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Lewis Acid Mediated Cyclizations: Diastereoselective Synthesis of Six- to Eight-Membered Substituted Cyclic Ethers

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Abstract

Cyclic ethers are widely abundant in natural products. Cyclic ether templates are also utilized in drug design and medicinal chemistry. Although the synthetic processes for this class of compounds have been studied extensively with respect to five- and six-membered rings, medium-sized cyclic ethers are synthetically more challenging due to a variety of factors. Herein, we report our results on the Lewis acid catalyzed synthesis of medium-sized cyclic ethers in a diastereoselective manner.

Abstract

Keywords

cyclization; cyclic ethers; diastereoselectivity; Lewis acids; oxacycles; oxepanes; oxocenes; polycycles

Functionalized cyclic ethers are structural features of a variety of bioactive natural products.
1,2 There are numerous six- to nine-membered cyclic ethers embedded in a variety of natural

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products. These include polyether antibiotics,³ macrolide antibiotics,⁴ C-glycosides,⁵ C-nucleotides,⁶ marine toxins,^{7,8} lauroxanes,⁹ and annonaceous acetogenins.¹⁰ Many marine polycyclic ethers, like brevetoxins, ciguatoxins, and maitotoxin, possess unique six-, seven-, and eight-membered fused cyclic ether ring systems. Numerous synthetic methods were developed for the construction of these fused polyethers.^{11,12} Cyclic ether subunits have also been utilized in drug discovery and medicinal chemistry. We have designed a range of cyclic-ether-derived templates and scaffolds in the context of our nonpeptide enzyme inhibitor research.^{13,14} A few representative examples of cyclic-ether-containing natural products, isolaurepan (**1**),¹⁵ laurencin (**2**),¹⁶ HIV-1 protease inhibitor **3**,¹⁷ and prostacyclin derivative **4**,¹⁸ are shown in Figure 1. Over the years, considerable interest and research efforts have been devoted toward the synthesis of various polyether ring sizes and their application in synthesis.^{2,19,20} In general, five- and six-membered cyclic ethers are widely prevalent in natural products and a number of general synthetic strategies have been reported for their construction.^{21–23} For six-membered ether ring cycles, particularly for substituted tetrahydropyrans, hetero-Diels–Alder reactions,²⁴ Prins cyclizations,²⁵ Petasis–Ferrier rearrangements,²⁶ and domino Michael/cyclization reactions²⁷ have been extensively utilized to construct multiple stereocenters. Interestingly, the synthesis of substituted medium-sized cyclic ethers, particularly seven-, eight-, and nine-membered rings, is vastly unexplored due to increased enthalpic and entropic penalties contributing to medium-size-ring formation.²⁸ Herein, we describe our work on the Lewis acid catalyzed synthesis of substituted medium-sized cyclic ether ring systems.

As part of our continuing interest in the synthesis of cyclic ethers, we developed a number of synthetic methodologies to construct these subunits. As represented in Scheme 1, Hosomi and co-workers reported the PtCl₂ (0.5 mol%) and AgOTf (1 mol%) catalyzed reaction of alkenol **5a** and benzaldehyde to achieve a diastereoselective synthesis of *trans*-2,3-disubstituted tetrahydropyran derivative **6a**.²⁹ Loh and co-workers showed that the In(OTf)₃-catalyzed reaction of alkenol **5a** and furfural provided a *trans*-2,3,6-tri-substituted tetrahydropyran ring via an oxonium–ene-type reaction, to provide **7a**.³⁰ The reaction proceeded with an olefin migration followed by Prins-type cyclization. On the basis of these previous results, we subsequently developed an inexpensive catalytic system to promote the synthesis of substituted tetrahydropyran rings with high diastereoselectivity and good yields.³¹

As shown in Scheme 2, the reaction of alkenol **8** and benzaldehyde in the presence of a catalytic amount of Cu(OTf)₂ (15 mol%) and *cis*-1,2-bis(diphenylphosphino)ethylene (15 mol%) provided *trans*-tetrahydropyran derivative **9a** with high diastereoselectivity. Similarly, the reaction of alkenol **8** with benzyloxyacetaldehyde afforded *trans*-tetrahydropyran **10a** in a highly diastereoselective manner (most results indicated >20:1 dr).

We have carried out this reaction with an optically active phenyl-substituted alkenol and showed that the resulting optically active tetrahydropyran derivative was obtained without erosion of optical purity.³¹ This indicates that the reaction does not involve a [3,3]-sigmatropic rearrangement pathway.³² We then attempted an FeCl₃-catalyzed reaction with *cis*-alkenol **11** and *p*-nitrobenzaldehyde. As shown in Scheme 3, this resulted in a tandem Prins and Friedel–Crafts cascade cyclization, leading to polycyclic fused hexahydro-1*H*-

benzo[*f*]isochromene derivative **12** in excellent yield (81%) and diastereoselectivity (dr >20:1). Subsequently, we found that this cascade reaction can be carried out efficiently using inexpensive FeCl₃ as the catalyst (10 to 15 mol%) in the presence of 4 Å molecular sieves in CH₂Cl₂.³³ Thus, *cis*-alkenol **11** provided *cis*-fused hexahydro-2*H*-benzo[*f*]isochromene derivative **12** in high yield and excellent diastereoselectivity (Scheme 3). Similarly, the reaction of *trans*-alkenol **13** provided *trans*-ring-fused product **14** in high diastereoselectivity. Further, the reaction of secondary alkenol **15** with benzaldehyde afforded the highly functionalized tetrahydropyran derivative **16** in excellent yield and diastereoselectivity.

We have expanded the scope of the Cu(OTf)₂- and bisphosphine-catalyzed reactions to a variety of substituted alkenols and aldehydes, to provide highly functionalized tetrahydropyran derivatives in good to excellent yields and generally with excellent diastereoselectivity (dr >20:1).³¹ During the course of these olefin migration and Prins cyclization studies, we observed that the reaction of methyl-substituted alkenol **5a** and aromatic aldehydes afforded substituted tetrahydropyran derivatives as the only isolated product. However, as shown in Scheme 4, although the reaction of substituted alkenol **5a** and benzyloxyacetaldehyde in the presence of Cu(OTf)₂ (15 mol%) and bisphosphine (15 mol%) provided the desired tetrahydropyran derivative **19** as the major product in 55% yield as a single diastereomer, in this reaction an eight-membered cyclic ether, 3,4,7,8-tetrahydro-2*H*-oxocene **20**, was obtained as a minor product in 11% isolated yield. The stereochemical outcome for the formation of tetrahydropyran derivative **19** can be rationalized based on the Zimmerman–Traxler³² transition-state models **17a** and **17b** (Scheme 4). Olefin migration followed by cyclization could proceed through favored transition state **17b**, leading to product **19**. For the formation of the eight-membered oxocene derivative, minor product **20**, we presume a direct nucleophilic attack by the olefin onto the oxocarbenium ion **18a**. The resulting carbenium ion may be stabilized through an alternative oxocarbenium ion **18b**, which upon proton elimination forms the minor oxocene product **20**. To further expand the scope of this reaction to form medium-sized ring systems, we then investigated other Lewis acid catalyzed reactions to improve the ratio of oxocene product over tetrahydropyran derivatives. Kobayashi and co-workers have demonstrated the utility of Sc(OTf)₃ as an efficient Lewis acid in the Diels–Alder reaction.³⁴ Recently, Sc(OTf)₃ has been employed in a variety of carbon–carbon and carbon–heteroatom bond-forming reactions.³⁵

We first explored the cyclization reaction of alkenol **5a** with *p*-nitrobenzaldehyde in the presence of a catalytic amount of Sc(OTf)₃ and *p*-toluenesulfonic acid (*p*-TSA). The results are shown in Table 1. The reaction performed in the presence of Sc(OTf)₃ (10 mol%), without *p*-TSA, in CH₂Cl₂ at 0 °C to 23 °C for 12 hours provided only a small amount of substituted oxocene derivative **22a** (entry 1). We then investigated this cyclization in the presence of a combination of *p*-TSA (30 mol%) and Sc(OTf)₃ (10 mol%). Similar conditions were utilized by Yadav and co-workers for a Prins cyclization.³⁶ These reactions were carried out in CH₂Cl₂ and toluene, to provide tetrahydropyran derivative **21** as the major product (entries 2 and 3). In MeCN, the reaction provided oxocene **22a** as the major product (**22a**/**21** 10:1); however, the yield of the combined products was only 27% (entry 4). When the reaction was carried out in a mixture (1:1) of MeCN and CH₂Cl₂, oxocene derivative **22a**

was obtained as the major product (**22a**/**21** 5:1) and the combined yield improved to 37% (entry 6). The cyclization reaction performed in CH₂Cl₂–MeCN with Sc(OTf)₃ (10 mol%) in the absence of Brønsted acid provided a similar product ratio, but the combined yield was slightly lower (entry 7). Interestingly, increasing the Sc(OTf)₃ to 20 mol% improved the reaction yield, but decreased the oxocene to tetrahydropyran ratio significantly (entry 8). Also, reducing *p*-TSA to 10 mol% resulted in a decreased combined yield, with oxocene **22a** being obtained as the major product (2.4:1, entry 9).

We then investigated the substrate scope of this cyclization using Sc(OTf)₃ (10 mol%) and *p*-TSA (30 mol%) in a mixture (1:1) of MeCN and CH₂Cl₂. The results are summarized in Table 2. With *p*-fluoro-*m*-nitrobenzaldehyde, the reaction provided a 1:1 mixture of tetrahydropyran derivative **23** and oxocene **22b** in 32% yield (entry 1). The reaction with *p*-bromobenzaldehyde provided tetrahydropyran derivative **24** exclusively. Reaction with benzyloxyacetaldehyde afforded a 60:40 mixture of oxocene **20** and tetrahydropyran derivative **19** in 23% yield (entry 3). Reaction of *p*-methoxybenzaldehyde or 3-phenylpropionaldehyde provided the respective tetrahydropyran derivatives, **25** and **26**, exclusively (entries 4 and 5).

We have also investigated the effect of lanthanide(III) triflates to improve the product ratio in favor of the oxocene. In particular, we examined dysprosium(III) triflate [Dy(OTf)₃] for this cyclization reaction. Dy(OTf)₃ is commercially available, inexpensive, and less toxic and much less sensitive to moisture than Sc(OTf)₃.³⁷ Dy(OTf)₃ has been utilized as a Lewis acid in a variety of Lewis acid catalyzed carbon–carbon bond-forming reactions.³⁸ In an effort to assess the scope and utility of Dy(OTf)₃ over Sc(OTf)₃, we initially carried out the cyclization of 6-methylhept-6-en-2-ol (**5a**) with *p*-nitrobenzaldehyde in a mixture (1:1) of MeCN and CH₂Cl₂ in the presence of *p*-TSA (30 mol%), and the results are summarized in Table 3. The use of Dy(OTf)₃ (10 mol%) alone, without *p*-TSA, did not provide any appreciable yield of oxocene product (entry 1). The use of *p*-TSA (30 mol%) in combination with Dy(OTf)₃ (10 mol%) afforded oxocene product **22a** as the only isolated product, in 26% yield (entry 2). The use of camphorsulfonic acid (CSA, 30 mol%) in place of *p*-TSA showed comparable results (entry 3). The use of 2 equivalents of aldehyde resulted in the retention of oxocene product **22a** as the major product (77:23), with an improved combined yield of 70% (entry 4). Further reactions with 20 mol% and 30 mol% of Dy(OTf)₃ and 2 equivalents of aldehyde in the presence of *p*-TSA (30 mol%) did not result in an improved product ratio in favor of **22a**; furthermore, the overall combined yields were also reduced (entries 5 and 6).

The substrate scope for the Dy(OTf)₃-catalyzed reactions is summarized in Table 4. The reaction proceeded best when the aromatic aldehyde contained electron-withdrawing substituents. With *p*-fluoro-*m*-nitrobenzaldehyde, oxocene product **22b** and tetrahydropyran **23** were obtained in a nearly 1:1 ratio, in 46% combined yield (entry 1). The reaction with *p*-bromobenzaldehyde provided only 6% yield of the combined products (entry 2). The cyclization reaction with *p*-methoxybenzaldehyde also provided a very poor yield, in this case with no oxocene product (entry 4). The reaction with benzyloxyacetaldehyde afforded oxocene product **20** as the major product (**20**/**19** 2:1); however, the reaction yield was very

low (entry 3). The reaction of *m*-tolualdehyde gave oxocene product **22f** and tetrahydropyran derivative **27** in a 1:1 ratio, with a combined yield of only 7% (entry 5).

Aiming to form the oxocene core as the major product, we further explored other Lewis acids. Overman and co-workers reported a $\text{BF}_3 \cdot \text{OEt}_2$ -catalyzed intramolecular Prins reaction, during the synthesis of (+)-laurencin.³⁹ As shown in Scheme 5, the $\text{BF}_3 \cdot \text{OEt}_2$ -catalyzed cyclization of vinyl sulfide **28** afforded oxocene derivative **29** in 57% yield. In this reaction, the corresponding tetrahydropyran derivative **30** was obtained in 4% yield.

Based upon this result, we elected to investigate $\text{BF}_3 \cdot \text{OEt}_2$ as catalyst in our cyclization of **5a** and *p*-nitrobenzaldehyde.⁴⁰ The results are summarized in Table 5. The reaction of alkenol **5a** and *p*-nitrobenzaldehyde in the presence of 3 equivalents of $\text{BF}_3 \cdot \text{OEt}_2$ in *t*-BuOMe at 0 °C resulted in the formation of oxocene derivative **22a** and a new *exo*-olefin derivative **31a** in a 76:24 ratio and 33% combined yield (entry 1). Interestingly, in this reaction we were not able to identify the six-membered Prins cyclization product **21** by ¹H NMR analysis of the crude product. In an effort to improve the yield of *endo*-oxocene product **22a**, we examined reactions in CH_2Cl_2 with decreased amounts of $\text{BF}_3 \cdot \text{OEt}_2$ (entries 2–4). The use of 0.2 equivalents of $\text{BF}_3 \cdot \text{OEt}_2$ in CH_2Cl_2 provided the best results with an *endo/exo*-olefin oxocene ratio of 98:2 and a modest yield of 38% (entry 3).⁴⁰ In 2011, Cho and co-workers reported TMSOTf-catalyzed Prins-type cyclization, leading to oxepane derivatives.⁴¹ We therefore explored TMSOTf-catalyzed reactions, aiming to improve the yield of oxocene product **22a**. Reaction of alkenol **5a** and *p*-nitrobenzaldehyde with 1 equivalent of TMSOTf in *t*-BuOMe at 0 °C resulted in the improvement of yield and *endo/exo*-olefin oxocene product ratio over the $\text{BF}_3 \cdot \text{OEt}_2$ -catalyzed reaction (entries 1 and 5). A further survey of solvents showed that the cyclization reaction in THF with 1 equivalent of TMSOTf was optimum (entries 6–10).

The substrate scope of the TMSOTf-catalyzed reaction with a number of alkenols was examined, with a variety of substituted aromatic aldehydes, 3-phenylpropionaldehyde, and benzyloxyacetaldehyde. The results are shown in Table 6, where the structure of the major *endo*-olefin oxocene product is given for each entry, along with the ratio of *endo/exo*-olefin isomer as determined by ¹H NMR analysis. We first examined the compatibility of alkyl substituents on the alkenol substrate in reactions with *p*-nitrobenzaldehyde (entries 2–5); the TMSOTf-catalyzed conditions provided consistently good to excellent yields of *endo*-olefin products with excellent *endo*-olefin selectivity.

Next, we tested a variety of aldehyde substrates using alkenol **5a** (R = Me) as the starting material. *m*-Nitrobenzaldehyde provided a 65% yield of *endo*-olefin product **22k** and its *exo*-isomer **31k** in a 91:9 ratio (entry 6). *o*-Nitrobenzaldehyde also provided a 58% yield of cyclization products with good *endo*-olefin selectivity (entry 7). Reactions with moderately electron-deficient aldehydes, such as *p*-fluoro-, *p*-(trifluoromethyl)-, and *p*-chlorobenzaldehyde, gave the corresponding *endo*-olefin oxocenes as the major product; however, yields were moderate (entries 8–10). Reactions of alkenol **5a** with 3-phenylpropionaldehyde and benzyloxyacetaldehyde also provided the *endo*-olefin oxocenes as the major product (entries 11 and 12), but with a substantial reduction in yields compared to electron-deficient aromatic aldehydes. Unfortunately, moderately electron-donating *m*-

tolualdehyde provided a very low yield of cyclization product (entry 13). Similarly, 2-naphthaldehyde provided only 16% yield of oxocene products (entry 14). Finally, the reaction of alkenol **5a** with *p*-fluoro-*m*-nitrobenzaldehyde gave 41% yield of oxocene products with an *endo/exo*-olefin ratio of 91:9 (entry 15).

In general, these *endo/exo*-isomer pairs are difficult to separate by silica gel chromatography. To provide conclusive structural evidence, we have carried out ozonolytic cleavage of the mixture of **22k/31k** isomers, as shown in Scheme 6. The resulting products **32** and **33** were separated by silica gel chromatography. Wittig olefination of ketone **33** afforded the *exo*-olefin product **31k** which showed identical ¹H NMR and ¹³C NMR data corresponding to the minor product formed during the TMSOTf-catalyzed cyclization (Table 6, entry 6). ¹H NMR NOESY experiments were used for assignment of the stereochemistry of the oxocene products. Further support of the structural assignment was obtained by determination of the X-ray crystal structure of the corresponding sulfonamide derivative of the major oxocene product **22a**.⁴⁰

In efforts to expand our cyclic ether synthetic method, seven-membered oxepines have been synthesized. Using 5-methylhex-5-en-2-ol (**34**), TMSOTf, 4 Å molecular sieves, and a variety of aldehydes, oxepines were synthesized with high diastereoselectivity (dr >20:1), with an unidentified minor isomer. The results are summarized in Table 7. The presence of one electron-withdrawing substituent on the aromatic aldehyde (entries 1 and 2) resulted in moderate yields of the corresponding oxepine products **35** and **36**. The reaction with 3-phenylpropionaldehyde gave oxepine product **37** in moderate yield (entry 3), while the use of benzyloxyacetaldehyde led to a decreased yield of product **38** (entry 4). Similarly, electron-deficient *p*-fluoro-*m*-nitrobenzaldehyde produced oxepine **39** in only 28% yield (entry 5). Interestingly, an aldehyde with both an electron-donating and an electron-withdrawing substituent (entry 6) gave a moderate yield (48%) of oxepine **40**. Finally, ethyl glyoxylate as the substrate provided a 23% yield of oxepine **41** (entry 7), displaying the potential for further modifications external to the oxepine framework.

Further assignment of the relative stereochemistry was carried out using ¹H NMR NOESY experiments on compound **35** (Figure 2). The depicted conformation is based on the observed strong NOESY correlations. Thus, the strong NOESY correlation between H_E and H_D supports the *cis* stereochemical assignment between the methyl and aromatic substituents. The additional NOESY correlations between H_C–H_I, H_I–H_K, and H_H–H_J support the conformation shown.

The *cis* stereochemical outcome can be rationalized based on the transition-state models shown in Scheme 7. Steric clash, as seen in structure **42b**, is likely the driving force which favors the *cis* outcome over the *trans* outcome. Successive cyclization, followed by proton elimination, yields the *cis*-product **43a**; formation of the *trans*-product **43b** was not observed by ¹H NMR analysis.

In addition to the seven-membered oxepine syntheses, we were able to construct seven-membered oxepanes using 7-methyloct-7-en-2-ol (**44**) as the substrate. After constructing **44**, we then subjected it to reaction conditions which included TMSOTf, 4 Å molecular

sieves, and nitrobenzaldehydes. For this reaction, it was necessary to increase the amount of TMSOTf to 1.2 equivalents, relative to **44**. As summarized in Table 8, the reaction with *p*-nitrobenzaldehyde yielded oxepane **45** in 14% yield (entry 1), while *m*-nitrobenzaldehyde as the substrate gave oxepane **46** in 29% yield (entry 2). The diastereomers shown were isolated from a reaction mixture with compounds that have not been fully analyzed.

The oxepane outcome is a similar result to that observed with our Cu(OTf)₂-bisphosphine ligand protocol. It was suspected that the olefin migrates to the internal position, subsequently cyclizing to form the oxepane core. We tested our hypothesis by first subjecting 7-methyloct-7-en-2-ol (**44**) to TMSOTf in THF with 4 Å molecular sieves at 0 °C. These conditions provided **47** in 93% yield (Scheme 8). Subsequently, product **47** was subjected to the Prins-type cyclization conditions with *p*-nitrobenzaldehyde, and indeed gave oxepane **45** in 42% yield. Based upon this, the isomerization seems to occur first, under the reaction conditions to form **47** *in situ*, followed by cyclization and proton elimination to give the oxepane scaffold.

To determine the X-ray crystal structure, oxepane derivative **45** was first subjected to reduction conditions using zinc dust and acetic acid, as shown in Scheme 9. The resulting aniline derivative was then reacted with *p*-bromobenzenesulfonyl chloride to yield sulfonamide **48**. This compound was then recrystallized from CH₂Cl₂/MeOH at 23 °C to yield white needles. The single-crystal X-ray analysis supports the *cis* stereochemical assignment shown.⁴¹

Further assignment of the relative stereochemistry was carried out using ¹H NMR NOESY experiments on compound **45** (Figure 3). The depicted conformation is based on the X-ray crystal structure of **48**. The observed strong NOESY correlation between H_E and H_C supports the *cis* stereochemical assignment between the methyl and aromatic substituents of **45**. Additional NOESY correlations between H_C-H_K, H_E-H_K, and H_F-H_K support the notion of all substituents on the oxepane core having a *cis* relationship. The observed NOESY correlations between H_M-H_J and H_M-H_L further support the *cis* relationship.

The *cis* stereochemical outcome can be rationalized based on the transition-state models shown in Scheme 10. The transition-state structures **49a** and **49b** are based on the X-ray crystal structure of **48** and the positive charge distribution is based upon the results of our isomerization studies. After the olefin has migrated to the internal position, steric hindrance is likely the driving force which favors the *cis* stereochemistry (**50a**), as seen with the oxepine systems.

In summary, medium-sized cyclic ethers are subunits of numerous biologically active molecules; however, the direct synthesis of these subunits is limited. Over the years, we have investigated a variety of catalytic methods for the synthesis of functionalized cyclic ethers with high diastereoselectivity and yields. In particular, a mild Cu(OTf)₂ and bisphosphine complex provided access to substituted tetrahydropyran rings through an olefin migration, followed by Prins-type cyclization. Interestingly, this reaction protocol with benzyloxyacetaldehyde provided the tetrahydropyran derivative as the major product and an eight-membered oxocene derivative as the minor product. We subsequently investigated a

number of other Lewis acid catalyzed conditions, including $\text{Sc}(\text{OTf})_3$ and $\text{Dy}(\text{OTf})_3$ in the presence of a catalytic amount of Brønsted acid. As it turned out, with 6-methylhept-6-en-2-ol and *p*-nitrobenzaldehyde, $\text{Sc}(\text{OTf})_3$ (10 mol%) and *p*-TSA (30 mol%) in a mixture of CH_2Cl_2 and MeCN resulted in the oxocene product as the major product over the tetrahydropyran derivative, as a 83:17 mixture. However, the yield of the combined products was 37%. Our optimization efforts with $\text{Dy}(\text{OTf})_3$ also provided similar results. We subsequently developed a TMSOTf-catalyzed Prins-type cyclization for the synthesis of a variety of substituted oxocene derivatives with 1-alkyl-5-methylhexenols and aromatic aldehydes. This protocol is also suitable for the synthesis of seven-membered cyclic ethers with excellent diastereoselectivity and good yields. Further studies, particularly on the subject of substrate scopes and application, are currently underway in our laboratory.

All reagents were purchased from Sigma-Aldrich, Fisher-Acros, Oakwood Chemical, or Alfa-Aesar. Liquid reagents were distilled and solid reagents were solvated in EtOAc, followed by washes with sat. NaHCO_3 , drying over Na_2SO_4 , and finally removal of the solvent in vacuo. Methyltriphenylphosphonium bromide was dried by heating at 150 °C under reduced pressure overnight. The following reaction solvents were distilled prior to use: CH_2Cl_2 and toluene from CaH_2 ; Et_2O and THF from Na/benzophenone. MeCN and DME were dried over activated 4 Å molecular sieves. All reactions were performed at 0 °C under an argon atmosphere in oven-dried glassware. TLC analysis was run using glass-backed thin-layer silica gel chromatography plates (SiliCycle; 60 Å, 250 µm thickness, F-254 indicator). All solvent systems are given as volume/volume ratios. Flash chromatography was performed using 230–400 mesh, 60 Å pore diameter silica gel (SiliCycle). Preparative HPLC was performed on all compounds where impurities remained after flash column chromatography. The system used was comprised of an Agilent 1100 series dual-piston pump, YMC-Pack ODS-A column (250 × 20 mm i.d.), variable wavelength detector, and Agilent 1260 series fraction collector. The mobile phase was HPLC-grade MeCN at 10 mL/min and the hardware was controlled by ChemStation software. ^1H and ^{13}C NMR spectra were recorded at room temperature on a Bruker AV-500 spectrometer, using a CryoProbe. Chemical shifts (δ values) are reported in parts per million, and are referenced to the CDCl_3 residual solvent peak (7.26 ppm). Data are reported as: δ value (multiplicity, *J* value, integration), where s = singlet, d = doublet, t = triplet, q = quartet, p = quintet, h = hexet, and m = multiplet. Mass spectrometry experiments were performed under EI/CI, ESI+, or APCI conditions (Hewlett Packard Engine, Agilent 1290, 6320 LCMS, Thermofisher LTQ). The ratios of eight- to six-membered-ring compounds were determined by ^1H NMR analysis.

Substituted Cyclic Ethers; General Procedure

To a 10-mL round-bottomed flask with a stir bar and activated molecular sieves, under argon, was added THF (0.2 M) and aldehyde (1.2 equiv). The flask was cooled to 0 °C for 10 min, after which TMSOTf (1.0 or 1.2 equiv) was added dropwise. After stirring for 5 min, a chilled solution (−78 °C) of 6-methylhept-6-en-2-ol (**5a**) or 5-methylhex-5-en-2-ol (**34**) (50 mg, 1.0 equiv) in THF (0.2 M) was added drop-wise over 5 min. The reaction was monitored by TLC (EtOAc–hexanes, 5:95) until completion. The reaction was then quenched with sat. NaHCO_3 and the mixture was extracted with EtOAc (3 ×). Then, Na_2SO_4

was added to the combined organic layers, which were then filtered, concentrated, and purified by column chromatography (EtOAc–hexanes, 5:95) to yield the cyclic ether products.

(Z)-2,6-Dimethyl-8-(*p*-nitrophenyl)-3,4,7,8-tetrahydro-2*H*-oxocine (22a)

Following the general procedure, activated molecular sieves (60 mg), *p*-nitrobenzaldehyde (71 mg, 0.47 mmol, 1.2 equiv) in THF (2.4 mL, 0.2 M), TMSOTf (0.07 mL, 0.39 mmol, 1.0 equiv), and 6-methylhept-6-en-2-ol (50 mg, 0.39 mmol, 1.0 equiv) in THF (2.0 mL, 0.2 M) gave **22a** as a clear, pale yellow oil; yield: 74 mg (73%); 98:2 (*endo/exo*).

¹H NMR (500 MHz, CDCl₃): δ = 8.18 (d, *J* = 8.7 Hz, 2 H), 7.54 (d, *J* = 8.8 Hz, 2 H), 5.58–5.49 (m, 1 H), 4.45 (d, *J* = 9.1 Hz, 1 H), 3.77–3.66 (m, 1 H), 2.71 (dd, *J* = 13.9, 9.5 Hz, 1 H), 2.55–2.44 (m, 1 H), 2.14 (dd, *J* = 14.0, 1.8 Hz, 1 H), 2.04–1.96 (m, 1 H), 1.78 (s, 3 H), 1.75–1.67 (m, 1 H), 1.63–1.54 (m, 1 H), 1.14 (d, *J* = 6.3 Hz, 3 H).

¹³C NMR (125 MHz, CDCl₃): δ = 151.78, 146.81, 134.37, 126.63, 126.05, 123.42, 80.34, 76.07, 42.47, 38.18, 25.30, 24.42, 22.3.

HRMS (EI/CI)⁺: *m/z* [M + H]⁺ calcd for C₁₅H₂₀NO₃: 262.1443; found: 262.1440.

(Z)-6-Methyl-8-(*p*-nitrophenyl)-3,4,7,8-tetrahydro-2*H*-oxocine (22g)

Following the general procedure, activated molecular sieves (60 mg), *p*-nitrobenzaldehyde (80 mg, 0.53 mmol, 1.2 equiv) in THF (2.64 mL, 0.2 M), TMSOTf (0.08 mL, 0.44 mmol, 1.0 equiv), and 5-methylhex-5-en-1-ol (50 mg, 0.44 mmol, 1.0 equiv) in THF (2.0 mL, 0.2 M) gave **22g** as a clear, pale yellow oil; yield: 76 mg (70%); 90:10 (*endo/exo*).

¹H NMR (500 MHz, CDCl₃): δ = 8.19 (d, *J* = 8.8 Hz, 2 H), 7.53 (d, *J* = 8.7 Hz, 2 H), 5.53 (ddt, *J* = 9.7, 6.8, 1.5 Hz, 1 H), 4.47 (dd, *J* = 9.3, 2.0 Hz, 1 H), 4.04 (ddd, *J* = 12.0, 5.0, 2.1 Hz, 1 H), 3.52 (dt, *J* = 11.9, 3.3 Hz, 1 H), 2.69 (dd, *J* = 14.0, 9.3 Hz, 1 H), 2.49–2.38 (m, 1 H), 2.17 (dd, *J* = 14.0, 2.1 Hz, 1 H), 2.11–1.95 (m, 2 H), 1.77 (s, 3 H), 1.54–1.44 (m, 1 H).

¹³C NMR (125 MHz, CDCl₃): δ = 151.29, 134.52, 126.63, 125.60, 123.49, 81.30, 69.30, 41.78, 31.07, 25.04, 24.07.

LRMS (EI/CI)⁺: *m/z* [M + H]⁺ = 248.

HRMS (EI/CI)⁺: *m/z* [M + H]⁺ calcd for C₁₄H₁₈NO₃: 248.1281; found: 248.1281.

(Z)-2-Ethyl-6-methyl-8-(*p*-nitrophenyl)-3,4,7,8-tetrahydro-2*H*-oxocine (22h)

Following the general procedure, activated molecular sieves (60 mg), *p*-nitrobenzaldehyde (63 mg, 0.42 mmol, 1.2 equiv) in THF (2.1 mL, 0.2 M), TMSOTf (0.06 mL, 0.35 mmol, 1.0 equiv), and 7-methyloct-7-en-3-ol (50 mg, 0.35 mmol, 1.0 equiv) in THF (2.0 mL, 0.2 M) gave **22h** as a clear, pale yellow oil; yield: 85 mg (87%); 90:10 (*endo/exo*).

^1H NMR (500 MHz, CDCl_3): δ = 8.19 (d, J = 8.8 Hz, 2 H), 7.55 (d, J = 8.4 Hz, 2 H), 5.52 (ddt, J = 9.9, 6.7, 1.5 Hz, 1 H), 4.39 (dd, J = 9.6, 1.6 Hz, 1 H), 3.48–3.39 (m, 1 H), 2.73 (dd, J = 14.1, 9.6 Hz, 1 H), 2.57–2.45 (m, 1 H), 2.09 (dd, J = 14.0, 1.7 Hz, 1 H), 2.04–1.96 (m, 1 H), 1.79 (s, 3 H), 1.70 (dddd, J = 14.4, 11.1, 5.1, 3.4 Hz, 1 H), 1.63–1.53 (m, 1 H), 1.47–1.38 (m, 2 H), 0.81 (t, J = 7.4 Hz, 3 H).

^{13}C NMR (125 MHz, CDCl_3): δ = 151.63, 146.83, 134.34, 126.59, 126.08, 123.44, 81.77, 81.57, 42.80, 36.31, 29.80, 25.31, 24.26, 10.49.

LRMS (EI/CI) $^+$: m/z $[\text{M} + \text{H}]^+ = 276$.

HRMS (EI/CI) $^+$: m/z $[\text{M} + \text{H}]^+$ calcd for $\text{C}_{16}\text{H}_{22}\text{NO}_3$: 276.1594; found: 276.1596.

(Z)-2-Isopropyl-6-methyl-8-(*p*-nitrophenyl)-3,4,7,8-tetrahydro-2*H*-oxocine (22i)

Following the general procedure, activated molecular sieves (60 mg), *p*-nitrobenzaldehyde (21 mg, 0.13 mmol, 1.2 equiv) in THF (0.7 mL, 0.2 M), TMSOTf (0.02 mL, 0.12 mmol, 1.0 equiv), and 2,7-dimethyloct-7-en-3-ol (18 mg, 0.12 mmol, 1.0 equiv) in THF (0.58 mL, 0.2 M) gave **22i** as a clear, pale yellow oil; yield: 21 mg (62%); 91:9 (*endo/exo*).

^1H NMR (500 MHz, CDCl_3): δ = 8.19 (d, J = 8.8 Hz, 2 H), 7.55 (d, J = 8.2 Hz, 2 H), 5.51 (ddt, J = 9.9, 6.6, 1.5 Hz, 1 H), 4.35 (d, J = 8.6 Hz, 1 H), 3.26 (ddd, J = 11.4, 6.1, 3.6 Hz, 1 H), 2.72 (dd, J = 14.0, 9.5 Hz, 1 H), 2.60–2.43 (m, 1 H), 2.06 (dd, J = 14.0, 1.7 Hz, 1 H), 2.04–1.96 (m, 1 H), 1.80 (s, 3 H), 1.74 (dddd, J = 13.6, 11.4, 5.0, 3.4 Hz, 1 H), 1.65–1.56 (m, 2 H), 0.82 (dd, J = 6.7, 1.6 Hz, 6 H).

^{13}C NMR (125 MHz, CDCl_3): δ = 151.68, 146.81, 134.35, 126.54, 126.14, 123.44, 85.16, 81.93, 43.09, 34.15, 33.51, 25.35, 24.27, 19.27, 18.22.

LRMS (EI/CI) $^+$: m/z $[\text{M} + \text{H}]^+ = 290$.

HRMS (EI/CI) $^+$: m/z $[\text{M} + \text{H}]^+$ calcd for $\text{C}_{17}\text{H}_{24}\text{NO}_3$: 290.1751; found: 290.1749.

(Z)-6-Methyl-8-(*p*-nitrophenyl)-2-phenyl-3,4,7,8-tetrahydro-2*H*-oxocine (22j)

Following the general procedure, activated molecular sieves (60 mg), *p*-nitrobenzaldehyde (47 mg, 0.312 mmol, 1.2 equiv) in THF (1.56 mL, 0.2 M), TMSOTf (0.045 mL, 0.26 mmol, 1.0 equiv), and 5-methyl-1-phenylhex-5-en-1-ol (50 mg, 0.26 mmol, 1.0 equiv) in THF (1.3 mL, 0.2 M) gave **22j** as a clear, pale yellow oil; yield: 33 mg (39%); 91:9 (*endo/exo*).

^1H NMR (500 MHz, CDCl_3): δ = 8.20 (d, J = 8.8 Hz, 2 H), 7.59 (d, J = 8.2 Hz, 2 H), 7.32–7.22 (m, 3 H), 7.24–7.15 (m, 2 H), 5.64 (ddt, J = 9.9, 6.8, 1.5 Hz, 1 H), 4.66 (dd, J = 11.3, 4.0 Hz, 1 H), 4.55 (dd, J = 9.7, 1.6 Hz, 1 H), 2.85 (dd, J = 14.0, 9.7 Hz, 1 H), 2.73–2.60 (m, 1 H), 2.18 (dd, J = 14.0, 1.7 Hz, 1 H), 2.17–2.09 (m, 1 H), 2.00–1.88 (m, 2 H), 1.87 (d, J = 1.5 Hz, 3 H).

^{13}C NMR (125 MHz, CDCl_3): δ = 151.29, 146.89, 144.22, 134.88, 128.18, 126.80, 126.59, 125.83, 125.22, 123.49, 81.22, 81.00, 42.99, 38.85, 25.43, 24.58.

LRMS (EI/CI) $^+$: m/z $[\text{M} + \text{H}]^+ = 324$.

HRMS (EI/CI) $^+$: m/z $[\text{M} + \text{H}]^+$ calcd for $\text{C}_{20}\text{H}_{22}\text{NO}_3$: 324.1594; found: 324.1595.

(Z)-2,6-Dimethyl-8-(*m*-nitrophenyl)-3,4,7,8-tetrahydro-2*H*-oxocine (22k)

Following the general procedure, activated molecular sieves (100 mg), *m*-nitrobenzaldehyde (0.51 g, 3.4 mmol, 1.2 equiv) in THF (17 mL, 0.2 M), TMSOTf (0.51 mL, 2.8 mmol, 1.0 equiv), and 6-methylhept-6-en-2-ol (0.36 g, 2.8 mmol, 1.0 equiv) in THF (14 mL, 0.2 M) gave **22k** as a clear, pale yellow oil; yield: 476 mg (65%); 91:9 (*endo/exo*).

^1H NMR (500 MHz, CDCl_3): δ = 8.25 (t, J = 2.0 Hz, 1 H), 8.10 (ddd, J = 8.2, 2.4, 1.1 Hz, 1 H), 7.71 (ddt, J = 7.7, 1.7, 0.8 Hz, 1 H), 7.49 (t, J = 7.9 Hz, 1 H), 5.52 (ddt, J = 9.9, 6.7, 1.5 Hz, 1 H), 4.45 (dd, J = 9.6, 1.6 Hz, 1 H), 3.73 (dtt, J = 12.6, 6.3, 3.1 Hz, 1 H), 2.75 (dd, J = 14.0, 9.6 Hz, 1 H), 2.57–2.46 (m, 1 H), 2.15 (dd, J = 14.0, 1.7 Hz, 1 H), 2.04–1.96 (m, 1 H), 1.80 (dd, J = 0.6, 0.6 Hz, 3 H), 1.76–1.66 (m, 1 H), 1.63–1.51 (m, 1 H), 1.15 (d, J = 6.3 Hz, 3 H).

^{13}C NMR (125 MHz, CDCl_3): δ = 148.18, 146.57, 134.42, 132.11, 129.01, 125.99, 121.88, 120.98, 80.12, 76.01, 42.44, 38.12, 25.33, 24.38, 22.34.

LRMS (EI/CI) $^+$: m/z $[\text{M} + \text{H}]^+ = 262$.

HRMS (EI/CI) $^+$: m/z $[\text{M} + \text{H}]^+$ calcd for $\text{C}_{15}\text{H}_{20}\text{NO}_3$: 262.1438; found: 262.1429.

(Z)-2,6-Dimethyl-8-(*o*-nitrophenyl)-3,4,7,8-tetrahydro-2*H*-oxocine (22l)

Following the general procedure, activated molecular sieves (60 mg), *o*-nitrobenzaldehyde (71 mg, 0.47 mmol, 1.2 equiv) in THF (2.4 mL, 0.2 M), TMSOTf (0.07 mL, 0.39 mmol, 1.0 equiv), and 6-methylhept-6-en-2-ol (50 mg, 0.39 mmol, 1.0 equiv) in THF (2.0 mL, 0.2 M) gave **22l** as a clear, colorless oil; yield: 59 mg (58%); 97:3 (*endo/exo*).

^1H NMR (500 MHz, CDCl_3): δ = 7.92 (dd, J = 8.2, 1.2 Hz, 1 H), 7.87 (dd, J = 7.9, 1.2 Hz, 1 H), 7.61 (td, J = 7.8, 1.2 Hz, 1 H), 7.41–7.36 (m, 1 H), 5.50 (ddt, J = 9.9, 6.7, 1.5 Hz, 1 H), 4.94 (d, J = 9.2 Hz, 1 H), 3.75–3.66 (m, 1 H), 2.68 (dd, J = 13.8, 9.2 Hz, 1 H), 2.60–2.48 (m, 1 H), 2.15 (dd, J = 13.8, 1.4 Hz, 1 H), 2.03–1.95 (m, 1 H), 1.87 (s, 3 H), 1.69 (dddd, J = 14.0, 11.2, 5.3, 2.9 Hz, 1 H), 1.61–1.50 (m, 1 H), 1.08 (d, J = 6.3 Hz, 3 H).

^{13}C NMR (125 MHz, CDCl_3): δ = 146.67, 140.07, 135.40, 133.27, 128.55, 127.49, 125.45, 124.08, 76.91, 76.02, 42.39, 38.29, 24.77, 24.31, 22.14.

LRMS (EI/CI) $^+$: m/z $[\text{M} + \text{H}]^+ = 262$.

HRMS (EI/CI) $^+$: m/z $[\text{M} + \text{H}]^+$ calcd for $\text{C}_{15}\text{H}_{20}\text{NO}_3$: 262.1438; found: 262.1428.

(Z)-8-(p-Fluorophenyl)-2,6-dimethyl-3,4,7,8-tetrahydro-2H-oxocine (22m)

Following the general procedure, activated molecular sieves (60 mg), *p*-fluorobenzaldehyde (0.05 mL, 0.47 mmol, 1.2 equiv) in THF (2.4 mL, 0.2 M), TMSOTf (0.07 mL, 0.39 mmol, 1.0 equiv), and 6-methylhept-6-en-2-ol (50 mg, 0.39 mmol, 1.0 equiv) in THF (2.0 mL, 0.2 M) gave **22m** as a clear, colorless oil; yield: 18 mg (20%); 90:10 (*endo/exo*).

¹H NMR (500 MHz, CDCl₃): δ = 7.38–7.30 (m, 2 H), 7.04–6.96 (m, 2 H), 5.49 (ddt, *J* = 9.9, 6.7, 1.5 Hz, 1 H), 4.33 (d, *J* = 9.6 Hz, 1 H), 3.75–3.64 (m, 1 H), 2.77 (dd, *J* = 13.9, 9.8 Hz, 1 H), 2.58–2.46 (m, 1 H), 2.11 (dd, *J* = 13.9, 1.6 Hz, 1 H), 2.02–1.93 (m, 1 H), 1.78 (s, 3 H), 1.73–1.63 (m, 1 H), 1.59–1.48 (m, 1 H), 1.14 (d, *J* = 6.3 Hz, 3 H).

¹³C NMR (125 MHz, CDCl₃): δ = 161.79 (d, *J* = 244.3 Hz), 140.24, 135.12, 127.50 (d, *J* = 7.9 Hz), 125.43, 114.89 (d, *J* = 21.1 Hz), 80.66, 75.72, 42.18, 38.21, 25.38, 24.37, 22.38.

¹⁹F NMR (471 MHz, CDCl₃): δ = –117.40 to –117.51 (m).

LRMS (EI/CI)⁺: *m/z* [M]⁺ = 234.

HRMS (ESI⁺): *m/z* [M + H]⁺ calcd for C₁₅H₂₀FO: 235.1498; found: 235.1494.

(Z)-2,6-Dimethyl-8-(p-(trifluoromethyl)phenyl)-3,4,7,8-tetrahydro-2H-oxocine (22n)

Following the general procedure, activated molecular sieves (60 mg), *p*-(trifluoromethyl)benzaldehyde (0.06 mL, 0.47 mmol, 1.2 equiv) in THF (2.4 mL, 0.2 M), TMSOTf (0.07 mL, 0.39 mmol, 1.0 equiv), and 6-methylhept-6-en-2-ol (50 mg, 0.39 mmol, 1.0 equiv) in THF (2.0 mL, 0.2 M) gave **22n** as a clear, colorless oil; yield: 41 mg (37%); 92:8 (*endo/exo*).

¹H NMR (500 MHz, CDCl₃): δ = 7.58 (d, *J* = 8.2 Hz, 2 H), 7.49 (d, *J* = 8.1 Hz, 2 H), 5.51 (ddt, *J* = 10.3, 7.0, 1.8 Hz, 1 H), 4.40 (d, *J* = 9.5 Hz, 1 H), 3.77–3.64 (m, 1 H), 2.75 (dd, *J* = 13.9, 9.7 Hz, 1 H), 2.58–2.47 (m, 1 H), 2.13 (dd, *J* = 13.9, 1.7 Hz, 1 H), 2.04–1.93 (m, 1 H), 1.79 (s, 3 H), 1.75–1.65 (m, 1 H), 1.62–1.49 (m, 1 H), 1.14 (d, *J* = 6.3 Hz, 3 H).

¹³C NMR (125 MHz, CDCl₃): δ = 148.38, 134.81, 129.04 (q, *J* = 32.3 Hz), 126.16, 125.70, 125.09 (q, *J* = 3.5 Hz), 124.25 (q, *J* = 272.0 Hz), 80.72, 75.90, 42.44, 38.22, 25.33, 24.39, 22.35.

¹⁹F NMR (471 MHz, CDCl₃): δ = –63.55.

HRMS (ESI⁺): *m/z* [M + H]⁺ calcd for C₁₆H₂₀F₃O: 285.1466; found: 285.1460.

(Z)-8-(p-Chlorophenyl)-2,6-dimethyl-3,4,7,8-tetrahydro-2H-oxocine (22o)

Following the general procedure, activated molecular sieves (50 mg), *p*-chlorobenzaldehyde (66 mg, 0.47 mmol, 1.2 equiv) in THF (2.4 mL, 0.2 M), TMSOTf (0.07 mL, 0.39 mmol, 1.0

equiv), and 6-methylhept-6-en-2-ol (50 mg, 0.39 mmol, 1.0 equiv) in THF (2.0 mL, 0.2 M) gave **22o** as a clear, colorless oil; yield: 18 mg (18%); 93:7 (*endo/exo*).

¹H NMR (500 MHz, CDCl₃): δ = 7.34–7.27 (m, 4 H), 5.49 (ddt, *J* = 9.9, 6.7, 1.5 Hz, 1 H), 4.32 (dd, *J* = 9.7, 1.1 Hz, 1 H), 3.75–3.63 (m, 1 H), 2.74 (dd, *J* = 13.9, 9.7 Hz, 1 H), 2.57–2.45 (m, 1 H), 2.10 (dd, *J* = 13.9, 1.6 Hz, 1 H), 2.02–1.93 (m, 1 H), 1.78 (s, 3 H), 1.72–1.64 (m, 1 H), 1.60–1.49 (m, 1 H), 1.13 (d, *J* = 6.3 Hz, 3 H).

¹³C NMR (125 MHz, CDCl₃): δ = 142.95, 134.99, 132.49, 128.23, 127.29, 125.50, 80.62, 75.78, 42.24, 38.20, 25.35, 24.36, 22.36.

LRMS (EI/CI)⁺: *m/z* [M]⁺ = 250.

HRMS (ESI⁺): *m/z* [M + H]⁺ calcd for C₁₅H₂₀ClO: 251.1203; found: 251.1199.

(Z)-2,6-Dimethyl-8-phenethyl-3,4,7,8-tetrahydro-2H-oxocine (22e)

Following the general procedure, activated molecular sieves (50 mg), 3-phenylpropionaldehyde (0.06 mL, 0.47 mmol, 1.2 equiv) in THF (2.4 mL, 0.2 M), TMSOTf (0.07 mL, 0.39 mmol, 1.0 equiv), and 6-methylhept-6-en-2-ol (50 mg, 0.39 mmol, 1.0 equiv) in THF (2.0 mL, 0.2 M) gave **22e** as a clear, colorless oil; yield: 33 mg (35%); 94:6 (*endo/exo*).

¹H NMR (500 MHz, CDCl₃): δ = 7.31–7.26 (m, 2 H), 7.23–7.15 (m, 3 H), 5.40 (dddd, *J* = 8.2, 6.7, 3.0, 1.5 Hz, 1 H), 3.56–3.47 (m, 1 H), 3.28 (tdd, *J* = 9.5, 3.4, 1.5 Hz, 1 H), 2.89 (ddd, *J* = 15.0, 10.1, 5.3 Hz, 1 H), 2.63 (ddd, *J* = 13.8, 10.0, 6.3 Hz, 1 H), 2.52–2.39 (m, 2 H), 1.96–1.82 (m, 3 H), 1.78–1.73 (m, 3 H), 1.72–1.58 (m, 2 H), 1.57–1.46 (m, 1 H), 1.15 (d, *J* = 6.3 Hz, 3 H).

¹³C NMR (125 MHz, CDCl₃): δ = 142.51, 135.64, 128.48, 128.30, 125.64, 124.68, 79.78, 75.07, 40.81, 39.07, 38.09, 32.95, 25.55, 24.28, 22.06.

LRMS (EI/CI)⁺: *m/z* [M]⁺ = 244.

HRMS (ESI⁺): *m/z* [M + H]⁺ calcd for C₁₇H₂₅O: 245.1906; found: 245.1898.

(Z)-8-((Benzyloxy)methyl)-2,6-dimethyl-3,4,7,8-tetrahydro-2H-oxocine (20)

Following the general procedure, activated molecular sieves (30 mg), benzyloxyacetaldehyde (0.033 mL, 0.23 mmol, 1.2 equiv) in THF (1.2 mL, 0.2 M), TMSOTf (0.036 mL, 0.2 mmol, 1.0 equiv), and 6-methylhept-6-en-2-ol (25 mg, 0.2 mmol, 1.0 equiv) in THF (1.0 mL, 0.2 M) gave **20** as a clear, colorless oil; yield: 12 mg (24%); *endo*-isomer, with trace amounts of an unidentified minor isomer.

¹H NMR (500 MHz, CDCl₃): δ = 7.38–7.31 (m, 4 H), 7.31–7.27 (m, 1 H), 5.42 (ddt, *J* = 9.9, 6.7, 1.5 Hz, 1 H), 4.61 (d, *J* = 12.0 Hz, 1 H), 4.56 (d, *J* = 12.0 Hz, 1 H), 3.59–3.46 (m, 3 H), 3.40 (tt, *J* = 8.6, 4.8 Hz, 1 H), 2.50–2.38 (m, 2 H), 1.97 (d, *J* = 14.0 Hz, 1 H), 1.94–1.87 (m, 1 H), 1.77 (s, 3 H), 1.65–1.56 (m, 1 H), 1.53–1.45 (m, 1 H), 1.13 (d, *J* = 6.3 Hz, 3 H).

^{13}C NMR (125 MHz, CDCl_3): δ = 138.54, 135.31, 128.30, 127.59, 127.47, 124.98, 79.18, 75.52, 74.03, 73.29, 38.12, 36.99, 25.38, 24.27, 22.21.

HRMS (ESI⁺): m/z $[\text{M} + \text{Na}]^+$ calcd for $\text{C}_{17}\text{H}_{24}\text{O}_2\text{Na}$: 283.1674; found: 283.1667.

(Z)-2,6-Dimethyl-8-(*m*-tolyl)-3,4,7,8-tetrahydro-2H-oxocine (22f)

Following the general procedure, activated molecular sieves (60 mg), *m*-tolualdehyde (0.05 mL, 0.47 mmol, 1.2 equiv) in THF (2.4 mL, 0.2 M), TMSOTf (0.07 mL, 0.39 mmol, 1.0 equiv), and 6-methylhept-6-en-2-ol (50 mg, 0.39 mmol, 1.0 equiv) in THF (2.0 mL, 0.2 M) gave **22f** as a clear, colorless oil; yield: 7 mg (8%); 92:8 (*endo/exo*).

^1H NMR (500 MHz, CDCl_3): δ = 7.24–7.14 (m, 3 H), 7.07–7.03 (m, 1 H), 5.47 (ddt, J = 9.8, 6.6, 1.5 Hz, 1 H), 4.31 (d, J = 9.7 Hz, 1 H), 3.75–3.64 (m, 1 H), 2.82 (dd, J = 13.9, 10.0 Hz, 1 H), 2.62–2.49 (m, 1 H), 2.36 (s, 3 H), 2.10 (dd, J = 13.9, 1.4 Hz, 1 H), 2.01–1.93 (m, 1 H), 1.84–1.75 (m, 3 H), 1.69 (dddd, J = 14.1, 11.3, 5.2, 3.1 Hz, 1 H), 1.59–1.49 (m, 1 H), 1.14 (d, J = 6.3 Hz, 3 H).

^{13}C NMR (125 MHz, CDCl_3): δ = 144.39, 137.77, 135.51, 128.08, 127.66, 126.57, 125.15, 123.03, 81.59, 75.67, 42.29, 38.28, 25.36, 24.32, 22.35, 21.51.

HRMS (ESI⁺): m/z $[\text{M} + \text{H}]^+$ calcd for $\text{C}_{16}\text{H}_{23}\text{O}$: 231.1749; found: 231.1741.

(Z)-2,6-Dimethyl-8-(2-naphthyl)-3,4,7,8-tetrahydro-2H-oxocine (22p)

Following the general procedure, activated molecular sieves (60 mg), 2-naphthaldehyde (73 mg, 0.47 mmol, 1.2 equiv) in THF (2.4 mL, 0.2 M), TMSOTf (0.07 mL, 0.39 mmol, 1.0 equiv), and 6-methylhept-6-en-2-ol (50 mg, 0.39 mmol, 1.0 equiv) in THF (2.0 mL, 0.2 M) gave **22p** as a clear, colorless oil; yield: 16 mg (16%); 94:6 (*endo/exo*).

^1H NMR (500 MHz, CDCl_3): δ = 7.88–7.76 (m, 4 H), 7.53–7.40 (m, 3 H), 5.52 (ddq, J = 9.9, 6.7, 1.5 Hz, 1 H), 4.51 (d, J = 9.5 Hz, 1 H), 3.82–3.72 (m, 1 H), 2.89 (dd, J = 13.9, 9.7 Hz, 1 H), 2.66–2.55 (m, 1 H), 2.24 (dd, J = 13.9, 1.6 Hz, 1 H), 2.05–1.97 (m, 1 H), 1.86–1.79 (m, 3 H), 1.79–1.69 (m, 1 H), 1.63–1.55 (m, 1 H), 1.18 (d, J = 6.3 Hz, 3 H).

^{13}C NMR (125 MHz, CDCl_3): δ = 141.86, 135.39, 133.31, 132.61, 128.01, 127.79, 127.56, 125.88, 125.50, 125.35, 124.79, 124.02, 81.56, 75.88, 42.24, 38.31, 25.41, 24.42, 22.42.

LRMS (EI/CI)⁺: m/z $[\text{M}]^+$ = 266.

HRMS (ESI⁺): m/z $[\text{M} + \text{H}]^+$ calcd for $\text{C}_{19}\text{H}_{23}\text{O}$: 267.1749; found: 267.1742.

(Z)-8-(*p*-Fluoro-*m*-nitrophenyl)-2,6-dimethyl-3,4,7,8-tetrahydro-2H-oxocine (22b)

Following the general procedure, activated molecular sieves (60 mg), *p*-fluoro-*m*-nitrobenzaldehyde (79 mg, 0.47 mmol, 1.2 equiv) in THF (2.4 mL, 0.2 M), TMSOTf (0.07 mL, 0.39 mmol, 1.0 equiv), and 6-methylhept-6-en-2-ol (50 mg, 0.39 mmol, 1.0 equiv) in

THF (2.0 mL, 0.2 M) gave **22b** as a clear, colorless oil; yield: 45 mg (41%); 91:9 (*endo/exo*).

¹H NMR (500 MHz, CDCl₃): δ = 8.07 (dd, *J* = 7.2, 2.2 Hz, 1 H), 7.64 (ddd, *J* = 8.6, 4.2, 2.3 Hz, 1 H), 7.23 (dd, *J* = 10.6, 8.6 Hz, 1 H), 5.52 (ddt, *J* = 9.8, 6.7, 1.5 Hz, 1 H), 4.39 (d, *J* = 9.4 Hz, 1 H), 3.75–3.66 (m, 1 H), 2.70 (dd, *J* = 13.9, 9.6 Hz, 1 H), 2.53–2.43 (m, 1 H), 2.12 (dd, *J* = 14.0, 1.7 Hz, 1 H), 2.03–1.95 (m, 1 H), 1.79 (s, 3 H), 1.74–1.65 (m, 1 H), 1.62–1.51 (m, 1 H), 1.14 (d, *J* = 6.3 Hz, 3 H).

¹³C NMR (125 MHz, CDCl₃): δ = 154.31 (d, *J* = 263.7 Hz), 141.66 (d, *J* = 4.3 Hz), 134.17, 132.92 (d, *J* = 8.5 Hz), 126.12, 123.37, 118.01, 117.85, 79.39, 76.07, 42.38, 38.04, 25.32, 24.36, 22.32.

¹⁹F NMR (471 MHz, CDCl₃): δ = –121.82 (ddd, *J* = 10.9, 7.1, 4.5 Hz).

LRMS (EI/CI)⁺: *m/z* [M]⁺ = 279.

HRMS (EI/CI)⁺: *m/z* [M + H]⁺ calcd for C₁₅H₁₉FNO₃: 280.1343; found: 280.1356.

4-(1-(*m*-Nitrophenyl)-3-oxobutoxy)pentanal (**32**) and 8-Methyl-2-(*m*-nitrophenyl)oxocan-4-one (**33**)

To a 10-mL round-bottomed flask with a stir bar and a 9:1 mixture of **22k/31k** (0.226 g, 0.86 mmol, 1 equiv) was added CH₂Cl₂–MeOH (1:1, 5 mL). The reaction solution was then cooled to –78 °C and ozone was bubbled through the solution. Once the reaction mixture was saturated with ozone, the solution turned blue, whereupon oxygen was bubbled through the solution to quench the excess ozone. Once the solution was no longer blue, Me₂S (630 μL, 8.64 mmol, 10 equiv) was added directly to the reaction flask. This solution was then allowed to stir overnight and warm to room temperature. The solvent was then removed in vacuo and the remainder directly transferred to a column, where the products were eluted with EtOAc–hexanes (20:80), giving **32** and **33** as clear, pale yellow oils.

Compound 32

Yield: 0.22 g (96%, based on **22k**).

¹H NMR (500 MHz, CDCl₃): δ = 9.79 (s, 1 H), 8.21 (s, 1 H), 8.12 (dd, *J* = 8.1, 2.0 Hz, 1 H), 7.66 (d, *J* = 7.6 Hz, 1 H), 7.51 (t, *J* = 7.9 Hz, 1 H), 4.97 (dd, *J* = 8.8, 3.9 Hz, 1 H), 3.57 (h, *J* = 6.1 Hz, 1 H), 2.98 (dd, *J* = 17.0, 8.8 Hz, 1 H), 2.60–2.39 (m, 3 H), 2.17 (s, 3 H), 1.90–1.77 (m, 2 H), 0.94 (d, *J* = 6.2 Hz, 3 H).

¹³C NMR (125 MHz, CDCl₃): δ = 205.44, 202.44, 148.42, 145.38, 132.46, 129.47, 122.65, 121.23, 74.96, 74.48, 51.81, 39.59, 31.01, 28.15, 20.69.

HRMS (ESI⁺): *m/z* [M + Na]⁺ calcd for C₁₅H₁₉NO₅Na: 316.1161; found: 316.1149.

Compound 33

Yield: 0.013 g (59%, based on **31k**).

^1H NMR (500 MHz, CDCl_3): δ = 8.30 (s, 1 H), 8.14 (dd, J = 8.2, 1.3 Hz, 1 H), 7.69 (d, J = 7.7 Hz, 1 H), 7.52 (t, J = 7.9 Hz, 1 H), 4.82 (dd, J = 10.8, 2.4 Hz, 1 H), 3.59–3.50 (m, 1 H), 3.12 (t, J = 11.1 Hz, 1 H), 2.68 (ddd, J = 13.7, 7.2, 2.0 Hz, 1 H), 2.57 (dd, J = 11.4, 2.5 Hz, 1 H), 2.46–2.32 (m, 2 H), 1.87 (dddd, J = 14.2, 9.9, 4.5, 2.3 Hz, 1 H), 1.79–1.71 (m, 1 H), 1.69–1.61 (m, 1 H), 1.18 (d, J = 6.1 Hz, 3 H).

^{13}C NMR (125 MHz, CDCl_3): δ = 213.94, 148.38, 144.52, 131.78, 129.35, 122.52, 120.78, 80.00, 75.73, 51.07, 44.06, 36.27, 22.38, 21.01.

HRMS (ESI⁺): m/z $[\text{M} + \text{Na}]^+$ calcd for $\text{C}_{14}\text{H}_{17}\text{NO}_4\text{Na}$: 286.1056; found: 286.1050.

8-Methyl-4-methylene-2-(*m*-nitrophenyl)oxocane (31k)

To a 5-mL round-bottomed flask with a stir bar, under argon, containing anhyd methyltriphenylphosphonium bromide (46 mg, 0.12 mmol, 2.5 equiv) and anhyd THF (1 mL, 0.12 M) at 0 °C was added 1.6 M *n*-BuLi (0.08 mL, 0.13 mmol, 2.6 equiv). After 5 min, the red-orange reaction mixture was cooled to –78 °C and cannulated over 2 min into a mixture of **33** (13.5 mg, 0.05 mmol, 1 equiv) and THF (0.5 mL, 0.1 M) in a dry 5-mL round-bottomed flask with a stir bar, under argon. The reaction was gradually warmed to 0 °C and, after stirring for 5 h at 0 °C, salts had formed and the reaction mixture was quenched with H_2O . The organic and aqueous layers were then separated, after which the aqueous layer was extracted with EtOAc (3 $\times$). The organic layers were then combined, dried over Na_2SO_4 , and concentrated. After purification by column chromatography (EtOAc–hexanes, 5:95), **31k** was isolated as a clear, colorless oil; yield: 7 mg (52%).

^1H NMR (500 MHz, CDCl_3): δ = 8.26 (s, 1 H), 8.11 (dd, J = 8.2, 1.3 Hz, 1 H), 7.72 (d, J = 7.7 Hz, 1 H), 7.50 (t, J = 7.9 Hz, 1 H), 4.95 (s, 1 H), 4.91 (s, 1 H), 4.62 (dd, J = 10.5, 2.7 Hz, 1 H), 3.98–3.89 (m, 1 H), 2.59 (dd, J = 13.4, 2.6 Hz, 1 H), 2.47–2.30 (m, 3 H), 2.14–2.01 (m, 1 H), 1.82–1.72 (m, 1 H), 1.64–1.55 (m, 2 H), 1.17 (d, J = 6.3 Hz, 3 H).

^{13}C NMR (125 MHz, CDCl_3): δ = 148.82, 148.24, 146.29, 132.02, 129.08, 122.00, 120.92, 113.71, 81.73, 75.55, 45.47, 35.57, 35.12, 23.38, 22.13.

LRMS (EI/CI)⁺: m/z $[\text{M} + \text{H}]^+$ = 262.

HRMS (EI/CI)⁺: m/z $[\text{M} + \text{H}]^+$ calcd for $\text{C}_{15}\text{H}_{20}\text{NO}_3$: 262.1438; found: 262.1441.

4,7-Dimethyl-2-(*p*-nitrophenyl)-2,3,6,7-tetrahydrooxepine (35)

Following the general procedure, activated molecular sieves (40 mg), *p*-nitrobenzaldehyde (80 mg, 0.52 mmol, 1.2 equiv) in THF (2.6 mL, 0.2 M), TMSOTf (0.08 mL, 0.44 mmol, 1.0 equiv), and 5-methylhex-5-en-2-ol (50 mg, 0.44 mmol, 1.0 equiv) in THF (2.2 mL, 0.2 M) gave **35** as a clear, pale yellow oil; yield: 39 mg (36%).

^1H NMR (500 MHz, CDCl_3): δ = 8.17 (d, J = 8.7 Hz, 2 H), 7.54 (d, J = 8.7 Hz, 2 H), 5.62 (d, J = 7.6 Hz, 1 H), 4.60 (d, J = 10.1 Hz, 1 H), 3.74 (dq, J = 12.5, 6.2 Hz, 1 H), 2.65 (dd, J = 15.9, 10.4 Hz, 1 H), 2.43–2.30 (m, 1 H), 2.27–2.11 (m, 2 H), 1.78 (s, 3 H), 1.24 (d, J = 6.3 Hz, 3 H).

^{13}C NMR (125 MHz, CDCl_3): δ = 151.51, 146.86, 137.33, 126.54, 124.29, 123.45, 79.46, 76.40, 45.02, 37.90, 26.61, 23.13.

LRMS (ESI⁺): m/z $[\text{M} + \text{H}]^+ = 248$.

HRMS (ESI⁺): m/z $[\text{M} + \text{H}]^+$ calcd for $\text{C}_{14}\text{H}_{18}\text{NO}_3$: 248.1287; found: 248.1282.

4,7-Dimethyl-2-(*m*-nitrophenyl)-2,3,6,7-tetrahydrooxepine (36)

Following the general procedure, activated molecular sieves (40 mg), *m*-nitrobenzaldehyde (81 mg, 0.52 mmol, 1.2 equiv) in THF (2.6 mL, 0.2 M), TMSOTf (0.08 mL, 0.44 mmol, 1.0 equiv), and 5-methylhex-5-en-2-ol (51 mg, 0.44 mmol, 1.0 equiv) in THF (2.2 mL, 0.2 M) gave **36** as a clear, pale yellow oil; yield: 53 mg (49%).

^1H NMR (500 MHz, CDCl_3): δ = 8.25 (s, 1 H), 8.10 (dd, J = 8.1, 1.9 Hz, 1 H), 7.71 (d, J = 8.1 Hz, 1 H), 7.49 (t, J = 7.9 Hz, 1 H), 5.63 (d, J = 7.6 Hz, 1 H), 4.60 (d, J = 10.2 Hz, 1 H), 3.80–3.68 (m, 1 H), 2.70 (dd, J = 15.8, 10.4 Hz, 1 H), 2.42–2.30 (m, 1 H), 2.27–2.10 (m, 2 H), 1.79 (s, 3 H), 1.25 (d, J = 6.2 Hz, 3 H).

^{13}C NMR (125 MHz, CDCl_3): δ = 148.20, 146.36, 137.36, 132.02, 129.07, 124.35, 121.99, 120.95, 79.29, 76.51, 45.01, 37.91, 26.64, 23.18.

LRMS (ESI⁺): m/z $[\text{M} + \text{H}]^+ = 248$.

HRMS (ESI⁺): m/z $[\text{M} + \text{H}]^+$ calcd for $\text{C}_{14}\text{H}_{18}\text{NO}_3$: 248.1287; found: 248.1282.

4,7-Dimethyl-2-phenethyl-2,3,6,7-tetrahydrooxepine (37)

Following the general procedure, activated molecular sieves (40 mg), 3-phenylpropionaldehyde (0.06 mL, 0.52 mmol, 1.2 equiv) in THF (2.6 mL, 0.2 M), TMSOTf (0.08 mL, 0.44 mmol, 1.0 equiv), and 5-methylhex-5-en-2-ol (50 mg, 0.44 mmol, 1.0 equiv) in THF (2.2 mL, 0.2 M) gave **37** as a clear, colorless oil; yield: 49 mg (49%).

^1H NMR (500 MHz, CDCl_3): δ = 7.34–7.24 (m, 2 H), 7.24–7.13 (m, 3 H), 5.48 (d, J = 7.3 Hz, 1 H), 3.61–3.41 (m, 1 H), 3.34 (dt, J = 9.3, 3.6 Hz, 1 H), 2.81 (ddd, J = 13.9, 8.9, 5.2 Hz, 1 H), 2.75–2.62 (m, 1 H), 2.50–2.38 (m, 1 H), 2.30–2.16 (m, 1 H), 2.07 (dd, J = 15.7, 7.9 Hz, 1 H), 1.98–1.80 (m, 2 H), 1.77–1.61 (m, 4 H), 1.23 (d, J = 6.3 Hz, 3 H).

^{13}C NMR (125 MHz, CDCl_3): δ = 142.42, 138.09, 128.55, 128.26, 125.60, 123.26, 77.47, 76.09, 43.26, 38.77, 38.03, 32.36, 26.79, 23.06.

LRMS (APCI⁺): m/z $[\text{M} + \text{H}]^+ = 231$.

HRMS (ESI⁺): m/z $[\text{M} + \text{H}]^+$ calcd for $\text{C}_{16}\text{H}_{23}\text{O}$: 231.1749; found: 231.1745.

2-((Benzyloxy)methyl)-4,7-dimethyl-2,3,6,7-tetrahydrooxepine (38)

Following the general procedure, activated molecular sieves (40 mg), benzyloxyacetaldehyde (0.08 mL, 0.53 mmol, 1.2 equiv) in THF (2.6 mL, 0.2 M), TMSOTf

(0.08 mL, 0.44 mmol, 1.0 equiv), and 5-methylhex-5-en-2-ol (51 mg, 0.44 mmol, 1.0 equiv) in THF (2.2 mL, 0.2 M) gave **38** as a clear, colorless oil; yield: 29 mg (27%).

^1H NMR (500 MHz, CDCl_3): δ = 7.35 (d, J = 4.6 Hz, 3 H), 7.31–7.25 (m, 2 H), 5.53–5.47 (m, 1 H), 4.62–4.52 (m, 2 H), 3.68–3.61 (m, 1 H), 3.61–3.55 (m, 1 H), 3.52–3.47 (m, 1 H), 3.37 (dd, J = 9.7, 5.9 Hz, 1 H), 2.42–2.32 (m, 1 H), 2.28–2.17 (m, 1 H), 2.14–2.01 (m, 2 H), 1.74 (s, 3 H), 1.19 (d, J = 6.3 Hz, 3 H).

^{13}C NMR (125 MHz, CDCl_3): δ = 138.46, 137.90, 128.32, 127.68, 127.51, 123.41, 77.45, 76.09, 73.78, 73.29, 39.47, 37.89, 26.63, 23.14.

LRMS (APCI) $^+$: m/z [$\text{M} + \text{H}$] $^+$ = 247.

HRMS (ESI $^+$): m/z [$\text{M} + \text{Na}$] $^+$ calcd for $\text{C}_{16}\text{H}_{22}\text{O}_2\text{Na}$: 269.1518; found: 269.1513.

2-(*p*-Fluoro-*m*-nitrophenyl)-4,7-dimethyl-2,3,6,7-tetrahydrooxepine (**39**)

Following the general procedure, activated molecular sieves (40 mg), *p*-fluoro-*m*-nitrobenzaldehyde (91 mg, 0.53 mmol, 1.2 equiv) in THF (2.6 mL, 0.2 M), TMSOTf (0.08 mL, 0.44 mmol, 1.0 equiv), and 5-methylhex-5-en-2-ol (51 mg, 0.44 mmol, 1.0 equiv) in THF (2.2 mL, 0.2 M) gave **39** as a clear, colorless oil; yield: 33 mg (28%).

^1H NMR (500 MHz, CDCl_3): δ = 8.07 (dd, J = 7.2, 2.3 Hz, 1 H), 7.64 (ddd, J = 8.6, 4.3, 2.3 Hz, 1 H), 7.23 (dd, J = 10.6, 8.6 Hz, 1 H), 5.65–5.59 (m, 1 H), 4.58–4.52 (m, 1 H), 3.77–3.68 (m, 1 H), 2.71–2.61 (m, 1 H), 2.39–2.29 (m, 1 H), 2.23–2.12 (m, 2 H), 1.78 (s, 3 H), 1.24 (d, J = 6.2 Hz, 3 H).

^{13}C NMR (125 MHz, CDCl_3): δ = 154.37 (d, J = 263.6 Hz), 141.47 (d, J = 4.2 Hz), 137.11, 132.85 (d, J = 8.4 Hz), 124.45, 123.38, 118.07, 117.90, 78.58, 76.53, 44.93, 37.86, 26.63, 23.14.

LRMS (CI) $^+$: m/z [$\text{M} + \text{H}$] $^+$ = 266.

2-(*p*-Methoxy-*m*-nitrophenyl)-4,7-dimethyl-2,3,6,7-tetrahydrooxepine (**40**)

Following the general procedure, activated molecular sieves (40 mg), *p*-methoxy-*m*-nitrobenzaldehyde (96 mg, 0.53 mmol, 1.2 equiv) in THF (2.6 mL, 0.2 M), TMSOTf (0.08 mL, 0.44 mmol, 1.0 equiv), and 5-methylhex-5-en-2-ol (51 mg, 0.44 mmol, 1.0 equiv) in THF (2.2 mL, 0.2 M) gave **40** as a clear, yellow oil; yield: 57 mg (48%).

^1H NMR (500 MHz, CDCl_3): δ = 7.87 (d, J = 2.2 Hz, 1 H), 7.56 (dd, J = 8.7, 2.2 Hz, 1 H), 7.04 (d, J = 8.7 Hz, 1 H), 5.63–5.58 (m, 1 H), 4.52–4.47 (m, 1 H), 3.95 (s, 3 H), 3.75–3.67 (m, 1 H), 2.72–2.64 (m, 1 H), 2.38–2.28 (m, 1 H), 2.22–2.10 (m, 2 H), 1.78 (s, 3 H), 1.22 (d, J = 6.2 Hz, 3 H).

^{13}C NMR (125 MHz, CDCl_3): δ = 151.87, 139.27, 137.40, 137.02, 131.59, 124.24, 123.20, 113.27, 78.82, 76.45, 56.61, 44.83, 37.91, 26.65, 23.19.

LRMS (APCI) $^+$: m/z [$\text{M} + \text{H}$] $^+$ = 278.

HRMS (ESI⁺): m/z [M + H]⁺ calcd for C₁₅H₂₀NO₄: 278.1393; found: 278.1384.

Ethyl 4,7-Dimethyl-2,3,6,7-tetrahydrooxepine-2-carboxylate (41)

Following the general procedure, activated molecular sieves (40 mg), ethyl glyoxylate (0.05 mL, 0.53 mmol, 1.2 equiv, in toluene) in THF (2.6 mL, 0.2 M), TMSOTf (0.08 mL, 0.44 mmol, 1.0 equiv), and 5-methylhex-5-en-2-ol (51 mg, 0.44 mmol, 1.0 equiv) in THF (2.2 mL, 0.2 M) gave **41** as a clear, colorless oil; yield: 20 mg (23%).

¹H NMR (500 MHz, CDCl₃): δ = 5.57–5.51 (m, 1 H), 4.26–4.18 (m, 2 H), 4.10 (dd, J = 10.2, 1.6 Hz, 1 H), 3.71–3.61 (m, 1 H), 2.70–2.58 (m, 1 H), 2.38–2.27 (m, 2 H), 2.12–2.04 (m, 1 H), 1.77 (d, J = 1.4 Hz, 3 H), 1.29 (t, J = 7.1 Hz, 3 H), 1.25 (d, J = 6.3 Hz, 3 H).

¹³C NMR (125 MHz, CDCl₃): δ = 171.75, 136.80, 124.11, 77.92, 76.31, 60.95, 39.25, 37.61, 26.44, 22.87, 14.20.

LRMS (APCI)⁺: m/z [M + H]⁺ = 199.

HRMS (ESI⁺): m/z [M + Na]⁺ calcd for C₁₁H₁₈O₃Na: 221.1154; found: 221.1149.

7-Methyl-2-(*p*-nitrophenyl)-3-(prop-1-en-2-yl)oxepane (45)

To a 25-mL round-bottomed flask with a stir bar and activated molecular sieves (50 mg), under argon, were added THF (10.6 mL, 0.2 M) and *p*-nitrobenzaldehyde (320 mg, 2.11 mmol, 1.2 equiv). The flask was cooled to 0 °C for 10 min, after which TMSOTf (0.380 mL, 2.11 mmol, 1.2 equiv) was added dropwise. After stirring for 5 min, a chilled solution (–78 °C) of 7-methyloct-7-en-2-ol (0.251 g, 1.76 mmol, 1.0 equiv) in THF (8.80 mL, 0.2 M) was added dropwise over 5 min. The reaction was slowly warmed to room temperature and monitored by TLC (EtOAc–hexanes, 5:95) until completion. After 3 h, the reaction was quenched with sat. NaHCO₃ and the mixture was extracted with EtOAc (3 ×). Then, Na₂SO₄ was added to the combined organic layers, which were then filtered, concentrated, and purified by column chromatography (EtOAc–hexanes, 5:95) to give **45** as a clear, pale yellow oil; yield: 67 mg (14%).

¹H NMR (500 MHz, CDCl₃): δ = 8.12 (d, J = 8.8 Hz, 2 H), 7.47 (d, J = 8.5 Hz, 2 H), 4.89 (d, J = 5.3 Hz, 1 H), 4.54 (s, 1 H), 4.50 (s, 1 H), 3.72–3.59 (m, 1 H), 2.89 (dt, J = 9.6, 6.1 Hz, 1 H), 2.01–1.83 (m, 3 H), 1.82–1.62 (m, 2 H), 1.61–1.48 (m, 1 H), 1.42 (s, 3 H), 1.30 (d, J = 6.2 Hz, 3 H).

¹³C NMR (125 MHz, CDCl₃): δ = 150.68, 146.39, 145.86, 126.77, 122.74, 113.63, 81.76, 79.68, 52.42, 40.31, 31.37, 24.07, 22.86, 20.53.

LRMS (APCI)⁺: m/z [M + H]⁺ = 276.

7-Methyl-2-(*m*-nitrophenyl)-3-(prop-1-en-2-yl)oxepane (46)

To a 10-mL round-bottomed flask with a stir bar and activated molecular sieves (40 mg), under argon, were added THF (2.1 mL, 0.2 M) and *m*-nitrobenzaldehyde (63 mg, 0.42

mmol, 1.2 equiv). The flask was cooled to 0 °C for 10 min, after which TMSOTf (0.07 mL, 0.42 mmol, 1.2 equiv) was added dropwise. After stirring for 5 min, a chilled solution (–78 °C) of 7-methyloct-7-en-2-ol (51 mg, 0.35 mmol, 1.0 equiv) in THF (1.8 mL, 0.2 M) was added dropwise over 5 min. The reaction was slowly warmed to room temperature and monitored by TLC (EtOAc–hexanes, 5:95) until completion. After 4 h, the reaction was quenched with sat. NaHCO₃ and the mixture was extracted with EtOAc (3 ×). Then, Na₂SO₄ was added to the combined organic layers, which were then filtered, concentrated, and purified by column chromatography (EtOAc–hexanes, 5:95) to give **46** as a clear, pale yellow oil; yield: 23 mg (24%).

¹H NMR (500 MHz, CDCl₃): δ = 8.19 (s, 1 H), 8.04 (d, *J* = 8.0 Hz, 1 H), 7.63 (d, *J* = 7.7 Hz, 1 H), 7.42 (t, *J* = 7.9 Hz, 1 H), 4.89 (d, *J* = 5.3 Hz, 1 H), 4.56 (s, 1 H), 4.51 (s, 1 H), 3.71–3.61 (m, 1 H), 2.90 (dt, *J* = 9.7, 5.9 Hz, 1 H), 1.97–1.85 (m, 3 H), 1.82–1.73 (m, 2 H), 1.67 (dd, *J* = 13.3, 11.8 Hz, 1 H), 1.42 (s, 3 H), 1.31 (d, *J* = 6.2 Hz, 3 H).

¹³C NMR (125 MHz, CDCl₃): δ = 147.84, 145.95, 145.03, 132.23, 128.25, 121.27, 121.15, 113.72, 81.37, 79.49, 52.28, 40.25, 31.16, 24.17, 22.91, 20.59.

LRMS (ESI⁺): *m/z* [M + H]⁺ = 276.

4-Bromo-*N*-((4-bromophenyl)sulfonyl)-*N*-(4-(7-methyl-3-(prop-1-en-2-yl)oxepan-2-yl)phenyl)benzenesulfonamide (**48**)

To a 10-mL round-bottomed flask with a stir bar and **45** (67 mg, 0.24 mmol, 1.0 equiv) was added CH₂Cl₂ (2.4 mL, 0.1 M). The flask was cooled to 0 °C for 10 min, after which AcOH (0.14 mL, 2.4 mmol, 10 equiv) was added dropwise, followed by activated Zn dust (0.11 g, 1.7 mmol, 7 equiv). The reaction was allowed to warm to room temperature and was monitored by TLC (EtOAc–hexanes, 20:80) until completion. After 30 min, the reaction mixture was filtered through Celite and stirred overnight in sat. NaHCO₃. The biphasic solution was then transferred to a separatory funnel, where the organic layer was removed and the aqueous layer was back-extracted with CH₂Cl₂ (3 ×). The combined organic layer was then dried with Na₂SO₄, filtered, concentrated, and purified by column chromatography (EtOAc–hexanes, 20:80) to give 4-(7-methyl-3-(prop-1-en-2-yl)oxepan-2-yl)aniline as a pale yellow oil; yield: 41 mg (70%).

¹H NMR (500 MHz, CDCl₃): δ = 7.10 (d, *J* = 8.1 Hz, 2 H), 6.60 (d, *J* = 8.3 Hz, 2 H), 4.73 (d, *J* = 5.4 Hz, 1 H), 4.57 (s, 1 H), 4.54 (s, 1 H), 3.72–3.62 (m, 1 H), 3.54 (s, 2 H), 2.81 (dt, *J* = 10.2, 5.5 Hz, 1 H), 1.93–1.71 (m, 4 H), 1.67–1.45 (m, 2 H), 1.39 (s, 3 H), 1.25 (d, *J* = 6.2 Hz, 3 H).

¹³C NMR (125 MHz, CDCl₃): δ = 147.31, 144.45, 132.88, 127.10, 114.44, 112.48, 81.88, 77.87, 52.42, 40.17, 30.73, 24.81, 23.09, 20.68.

LRMS (ESI⁺): *m/z* [M + H]⁺ = 246.

HRMS (ESI⁺): *m/z* [M + H]⁺ calcd for C₁₄H₁₈NO: 246.1858; found: 246.1852.

To a 5-mL round-bottomed flask with a stir bar containing the above aniline (41 mg, 0.17 mmol, 1.0 equiv) was added CH_2Cl_2 (1.7 mL, 0.1 M) and Et_3N (0.07 mL, 0.51 mmol, 3 equiv), followed by the addition of *p*-bromobenzenesulfonyl chloride (0.13 g, 0.51 mmol, 3 equiv). The reaction mixture was then stirred for 12 h at room temperature. Then, H_2O was added to the reaction mixture. The resulting mixture was then extracted with CH_2Cl_2 , dried over Na_2SO_4 , and concentrated. The crude mixture was then purified by column chromatography (EtOAc –hexanes, 20:80) to give **48** as a white solid; yield: 40 mg (35%); mp 162–164 °C.

^1H NMR (500 MHz, CDCl_3): δ = 7.74 (d, J = 8.5 Hz, 4 H), 7.67 (d, J = 8.4 Hz, 4 H), 7.31 (d, J = 8.2 Hz, 2 H), 6.89 (d, J = 8.1 Hz, 2 H), 4.84 (d, J = 5.3 Hz, 1 H), 4.54 (s, 2 H), 3.73–3.59 (m, 1 H), 2.84 (dt, J = 10.1, 5.4 Hz, 1 H), 1.97–1.83 (m, 3 H), 1.76 (q, J = 11.2 Hz, 1 H), 1.71–1.59 (m, 1 H), 1.59–1.46 (m, 1 H), 1.39 (s, 3 H), 1.27 (d, J = 6.0 Hz, 3 H).

^{13}C NMR (125 MHz, CDCl_3): δ = 146.30, 145.67, 138.20, 132.27, 131.36, 130.36, 130.03, 129.36, 127.12, 113.18, 81.69, 78.92, 52.61, 40.23, 30.93, 24.44, 22.93, 20.63.

LRMS (APCI) $^+$: m/z [$\text{M} + \text{H}$] $^+$ = 682.

HRMS (ESI $^+$): m/z [$\text{M} + \text{Na}$] $^+$ calcd for $\text{C}_{28}\text{H}_{29}\text{Br}_2\text{NO}_5\text{S}_2\text{Na}$: 703.9752; found: 703.9736.

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Figure 1.
Structures of oxacyclic bioactive molecules

Figure 2.
NOE correlations of oxepine derivative **35**

Figure 3.
NOE correlations of oxepane derivative **45**

Scheme 1.

Synthesis of tetrahydropyrans by Hosomi²⁹ and Loh³⁰ and their co-workers

Scheme 2. Tetrahydropyran synthesis by Ghosh and Nicponski³¹

Scheme 3.
Polycyclic ring formations by Ghosh and co-workers³³

Scheme 4.

Formation of oxocene product as a minor isomer, with benzyloxyacetaldehyde

Scheme 5.
Oxocene synthesis by Overman and co-workers³⁹

Scheme 6.
Preparation of *exo*-oxacyclic isomer **31k**

Scheme 7.
Transition-state analysis for the oxepine products

Scheme 8.TMSOTf-catalyzed isomerization of alkenol **44**

Scheme 9.

X-ray crystal structure determination of **48** (white = hydrogen, black = carbon, red = oxygen, blue = nitrogen, yellow = sulfur, brown = bromine)

Scheme 10.
Transition-state analysis for the oxepane products

Table 1 Sc(OTf)₃- and *p*-TSA-Catalyzed Cyclization^a

Entry	Solvent	Ratio (21/22a)	Yield (%) ^b
1 ^c	CH ₂ Cl ₂	71:29 ^d	N/A
2	CH ₂ Cl ₂	90:10	43
3	toluene	74:26	54
4	MeCN	9:91	27
5	THF	N/A	N/A
6	CH ₂ Cl ₂ -MeCN, 1:1	17:83	37
7 ^c	CH ₂ Cl ₂ -MeCN, 1:1	17:83	33
8 ^e	CH ₂ Cl ₂ -MeCN, 1:1	64:36	42
9 ^f	CH ₂ Cl ₂ -MeCN, 1:1	29:71	27

^aReaction conditions: **5a** (1 equiv), *p*-nitrobenzaldehyde (1 equiv), Sc(OTf)₃ (10 mol%), *p*-TSA (30 mol%), 0.05 M solution; N/A = not applicable.^bIsolated yield of combined products.^cNo *p*-TSA was used.^dNo purification done; starting material remained after 48 h.^eSc(OTf)₃ (20 mol%) used.^f*p*-TSA (10 mol%) used.

Table 2 Sc(OTf)₃-Catalyzed Reactions: Selected Substrate Scope^a

Entry	R	Product ^b	Yield (%) ^c
1	<i>p</i> -F- <i>m</i> -NO ₂ C ₆ H ₃	23 + 24 50:50	32
2	<i>p</i> -BrC ₆ H ₄	24 + 22c 100:0	16
3	CH ₂ OBn	19 + 20 40:50	23
4 ^d	<i>p</i> -MeOC ₆ H ₄	25 + 22d 100:0	19
5	(CH ₂) ₂ Ph	26 + 22e 100:0	9

^aReaction conditions: as per entry 6, Table 1.^bRatio of pyran/oxocene is given.^cYield of combined products.^dAldehyde (2 equiv) used.

Table 3 Dy(OTf)₃- and *p*-TSA-Catalyzed Cyclization^a

Entry	Conditions	Ratio (21/22a)	Yield (%) ^b
1 ^c	Dy(OTf) ₃ (10 mol%)	N/A	N/A
2	Dy(OTf) ₃ (10 mol%) and <i>p</i> -TSA (30 mol%)	0:100	26
3	Dy(OTf) ₃ (10 mol%) and CSA (30 mol%)	0:100	22
4 ^d	Dy(OTf) ₃ (10 mol%) and <i>p</i> -TSA (30 mol%)	23:77	70
5 ^d	Dy(OTf) ₃ (20 mol%) and <i>p</i> -TSA (30 mol%)	41:59	55
6 ^d	Dy(OTf) ₃ (30 mol%) and <i>p</i> -TSA (30 mol%)	47:53	52

^aReaction conditions: **5a** (1 equiv), *p*-nitrobenzaldehyde (1 equiv), Dy(OTf)₃ (10 mol%), *p*-TSA (30 mol%), 0.05 M solution; N/A = not applicable.

^bYield of combined products.

^cOnly starting materials remained after 48 h.

^dAldehyde (2 equiv) used.

Table 4 Dy(OTf)₃-Catalyzed Reactions: Substrate Scope^a

Entry	R ¹	Product ^b	Yield (%) ^c
1	<i>p</i> -F- <i>m</i> -NO ₂ C ₆ H ₃		46
2	<i>p</i> -BrC ₆ H ₄		6
3	CH ₂ OBn		6
4	<i>p</i> -MeOC ₆ H ₄		5
5	<i>m</i> -MeC ₆ H ₄		7

^aReaction conditions: as per entry 2, Table 3.^bRatio of pyran/oxocene is given.^cYield of combined products.

Table 5TMSOTf- and BF₃·OEt₂-Catalyzed Cyclization^a

Entry	Solvent	Lewis acid	Equiv ^b	Ratio (22a/31a) ^c	Yield (%) ^d
1 ^e	<i>t</i> -BuOMe	BF ₃ ·OEt ₂	3.0	76:24	33
2 ^e	CH ₂ Cl ₂	BF ₃ ·OEt ₂	0.1	98:2	14
3 ^e	CH ₂ Cl ₂	BF ₃ ·OEt ₂	0.2	98:2	38
4 ^e	CH ₂ Cl ₂	BF ₃ ·OEt ₂	0.4	98:2	21
5	<i>t</i> -BuOMe	TMSOTf	1.0	88:12	46
6 ^e	Et ₂ O	TMSOTf	1.0	95:5	60
7	DME	TMSOTf	1.0	81:19	58
8	THF	TMSOTf	1.0	98:2	73
9	CH ₂ Cl ₂ -THF, 1:1	TMSOTf	1.0	98:2	68
10	CH ₂ Cl ₂ -THF, 3:1	TMSOTf	1.0	98:2	68

^aReaction conditions: 5a (1 equiv), *p*-nitrobenzaldehyde (1.2 equiv), 0.1 M solution, molecular sieves (60 mg).^bEquivalents of Lewis acid.^cRatio of *endo*/*exo*-olefin.^dYield of combined products.^eNo molecular sieves were used.

Table 6TMSOTf-Catalyzed Reactions: Substrate Scope^a

Entry	R	R ¹	Product ^{b,c}	Yield (%) ^d
1	Me	<i>p</i> -NO ₂ C ₆ H ₄	 22a/31a, 98:2	73
2	H	<i>p</i> -NO ₂ C ₆ H ₄	 22g/31g, 90:10	70
3	Et	<i>p</i> -NO ₂ C ₆ H ₄	 22h/31h, 90:10	87

Entry	R	R ¹	Product ^{b,c}	Yield (%) ^d
4	<i>i</i> -Pr	<i>p</i> -NO ₂ C ₆ H ₄	 22l/31l , 91:9	62
5	Ph	<i>p</i> -NO ₂ C ₆ H ₄	 22j/31j , 91:9	39
6	Me	<i>m</i> -NO ₂ C ₆ H ₄	 22k/31k , 91:9	65
7	Me	<i>o</i> -NO ₂ C ₆ H ₄	 22l/31l , 97:3	58
8	Me	<i>p</i> -FC ₆ H ₄	 22m/31m , 90:10	20
9	Me	<i>p</i> -F ₃ CC ₆ H ₄	 22n/31n , 92:8	37
10	Me	<i>p</i> -ClC ₆ H ₄	 22o/31o , 93:7	18

Entry	R	R ¹	Product ^{b,c}	Yield (%) ^d
11	Me	(CH ₂) ₂ Ph	 22e/31e , 94:6	35
12	Me	CH ₂ OBn	 20/19 , 98:2	24
13	Me	<i>m</i> -MeC ₆ H ₄	 22f/31f , 92:8	8
14	Me	2-Naph	 22p/31p , 94:6	16
15	Me	<i>p</i> -F- <i>m</i> -NO ₂ C ₆ H ₃	 22b/31b , 91:9	41

^aReaction conditions: as per entry 8, Table 5.

^bThe *endo/exo*-olefin ratio was determined by ¹H NMR analysis.

^c*endo*-Oxocene dr >20:1, as determined by ¹H NMR analysis.

^dIsolated yield of combined products.

Table 7 Preliminary Oxepine Syntheses^a

Entry	R	Product	Yield (%)
1	<i>p</i> -NO ₂ C ₆ H ₄	35	36
2	<i>m</i> -NO ₂ C ₆ H ₄	36	49
3	(CH ₂) ₂ Ph	37	49
4	CH ₂ OBn	38	27
5	<i>p</i> -F- <i>m</i> -NO ₂ C ₆ H ₃	39	28
6	<i>p</i> -MeO- <i>m</i> -NO ₂ C ₆ H ₃	40	48

Entry	R	Product	Yield (%)
7	CO ₂ Et	 41	23

^aReaction conditions: **34** (1 equiv), aldehyde (1.2 equiv), TMSOTf (1 equiv), 0.1 M solution, 0 °C, molecular sieves (40 mg).

Table 8 Synthesis of Oxepane Derivatives^a

Entry	R	Product	Yield (%)
1	<i>p</i> -NO ₂ C ₆ H ₄	 45	14
2	<i>m</i> -NO ₂ C ₆ H ₄	 46	29

^aReaction conditions: **44** (1 equiv), aldehyde (1.2 equiv), TMSOTf (1.2 equiv), 0.1 M solution, 0 °C, molecular sieves (40 mg).