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Cobalt Catalyzed Intramolecular Cyclization of Acyclic Alkenols for Polycyclic Ether Synthesis

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An abstract of
A thesis submitted to the Faculty of the
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Abstract

Cobalt Catalyzed Intramolecular Cyclization of Acyclic Alkenols for Polycyclic Ether Synthesis

By Zakiria Brishuna Mays

Intramolecular cyclization reactions are useful to form fused cyclic ether rings like those observed in the natural product, brevenal. Stoichiometric amounts of mercury and iodide have been applied to acyclic alkenol substrates that resulted in brevenal's ABC cyclic ether core with some limitations. We present a new metal catalyzed approach that will expand bis(1,3-diketonato)cobalt(II) intramolecular cyclizations beyond 5-membered tetrahydrofuran compounds. Studies with substituted alkenol substrates has provided suitable preliminary reaction conditions for product formation. Optimized reaction conditions will include the appropriate cobalt catalyst and efficient catalyst regeneration for successful product isolation.

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List of Schemes:

List of Abbreviations

***K. Brevis*:** *Karenia Brevis*

PbTxs: brevetoxins

NSP: neurotoxic shellfish poisioning

VGSC: voltage-gated sodium channels

NOE: Nuclear Overhauser Effect

COPD: chronic obstructive pulmonary disease

THP: tetrahydropyran

THF: tetrahydrofuran

$Hg(OTFA)_2$: mercury(II) trifluoroacetate

LiBr: lithium bromide

TBAF: tetra-n-butylammonium fluoride

Co(II): cobalt(II)

$Co(OAc)_2 \cdot 4\ H_2O$: cobalt(II) acetate tetrahydrate

$Co(MODP)_2$: bis(1-morpholinocarbamoyl-4,4-dimethyl-1,3-pentanedionato)cobalt(II)

CHD: 1,4-Cyclohexadiene

$Na_2S_2O_3$: sodium thiosulfate

^{1}H NMR: proton nuclear magnetic resonance

Co(III): cobalt(III)

h: hour

$CDCl_3$: deuterated chloroform

EtOAc: ethyl acetate

R_f: retardation factor

Introduction:

I. Background

The red tide is a phenomenon that was first reported in 1844, caused by marine dinoflagellate *Karenia Brevis* (*K. brevis*). Once the harmful alga bloom is initiated, *K. brevis* is transported into the ocean to retrieve nutrients and results in red-colored tides.[1] Harmful alga blooms occur annually in Florida, Texas, North Carolina, and all coastal regions along the Gulf of Mexico.[2]

Blooms of *K. brevis* is linked to increased mortality of marine organisms.[3] This led to studies that revealed the source of damaging effects to be neurotoxins termed brevetoxins, or PbTxs derived from a numbering system of the polyethers.[1] Brevetoxins, analogs, and its metabolites are categorized by their trans-fused polycyclic ether backbone. Toxins accumulate in shellfish and finfish, which in turn poison other animals that eat brevetoxin-contaminated fish. For example, in 2004, the death of 107 bottle nose dolphins was proven to result from the consumption of finfish with elevated levels of brevetoxin found in their guts.[1] In addition, human consumption of shellfish leaves us susceptible to brevetoxin exposure and neurotoxic shellfish poisoning (NSP). These compounds have an affinity for site 5 of the alpha subunit of voltage-gated sodium channels (VGSC) and cause depolarization and spontaneous firing that results in neurological and gastrointestinal symptoms. Cell fragments that contain brevetoxins can be released as aerosols and act as potent respiratory toxins.[4] This raises a threat to people with underlying respiratory complications such as asthma and cystic fibrosis.

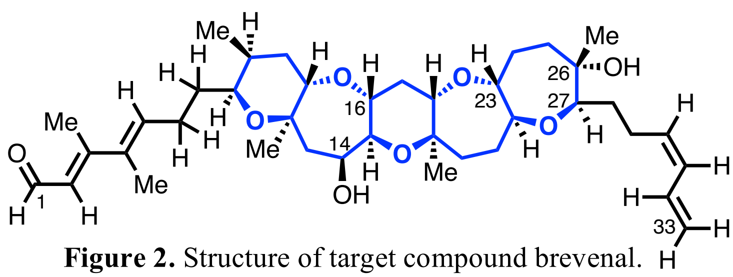


Figure 2. Structure of target compound brevenal.

More than 50 fused polycyclic ether natural products have been characterized with 5- to 9-membered rings.[5] In 2004, the Bourdelais laboratory described the isolation and characterization of a new polycyclic ether. Brevenal is an antagonist for brevetoxins on the VGSC receptor confirmed by various binding assays (Figure 1).[6] Nuclear Overhauser Effect (NOE) spectroscopy correlations confirmed trans-fused polycyclic ether rings consistent with those observed in brevetoxins.[6] Cell model studies have shown brevenal can reduce cell death in highly toxic concentrations of PbTxs, and in vivo models have proven brevenal's ability to increase tracheal mucous velocity and mucocilliary clearance.[7] Brevenal is patented as a treatment for COPD, cystic fibrosis, and asthma.[8] One of the most recent total synthesis of brevenal was performed in the Rainier laboratory, and required 38 total steps with an overall yield of 0.99%.[9]

Nakanishi proposed a biosynthetic mechanism to synthesize fused cyclic ether scaffolds. His hypothesis involved monooxidase-catalyzed epoxidation of polyketide derivatives to generate precursors that undergo a cascade of 6-endo-selective epoxide-opening cyclizations.[10] To bypass Baldwin's rules, reactions often require directing groups and a lewis-acid catalyst to stabilize the transition state.[11] This mechanism has been successfully applied to the synthesis of fused cyclic ethers over the past 20 years.[12, 13, 14]

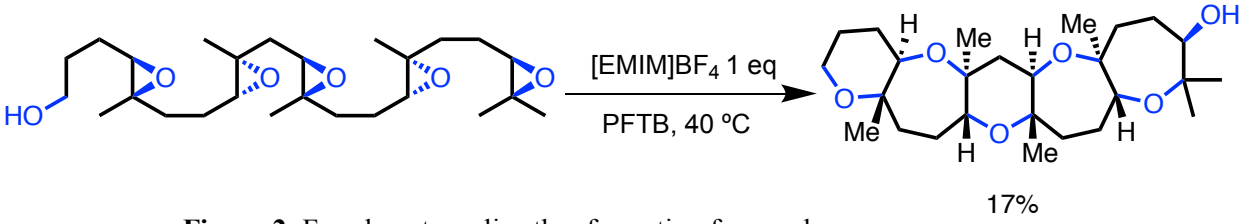


Figure 2. Fused pentacyclic ether formation from polyepoxy precursors.

The Qu Laboratory expanded upon these methods and produced a 7/7/6/7/6 polycyclic ether core with five fused rings (Figure 2).[15] Despite the production of a motif similar to

brevenal's core, restrictions arose from the cyclization of polysubstituted epoxide substrates and the use of directing groups for desired regioselectivity. Results display the misplacement of substituents observed in brevenal's structure. This includes absence of C14 hydroxyl group, hydrogen atoms at C16, C23, and C27, and an additional methyl substituent at C26 (Figure 2).

II. This Work

Our group saw potential in linear alkenol substrates that undergo cyclization to overcome these challenges. Oxacyclizations with linear alkenol substrates are exo-regioselective, rather than endo-regioselective polyepoxide opening cyclizations that brought forth limitations in regard to substituent patterns at rung fusions.[16] In 2013, the McDonald group achieved cyclization of linear alkenol substrates initiated by stoichiometric amounts of iodide and mercury.[17] Substituted erythro THP products were produced following the Chamberline-Hehre model, and consistent with brevenal's stereochemical structure.[18]

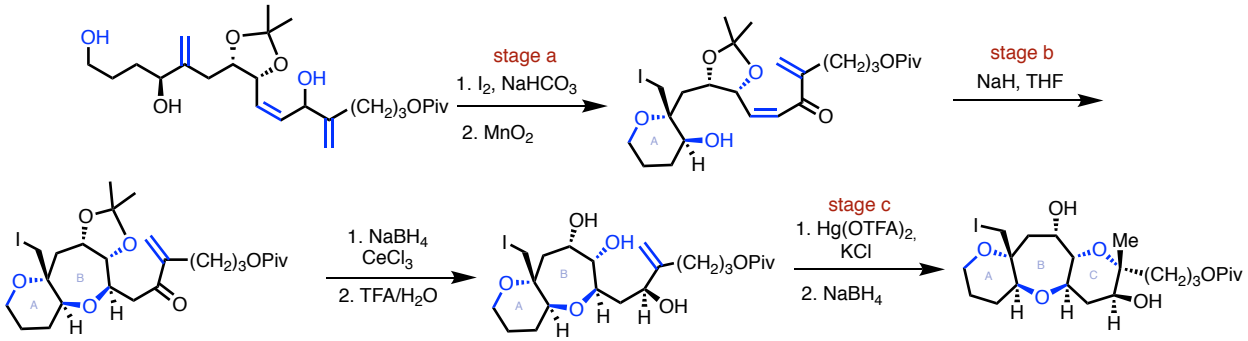


Figure 3. Formation of brevenal's ABC structure from acyclic starting materials.

This work was expanded within the lab to access brevenal's ABC structure (Figure 3). Diastereoselective iodocyclizations of acyclic starting material provided the THP A ring in one-step. The 7-membered B ring was formed from diastereoselective intramolecular conjugate addition. Stoichiometric amounts of $Hg(OTFA)_2$ initiated diastereoselective cyclization to access the THP C ring. Demercuration was successful, however, iodide could not be removed from final fused tricyclic either product under various conditions.[16]

After some success with stoichiometric reagents, we are inspired to discover a catalytic method to access fused cyclic ether rings. In 1989, the Mukaiyama laboratory studied the oxygenation of olefins to form alcohols. Reactions were conducted under aerobic conditions with bis(1,3-diketonato)cobalt(II) catalysts.[19] Mukaiyama's work was later extended to bis(1,3-diketonato)cobalt(II) catalyzed oxidative cyclizations of alkenol substrates that formed trans-2-hydroxymethyltetrahydrofuran products with >99% selectivity (Figure 4).[20] Over the years this method was used as a stereospecific catalytic solution for the total synthesis of natural products such as asimilobin, mucocin, and cyclocapitelline.[21, 22, 23]

Further advancement with linear substrates involves a selective procedure that will successively produce fused 6- and 7-membered heterocyclic ether structures. Hartung's laboratory reported data for cobalt catalyzed cyclizations of monosubstituted 5-hexenol substrates to form 6-membered THP rings (Figure 4).[24] A radical intermediate was proposed that could be trapped with various substituents (Figure 4). Herein, we will revisit cobalt catalyzed cyclization chemistry to increase the complexity of acyclic alkenol substrates, study the catalytic activity of various bis(1,3-diketonato)cobalt(II) complexes, and optimize reaction conditions.

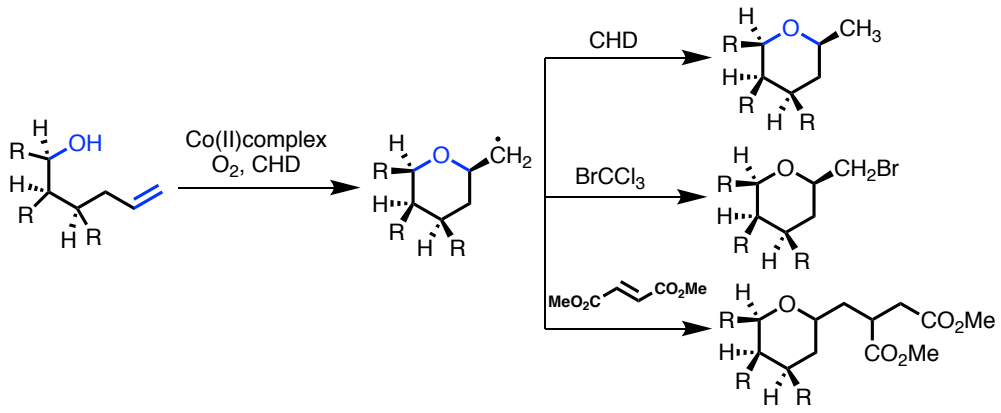
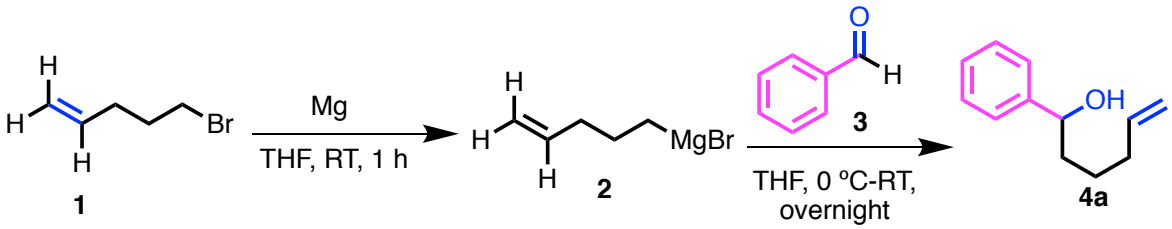


Figure 4. Previous formation of functionalized THP rings from cobalt catalyzed cyclizations.

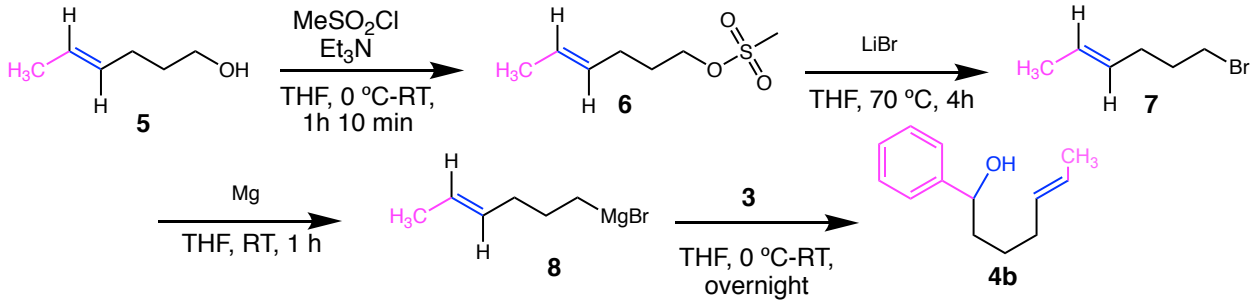
Results and Discussion:

I. Substrate Synthesis



Scheme 1. Synthesis of acyclic monosubstituted alkenol **4a**.

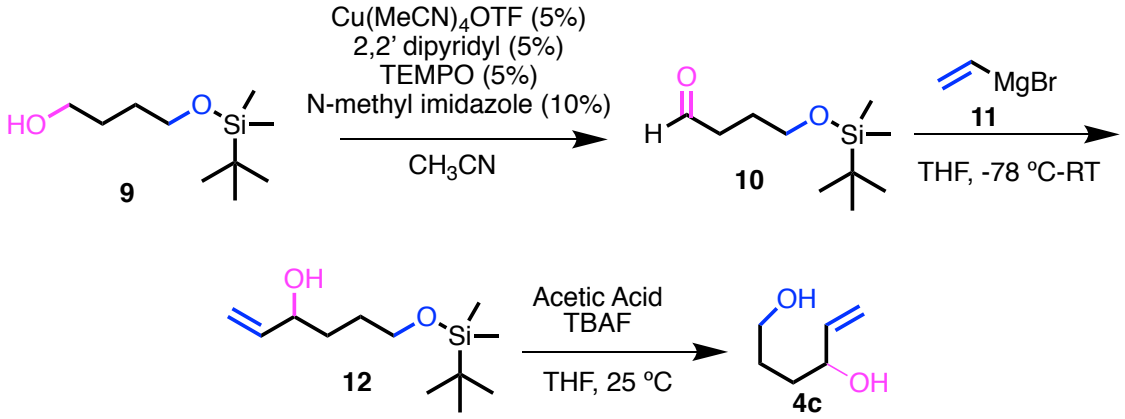
We performed a control experiment with C1 phenyl substituted alkenol **4a** to confirm formation of THP product and cobalt catalyst reactivity. Commercially available alkenyl bromide (**1**) was reacted with magnesium to undergo addition with benzaldehyde via a Grignard reaction (Scheme 1). Monosubstituted alkenol **4a** was produced with a 60% yield.[25] Calculated yields indicated presence of unreactive magnesium oxide and low reactivity when oxygen is absorbed into the reaction solution.



Scheme 2. Synthesis of acyclic disubstituted alkenol **4b**.

Next, we incorporated a methyl substituent at the terminal olefin position to gather preliminary data on disubstituted alkenols. Previous reports show that olefin stereochemistry is lost during cobalt catalyzed oxacyclizations because of an assumed radical pathway.[26] Therefore, (*E*)-1-phenyl-5-hepten-1-ol (**4b**) was prepared from commercially available (*E*)-hex-4-en-1-ol (**5**) (Scheme 2). **5** was mesylated for LiBr substitution that produced (**7**).[27] Addition of crude alkenyl bromide reaction mixture inhibited the Grignard reaction. This resulted in byproducts caused by unreacted benzaldehyde and alkenyl bromide. Moreover, distillation of **7** on a small-

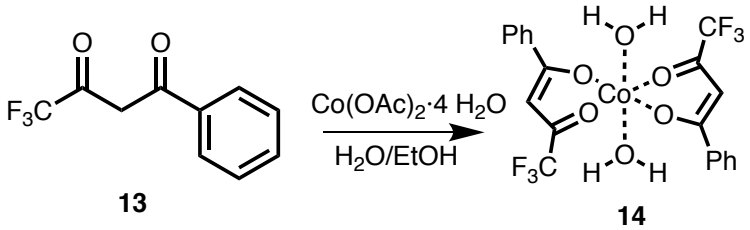
scale would result in lost product and attempts to purify via flash column chromatography gave a 45% yield, so pure **7** was difficult to obtain. Nevertheless, Grignard reaction produced **4b** as a slightly yellow oil at 35% yield.[25] NMR data was not previously reported in literature, so further characterization of **4b** is presented.



Scheme 3. Synthesis of acyclic disubstituted alkenol **4c**.

Diol **4c** was produced to further increase substrate complexity and study stereoinductive effects of an allylic alcohol (Scheme 3). Synthesis started with Stahl oxidation of **9** to afford **10** at 90% yield.[28] Grignard addition with vinyl magnesium bromide (**11**) produced **12** at 90% yield.[29] Deprotection with TBAF and acetic acid lead to final diol product at 62% yield after purification.[18]

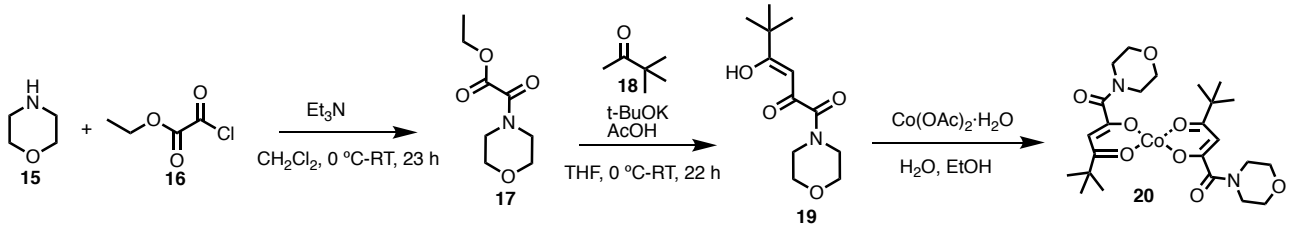
II. Synthesis of Co(II)diketonate complexes



Scheme 4. Formation of Bis-[1,1,1-trifluoro-4-phenyl-2-(oxo-κO)- but-3-en-4-(olato-κO)]cobalt(II) dihydrate catalyst.

Various Co(II) complexes have been reported to catalyze aerobic cyclization of acyclic alkenols. Control cyclization with monosubstituted alkenol **4a** was performed under conditions

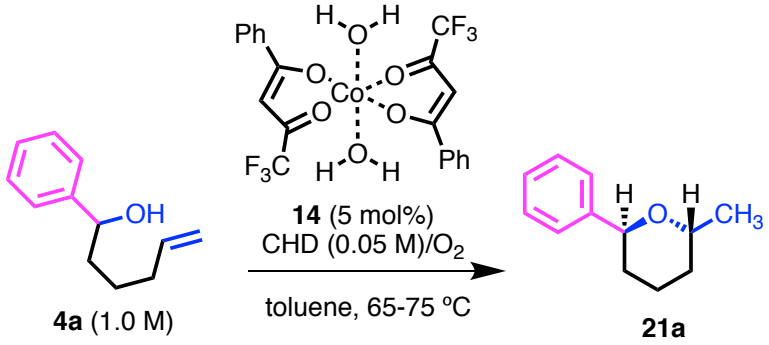
recorded in Hartung's laboratory with trifluoro substituted ligand **13**. Ligand exchange with $Co(OAc)_2$•4 H_2O produced catalyst **14** as an orange solid with a 90% yield.[30]



Scheme 5. Synthesis of $Co(MODP)_2$ catalyst.

The next catalyst of interest was morpholine derived bis(1-morpholinocarbamoyl-4,4-dimethyl-1,3-pentanedionato)cobalt(II), or $Co(MODP)_2$. Ligand precursor **17** was achieved by nucleophilic addition of morpholine (**15**) into ethyl chlorooxoacetate (**16**). Addition of pinacolone (**18**) produced MODP ligand **19**. Reaction with $Co(OAc)_2$•4 H_2O formed $Co(MODP)_2$ (**20**) as a light pink solid with a 69% yield.[31]

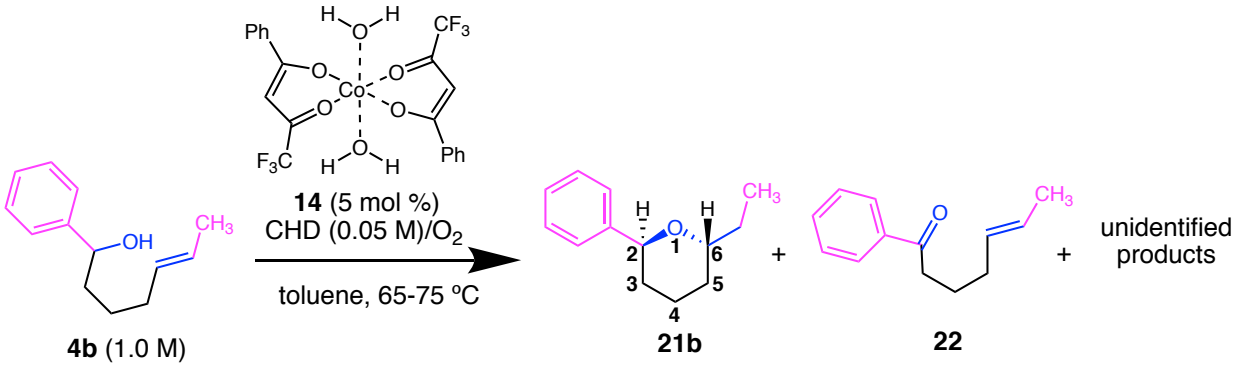
III. Cobalt Catalyzed Cyclizations



Scheme 6. Control cobalt catalyzed cyclization experiment with monosubstituted alkenol.

Control experiment with **4a** applied 5% of catalyst **14**, atmospheric oxygen as a terminal oxidant, 1,4-Cyclohexadiene (CHD) for a hydrogen source, and toluene (Scheme 6).[25] All cyclization temperatures were maintained between 65-80 ºC. THP product **21a** was produced and confirmed by previous reports.[25] Oxacyclization of **4a** is reported to give 11:89 cis/trans selectivity, and >99% conversion in 22 h. However, after 22h, there was still presence of starting material. Attempts to terminate the reaction and remove cobalt remnants by filtering through a

short pad of $Na_2S_2O_3$ resulted in a green filtrate, and was unsuccessful.[25] Purification of the reaction mixture afforded **21a** as a green oil. ^{1}H NMR analysis presented evidence for product **21a**, with some presence of unidentified cobalt species. Unfortunately, following the published experimental procedure did not afford pure product.

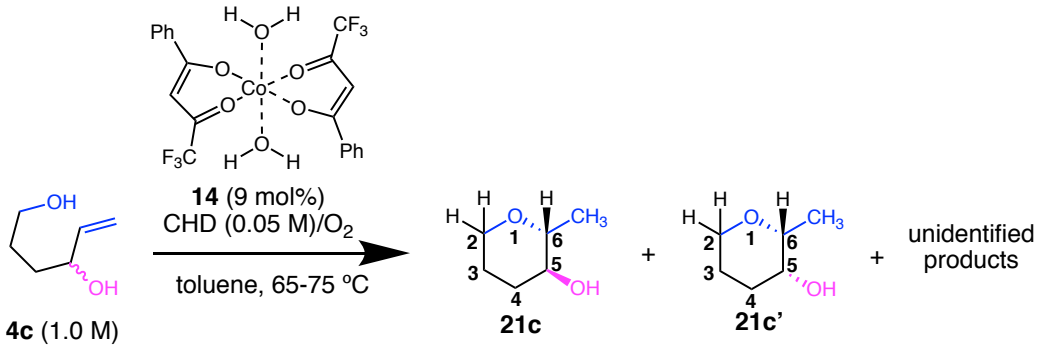


Scheme 7. Cobalt catalyzed cyclization experiment with disubstituted alkenol substrate.

Our initial goal involved preliminary results for the removal of oxygen from reaction conditions to extend the substrate scope of cobalt catalyzed cyclizations and avoid predicted epoxidation. A hydroperoxy intermediate that forms during slow cyclizations is predicted to leave pi bonds susceptible to oxygenation with methyl substituted alkenols.[32] This results in hydroxyl products and reversed diastereoselectivity. We chose 2,3-Dichloro-5,6-dicyano-1,4-benzoquinone and 2,6-Dichloro-1,4-benzoquinone as alternative terminal oxidants to test if reactions could be performed in the absence of oxygen with substrate **4a** and catalyst **14**. Reaction conditions were derived from the control experiment at various concentrations and under inert conditions to exempt oxygen. Attempts also incorporated triethylsilane as an alternative reductant to CHD. Unfortunately, Co(II) was not oxidized to its Co(III) state required for reactivity. Cobalt oxidation can be visualized by a color change to green. Only starting material was recovered, and we decided to move on without further investigation.

Although epoxidation is predicted to occur when the alkenol chain is extended, there has been minimal investigation for cobalt catalyzed cyclizations to form 6-membered THP rings. It is

important that the alkenol chain can be extended for future application in natural product synthesis. Methyl substituted alkenol **4b** was tested under various cyclization conditions. Trifluoro diketonate ligands have played a significant role in expanding the substrate scope to produce 5-membered THF rings, so we continued with catalyst **14** for further investigation. Evidence of THP product **21b** was first observed at 1.0 M of **4b** in toluene added to 5% of **14** dissolved in 0.05 M of CHD and heated under reflux for 48 h (Scheme 7). A complex mixture was recovered that was difficult to analyze because of cobalt compounds and other impurities. However, ^{1}H NMR peaks (400 MHz, $CDCl_3$) that correlate with expected cyclic ether product were observed at 4.82 (t, C2: 1H) and 3.63 ppm (m, C6: 1H). We identified ketone **22** as a prominent byproduct, which lead us to conclude that oxidation of the secondary benzylic alcohol occurred at a faster rate. The rate of cyclization for known THF cyclization procedure is 24x faster than THP formation, which leaves starting material susceptible to side reactions and decomposition.[25] Since substitution at the C1 position is reported to affect selectivity, methyl substitution at the terminal olefin position could cause steric hindrance with coordinated catalyst ligand, or affect catalyst accessibility to the pi bond.



Scheme 8. Cobalt catalyzed cyclization with diol substrate.

The next step was to study the stereoinductive effects of an allylic alcohol. The first cyclization attempt with diol **4c** was conducted over the course of three days with catalyst **14**.

Concentration was kept constant based off previous literature procedures.[25] Upon return, the reaction solution had reverted to its original orange color. Therefore, cyclizations started with 5% catalyst and an additional 2% catalyst dissolved in 0.05 M CHD was added each day (Entry 1). All starting material was consumed at 9% catalyst loading, and this parameter was kept constant for following cyclizations. We repeated the experiment with established 9% catalyst loading, and evidence for formation of hydroxyl substituted THP product was observed after 48 h. Unfortunately, product was not successfully purified from unidentified cobalt(III) products and other impurities. Further analysis of crude ^{1}H NMR (400 MHz; $CDCl_3$) spectra allowed us to identify signature peaks of trans product **21c** and cis product **21c'**. We predicted a mixture of trans and cis diastereomers was recovered with C6 methyl doublets at 1.26 (J = 5.8 Hz) and 1.14 ppm (J = 6.5 Hz) respectively. Crude spectra displayed trans selectivity with a 1:2 cis/trans ratio. Peaks associated with trans product were confirmed by previous literature reports.[33] Additional peaks of importance appeared within a range of 3.99-3.71 ppm (C2: 2H, C5: 1H, C6: 1H).

Cyclization product **21a** was reported as a clear oil after flash column chromatography purification with 1:1:20 acetone:ether:pentanes solvent mixture. However, attempts to isolate compound **21a** resulted in green cobalt impurities. The same challenges with isolation were faced with disubstituted alkenol **4b** and diol **4c** cyclizations. Major ^{1}H NMR peaks were signature peaks for THP product in the green crude spectra, and colorless fractions recovered from flash column chromatography purification with EtOAc:hexanes solution presented ^{1}H NMR peaks for byproducts that have not yet been identified. Evidence for THP product was only observed in fractions that contained green cobalt impurities.

Separation of trifluoro substituted catalyst **14** in Co(III) state from organic cyclic ether products was difficult due to high solubility in organic solvents. Suggested work ups from

literature to remove cobalt compounds with satd. aq. $Na_2S_2O_3$ washes and ether extraction were unsuccessful.[32] Attempts to terminate the reaction by filtering through a short pad of $Na_2S_2O_3$ resulted in a green filtrate, and was also unsuccessful.[25] To try and terminate the catalytic cycle and reduce Co(III) to Co(II), 1.0 mL of CHD was added to the crude reaction and heated under inert condition for approximately 2 h. A similar method was applied with 2-propanol as a hydrogen source.[20] However, the reaction solution remained green and cobalt remained in its oxidized state. Difficulty with purification of Co(II) catalyzed reactions was consistent with results reported by Pagenkopf and lab members in 2009, that included decomposed cobalt catalysts at varying R_f values during flash column chromatography purification that overlapped with cyclized products.[34]

With hopes to improve separation, we synthesized morpholine derived MODP ligand to produce catalyst **20**. Due to paramagnetic activity, cobalt catalysts cannot be identified by ^{1}HNMR. Qualitative observation of a color change from pink to green reaction solution indicated cobalt catalyst was activated by CHD and O_2.[34] An ideal catalyst would decrease impurities, but initial cyclizations with catalyst **20** increased byproducts. Activated green Co(III) complex also remained highly soluble in organic solvents, and similar isolation difficulties were faced as previously described with **14**.

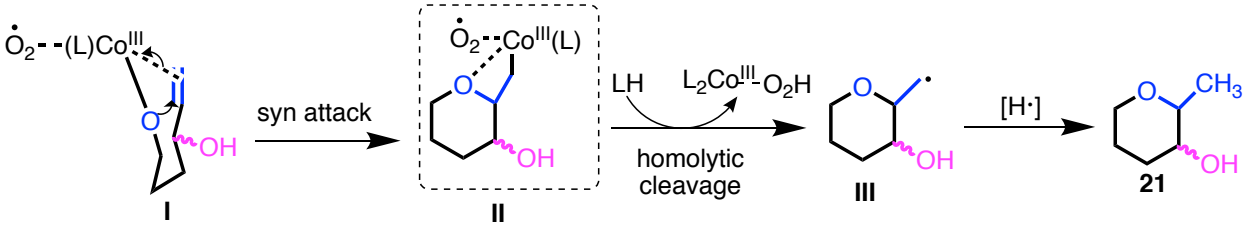


Figure 5. Proposed mechanism that leads to Co-C intermediate **II**.

Based on recent mechanistic studies from Ferreira's laboratory, the pi bond undergoes syn attack from oxygen upon coordination with cobalt catalyst followed by addition into Co(III) complex (Figure 5).[35] Addition of the cyclized product into Co(III) forms a covalent Co-C bond

(**II**), and the intermediate undergoes homolytic cleavage and ligand exchange to form a free radical and Co(III) peroxide complex. During our studies, we predicted that the free radical is trapped by a CHD hydrogen. However, difficulties with isolation is possibly due to presence of Co-C intermediate and an inability to overcome energy barriers to homolytically cleave the bond for access to the free radical and reductive termination. Here a gap in knowledge arose regarding catalyst regeneration, and reduction of Co(III) to Co(II).

Conclusion and Future Work:

Thus far, this project presents the synthesis of acyclic alkenol substrates with fair yields, the ability of Co(II)diketonate complexes to produce substituted THP rings from intramolecular cyclizations with reductive termination, and reaction conditions that will be optimized for satisfactory mass balance. Final cyclic ether products have not been successfully isolated, but ^{1}H NMR data has provided evidence that supports literature reports. We also concluded substrates that have an allylic alcohol appear to be moderately selective for trans configurations.

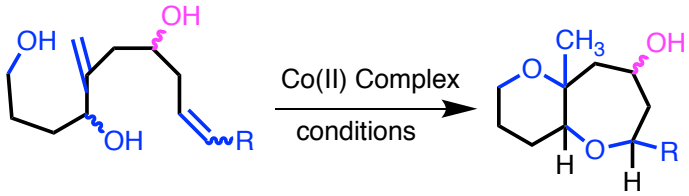


Figure 6. Acyclic substrates for future tandem cyclizations.

After THP products are successfully isolated, we will continue to build our library of alkenol substrates. Our goal is to strategically extend the alkyl chain, so brevenal's trans fused cyclic ether core can be produced with stereo- and regioselectivity in a tandem cyclizations (Figure 6). We also hope to explore a method for the reductive coupling of alkynes with aldehydes that is both enantioselective and regioselective. It is vital to access pure starting

material more efficiently and with fewer steps for cyclization studies. In addition to substrate synthesis, we will establish conditions to form 7-membered rings.

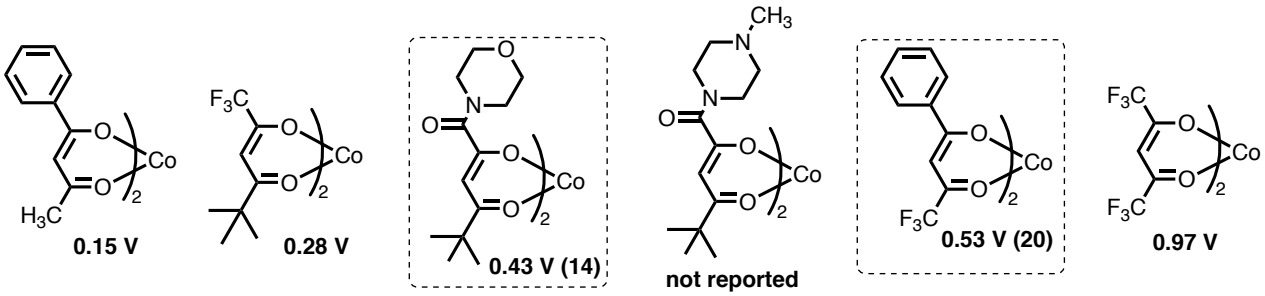


Figure 7. Redox potentials reported for various cobalt(II)diketonate complexes. Cyclization results for catalysts **14** and **21** are described herein.

As stated earlier, various Co(II) catalysts have been reported to successfully cyclize acyclic alkenol substrates to form 5-membered rings. Redox potentials have been reported for cobalt catalysts dependent upon a range of diketonate ligands.[36] Results herein have been obtained with cobalt catalysts **14** and **20** that have redox potentials of 0.53 and 0.43 V respectively. A gap in knowledge arises with alkenol substrates that have electron rich pi bonds from alkyl substituents. We will synthesize catalysts above and below the reported range for selective reactivity (Figure 7). It will also be important to consider steric effects. We will also work to discover the optimal concentrations, time, and temperatures for catalyst turnover and selectivity. Experiments that efficiently terminate the reaction and regenerate cobalt catalyst will be explored such as addition of traditional Co(III) to Co(II) reductants.[32] Isolation of organic compounds from cobalt residues will allow for complete characterization of THP compounds as we advance towards brevenal's complex trans fused polycyclic ether core.

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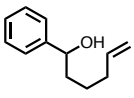
Experimental:

General Information:

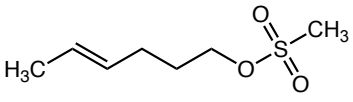
Compound numbering is consistent with the accompanying report. References herein refer exclusively to the supporting information. Flash chromatography purification was carried out using Siliaflash® P60 silica gel obtained from Silicycle. ^{1}H NMR data was consistent with published literature results, unless otherwise stated. ^{1}H NMR spectra were obtained from the Emory University NMR facility and recorded on INOVA 600 (600 MHz), Bruker 600 (600 MHz), INOVA 500 (500 MHz), Bruker 400 (400 MHz), INOVA 400 (400 MHz), and VNMR 400 (400 MHz). Chemical shifts (δ) are referenced using $CDCl_3$ as solvent (δ 7.26). Coupling constants *J* are given in Hz. Reaction progress was monitored via thin layer chromatography (tlc) on aluminum sheets coated with TLC Silica gel 60 F_{254} obtained from MilliporeSigma. Compounds were detected by staining with phosphomolybdic acid (PMA) stain. Anhydrous LiBr was dried overnight under vacuum at 110 ºC before use. Remaining commercial reagents were used without any further preparation. All reactions were carried out with oven-dried glassware and stir bar. Organic solutions were concentrated under vacuo using a water bath.

Synthesis of alkenols:

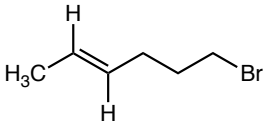


1-phenylpent-4-en-1-ol (4a):[25] Alkenyl bromide (1.2 equiv., 24.0 mmol, 2.85 mL) in dry THF (0.5 M) was added dropwise to magnesium turnings in a 100 mL oven-dried pear shaped flask under Ar atmosphere. The reaction was left to stir for 1 h. Next, the gray magnesium bromide solution was added dropwise to a solution of benzaldehyde (1.0 equiv., 20.0 mmol, 2.03 mL) and THF (0.5 M) in a dry 250 mL round bottom flask under inert conditions at 0 ºC. After addition, the solution was warmed to room temperature and left to stir overnight. The

reaction was monitored by TLC (10% EtOAc/hexanes). Upon completion, the reaction was quenched with saturated NH_4Cl, extracted with EtOAc (2x) and the combined organic extracts were washed with brine and dried over $MgSO_4$. After removing remaining solvents in vacuo, the crude light yellow product was purified by column chromatography (SiO_2,10% EtOAc/hexanes). The final product **4a**, was a light yellow oil (3.52 g, 60% yield). **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.68 – 7.26 (m, 5H), 5.78 (ddt, *J* = 17.0, 10.2, 6.7 Hz, 1H), 5.17 – 4.87 (m, 2H), 4.67 (ddd, *J* = 7.5, 5.8, 3.4 Hz, 1H), 2.13 – 1.97 (m, 2H), 1.92 – 1.65 (m, 2H), 1.62 – 1.27 (m, 2H).

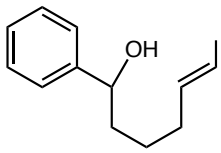


(E)-hex-4-en-1-yl methanesulfonate (6):[27] $MeSO_2Cl$ (1.8 mL, 23.2 mmol, 1.21 equiv.) was added dropwise to a solution of **5** (2.3 mL, 19.2 mmol, 1.0 equiv.), and Et_3N (3.3 mL, 23.2 mmol, 1.21 equiv.) in dry THF (40 mL) at 0 ºC. The solution was allowed to stir for 40 min, then warmed to room temperature and stirred for 30 min. Upon completion, the reaction was quenched with water (25 mL) and diluted with CH_2Cl_2 (100 mL). The organic layer was separated, and the aqueous layer was extracted with CH_2Cl_2 (2x). The combined organic extracts were dried with $MgSO_4$ and the solvent was evaporated to give crude **6** as a light yellow oil that was carried on to the next step (3.10 g, 91% yield). **^{1}H NMR** (400 MHz, $CDCl_3$) δ 5.54 – 5.44 (m, 1H), 5.42 – 5.32 (m, 1H), 4.22 (t, *J* = 6.5 Hz, 2H), 3.00 (s, 4H), 2.10 (dtt, *J* = 7.6, 6.4, 1.3 Hz, 2H), 1.81 (dt, *J* = 7.9, 6.6 Hz, 2H), 1.65 (dq, *J* = 6.3, 1.3 Hz, 3H).

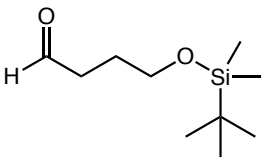


(Z)-6-Bromo-2-hexene (7):[27] Anhydrous LiBr was dried overnight at 110 ºC under vacuum (2.98 g, 33.8 mmol, 3.0 equiv.), then poured into a stirred solution of **6** (2.00 g, 11.28 mmol, 1.0 equiv.) in dry THF (40 mL). The solution was refluxed for 4h, or until all the starting material was consumed by TLC (1:4 EtOAc/hexanes). Upon completion, the reaction

mixture was cooled and pentane was added (200 mL). The resulting solution was washed with water, dried with $MgSO_4$ and the solvent was evaporated to yield crude **7** as a light yellow oil. The crude oil was applied to a silica plug and washed with EtOAc to yield **7** as a clear oil (0.828 g, 45% yield). **^{1}H NMR** (400 MHz, $CDCl_3$) δ 5.83 – 5.47 (m, 1H), 5.42 – 5.25 (m, 2H), 3.40 (t, *J* = 6.8 Hz, 5H), 2.13 (dt, *J* = 6.6, 1.3 Hz, 3H), 2.02 – 1.74 (m, 5H), 1.65 (dq, *J* = 6.3, 1.3 Hz, 7H).

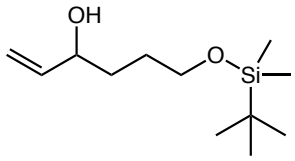


(E)-1-phenylhex-4-en-1-ol (4b):[25] Alkenyl bromide **7** (2.45 mmol, 1.2 equiv.) in dry THF (0.5 M) was added dropwise to magnesium turnings. The reaction was left to stir for 1 h. The gray magnesium bromide solution was added to a solution of benzaldehyde (2.04 mmol, 1.0 equiv.) and dry THF (0.5 M). After addition, the solution was warmed to room temperature and left to stir overnight. The reaction was monitored by TLC (10% EtOAc/hexanes). Upon completion, the reaction was quenched with saturated NH_4Cl, extracted with EtOAc (2x) and the combined organic extracts were washed with brine and dried over $MgSO_4$. After removing remaining solvents in vacuo, the crude light yellow product was purified by column chromatography (SiO_2, 10% EtOAc/hexanes). The final product **4b** was a light yellow oil (35% yield). **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.38 – 7.26 (m, 5H), 5.42 – 5.37 (m, 2H), 4.67 (dd, *J* = 3.1, 1.7 Hz, 1H), 1.86 – 1.65 (m, 2H), 1.64 – 1.62 (m, 3H), 1.54 – 1.41 (m, 2H), 1.42 – 1.14 (m, 2H).

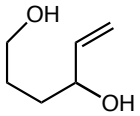


4-((tert-butyldimethylsilyl)oxy)butanal (10):[28] To a solution of **9** (2.30 mL, 10.0 mmol, 1.0 equiv.) in dry CH_3CN (10 mL), $Cu(MeCN)_4OTF$ (5% in 10 mL CH_3CN), 2,2' dipyridyl (5% in 10 mL CH_3CN), TEMPO (5% in 10 mL CH_3CN), and N-methyl imidazole

(10% in 10 mL CH_3CN) was added. The solution stirred rapidly for 5 h at room temperature and open to the air. Upon completion confirmed by TLC (10% EtOAc/hexane), solvent was removed in vacuo, and crude mixture was filtered through a silica plug and washed with EtOAc to yield aldehyde **10** as a clear oil (1.82 g, 90% yield). **^{1}H NMR** (600 MHz, $CDCl_3$) δ 9.79 (t, *J* = 1.7 Hz, 1H), 3.65 (t, *J* = 6.0 Hz, 2H), 2.50 (td, *J* = 7.1, 1.8 Hz, 2H), 1.89 – 1.82 (m, 2H), 0.88 (s, 10H), 0.04 (s, 6H).



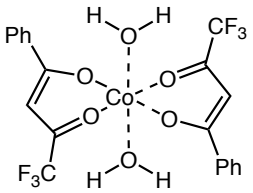
6-((tert-butyldimethylsilyl)oxy)hex-1-en-3-ol (12):[29] To a solution of vinyl magnesium bromide (1M in THF, 10.19 mmol, 1.25 equiv.), **10** was added dropwise over 15 min. The reaction was stirred for 5 min, then warmed to 0 ºC and stirred for 15 min. After starting material was consumed verified by TLC (10% EtOAc/hexanes) 2-propanol was added, followed by ether and NH_4Cl. Next, the solution was extracted with ether (3x), washed with brine, diluted with hexanes, and dried over sodium sulfate. Solvent was removed via vacuo to afford a yellow oil (1.88 g, 90% yield). **^{1}H NMR** (400 MHz, $CDCl_3$) 5.88 (ddd, *J* = 17.3, 10.4, 5.9 Hz, 1H), 5.24 (dt, *J* = 17.2, 1.6 Hz, 1H), 5.10 (dt, *J* = 10.4, 1.5 Hz, 1H), 4.23 – 4.05 (m, 1H), 3.66 (t, *J* = 5.9 Hz , 2H), 2.67 – 2.61 (m, 1H), 1.73 – 1.53 (m, 4H), 0.90 (S, 9H), 0.07 (s, 6H).



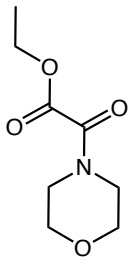
hex-5-ene-1,4-diol (4c):[18] **12** was dissolved in THF and cooled to 0 ºC. Acetic acid (13.02 mmol, 2.0 equiv.) was added followed by TBAF (9.77 mmol, 1.5 equiv). The solution was gradually warmed to room temperature and left to stir overnight. Solvent was removed via vacuo and the resulting oil was purified by column chromatography (SiO_2, 100% EtOAc) to yield **4c** as a light yellow oil (0.17 g, 62% yield). **^{1}H NMR** (500 MHz, $cdcl_3$) δ 5.89 (dddt, *J* =

17.1, 10.5, 6.0, 1.7 Hz, 1H), 5.25 (ddd, *J* = 17.2, 1.6 Hz, 1H), 5.12 (ddd, *J* = 10.4, 1.5 Hz, 1H), 4.21 – 4.12 (m, 1H), 3.75 – 3.63 (m, 2H), 2.20 (s, 2H), 1.86 – 1.52 (m, 4H).

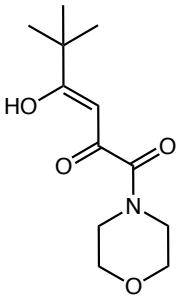
Synthesis of cobalt catalysts:



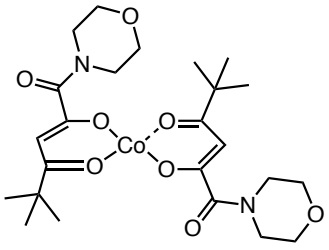
Bis-[1,1,1-trifluoro-4-phenyl-2-(oxo-kO)- but-3-en-4-(olato-κO)]cobalt(II) dehydrate (14):[25] Trifluoro diketonate ligand **13** (2.01 g , 9.27 mmol, 2.1 equiv.) in 6.0 mL of ethanol was added to an aqueous solution of cobalt (II) acetate tetrahydrate (1.11 g, 2.07 mmol, 1.0 equiv., in 20 mL H_20). The reaction was left to stir at 20 ºC for 1 h. After completion, the orange precipitate was filtered and washed with hexanes to give **14** (2.83 g, 90% yield).



Ethyl 2-morpholino-2-oxoacetate (17):[31] To a solution of morpholine **3** (0.87 mL, 10 mmol) and Et_3N (1.4 mL, 10 mmol) in CH_2Cl_2 (20 mL) at 0 ºC, **15** (1.5 mL, 10 mmol) was added. The reaction was left to stir at room temperature for 22 h. Next, the reaction mixture was washed with 1 M HCl (2x), saturated $NaHCO_3$, and brine then dried with $MgSO_4$. After removing solvent in vacuo, amide **17** was recovered as an orange oil (50% yield). **^{1}H NMR** (400 MHz, $CDCl_3$) δ 4.33 (q, *J* = 7.2 Hz, 1H), 3.72 (qd, *J* = 5.0, 2.3 Hz, 2H), 3.67 – 3.63 (m, 1H), 3.50 – 3.43 (m, 1H), 1.36 (t, *J* = 7.2 Hz, 1H).



5,5-dimethyl-1-morpholinohexane-1,2,4-trione (19):[31] A solution of t-BuOK (1.70 g, 15 mmol, 2.1 equiv.) in THF (13.3 mL) was added dropwise to a solution of amide **17** (1.35 g, 7.22 mmol, 1.0 equiv.) and pinacolone **18** (1.0 mL, 7.22 mmol, 1.0 equiv.). After 3 h, AcOH (1.5 mL, 26 mmol, 3.6 equiv.) was added dropwise and the resulting reaction mixture was filtered and the solids were washed with $NaHCO_3$ and brine, dried with $MgSO_4$. Excess solvent was removed in vacuo to yield crude **19** (modp) as a crude yellow oil. **^{1}H NMR** (400 MHz, $CDCl_3$) 6.03 (s, 1H), 3.80 – 3.60 (m, 8H), 1.21 (s, 9H).

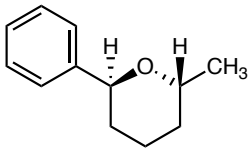


bis(1-morpholinocarbamoyl-4,4-dimethyl-1,3-pentanedionato)cobalt(II) (20):[37] MODP ligand **19** (2.54 mmol, 2.0 equiv.) in 15.9 mL of toluene was added to an aqueous solution of cobalt (II) acetate tetrahydrate (1.27 mmol, 1.0 eq.) in H_2O (4.0 eq., 0.9 mL) after 30 min. The reaction was left to stir at 20 ºC for 23 h. Hexanes (25 mL) were added, and the light pink precipitate was filtered and washed with hexanes to give **20** (0.69 g, 69% yield).

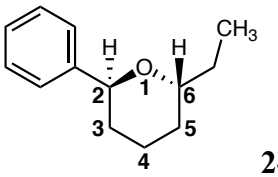
Cobalt catalyzed cyclization products:

General procedure: Catalyst **14** was dissolved in CHD (0.05 M) and heated to 65-75 ºC under reflux. Once the orange solution turned green, alkenol (1.0 eq.) dissolved in toluene (1.0 M) was added. The resulting solution was left to stir under reflux for 22-48 h. Next, the mixture was cooled to room temperature, and solvent was removed via vacuo for further TLC and ^{1}H NMR analysis.

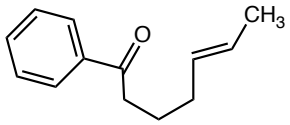
Note: ^{1}H NMR data reported from crude spectra due to difficulty with separation of inorganic products from organic products.



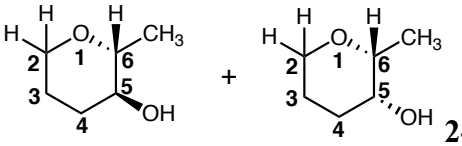
6-methyl-2-phenyltetrahydropyran (21a):[25] **^{1}H NMR** (400 MHz; $CDCl_3$): 7.40-7.25 (m, 5H), 4.87 (t, J = 5.3 Hz, 1H), 3.95 (qd, J = 6.4, 3.7 Hz, 1H), 1.91-1.42 (m, 6H), 1.27 (d, J = 6.5 Hz, 3H).



2-ethyl-6-phenyltetrahydro-2H-pyran (21b): ^{1}H NMR (400 MHz; $CDCl_3$): 4.82 (t, C2: 1H) and 3.63 ppm (m, C6: 1H).

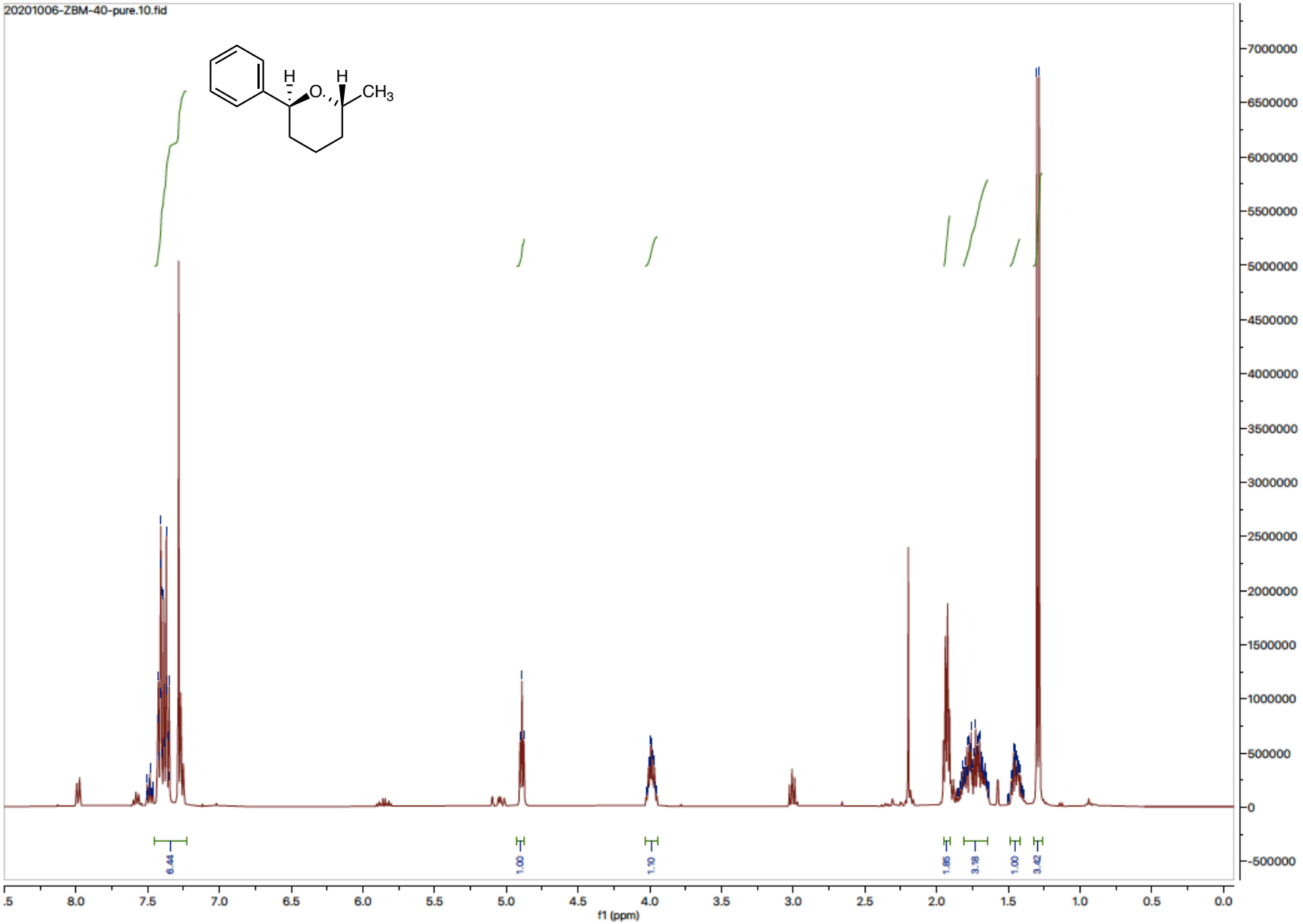


(E)-1-phenylhept-5-en-1-one (22):[38] **^{1}H NMR** (400 MHz; $CDCl_3$): 7.95-734 (m, 5H), 5.43 (m, 1H), 2.96 (t, J = 7.4 Hz, 2 H), 2.08 (m, 2H), 1.80 (m, 2H) 1.65 (m, 3H).



2-methyltetrahydro-2H-pyran-3-ol (21c, 21c', 1:2 cis/trans):[33] **^{1}H NMR (400 MHz; $CDCl_3$):**[33] 3.99-3.71 (m, C2: 2H, C5: 1H, C6: 1H),

trans-diastereomer: 1.26 (d, J = 5.8 Hz, C6: 3 H), *cis*-diastereomer: 1.14 ppm (d, J = 6.5 Hz, C6: 3 H).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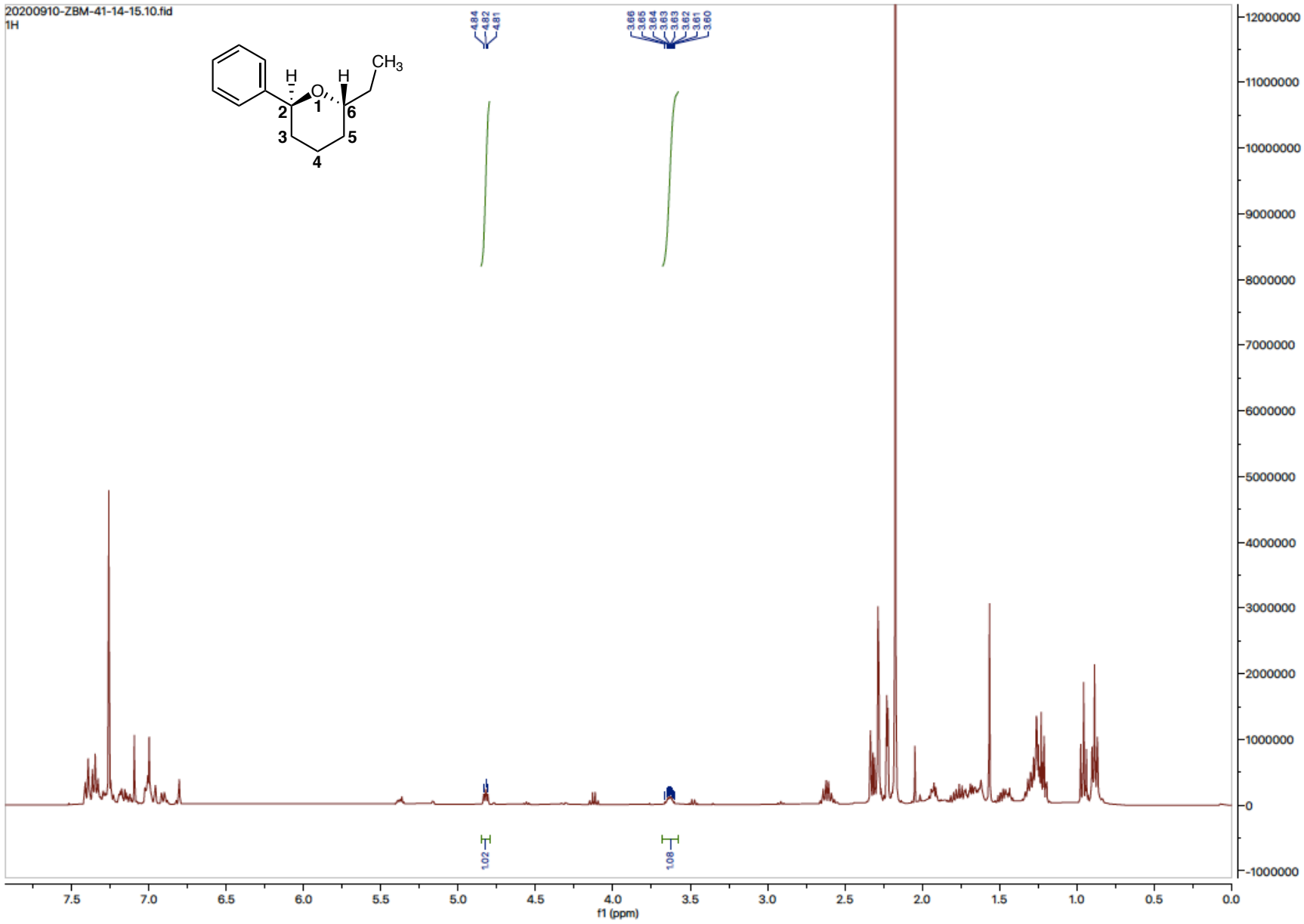
f1 (ppm)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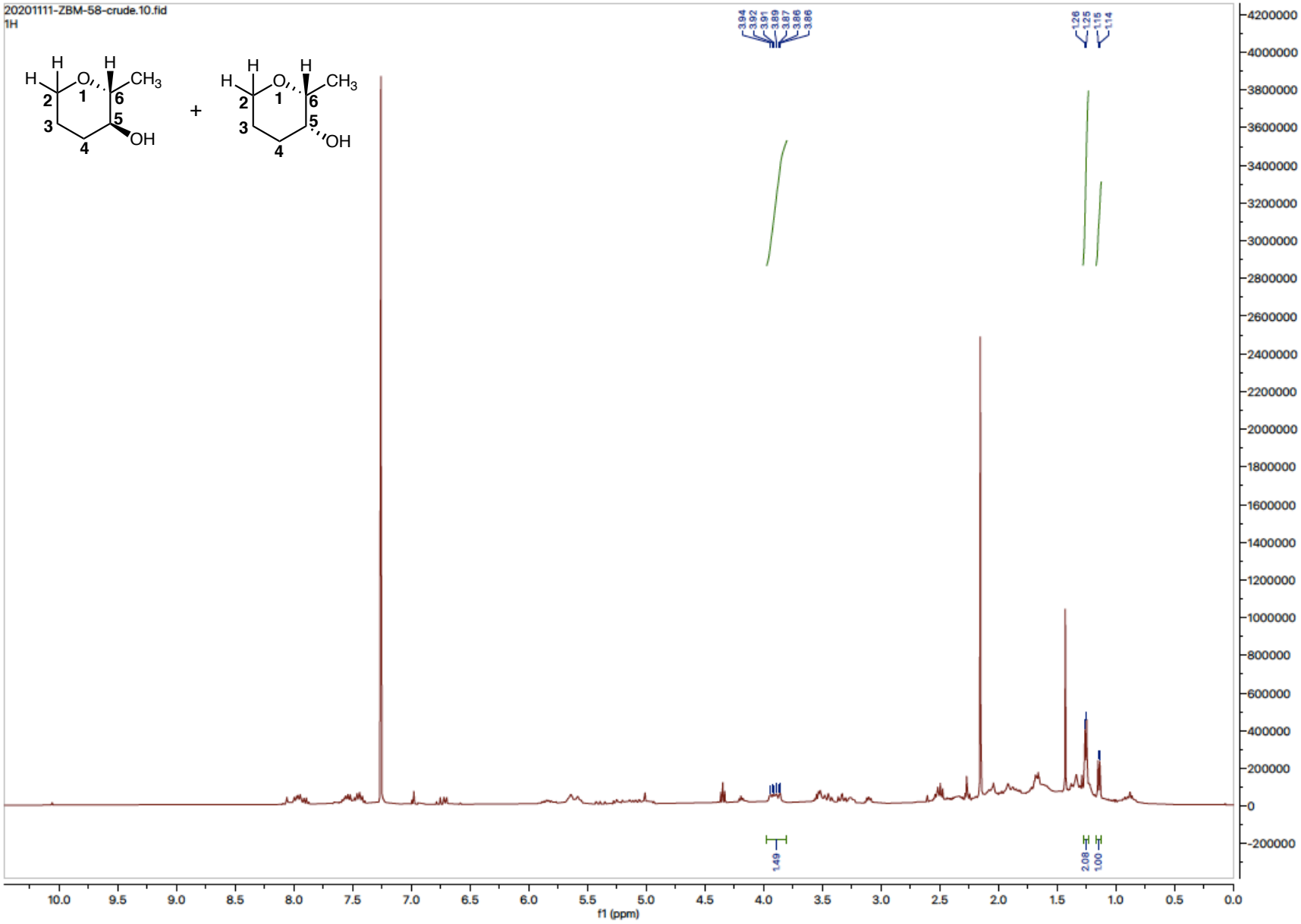
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