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Medium-Ring Effects on the *Endo/Exo* Selectivity of the Organocatalytic Intramolecular Diels–Alder Reaction

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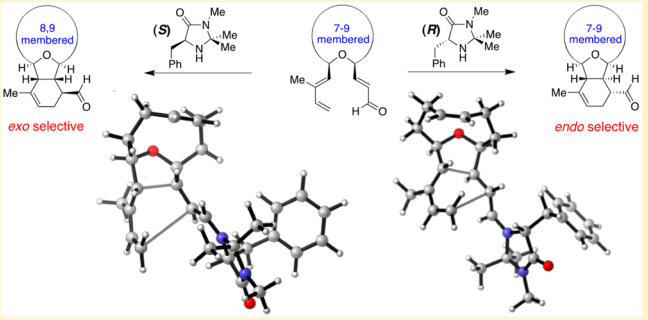
Supporting Information

ABSTRACT: The intramolecular Diels–Alder reaction has been used as a powerful method to access the tricyclic core of the eunicellin natural products from a number of 9-membered-ring precursors. The *endo/exo* selectivity of this reaction can be controlled through a remarkable organocatalytic approach, employing MacMillan's imidazolidinone catalysts, although the mechanistic origin of this selectivity remains unclear. We present a combined experimental and density functional theory investigation, providing insight into the effects of medium-ring constraints on the organocatalyzed intramolecular Diels–Alder reaction to form the isobenzofuran core of the eunicellins.



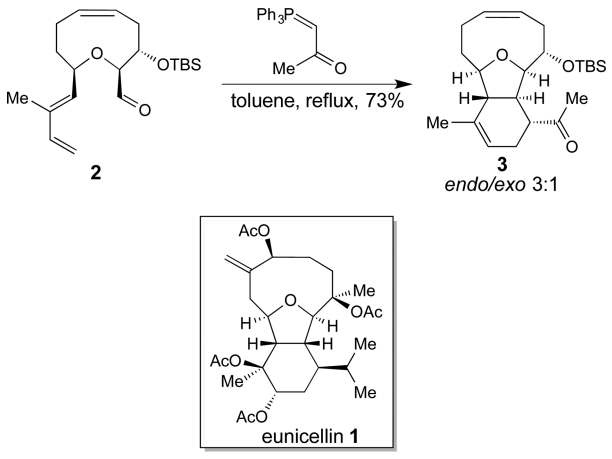
INTRODUCTION

The eunicellins (e.g., eunicellin **1**, Scheme 1) are a class of diterpenoid natural products, which, because of their structural complexity and broad range of biological activities, have attracted much attention from synthetic organic chemists.[1] Among the range of methods used to synthesize the tricyclic eunicellin core, several groups have adopted a Diels–Alder cycloaddition strategy to form the isobenzofuran ring system. Paquette first described an *endo* selective intermolecular Diels–Alder approach employing Danishefsky's diene in the synthesis of sclerophytin A.[2] Clark later reported an intermolecular [4 + 2] cycloaddition en route to vigulariol, resulting in a 2:1 mixture of isomers.[3]

An alternative strategy is to employ an intramolecular Diels–Alder reaction of an appropriately substituted 9-membered-ring precursor to form the tricyclic ring system of the eunicellins. While this is clearly a powerful method for the construction of the eunicellin core, controlling the *endo/exo* selectivity of this reaction to obtain the desired *exo* cycloadduct has proven critical for the success of this method. Crimmins and co-workers have shown that strong *exo* selectivity can be obtained by careful substrate control, in which the protecting group on the C3 hydroxyl is critical for high *exo* selectivity.[4] The success of this approach has been further demonstrated by the work of Kim and co-workers.[5]

Our group has reported an intramolecular Diels–Alder approach to the eunicellin core, where the *endo/exo* selectivity of the cycloaddition reaction can be controlled through the use of an appropriate catalyst. In a first generation approach,[6]

Scheme 1. A Thermal Intramolecular Diels–Alder Approach to the Tricyclic Core of the Eunicellins



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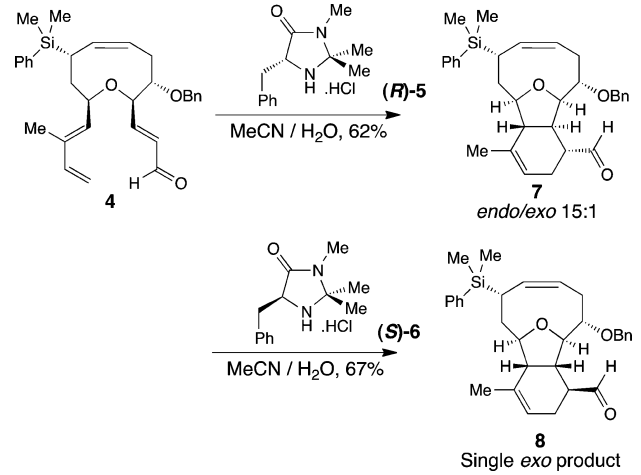
treatment of the aldehyde **2** with a Wittig reagent generated the reactive triene *in situ*. Thermal cycloaddition of this intermediate resulted in a 3:1 mixture of adducts, favoring the undesired *endo* product **3** (Scheme 1).

In further approaches to the synthesis of these compounds, we discovered a remarkable case of stereocontrolled cycloaddition employing the first generation MacMillan imidazolidinone organocatalysts.[7] Treatment of aldehyde **4** with the MacMillan catalyst (*R*)-**5** resulted in a 15:1 mixture of *endo* and *exo* cycloadducts, favoring the *endo* product **7** (Scheme 2). In

Scheme 2. An *Exo* Selective Diels–Alder Approach to the Eunicellin Core

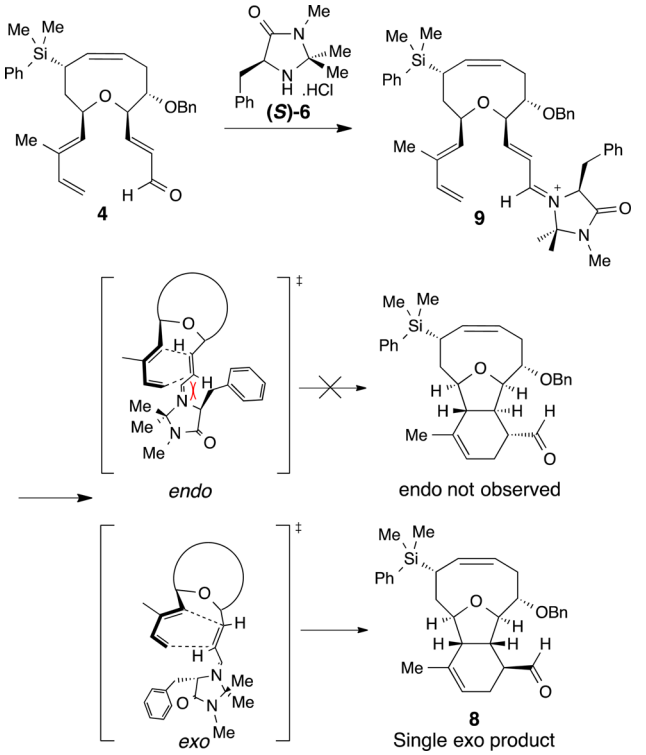


contrast, exposure of **4** to the (*S*)-catalyst **6** gave the desired *exo* product **8** as a single diastereoisomer. We believe that this represents the first example of near-complete *endo*/*exo* control in an organocatalytic Diels–Alder reaction. The purpose of this investigation is to explain the origin of this stereoselectivity from a synthetic and computational perspective.

Scheme 3 shows a possible explanation for the diastereoselectivity observed in the organocatalytic Diels–Alder cycloaddition of **4**. Condensation of the α,β-unsaturated aldehyde **4** with the catalyst (*S*)-**6** results in the iminium ion **9**, believed to favor the (*E*′)-iminium configuration.[8] This intermediate may adopt either an *endo* or *exo* transition geometry in the Diels–Alder reaction. In the *endo* transition state, the diene would approach the dienophile from the more hindered *si* face of the iminium ion, resulting in an unfavorable nonbonding interaction between the benzyl group of the catalyst and the diene. In the *exo* transition state, the diene would approach the dienophile from the less hindered *re* face of the iminium ion, resulting in a high level of *exo* diastereoselectivity, consistent with the experimental finding. Similarly, the use of the (*R*)-catalyst **5** results in a more hindered *re* face, thus favoring addition of the dienophile to the *si* face of the iminium ion, which would provide the *endo* cycloadduct.

While the model described above provides a general rationalization of the observed *endo*/*exo* selectivity in the organocatalyzed cycloaddition reactions of **4**, it remains unclear how the conformational restrictions imposed by the 9-membered ring affect the catalysts' ability to influence *endo*/*exo* selectivity, and whether this could be applied to other ring sizes. It also fails to account for the observation that addition to the *re* face (or the "top" face as drawn) of the diene is not

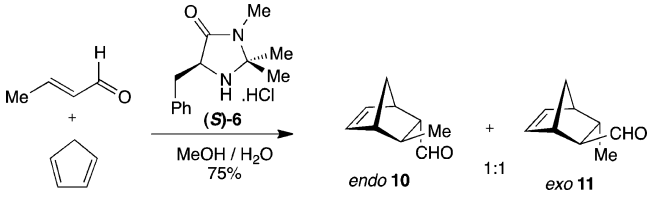
Scheme 3. A Possible Explanation for the Observed *Exo* Selectivity in the Cycloaddition of 4



observed. In this paper, we detail the reactivity of a series of Diels–Alder precursors in an attempt to explain the *exo* selectivity observed in the presence of the (*S*)-MacMillan catalyst. This includes an investigation of the acyclic substrate and corresponding 7-, 8-, and 9-membered-ring ether analogues, in an effort to determine how a medium-sized ring affects the diastereoselectivity preferences. We report herein an experimental study of these reactions and a theoretical study that predicts the trends observed experimentally and explains the steric and electronic factors that control stereochemistry.

The imidazolidinones (*R*)-**5** and (*S*)-**6** were first reported in 2000 by MacMillan and co-workers as catalysts for asymmetric synthesis.[8] These catalysts are known to react with α,β-unsaturated aldehydes, reversibly forming an iminium ion and lowering the LUMO of the alkene. MacMillan and co-workers demonstrated the use of these organocatalysts in highly enantioselective Diels–Alder reactions. The reaction of cyclopentadiene with a variety of α,β-unsaturated aldehydes was investigated, and it was observed that catalyst **6** gave high levels of enantioselectivity. However, the reaction resulted in 1:1 mixtures of *endo* and *exo* isomers **10** and **11**, indicating that the catalyst could not control *endo*/*exo* selectivity in the reported intermolecular cycloadditions (Scheme 4).

Scheme 4. First Example of Enantioselective Diels–Alder Cycloadditions Employing Imidazolidinone Catalysts



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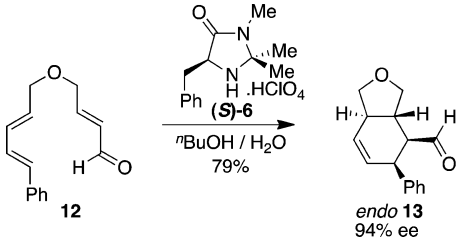
Chiral imidazolidinones have been used by MacMillan and co-workers for the stereoselective total synthesis of solanapyrone D, a marine metabolite.[9] In course of this investigation it was determined that the imidazolidinone catalysts are effective in promoting enantioselective intramolecular cycloadditions of a variety of trienes, including trienes that incorporate heteroatoms. It was noted that Lewis acid catalyzed reactions involving heteroatoms in the tether were problematic due to substrate decomposition,[9] but by using catalyst **6**, MacMillan and co-workers found that the ether−aldehyde triene **12** underwent cyclization to give the resulting *endo* isobenzofuran adduct **13** in good yield and with high stereoselectivity (Scheme 5).

Scheme 5. MacMillan's *Endo* Selective Intramolecular Diels−Alder Cycloaddition Using Catalyst 6



The MacMillan group employed MM3 force field calculations to account for the selectivities obtained with catalyst (*S*)-**6**.[8] It was suggested that, upon condensation of the catalyst with an α,β-unsaturated aldehyde, the (*E*)-iminium ion is favored to avoid nonbonding interactions between the appendent olefin and the *geminal* dimethyl group. MacMillan also suggested that the benzyl group of the catalyst shields the *re* face of the alkene, stabilized by an iminium−π interaction. Kozlowski et al. found the same lowest energy conformation also using the MM2 force field method.[10]

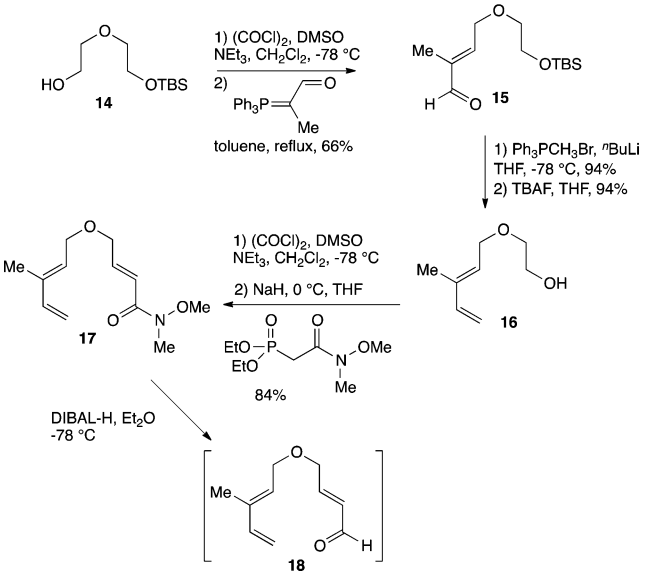
Houk and co-workers studied the conformations of the iminium ion formed from (*E*)-crotonaldehyde and **6** using density functional theory calculations (B3LYP/6-31G(d)) and showed that the (*E*)- and (*Z*)-iminium ions differ in energy by only 1.2 kcal/mol,[11] suggesting that both isomers may be relevant in catalysis. This is supported by experimental work from Seebach[12] and Gilmour.[13] They also found that, contrary to previous results, the lowest energy conformer included a stabilizing C−H···π interaction between the *syn*-methyl group and the phenyl shielding group. The importance of this interaction has been supported by experimental and computational studies.[14] Several other low-lying conformers were located, but calculations indicate that attack from the *si* face of the dienophile is always preferred.

In 2006, the Houk group studied the Diels−Alder reactions of cyclopentadiene with a variety of α,β-unsaturated aldehydes using density functional theory, suggesting that the catalyst (*S*)-**6** lowers the activation energies by approximately 13 kcal/mol versus the thermal cycloaddition.[15]

RESULTS AND DISCUSSION

Synthesis and Cycloaddition Reactions of an Acyclic Diels−Alder Precursor. To investigate the performance of the imidazolidinone catalysts **5** and **6** with an intramolecular Diels−Alder substrate in the absence of medium-ring constraints, the acyclic triene **18** was prepared from the silyl ether **14** (Scheme 6). Oxidation of the free hydroxyl-group of

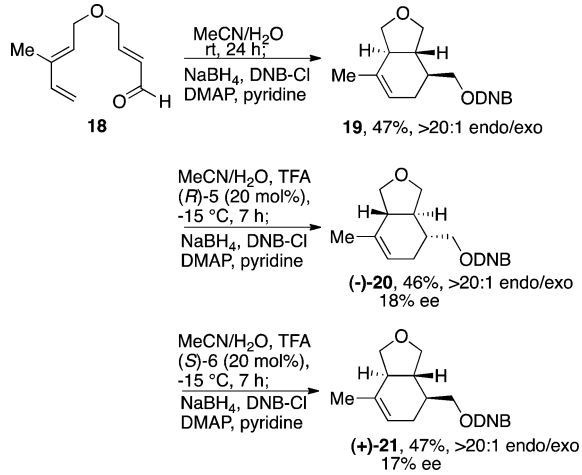
Scheme 6. Synthesis of the Diels−Alder Precursor 18



14 and Wittig olefination gave the α,β-unsaturated aldehyde **15**. Wittig methylenation and deprotection afforded the alcohol **16**, which was subjected to oxidation and Horner−Wadsworth−Emmons homologation to give the triene **17**. Reduction of the Weinreb amide **17** gave the α,β-unsaturated aldehyde **18**, which underwent spontaneous Diels−Alder cycloaddition at room temperature, but could be isolated and handled at low temperature without any observed cycloaddition.

Thermal cycloaddition of the α,β-unsaturated aldehyde **18** at room temperature gave the *endo* adduct exclusively, which was isolated after *in situ* reduction to the alcohol and subsequent esterification to the dinitrobenzoate ester **19** (Scheme 7).

Scheme 7. Thermal and Catalyzed Diels−Alder Cycloadditions of 18[a]



[a]DNB = 3,5-dinitrobenzoate.

When the α,β-unsaturated aldehyde **18** was treated with (*R*)-imidazolidinone catalyst **5** at −15 °C, considerable acceleration of the reaction rate was observed, and the cycloadduct was isolated as the dinitrobenzoate ester (−)-**20**. The cycloadduct **20** was isolated as the *endo* isomer only, although with a lower than expected enantiomeric excess of 18%. Exposure of the

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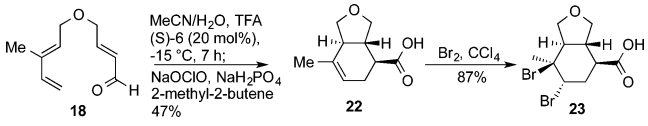
aldehyde **18** to the corresponding (*S*)-catalyst **6** gave, after derivatization to the ester, the enantiomeric cycloadduct (+)-**21**, with a similar level of enantiomeric excess (17%). Stirring the *α,β*-unsaturated aldehyde **18** in the absence of catalysts **5** and **6**, under otherwise identical reaction conditions (−15 °C, 20% TFA, MeCN/H_2O), resulted in recovery of the starting material, indicating that thermal cycloaddition is not competing with the catalyzed reaction under these conditions.

The assignment of *endo* selectivity to the products arising from both the thermal and the organocatalyzed Diels−Alder reactions of **18** was confirmed by X-ray crystallographic analysis of the brominated derivative **23** (Scheme 8). Assignment of the absolute configuration of the major enantiomers of (−)-**20** and (+)-**21** have been assumed by analogy to the previous reports of MacMillan[9] and Koskinen.[16]

Scheme 8. Preparation of the Dibromide Derivative 23 for X-ray Crystallographic Analysis



To analyze these trends and determine the steric and electronic effects involved, calculations using density functional theory (M06-2X/6-311G(d,p)//B3LYP/6-31+G(d)[17] with CPCM[18] for solvent effect of MeCN) were performed using Gaussian09.[19] All energies are given in kcal/mol and were calculated at standard conditions (1 atm, 273.15 K). The *endo* and *exo* transition states (**24** and **25**, Figure 1, each leading to

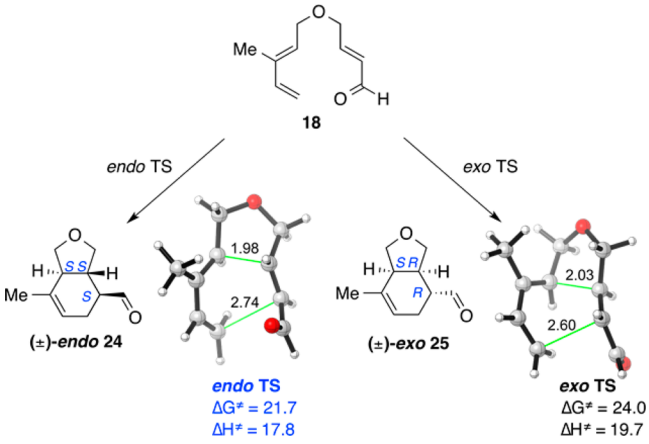


Figure 1. Calculated *endo* and *exo* Diels−Alder transition states for the uncatalyzed reaction of **18**.

two possible enantiomers) of the intramolecular reaction of the uncatalyzed ether-tethered triene **18** were investigated. The *endo* transiton states were found to be the most stable, with a 21.7 kcal/mol free energy of activation.

In our investigation of the reaction of the acyclic substrate catalyzed by the (*R*)-MacMillan catalyst **5** we attempted to locate all possible transition states of the reactive iminium ion. The *endo* transition state (*R*)-*endo-re* TS was found to have the lowest activation barrier of 13.1 kcal/mol (Figure 2). The other *endo* transition state (*R*)-*endo-si* TS is 1.3 kcal/mol higher in energy, which slightly overestimates the observed enantioselectivity of 18%. The *exo* transition states are significantly higher in energy, which is in good agreement with the experiment.

The (*R*)-*endo-re* TS features the optimal catalyst arrangement in which the benzyl group of the imidazolidinone shields one of the enantiofaces of the dienophile. The (*E*)-iminium isomer is preferred in order to avoid nonbonding interactions between the substrate olefin and the *geminal* dimethyl groups. Additionally, the lowest energy transition structure features a stabilizing C−H···*π* interaction between the *syn*-methyl group at the C2 position of the imidazolidinone and the *π* system of the phenyl group at the C5 position. These results are consistent with previous conformational studies by Houk of the iminium complex formed from (*E*)-crotonaldehyde and the MacMillan catalyst **6**[11] and correctly predict the preferred enantiomer.

Synthesis and Cycloaddition Reactions of Medium-Ring Diels−Alder Precursors. The 7- and 8-membered-ring ethers **32** and **33** were synthesized by a divergent ring closing metathesis approach from the enantiomerically pure allylic alcohol (+)-**26**, based on an approach developed by Crimmins (Scheme 9).[4a] The alcohol (+)-**26** was alkylated with bromoacetic acid, and the product was used to acylate the Evans oxazolidinone **27**[20] via the acid chloride intermediate, to yield the imide **28**. A one-carbon homologation[21] of the allylic ether **28** gave the homoallylic ether **29**, providing precursors to both the 7- and 8-membered rings. The imides **28** and **29** were alkylated under the conditions described by Crimmins,[22] to form the dienes **30** and **31**. Ring closing metathesis using Grubbs first generation catalyst[23] in dilute solutions of dichloromethane produced the 7- and 8-membered ethers in near quantitative yields. Reductive cleavage of the Evans auxiliary with $NaBH_4$ gave the alcohols **32** and **33**.

Oxidation of the primary alcohols **32** and **33** was followed by Wittig olefination to afford the *α,β*-unsaturated aldehydes **34** and **35** (Scheme 10). Benzyl deprotection was achieved by treatment with an excess of DDQ to give the alcohols **36** and **37**, and consequent one-pot oxidation/Wittig olefination gave the Weinreb amides **38** and **39**. A final Wittig methylenation gave the protected 7- and 8-membered Diels−Alder precursors **40** and **41**.

Treatment of the 7-membered-ring Weinreb amide **40** with DIBAL-H at −78 °C gave the aldehyde Diels−Alder precursor **42**, which was isolated at low temperature and used immediately in subsequent reactions (Table 1). Thermal intramolecular cycloaddition of the *α,β*-unsaturated aldehyde **42** proceeded at room temperature, and the product of this reaction was derivatized *in situ* to form the dinitrophenyl hydrazone **43** (entry 1). The structure of this compound was determined by single crystal X-ray diffraction and was found to have an *anti*-fused ring junction, resulting from an *endo* transition state.

In an attempt to shift the cycloaddition reaction toward the *exo* transition state, cycloaddition reactions were next attempted using the MacMillan catalysts. Treatment of the aldehyde **42** with either the (*R*)- or (*S*)-enantiomer of the catalyst (**5** and **6**) at −15 °C produced the *endo* adduct exclusively (entries 2 and 3). No discernible difference in the rate of cycloaddition catalyzed by the (*R*)- or (*S*)-enantiomer of the catalyst could be observed. Treatment of the aldehyde **42** at −15 °C with TFA in MeCN/H_2O in the absence of an amine catalyst afforded no reaction (entry 4), indicating that thermal cycloaddition is not competing with organocatalysis under these conditions.

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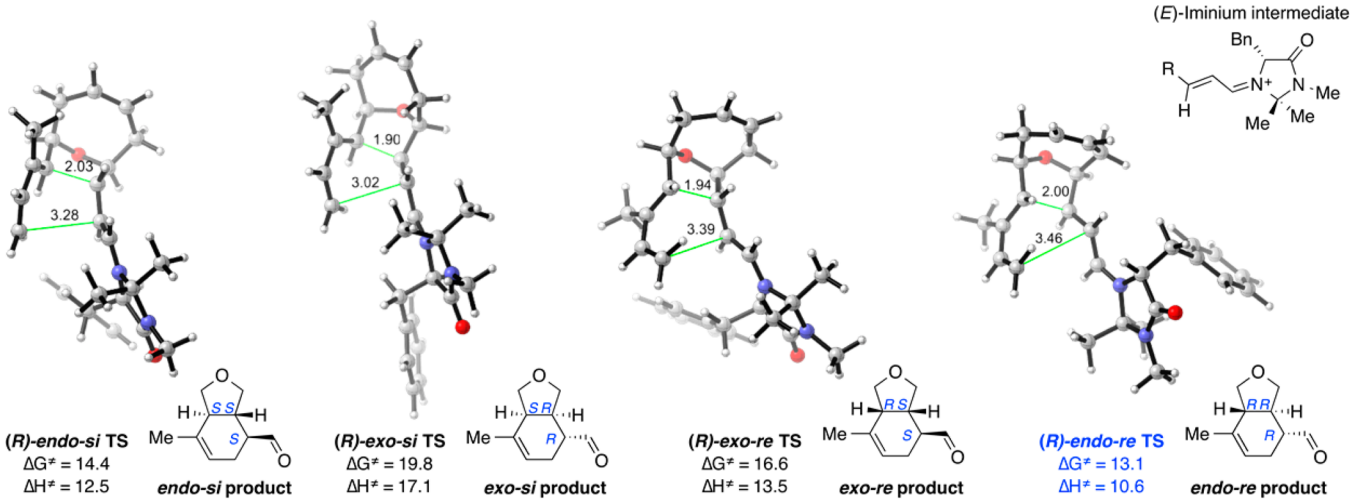
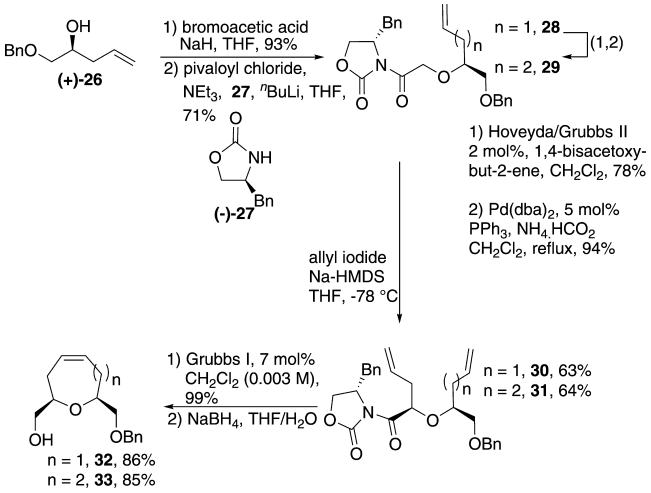
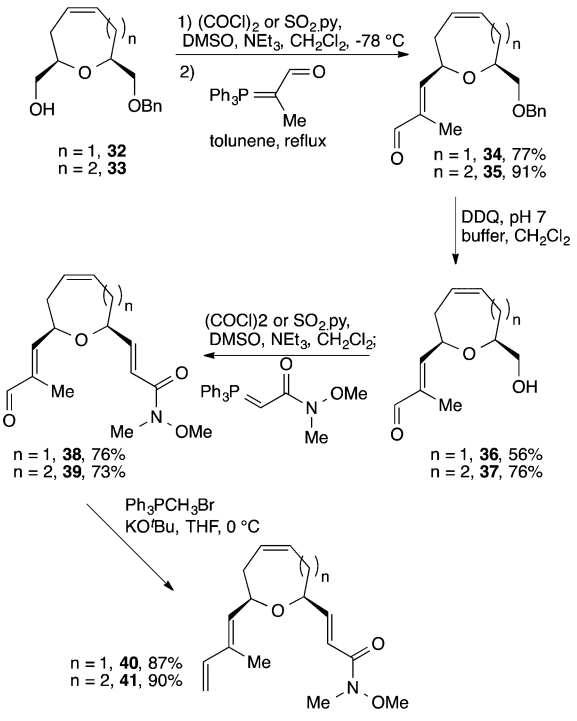


Figure 2. Calculated transition states of (*R*)-catalyzed Diels–Alder reaction **18**.

Scheme 9. Synthesis of the Medium-Ring Ethers 32 and 33



Scheme 10. Synthesis of the Weinreb Amides 40 and 41



The thermal and catalyzed cycloadditions of the 7-membered-ring ether **42** were computationally investigated. In contrast to the reactions of the acyclic precursor, the presence of a medium-sized ring imposes conformational restrictions on the accessible Diels–Alder transition states (Scheme 11). The ring system hinders the accessible orientations of the diene, causing unfavorable steric interactions in the *exo-re* TS and *endo-si* TS, in which the methyl group of the diene is in close proximity to the ring system. This observation is consistent with the experimental work of the Crimmins group and our own groups, where addition to the "top" or *re* face of the diene is not observed.

The thermal cycloaddition of the 7-membered-ring precursor favors the 7-*endo-re* TS, with an activation barrier of 25.0 kcal/mol (Figure 3). This transition state structure features the optimal arrangement of the diene with respect to the ring system, where the dienophile approaches from the *si* face of the diene and the diene methyl group is positioned away from the ring system. The effects of the unfavorable arrangement of the diene are most strongly observed in the 7-*exo-re* TS, in which the 7-membered ring is highly distorted to accommodate the transition state geometry, leading to an activation barrier of 38.2 kcal/mol. The 7-*exo-si* TS is still 2.9 kcal/mol higher in energy, which mirrors the observed large preference for the *endo* product.

In the organocatalyzed reactions of the ring-containing substrates, the interplay between the chiral substrate and the chiral catalyst determines the stereoinduction. The double stereodifferentiation arises when the facial selectivity of the substrate is either opposed or reinforced by the chiral auxiliary (Scheme 12). A matched case features the diene approaching the less hindered face of the dienophile, while the benzyl group of the imidazolidinone resides on the opposite face of the dienophile. In the mismatched cases, the attack of the diene is disfavored by the presence of the benzyl group on the same face. In the (*R*)-catalyzed reaction, the *endo-re* TS is a matched case, and in the (*S*)-catalyzed reactions, the facial preferences of the substrate and imidazolidinone are matched in the *exo-si* TS.

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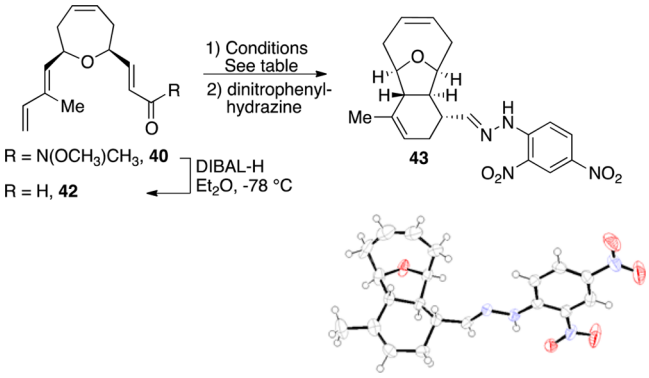
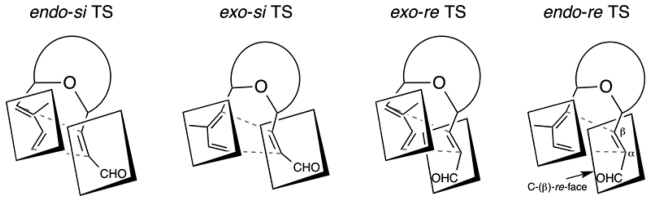
Table 1. Diels–Alder Cycloadditions of the 7-Membered Ether 42



entry	conditions	yield,[a] %	*endo*/*exo*[b]
1	room temperature, $CDCl_3$	50	>20:1
2	(*R*)-MacMillan·HCl **5**, TFA, MeCN/H_2O, −15 °C, 7 h	61	>20:1
3	(*S*)-MacMillan·HCl **6**, TFA, MeCN/H_2O, −15 °C, 7 h	63	>20:1
4	TFA, MeCN/H_2O, −15 °C, 24 h	0	n/a

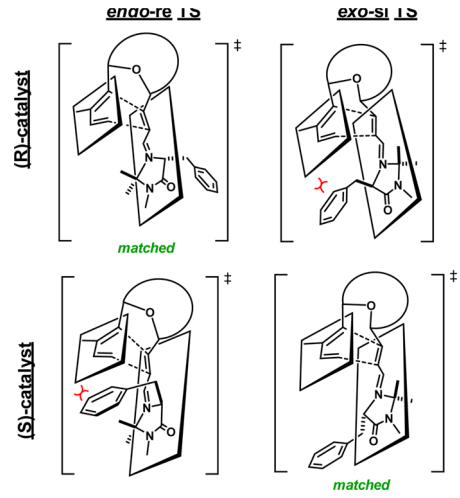
[a]Isolated yields. [b]Determined by ^1H NMR.

Scheme 11. Transition State Conformations in the Presence of a Medium-Sized Ring



The organocatalyzed reactions of the readily accessible *endo* and *exo* diastereomers were investigated with catalyst (*R*)-**5**, in which the diene reacts via the more accessible *si* face (Figure 4). In agreement with the experimental observations, the lowest energy optimized transition structure leads to an *endo* diastereomer. The (*R*)-7-*endo-re* TS is preferred over the (*R*)-7-*exo-si* TS by 8.3 kcal/mol.

Scheme 12. Double Stereodifferentiation between the (*R*)- and (*S*)-MacMillan Catalysts and Diels–Alder Transition States of Ring-Containing Substrates



In the presence of the (*S*)-catalyst **6**, the transition structure leading to the same *endo* diastereomer is preferred and has an activation barrier of 11.1 kcal/mol (Figure 5). These calculations suggest that while the catalyst is useful in lowering the activation barrier of the transition states, the substrate has a strong facial bias and controls the stereochemical outcome of the reaction. This is demonstrated in the reactions using the (*S*)-catalyst **6**, in which the *endo* transition state is preferred by 2.9 kcal/mol despite the fact that the *exo* transition state is a matched case. Again these results are in agreement with experiment.

Synthesis and Cycloaddition Reactions of an 8-Membered Diels–Alder Precursor. The 8-membered-ring precursor **41** was treated with DIBAL-H at −78 °C to give the *α*,*β*-unsaturated aldehyde **44** (Table 2). No reaction was observed after the substrate had been allowed to stand at room temperature for 24 h, indicating that the 8-membered-ring model is less reactive toward thermal cycloaddition than the 7-membered-ring system. Cycloaddition was achieved by heating the substrate at 100 °C in a microwave reactor for 3 h, and the cycloadducts were isolated as the dinitrophenyl hydrazone

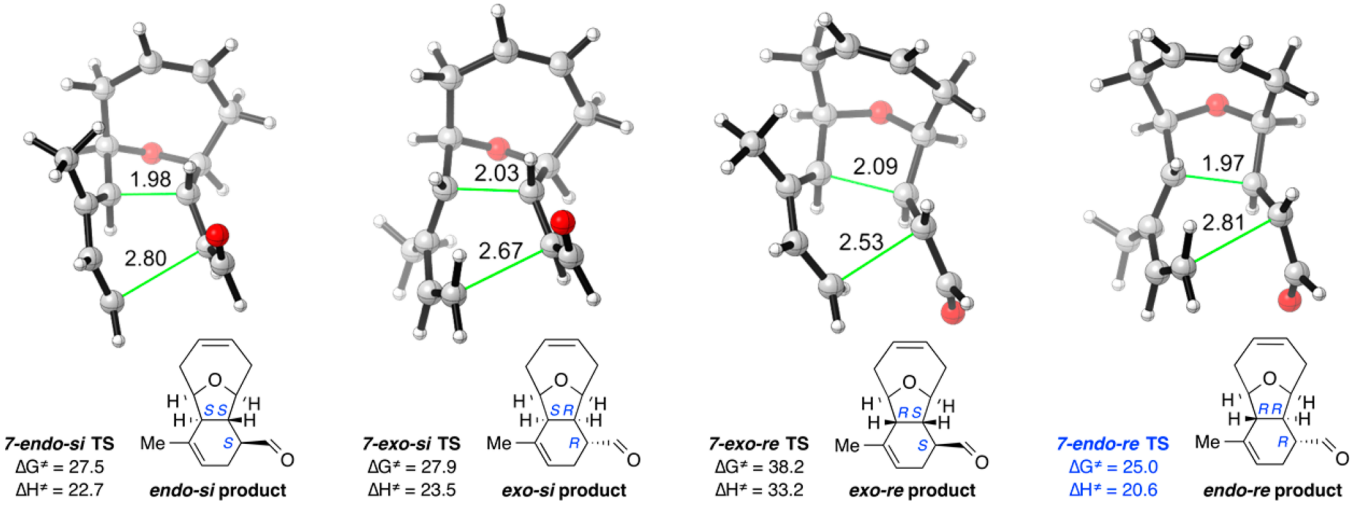


Figure 3. Diels–Alder transition states of aldehyde **42**.

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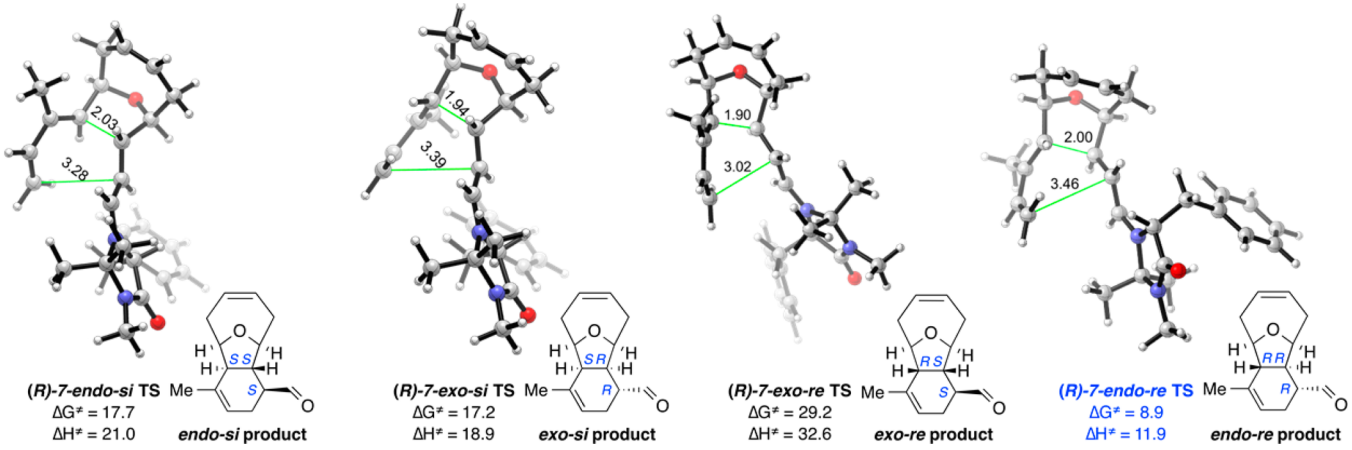


Figure 4. Diels–Alder transition states of aldehyde **42** catalyzed by the (*R*)-MacMillan catalyst **5**.

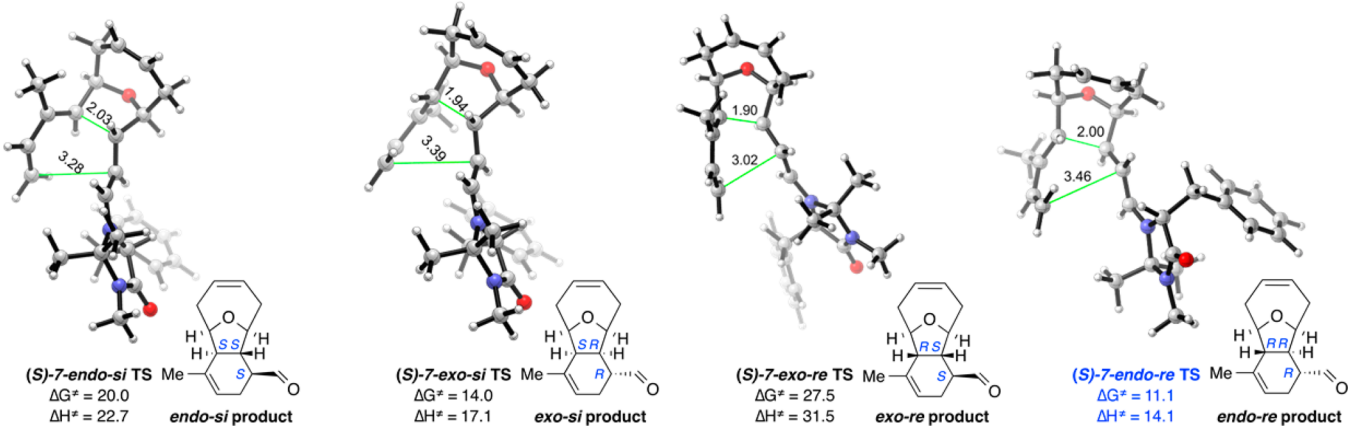
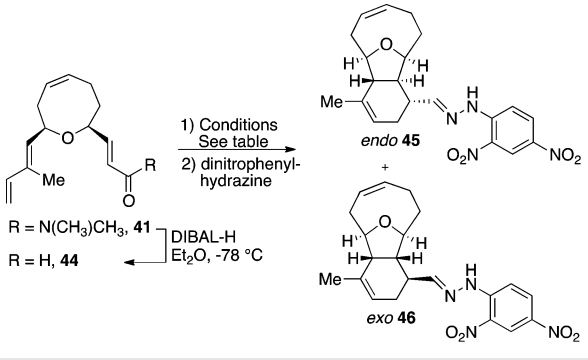


Figure 5. Diels–Alder transition states of aldehyde **42** in the presence of the (*S*)-MacMillan catalyst **6**.

Table 2. Diels–Alder Cycloadditions of the 8-Membered Ether 46



entry	conditions	yield,[a] %	*endo*/*exo*[b]
1	room temperature, 24 h, $CDCl_3$	0	n/a
2	100 °C, 3 h, $CDCl_3$, microwave	40	2.5:1
3	(*R*)-MacMillan·HCl **5**, TFA, $MeCN/H_2O$, 0 °C, 24 h	65	>20:1
4	(*S*)-MacMillan·HCl **6**, TFA, $MeCN/H_2O$, 0 °C, 24 h	72	1:1
5	TFA, $MeCN/H_2O$, −0 °C, 24 h	0	n/a

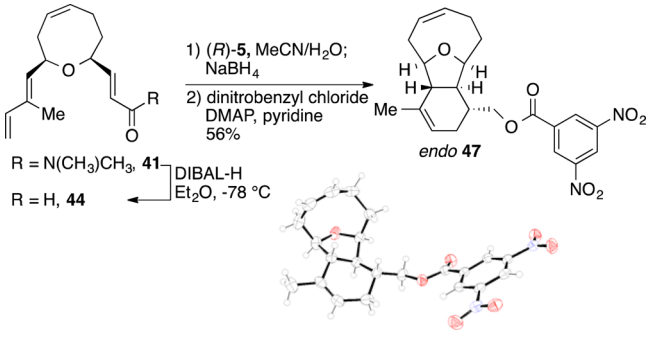
[a]Isolated yields. [b]Determined by ^1H NMR spectroscopy

derivatives in a 2.5:1 ratio of *endo*/*exo* products (entry 2, **45** and **46**). Treatment of the substrate **44** with the (*R*)-catalyst **5** at 0 °C produced the *endo* adduct exclusively (entry 3), which is consistent with the results obtained for the 7-membered-ring model, as well as the 9-membered-ring system previously reported.[24] In contrast, use of the (*S*)-catalyst **6** under the same conditions gave a 1:1 mixture of the *endo*/*exo* products (entry 4).

The assignment of *endo*/*exo* stereochemistry of the cycloadducts **45** and **46** was confirmed by X-ray crystallographic analysis of the dinitrobenzoate ester derivative **47** (Scheme 13).

In the Diels–Alder reactions of the 8-membered ether **44**, increased flexibility allows the ring to adopt improved conformations to better accommodate more stable transition state geometries. This is confirmed by examining the release of

Scheme 13. Synthesis and X-ray Crystal Structure of the *Endo* Adduct 47



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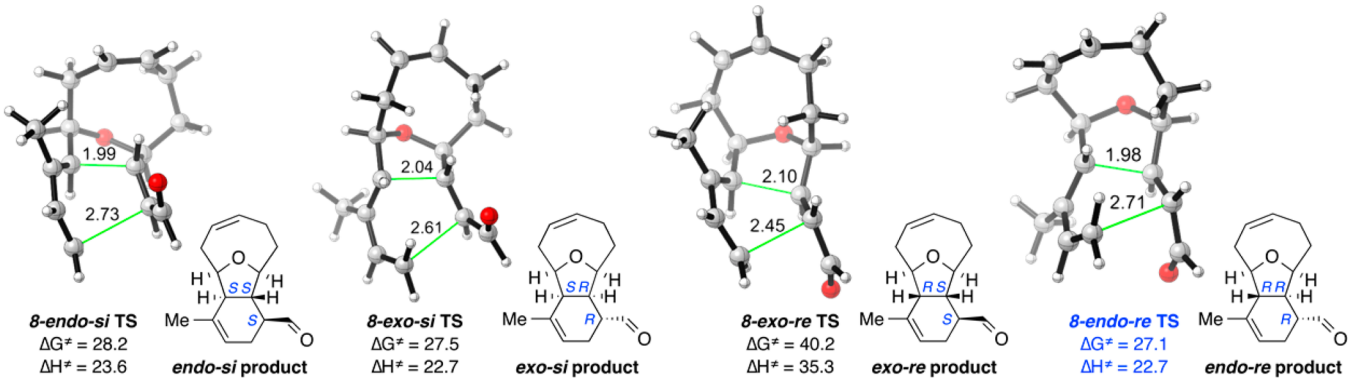

Figure 6. Diels–Alder transition states of aldehyde **44**.

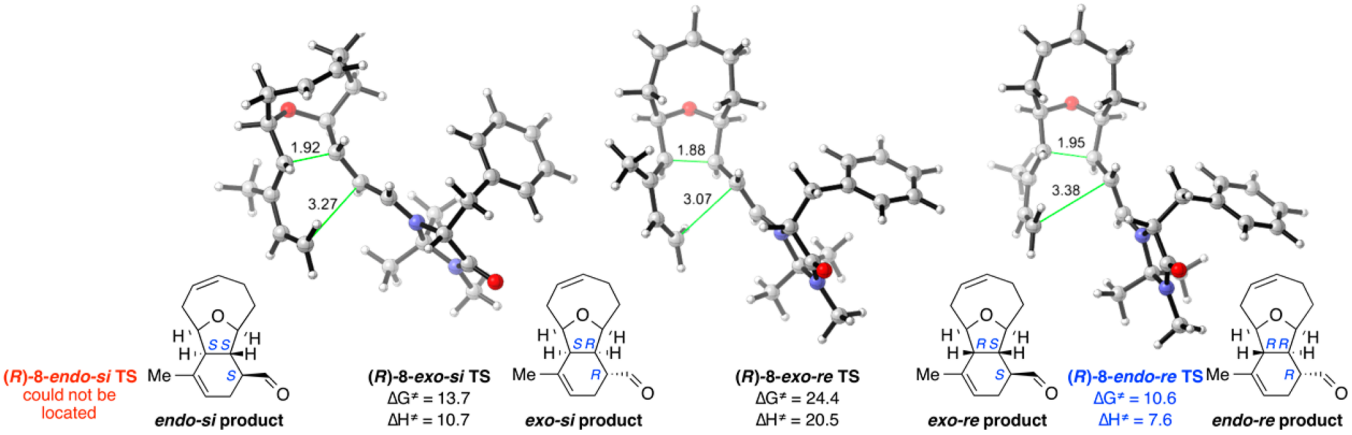

Figure 7. Calculated Diels–Alder transition states of aldehyde **44** in the presence of the (*R*)-MacMillan catalyst **5**.

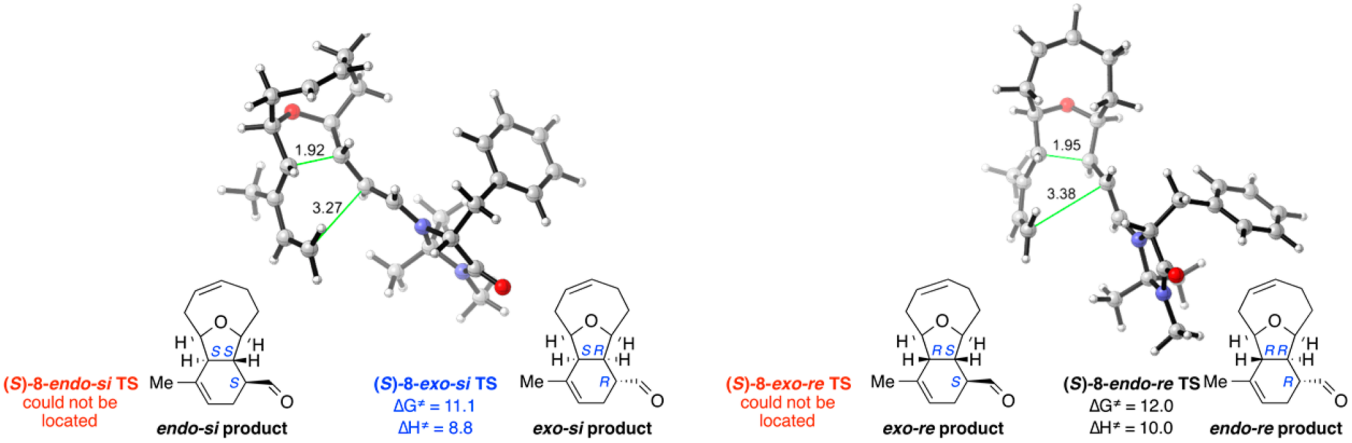

Figure 8. Calculated Diels–Alder transition states of aldehyde **46** in the presence of the (*S*)-MacMillan catalyst **6**.

torsional strain about the first C–C forming bond in the transition state. In the thermal reactions, the elevated temperature required to achieve cycloaddition is reflected by the increased activation barriers for the transition states. Calculations show that the 8-*endo-re* TS has the lowest activation barrier of 27.1 kcal/mol (Figure 6). The 8-*exo-si* TS was also found to be accessible with a free energy of activation 0.4 kcal/mol higher than the 8-*endo-re* TS, resulting in a predicted *endo*/*exo* ratio of 1.6:1 at 373 K (compare to 2.5:1 experimentally, Table 2).

In the (*R*)-catalyzed reaction, the *endo-re* diastereomer, a case of matched facial selectivity, has an activation barrier of 10.6 kcal/mol (Figure 7). The lowest lying *exo* TS was found to be 2.1 kcal/mol higher in energy. In the presence of the (*S*)-catalyst, both the *endo-re* and *exo-si* diastereomers are accessible (12.0 and 11.1 kcal/mol, respectively, Figure 8). While the experimental results show an *endo*/*exo* ratio of 1:1, our calculations based on M06-2X predict a slight preference for the *exo* diastereomer.

Computational Studies on a Model 9-Membered Substrate 48. Having examined the effects of 7- and 8-membered medium-ring constraints on the intramolecular Diels–Alder cycloaddition, we next examined the thermal and catalyzed cycloadditions of a 9-membered-ring precursor. Due

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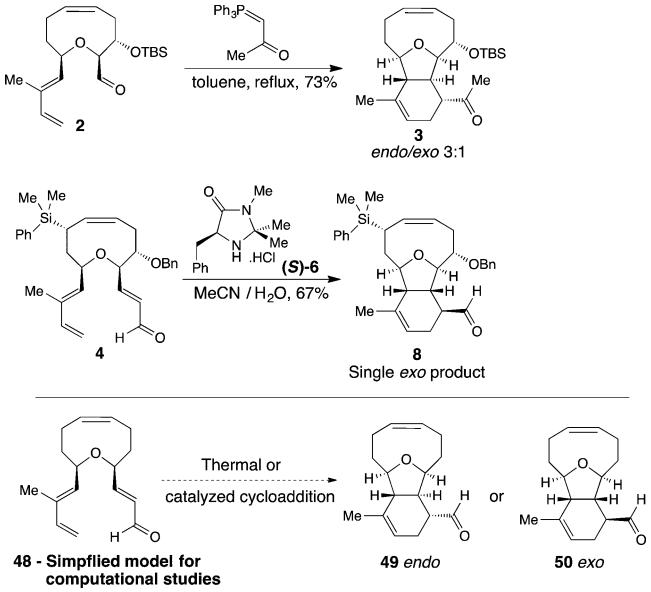
to the complexity of the reported 9-membered substrates **2** and **4**, we performed computations using aldehyde **48**, which served as a simplified model (Scheme 14).

Scheme 14. A Simplified Model of the 9-Membered Substrates 2 and 4



In the reported thermal cycloaddition, the reactive triene was generated *in situ* from **2** and resulted in a 3:1 mixture, favoring the *endo* product **3** (Scheme 1). Calculations performed on our simplified model system **48** are in agreement with the experimental results, but overestimate selectivity slightly (lowest *exo* TS is 1.9 kcal/mol higher in energy than lowest *endo* TS, Figure 9). Once again, the *endo-si* TS, in which the diene is approached from the *re* face, is more than 4 kcal/mol higher in energy than the favored *endo-re* transition state.

In the catalyzed reactions, the chiral information on the imidazolidinone is the controlling factor for stereodifferentiation. The (*R*)-catalyzed reaction of model substrate **48**, similar to all other (*R*)-catalyzed reactions in this series, favors the formation of the (*R*)-9-*endo-re* TS in which the stereochemical preferences of both the substrate and catalyst are conserved (Figure 10). This model predicts the *exo* TS to be 2.4 kcal/mol higher in energy.

The (*S*)-MacMillan (**6**) catalyzed reaction of the model substrate **48** was found to favor the *exo* transition state with an activation barrier of 18.3 kcal/mol (Figure 11). The cycloaddition of the 9-membered-ring substrate represents the first case in this series for which in the (*S*)-catalyzed reaction the matched case is preferred. In this case, the intrinsic *endo* bias of the 9-membered substrate (as seen in the thermal cycloadditions) is lower, and the catalyst is able to completely override this preference to favor the *exo* adduct. Consistent with earlier results, the (*S*)-9-*exo-si* TS features the (*E*)-iminium isomer and the benzyl group positioned on the bottom face of the dienophile. The lowest energy *endo* transition state, (*S*)-9-*endo-re* TS, was found to have a barrier 4.0 kcal/mol higher in energy than (*S*)-9-*exo-si* TS. While several *endo* transition states with the (*E*)-iminium geometry were located, the transition state with the (*Z*)-iminium isomer is preferred. This is due to the unfavorable interactions between the 9-membered ring and the benzyl group, when they are positioned on the same face. Although the (*Z*)-iminium geometry is generally disfavored, the energetic gain of positioning the benzyl group away from the medium ring is sufficient to make this the favored *endo* transition state.

This model substrate **48** is consistent with the experimental results obtained with substrate **4** and the (*S*)-catalyst (Scheme 2), in which only the *exo* isomer was observed. These calculations suggest that an interaction between the benzyl group of the catalyst and the medium ring is involved in disfavoring the *endo* TS, forcing the substrate/catalyst complex to adopt a (*Z*)-iminium geometry in the lowest energy *endo* transition state.

CONCLUSIONS

In contrast to the reactions of the acyclic precursor **18**, the presence of the 7-, 8-, and 9-membered-ring systems imposes conformational restrictions on the stereoselectivity observed in the Diels–Alder cycloaddition. The medium rings limit the accessibility of one *endo* and *exo* diastereomer, due to the unfavorable steric interactions between the diene and the ring system. This implies that the "top" or *si* face of the diene is unreactive, as seen by the experimental work of the Crimmins group and our own work.

In the organocatalyzed Diels–Alder reactions of these systems, several additional factors are introduced that affect the diastereoselectivity. As suggested from previous computational modeling, the catalyst-activated (*E*)-isomer of the iminium ion is expected to form selectively, to avoid nonbonding interactions between the substrate olefin and the *geminal* dimethyl substituents on the catalyst. In terms of facial

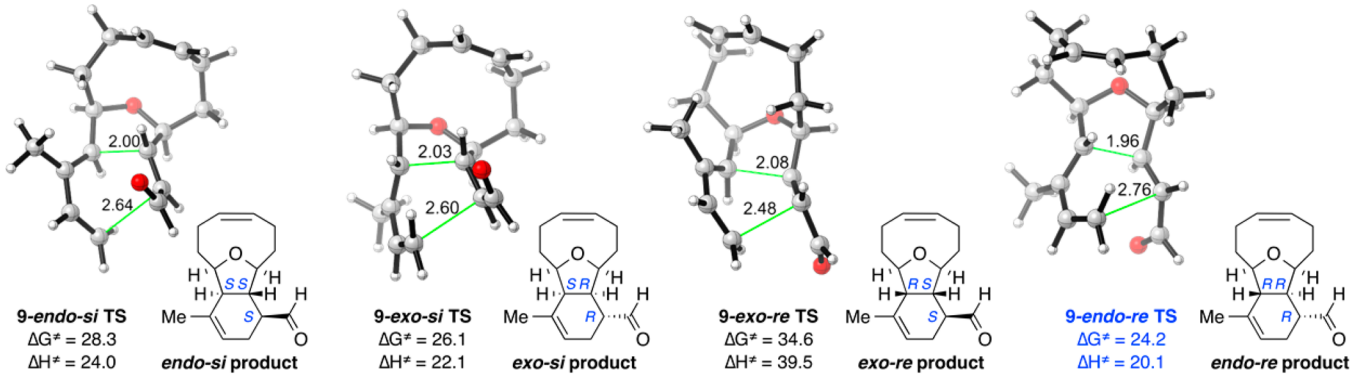


Figure 9. Diels–Alder transition states of the 9-membered-ring precursor model **48**.

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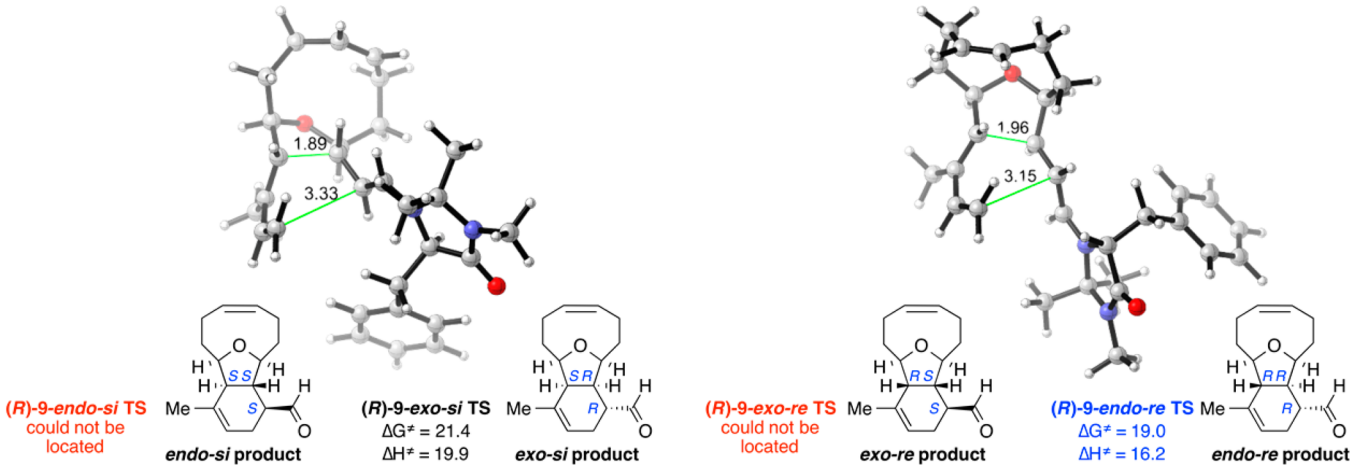

Figure 10. Calculated Diels–Alder transition states of the 9-membered-ring precursor **48** using catalyst (*R*)-**5**.

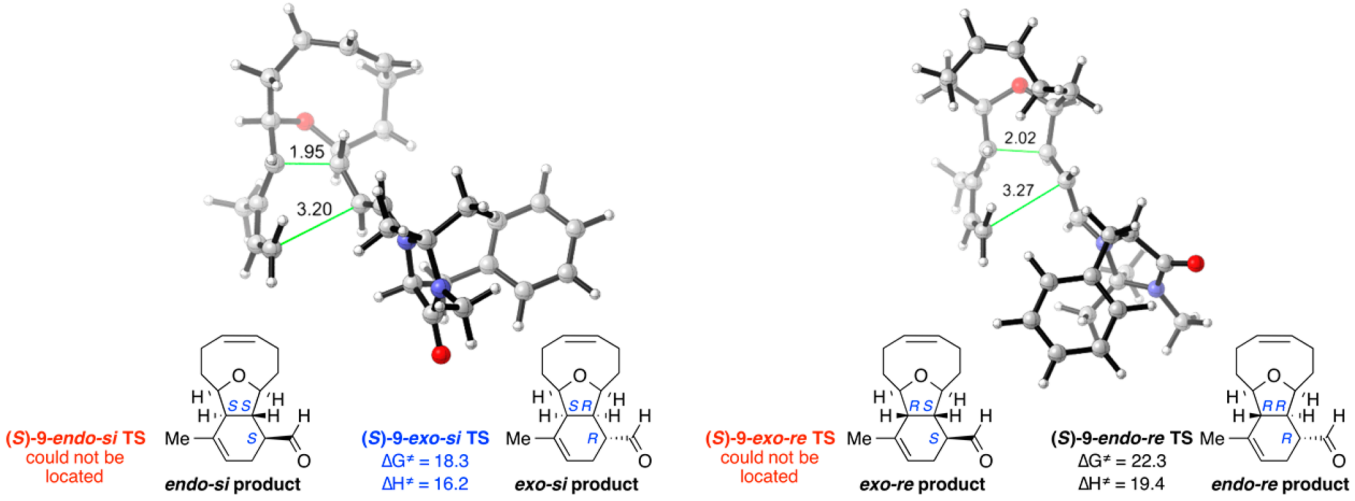

Figure 11. Calculated Diels–Alder transition states of the 9-membered-ring precursor **48** using catalyst (*S*)-**6**.

discrimination of the dienophile, the iminium structure revealed that the benzyl group of the (*R*)-imidazolidinone moiety **5** effectively shields the *si* face of the iminium ion and leave the *re* face exposed for selective bond formation.

All of the Diels–Alder substrates show an innate *endo* preference, as seen by the corresponding reactions under thermal conditions. As the ring size increases, the substrate control of the diastereoselectivity is reduced. In the reactions using catalyst (*R*)-**5**, the *endo-re* diastereomer is consistently preferred, regardless of ring size. This preference can be attributed to the favorable facial selectivity of both the catalyst and substrate in the transition state geometry. In the reactions employing catalyst (*S*)-**6** the reaction is increasingly controlled by the catalyst with increasing ring size. This leads to a change from the selective formation of the *endo-re* diastereomer in the 7-membered substrate to the selective formation of the *exo-si* product in the reactions of the 9-membered-ring substrate. This increase in catalyst control can be largely explained by the increased flexibility of the larger ring size, which allows the substrate to accommodate both the *endo* and *exo* transition geometries. The exquisite levels of *exo* selectivity seen in the (*S*)-catalyzed reaction of the 9-membered substrate are also due to an unfavorable interaction between the catalyst benzyl group and the medium ring in the *endo* transition state, which forces the catalyst to adopt a less favored (*Z*)-iminium ion geometry.

EXPERIMENTAL SECTION

General Experimental Techniques. ^{1}H nuclear magnetic resonance spectra were recorded for deuterochloroform, deuterobenzene, or deuteromethanol solutions on 400 and 500 MHz instruments. Chemical shifts are given in parts per million (ppm) quoted relative to tetramethylsilane (δ = 0 ppm) and referenced to residual solvent as internal standard. When quoting multiplicity, the following abbreviations are used: s, singlet; br s, broad singlet; d, doublet; t, triplet; q, quartet; sept, septet; m, multiplet. Coupling constants (J) are given in hertz (Hz), to the nearest 0.5 Hz. Two dimensional NMR spectra were recorded on a 500 MHz instrument fitted with gradient coils. Gradient COSY experiments were typically acquired with 256 slices in F1 and 2048 slices in F2. Proton decoupled ^{13}C nuclear magnetic resonance spectra were recorded in the solvent indicated. Chemical shifts are given in parts per million (ppm) quoted relative to tetramethylsilane (δ = 0 ppm) and referenced to residual solvent as internal standard.

Optical rotations were measured in a cell length of 1 dm. Specific rotations are given as $[\alpha]_D^T$ with implied units of deg dm^2 g^{-1}. Temperature (T) is given in °C, and concentration (c) is expressed as g/100 mL. Infrared spectra were recorded in the region of 4000–650 cm^{-1}. Samples were analyzed as thin films from chloroform, or from the solvent indicated.

Electrospray ionization (ESI) low- and high-resolution spectra were recorded using a hybrid linear ion trap and Fourier transform ion cyclotron resonance (FT-ICR) mass spectrometer.

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Melting points were determined and are uncorrected. Analytical thin layer chromatography was carried out on glass backed, precoated 0.25 mm silica plates. Spots were visualized by UV absorbance, or by staining with 20% w/w phosphomolybdic acid in ethanol. Flash chromatography was carried out on 230−400 mesh silica or, where indicated, neutral alumina (150 mesh) under a pressure of nitrogen.

Anhydrous THF, diethyl ether, and dichloromethane were dried by passage through a packed column of neutral alumina under a nitrogen atmosphere, and toluene was passed through a further column containing R3-11 copper based catalyst.[1] All other solvents were purified according to standard procedures. All nonaqueous reactions were carried out under an atmosphere of nitrogen (or argon where indicated) in a dual manifold using Schlenk techniques in anhydrous solvents. Petroleum spirit refers to the fraction boiling between 40 and 60 °C. Ether refers to diethyl ether. X-ray intensity data for compound **45** were collected using Cu Kα radiation, while that for compounds **41** and **S2** were collected using Mo Kα radiation. The temperature during data collections was maintained at 130.0(1). The structure was solved by direct methods and difference Fourier synthesis.[2] Thermal ellipsoid plots were generated using the program ORTEP-3[3] integrated within the WINGX[4] suite of programs.

*4-[2-(tert-Butyldiphenylsilanyloxy)ethoxy]-2-methylbut-2-enal (**15**).* To a solution of DMSO (0.82 mL, 11.6 mmol) in CH_2Cl_2 (50 mL) at −78 °C was added thionyl chloride (0.78 mL, 9 mmol) dropwise, and the mixture was stirred for 0.5 h. A solution of the alcohol **14** (2.0 g, 5.8 mmol) in CH_2Cl_2 (50 mL) was added dropwise and the solution stirred at −78 °C for 45 min. Triethylamine (4 mL, 29 mmol) was added dropwise and the solution stirred at −78 °C for 15 min and warmed to room temperature over 1 h. The reaction mixture was diluted with Et_2O (100 mL) and the organic phase washed with saturated aqueous $NaHCO_3$ (100 mL), water (100 mL), and brine (100 mL) and then dried ($MgSO_4$). The solvent was removed in vacuo to yield the aldehyde as a pale yellow oil (2.09 g).

To a stirred suspension of 2-(triphenylphosphoranylidene)-propionaldehyde (1.82 g, 5.8 mmol) in toluene (35 mL) was added the aldehyde (2.09 g, 5.8 mmol) in toluene (13 mL). The reaction was heated to reflux for 5 h, after which time the mixture was allowed to cool to room temperature before being passed through a plug of silica. The silica was flushed with CH_2Cl_2 (50 mL) to yield the α,β-unsaturated aldehyde **15** as a pale yellow oil (1.48 g, 66% 2 steps). This product was used immediately without further purification: R_f 0.69 (1:1 EtOAc/hexane); ^{1}H NMR (400 MHz) δ 9.43 (s, 1H, C*H*O), 7.68−7.79 (m, 4H, Ar), 7.36−7.43 (m, 6H,), 6.54 (dt, J = 5.5, 1.5 Hz, 1H, C=C*H*), 4.37 (dd, J = 5.5, 1 Hz, 2H,), 3.86 (t, J = 3.5 Hz, 2H,), 3.62 (t, J = 5 Hz, 2H), 1.73 (d, J = 1 Hz, 3H), 1.07 (s, 9H); ^{13}C NMR (100 MHz) δ 195.0, 150.1, 139.1, 135.6, 133.5, 129.7 and 127.6, 72.3, 68.7 and 63.4, 26.8, 19.2 9.5; ν_{max} (neat)/cm^{-1} 3071w, 2960m, 2930m, 2901m, 2858m, 1690s, 1473m, 1428s, 1251w, 1203w and 1105s. Found: C, 72.25; H, 7.92; $C_{23}H_{30}O_3Si$ requires C, 72.21; H, 7.90%; m/z (CI, NH_3) 400.4 [$(M + NH_4)^+$, 100%], 382.3 (M^+, 12), 318.3 (48) and 274 (88) [m/z (ES) Found: 400.2297 $(M + NH_4)^+$, $C_{23}H_{34}O_3NSi$ requires 400.2302].

*tert-Butyl[2-(3-methylpenta-2,4-dienyloxy)ethoxy]diphenylsilane (**15a**).* To a stirred suspension of methyltriphenylphosphonium bromide (4.50 g, 12.6 mmol, predried at 100 °C under high vacuum for 24 h) in THF (75 mL) at −78 °C was added *n*-BuLi (6.30 mL of 2.0 M solution in hexanes, 12.6 mmol) dropwise over a period of 5 min. After a further 5 min, the reaction mixture was allowed to warm to room temperature. After 1 h, the mixture was cooled to −78 °C, and a solution of the α,β-unsaturated aldehyde **15** (2.43 g, 6.36 mmol) in THF (17 mL) was added dropwise over 5 min. After 45 min, the reaction was quenched by the addition of saturated aqueous NH_4Cl solution (50 mL) and the aqueous phase was extracted with EtOAc (2 × 50 mL). The combined organic portions were washed with brine (25 mL) and dried ($MgSO_4$). The crude reaction mixture was passed through a plug of silica, eluted in 1:1 EtOAc/hexane, to yield the diene **15a** as a clear, colorless oil (2.28 g, 94%): R_f 0.69 (1:2 EtOAc/hexane); ^{1}H NMR (400 MHz) δ 7.70 (m, 4H), 7.40 (m, 6H), 6.40 (dd, J = 17.5, 10.5 Hz, 1H, C*H*=CH_2), 5.63 (t, J = 6.5 Hz, 1H, C*H*=$C(CH_3)$), 5.20 (d, J = 17.5 Hz, 1H, CH=CHH_{trans}), 5.05 (d, J = 10.5 Hz, 1H, CH=CHH_{cis}), 4.18 (d, J = 6.5 Hz, 2H, OCH_2) 3.83 (t, J = 5.5 Hz, 2H, OCH_2), 3.58 (t, J = 5.5 Hz, 2H, OCH_2), 1.77 (s, 3H, CH=C(CH_3)), 1.07 (s, 91H, SiC(CH_3)$_3$); ^{13}C NMR (100 MHz) δ 140.8, 135.6, 133.7, 129.6, 128.7, 127.6, 112.7, 71.5, 67.7, 63.6, 26.8, 19.2, 12.0; ν_{max} (neat)/cm^{-1} 3071w, 3050w, 2959m, 2930m, 2857m, 1428m, 1219m and 1111s. Found: C, 75.70; H, 8.40; $C_{24}H_{32}O_2Si$ requires C, 75.74; H, 8.47%.

*2-(3-Methylpenta-2,4-dienyloxy)ethanol (**16**).* To a stirred solution of the silyl ether **15a** (736 mg, 1.93 mmol) in THF (100 mL) at 0 °C was added TBAF (1.79 g, 5.8 mmol). The reaction mixture was stirred at 0 °C for 0.5 h and allowed to warm to room temperature over 18 h. The reaction was quenched by the addition of water (20 mL), and Et_2O (50 mL) was added. The layers were separated, and the aqueous phase was extracted with Et_2O (2 × 50 mL). The combined organic portions were washed with brine (100 mL) and dried ($MgSO_4$), and the solvent was removed *in vacuo*. Purification by flash chromatography (EtOAc/hexane, 1:1) furnished the alcohol **16** as a clear colorless oil (258 mg, 94%): R_f 0.24 (1:1 EtOAc/hexane); ^{1}H NMR (500 MHz) δ 6.39 (dd, J = 17.5, 10.5 Hz, 1H, C*H*=CH_2), 5.63 (t, J = 7 Hz, 1H, C*H*=C(CH_3)), 5.21 (d, J = 17.5 Hz, 1H, CH=CHH_{trans}), 5.06 (d, J = 10.5 Hz, 1H, CH=CHH_{tcis}), 4.18 (d, J = 7 Hz, 2H, C=CHCH_2O), 3.74 (m, 2H, OCH_2), 3.56 (m, 2H, OCH_2), 1.79 (s, 3H, CH=C(CH_3)); ^{13}C NMR (100 MHz) δ 140.6, 136.4, 127.7 113.1, 71.3, 67.5, 61.9, 29.7, 12.0; m/z (EI+, NH_3) 160.1 [$(M + NH_4)^+$, 92%], 98.1 ($C_6H_9OH^+$, 100%) and 81 (34).

*4-(3-Methylpenta-2,4-dienyloxy)but-2-enoic Acid N-Methoxy-N-methylamide (**17**).* To a solution of DMSO (360 μL, 5.0 mmol) in CH_2Cl_2 (3 mL) at −78 °C was added thionyl chloride (175 μL, 2.0 mmol), dropwise and the mixture was stirred for 0.5 h. A solution of the alcohol **16** (144 mg, 1.0 mmol) in CH_2Cl_2 (1 mL) was added dropwise and the solution stirred at −78 °C for 45 min. Triethylamine (0.5 mL, 3.6 mmol) was added dropwise and the solution stirred at −78 °C for 15 min and warmed to room temperature over 1 h. The reaction mixture was diluted with Et_2O (5 mL) and the organic phase washed with saturated aqueous $NaHCO_3$ (5 mL), water (5 mL), and brine (5 mL) and then dried ($MgSO_4$). The solvent was removed *in vacuo* to yield the aldehyde as a clear, colorless oil. The product was used without further purification. Sodium hydride (181 mg, 60% dispersion in mineral oil, 4.5 mmol) was washed twice with dry pentane (5 mL), dried *in vacuo*, and suspended in THF (2 mL). The suspension was cooled to 0 °C, and diethyl(*N*-methoxy-*N*-methyl carbamoylmethyl)phosphonate (915 mg, 3.8 mmol) was added dropwise. The mixture was stirred at 0 °C for 15 min, and a solution of the aldehyde (500 mg, 3.56 mmol) in THF (1 mL) was added dropwise. After stirring at 0 °C for 15 min the reaction was quenched by addition of saturated aqueous NH_4Cl solution (5 mL) and Et_2O (5 mL) was added. The aqueous layer was extracted with Et_2O (2 × 5 mL), and the combined organic portions were washed with water (5 mL) and brine (5 mL) and dried ($MgSO_4$). The solvent was removed *in vacuo* and the crude product purified by column chromatography, (1:2 EtOAc/hexane) to yield the Weinreb amide **17** as a pale yellow oil (686 mg, 84%): R_f 0.27 (1:1 EtOAc/hexane); ^{1}H NMR (500 MHz) δ 7.00 (dt, J = 15.5, 4.5 Hz, 1H, C*H*=CHCON), 6.66 (d, J = 15.5 Hz, 1H, CH=C*H*CON), 6.41 (dd, J = 17.5, 10.5 Hz, 1H, C*H*=CH_2), 5.64 (t, J = 6.5 Hz, 1H, C*H*=C(CH_3)), 5.22 (d, J = 17.5 Hz, 1H, CH=CHH_{trans}), 5.07 (d, J = 10.5 Hz, 1H, CH=CHH_{cis}), 4.19 (m, 4H), 3.71 (s, 3H, CH_3), 3.26 (s, 3H, CH_3), 1.79 (s, 3H, CH=C(CH_3)); ^{13}C NMR (100 MHz) δ 166.0, 142.6, 140.3, 127.6, 118.5, 112.7, 68.8, 66.8, 61.5, 32.0, 28.7, 11.8; IR (film) 2937, 2847, 2243, 1667, 1633, 1418, 1384, 1123, 992, 967, 910, 731 cm^{-1}; MS (EI) m/z (rel intensity) 236 [80], 225 [75, (M^+)], 217 [100]; HRMS (EI) 225.1356 (225.1359 calcd for $C_{12}H_{19}O_3N$, M^+).

*7-Methyl-1,3,3aS,4R,5,7aR-hexahydroisobenzofuran-4-carboxylic Acid (**22**).* To a solution of the amide **17** (70 mg, 0.31 mmol) in Et_2O (4 mL) at −78 °C was added DIBAL-H (300 μL, 2 M solution in toluene, 0.6 mmol) dropwise. The mixture was stirred at −78 °C for 1 h and quenched at −78 °C by addition of EtOAc (1 mL). After 30 min the mixture was warmed to 0 °C, and a solution of saturated aqueous sodium potassium tartrate (4 mL) was added. The organic layer was separated and washed with water (5 mL) and brine (5 mL). The

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solvent was removed by rotary evaporation at 0 °C to give the crude aldehyde as a clear colorless oil.

The aldehyde was dissolved in MeCN/H_2O (19:1, 4 mL) and cooled to −15 °C. (5*S*)-5-Benzyl-2,2,3-trimethylimidazolidin-4-one (18 mg, 0.071 mmol) was added, followed by trifluoroacetic acid (5.4 μL, 0.070 mmol). The mixture was stirred at −15 °C for 7 h, and Et_2O (5 mL) was added. The aqueous phase was extracted with Et_2O (2 × 5 mL), the organic fractions were washed with brine (5 mL) and dried ($MgSO_4$), and the solvent was removed *in vacuo* to yield the crude bicyclic aldehyde. This residue was dissolved in ^{t}BuOH (7 mL) and 2-methyl-2-butene (3.5 mL). To this was added a solution of NaH_2PO_4 (64 mg, 2.1 mmol) and NaOClO (81 mg, 2.8 mmol) in water (1.9 mL) dropwise over 10 min. The mixture was stirred at room temperature for 1 h, the solvents were removed *in vacuo*, and the residue was redissolved in water (10 mL). The aqueous layer was washed with hexane (3 × 5 mL), acidified to pH 3 by addition of 1 M HCl solution, and extracted with Et_2O (3 × 5 mL). The organic fractions were washed with water (5 mL) and brine (5 mL) and dried ($MgSO_4$), and the solvent was removed *in vacuo*. The crude product was recrystallized (EtOAc/hexane) to yield the carboxylic acid **22** (25 mg, 47%) as a colorless crystalline solid: R_f 0.13 (1:1 EtOAc/hexane); $[\alpha]_D^{22}$ +24.1 (*c* 1.0, CH_3OH); mp 126−128 °C; ^{1}H NMR (500 MHz, CD_3OD) δ 5.34 (s, 1H, C*H*═C(CH_3)), 4.19 (t, *J* = 7.5 Hz, 1H, OC*H*H), 4.12 (t, *J* = 7 Hz, 1H, OC*H*H), 3.59 (dd, *J* = 11, 8 Hz, 1H), 3.46 (dd, *J* = 11.5, 7 Hz, 1H, OC*H*H), 2.62 (td, *J* = 11, 6.5 Hz, 1H, C*H*CO_2H), 2.45−2.55 (m, 2H), 2.34−2.40 (m, 2H), 2.14 (qd, *J* = 11, 7 Hz, 1H), 1.67 (s, 3H, CH═C(C*H*$_3$)); ^{13}C NMR (125 MHz, $CDCl_3$) δ 179.7, 132.5, 120.8, 70.9, 69.6, 46.8, 44.5, 41.8, 29.7, 20.5; IR (film) 2953, 2878, 1719, 1443, 1255, 1203, 1192, 1003, 875 cm^{-1}; MS (EI) *m*/*z* (rel intensity) (EI) 182 [10 (M^+)], 107 [100], 91 [55] ; HRMS (EI) *m*/*z* 182.0938 (182.0937 calcd for $C_{10}H_{14}O_3$, M^+).

*((3aS,4R,7aR)-6,7-Dibromo-7-methyloctahydroisobenzofuran-4-carboxylic Acid (**23**).* To a solution of the carboxylic acid **22** (10 mg, 0.055 mmol) in CCl_4 (1 mL) was added Br_2 (3.5 μL, 0.07 mmol). The solution was stirred at room temperature for 2 h, and the solvent removed *in vacuo*. The crude product was purified by column chromatography (1:50 MeOH/EtOAc), to yield the dibromide **23** (16.5 mg, 87%) as a colorless crystalline solid. The product was recrystallized ($CHCl_3$) to give fine, colorless needles for X-ray analysis: R_f 0.14 (1:50 MeOH/EtOAc); $[\alpha]_D^{22}$ +1.8 (*c* 1.0, CH_3OH); mp 152−153 °C; ^{1}H NMR (500 MHz, CD_3OD) δ 4.78 (t, *J* = 3 Hz, 1H, C*H*Br), 4.24, (t, *J* = 7.5 Hz, 1H, OC*H*H), 4.04 (t, *J* = 7.5 Hz, 1H, OC*H*H), 3.63 (dd, *J* = 10, 7.5 Hz, 1H, OC*H*H), 3.61 (dd, *J* = 10.5, 8 Hz, 1H, OC*H*H), 2.92 (td, *J* = 11.5, 3.5 Hz, 1H), 2.82 (ddd, *J* = 15.5, 12, 3 Hz, 1H), 2.42- 2.50 (m, 2H), 2.23 (ddd, *J* = 11.5, 10, 7 Hz, 1H), 1.96 (s, 3H, CH═C(CH_3)); ^{13}C NMR (125 MHz, $CDCl_3$) δ 178.5, 71.5, 68.8, 68.7, 59.6, 48.2, 42.3, 40.3, 35.0, 33.2; IR (film) 2979, 2872, 1725, 1437, 1300, 1262, 1192, 1153, 1071, 1012 cm^{-1}; MS (EI) *m*/*z* (rel intensity) 342 [25, (M^+)], 181 [45], 107 [100]; HRMS (EI) *m*/*z* 339.9305 (339.9304 calcd for $C_{10}H_{14}O_3Br_2$). Crystal data for **23**: $C_{10}H_{14}Br_2O_3$, *M* = 342.03, *T* = 130.0 K, λ = 0.71073, monoclinic, space group $P2_1/c$, *a* = 6.1597(12), *b* = 24.878(5), *c* = 7.5576(15) Å, β = 111.066(3)°, *V* = 1080.7(4) Å^3, *Z* = 4, D_c = 2.102 mg M^{-3}, μ(Mo Kα) 7.484 mm^{-1}, *F*(000) = 672, crystal size 0.15 × 0.10 × 0.03 mm^3, 5580 reflections measured, 1899 independent reflections [*R*(int) = 0.0307], the final *R* was 0.0300 [$I > 2\sigma(I)$] and wR(F^2) was 0.0747 (all data).

*((3aS,4R,7aR)-1,3,3a,4,5,7a-Hexahydro-7-methylisobenzofuran-4-yl)methyl 3,5-Dinitrobenzoate (**21**).* To a solution of the amide **17** (200 mg, 0.89 mmol) in Et_2O (12 mL) at −78 °C was added DIBAL-H (870 μL, 1.5 M solution in toluene, 1.3 mmol) dropwise. The mixture was stirred at −78 °C for 1 h and quenched at −78 °C by addition of EtOAc (1 mL). After 30 min the mixture was warmed to 0 °C, and Et_2O (20 mL) and a solution of saturated aqueous sodium potassium tartrate (20 mL) were added. The organic layer was separated and washed with water (30 mL) and brine (30 mL). The solvent was removed by rotary evaporation at 0 °C to give the crude aldehyde as a clear colorless oil. The aldehyde was dissolved in MeCN/H_2O (19:1, 8 mL) and cooled to −15 °C. (5*S*)-5-Benzyl-2,2,3-trimethylimidazolidin-4-one **6** (20 mg, 0.078 mmol) was added, followed by trifluoroacetic acid (12 μL, 0.15 mmol). The mixture was stirred at −15 °C for 7 h, $NaBH_4$ (40 mg, 1.1 mmol) was added, and the mixture allowed to warm to room temperature. Water (10 mL) and CH_2Cl_2 (10 mL) were added, and the aqueous phase was extracted with CH_2Cl_2 (3 × 10 mL). The combined organic portions were dried ($MgSO_4$), and the solvent removed *in vacuo*. The resulting residue was dissolved in CH_2Cl_2 (5 mL), and 3,5-dinitrobenzoyl chloride (200 mg, 0.87 mmol), pyridine (120 μL, 1.5 mmol), and dimethylaminopyridine (10 mg, 0.09 mmol) were added. The mixture was stirred at room temperature for 1 h and was loaded directly onto a silica gel column. The product was eluted in 1:10 EtOAc, to yield a colorless crystalline solid (150 mg, 47%). The product was recrystallized (isopropanol) to give colorless plates. Analysis by chiral HPLC (Chiralcel OD-H column (10 × 250 mm) at a flow rate of 1 mL/min, eluted in 40% isopropanol/hexane, t_1 (major) = 28.7 min, t_2 (minor) = 32.9 min) showed that the product was formed in 18% enantiomeric excess: R_f 0.50 (1:2 EtOAc/petrol); $[\alpha]_D^{22}$ +12.5 (*c* 1.0, CH_3Cl); mp 124−125 °C; ^{1}H NMR (500 MHz, $CDCl_3$) δ 9.21 (t, *J* = 2 Hz, 1H, Ar), 9.09 (d, *J* = 2.16 Hz, 2H, Ar), 5.34−5.35 (m, 1H, CH═C(CH_3)), 4.41 (dd, *J* = 11, 6 Hz, 1H, OC*H*H), 4.27 (dd, *J* = 11, 7.5 Hz, 1H, OC*H*H), 4.08 (dt, *J* = 7, 6 Hz, 1H, OC*H*H), 3.57 (dd, *J* = 11, 7.5 Hz, 1H, OC*H*H), 3.42 (dd, *J* = 11.5, 7. Hz, 1H, OC*H*H), 2.39−2.52 (m, 2H), 2.20−2.28 (m, 1H), 1.94−2.01 (m, 1H), 1.87 (qd, *J* = 11, 7 Hz, 1H), 1.68 (s, 3H, CH═C(C*H*$_3$)); ^{13}C NMR (125 MHz, $CDCl_3$) δ 162.3, 148.6, 133.5, 133.0, 129.0, 122.4, 120.7, 70.6, 70.1, 69.5, 47.1, 46.2, 35.9, 29.9, 20.4; IR (film) 2856, 1730, 1629, 1543, 1343, 1272, 1163, 751, 720 cm^{-1}; MS (ESI) *m*/*z* (rel intensity) 363 [100, ($M + H)^+$] 360 [75] ; HRMS (ESI) *m*/*z* 363.11863 (363.11868 calc. for $C_{17}H_{19}N_2O7$ ($M + H)^+$). Anal. Calcd for $C_{17}H_{18}N_2O_7$: C, 56.4 ; H, 5.0; O 7.7. Found: C, 56.5 ; H, 5.2; O 7.7.

*((3aR,4S,7aS)-1,3,3a,4,5,7a-Hexahydro-7-methylisobenzofuran-4-yl)methyl 3,5-Dinitrobenzoate (**20**).* The above reaction was repeated using (5*R*)-5-benzyl-2,2,3-trimethylimidazolidin-4-one **5**, to yield compound **20** (147 mg, 46%) as colorless plates. Analysis by chiral HPLC (Chiralcel OD-H column (10 × 250 mm) at a flow rate of 1 mL/min, eluted in 40% isopropanol/hexane, t_1 (major) = 28.7 min, t_2 (minor) = 32.9 min) showed that the product was formed in 17% enantiomeric excess: R_f 0.50 (1:2 EtOAc/petrol); $[\alpha]_D^{22}$ −12.6 (*c* 1.0, CH_3Cl); mp 124−125 °C; ^{1}H NMR (500 MHz, $CDCl_3$) δ 9.21 (t, *J* = 2 Hz, 1H, Ar), 9.09 (d, *J* = 2.16 Hz, 2H, Ar), 5.34−5.35 (m, 1H, CH═C(CH_3)), 4.41 (dd, *J* = 11, 6 Hz, 1H, OC*H*H), 4.27 (dd, *J* = 11, 7.5 Hz, 1H, OC*H*H), 4.08 (dt, *J* = 7, 6 Hz, 1H, OC*H*H), 3.57 (dd, *J* = 11, 7.5 Hz, 1H, OC*H*H), 3.42 (dd, *J* = 11.5, 7. Hz, 1H, OC*H*H), 2.39−2.52 (m, 2H), 2.20−2.28 (m, 1H), 1.94−2.01 (m, 1H), 1.87 (qd, *J* = 11, 7 Hz, 1H), 1.68 (s, 3H, CH═C(C*H*$_3$)); ^{13}C NMR (125 MHz, $CDCl_3$) δ 162.3, 148.6, 133.5, 133.0, 129.0, 122.4, 120.7, 70.6, 70.1, 69.5, 47.1, 46.2, 35.9, 29.9, 20.4; HRMS (ESI) *m*/*z* 363.1184 (363.1192 calcd for $C_{17}H_{19}N_2O_7$ ($M + H)^+$).

*(4R)-3-[1-Oxo-2-[(R)-1-(benzyloxymethyl)but-3-enyl-1-oxy]-4-benzyl-1,3-oxozolidinone (**28**).* To a solution of the carboxylic acid **26**[3] (6.17 g, 24.7 mmol) and triethyamine (3.78 mL, 27.2 mmol) in Et_2O (210 mL) at −78 °C was added pivaloyl chloride (3.35 mL, 27.2 mmol) slowly. After 5 min the mixture was warmed to room temperature and stirred for 1 h. In a separate flask, a solution of (*S*)-4-benzyl-2-oxazolidinone (5.25 g, 29.6 mmol) in THF (50 mL) was cooled to −78 °C, *n*-BuLi (2.0 M solution in hexane, 14.8 mL, 29.6 mmol) was added dropwise, and the solution was stirred at −78 °C for 15 min. The mixed anhydride solution was recooled to −78 °C, and the lithiated oxazolidinone solution was added dropwise by cannula. The mixture was stirred at −78 °C for 15 min and at 0 °C for 2 h. The reaction was quenched with saturated aqueous NH_4Cl (50 mL), and Et_2O (100 mL) was added. The aqueous phase was extracted into Et_2O (2 × 100 mL), the organic extracts were washed with water (200 mL) and brine (200 mL) and dried ($MgSO_4$), and the solvent was removed *in vacuo*. The crude product was purified by column chromatography (1:4 EtOAc/hexane) to yield the product **28** as a clear, colorless oil (6.88 g, 71%): R_f 0.38 (1:2 EtOAc/hexane); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.27−7.34 (m, 8H, Ar), 7.17−7.19 (m, 2H, Ar), 5.89 (ddt, *J* = 17, 10, 7 Hz, 1H, C*H*═CH_2), 5.10 (m, 2H, CH═CH_2), 4.89 (s, 2H, OCH_2CO), 4.62 (qd, *J* = 7, 3.5 Hz, 1H),

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4.54 (s, 2H, OCH_2Ph), 4.15 (m, 1H), 3.77 (m, 2H), 3.61 (ddd, J = 14, 10, 5 Hz, 1H), 3.30 (dd, J = 13.5, 3 Hz, 1H), 2.63 (dd, J = 13.5, 10 Hz, 1H), 2.42 (m, 2H).

These data are consistent with previously reported values.[22]

*4-(Benzyloxy)-3-((R)-2-((S)-1-(benzyloxy)pent-4-en-2-yloxy)pent-4-enoyl)oxazolidin-2-one (**30**).* To a solution of NaHMDS (1.0 M in THF, 12.0 mL, 12 mmol) in THF (40 mL) at −78 °C was added a solution of the oxazolidinone **28** (3.25 g, 8.22 mmol) in THF (20 mL) over 5 min. The solution was stirred at −78 °C for 30 min, and a solution of allyl iodide (3.64 mL, 40 mmol) in THF (20 mL) was added. The mixture was stirred at −78 °C for 2 h and quenched with saturated aqueous NH_4Cl (20 mL). The aqueous phase was extracted into Et_2O (2 × 60 mL), the organic extracts were washed with water (50 mL) and brine (50 mL) and dried ($MgSO_4$), and the solvent was removed *in vacuo*. The crude product was purified by column chromatography (1:6 EtOAc/hexane) to yield the diene **30** (2.34 g, 63%) as a clear, colorless oil: R_f 0.65 (1:2 EtOAc/hexane); $[\alpha]_D^{22}$ +72.8 (c 0.94, $CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.21−7.32 (m, 8H, Ar), 7.11−7.13 (m, 2H, Ar), 5.87−5.99 (m, 2H, 2 × C*H*═CH_2), 5.28 (dd, J = 8, 3.5 Hz, 1H, -OC*H*C═O) 5.06−5.17 (m, 4H), 4.43 (d, J = 12 Hz, 1H, OC*H*HPh), 4.34 (d, J = 12 Hz, 1H, OC*H*HPh), 4.18−4.21 (m, 1H) 3.79 (dd, J = 9, 3 Hz, 1H) 3.72−3.76 (m, 1H), 3.54−3.61 (m, 2H), 3.13 (dd, J = 13.5, 2.5 Hz, 1H), 3.03 (t, J = 8.5 Hz, 1H), 2.59 (dd, J = 13, 9.5 Hz, 1H) 2.48−2.51 (m, 1H), 2.35−2.43 (m, 2H), 2.22−2.28 (m, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 172.5, 153.2, 139.1, 135.9, 135.2, 134.6, 129.6, 128.9, 128.7, 127.4, 127.3, 126.5, 117.9, 117.1, 80.2, 79.3, 75.2, 72.4, 65.9, 54.9, 38.8, 38.1, 37.2; IR (film) 3076, 2912, 1778, 1712, 1641, 1392, 1351, 1276, 1212, 1110, 995, 914, 733, 699 cm^{-1}; MS (EI) m/z (rel intensity) 449 [25, M^+], 258 [25], 91 [100]; HRMS (EI) 449.2194 (449.2202 calcd for $C_{27}H_{31}NO_5$, M^+).

*4-(Benzyloxy)-3-((2R,7S,Z)-7-(benzyloxymethyl)-2,3,6,7-tetrahydrooxepine-2-carbonyl)oxazolidin-2-one (**30a**).* A solution of the diene **30** (1.98 g, 4.41 mmol) in CH_2Cl_2 (1360 mL, 0.003 M) was heated to reflux, and bis(tricyclohexylphosphine) benzylidine ruthenium(IV) chloride (243 mg, 0.31 mmol) was added. The mixture was heated at reflux for 2 h and cooled to room temperature, and air was bubbled through the solution for 3 h. The solvent was removed *in vacuo*, and the crude mixture was purified by column chromatography (1:5 EtOAc/hexane) to yield the product **30a** (1.85, 99%) as a colorless oil: R_f 0.24 (1:4 EtOAc/hexane); $[\alpha]_D^{22}$ +28.0 (c 1.18, $CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.13−7.25 (m, 2H, Ar), 7.26−7.35 (m, 8H, Ar), 5.75−5.82 (m, 2H, C*H*═C*H*), 4.91 (dd, J = 10.5, 1.5 Hz, 1H, OC*H*C═O), 4.57 (ddt, J = 10.5, 7.5, 3 Hz, 1H, OCH_2CHN), 4.45−4.51 (m, 2H, OCH_2Ph), 4.09−4.16 (m, 2H, OCH_2), 3.71 (dtd, J = 8.0, 5.5, 2.5 Hz, 1H, $OCHCH_2OBn$), 3.48 (dd, J = 10, 5 Hz, 1H, OC*H*H), 3.39 (dd, J = 10, 5.5 Hz, 1H, OC*H*H), 3.21 (dd, J = 13.5, 3.5 Hz, 1H, CC*H*HPh), 2.71 (dd, J = 13.5, 9.5 Hz, 1H, CC*H*HPh), 2.56−2.61 (m, 1H, C*H*H), 2.38−2.44, (m, 1H, C*H*H), 2.27−2.36 (m, 2H, CH_2); ^{13}C NMR (125 MHz, $CDCl_3$) δ 170.5, 152.7, 138.3, 135.1, 129.9, 129.0, 128.3, 128.2, 127.6, 127.5, 127.4, 79.5, 77.5, 73.2, 73.0, 66.5, 55.4, 37.8, 33.8, 33.3; IR (film) 3028, 2916, 2865, 1777, 1706, 1496, 1479, 1454, 1387, 1350, 1291, 1247, 1198, 1099, 1028, 994, 910, 730, 696 cm^{-1}; MS (EI) m/z (rel intensity) 421 [20, M^+], 362 [20], 91 [100]; HRMS (EI) 421.1881 (421.1884 calcd for $C_{25}H_{27}O_5N$, M^+).

*((2R,7S,Z)-7-(Benzyloxymethyl)-2,3,6,7-tetrahydrooxepin-2-yl)-methanol (**32**).* To a solution of the oxazolidinone **30a** (1.79 g, 4.27 mmol) in THF (35 mL) at 0 °C was added a solution of $NaBH_4$ (808 mg, 21.4 mmol) in water (9 mL) dropwise. The mixture was stirred at 0 °C for 1.5 h and quenched carefully by addition of 1 M HCl solution. The solvent (THF) was removed *in vacuo*, the aqueous phase was extracted into Et_2O (3 × 50 mL), the organic extracts were washed with water (100 mL) and brine (100 mL) and dried ($MgSO_4$), and the solvent was removed *in vacuo*. The crude product was purified by column chromatography (1:2 EtOAc/hexane) to yield the alcohol **32** (906 mg, 86%) as a clear colorless oil: R_f 0.23 (1:2 EtOAc/hexane); $[\alpha]_D^{22}$ +2.8 (c 1.6, $CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.14−7.29 (m, 5H, Ar), 5.68−5.70 (m, 2H, C*H*═C*H*), 4.48 (s, 2H, OCH_2Ph), 3.58 (ddd, J = 12, 7 5 Hz, 1H), 3.41−3.48 (m, 4H), 3.36 (dd, J = 10, 4.5 Hz, 1H), 2.51 (br. s, 1H, O*H*) 2.19−2.21 (m, 2H), 2.13−2.16 (m, 1H), 2.01−2.07 (m, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 138.1, 128.8, 128.7, 128.4, 127.6, 127.5, 80.7, 79.1, 73.4, 73.2, 65.9, 34.0, 33.4; IR (film) 3452, 3025, 2878, 1738, 1652, 1496, 1454, 1364, 1205, 1100, 1061, 910, 734, 697 cm^{-1}; MS (EI) m/z (rel intensity) 449 [5, M^+], 171 [10], 127 [20], 91 [100]; HRMS (EI) 248.1417 (248.1407 calcd for $C_{15}H_{20}O_3$, M^+).

*(E)-3-((2R,7S,Z)-7-(Benzyloxymethyl)-2,3,6,7-tetrahydrooxepin-2-yl)-2-methylacrylaldehyde (**34**).* To a solution of DMSO (170 μL, 2.16 mmol) in CH_2Cl_2 (3 mL) at −78 °C was added thionyl chloride (145 μL, 1.68 mmol) dropwise, and the mixture was stirred for 0.5 h. A solution of the alcohol **32** (268 mg, 1.08 mmol) in CH_2Cl_2 (1 mL) was added dropwise and the solution stirred at −78 °C for 1 h. Triethylamine (0.75 mL, 5.4 mmol) was added dropwise and the solution stirred at −78 °C for 15 min and warmed to room temperature over 2 h. The reaction mixture was diluted with Et_2O (5 mL), and the organic phase was washed with saturated aqueous $NaHCO_3$ (5 mL), water (5 mL), and brine (5 mL) and then dried ($MgSO_4$). The solvent was removed *in vacuo* to yield the crude aldehyde **32a** as a clear colorless oil. The aldehyde was dissolved in toluene (5 mL), and 2-(triphenylphosphoranylidene)propionaldehyde (268 mg, 1.09 mmol) was added. The resulting mixture was heated to reflux for 16 h, after which time the mixture was allowed to cool to room temperature before being passed through a plug of silica. The silica was flushed with CH_2Cl_2 (50 mL), and the solvent was removed *in vacuo* to yield the α,β-unsaturated aldehyde **34** (228 mg, 73%) as a pale yellow oil: R_f 0.59 (1:2 EtOAc/hexane); $[\alpha]_D^{22}$ −47.5 (c 1.0, $CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$) δ 9.34 (s, 1H, C*H*═O), 7.19−7.28 (m, 5H, Ar), 6.42 (d, J = 7.5 Hz, 1H, C*H*═C(CH_3) (CHO)), 5.71−5.80 (m, 2H, C*H*═C*H*), 4.49 (s, 2H, OCH_2Ph), 4.39 (t, J = 9 Hz, 1H, OC*H*CH═C), 3.62 (quin, J = 5.5 Hz, 1H, OC*H*OBn), 3.46 (dd, J = 10, 5.5 Hz, 1H, C*H*HOBn), 3.36 (dd, J = 10, 5.5 Hz, 1H, C*H*HOBn), 2.43 (t, J = 12 Hz, 1H, C*H*H), 2.30 (t, J = 5 Hz, 2H, CH_2), 2.14 (dd, J = 16.5, 8 Hz, 1H, C*H*H), 1.69 (s, 3H, CH_3); ^{13}C NMR (125 MHz, C_6D_6) 194.0, 152.5, 139.0, 138.2, 130.4, 128.9, 128.6, 127.8, 127.7, 79.2, 77.2, 73.8, 73.4, 36.7, 34.9, 9.6; IR (film) 2922, 2861, 1687, 1496, 1453, 1315, 1097, 1027, 1014, 736, 697 cm^{-1}; MS (ESI$^+$) m/z (rel intensity) 501 [50], 309 [100, $(M + Na)^+$], 304 [25]; HRMS (ESI$^+$) 309.1461 (309.1461 calcd for $C_{18}H_{22}O_3Na$, $(M + Na)^+$). Anal. Calcd for $C_{18}H_{22}O_3$: C, 75.5; H, 7.7; Found: C, 75.5; H, 7.8.

*2(R),7(S)-3-(7-Methoxy-2,3,6,7-tetrahydrooxepin-2-yl)-2-methylpropenal (**36**).* To a stirred solution of the benzyl ether **34** (237 mg, 0.82 mmol) in CH_2Cl_2 (5 mL) was added pH 7 buffer (0.5 mL, 0.05 M NaH_2PO_4, 0.29 M NaOH in H_2O) and DDQ (130 mg, 0.57 mmol). The resulting mixture was stirred at room temperature for 16 h and quenched by addition of saturated aqueous $NaHCO_3$ solution (5 mL). The organic phase was washed with saturated aqueous $NaHCO_3$ solution (5 × 10 mL) until the washings ran clear. The organic phase was dried (Mg_2SO_4), the solvent was removed *in vacuo*, and the crude material was purified by flash chromatography (1:2 EtOAc/petrol) to yield the alcohol **36** (91 mg, 56%) as a yellow oil: R_f 0.39 (1:1 EtOAc/hexane); $[\alpha]_D^{22}$ −69.0 (c 1.1, $CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$) δ 9.41 (s, 1H, C*H*═O), 6.47 (dd, J = 7.5, 1 Hz, 1H, C*H*═C(CH_3) (CHO)), 5.88−5.77 (m, 2H), 4.39 (ddd, J = 11, 8, 1.5 Hz, 1H, OC*H*), 3.62−3.49 (m, 3H), 2.49 (dddd, J = 16.5, 8.5, 6, 3 Hz, 1H, C*H*H), 2.32 (dddd, J = 15.5, 8, 5, 2.5 Hz, 1H, C*H*H), 2.25−2.16 (m, 2H), 2.14 (br s, 1H, O*H*), 1.76 (s, 3H, CH_3); ^{13}C NMR (125 MHz, $CDCl_3$) δ 194.9, 152.6, 138.0, 129.8, 128.5, 80.3, 76.9, 65.9, 36.3, 33.5, 9.6; IR (film) 3459, 2925, 2881, 1685, 1421, 1361, 1319, 1222, 1116, 1047, 1016, 917, 731, 701 cm^{-1}; MS (EI) m/z (rel intensity) 196 [5, M^+], 98 [60], 80 [100]; HRMS (EI) 196.1089 (196.1099 calcd for $C_{11}H_{16}O_3$, M^+).

*(E)-N-Methoxy-N-methyl-3-((2S,7R,Z)-7-((E)-2-methyl-3-oxoprop-1-enyl)-2,3,6,7-tetrahydrooxepin-2-yl)acrylamide (**38**).* To a solution of DMSO (180 μL, 2.5 mmol) in CH_2Cl_2 (12 mL) at −78 °C was added $(COCl)_2$ (168 μL, 1.9 mmol) dropwise, and the mixture was stirred at −78 °C for 30 min. A solution of the alcohol **36** (241 mg, 1.23 mmol) in CH_2Cl_2 (12 mL) was added, and the mixture was stirred at −78 °C for 45 min. Triethylamine (850 μL, 6.1 mmol) was added, and the mixture was stirred at −78 °C for 15 min and at room

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temperature for 1 h. After oxidation was deemed to be complete by TLC analysis, *N*-methoxy-*N*-methyl-2-(triphenylphosphoranylidene) acetamide (670 mg, 1.85 mmol) was added and the resulting solution stirred at room temperature for 1 h. The crude reaction mixture was filtered through a plug of silica and eluted with 1:2 EtOAc/petrol, and the solvent was removed *in vacuo* to yield a waxy white solid. This material was recrystallized (CH_2Cl_2/petrol) to yield the amide **38** (258 mg, 76%) as fine colorless needles: R_f 0.26 (1:1 EtOAc/hexane); $[\alpha]_D^{22}$ −149.2 (*c* 0.87, $CHCl_3$); mp 110−111 °C; ^{1}H NMR (500 MHz, $CDCl_3$) δ 9.44 (s, 1H, C*H*═O), 6.92 (dd, *J* = 15.5, 4.5 Hz, 1H, C*H*═CH(CO)N), 6.63 (d, *J* = 15.5 Hz, 1H, C*H*═CH(CO)N), 5.51 (dd, *J* = 7, 1 Hz, 1H, C*H*═C(CH_3) (CHO)), 6.89−6.82 (m, 2H, C*H*═C*H*), 4.43, (t, *J* = 10 Hz, 1H, OC*H*), 4.21 (dd, *J* = 11.5, 5.5 Hz, 1H, OC*H*), 3.70 (s, 3H, CH_3), 3.24 (s, 3H, CH_3), 2.54 (dd, *J* = 16.5, 11 Hz, 1H, C*H*H), 2.42 (t, *J* = 5 Hz, 2H, CH_2), 2.26 (dd, *J* = 16.5, 6.5 Hz, 1H, CH*H*), 1.78 (s, 3H, CH═C(CH_3) (CHO)); ^{13}C NMR (125 MHz, C_6D_6) δ 193.8, 166.6, 152.0, 146.4, 138.4, 130.0, 129.1, 118.3, 78.9, 77.1, 61.1, 37.5, 36.6, 32.2, 9.7; IR (film) 3018, 2987, 2944, 2884, 2857, 2832, 1684, 1661, 1633, 1419, 1386, 1320, 1243, 1180, 1117, 1026, 1010, 965, 918, 706 cm^{-1}; MS (EI) *m*/*z* (rel intensity) 279 [5, M^+], 219 [15], 181 [25], 136 [70], 121 [100]; HRMS (EI) 279.1473 (279.1471 calcd for $C_{15}H_{21}NO_4$, M^+). Anal. Calcd for $C_{15}H_{21}NO_4$: C, 64.5 ; H, 7.6 ; N, 5.0 ; Found: C, 64.0 ; H, 7.4 ; N, 4.9.

*(E)-N-Methoxy-N-methyl-3-((2S,7R,Z)-7-((E)-2-methylbuta-1,3-dienyl)-2,3,6,7-tetrahydrooxepin-2-yl)acrylamide (**40**).* To a solution of methyltriphenylphosphonium bromide (8 mg, 0.064 mmol) in THF (1 mL) at 0 °C was added KO^{t}Bu solution (64 μL, 1.0 M solution in THF, 0.064 mmol). The resulting yellow solution was stirred at 0 °C for 30 min, and a solution of the aldehyde **38** (23 mg, 0.064 mmol) in THF (1 mL) was added. The mixture was stirred at 0 °C for 1 h and quenched by addition of saturated aqueous $NaHCO_3$ solution (1 mL). The solvent (THF) was removed *in vacuo*, Et_2O (5 mL) was added, and the aqueous phase was further extracted with Et_2O (2 × 5 mL). The organic portions were dried (Mg_2SO_4), the solvent was removed *in vacuo*, and the crude material was purified by flash chromatography (1:2 EtOAc/petrol) to yield the diene **40** (20 mg, 86%) as a colorless oil: R_f 0.42 (1:1 EtOAc/hexane); $[\alpha]_D^{22}$ −171.3 (*c* 1.0, $CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$) δ 6.90 (dd, *J* = 15.5, 4.0 Hz, 1H), C*H*═CH(CO)N), 6.62 (d, *J* = 15.5 Hz, 1H, CH═C*H*(CO)N), 6.35 (dd, *J* = 17.5, 10.5 Hz, 1H, C*H*═CH_2), 5.83−5.77 (m, 2H, C*H*═C*H*), 5.57 (d, *J* = 7.5 Hz, 1H, C*H*═C(CH_3) ($CHCH_2$)), 5.18 (d, *J* = 17.5 Hz, 1H, CH═CHH_{trans}), 5.02 (d, *J* = 10.5 Hz, 1H, CH═CHH_{cis}), 4.28 (td, *J* = 8.5, 1.5 Hz, 1H, OC*H*), 4.19 (ddd, *J* = 12, 4.5, 2 Hz, 1H, OC*H*), 3.69 (s, 3H, CH_3), 3.24 (s, 3H, CH_3), 2.48 (dd, *J* = 16, 10.5 Hz, 1H), 2.39−2.37 (m, 2H), 2.27−2.14 (m, 1H), 1.76 (s, 3H, C*H*═C(CH_3) ($CHCH_2$)); ^{13}C NMR (125 MHz, C_6D_6) δ 166.9, 147.0, 141.4, 134.4, 129.8, 129.7, 128.3, 118.1, 112.6, 78.8, 77.4, 61.0, 38.2, 37.6, 32.2, 12.4; IR (film) 2965, 2933, 2883, 1665, 1635, 1414, 1376, 1315, 1177, 1121, 990, 974, 899, 846, 704 cm^{-1}; MS (ESI$^+$) *m*/*z* (rel intensity) 577 [75, $(2M + Na)^+$], 300 [100, $(M + Na)^+$], 278 [30, $(M + H)^+$]; HRMS (ESI$^+$) 300.1670 (300.1670 calcd for $C_{16}H_{23}NO_3Na$, $(M + Na)^+$).

*(E)-1-(2,4-dinitrophenyl)-2-(((1R,4aR,5R,10S,10aS)-4-methyl-1,2,4a,5,6,9,10,10a-octahydro-5,10-epoxybenzo[8]annulen-1-yl)-methylene)hydrazine (**43**).* To a solution of the amide **40** (52 mg, 0.19 mmol) in Et_2O (2 mL) at −78 °C was added DIBAL-H solution (190 μL of a 1.5 M solution in toluene, 0.28 mmol), and the solution was stirred at −78 °C for 1 h. EtOAc (0.5 mL) was added, and the mixture was stirred at −78 °C for 15 min before being allowed to warm to room temperatute. Et_2O (10 mL) and saturated aqueous sodium potassium tartrate (10 mL) were added, and the aqueous phase was extracted with Et_2O (2 × 20 mL). The combined organic portions were washed with water (30 mL) and brine (30 mL) and dried (Mg_2SO_4), and the solvent was removed *in vacuo* at 0 °C to yield the crude aldehyde. The aldehyde was dissolved in MeCN/H_2O (19:1, 2 mL) and cooled to −15 °C. (5*R*)-5-Benzyl-2,2,3-trimethylimidazolidin-4-one **5** (9.7 mg, 0.038 mmol) was added, followed by trifluoroacetic acid (3 μL, 0.04 mmol). The mixture was stirred at −15 °C for 7 h, 2,4-dinitrophenylhydrazine (38 mg, 0.19 mmol) was added, and the mixture was allowed to warm to room temperature. Water (10 mL) and CH_2Cl_2 (20 mL) were added, and the aqueous phase was extracted with CH_2Cl_2 (2 × 20 mL). The combined organic portions were dried ($MgSO_4$), and the solvent removed *in vacuo*. The crude product was purified by column chromatography (1:5 EtOAc/petrol) to yield the title compound **43** as a yellow crystalline solid. The product was recrystallized (Et_2O) to give bright yellow prisms (62 mg, 82%): R_f 0.59 (1:2 EtOAc/hexane); $[\alpha]_D^{22}$ −150.7 (*c* 0.59, $CHCl_3$); mp 172−174 °C; ^{1}H NMR (500 MHz, $CDCl_3$) δ 11.03 (br s, 1H, N*H*), 9.12 (d, *J* = 2.5, 1H, Ar), 8.31 (ddd, *J* = 9.5, 2.5, 0.5 Hz, 1H, Ar), 7.88 (d, *J* = 9.5 Hz, 1H,) Ar), 7.46 (d, *J* = 6 Hz, 1H, C*H*═N), 5.53−5.58 (m, 1H, C*H*═CH), 5.39−5.42 (m, 1H, C*H*═CH), 5.24 (br s, 1H, C*H*═C(CH_3)), 4.49 (dd, *J* = 8, 5.5 Hz, 1H, OC*H*), 4.39−4.41 (m, 1H, OC*H*), 2.92−2.95 (m, 1H), 2.86 (tt, *J* = 12.5, 6.5 Hz, 1H), C*H*CH═N), 2.76−2.83 (m, 1H), 2.56−2.63 (m, 1H), 2.44−2.52 (m, 1H), 2.32−2.36 (m, 1H), 2.27 (dt, *J* = 12, 5.5 Hz, 1H), 2.18−2.25 (m, 1H), 1.74 (s, 3H, CH═C(CH_3)); ^{13}C NMR (125 MHz, $CDCl_3$) δ 153.2, 145.0, 138.0, 136.1, 130.1, 129.1, 128.3, 123.8, 123.5, 118.9, 116.4, 77.6, 76.9, 50.7, 46.8, 39.5, 39.1, 32.3, 31.2, 19.8; IR (film) 3299, 3110, 3008, 2912, 1616, 1589, 1517, 1422, 1330, 1308, 1275, 1219, 1138, 1079, 1010, 922, 833, 744, 664 cm^{-1}; MS (ESI$^+$) *m*/*z* (rel intensity) 421 [100, $(M + Na)^+$], 399 [65, $(M + H)^+$]; HRMS (ESI$^+$) 421.1481 (421.1482 calcd for $C_{20}H_{22}N_4O_5Na$, M^+).

Crystal data for **43**: $C_{20}H_{23}N_4O_5$, *M* = 399.42, *T* = 130.0 K, λ = 0.71073, tetragonal, space group $P4_32_12$, *a* = 10.7298(4), *c* = 35.040(3) Å, *V* = 4034.2(4) Å^3, *Z* = 8, D_c = 1.315 mg M^{-3} μ(Mo Kα) 0.096 mm^{-1}, *F*(000) = 1688, crystal size 0.2 × 0.2 × 0.2 mm^3, 21393 reflections measured, 3556 independent reflections [*R*(int) = 0.0788], the final *R* was 0.0444 [$I > 2\sigma(I)$], and wR(F^2) was 0.0891 (all data).

*(5R,E)-6-(4-(Benzyloxy)-2-oxooxazolidin-3-yl)-5-(2-(benzyloxy)-ethoxy)-6-oxohex-2-enyl Acetate (**28a**).* To a solution of the alkene **28** (3.0 g, 7.59 mmol) in CH_2Cl_2 (150 mL) were added 1,4-bisacetoxy-*cis*-2-butene (2.61 g, 15.2 mmol) and (1,3-bis(2,4,6-trimethylphenyl)-2-imidazolidinylidene)dichloro(o-isopropoxyphenylmethylene)ruthenium (94 mg, 0.15 mmol). The resulting solution was heated to reflux for 1.5 h and filtered through a plug of silica, and the silica was washed with CH_2Cl_2 (500 mL). The solvent was removed *in vacuo* to yield a green colored oil, which was purified by column chromatography (1:4 EtOAc/petrol) to yield the allylic acetate **28a** (2.85 g, 78%) as a pale brown oil: R_f 0.21 (1:2 EtOAc/hexane); $[\alpha]_D^{22}$ −64.5 (*c* 0.68, $CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.19−7.29 (m, 8H, Ar), 7.09−7.11 (m, 2H, Ar), 5.79 (dt, *J* = 15.5, 7 Hz, 1H, OCH_2C*H*═C*H*), 5.61 (dt, *J* = 15.5, 6.5 Hz, 1H, OCH_2C*H*═CH), 4.84 (d, *J* = 18 Hz, 1H, OC*H*HPh), 4.76 (d, *J* = 18 Hz, 1H, OC*H*HPh), 4.37−4.48 (m, 5H), 4.06 (dd, *J* = 14.5, 7 Hz, 1H), 4.02 (dd, *J* = 9, 3 Hz, 1H), 3.84 (t, *J* = 8.5 Hz, 1H), 3.70 (ddd, *J* = 12.5, 6.5, 2.5 Hz, 1H), 3.51−3.58 (m, 2H), 3.19 (dd, *J* = 13.5, 2.5 Hz, 1H), 2.65 (dd, *J* = 13.5, 9.5 Hz, 1H), 2.30−2.42 (m, 2H), 1.98−2.03 (m, 4H), 1.20 (t, *J* = 7 Hz, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 170.5, 153.3, 138.2, 135.0, 131.2, 129.3, 127.5, 127.3, 127.1, 126.7, 79.4, 73.1, 73.0, 70.5, 70.0, 64.9, 54.7, 37.6, 34.7, 21.0, 14.2; IR (film) 2919, 1777, 1733, 1391, 1363, 1227, 1132, 1026, 974, 738, 700 cm^{-1}; MS (ESI$^+$) *m*/*z* (rel intensity) 499.3 [100, $(M + NH_4)^+$], 482 [20, $(M + H)^+$]; HRMS (ESI$^+$) 499.2442 (499.2439 calcd for $C_{27}H_{35}O_7N_2$, $[M + NH_4]^+$).

*4-(Benzyloxy)-3-((R)-2-(2-(benzyloxy)ethoxy)hex-5-enoyl)-oxazolidin-2-one (**29**).* To a solution of the allylic acetate **28a** (2.68 g, 5.57 mmol) in CH_2Cl_2 (150 mL) were added $Pd(dba)_2$ (160 mg, 0.28 mmol), triphenylphosphine (294 mg, 1.12 mmol) and ammonium formate (758 mg, 11.1 mmol). The mixture was heated to reflux for 18 h and allowed to cool to room temperature. The product was absorbed onto silica and purified by column chromatography (1:5 EtOAc/petrol) to yield the alkene **29** (2.15 g, 94%) as a colorless oil: R_f 0.45 (1:2 EtOAc/hexane); $[\alpha]_D^{22}$ 79.8 (*c* 0.68, $CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.25−7.33 (m, 8H, Ar), 7.15−7.17 (m, 2H, Ar), 5.84 (ddt, *J* = 17, 10, 6.5 Hz, 1H, C*H*═CH_2), 5.05 (ddd, *J* = 17, 3.5, 1.5 Hz, 1H, CH═CHH_{trans}), 4.89 (ddt, *J* = 10, 2, 1.5 Hz, 1H, CH═CHH_{cis}), 4.94 (d, *J* = 18 Hz, 1H, OC*H*HPh), 4.80 (d, *J* = 18 Hz, 1H, OC*H*HPh), 4.49 (dd, *J* = 28.5, 12 Hz, 2H), 4.42 (ddt, *J* = 9.5, 8, 3 Hz, 1H), 4.05 (dd, *J* = 9, 3 Hz, 1H), 3.82 (t, *J* = 8.5 Hz, 1H), 3.69−3.74 (m, 1H), 3.56−3.66 (m, 2H), 3.24 (dd, *J* = 13.5, 3 Hz, 1H), 2.72 (dd, *J*

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= 13.5, 9.5 Hz, 1H), 2.16−2.29 (m, 1H), 1.74 (ddt, J = 17, 7.5, 5.5 Hz, 1H), 1.59−1.68 (m, 2H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 170.8, 153.3, 138.4, 138.2, 135.1, 129.3, 128.9, 128.4, 127.4, 127.3, 127.0, 114.9, 79.6, 74.1, 72.9, 70.7, 70.0, 54.7, 37.7, 31.0, 29.7; IR (film) 2919, 1777, 1733, 1391, 1363, 1227, 1132, 1026, 974, 738, 700 cm^{-1}; MS (ESI$^+$) m/z (rel intensity) 446 [30, (M + Na)$^+$], 441 [100, (M + NH_4)$^+$], 424 [60, (M + H)$^+$]; HRMS (ESI$^+$) 424.2120 (424.2118 calcd for $C_{25}H_{30}O_5N$, [M + H]$^+$).

*4-(Benzyloxy)-3-((R)-2-((S)-1-(benzyloxy)hex-5-en-2-yloxy)pent-4-enoyl)oxazolidin-2-one (**31**).* To a solution of NaHMDS (6.86 mL, 1.0 M in THF, 6.86 mol.) in THF (25 mL) at −78 °C was added a solution of the oxazolidinone **29** (2.15 g, 5.24 mmol) in THF (20 mL) over 5 min. The solution was stirred at −78 °C for 30 min, and a solution of allyl iodide (955 μL, 10.5 mmol) in THF (20 mL) was added. The mixture was stirred at −78 °C for 2 h and quenched with saturated aqueous NH_4Cl (20 mL). The aqueous phase was extracted into Et_2O (3 × 40 mL), the organic extracts were washed with water (60 mL) and brine (60 mL) and dried ($MgSO_4$), and the solvent was removed *in vacuo*. The crude product was purified by column chromatography (1:6 EtOAc/hexane) to yield a colorless solid. Proton NMR analysis of this material indicated a 14:1 mixture of diastereoisomers. This material was recrystallized from Et_2O/hexane to give the diene **31** (1.56 g, 64%) as a white powder: R_f 0.46 (1:2 EtOAc/hexane); $[\alpha]_D^{22}$ +114.5 (c 0.65, $CHCl_3$); mp 76−77 °C; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.22−7.32 (m, 8H, Ar), 7.10−7.11 (m, 2H, Ar), 5.95 (ddt, J = 14.5, 7.5, 6.5 Hz, 1H, CH═CH_2), 5.83 (ddt, J = 13.5, 10, 7 Hz, 1H, CH═CH_2), 5.28 (dd, J = 8, 3.5 Hz, 1H), 4.98−5.17 (m, 4H), 4.42 (d, J = 12 Hz, 1H, OCHHPh). 4.34 (d, J = 12 Hz, 1H, OCHHPh), 4.15−4.20 (m, 1H), 3.77 (dd, J = 9, 3 Hz, 1H), 3.69−3.73 (m, 1H), 3.60 (t, J = 9 Hz, 1H), 3.50 (dd, J = 9.5, 1 Hz, 1H), 3.12 (dd, J = 13.5, 3 Hz, 1H), 2.95 (t, J = 8.5 Hz, 1H), 2.58 (dd, J = 13.5, 9.5 Hz, 1H), 2.48−2.53 (m, 1H), 2.36−2.41 (m, 1H), 2.29−2.34 (m, 1H), 2.19 (dtd, J = 14, 9, 5.5 Hz, 1H), 1.68−1.75 (m, 1H), 1.45−1.51 (m, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 172.9, 153.0, 138.5, 138.2, 135.3, 133.7, 129.3, 128.8, 128.5, 127.3, 127.2, 126.0, 118.0, 114.9, 80.1, 79.3, 76.0, 72.2, 66.1, 54.7, 38.4, 38.0, 31.3, 29.9; IR (film) 2970, 2920, 1774, 1738, 1715, 1353, 1216, 1108, 912, 735, 698 cm^{-1}; MS (ESI$^+$) m/z (rel intensity) 481 [40, (M + NH_4)$^+$], 464 [85, (M + H)$^+$], 258 [100]; HRMS (ESI$^+$) 464.2428 (464.2431 calcd for $C_{28}H_{33}O_5N$, [M + H]$^+$).

*4-(Benzyloxy)-3-((2R,8S,Z)-8-(benzyloxymethyl)-2,3,6,7-tetrahydrooxocine-2(8H)-carbonyl)oxazolidin-2-one (**31a**).* A solution of the diene **31** (230 mg, 0.50 mmol) in CH_2Cl_2 (167 mL, 0.003 M) was heated to reflux, and bis(tricyclohexylphosphine) benzylidine ruthenium(IV) chloride (29 mg, 0.035 mmol) was added. The mixture was stirred at reflux for 1 h and cooled to room temperature, and air was bubbled through the solution for 3 h. The solvent was removed *in vacuo* and the crude mixture purified by column chromatography (1:4 EtOAc/hexane) to yield the title compound **31a** (219 mg, 99%) as a colorless oil: R_f 0.08 (1:4 EtOAc/hexane); $[\alpha]_D^{22}$ +79.8 (c 1.69, $CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.22−7.34 (m, 8H, Ar), 7.18−7.20 (m, 2H, Ar), 5.79−5.91 (m, 2H, CH═CH), 5.00 (dd, J = 9, 2 Hz, 1H, OCHC═O), 4.61 (ddt, J = 9.5, 7, 3.5 Hz, 1H, CHN), 4.50 (s, 2H, OCH_2Ph), 4.10−4.18 (m, 2H, OCH_2), 3.80 (qd J = 8, 4 Hz, 1H, OCHCH_2OBn), 3.44−3.53 (m, 2H, CH_2OBn), 3.23 (dd, J = 13.5, 3.5 Hz, 1H, CHCHHPh), 2.80 (dd, J = 13.5, 9.5 Hz, 1H, CHCHHPh), 2.57−2.65 (m, 2H), 2.37 (ddd, J = 14, 8, 2 Hz, 1H, CHH), 2.03−2.09 (m, 1H, CHH), 1.72−1.79 (m, 1H, CHH), 1.59−1.65 (m, 1H, CHH); ^{13}C NMR (125 MHz, $CDCl_3$) δ 170.3, 152.6, 138.3, 135.0, 129.8, 129.3, 128.8, 128.14, 128.05, 127.5, 127.34, 127.29, 127.2, 79.3, 77.3, 73.1, 72.9, 66.4, 55.3, 37.6, 33.7, 33.2; IR (film) 2932, 1776, 1710, 1388, 1285, 1211, 1104, 749, 699 cm^{-1}; MS (ESI$^+$) m/z (rel intensity) 893 [100, (2M + Na)$^+$], 458 [65, (M + Na)$^+$]; HRMS (ESI$^+$) 458.1937 (458.1938 calcd for $C_{26}H_{29}O_5NNa$, [M + Na]$^+$)

*((2R,8S,Z)-8-(Benzyloxymethyl)-2,3,6,7-tetrahydrooxocin-2(8H)-yl)methanol (**33**).* To a solution of the oxazolidinone **31a** (877 mg, 2.02 mmol) in THF (20 mL) at 0 °C was added a solution of $NaBH_4$ (382 mg, 10.1 mmol) in water (5 mL) dropwise. The mixture was stirred at 0 °C for 2 h and quenched carefully by addition of 1 M HCl solution. The solvent (THF) was removed *in vacuo*, the aqueous phase was extracted into Et_2O (3 × 20 mL), the combined organic extracts were washed with water (30 mL) and brine (30 mL) and dried ($MgSO_4$), and the solvent was removed *in vacuo*. The crude product was purified by column chromatography (1:4 EtOAc/hexane) to yield the alcohol **33** (448 mg, 85%) as a clear, colorless oil: R_f 0.30 (1:2 EtOAc/hexane); $[\alpha]_D^{22}$ −26.6 (c 0.69, $CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.27−7.36 (m, 5H, Ar), 5.76−5.81 (m, 1H, CH═CH), 5.67−5.73 (m, 1H, CH═CH), 4.51−4.56 (m, 2H, OCH_2Ph), 3.72 (dtt, J = 13.5, 5, 3 Hz, 1H, OCH), 3.37−3.56 (m, 5H), 3.22 (dd, J = 9, 1.5 Hz, 1H, OH), 2.54 (dtd, J = 12, 10.5, 6.5 Hz, 1H, CHH), 2.24−2.30 (m, 1H, CHH), 1.97−2.03 (m, 1H, CHH), 1.94 (ddd, J = 14, 8, 1 Hz, 1H, CHH), 1.50−1.55 (m, 2H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 137.6, 131.1, 128.3, 127.76, 127.73, 127.68, 84.5, 78.2, 74.4, 73.2, 66.2, 31.5, 30.4, 22.7; IR (film) 3470, 3016, 2930, 1738, 1364, 1217, 1094, 752, 698 cm^{-1}; MS (EI) m/z (rel intensity) 262 [5, M$^+$], 91 [100]; HRMS (EI) 262.1552 (262.1569 calcd for $C_{16}H_{22}O_3$, M$^+$).

*(E)-3-((2R,8S,Z)-8-(Benzyloxymethyl)-2,3,6,7-tetrahydrooxocin-2(8H)-yl)-2-methylacrylaldehyde (**35**).* To a solution of the alcohol **33** (432 mg, 1.65 mmol) in CH_2Cl_2 (12 mL) at 0 °C was added triethylamine (920 μL, 6.6 mmol), and the mixture was stirred for 10 min. To this was added a solution of SO_3·pyridine (795 mg, 5.0 mmol) in DMSO (5 mL) dropwise. The resulting mixture was stirred at 0 °C for 2 h, until oxidation was deemed complete by TLC analysis. 2-(Triphenylphosphoranylidene)propionaldehyde (1.05 g, 3.3 mmol) was added and the mixture heated to reflux for 40 h. The reaction mixture was diluted with Et_2O (20 mL) and the organic phase washed with saturated aqueous $NaHCO_3$ (20 mL), water (20 mL), and brine (20 mL) and then dried ($MgSO_4$). The solvent was removed *in vacuo*, and the crude product was purified by column chromatography (1:10 EtOAc/hexane) to yield the α,β-unsaturated aldehyde **35** (367 mg, 74%) as a colorless oil: R_f 0.37 (1:4 EtOAc/hexane); $[\alpha]_D^{22}$ −51.9 (c 1.22, $CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$) δ 9.44 (s, 1H, CH═O), 7.25−7.32 (m, 5H, Ar), 6.48 (ddd, J = 8, 1.5, 1 Hz, 1H, CH═C(CH_3)(CHO)), 5.79−5.82 (m, 2H, CH═CH), 4.50 (s, 2H,, OCH_2Ph), 4.38−4.42 (m, 1H, OCH), 3.82 (ddt, J = 11, 6.5, 4 Hz, 1H, OCH), 3.41−3.42 (m, 2H, OCH_2OBn), 2.51−2.59 (m, 1H, CHH), 2.45−2.51 (m, 1H, CHH), 2.12−2.17 (m, 1H, CHH), 2.05−2.11 (m, 1H, CHH), 1.74 (d, J = 1.5 Hz, 3H, CH═C(CH_3)(CHO)) 1.54−1.65 (m, 2H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 195.2, 153.1, 138.3, 137.8, 132.6, 128.3, 127.5, 127.4, 126.6, 78.4, 78.0, 74.3, 73.3, 33.6, 31.8, 23.2, 9.5; IR (film) 2930, 2855, 1689, 1453, 1364, 1314, 1092, 1055, 733, 698 cm^{-1}; MS (ESI$^+$) m/z (rel intensity) 625 [45], 339 [55, (M + K)$^+$], 323 [100, (M + Na)$^+$]; HRMS (ESI$^+$) 323.1617 (323.1618 calcd for $C_{19}H_{24}O_3Na$, [M + Na]$^+$)

*(E)-3-((2R,8S,Z)-8-(Methoxy)-2,3,6,7-tetrahydrooxocin-2(8H)-yl)-2-methylacrylaldehyde (**37**).* To a stirred solution of the benzyl ether **35** (455 mg, 1.45 mmol) in CH_2Cl_2 (30 mL) were added pH 7 buffer (3 mL, 0.05 M NaH_2PO_4, 0.29 M NaOH in H_2O) and DDQ (1.64 g, 7.24 mmol). The resulting mixture was stirred at room temperature for 16 h and quenched by addition of saturated aqueous $NaHCO_3$ solution (20 mL). The organic phase was washed with saturated aqueous $NaHCO_3$ solution (5 × 20 mL) until the washings ran clear. The organic phase was dried (Mg_2SO_4), the solvent was removed *in vacuo*, and the crude material was purified by flash chromatography (1:2 EtOAc/petrol) to yield the alcohol as a white solid. The product was recrystallized (Et_2O/hexane) to yield the alcohol **37** (233 mg, 76%) as colorless needles: R_f 0.10 (1:2 EtOAc/hexane); $[\alpha]_D^{22}$ −53.5 (c 0.69, $CHCl_3$); mp 48 °C; ^{1}H NMR (500 MHz, $CDCl_3$) δ 9.41 (s, 1H, CH═O), 6.47 (dd, J = 8, 1.5 Hz, 1H, CH═C(CH_3)(CHO)), 5.76−5.787 (m, 2H, CH═CH), 4.40 (td, J = 8.5, 2.5 Hz, 1H, OCHCH═C), 3.70 (qd, J = 11, 3 Hz, 1H, OCHCH_2OH), 3.54 (ddd, J = 11.5, 8.5, 3.5 Hz, 1H, CHHOH), 3.43 (ddd, J = 11.5, 8, 4 Hz, 1H, CHHOH), 2.44−2.54 (m, 2H), 2.19 (ddd, J = 19, 8, 2.5 Hz, 1H, CHH), 2.07−2.13 (m, 1H, CHH), 1.89 (dd, J = 8.5, 4.5 Hz, 1H, CHH), 1.78 (d, J = 1.5 Hz, 3H, CH═C(CH_3)(CHO)), 1.60−1.68 (m, 1H, CHH), 1.45−1.55 (m, 1H, CHH); ^{13}C NMR (125 MHz, $CDCl_3$) δ 195.0, 152.6, 137.7, 132.8, 126.3, 79.9, 78.6, 66.3, 33.4, 31.4, 23.1, 9.6; IR (film) 3446, 2931, 1683, 1361, 1314, 1105, 1048, 1014, 753, 725 cm^{-1}; MS (EI) m/z (rel intensity) 210 [5, M$^+$], 127 [25], 79

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[75], 54 [100]; HRMS (EI) 210.1249 (210.1256 calcd for $C_{12}H_{18}O_3$, M^+).

*(E)-N-Methoxy-N-methyl-3-((2S,8R,Z)-8-((E)-2-methyl-3-oxoprop-1-enyl)-2,3,6,7-tetrahydrooxocin-2(8H)-yl)acrylamide (**39**).* To a solution of the alcohol **37** (47 mg, 0.62 mmol) in CH_2Cl_2 (2 mL) at 0 °C was added triethylamine (150 μL, 1.1 mmol), and the mixture was stirred for 10 min. To this was added a solution of SO_3·pyridine (1.5 mg, 0.66 mmol) in DMSO (0.65 mL) dropwise. The resulting mixture was stirred at 0 °C for 3 h, until oxidation was deemed complete by TLC analysis. *N*-Methoxy-*N*-methyl-2-(triphenylphosphoranylidene) acetamide (96 mg, 0.26 mmol) was added and the mixture stirred at room temperature for 3 h. The reaction mixture was absorbed onto silica and purified by column chromatography (1:2 EtOAc/hexane), to yield the amide **39** (46 mg, 73%) as a colorless oil: R_f 0.24 (1:1 EtOAc/hexane); $[\alpha]_D^{22}$ −165.9 (*c* 0.82, $CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$) δ 9.43 (s, 1H, C*H*═O), 6.90 (dd, *J* = 15.5, 3.5 Hz, 1H, C*H*═CH(CO)N), 6.49−6.52 (m, 2H), 5.79−5.88 (m, 2H, C*H*═C*H*), 4.24−4.30 (m, 2H), 3.60 (s, 3H, CH_3), 3.20 (s, 3H, CH_3), 2.52−2.62 (m, 2H), 2.11−2.18 (m, 2H), 1.76 (s, 3H, CH═C(CH_3)(CHO)), 1.69−1.83 (m, 2H); ^{13}C NMR (125 MHz, $CDCl_3$) 194.0, 166.8, 151.7, 147.5, 138.1, 132.2, 127.2, 117.7, 78.3, 77.9, 61.0, 35.0, 33.7, 32.2, 23.8, 9.6; IR (film) 2934, 1688, 1664, 1635, 1413, 1379, 1120, 1090, 823, 728 cm^{-1}; MS (EI) *m*/*z* (rel intensity) 293 [2, M^+], 277 [15], 135 [65], 81 [100]; HRMS (EI) 293.1614 (293.1627 calcd for $C_{16}H_{23}NO_4$, M^+).

*(E)-N-Methoxy-N-methyl-3-((2S,8R,Z)-8-((E)-2-methylbuta-1,3-dienyl)-2,3,6,7-tetrahydrooxepin-2(8H)-yl)acrylamide (**41**).* To a solution of methyltriphenylphosphonium bromide (112 mg, 0.31 mmol, predried at 100 °C under high vacuum for 2 h) in THF (6 mL) at 0 °C was added a solution of KO^{t}Bu (310 μL, 1.0 M in THF, 0.31 mmol) dropwise. The resulting solution was stirred at 0 °C for 0.5 h, and a solution of the α,β-unsaturated aldehyde **39** (46 mg, 0.16 mmol) in THF (6 mL) was added dropwise by cannula. The mixture was stirred at 0 °C for 2 h, loaded directly onto a column of neutral alumina, and eluted in 1:10 EtOAc/hexane, and the solvent was removed *in vacuo*. The resulting product was recrystallized (Et_2O/hexane) to yield the product **41** (42 mg, 90%) as fine colorless needles: R_f 0.35 (1:1 EtOAc/hexane); $[\alpha]_D^{22}$ −224.0 (*c* 1.0, $CHCl_3$); mp 73−76 °C; ^{1}H NMR (500 MHz, $CDCl_3$) δ 6.93 (dd, *J* = 15, 3.5 Hz, 1H, C*H*═CH(CO)N), 6.58 (d, *J* = 15 Hz, 1H, CH═C*H*(CO)N), 6.38 (ddd, *J* = 17.5, 10.5, 0.5 Hz, 1H, C*H*═CH_2), 5.97 (dt, *J* = 11, 8 Hz, 1H, C*H*═CH), 5.76 (dtd, *J* = 11, 7, 1.5 Hz, 1H, C*H*═CH), 5.61 (dd, *J* = 8.5, 1 Hz, 1H, C*H*═C(CH_3)(CH═CH_2))), 5.20 (d, *J* = 17.5 Hz, 1H, CH═CHH_{trans}), 5.05 (dd, *J* = 10.5 Hz, 1H, CH═CHH_{cis}), 4.30−4.26 (m, 1H, OC*H*), 4.15−4.11 (m, 1H, OC*H*), 3.61 (s, 3H, CH_3), 3.21 (s, 3H, CH_3), 2.48−2.63 (m, 2H), 2.14 (ddd, *J* = 14, 8.5, 2 Hz, 1H, C*H*H), 2.07−2.13 (m, 1H, CH*H*), 1.77 (d, *J* = 1 Hz, 3H, CH═C(CH_3)(CH═CH_2)), 1.70−1.66 (m, 2H); ^{13}C NMR (125 MHz C_6D_6) 148.1, 141.4, 134.1, 134.0, 131.4, 127.7, 127.6, 117.6, 112.5, 78.0, 77.9, 60.9, 34.9, 34.8, 32.1, 23.6, 12.2; IR (film) 3016, 2934, 1665, 1637, 1412, 1376, 1175, 1121, 1088, 990, 900, 728 cm^{-1}; MS (EI) *m*/*z* (rel intensity) 291 [3, M^+], 195 [15], 136 [40], 81 [100]; HRMS (EI) 291.1828 (219.1834 calcd for $C_{17}H_{25}NO_3$, M^+).

*(E)-3-((2S,8R,Z)-8-((E)-2-Methylbuta-1,3-dienyl)-2,3,6,7-tetrahydrooxepin-2(8H)-yl)acrylaldehyde (**44**).* To a solution of the amide **41** (6 mg, 0.020 mmol) in Et_2O (1 mL) at −78 °C was added DIBAL-H solution (28 μL of a 1.5 M solution in toluene, 0.40 mmol), and the solution was stirred at −78 °C for 1 h. EtOAc (0.1 mL) was added, and the mixture was stirred at −78 °C for 15 min before being allowed to warm to room temperature. Et_2O (2 mL) and saturated aqueous sodium potassium tartrate (2 mL) were added, and the aqueous phase was extracted with Et_2O (3 × 5 mL). The combined organic portions were washed with water and brine and dried (Mg_2SO_4), and the solvent was removed *in vacuo* to yield the aldehyde **44** (5 mg). This compound was used immediately without further purification: R_f 0.74 (1:1 EtOAc/hexane); $[\alpha]_D^{22}$ −104.0 (*c* 1.0, $CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$) 9.56 (d, *J* = 8 Hz, 1H), 6.78 (dd, *J* = 15, 4 Hz, 1H), 6.35 (ddd, *J* = 17.5, 10.5, 0.5 Hz, 1H), 6.26 (ddd, *J* = 15.5, 8, 2 Hz, 1H), 5.95−5.83 (m, 1H), 5.86−5.91 (m, 1H), 5.77 (ddt, *J* = 10, 6.5, 1.5 Hz, 1H), 5.57 (d, *J* = 8 Hz, 1H), 5.21 (d, *J* = 17.5 Hz, 1H), 5.07 (d, *J* = 10.5 Hz, 1H), 4.35 (dtd, *J* = 8.5, 4, 2 Hz, 1H), 4.15 (ddd, *J* = 10, 8.5, 2 Hz, 1H), 2.57−2.65 (m, 1H), 2.48−2.54 (m, 1H), 2.15 (ddd, *J* = 14.5, 8.5, 2 Hz, 1H), 2.10−2.16 (m, 1H), 1.75 (d, *J* = 1.5 Hz, 1H); ^{13}C NMR (125 MHz $CDCl_3$) 193.5, 158.8, 140.7, 133.1, 132.3, 131.1, 130.3, 128.3, 113.2, 112.7, 78.2, 77.2, 34.7, 34.5, 23.2, 12.3; IR (film) 2917, 1730, 1513, 1247, 1127, 1089, 1032, 916 cm^{-1}; MS (ESI^+) *m*/*z* (rel intensity)) 246 [100], 233 [20, $(M + H)^+$], 220 [40], 215 [40]; HRMS (ESI^+) 233.15359 (233.15361 calcd for $C_{15}H_{21}O_2N$, $(M + H)^+$).

*(E)-1-(2,4-Dinitrophenyl)-2-(((1R,4aR,5R,11S,11aS,Z)-4-methyl-2,4a,5,6,9,10,11,11a-octahydro-1H-5,11-epoxybenzo[9]annulen-1-yl)methylene)hydrazine (**45**).* The aldehyde **44** (6 mg) was dissolved in MeCN/H_2O (19:1, 1 mL) and cooled to −15 °C. (5*R*)-5-Benzyl-2,2,3-trimethylimidazolidin-4-one **5** (1 mg, 0.004 mmol) was added, followed by trifluoroacetic acid (1 μL, 0.01 mmol). The mixture was stirred at −15 °C for 7 h, and at 0 °C for 16 h. 2,4-Dinitrophenylhydrazine (6 mg, 0.03 mmol) was added, and the mixture was allowed to warm to room temperature. Water (3 mL) and CH_2Cl_2 (5 mL) were added, and the aqueous phase was extracted with CH_2Cl_2 (2 × 5 mL). The combined organic portions were dried ($MgSO_4$), and the solvent was removed *in vacuo*. The crude product was purified by column chromatography (1:10 EtOAc/petrol), to yield the *endo* cycloadduct **45** (5.4 mg, 65%) as a yellow amorphous solid: R_f 0.74 (1:1 EtOAc/hexane); $[\alpha]_D^{22}$ −202.0 (*c* 0.56, $CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$) δ 11.0 (s, 1H, N*H*), 9.12 (d, *J* = 2.5 Hz, 1H, Ar), 8.31 (dd, *J* = 9.5, 2.5 Hz, 1H, Ar), 7.87 (d, *J* = 9.5 Hz, 1H, Ar), 7.45 (d, *J* = 5.5 Hz, 1H, C*H*═N), 5.87 (dtd, *J* = 11.5, 8.5, 3 Hz, 1H, C*H*═CH), 5.53 (dddd, *J* = 13, 5.5, 4, 1 Hz, 1H, C*H*═CH), 5.29 (br s, 1H), C*H*═C(CH_3)), 4.34 (dt, *J* = 9, 6 Hz, 1H, OC*H*), 4.10 (dt, *J* = 9.5, 3 Hz, 1H, OC*H*), 2.77 (m, 1H), 2.71 (ddd, *J* = 9, 6.5, 3 Hz, 1H, C*H*CH═N), 2.63−2.58 (m, 1H), 2.46−2.41 (m, 1H), 2.37−2.18 (m, 4H), 1.97 (dt, *J* = 13, 8.5 Hz, 1H), 1.85 (dt, *J* = 14, 9 Hz, 1H), 1.72 (s, 3H, CH═C(C*H*$_3$)); ^{13}C NMR (125 MHz $CHCl_3$) δ 153.3, 145.0, 138.0, 134.5, 133.4, 130.1, 129.0, 125.7, 123.5, 119.4, 116.4, 78.3, 74.2, 49.9, 43.9, 38.0, 33.0, 30.8, 29.6, 21.8, 20.7; IR (film) 3458, 3297, 3016, 2970, 2945, 1738, 1617, 1517, 1434, 1365, 1228, 1217, 1206 cm^{-1}; MS (ESI^+) *m*/*z* (rel intensity) 413 [100, $(M + H)^+$], 324 [25]; HRMS (ESI^+) 413.1819 (413.1820 calcd for $C_{21}H_{25}N_4O_5$, $(M + H)^+$).

*(E)-1-(2,4-Dinitrophenyl)-2-(((1S,4aR,5R,11S,11aR,Z)-4-methyl-2,4a,5,6,9,10,11,11a-octahydro-1H-5,11-epoxybenzo[9]annulen-1-yl)methylene)hydrazine (**46**).* The above reaction was repeated using the (5*S*)-5-benzyl-2,2,3-trimethylimidazolidin-4-one catalyst **6**, to yield a 1:1 mixture of the *endo* and *exo* cycloadducts **45** and **46** as a yellow amorphous solid. (7.7 mg, 72%). The isomers were separated by column chromatography (1:10 EtOAc/petrol), and *exo* adduct was recrystallized (MeOH/hexane) to yield thin yellow needles (3 mg).

Data for *exo* cycloadduct **46**: R_f 0.63 (1:1 EtOAc/hexane); $[\alpha]_D^{22}$ +71.9 (*c* 0.14, $CHCl_3$); mp 185−188 °C; ^{1}H NMR (500 MHz, $CDCl_3$) δ 10.98 (s 1H, N*H*), 9.12 (d, *J* = 2.5 Hz, 1H), Ar), 8.32 (dd, *J* = 9.5, 2.5 Hz, 1H, Ar), 7.87 (dd, *J* = 9.5 Hz, 1H, Ar), 7.43 (d, *J* = 5.5 Hz, 1H, C*H*═N), 5.95 (dddd, *J* = 10, 8.5, 6.5, 1.5 Hz, 1H, C*H*═CH), 5.81−5.75 (m, 1H, C*H*═CH), 5.48 (d, *J* = 5.5 Hz, 1H, C*H*═C(CH_3)), 4.29−4.28 (m, 1H, OC*H*), 4.19 (t, *J* = 6.5 Hz, 1H, OC*H*), 2.88 (td, *J* = 7, 3 Hz, 1H), 2.64−2.61 (m, 1H), 2.58−2.54 (m, 1H), 2.51−2.41 (m, 3H), 2.19 (ddd, *J* = 14, 9, 5 Hz, 1H), 2.14−2.05 (m, 3H), 1.71 (s, 3H, CH═C(C*H*$_3$)); ^{13}C NMR (125 MHz $CHCl_3$) 155.0, 145.1, 137.9, 135.0, 134.0, 130.0, 128.9, 127.6, 123.5, 120.0, 116.3, 83.3, 80.6, 46.7, 45.9, 36.2, 34.6, 33.2, 23.7, 22.3, 22.2; IR (film) 3301, 2916, 2845, 1617, 1591, 1518, 1427, 1335, 1310, 1280, 1133, 1090, 1068, 925, 828, 743 cm^{-1}; MS (ESI^+) *m*/*z* (rel intensity) 413 [100, $(M + H)^+$], 360 [50]; HRMS (ESI^+) 413.1820 (413.1820 calcd for $C_{21}H_{25}N_4O_5$, $(M + H)^+$).

*((1R,4aR,5R,11S,11aS,Z)-4-Methyl-2,4a,5,6,9,10,11,11a-octahydro-1H-5,11-epoxybenzo[9]annulen-1-yl)methyl 2,4-dinitrobenzoate (**47**).* The aldehyde **44** (10 mg) was dissolved in MeCN/H_2O (19:1, 1 mL) and cooled to −15 °C. (5*R*)-5-Benzyl-2,2,3-trimethylimidazolidin-4-one **5** (1.5 mg, 0.006 mmol) was added, followed by trifluoroacetic acid (2 μL, 0.02 mmol). The mixture was stirred at 0 °C for 16 h, $NaBH_4$ (40 mg, 1.1 mmol) was added, and the mixture was allowed to warm to room temperature. Water (5 mL) and

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CH_2Cl_2 (5 mL) were added, and the aqueous phase was extracted with CH_2Cl_2 (3 × 5 mL). The combined organic portions were dried ($MgSO_4$), and the solvent was removed *in vacuo*. The resulting residue was dissolved in CH_2Cl_2 (5 mL), and 3,5-dinitrobenzoyl chloride (200 mg, 0.87 mmol), pyridine (120 μL, 1.5 mmol), and dimethylaminopyridine (10 mg, 0.09 mmol) were added. The mixture was stirred at room temperature for 1 h and was loaded directly onto a silica gel column. The product was eluted in 1:10 EtOAc, to yield a colorless crystalline solid **47** (8 mg, 56%). The product was recrystallized (isopropanol) to yield fine, colorless needles: R_f 0.74 (1:1 EtOAc/hexane); $[\alpha]_D^{22}$ −98.7 (*c* 0.23, $CHCl_3$); mp 107−109.5 °C; ^{1}H NMR (500 MHz, $CDCl_3$) δ 9.23−9.24 (m, 1H, Ar), 9.13−9.14 (m, 2H, Ar), 5.85 (ddd, *J* = 11.5, 8.5, 2.5 Hz, 1H, C*H*═CH), 5.53 (td, *J* = 12, 4 Hz, 1H, C*H*═CH), 5.27 (br s, 1H, C*H*═C(CH_3)), 4.35 (m, 2H, OCH_2), 4.24 (dt, *J* = 8.5, 5.5 Hz, 1H, OC*H*), 4.08 (dt, *J* = 9, 2 Hz, 1H, OC*H*), 2.69 (dd, *J* = 16, 2.5 Hz, 1H, C*H*H), 2.58 (t, *J* = 11 Hz, 1H, C*H*H), 2.41 (d, *J* = 18 Hz, 1H, C*H*H), 2.21−2.34 (m, 3H), 2.06 (td *J* = 12, 5.5 Hz, 1H), 1.81−2.01 (m, 3H), 1.70 (s, 3H, CH═C(CH_3)), 1.26 (ddd, *J* = 13, 12, 6 Hz, 1H, C*H*H); ^{13}C NMR (125 MHz $CHCl_3$) 162.5, 148.7, 134.2,133.8, 133.3, 129.3, 125.8, 122.5, 119.8, 78.5, 74.0, 70.2, 49.7, 43.8, 33.5, 32.8, 30.5, 29.8, 21.7, 20.7; IR (film) 2926, 1731, 1545, 1344, 1282, 1163, 729, 721 cm^{-1}; MS (EI) *m*/*z* (rel intensity) 428 [100, (M)$^+$], 255 (5), 195 (50); Anal. Calcd for $C_{22}H_{24}N_2O_7$: C, 61.7 ; H, 5.7; O 6.6. Found: C, 61.9 ; H, 5.9; O 6.5. Crystal data for **47**: $C_{22}H_{24}N_2O_7$, *M* = 428.43, *T* = 130.0 K, λ = 1.54180, orthorhombic, space group $P2_12_12_1$, *a* = 5.8916(2), *b* = 9.3511(3), *c* = 37.0887(11) Å, *V* = 2043.3(1) Å^3, *Z* = 4, D_c = 1.393 mg M^{-3} μ(Cu Kα) 0.875 mm^{-1}, *F*(000) = 904, crystal size 0.6 × 0.07 × 0.05 mm^3, 6027 reflections measured, 3267 independent reflections [*R*(int) = 0.0432], the final *R* was 0.0576 [$I > 2\sigma(I)$] and wR(F^2) was 0.1320 (all data).

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.joc.5b02037.

NMR spectra, Cartesian coordinates and energies, and thermal ellipsoid plots (PDF)
X-ray crystallographic data for **23** (CIF)
X-ray crystallographic data for **43** (CIF)
X-ray crystallographic data for **47** (CIF)

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Notes

The authors declare no competing financial interest.

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