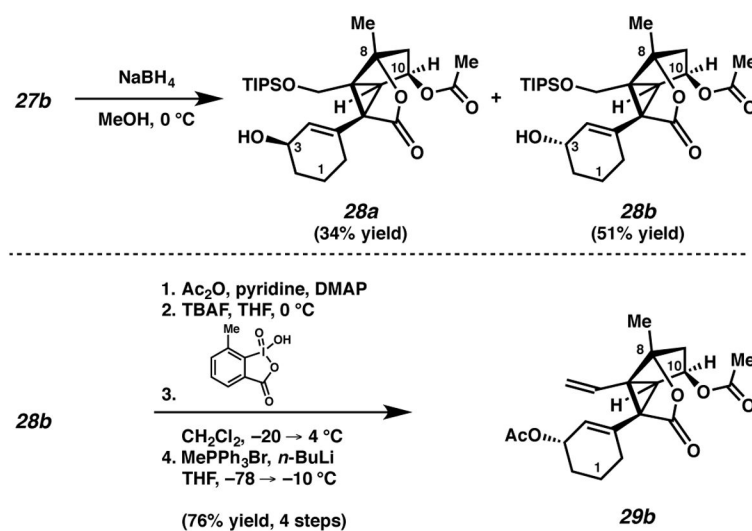
**Scheme 5.**  
Successful cyclopropanation of silyl ether 24

**Scheme 6.**

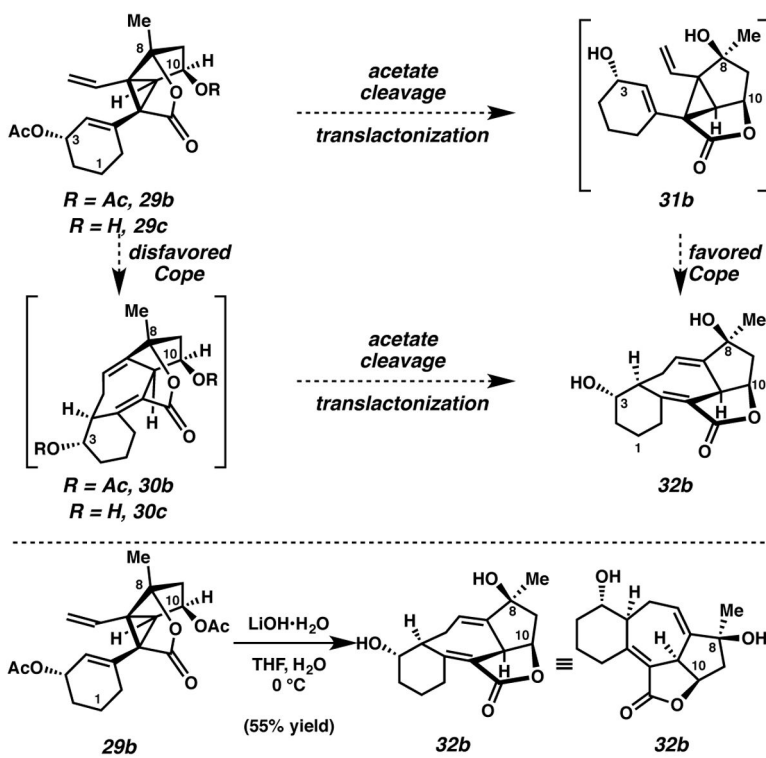
Byproduct formed in the desilylation–oxidation sequence

**Scheme 7.**

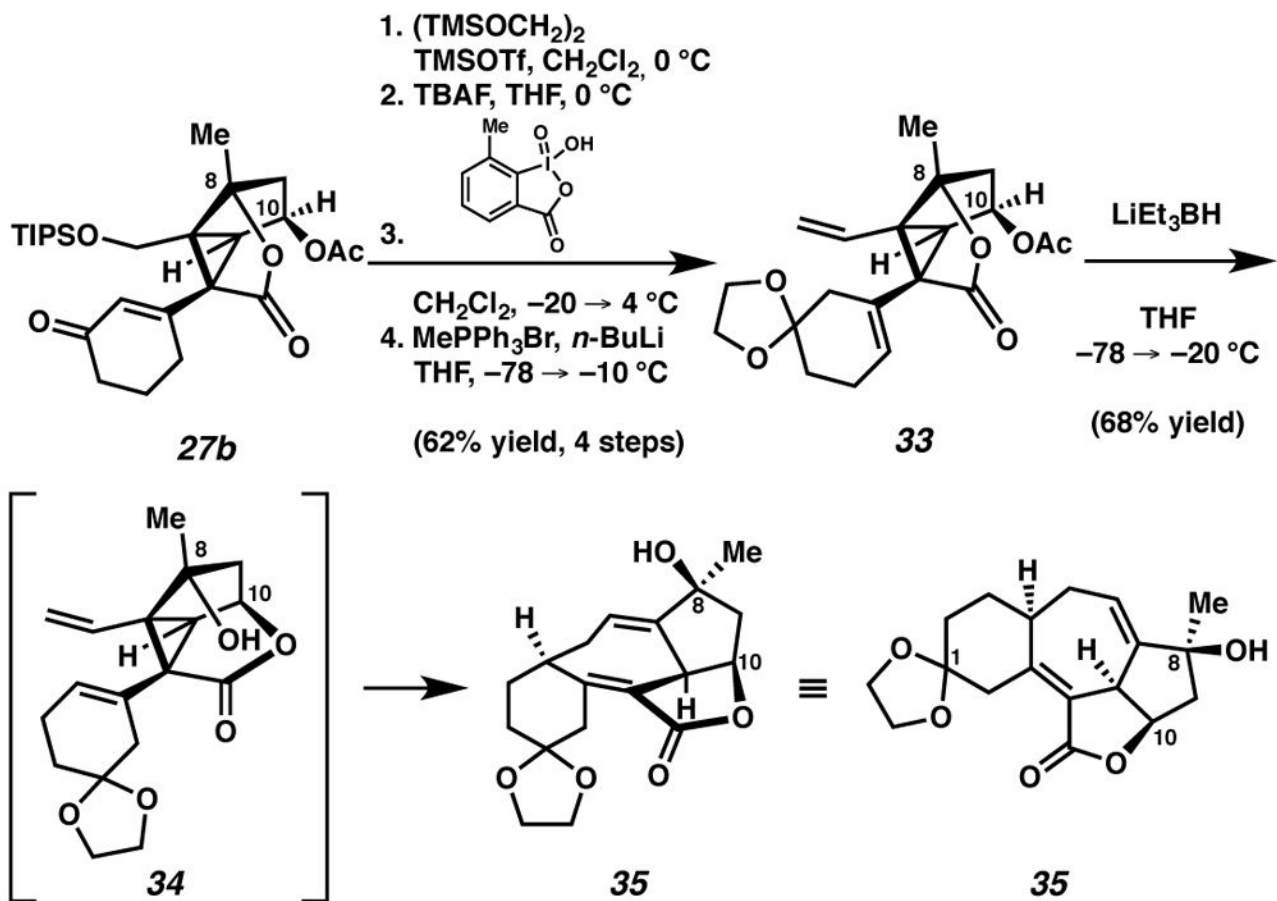
Translactonization to form benzyl ether and acetyl ester



**Scheme 8.**  
Access to divinylcyclopropane 29b

**Scheme 9.**

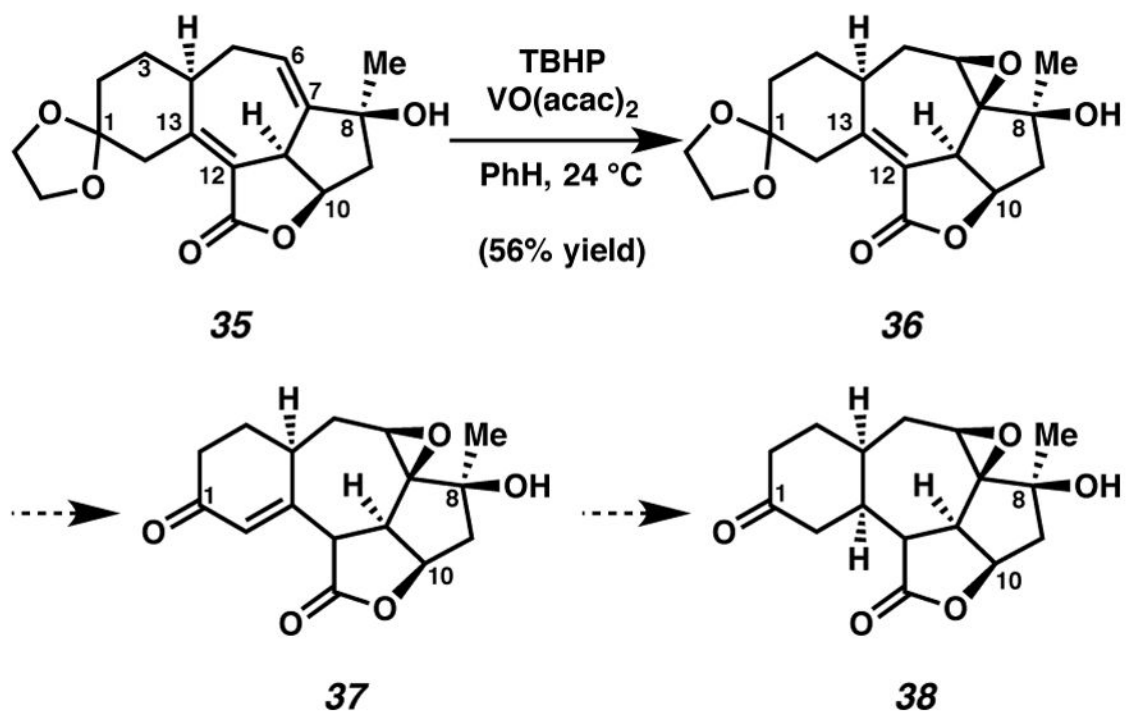
Translactonization-Cope approach to access cycloheptadiene 32b



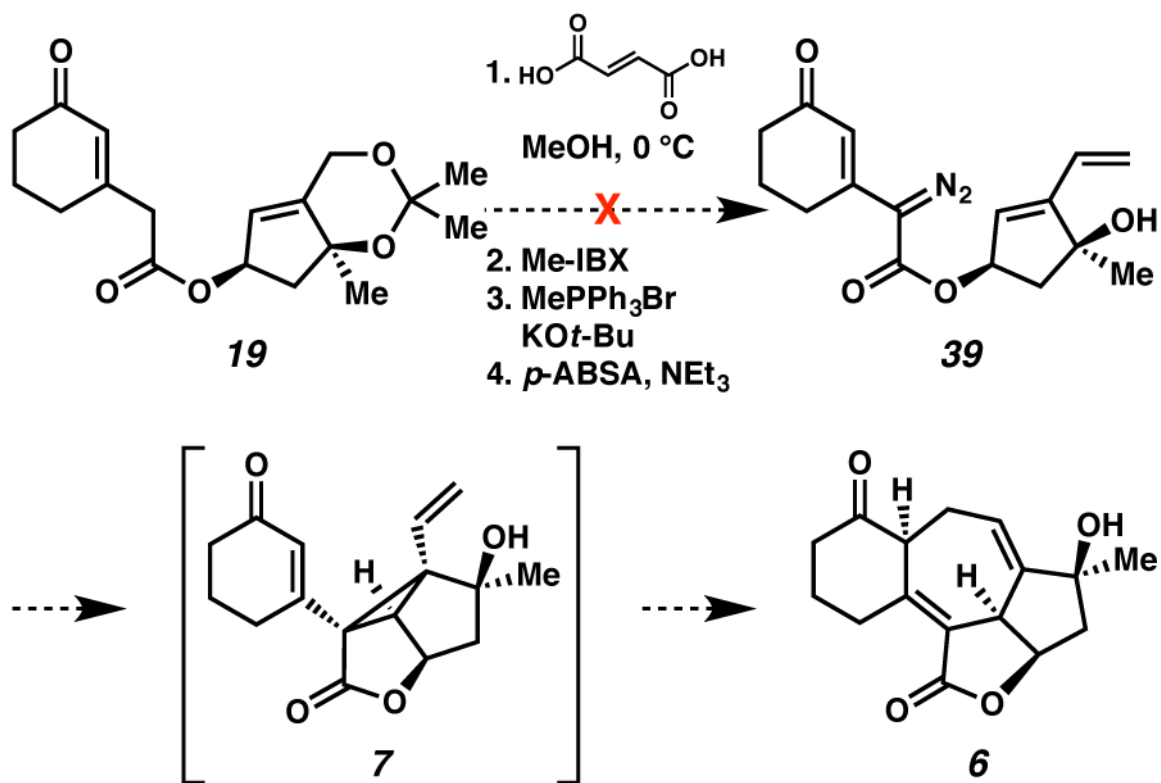
Scheme 10.

Ketalization with undesired olefin isomerization and subsequent transactonization-Cope rearrangement sequence



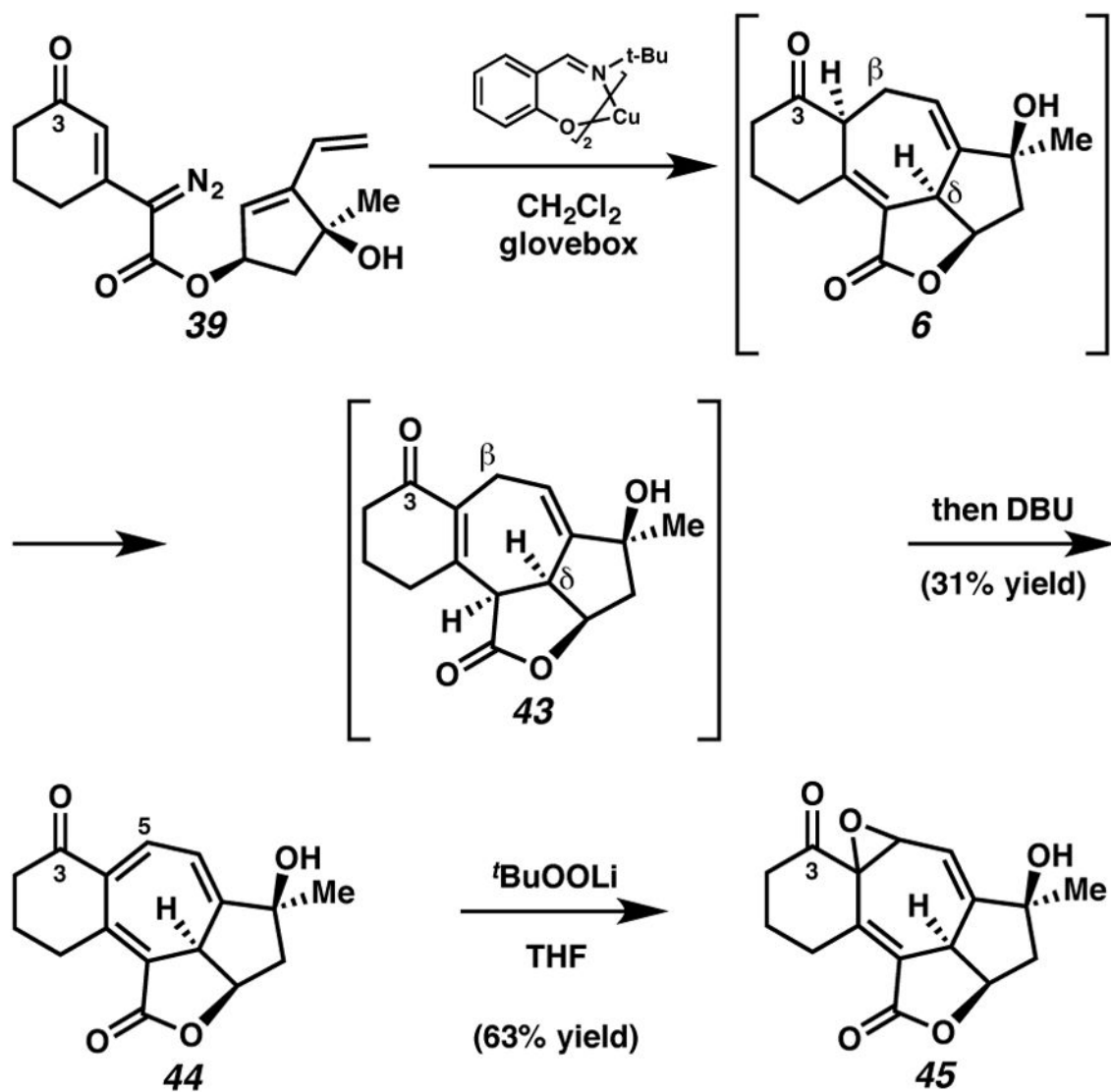


**Scheme 11.**  
Olefin differentiation from cycloheptadiene 35

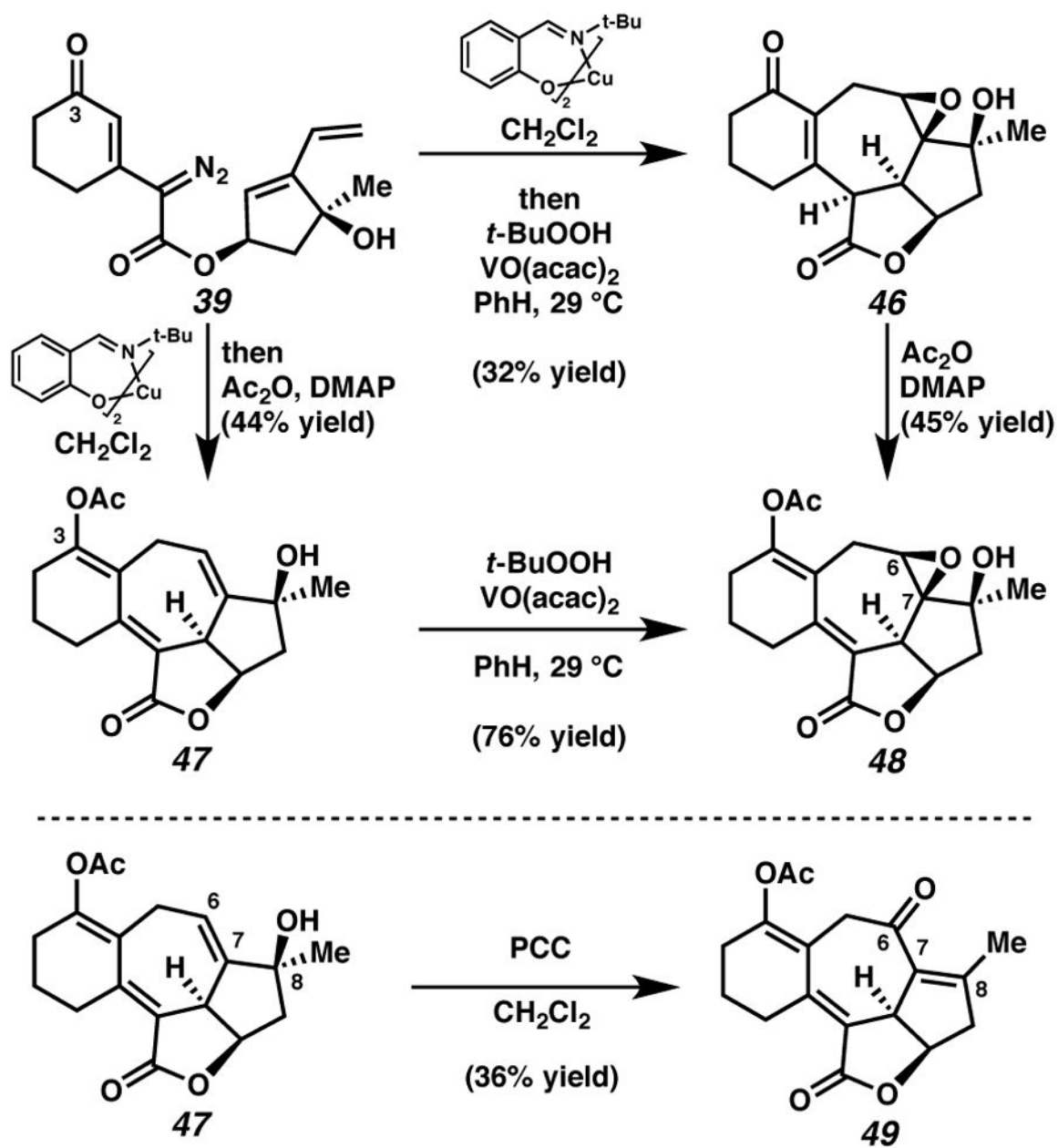


**Scheme 12.**  
 Alternative plan to access cycloheptadiene 6





Scheme 14.  
Cyclopropanation-Cope-oxidation sequence with nucleophilic epoxidation



Scheme 15.

Cyclopropanation-Cope-epoxidation and cyclopropanation-Cope-enolate trapping sequences