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Cycloaddition Reactions of Cobalt-Complexed Macrocyclic Alkynes: The Transannular Pauson–Khand Reaction

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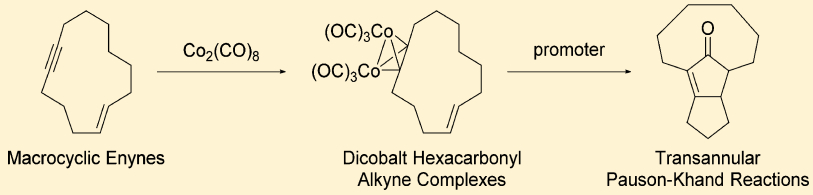
Supporting Information



ABSTRACT: The Pauson–Khand reaction is a powerful tool for the synthesis of cyclopentenones through the efficient [2 + 2 + 1] cycloaddition of dicobalt alkyne complexes with alkenes. While intermolecular and intramolecular variants are widely known, transannular versions of this reaction are unknown and the basis of this study. Macrocyclic enyne and dienyne complexes were readily synthesized by palladium(II)-catalyzed oxidative macrocyclizations of bis(vinyl boronate esters) or ring-closing metathesis reactions followed by complexation with dicobalt octacarbonyl. Several reaction modalities of these macrocyclic complexes were uncovered. In addition to the first successful transannular Pauson–Khand reactions, other intermolecular and transannular cycloaddition reactions included intermolecular Pauson–Khand reactions, transannular [4 + 2] cycloaddition reactions, intermolecular [2 + 2 + 2] cycloaddition reactions, and intermolecular [2 + 2 + 1 + 1] cycloaddition reactions. The structural and reaction requirements for each process are presented.

INTRODUCTION

Of the modes of reactivity exhibited by dicobalt hexacarbonyl alkyne complexes, the most useful and well-studied is the Pauson–Khand (PK) reaction. The reaction allows for efficient synthesis of cyclopentenones from simple alkene and alkyne starting materials in the presence of dicobalt octacarbonyl catalyst or from alkenes and dicobalt hexacarbonyl alkyne complexes.[1] The method's utility and efficiency is demonstrated in enantioselective[2] and diasteoselective[3] variants, as well as many total syntheses.[4] Generally, intermolecular and intramolecular modes give complementary regiochemistries.[1c,5] Intermolecular PK reactions preferentially give cyclopentenones with large substituents at the α positions (Figure 1a). Intramolecular reactions of 1,6- and 1,7,-enynes give bicyclic 3,4-disubstituted cyclopentenones (Figure 1b). On the other hand, a transannular PK (TAPK) reaction would be expected to yield bridged tricyclic cyclopentenone derivatives (Figure 1c), but the reaction is unprecedented in the PK literature. Many formidable synthetic targets of this type exist, which provided us the impetus to discover this novel mode of reactivity.[6] Moreover, transannular reactions catalyzed or promoted by organometallic species are not well explored.[7] Since transannular reactions are exceptionally powerful at generating molecular complexity,[8] as exemplified by the transannular Diels–Alder reaction,[9,10] we seized this opportunity to expand the scope of these methodologies to the first transannular Pauson–Khand reactions and discovered an apparent large steric demand for this transformation.

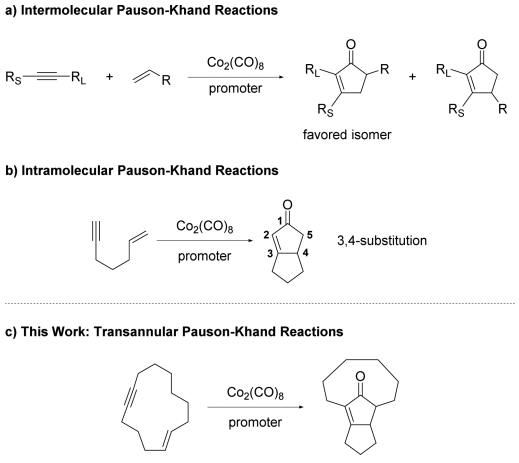


Figure 1. Regioselectivity of inter- and intramolecular Pauson–Khand reactions and proposed transannular Pauson–Khand reaction.

RESULTS

Macrocyclic dicobalt hexacarbonyl dienyne complexes served as entry points for the proposed TAPK reaction. We prepared dienynes employing our palladium-catalyzed oxidative macrocyclization of terminal bis(vinyl boronate esters) (Scheme 1).[11,12] Bis(vinyl boronate esters) were readily accessible from

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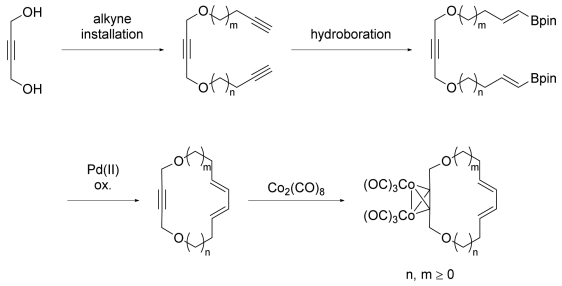
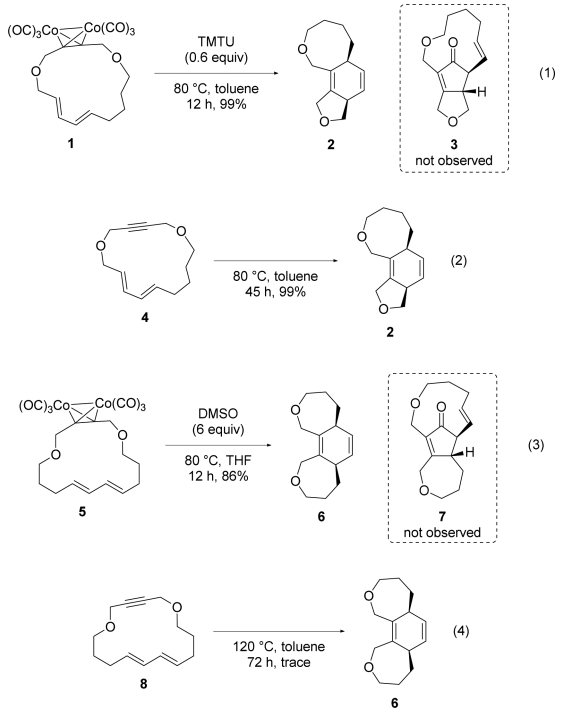
Scheme 1. Prior Syntheses of Macrocyclic Dicobalt Hexacarbonyl Dienyne Complexes[a]



[a]See refs 11 and 12 for synthetic details.

terminal bis(alkynes) by hydroboration catalyzed by Schwartz's reagent.[13] Alkyne complexes were prepared by the reaction of macrocyclic dienynes with dicobalt octacarbonyl at ambient temperature.[14]

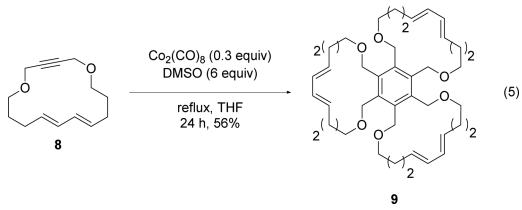
We previously reported the serendipitous discovery that dienyne complexes **1** and **5** undergo smooth cobalt-promoted transannular Diels–Alder (TADA) reactions (eqs 1 and 3)



under mild reaction conditions, rather than the TAPK reaction.[12] This mode of reactivity is due to low transition state distortion energies imparted on the diene and dienophile by their linking tethers and the strain release of those tethers in the transition state.[15] Choice of promoter to activate loss of a carbonyl group was critical for success of the reaction, as is known for many reactions with dicobalt hexacarbonyl alkyne complexes.[16] Tetramethylthiourea (TMTU)[17] and DMSO[18] were found to be the optimal promoters for **1** and **5**, respectively.

A critical question was whether the TADA reactions involved cobalt or if the promoters merely removed cobalt to allow standard thermal Diels–Alder reactions. Control TADA reactions of complexes **1** and **5** without promoter were less efficient. Complex **1** does not undergo the TADA reaction without a promoter, and product **6** was accessible only at elevated temperature from complex **5** in the absence of promoter. Reactions were less efficient without cobalt complexation as well. Cobalt-free dienyne **4** underwent the TADA reaction but required elevated temperatures and extended reaction times (eq 2). Dienyne **8** only gave trace amounts of the TADA product **6** upon heating at 120 °C for an extended period (eq 4). Thus, the reactions of complexes **1** and **5** were cobalt-promoted transannular [4 + 2] cycloaddition reactions.

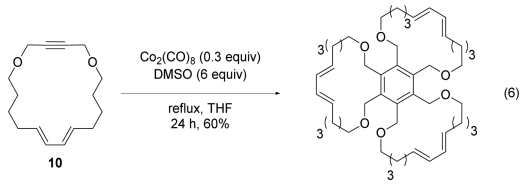
We next tested reaction conditions with free alkynes that were catalytic in dicarbonyl octacarbonyl for the TAPK mode of reactivity. Heating dienyne **8** in the presence of catalytic dicobalt octacarbonyl (0.3 equiv) gave trimer **9** from a [2 + 2 + 2] cycloaddition reaction in moderate yield (eq 5). Neither

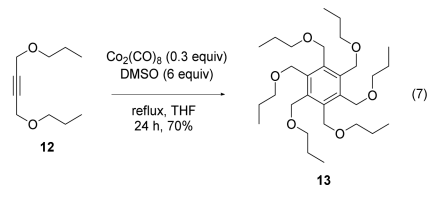


TADA or TAPK reaction products were observed. In contrast, the preformed dicobalt alkyne complex **5** underwent the TADA reaction under identical reaction conditions (eq 3).

This [2 + 2 + 2] cycloaddition reaction of **8** was not unexpected. Many transition metals are known to catalyze [2 + 2 + 2] cycloaddition reactions,[19] and cobalt is particularly efficient.[20] Specifically, dicobalt octacarbonyl has been used in many [2 + 2 + 2] cycloadditions.[21] Transannular [2 + 2 + 2] cycloadditions of macrocyclic triynes are also known;[22] however, to the best of our knowledge, this is the first example of an intermolecular cyclotrimerization involving a macrocyclic dicobalt hexacarbonyl alkyne complex.

The larger 18-membered dienyne **10**[12] was tested under the same reaction conditions. The [2 + 2 + 2] cyclotrimerization product **11** was obtained as the sole cycloaddition product in 60% yield (eq 6). Interestingly, this substrate also did not





undergo TADA or TAPK reactions. These cyclotrimerization reaction conditions were also applied to the nonmacrocyclic alkyne **12** providing the [2 + 2 + 2] cycloaddition product **13** in good yield (eq 7).

Benzene derivatives with hexa-(CH_2OR) substituents as found in **9**, **11**, and **13** are useful in a variety of applications.[23] The key hexasubstituted benzene pattern is found in sugar clusters with protein cross-linker properties,[21b] crown ethers

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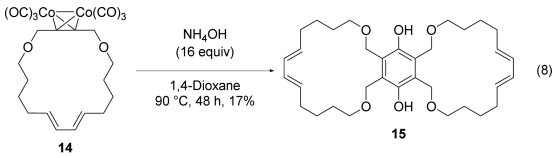
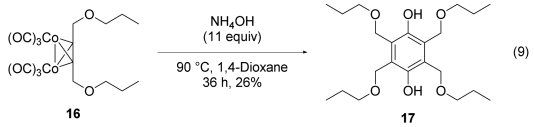
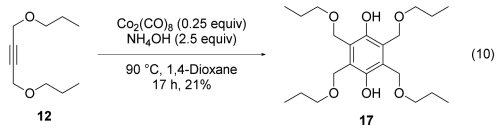
(or hexahosts for inclusion complexes),[24] active ligands for transition-metal catalysts,[25] dendrimers for production of scratch-free, self-standing cross-linked transparent films,[26] biodegradable polymers,[27] and metal−organic frameworks (MOFs).[28] The intermolecular [2 + 2 + 2] cycloaddition products derived from macrocyclic dienyne substrates warrant further investigation as novel structural motifs for these applications.

We predicted that different promoters could affect the CO dissociation step leading to alternative reaction pathways. The 18-membered diene **10**, shown to undergo a [2 + 2 + 2] cycloaddition in the presence of catalytic dicobalt octacarbonyl (eq 6), was tested as the dicobalt hexacarbonyl complex **14**[12] but failed to show productive reactivity with promoters such as DMSO, NMO, and TMTU. Finally, ammonium hydroxide was employed as a promoter,[29] and under these conditions a new mode of reactivity was uncovered. The [2 + 2 + 1 + 1] cycloaddition product **15** was formed as the sole identifiable product, albeit in low yield (eq 8). It is noteworthy that while



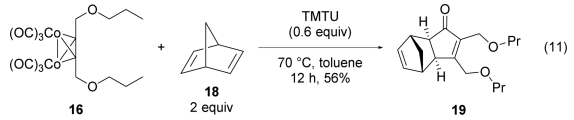




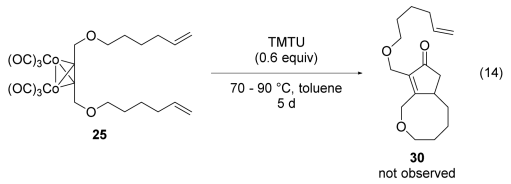
complex **14** and its cobalt-free analogue **10** participated in the [2 + 2 + 2] and [2 + 2 + 1 + 1] cycloaddition reactions (eq 6 and 8, respectively), neither gave a successful TADA reaction.[12] A non-macrocyclic example of the [2 + 2 + 1 + 1] process was also discovered by converting alkyne complex **16** to hydroquinone **17**, again in low yield (eq 9). Interestingly, this reactivity mode promoted by ammonium hydroxide was even observed for the cobalt-free alkyne **12** (eq 10) in the presence of catalytic dicobalt octacarbonyl.

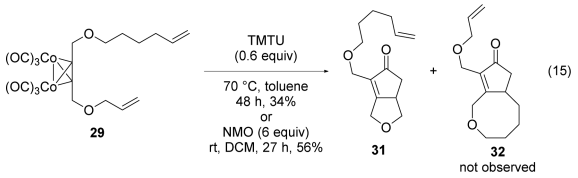
These results are significant due to the importance of hydroquinone derivatives[30] and the scarcity of hydroquinone or quinone syntheses mediated by cobalt−carbonyl complexes.[31] The reported examples of participation of $Co_2(CO)_8$ in hydroquinone/quinone synthesis are limited to dicobalt octacarbonyl-promoted intramolecular *rearrangement* of 1-(1,2-propadienyl)cyclopropanols to 1,4-hydroquinones[32] and synthesis of η^4-quinone cobalt complexes.[33] There have been no reports of $Co_2(CO)_8$ directly promoting hydroquinone synthesis via cycloaddition. Overall, the transformation of **14** to **15** (eq 8) in the presence of an amine promoter resembles the industrially significant hydroquinone synthesis process investigated by Reppe and co-workers in the 1940s.[34] Reppe's investigations showed that alkynes undergo [2 + 2+1 + 1] cycloaddition reactions with metal carbonyl complexes yielding 1,4-hydroquinones under high pressures of CO gas in the presence of water. Although $Fe(CO)_5$ is used most frequently, this process can be catalyzed by metal amine salts such as $[Fe(NH_3)_6][Co(CO)_4]_2$ or $[Co(NH_3)_6][Co(CO)_4]_2$.[34c] In addition, Liebeskind and co-workers demonstrated more recently that various quinones can be prepared by reacting alkynes with maleoylcobalt complexes carrying amino ligands.[35]

Propargylic heteroatom substituents are known to cause side reactions in PK reactions,[5a] which we suspected may prevent the TAPK process for substrates **1**, **5**, and **14**. We tested an acyclic model substrate with bis(propargylic ethers) in a control experiment to verify the ability of this functionality to undergo the PK reaction in our hands. Complex **16** reacted with 2 equiv of norbornadiene (**18**) in the presence of DMSO, NMO, or TMTU promoters to afford the intermolecular PK product **19**, but the best yield employed TMTU in toluene (eq 11). This result verified the viability of bis(propargylic ether) substrates and identified reaction conditions that could be used for subsequent PK reactions.

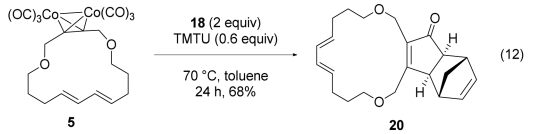


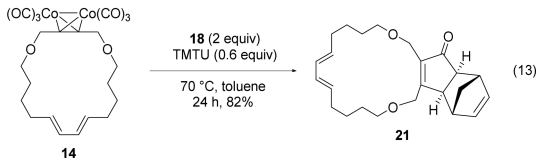
To verify that our macrocyclic complexes could undergo PK reactions, eqs 5 and 14 were tested under the intermolecular





PK reaction conditions employing TMTU in the presence of norbornadiene. To our delight, the complexes were quite reactive, and novel PK reaction products **20** and **21** were obtained in 68 and 82% yields, respectively (eqs 12 and 13).





These results provided two key results. First, the macrocyclic bis(propargylic ether) complexes efficiently participated in PK reactions. Second, and more importantly, the intermolecular PK reaction mode was favored over a transannular reaction mode. This suggested that further structural refinements would be required to achieve the desired TAPK process. This is a further example of how slight modification of reaction conditions gives unique reaction pathways for the macrocyclic

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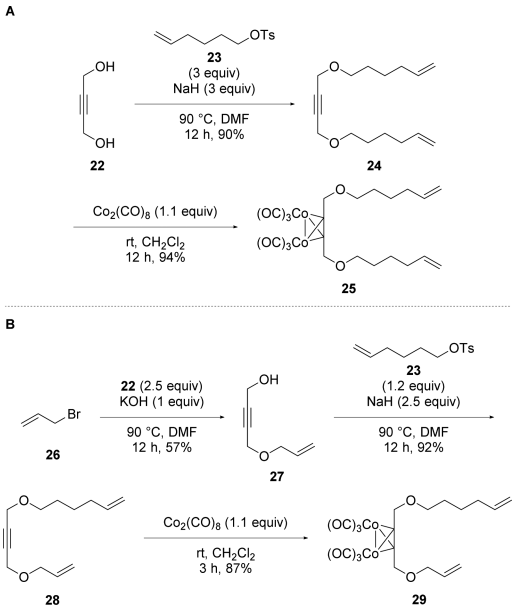
dicobalt hexacarbonyl dienyne complexes. Complex **5** previously underwent the transannular [4 + 2] reaction to give **6** in the presence of DMSO (eq 3), while complex **14** gave the [2 + 2 + 1 + 1] cycloaddition product **15** with ammonium hydroxide as the promoter (eq 8).

We next investigated the effect of chain length between the alkene and dicobalt hexacarbonyl alkyne moieties on the possible TAPK reactions of macrocyclic dienynes with propargylic ether linkers. Acyclic dienes **25** and **29** with propargylic ethers were prepared to determine ring sizes allowed in the intramolecular PK reaction (Scheme 2A and 2B,

Scheme 2. (A) Synthesis of Linear Dicobalt Hexacarbonyl Dienyne Complex 25; (B) Synthesis of Linear Dicobalt Hexacarbonyl Dienyne Complex 29

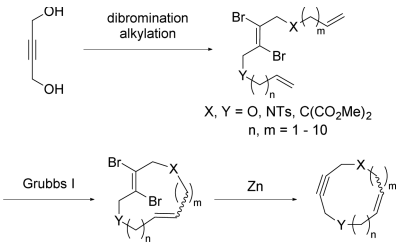


respectively). Complex **25** was prepared by double alkylation of diol **22**, followed by complexation with dicobalt octacarbonyl. A two-step sequential alkylation of **22** gave asymmetric dienyne **28**, which upon cobalt complexation gave complex **29**.

Gradually heating dienyne complex **25** in toluene over 5 days in the presence of TMTU gave a complex mixture of inseparable and unidentifiable compounds (eq 14). The expected intramolecular PK reaction product **30** could not be isolated or detected. In contrast, unsymmetrical acyclic dienyne complex **29** gave cyclopentenone product **31** in 34% yield in the presence of TMTU (eq 15). Regioisomer **32** from the reaction with the alkene separated by the longer tether which would form an unfavored 8-membered ring was not observed. This demonstrated that the linking chain's length would affect the TAPK process, rather than the bis(propargylic ether) unit, and that a successful TAPK reaction might require formation of a 5-membered ring fused at the 3,4 positions of the cyclopentenone ring.

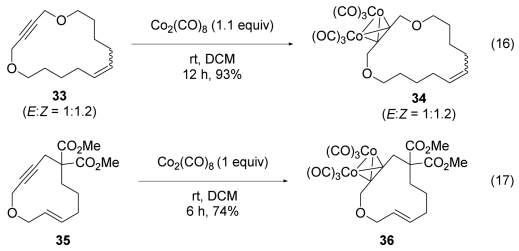
With this information in hand, and since macrocyclic dienyne complexes were shown to undergo transannular [4 + 2] cycloadditions, we expected that unsymmetrical cyclic enynes could undergo the desired TAPK reaction. Attempts to prepare cyclic enynes by ring-closing metathesis of linear dienynes were unsuccessful, likely due to a competitive intramolecular enyne metathesis pathway. Similar low yields were observed when dicobalt hexacarbonyl-protected dienyne complexes underwent metathesis, possibly due to carbon monoxide poisoning of the ruthenium catalyst. Our successful synthetic strategy involved ruthenium-catalyzed ring-closing metathesis of trienes, where the central alkyne unit was protected as a vicinal dibromoalkene (Scheme 3). Ring-closing metathesis gave cyclic dienes, which upon deprotection with zinc gave cyclic enynes.[36]

Scheme 3. Prior Synthesis of Enynes by Alkyne Protection, Ring-Closing Metathesis, and Deprotection[a]



[a]For details see ref 36.

We hypothesized that substrates with one short and one long linking chain between the alkene and alkyne moieties should be more likely to undergo TAPK reactions. Two new dicobalt hexacarbonyl complexes were prepared from enynes to test structural limitations for the TAPK reaction. Dicobalt hexacarbonyl complexes of cyclic enynes **33** and **35**[36] were easily prepared by complexation with dicobalt octacarbonyl to give **34** and **36** (eqs 16 and 17).



Treatment of three substrates with several PK reaction conditions including NMO established the basis for optimal chain lengths between the alkene and dicobalt hexacarbonyl moieties. As expected from the failed intramolecular PK reaction of complex **25** (eq 14), complex **34** was unable to form the fused eight-membered cyclopentenone TAPK product **37** (eq 18). Enyne **38**[36] was expected to form the fused five-membered cyclopentenone TAPK product **39** (eq 19) based on the successful intramolecular PK reaction of **29** to give **31** (eq 15), but did not do so. These data suggested the length of the second bridging chain should be modified to find an optimal TAPK substrate. The inability of complex **36** to undergo the TAPK reaction to give cyclopentenone **40** confirmed that the length of the second chain was an opportunity for further substrate modification (eq 20).

These results led us to predict that even when forming 5-membered rings fused at the 3 and 4 positions of the cyclopentenone, TAPK reactions may require significantly longer bridging chains between the 2 and 5 positions, a challenging reaction requiring formation of medium or large-sized rings in the TAPK product. Previously, the Krafft group demonstrated preparation of medium-sized rings in intramolecular PK reactions of 1,8-, 1,10-, and 1,11-enynes.

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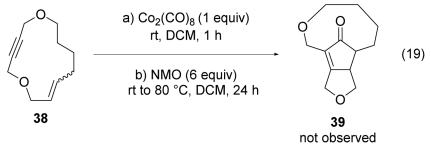
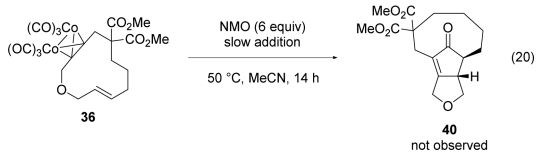
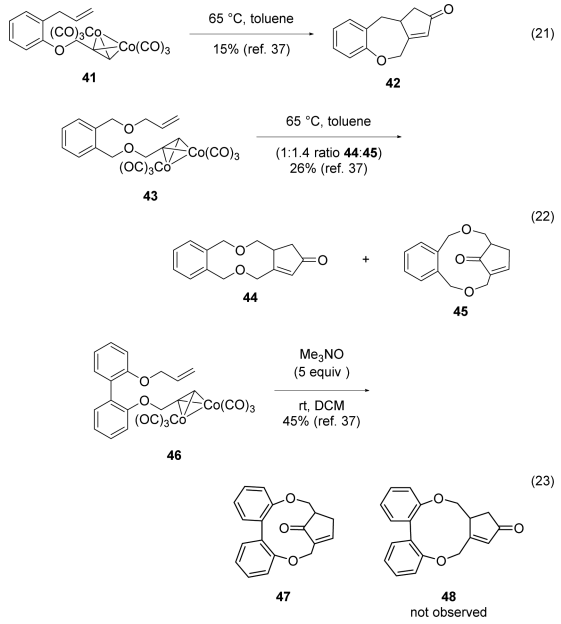




Intramolecular PK reactions were not successful for 1,9-enynes. Successful reactions stemmed from rigid aromatic linkers which placed the alkene and alkyne termini in close proximity to allow cyclization.[37] 1,8-Enyne complex **41** proceeded with the standard intramolecular regiochemistry giving 3,4-disubstituted cyclopentenone **42** (eq 21). On the other hand, complex **43**



gave a mixture of isomers **44** and **45** (eq 22), while **46** gave a single PK product as the 2,5 disubstituted cyclopentenone **47** (eq 23). This demonstrated that as the length of linking chains increased, regioselectivity could switch to favor 2,5-disubstituted cyclopentenones with similar regioselectivity to intermolecular reactions.

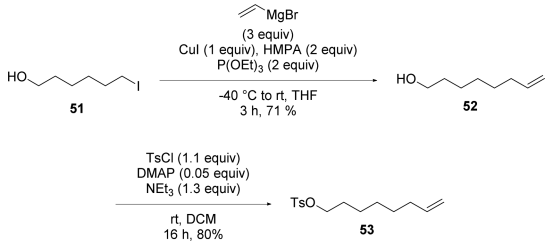
With this information in mind, we designed substrates **49** and **50**, expecting that a small linking chain would favor formation of a 5-membered ring fused at the 3 and 4 positions of the cyclopentenone while a significantly longer linking chain would bridge the 2 and 5 positions (Figure 2). Substrate **50** benefits from incorporation of the rigid aryl group to restrict the conformational freedom for cyclization similar to the work of the Krafft group (eqs 21–23).[37]

We embarked upon the synthesis of TAPK substrates **49** and **50**. Preparation of **49** was achieved by cobalt complexation of

Figure 2. Designed substrates for the TAPK reaction.

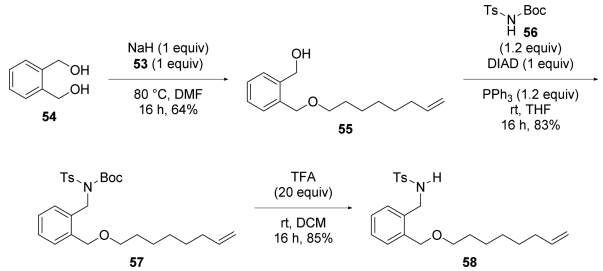
the known alkyne obtained during our previous studies on macrocyclic enyne synthesis.[36] The synthesis of **50** began from alcohol **51** (Scheme 4).[38] Gilman coupling with vinyl magnesium bromide followed by tosylation gave the requisite terminal alkene linker **53**.

Scheme 4. Synthesis of Alkene 53



The aryl backbone of **50** originated from diol **54** which was attached to alkene **53** by an ether linkage found in **55** (Scheme 5). A Mitsunobu reaction gave the Boc-protected sulfonamide **57** which was deprotected with trifluoroacetic acid to give sulfonamide **58**.

Scheme 5. Synthesis of Sulfonamide 58



Dibromoalkene **61**, prepared by alkylation of malonate **59**, was attached to the aryl linker **58** to form the substituted dibromoalkene **62** (Scheme 6). Metathesis with Grubbs second generation catalyst gave macrocyclic alkene **63** as a 3:1 *E*:*Z* ratio in good yield. Facile deprotection with zinc gave the cyclic enyne **64** which was converted to the dicobalt hexacarbonyl alkyne complex **50**.

With complexes **49** and **50** in hand we tested the TAPK reactions. When complex **49** was submitted to the NMO-promoted PK reaction conditions we were delighted to find that the TAPK reaction had occurred to give the tricyclic cyclopentenone **65** in a 44% yield (eq 24). Lower yields were obtained with TMTU or NMO in DCM. Similarly, enyne complex **50**, featuring the same required structural characteristics as **49** plus the rigid aryl linker, gave the TAPK reaction product **66** in 40% yield (eq 25) using slow addition of NMO promoter. In this case, the starting 3:1 *E*/*Z* ratio, derived from the limited selectivity in the metathesis macrocyclization reaction, led to a 5.5:1 diastereomeric ratio of products.

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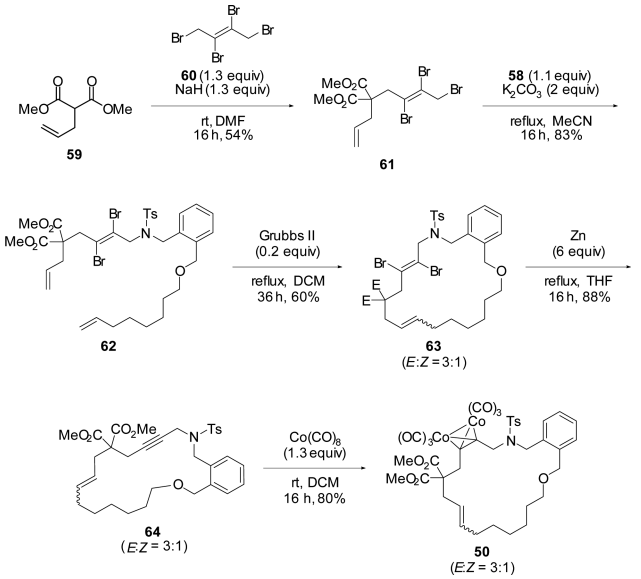
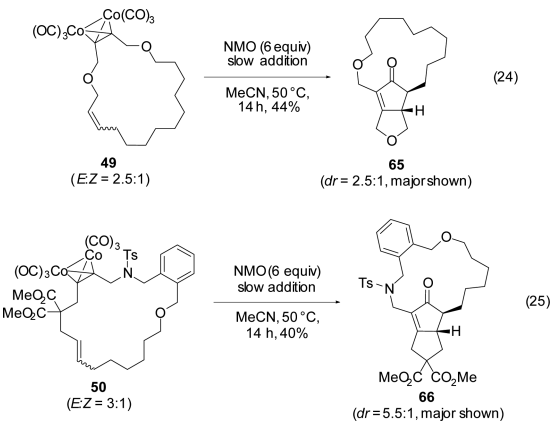
Scheme 6. Synthesis of Dicobalt Alkyne Complex 50



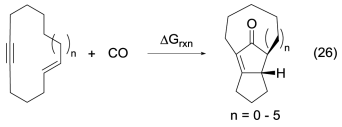


Thus, the *E*-isomer undergoes a more productive TAPK reaction than the *Z*-isomer, as shown by the increase in the diastereomeric ratio compared to the starting material.

DISCUSSION

The TAPK reaction was successfully demonstrated in two cases. The cyclic enyne substrates required one long chain and one three-atom chain linking the alkene and alkyne moieties. Decreasing the length of the long linking chain rendered the TAPK unsuccessful. To improve our understanding of the TAPK reaction we sought to determine whether the unsuccessful TAPK reactions were favored thermodynamically, yet the steric interactions between the dicobalt carbonyl moiety and the linking chain disfavored the transformation kinetically.

Calculations were performed to determine the change in Gibbs free energy for the formation of TAPK products from cyclic enynes and carbon monoxide using substrates with a variety of linking chains bridging the 2 and 5 positions of the cyclopentenone (eq 26, Figure 3).[39] Energies of products and



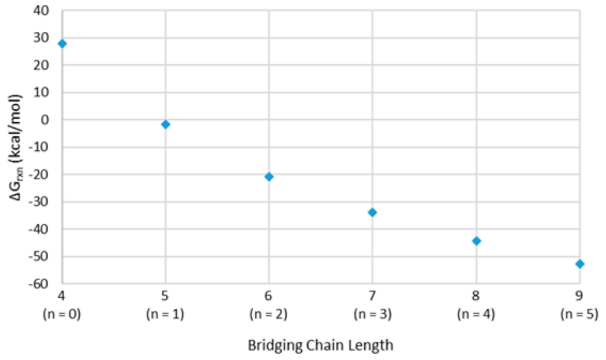


Figure 3. Gibbs free energy of reaction for TAPK products (energies calculated at the M06-2X/6-311+G(d,p)//B3LYP/6-31G(d) level of theory).

reactants were calculated at the M06−2*x*/6-311+G(d,p)//B3LYP/6-31G(d) level of theory.[40] The linking chains ranged from 4 (n = 0) to 9 (n = 5) atoms. As the number of carbon atoms in the linking chain increases, the Gibbs free energy of the TAPK reaction decreases. This is attributed to decreasing ring strain, although none of these products are technically Bredt's Rule violations.[41] The computational results show that ring sizes where n = 0 (or smaller) are disfavored thermodynamically with a positive Gibbs free energy, whereas ring sizes with n = 1 and larger are thermodynamically favorable with negative Gibbs free-energies.

According to the calculation results, substrates such as **36** and **38** could be expected to undergo the TAPK reaction due to a thermodynamically favorable reaction, although experimentally they do not. We propose that these TAPK reactions are disfavored kinetically due to the steric demands of the dicobalt carbonyl moiety and macrocylic ring in the reaction mechanism (Scheme 7).[1c,42] Although each macrocyclic substrate is achiral, the two faces of the alkene are enantiotopic and the two cobalt atoms are enantiotopic, so there is the potential for diastereomeric alkene insertion adducts, of which one is shown. However, they merely lead to enantiomeric products. Enyne complexes such as **49** and **50** must have enough conformational freedom to prevent unfavorable steric interactions between the linking chain and the dicobalt carbonyl moiety during the TAPK reaction. In addition, there could be conformational constraints on the reaction intermediates requiring specific geometries of substituents. Dienyne substrates **1** and **5** that led to cobalt-promoted [4 + 2] cycloaddition products **2** and **6** (eq 1 and 3) rather than PK adducts are the consequence of a cobalt 1,3-shift rather than a CO insertion (Scheme 7). Further studies will be required to discriminate between these possibilities.

CONCLUSIONS

We found the first examples of the transannular Pauson−Khand reaction and determined that the reaction has considerable steric requirements necessitating a long chain linking the 2,5 positions of the tricyclic cyclopentenone product. In a smaller macrocyclic ring substrate, an intermolecular Pauson−Khand reaction could outcompete a transannular reaction process. During development of the transannular Pauson−Khand reaction, we also discovered cobalt-promoted [4 + 2] cycloaddition reactions, dicobalt octacarbonyl catalyzed [2 + 2 + 2] cycloaddition reactions of macrocyclic dienynes, and the first direct hydroquinone

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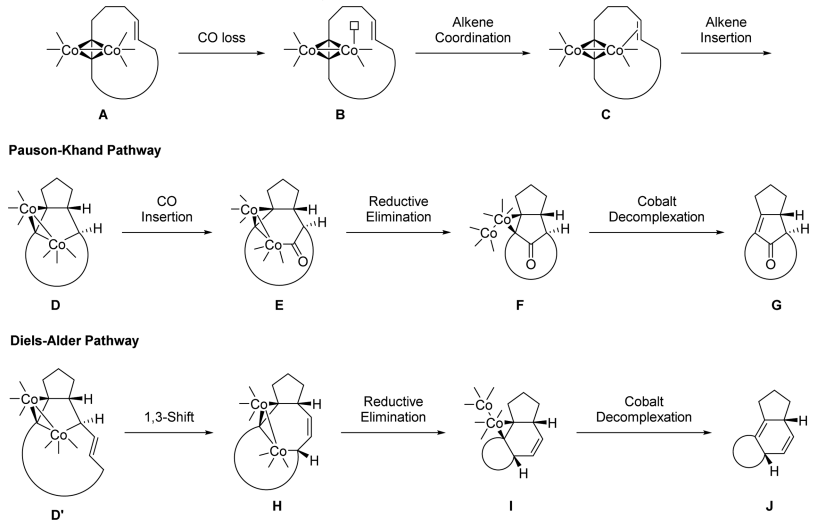
Scheme 7. Mechanisms of Cobalt-Promoted Pauson–Khand and [4 + 2] Reactions.[a,b]



[a]CO ligands omitted for clarity. [b]Substrates with *trans*-alkenes shown.

synthesis from dicobalt hexacarbonyl alkyne complexes via a [2 + 2+1 + 1] cycloaddition reaction. Only minor modifications of the reaction conditions and substrates allowed switching between the different reaction modalities. Overall, these new transformations of macrocyclic enynes and dienynes will provide a platform for further explorations of transition metal-mediated macrocycle chemistry.

EXPERIMENTAL SECTION

General Information. All commercial compounds were used as received unless otherwise noted. Dicobalt octacarbonyl was purchased from Strem Chemicals, Inc., as a solid, stabilized with 1–5% hexane, and was stored at 0 °C. Dichloromethane, triethylamine, and acetonitrile were purified by distillation over CaH_2. Methanol was distilled over Mg. Tetrahydrofuran and ether were distilled prior to use from sodium-benzophenone ketyl. All reactions were carried out in flame-dried glassware under a nitrogen atmosphere, unless otherwise stated. Schwartz's catalyst (Strem) and metathesis catalysts (Materia) were stored in a glovebox and used as received. Reactions were monitored using TLC and the plates were developed using vanillin, cerium ammonium molybdate, or potassium permanganate stains. Column chromatography was performed using silica gel (40–63 μm) and reagent grade solvents without deactivation, unless noted. NMR spectra were recorded at 400 or 500 MHz as noted and calibrated to the solvent signal ($CDCl_3$ δ = 7.26 ppm or C_6D_6 δ = 7.16 ppm for ^{1}H NMR, and $CDCl_3$ δ = 77.0 ppm or C_6D_6 δ = 128.1 for ^{13}C NMR). Multiplicities are indicated by s (singlet), d (doublet), t (triplet), q (quartet), p (pentet), m (multiplet), or b (broadened). IR spectra were recorded with an ATR attachment and selected peaks are reported in cm^{-1}. High resolution mass spectral data was recorded with an IonSense ID-CUBE DART source or an Agilent 6530 Q-TOF ESI.

Safety. Experiments contained in this section were conducted with proper personal protective equipment (gloves, lab coat, safety glasses) and engineering controls (fume hood). Hazardous substances used in this experimental include Schwartz's reagent (Cp_2ZrHCl, water reactive), lithium aluminum hydride (pyrophoric), trifluoroacetic acid (acute toxin), toluene (reproductive toxin), 1,4-dioxane (carcinogen), tetrahydrofuran (acute toxin), dichloromethane (carcinogen), allyl bromide (acute toxin), ammonium hydroxide (acute toxin), dicobalt octacarbonyl (acute toxin), tetramethyl thiourea (acute toxin), sodium hydride (pyrophoric), dimethylformamide (reproductive toxin), and vinylmagnesium bromide (1 M, hexanes, pyrophoric).

Trimer 9. Dienyne **8** (158 mg, 0.72 mmol)[12] was dissolved in THF (14 mL). Dicobalt octacarbonyl (74 mg, 0.21 mmol) and DMSO (0.3 mL, 4.30 mmol) were added, and the solution was refluxed for 24 h. Solvent was removed in vacuo, and column chromatography with 4:1 hexanes/EtOAc gave 88 mg (56% yield) of a white solid: ^{1}H NMR (400 MHz, $CDCl_3$, ppm) δ 6.23–6.16 (m, 6H), 5.65–5.55 (m, 6H), 4.57 (s, 12 H), 3.45 (t, J = 4.8 Hz, 12H), 2.22 (td, J = 6.8, 6.0 Hz, 12 H), 1.67–161 (m, 12H); ^{13}C NMR (100 MHz, $CDCl_3$, ppm) δ 138.1, 132.0, 130.8, 69.4, 66.9, 30.9, 28.6; IR (neat ATR) 2908, 2851, 1107, 1085, 983; HRMS (DART) m/z [M + H]$^+$ calcd for $C_{42}H_{61}O_6$ 661.4463, found 661.4447.

Trimer 11. Dienyne **10** (43 mg, 0.17 mmol)[12] was dissolved in THF (4 mL). Dicobalt octacarbonyl (18 mg, 0.05 mmol) and DMSO (0.07 mL, 1.04 mmol) were added, and the solution was refluxed for 24 h. Solvent was removed in vacuo, and column chromatography with 6:1 hexanes/EtOAc gave 26 mg (60% yield) of a white solid: ^{1}H NMR (400 MHz, $CDCl_3$, ppm) δ 6.11–6.04 (m, 6H), 5.54–5.47 (m, 6H), 4.47 (s, 12H), 3.48 (t, J = 8.0 Hz, 12H), 2.15 (td, J = 7.2, 4.4 Hz, 12H), 1.66–1.59 (m, 12H), 1.49–1.42 (m, 12H); ^{13}C NMR (100 MHz, $CDCl_3$, ppm) δ 137.7, 132.4, 131.3, 71.1, 66.0, 33.0, 28.3, 23.8; IR (neat ATR) 2927, 2857, 1443, 1356, 1081, 989, 907, 727; HRMS (DART) m/z [M – H]$^-$ calcd for $C_{48}H_{71}O_6$ 743.5256, found 743.5223.

1,4-Dipropoxybut-2-yne (12). But-2-yne-1,4-diol (1.07 g, 12.5 mmol) was dissolved in a H_2O/DMSO mixture (5 mL/20 mL) and cooled to 0 °C. Potassium hydroxide (1.75 g, 31.2 mmol) was added prior to dropwise addition of 1-bromopropane (2.5 mL, 27.5 mmol). The solution was warmed to rt and stirred for 48 h. The reaction mixture was diluted with water and extracted with diethyl ether. Organic extracts were washed with brine, dried over $MgSO_4$, and filtered through a short silica plug. Removal of solvent in vacuo gave 1.67 g (78% yield) of the known[43] colorless oil: ^{1}H NMR (400 MHz, $CDCl_3$, ppm) δ 4.18 (s, 4H), 3.46 (t, J = 6.8 Hz, 4H), 1.66–1.57 (m, 4H), 0.93 (t, J = 7.4 Hz, 6H).

1,2,3,4,5,6-Hexakis(propoxymethyl)benzene (13). Alkyne **12** (126 mg, 0.74 mmol) was dissolved in THF (15 mL). Dicobalt octacarbonyl (76 mg, 0.22 mmol) and DMSO (0.3 mL, 4.44 mmol) were added, and the solution was refluxed for 24 h. Solvent was removed in vacuo, and column chromatography with 4:1 hexanes/EtOAc gave 88 mg (70% yield) of a white solid: ^{1}H NMR (400 MHz, $CDCl_3$, ppm) δ 4.63 (s, 12H), 3.46 (t, J = 6.6 Hz, 12H), 1.60 (sext, J = 7.0 Hz, 12H), 0.92 (t, J = 7.4 Hz, 18H); ^{13}C NMR (100 MHz, $CDCl_3$, ppm) δ 137.7, 72.4, 66.2, 22.9, 10.6; IR (neat ATR) 2962, 2936, 2873, 1353, 1087, 908, 728; HRMS (DART) m/z [M + H]$^+$ calcd for $C_{30}H_{55}O_6$ 511.3993, found 511.3981.

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Hydroquinone 15. Complex **14** (145 mg, 0.27 mmol),[12] NH_4OH (2.2 mL, 2 M), and 1,4-dioxane (6 mL) were mixed in a round-bottom flask. The reaction solution was heated at 90 °C for 48 h. The reaction mixture was diluted with ether, filtered through Celite, and dried with $MgSO_4$. Column chromatography with 9:1 hexanes/EtOAc gave 13 mg (17% yield) of a white solid: ^{1}H NMR (400 MHz, $CDCl_3$, ppm) δ 8.30 (s, 2H), 6.08−6.01 (m, 4H), 5.55−5.47 (m, 4H), 4.59 (s, 8H), 3.48 (t, J = 7.4 Hz, 8H), 2.13 (td, J = 7.0, 4.8 Hz, 8H), 1.66−1.59 (m, 8H), 1.51−1.44 (m, 8H); ^{13}C NMR (100 MHz, $CDCl_3$, ppm) δ 148.3, 132.2, 131.5, 122.5, 69.8, 65.5, 32.0, 27.6, 23.6; IR (neat ATR) 3361, 2922, 2857, 1691, 1541, 1432, 1375, 1267, 1089, 1035, 985; HRMS (DART) m/z $[M + H]^+$ calcd for $C_{34}H_{51}O_6$ 555.3680, found 555.3655.

2,3,5,6-Tetrakis(propoxymethyl)benzene-1,4-diol (17). Complex **16** (280 mg, 0.61 mmol),[12] NH_4OH (1.7 mL, 4 M), and 1,4-dioxane (5 mL) were mixed in a round-bottom flask. The reaction solution was heated at 90 °C for 36 h. The reaction mixture was diluted with ether, filtered through Celite, and dried with $MgSO_4$. Column chromatography with 9:1 petroleum ether/Et_2O gave 32 mg (26% yield) of a white solid.

Alternatively, the reaction may be carried out by combining the free alkyne **12** (163 mg, 0.957 mmol), catalytic dicobalt octacarbonyl (82 mg, 0.239 mmol) in 1,4-dioxane (2 mL), followed by addition NH_4OH (0.6 mL, 4 M). The reaction was heated at 90 °C for 17 h. The reaction solution was cooled to rt, diluted with ether, filtered through Celite, and dried with $MgSO_4$. Column chromatography with 9:1 petroleum ether/Et_2O gave 40 mg (21% yield) of a white solid: ^{1}H NMR (400 MHz, $CDCl_3$, ppm) δ 8.11 (s, 2H), 4.71 (s, 8H), 3.45 (t, J = 6.6 Hz, 8H), 1.66−1.57 (m, 8H), 0.91 (t, J = 7.4 Hz, 12H); ^{13}C NMR (100 MHz, $CDCl_3$, ppm) δ 148.4, 122.8, 72.0, 65.7, 22.8, 10.6; IR (neat ATR) 3748, 1558, 1540, 1363, 1215, 1077; HRMS (DART) m/z $[M]^+$ calcd for $C_{22}H_{38}O_6$ 398.2668, found 398.2650.

2,3-Bis(propoxymethyl)-3a,4,7,7a-tetrahydro-1*H*-4,7-methanoinden-1-one (19). A flame-dried round-bottom flask was charged with TMTU (52 mg, 0.39 mmol) and flushed with nitrogen. A solution of complex **16** (300 mg, 0.65 mmol)[12] in toluene (10 mL) and norbornadiene (**18**, 0.13 mL, 1.31 mmol) was added. The reaction solution was stirred at 70 °C for 12 h. Solvent was removed in vacuo and column chromatography with 4:1 hexanes/EtOAc gave 106 mg (56% yield) of a colorless oil: ^{1}H NMR (400 MHz, C_6D_6, ppm) δ 5.99 (dd, J = 5.6, 3.2 Hz, 1H), 5.86 (dd, J = 5.6, 2.8 Hz, 1H), 4.33 (d, J = 15.2 Hz, 1H), 4.16 (dd, J = 15.2, 0.8 Hz, 1H), 4.15 (d, J = 12.0 Hz, 1H), 4.06 (d, J = 12.0 Hz, 1H), 3.17 (t, J = 6.6 Hz, 2H), 3.13 (ddt, J = 19.6, 9.2, 6.4 Hz, 2H), 2.91 (bs, 1H), 2.74 (bs, 1H), 2.73 (d, J = 5.2 Hz, 1H), 2.14 (d, J = 5.2 Hz, 1H), 1.50−1.36 (m, 4H), 1.26−1.21 (m, 2H), 0.81 (t, J = 7.4 Hz, 3H), 0.78 (t, J = 7.4 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$, ppm) δ 208.1, 174.9, 140.9, 138.4, 137.1, 73.0, 72.5, 67.3, 61.5, 52.3, 48.7, 43.6, 42.6, 41.3, 22.80, 22.76, 10.51, 10.50; IR (neat ATR) 2964, 2938, 2874, 1698, 1100, 693; HRMS (DART) m/z $[M + H]^+$ calcd for $C_{18}H_{27}O_3$ 291.1955, found 291.1948.

(6*E*,8*E*)-1,3,4,5,10,11,12,14,14b,15,18,18a-Dodecahydro-19*H*-15,18-methanoindeno[1,2 c][1,6]dioxacyclohexadecin-19-one (20). A flame-dried round-bottom flask was charged with TMTU (26 mg, 0.19 mmol) and flushed with nitrogen. A solution of complex **5** (166 mg, 0.33 mmol)[12] in toluene (6 mL) and norbornadiene (**18**, 0.10 mL, 0.65 mmol) was added. The reaction solution was stirred at 70 °C for 24 h. Solvent was removed in vacuo and column chromatography with 4:1 hexanes/EtOAc gave 76 mg (68% yield) of a colorless oil. ^{1}H NMR (400 MHz, $CDCl_3$, ppm) δ 6.32 (dd, J = 5.6, 2.8, 1H), 6.20 (dd, J = 5.6, 2.8 Hz, 1H), 6.02 (dd, J = 14.6, 6.6 Hz, 1H), 5.93 (dd, J = 14.4, 6.4 Hz, 1H), 5.62−5.47 (m, 2H), 4.36 (d, J = 15.2 Hz, 1H), 4.31 (d, J = 15.2 Hz, 1H), 3.90 (s, 2H), 3.54 (ddd, J = 9.8, 6.0, 3.8 Hz, 1H), 3.49−3.38 (m, 3H), 3.01 (bs, 1H), 2.94 (bs, 1H), 2.90 (d, J = 5.2 Hz, 1H), 2.31 (d, J = 5.2 Hz, 1H), 2.28−2.09 (m, 4H), 1.76−1.66 (m, 4H), 1.40 (dt, J = 9.2, 1.2 Hz, 1H), 1.24 (bd, J = 9.2 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$, ppm) δ 208.3, 175.9, 139.7, 138.6, 137.0, 133.0, 131.9, 129.9, 129.3, 71.7, 70.1, 67.9, 60.7, 52.2, 48.7, 43.7, 42.7, 41.1, 31.9, 30.6, 28.5 (2 C signals overlap); IR (neat ATR) 2916, 2868, 1692, 1095, 985, 911, 727; HRMS (DART) m/z $[M + H]^+$ calcd for $C_{22}H_{29}O_3$ 341.2111, found 341.2102.

(7*E*,9*E*)-1,3,4,5,6,11,12,13,14,16,16b,17,20,20a-Tetradecahydro-21*H*-17,20-methanoindeno[1,2-*c*][1,6]-dioxacyclooctadecin-21-one (21). A flame-dried round-bottom flask was charged with TMTU (17 mg, 0.13 mmol) and flushed with nitrogen. A solution of complex **14** (115 mg, 0.22 mmol)[12] in toluene (5 mL) and norbornadiene (0.04 mL, 0.43 mmol) was added. The reaction solution was stirred at 70 °C for 24 h. Solvent was removed in vacuo, and column chromatography with 4:1 hexanes/EtOAc gave 65 mg (82% yield) of a colorless oil: ^{1}H NMR (400 MHz, $CDCl_3$, ppm) δ 6.30 (dd, J = 5.4, 3.0, 1H), 6.19 (dd, J = 5.4, 3.0 Hz, 1H), 6.05 (dd, J = 14.4, 10.4 Hz, 1H), 5.98 (dd, J = 14.4, 10.4 Hz, 1H), 5.55−5.44 (m, 2H), 4.46 (d, J = 16 Hz, 1H), 4.32 (d, J = 15.6 Hz, 1H), 4.08 (dd, J = 18.8, 12.4 Hz, 2H), 3.50 (td, J = 7.2, 2.4 Hz, 2H), 3.30 (t, J = 7.2 Hz, 2H), 2.94−2.91 (m, 3H), 2.29 (d, J = 5.2 Hz, 1H), 2.21−2.03 (m, 4H), 1.66−1.60 (m, 2H), 1.58−1.47 (m, 4H), 1.45−1.40 (m, 2H), 1.38 (bd, J = 9.2 Hz, 1H), 1.21 (bd, J = 9.2 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$, ppm) δ 208.1, 175.6, 140.1, 138.6, 137.1, 132.6, 131.8, 131.5, 131.3, 70.3, 70.1, 66.7, 61.9, 52.3, 48.8, 43.7, 42.8, 41.3, 32.0, 31.3, 27.42, 27.32, 24.1, 23.5; IR (neat ATR) 2937, 2861, 1690, 1637, 1372, 1107, 990, 913, 731; HRMS (DART) m/z $[M + H]^+$ calcd for $C_{24}H_{33}O_3$ 369.2424, found 369.2414.

Hex-5-en-1-yl 4-Methylbenzenesulfonate (23). Tosyl chloride (5.2 g, 27.5 mmol) was added portionwise to a stirred and ice-cooled solution of hex-5-en-1-ol (3 mL, 25 mmol), DMAP (0.06 g, 0.50 mmol), and Et_3N (4.5 mL, 32.5 mmol) in DCM (55 mL). The mixture was stirred for 1 h at 0 °C and 12 h at rt. After completion, the reaction solution was diluted with DCM, washed with brine, and dried over $MgSO_4$. The solution was filtered through silica gel and concentrated in vacuo to give 6.25 g (98% yield) of the known[44] colorless oil: ^{1}H NMR (400 MHz, $CDCl_3$, ppm) δ 7.78 (d, J = 8.4 Hz, 2H), 7.34 (d, J = 8.0 Hz, 2H), 5.71 (ddt, J = 17.0, 10.2, 6.8 Hz, 1H), 4.98−4.92 (m, 2H), 4.02 (t, J = 6.4 Hz, 2H), 2.44 (s, 3H), 2.03−1.97 (m, 2H), 1.68−1.61 (m, 2H), 1.44−1.37 (m, 2H).

1,4-Bis(hex-5-en-1-yloxy)but-2-yne (24). A flame-dried flask was charged with NaH (314 mg, 7.86 mmol, 60% w/w dispersion in mineral oil) and dry DMF (5 mL). The suspension was cooled to 0 °C, and a solution of but-2-yne-1,4-diol (**22**, 0.23 g, 2.62 mmol) in dry DMF (5 mL) was added dropwise. The mixture was stirred for 45 min at 0 °C prior to the addition of **23** (2.0 g, 7.86 mmol) in 3 mL of dry DMF. The reaction solution was stirred at 90 °C for 12 h. Upon completion, water was added, and the crude mixture was extracted with DCM. The combined organic layers were washed with water and brine and dried over $MgSO_4$. Solvent was removed in vacuo. Chromatography with 9:1 hexanes/EtOAc gave 0.59 g (90% yield) of a colorless oil: ^{1}H NMR (400 MHz, $CDCl_3$, ppm) δ 5.80 (ddt, J = 17.0, 10.2, 6.8 Hz, 2H), 5.00 (bdd, J = 17.0, 1.8 Hz, 2H), 4.94 (bdd, J = 10.4, 0.8 Hz, 2H), 4.17 (s, 4H), 3.50 (t, J = 6.5, 4H), 2.07 (bq, J = 7.2 Hz, 4H), 1.64−1.57 (m, 4H), 1.40−1.42 (m, 4H); ^{13}C NMR (100 MHz, $CDCl_3$, ppm) δ 138.5, 114.4, 82.2, 69.9, 58.2, 33.4, 28.8, 25.3; IR (neat ATR) 3324, 2930, 2855, 1640, 1541, 1438, 1348, 1118, 1103, 1084, 992, 908; HRMS (DART) m/z $[M + H]^+$ calcd for $C_{16}H_{27}O_2$ 251.2006, found 251.1998.

Complex 25. To a solution of **24** (0.58 g, 2.32 mmol) in DCM (30 mL) was added $Co_2(CO)_8$ (0.87 g, 2.55 mmol). The mixture was stirred at rt for 12 h. The solvent was removed in vacuo. Chromatography with 15:1 hexanes/EtOAc gave 1.17 g (94% yield) of a red oil: ^{1}H NMR (400 MHz, $CDCl_3$, ppm) δ 5.85−5.75 (m, 2H), 5.00 (d, J = 17.2 0048z, 2H), 4.94 (d, J = 10.0 Hz, 2H), 4.61 (s, 4H), 3.59 (t, J = 6.0 Hz, 4H), 2.07 (bq, J = 6.8 Hz, 4H), 1.63 (bp, J = 7.0 Hz, 4H), 1.48 (bp, J = 7.0 Hz, 4H); ^{13}C NMR (100 MHz, C_6D_6, ppm) δ 199.8, 138.5, 114.4, 92.8, 70.73, 70.63, 33.4, 29.1, 25.3; IR (neat ATR) 2940, 2861, 2092, 2049, 2007, 1644, 1435, 1338, 1100, 992, 909; HRMS (DART) m/z $[M - O(CH_2)_4CH{=}CH_2]^+$ calcd for $C_{16}H_{15}Co_2O_7$ 436.9476, found 436.9469.

4-(Allyloxy)but-2-yn-1-ol (27). To a suspension of KOH (2.30 g, 41.3 mmol) in DMSO (20 mL) were added allyl bromide (**26**, 1.4 mL, 16.2 mmol) and but-2-yne-1,4-diol (**22**, 3.5 g, 41.3 mmol). The mixture was stirred for 1 h, poured into water, and extracted with ether. The aqueous phase was acidified with aqueous HCl (6 M) and extracted further with ether. The combined organic phases were

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reduced in volume, washed with water, dried with $MgSO_4$, and concentrated in vacuo. Chromatography with 3:1 hexanes/Et_2O gave 1.15 g (57% yield) of the known[45] colorless oil: ^{1}H NMR (400 MHz, $CDCl_3$, ppm) δ 5.90 (ddt, J = 17.2, 10.4, 5.6 Hz, 1H), 5.31 (ddt, J = 17.2, 1.6, 1.6 Hz, 1H), 5.22 (ddt, J = 10.4, 1.6, 1.2 Hz, 1H), 4.32−4.30 (m, 2H), 4.19 (t, J = 1.6 Hz, 2H), 4.05 (dt, J = 5.6, 1.2 Hz, 2H), 1.74 (bt, J = 5.6 Hz, 1H).

6-((4-(Allyloxy)but-2-yn-1-yl)oxy)hex-1-ene (28). A flame-dried flask was charged with NaH (261 mg, 6.53 mmol, 60% w/w dispersion in mineral oil) and dry DMF (6 mL). The suspension was cooled to 0 °C, and a solution of 4-(allyloxy)but-2-yn-1-ol (**27**, 343 mg, 2.72 mmol) in dry DMF (6 mL) was added dropwise. The mixture was stirred for 45 min at 0 °C prior to the addition of **23** (830 mg, 3.26 mmol). The reaction solution was stirred at rt for 24 h. Upon completion, water was added, and the crude mixture was extracted with DCM. The combined organic layers were washed with water ans brine and dried over $MgSO_4$. Solvent was removed in vacuo. Chromatography with 9:1 hexanes/EtOAc gave 520 mg (92% yield) of a colorless oil: ^{1}H NMR (400 MHz, $CDCl_3$, ppm) δ 5.90 (ddt, J = 17.2, 10.4, 5.6 Hz, 1H), 5.79 (ddt, J = 17.0, 10.4, 6.8 Hz, 1H), 5.29 (ddt, J = 17.2, 1.6, 1.6 Hz, 1H), 5.21 (ddt, J = 10.4, 1.2, 1.2 Hz, 1H), 4.99 (ddt, J = 17.2, 1.6, 1.6 Hz, 1H), 4.94 (ddt, J = 10.0, 1.2, 1.2 Hz, 1H), 4.19−4.16 (m, 4H), 4.05 (dt, J = 5.6, 1.2 Hz, 2H), 3.50 (t, J = 6.6 Hz, 2H), 2.09−2.04 (m, 2H), 1.64−1.56 (m, 2H), 1.49−1.41 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$, ppm) δ 138.6, 133.9, 117.8, 114.5, 82.6, 81.9, 70.6, 70.0, 58.2, 57.4, 33.4, 28.9, 25.4; IR (neat ATR) 2937, 2857, 1439, 1349, 1117, 1080, 992, 909; HRMS (DART) m/z $[M + H]^+$ calcd for $C_{13}H_{21}O_2$ 209.1536, found 209.1537.

Complex 29. To a solution of **28** (156 mg, 0.75 mmol) in DCM (10 mL) was added $Co_2(CO)_8$ (282 mg, 0.82 mmol). The mixture was stirred at rt for 3 h. The solvent was removed in vacuo. Chromatography with hexanes gave 323 mg (87% yield) of red oil: ^{1}H NMR (400 MHz, $CDCl_3$, ppm) δ 5.93 (ddt, J = 17.2, 10.8, 5.4 Hz, 1H), 5.80 (ddt, J = 17.0, 10.2, 6.6 Hz, 1H), 5.35−5.30 (m, 1H), 5.20 (dd, J = 10.4, 1.2 Hz, 1H), 5.00 (dd, J = 17.2, 1.6 Hz, 1H), 4.94 (bd, J = 10.4 Hz, 1H), 4.65 (s, 2H), 4.62 (s, 2H), 4.15 (bd, J = 5.2 Hz, 2H), 3.60 (t, J = 6.4 Hz, 2H), 2.10−2.05 (m, 2H), 1.66−1.59 (m, 2H), 1.52−1.45 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$, ppm) δ 138.7, 134.3, 116.8, 114.4, 71.6, 70.99, 70.95, 70.2, 67.9 33.5, 29.2, 25.3 (cobalt coordinated alkyne carbons absent and CO signal was not observed); IR (neat ATR) 3016, 2969, 2942, 2093, 2049, 1997, 1439, 1365, 1228, 1216, 1091, 910; HRMS (DART) m/z $[M - OCH_2CH{=}CH_2]^+$ calcd for $C_{16}H_{15}Co_2O_7$ 436.9476, found 436.94797, $[M - O(CH_2)_4CH{=}CH_2]^+$ calcd for $C_{13}H_9Co_2O_7$ 394.9007, found 394.9010.

6-((Hex-5-en-1-yloxy)methyl)-3a,4-dihydro-1*H*-cyclopenta-[c]furan-5(3*H*)-one (31). A flame-dried round-bottom flask was charged with NMO (388 mg, 2.89 mmol) and flushed with nitrogen. A solution of complex **29** (238 mg, 0.48 mmol) in DCM (10 mL) was added, and the resultant solution was stirred at rt for 27 h. DCM was removed in vacuo, and column chromatography with 4:1 hexanes/EtOAc gave 64 mg (56% yield) of a colorless oil. ^{1}H NMR (400 MHz, C_6D_6, ppm) δ 5.66 (ddt, J = 17.0, 10.2, 6.8 Hz, 1H), 4.98−4.89 (m, 2H), 4.48 (d, J = 16.4 Hz, 1H), 4.41 (dd, J = 16.4, 1.6 Hz, 1H), 4.07 (ddt, J = 14.4, 2.8, 2.0 Hz, 1H), 4.01 (dtd, J = 14.4, 2.4, 1.4 Hz, 1H), 3.71 (t, J = 7.8 Hz, 1H), 3.06 (t, J = 6.2 Hz, 2H), 2.58 (dd, J = 11.2, 8.0 Hz, 1H), 2.42−2.37 (m, 1H), 2.05 (ddd, J = 17.6, 6.4, 0.4 Hz, 1H), 1.89−1.83 (m, 2H), 1.50 (dd, J = 17.4, 3.8 Hz, 1H), 1.37−1.30 (m, 2H), 1.29−1.21 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$, ppm) δ 207.1, 178.6, 138.4, 133.8, 114.5, 71.37, 71.20, 65.5, 64.7, 44.0, 39.0, 33.3, 28.9, 25.2; IR (neat ATR) 2934, 2857, 1710, 1680, 1374, 1272, 1121, 1024, 911, 887, 732; HRMS (DART) m/z $[M + H]^+$ calcd for $C_{14}H_{21}O_3$ 237.1485, found 237.1489.

Complex 34. To a solution of **33** (41 mg, 0.184 mmol)[36] in DCM (2 mL) was added $Co_2(CO)_8$ (69 mg, 0.203 mmol). The mixture was stirred at rt for 2 h. The solvent was removed in vacuo. Chromatography with 20:1 hexanes/EtOAc gave 94 mg (84% yield, E:Z ratio 1:1.2) of a red oil: ^{1}H NMR (400 MHz, $CDCl_3$, ppm) δ (E) 5.42−5.39 (m, 2H), 4.67 (s, 4H), 3.58 (t, J = 8.3 Hz, 4 H), 2.09−2.01 (m, 4H), 1.68−1.61 (m, 4H), (1.51−1.42 (m, 2H); (Z) 5.42−5.39 (m, 2H), 4.70 (s, 4H), 3.64 (t, J = 7.5 Hz, 4H), 2.09−2.01 (m, 4H), 1.68−1.61 (m, 4H), (1.51−1.42 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$, ppm) δ 199.4 (b), 131.1, 130.0, 92.9, 71.6, 71.0, 70.7, 70.4, 31.3, 28.5, 27.7, 26.2, 25.9, 24.9; IR (neat ATR) 3009, 2936, 2360, 2336, 2090, 2050, 2022, 1622, 1345, 1099, 910, 736; HRMS (DART) m/z $[M + H]^+$ calcd for $C_{20}H_{23}Co_2O_8$ 509.0051, found 509.0025.

Complex 36. To a solution of **35** (95 mg, 0.34 mmol)[36] in DCM (7 mL) was added $Co_2(CO)_8$ (116 mg, 0.34 mmol). The mixture was stirred at rt for 6 h. The solvent was removed in vacuo. Chromatography with 9:1 petroleum ether/Et_2O gave 142 mg (74% yield) of a red solid: ^{1}H NMR (400 MHz, $CDCl_3$, ppm) δ 5.88−5.65 (m, 2H), 4.66 (s, 2H), 4.00 (d, J = 1.6 Hz, 2H), 3.74 (s, 6H), 3.65 (s, 2H), 2.14 (bs, 2H), 2.02−1.96 (m, 2H), 1.41 (bs, 2H); ^{13}C NMR (100 MHz, $CDCl_3$, ppm) δ 199.4, 170.8 (C═O), 136.2, 128.4, 95.0, 87.0, 70.5, 66.6, 58.0, 52.6, 38.2, 28.7, 28.2, 23.2; IR (neat ATR) 2947, 2855, 2089, 2050, 1998, 1730, 1301, 1242, 1205, 1182, 1059, 1013; HRMS (DART) m/z $[M + H]^+$ calcd for $C_{21}H_{21}Co_2O_{11}$ 566.9742, found 566.9717.

6-Iodohexan-1-ol (51). A flame-dried flask containing 6-bromohexan-1-ol (8.363 g, 46.2 mmol)[46] was flushed and with nitrogen, and then acetone (123 mL) was added. After the addition of sodium iodide (24.260 g, 161 mmol) the mixture was heated to reflux and stirred 16 h. The mixture was diluted with water and extracted with EtOAc. The organic layers were washed with 1% aq sodium thiosulfate and brine, then dried with $MgSO_4$. Solvent was removed in vacuo. Chromatography with 2:1 hexanes/EtOAc gave 9.542 g (80% yield) of the known[38] clear light yellow oil: ^{1}H NMR (400 MHz, $CDCl_3$, ppm) δ 3.63 (t, J = 6.6 Hz, 2H), 3.18 (t, J = 7.0 Hz, 2H), 1.83 (p, J = 7.0 Hz, 2H), 1.57 (p, J = 6.9 Hz, 2H), 1.47−1.34 (m, 4H).

Oct-7-en-1-ol (52). A flame-dried flask with copper(I) iodide (7.634 g, 40.1 mmol) was flushed with nitrogen, and then THF (55 mL) was added. The flask was cooled to −40 °C, then vinylmagnesium bromide (120 mL, 120 mmol, 1 M in hexanes), was added, and the mixture was stirred for 15 min at that temperature. Next, HMPA (13.9 mL, 80.2 mmol), triethyl phosphite (13.7 mL, 80.2 mmol), and a solution of 6-iodohexanol (**51**, 9.142 g, 40.1 mmol) in THF (55 mL) were added sequentially at −40 °C, and then the mixture was stirred 1 h. The mixture was warmed to rt and stirred for 2 h, then the reaction was quenched with saturated aq NH_4Cl, extracted with EtOAc, washed with brine, and dried with $MgSO_4$. Solvent was removed in vacuo. Chromatography with 3:1 hexanes/Et_2O gave 3.638 g (71% yield) of the known[47] clear light yellow oil: ^{1}H NMR (400 MHz, $CDCl_3$, ppm) δ 5.80 (dtd, J = 17.1, 10.3, 6.7 Hz, 1H), 4.99 (d, J = 17.2 Hz, 1H), 4.93 (d, J = 10.0 Hz, 1H), 3.63, (t, J = 6.6 Hz, 2H) 2.04 (td, J = 6.8 Hz, 2H), 1.56 (p, J = 6.9 Hz, 2H), 1.43−1.27 (m, 6H).

Oct-7-en-1-yl 4-Methylbenzenesulfonate (53). A flame-dried flask with 4-dimethylaminopyridine (69 mg, 0.567 mmol) was flushed with nitrogen, and then DCM (57 mL) was added. After the addition of oct-7-en-1-ol (**52**, 3.638 g, 28.4 mmol) and triethylamine (5.14 mL, 36.9 mmol), the flask was cooled to 0 °C, and tosyl chloride (5.950 g, 31.2 mmol) was added slowly. The mixture was warmed to rt and stirred 16 h. The mixture was diluted with water, washed with brine, and dried with $MgSO_4$. Solvent was removed in vacuo. Chromatography with 5:1 hexanes/Et_2O gave 6.437 g (80% yield) of a clear colorless oil: R_f = 0.42 (5:1 hexanes/Et_2O); ^{1}H NMR (400 MHz, $CDCl_3$, ppm) δ 7.79 (d, J = 8.0 Hz, 2H), 7.34 (d, J = 8.0 Hz, 2H), 5.76 (ddt, J = 17.0, 10.2, 6.7 Hz, 1H), 4.97 (dtd, J = 17.2, 1.8, 1.6 Hz, 1H), 4.92 (ddt, J = 10.3, 2.1, 1.1 Hz, 1H) 4.01 (t, J = 6.6 Hz, 2H), 2.44 (s, 3H) 1.99 (q, J = 7.1 Hz, 2H), 1.63 (p, J = 6.9 Hz, 2H), 1.359−1.186 (m, 6H); ^{13}C NMR (100 MHz, $CDCl_3$, ppm) δ 144.6, 138.8, 133.3, 129.8, 127.9, 114.4, 70.6, 33.6, 28.8, 28.6, 28.4, 25.2, 21.6; IR (neat, ATR, cm^{-1}) 3077, 2973, 2930, 2855, 1358, 1174, 956, 912, 812; HRMS (DART) m/z $[M + H]^+$ calcd for $C_{15}H_{23}O_3S$ 283.1362, found 283.1368.

1,2-Phenylenedimethanol (54). A flame-dried flask with lithium aluminum hydride (5.210 g, 137.3 mmol) was flushed with nitrogen, and then THF (145 mL) was added. The flask was cooled to 0 °C, and then a solution of phthalic anhydride (10.719g, 72.4 mmol) in THF (106 mL) was added dropwise. The mixture was stirred at rt for 30 min and then at reflux for 3 h. The mixture was cooled to 0 °C and

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diluted with ether, and water (5.5 mL) was added dropwise, followed by 15% aq NaOH (5.5 mL) and then water (13.7 mL). The solution was warmed to rt, stirred 15 min, and then stirred another 15 min after addition of magnesium sulfate. The mixture was filtered through Celite, and solvent was removed in vacuo. Crystallization with hexanes gave 6.002 g (60% yield) of the known compound[48] as off white crystals: ^{1}H NMR (400 MHz, $CDCl_3$, ppm) δ 7.30 (s, 4H), 4.62 (s, 4H), 3.77 (s, 2H).

(2-((Oct-7-en-1-yloxy)methyl)phenyl)methanol (55). A flame-dried flask with sodium hydride (603 mg, 15.1 mmol) was flushed with nitrogen, and then DMF (16 mL) was added. A solution of 1,2-phenylenedimethanol (**54**, 2.092 g, 15.1 mmol) in DMF (16 mL) was added dropwise at 0 °C, then stirred 15 min. Next, a solution of oct-7-en-1-yl 4-methylbenzenesulfonate (**53**, 4.257 g, 15.1 mmol) in DMF (16 mL) was added at 0 °C, then stirred 15 min. The mixture was warmed to 80 °C and stirred 16 h. The mixture was diluted with water, extracted with ether, and dried with $MgSO_4$. Solvent was removed in vacuo. Chromatography with 3:2 hexanes/Et_2O gave 2.379 g (64% yield) of a clear light yellow oil: R_f = 0.36 (2:1 hexanes/Et_2O); ^{1}H NMR (400 MHz, $CDCl_3$, ppm) δ 7.40 (d, J = 6.8 Hz, 1H), 7.36−7.27 (m, 2H), 5.79 (ddt, J = 16.8, 10.4, 6.7, 1H), 4.98 (dtd, J = 17.1, 1.8, 1.8, 1H), 4.92 (ddt, J = 10.2, 2.2, 1.1 Hz, 1H), 4.66 (d, J = 6.4 Hz, 2H), 4.60 (s, 2H), 3.52 (t, J = 6.6 Hz, 3H), 3.31 (t, J = 6.4 Hz, 1H), 2.03 (td, J = 7.1, 7.1 Hz, 2H), 1.61 (p, J = 7.1 Hz, 2H), 1.41−1.27 (m, 6H); ^{13}C NMR (100 MHz, $CDCl_3$, ppm) δ 140.9, 139.0, 136.3, 130.1, 129.8, 128.9, 128.0, 114.3, 72.4, 70.9, 64.0, 33.7, 29.6, 28.9, 28.8, 26.0; IR (neat, ATR, cm^{-1}) 3401, 3074, 2926, 2855, 1641, 1362, 1089, 1006, 908, 747; HRMS (DART) m/z $[M + H]^+$ calcd for $C_{16}H_{24}O_2$ 249.1849, found 249.1846.

***tert*-Butyl (2-((oct-7-en-1-yloxy)methyl)benzyl)(tosyl)-carbamate (57).** A flame-dried flask with (2-((oct-7-en-1-yloxy)-methyl)phenyl)methanol (**55**, 614 mg, 2.47 mmol), triphenylphosphine (778 mg, 2.97 mmol), and *tert*-butyl tosylcarbamate (**56**, 805 mg, 2.97 mmol)[49] was flushed with nitrogen, and then THF (5 mL) was added. The mixture was cooled to 0 °C, then diisopropyl azodicarboxylate (0.49 mL, 2.47 mmol) was added dropwise. The mixture warmed to rt and stirred for 16 h. Solvent was removed in vacuo. Chromatography with 6:1 hexanes/EtOAc gave 1.031 g (83% yield) of a clear colorless oil: ^{1}H NMR (400 MHz, $CDCl_3$, ppm) δ 7.68 (d, J = 8.4 Hz, 2H), 7.32−7.21 (m, 6H), 5.80 (ddt, J = 17.2, 10.4, 6.7 Hz), 5.14 (s, 2H), 4.98 (dtd, J = 17.2, 1.9, 1.9 Hz, 1H), 4.92 (ddt, J = 10.1, 2.3, 1.1 Hz, 1H), 4.60 (s, 2H) 3.44 (t, J = 6.6 Hz, 2H), 2.43 (s, 3H), 2.04 (td, J = 6.9, 6.9 Hz, 2H), 1.60 (p, J = 6.9 Hz, 2J), 1.42−1.33 (m, 6H), 1.31 (s, 9H); ^{13}C NMR (125 MHz, $CDCl_3$, ppm) δ 151.2, 144.2, 139.1, 137.0, 136.5, 135.3, 129.12, 129.08, 128.3, 128.2,126.9, 126.5, 114.2, 84.3, 71.3, 70.3, 47.0, 33.7, 29.7, 29.0, 28.9, 27.8, 26.1, 21.6; IR (neat, ATR, cm^{-1}) 3070, 2977, 2930, 2858, 1727, 1358, 1153, 1089; HRMS (DART) m/z $[M - C_5H_9O_2]^+$ calcd for $C_{23}H_{30}NO_3S$ 400.1946, found 400.1937.

4-Methyl-*N*-(2-((oct-7-en-1-yloxy)methyl)benzyl)benzene-sulfonamide (58). A flame-dried flask with *tert*-butyl (2-((oct-7-en-1-yloxy)methyl)benzyl)(tosyl)carbamate (**57**, 1.031 g, 2.05 mmol) was flushed with nitrogen, and then DCM (35 mL) was added. Trifluoroacetic acid (3.3 mL, 42.5 mmol) was added dropwise, and the mixture was warmed to rt and stirred 16 h. The mixture was quenched with saturated aqueous sodium bicarbonate, extracted with DCM, and dried with $MgSO_4$. Solvent was removed in vacuo. Chromatography with 4:1 hexanes/EtOAc gave 702 mg (85% yield) of a clear colorless oil: ^{1}H NMR (400 MHz, $CDCl_3$, ppm) δ 7.72 (d, J = 8.4 Hz, 2H), 7.27−7.14 (m, 6H), 5.80 (ddt, J = 17.2, 10.4, 6.7 Hz, 1H), 5.65 (t, J = 5.8 Hz, 1H), 4.99 (dtd, J = 17.2, 1.8, 1.8 Hz, 1H), 4.93 (ddt, J = 10.3, 2.3, 1.3 Hz, 1H), 4.39 (s, 3H), 4.14 (d, J = 8.0 Hz, 2H), 3.42 (t, J = 6.8 Hz, 2H), 2.07 (s, 3H), 2.05 (td, J = 7.0 Hz, 2H), 1.60 (p, J = 6.0 Hz, 2H), 1.43−1.30 (m, 6H); ^{13}C NMR (100 MHz, $CDCl_3$, ppm) δ 143.2, 139.1, 137.2, 136.2, 135.8, 130.4 (2C), 129.6, 128.7, 128.2, 127.2, 114.3, 70.7, 70.8, 45.7, 33.7, 29.6, 28.9, 28.8, 26.0, 21.5; IR (neat, ATR, cm^{-1}) 3282, 3066, 2926, 2858, 1738, 1329, 1156, 1092; HRMS (DART) m/z $[M + H]^+$ calcd for $C_{23}H_{32}NO_3S$ 402.2097, found 402.2086.

Dimethyl 2-Allylmalonate (59). Dimethyl malonate (1.0 mL, 8.74 mmol) was added dropwise to a suspension of NaH (350 mg, 8.74 mmol, 60% w/w dispersion in mineral oil) in THF (30 mL) at 0 °C. The mixture was stirred for 30 min at this temperature, and then 3-bromoprop-1-ene (0.6 mL, 7.30 mmol) was added slowly. The reaction mixture was refluxed 16 h and was then quenched with H_2O. The heterogeneous mixture was diluted with ether and the organic layer was washed with water and brine, dried over $MgSO_4$, and concentrated in vacuo. Chromatography with 4:1 petroleum ether/Et_2O gave 0.70 g (57% yield) of the known[50] colorless oil: ^{1}H NMR (400 MHz, $CDCl_3$, ppm) δ 5.76 (ddt, J = 17.0, 10.2, 6.8 Hz, 1H), 5.12 (ddt, J = 17.2, 1.6, 1.4 Hz, 1H), 5.06 (dd, J = 10.4, 1.2 Hz, 1H), 3.73 (s, 6H), 3.46 (t, J = 7.6 Hz, 1H), 2.67−2.63 (m, 2H).

***(E)*-1,2,3,4-Tetrabromobut-2-ene (60).** Phosphorus tribromide (0.6 mL, 6.50 mmol) was slowly added to a solution of (*E*)-2,3-dibromobut-2-ene-1,4-diol (2 g, 8.13 mmol)[51] and pyridine (0.1 mL, 1.46 mmol) in Et_2O (10 mL) at 0 °C. The solution was stirred at 0 °C for 30 min and then refluxed for 4 h. After cooling, the reaction was quenched with water, and the aqueous layer was extracted with ether. The combined organic extracts were washed with saturated $NaHCO_3$ and brine and dried over $MgSO_4$. The solution was passed through a silica gel plug and concentrated in vacuo to afford 2.07 g (70% yield) of the known[36,52] white solid: ^{1}H NMR (400 MHz, $CDCl_3$, ppm) δ 4.34 (s, 4H).

Dimethyl (*E*)-2-Allyl-2-(2,3,4-tribromobut-2-en-1-yl)-malonate (61). A solution of dimethyl 2-allylmalonate (**59**, 0.42 g, 2.42 mmol) in DMF (4 mL) was added dropwise to a suspension of NaH (126 mg, 3.16 mmol, 60% w/w dispersion in mineral oil) in DMF (10 mL) at 0 °C. The mixture was stirred for 30 min at this temperature then **60** (1.2 g, 3.16 mmol) was added slowly. The reaction mixture stirred 16 h at rt and was then quenched with H_2O. The crude product was extracted with Et_2O, and the combined organic layers were washed with water and brine, dried over $MgSO_4$, and concentrated in vacuo. Chromatography with 9:1 petroleum ether/Et_2O gave 0.73 g (65% yield) of a colorless oil: ^{1}H NMR (400 MHz, $CDCl_3$, ppm) δ 5.79 (ddt, J = 17.0, 10.2, 7.2 Hz, 1H), 5.14−5.08 (m, 2H), 4.45 (s, 2H), 3.73 (s, 6H), 3.51 (s, 2H), 2.71 (bd, J = 7.2 Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$, ppm) δ 170.2, 132.2, 121.6, 120.3, 119.5, 57.7, 52.6, 42.7, 37.7, 37.0; IR (neat ATR) 2954, 1729, 1433, 1290, 1201, 914, 875; HRMS (DART) m/z $[M + H]^+$ calcd for $C_{12}H_{16}Br_3O_4$ 462.8573, found 462.8564.

Dimethyl (*E*)-2-Allyl-2-(2,3-dibromo-4-((4-methyl-*N*-(2-((oct-7-en-1-yloxy)methyl)benzyl)phenyl)sulfonamido)but-2-en-1-yl)malonate (62). A flame-dried flask with **61** (702 mg, 1.75 mmol), **58** (890 mg, 1.92 mmol), and potassium carbonate (483 mg, 3.50 mmol) was flushed with nitrogen, and then acetonitrile (8.7 mL) was added. The mixture was heated at reflux 16 h with stirring. The mixture was passed through a silica plug with DCM, and then solvent was removed in vacuo. Chromatography with 4:1 hexanes/EtOAc gave 1.138 g (83% yield) of a clear light yellow oil: ^{1}H NMR (500 MHz, $CDCl_3$, ppm) δ 7.73 (d, J = 8.0 Hz, 2H), 7.33−7.27 (m, 2H), 7.30 (d, J = 8.0 Hz, 2H), 7.23−7.20 (m, 2H), 5.80 (ddt, J = 17.1, 10.1, 6.8 Hz, 1H), 5.78−5.71 (m, 1H), 5.03 (bd, J = 10.0 Hz, 1H), 5.02 (bd, J = 17.0 Hz, 1H), 4.99 (dtd, J = 17.0, 1.8, 1.8 Hz, 1H), 4.93, (ddt, J = 10.1, 2.1, 1.1 Hz, 1H), 4.52 (s, 2H), 4.48 (s, 2H), 4.33 (s, 2H), 3.67 (s, 6H), 3.43 (t, J = 6.8 Hz, 2H), 2.49, (d, J = 7.5 Hz, 2H, 2.44 (s, 3H), 2.04 (td, J = 7.0, 7.0 Hz, 2H), 1.58 (p, J = 6.7 Hz, 2H), 1.41−1.27 (m, 6H); ^{13}C NMR (125 MHz, $CDCl_3$, ppm) δ 170.5, 143.6, 139.1, 136.9, 136.4, 133.7, 132.7, 129.7, 129.2, 129.1, 127.9, 127.8, 127.6, 122.5, 119.2, 118.9, 114.3, 70.9, 70.6, 57.6, 54.8, 52.6, 49.8, 43.1, 36.7, 33.8, 29.7, 29.0, 28.9, 26.1, 21.6; IR (neat, ATR, cm^{-1}) 3073, 2930, 2855, 1735, 1437, 1343, 1218, 1160, 1092, 908; HRMS (ESI) m/z $[M + Na]^+$ calcd for $C_{35}H_{45}Br_2NO_7SNa$ 804.1181, found 804.1184.

Dimethyl (14*E*)-14,15-Dibromo-17-tosyl-4,5,6,7,8,11,13,16,17,18-decahydro-1*H*-benzo[*c*][1]oxa[6]-azacycloicosine-12,12(3*H*)-dicarboxylate (63). Grubbs' second-generation catalyst (123 mg, 0.145 mmol) was dissolved in DCM (600 mL). After addition of a solution of **62** (1.138 g, 1.45 mmol) in DCM (100 mL), the reaction was warmed to reflux for 16 h. Another portion of Grubbs' second generation catalyst was added (123 mg, 0.0145

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mmol), and the reaction was stirred under reflux another 24 h. Solvent was removed in vacuo. Chromatography with 1:1 hexanes/Et_2O gave 654 mg (60% yield, *E*:*Z* ratio 3:1) of a white foam: ^{1}H NMR (500 MHz, $CDCl_3$, ppm) δ (*E*) 7.73 (d, *J* = 8.5 Hz, 2H), 7.37 (d, *J* = 7.0 Hz, 1H), 7.29 (d, 2H), 7.27−7.19 (m, 3H), 5.48 (td, *J* = 14.3, 7.0 Hz, 1H), 5.19 (td, *J* = 15.0, 7.4 Hz, 1H), 4.57 (s, 2H), 4.47 (s, 2H), 4.34 (s, 2H), 3.709 (s, 6H), 3.53 (t, *J* = 6.5 Hz, 2H), 3.41 (s, 2H), 2.65 (d, *J* = 7.0 Hz, 2H), 2. 43 (s, 3H), 1.96 (p, *J* = 6.4 Hz, 2H), 1.62 (p, *J* = 6.7 Hz, 2H), 1.40−1.25 (m, 6H); (*Z*) 7.66 (d, *J* = 8.5 Hz, 2H), 7.41 (d, *J* = 7.5 Hz, 1H), 7.30−7.19 (m, 5H), 5.47−5.42 (m, 1H), 5.33 (td, *J* = 10.8, 6.8 Hz, 1H), 4.70 (s, 2H), 4.92 (s, 2H), 4.45 (s, 2H), 3.711 (s, 6H), 3.454 (t, *J* = 6.5 Hz, 2H), 3.450 (s, 2H), 2.55 (d, *J* = 8.0 Hz, 2H), 2.42 (s, 3H), 1.98−1.92 (m, 2H), 1.56−1.51 (m, 2H), 1.40−1.25 (m, 6H); ^{13}C NMR (125 MHz, $CDCl_3$, ppm) δ (*E*) 170.6, 143.6, 137.5, 136.4, 135.5 132.8, 129.6, 128.6, 128.0, 127.8, 127.63, 127.61, 123.5, 122.0, 119.6, 70.2, 69.8, 57.4, 53.9, 52.8, 49.5, 41.5, 35.3, 31.4, 28.8, 27.5, 27.0, 25.1, 21.6; (*Z*) 170.8, 143.4, 137.4, 136.3, 134.7, 133.2, 129.4, 128.4, 127.5, 127.4, 122.7, 123.9, 119.1, 71.1, 70.4, 57.0, 54.2, 52.7, 49.6, 44.1, 30.2, 29.3, 28.1, 27.7, 26.3, 24.9 (3 C's, absent); IR (neat, ATR, cm^{-1}) 3027, 2926, 2855, 1735, 1437, 1156, 1089; HRMS (ESI) *m*/*z* [M + Na]$^+$ calcd for $C_{33}H_{41}Br_2NNaO_7S$ 776.0868, found 776.0882.

Dimethyl 14,15-Dehydro-17-tosyl-4,5,6,7,8,11,13,16,17,18-decahydro-1*H*-benzo[*c*][1]oxa[6]azacycloicosine-12,12(3*H*)-dicarboxylate (64). A flame-dried flask equipped with a reflux condenser was charged with zinc dust (339 mg, 5.19 mmol). The zinc dust was stirred with 1 M HCl, rinsed with water, and flame-dried in a flask prior to use. A solution of **63** (654 mg, 0.866 mmol) in THF (43 mL) was added. The mixture was heated at reflux and stirred 16 h. The mixture was diluted with EtOAc and filtered over Celite. Solvent was removed in vacuo. Chromatography with 3:1 hexanes/EtOAc gave 452 mg (88% yield, *E*:*Z* ratio 3:1) of a white solid: ^{1}H NMR (500 MHz, $CDCl_3$, ppm) δ (*E*) 7.81 (d, *J* = 8.5 Hz, 2H), 7.59 (d, *J* = 8.0 Hz, 1H), 7.37 (d, *J* = 8.5 Hz, 2H), 7.34−7.24 (m, 3H), 5.07 (dt, *J* = 14.7, 7.1 Hz), 4.92 (dt, *J* = 14.8, 7.4 Hz, 1H), 4.49 (s, 2H), 4.48 (s, 2H), 3.98 (s, 2H), 3.72 (s, 6H), 3.45 (t, *J* = 6.0 Hz, 2H), 2.63 (s, 2H), 2.52 (d, *J* = 7.5 Hz, 2H), 2.42 (s, 3H), 1.96 (td, *J* = 6.0, 6.0 Hz, 2H), 1.58 (p, *J* = 6.3 Hz, 2H), 1.39−1.27 (m, 4H), 1.22−1.16 (m, 2H); (*Z*) 7.75 (d, *J* = 8.0 Hz, 2H), 7.54 (d, *J* = 7.5 Hz, 1H), 7.34−7.24 (m, 5H), 5.46 (dt, *J* = 11.0, 7.5 Hz, 1H), 4.95−4.89 (m, 1H), 4.55 (s, 2H), 4.48 (s, 2H), 4.07 (s, 2H), 3.72 (s, 6H), 3.40 (t, *J* = 5.7 Hz, 2H), 2.60 (d, *J* = 8.0 Hz, 2H), 2.59 (s, 2H), 2.43 (s, 3H), 1.88 (td, *J* = 7.2 Hz, 2H), 1.52 (p, *J* = 6.4 Hz, 2H), 1.39−1.27 (m, 4H), 1.22−1.16 (m, 2H); ^{13}C NMR (125 MHz, $CDCl_3$, ppm) δ (*E*) 170.23, 143.45, 137.1, 136.50, 135.2, 129.8, 129.6, 129.1, 128.8 127.6, 127.50, 122.7, 80.7, 76.7, 71.67, 69.4, 56.4, 52.82, 45.0, 36.2, 35.3, 31.9, 28.4, 27.9, 26.6, 24.9, 22.5, 21.5 (one C, absent); (*Z*) 170.19, 143.36, 136.48, 135.3, 134.8, 130.2, 129.5, 129.3, 128.6, 127.8, 127.52, 122.2, 80.8, 76.6, 71.73, 69.2, 56.8, 52.79, 46.5, 37.4, 30.2, 29.0, 28.6, 27.6, 26.5, 25.1, 23.1, 21.6 (one C, absent); IR (neat, ATR, cm^{-1}) 3027, 2926, 2858, 2359, 1735, 1437, 1347, 1210, 1160, 1089, 1066; HRMS (DART) *m*/*z* [M + H]$^+$ calcd for $C_{33}H_{42}NO_7S$ 596.2677, found 596.2675.

Complex 49. To a solution of 1,6-dioxacyclononadec-8-en-3-yne (132 mg, 0.50 mmol)[36] in DCM (10 mL) was added $Co_2(CO)_8$ (171 mg, 0.50 mmol). The mixture was stirred at rt for 9 h. The solvent was removed in vacuo. Chromatography with 19:1 petroleum ether/Et_2O gave 242 mg (88% yield, *E*:*Z* ratio 2.5:1) of a red oil: ^{1}H NMR (400 MHz, $CDCl_3$, ppm) δ (*E*) 5.71−5.51 (m, 2H), 4.64 (s, 2H), 4.61 (s, 2H), 4.14 (d, *J* = 5.6 Hz, 2H), 3.58 (t, *J* = 5.8 Hz, 2H), 2.08 (bd, *J* = 6.0 Hz, 2H), 1.59−1.55 (m, 2H), 1.40−1.28 (m, 14H), (*Z*) 5.71−5.51 (m, 2H), 4.67 (s, 2H), 4.64 (s, 2H), 4.23 (d, *J* = 6.0 Hz, 2H), 3.58 (t, *J* = 5.8 Hz, 2H), 2.08 (bd, *J* = 6.0 Hz, 2H), 1.59−1.55 (m, 2H), 1.40−1.28 (m, 14H); ^{13}C NMR (100 MHz, $CDCl_3$, ppm) δ (*E*) 199.5, 193.2, 135.1, 126.8, 94.23, 94.22, 71.33, 71.29, 71.0, 68.8, 31.6, 28.9, 27.9, 27.48, 27.39, 27.13, 27.09, 27.04, 24.7; (*Z*) 199.5, 193.2, 133.9, 126.3, 94.26, 94.19, 71.6, 70.9, 69.8, 66.4, 29.0, 28.3, 27.66, 27.59, 27.57, 27.26, 27.1 (2 C signals overlap), 26.9, 25.0; IR (neat ATR) 2928, 2857, 2092, 2049, 2013, 1622, 1460, 1348, 1095, 971; HRMS (DART) *m*/*z* [M + H]$^+$ calcd for $C_{23}H_{29}Co_2O_8$ 551.0521, found 551.0501.

Complex 50. A flame-dried flask with dicobalt octacarbonyl (236 mg, 0.690 mmol) and **64** (316 mg, 0.530 mmol) was flushed with nitrogen, and then DCM (22 mL) was added. The mixture was stirred at rt 16 h. Solvent was removed in vacuo. Chromatography with 3:1 hexanes/EtOAc gave 327 mg (80% yield, *E*:*Z* ratio 3:1) of a red viscous oil: ^{1}H NMR (500 MHz, $CDCl_3$, ppm) δ (*E*) 7.45 (d, *J* = 8.5 Hz, 2H), 7.19−7.04 (m, 4H), 7.12 (d, *J* = 8.0 Hz, 2H), 5.48 (dt, *J* = 14.5, 7.1 Hz, 1H), 5.24 (dt, *J* = 15.3, 7.6 Hz, 1H), 4.74 (s, 2H), 4.64 (s, 2H), 4.39 (s, 2H), 3.73 (s, 6H), 4.47 (t, *J* = 6.5 Hz, 2H), 3.40 (s, 2H), 2.82 (d, *J* = 7.5 Hz 2H), 2.36 (s, 3H), 2.01 (td, *J* = 5.8, 5.8 Hz, 2H), 1.56 (p, *J* = 6.6 Hz, 2H), 1.43−1.29 (m, 6H); (*Z*) 7.27−7.26 (m, 2H), 7.19−7.04 (m, 6H), 5.51−5.45 (m, 1H), 5.33 (dt, *J* = 11.0, 6.8 Hz, 1H), 4.73 (s, 2H), 4.60 (s, 2H), 4.22 (s, 2H), 3.75 (s, 6H), 3.68 (s, 2H), 3.33 (t, *J* = 6.0 Hz, 2H), 2.70 (d, *J* = 7.0 Hz, 2H), 2.33 (s, 3H), 2.04 (td, *J* = 7.0 Hz, 2H), 1.58−1.29 (m, 8H); ^{13}C NMR (125 MHz, $CDCl_3$, ppm) δ (*E*) 199.2, 170.7, 143.0, 137.1, 136.8, 135.7, 133.9, 129.6, 129.4, 129.3, 127.8, 127.6, 127.2, 123.5, 90.5, 90.3, 71.0, 70.2, 58.7, 53.0, 52.5, 50.5, 35.7, 34.7, 31.1, 29.0, 27.0, 26.5, 24.7, 21.4; (*Z*) 199.2, 170.7, 142.7, 137.3, 136.7, 134.0, 131.6, 129.7, 129.1, 128.0, 126.9, 122.8, 94.7, 90.4, 71.4, 70.4, 58.2, 54.2, 52.7, 51.7, 39.0, 32.0, 30.9, 27.7, 27.1, 25.7, 24.8 (3 C's, absent); IR (neat, ATR, cm^{-1}) 3031, 2934, 2093, 2051, 2018, 1735, 1437, 1207, 1160, 1092; HRMS (ESI) *m*/*z* [M + Na]$^+$ calcd for $C_{39}H_{41}Co_2NNaO_{13}S$ 904.0855, found 904.0874.

Cyclopentenone 65. A flame-dried flask was charged with complex **49** (115 mg, 0.21 mmol) and acetonitrile (20 mL). The solution was heated to 50 °C, and NMO (147 mg, 1.25 mmol in 10 mL MeCN) was added dropwise over 14 h. Upon completion, the reaction was cooled to rt, solvent was removed in vacuo, and chromatography with 1:1 hexanes/Et_2O gave 27 mg (44% yield) of a colorless oil: ^{1}H NMR (400 MHz, $CDCl_3$, ppm) δ (Major) 4.70 (d, *J* = 16.4 Hz, 1H), 4.53 (d, *J* = 16.0 Hz, 1H), 4.34 (dd, *J* = 14.0, 14.0 Hz, 1H), 4.24 (d, *J* = 12.8 Hz, 1H), 4.04 (d, *J* = 12.8 Hz, 1H), 3.50−3.44 (m, 1H), 3.42−3.36 (m, 1H), 3.24−3.18 (m, 2H), 2.26 (bt, *J* = 2.6 Hz, 1H), 2.19−2.11 (m, 1H), 1.76−1.64 (m, 1H), 1.65−1.50 (m, 2H), 1.47−1.14 (m, 14H), (Minor) 4.66 (d, *J* = 16.8 Hz, 1H), 4.60 (d, *J* = 16.4 Hz, 1H), 4.19 (dt, *J* = 11.6, 0.8 Hz, 1H), 4.15 (dd, *J* = 8.4, 8.4 Hz, 1H), 3.96 (d, *J* = 11.6 Hz, 1H), 3.56 (dd, *J* = 11.2, 8.4 Hz, 1H), 3.50−3.44 (m, 1H), 3.36−3.18 (m, 2H), 2.72−2.67 (m, 1H), 1.76−1.64 (m, 2H), 1.47−1.14 (m, 16H); ^{13}C NMR (100 MHz, CDCl3, ppm) δ (major) 209.7, 180.2, 133.9, 71.4, 69.5, 64.9, 61.4, 49.2, 47.5, 28.1, 27.7, 27.3, 26.7, 26.6, 26.4, 26.0, 25.61, 24.5; (minor) 210.4, 177.4, 130.9, 70.7, 67.3, 65.3, 61.8, 49.7, 47.7, 28.7, 27.8, 27.6, 26.9, 25.59, 25.2, 24.2, 23.7 (1 C signal overlaps around 27.0 ppm); IR (neat ATR) 2925, 2855, 1712, 1676, 1094, 1025, 986, 889, 733; HRMS (DART) *m*/*z* [M + H]$^+$ calcd for $C_{18}H_{29}O_3$ 293.2111, found 293.2101.

Cyclopentenone 66. Prior to reaction, glassware was soaked in concentrated nitric acid for 24 h, then KOH/*i*PrOH/H_2O for 24 h.[53] Acetonitrile was submitted to three freeze/pump/thaw cycles prior to use. A flame-dried flask with complex **50** (100 mg, 0.113 mmol) was flushed with nitrogen, and then acetonitrile (11 mL) was added. An acetonitrile (5.0 mL) solution of NMO (80 mg, 0.681 mmol) was added dropwise with stirring at 50 °C over 14 h. The mixture was stirred at 50 °C for another 4 h. Solvent was removed in vacuo. Chromatography with 3:1 hexanes/EtOAc gave 28 mg (40% yield, 5.5:1 diastereomeric ratio, *trans* major) of a clear colorless oil. Further chromatography was repeated with preparative TLC in 2:1 hexanes/EtOAc to yield pure diastereomers for characterization (see ***trans*-66** and ***cis*-66**, below).

***trans*-Cyclopentenone (*trans*-66):** ^{1}H NMR (400 MHz, $CDCl_3$, ppm) δ 7.69 (d, *J* = 8.4 Hz, 2H), 7.53−7.49 (m, 1H), 7.37−7.35 (m, 1H), 7.31 (2, *J* = 8.0 Hz, 2H), 7.19−7.16 (m, 2H), 4.37 (d, *J* = 16.4 Hz, 1H), 4.35 (d, *J* = 12.4 Hz, 1H), 4.30 (d, *J* = 12.8 Hz, 1H), 4.15 (d, *J* = 16.4 Hz, 1H), 4.13 (d, *J* = 14.0 Hz, 1H), 3.85 (d, *J* = 14.0 Hz, 1H), 3.80 (s, 3H), 3.76 (s, 3H), 3.58−3.47 (m, 2H), 3.32 (d, *J* = 19.6 Hz, 1H), 3.23 (d, *J* = 19.6 Hz, 1H), 2.63 (dd, *J* = 12.6, 7.8 Hz, 1H), 2.44 (s, 3H), 2.31 (bdd, *J* = 12.4, 7.8 Hz, 1H), 1.84 (m, 1H), 1.63−1.37 (m, 8H), 1.41 (dd, *J* = 12.4, 12.4 Hz, 1H), 1.27 (p, *J* = 6.5 Hz, 2H); ^{13}C NMR (125 MHz, $CDCl_3$, ppm) δ 210.1, 183.4, 171.7, 171.1, 143.6, 136.0, 135.8, 134.7, 130.7, 129.8, 127.5, 127.32, 127.30, 127.2, 127.0,

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70.0, 68.7, 60.9, 53.2, 53.1, 51.9, 48.9, 48.4, 42.1, 38.1, 34.7, 26.9, 26.8, 26.4, 24.1, 23.7, 21.5; IR (neat, ATR, cm^{-1}) 3006, 2951, 2864, 1737, 1715, 1365, 1218, 1159, 665; HRMS (DART) m/z $[M + H]^+$ calcd for $C_{34}H_{42}NO_8S$ 624.2653, found 624.2629.

***cis*-Cyclopentenone (*cis*-66):** ^1H NMR (500 MHz, C_6D_6, ppm) δ 7.69 (d, J = 7.0 Hz, 1H), 7.67 (d, J = 8.5 Hz, 2H), 7.29 (d, J = 8.0 Hz, 1H), 7.12−7.09 (m, 1H), 7.03, (t, J = 7.5 Hz, 1H), 6.75 (d, J = 8.0 Hz, 2H), 4.65 (d, J = 17.0 Hz, 1H), 4.43 (d, J = 12.0 Hz, 1H), 4.41 (d, J = 16.5 Hz, 1H), 4.24 (d, J = 15.0 Hz, 1H), 4.04 (d, J = 12.0 Hz, 1H), 3.91 (d, J = 14.5 Hz, 1H), 3.60 (d, J = 20.5 Hz, 1H), 3.50 (d, J = 20.0 Hz, 1H), 3.40−3.28 (m, 2H), 3.283 (s, 6H), 2.66 (ddd, J = 13.5, 6.8, 6.8 Hz, 1H), 2.28 (dd, J = 12.5, 7.5 Hz, 1H), 2.66 (ddd, J = 13.5, 6.8, 6.8 Hz, 1H), 1.97 (ddd, J = 11.0, 6.8, 4.0 Hz, 1H) 1.85 (s, 3H), 1.67 (dd, J = 13.0 Hz, 1H), 1.37−1.08 (m, 10H); ^{13}C NMR (125 MHz, $CDCl_3$, ppm) δ 211.1, 181.8, 171.9, 170.8, 143.3, 136.6, 135.8, 135.2, 129.6, 128.8, 128.6, 127.7, 127.5, 127.3, 126.9, 70.2, 69.6, 60.6, 53.3, 53.1, 48.6, 48.5, 47.9, 41.7, 34.4, 33.8, 27.19, 27.17, 27.1, 24.3, 24.2, 21.5; IR (neat, ATR, cm^{-1}) 3022, 3003, 2970, 1738, 1435, 1366, 1355, 1228, 1217, 1206; HRMS (DART) m/z $[M + H]^+$ calcd for $C_{34}H_{42}NO_8S$ 624.2653, found 624.2638.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.joc.7b01369.

NMR spectra, computational methods, computed coordinates, and computed energies (PDF)

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Notes

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