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# Highly Diastereoselective Intramolecular Asymmetric Oxidopyrylium-olefin [5 + 2] Cycloaddition and Synthesis of 8-Oxabicyclo[3.2.1]oct-3-enone Containing Ring Systems

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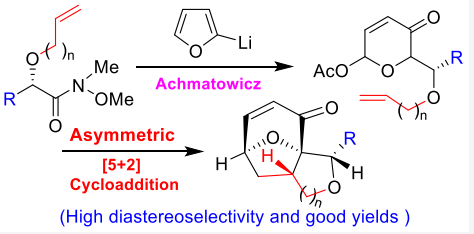
**ABSTRACT:** We have the investigated base mediated asymmetric intramolecular oxidopyrylium-alkene [5 + 2]-cycloaddition reaction which resulted in the synthesis of functionalized tricyclic ring systems containing an 8-oxabicyclo[3.2.1]octane core. Intramolecular cycloaddition constructed two new rings, three new stereogenic centers, and provided a tricyclic cycloadduct with high diastereoselectivity and isolated yield. We incorporated an $\alpha$-chiral center and an alkoxy alkene tether on the substrates and examined the effect of the size of alkyl groups and alkene tether length on diastereoselectivity. The requisite substrates for the oxidopyrylium-alkene cycloaddition reaction were synthesized in a few steps involving alkylation of optically active $\alpha$-hydroxy amide, furyllithium addition, reduction of resulting ketone, and Achmatowicz reaction followed by acylation of a lactol intermediate. We have proposed stereochemical models for the [5 + 2] cycloaddition reaction via the oxidopyrylium ylide. Interestingly, the alkoxy substituent on the stereocenter and the chain length are responsible for the degree of stereoselectivity of the cycloadduct.




## INTRODUCTION

The oxidopyrylium-alkene [5 + 2] cycloaddition reaction has emerged as an important synthetic method for the construction of complex seven-membered ring systems.[1−4] This reaction provides convenient access to a wide variety of highly functionalized seven-membered ring structures containing an oxygen bridge. Over the years, the development of new strategies and reaction protocols led this cycloaddition chemistry to become a reliable strategy for the synthesis of a diverse class of 8-oxabicyclo[3.2.1]octane heterocycles. Interestingly, these heterocyclic structural motifs are inherent to a wide variety of bioactive natural products.[4−6] Furthermore, these heterocyclic intermediates have been exploited in the design and synthesis of functionalized seven-membered ring compounds in medicinal chemistry.[7−9] Representative examples include phorbol (**1**, Figure 1), a tumor-promoting agent that works through activation of protein kinase C.[10,11] Resiniferatoxin (**2**) found in resin spurge shows extraordinary irritant properties.[12,13] Englerin B (**3**) and intricarene (**4**) possess very potent anticancer activity with medicinal potential.[14,15] Wender and co-workers elegantly utilized the intramolecular oxidopyrylium-alkene [5 + 2] cycloaddition reaction in the total synthesis of phorbol and (+)-resiniferatoxin.[16,17] Nicolaou and co-workers reported a racemic total synthesis of englerin A and englerin B utilizing the [5 + 2] cycloaddition.[18] Trauner and co-workers reported a biomimetic synthesis of (+)-intricarene using an intramolecular [5 + 2] cycloaddition.[19] A number of recent reviews highlighted

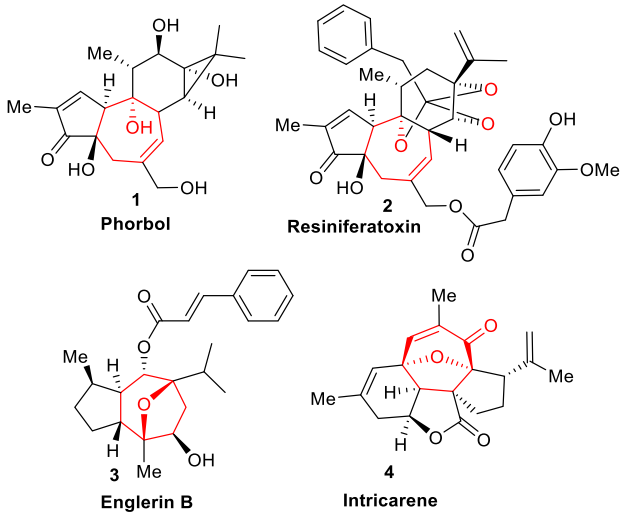



**Figure 1.** Natural products containing functionalized seven-membered and 8-oxabicyclo [3.2.1] octane core.

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important developments and applications of these cycloaddition reactions in organic synthesis.[4,6,20]

Among many developments, the generation of oxidopyrylium ylide through the elimination of the acetate or benzoate derivative of a 6-hydroxy-2*H*-pyran-3(6*H*)-one, which can be derived from an Achmatowicz reaction, greatly facilitated the use of oxidopyrylium-alkene [5 + 2] cycloaddition in synthesis. In 1980, Hendrickson and Farina first reported that acetoxypyranone can be used as a precursor to generate the oxidopyrylium ylide by elimination of the acetate group.[21,22] Later, Sammes and co-workers reported an intramolecular oxidopyrylium cycloaddition of **5** by using DBN as a base to provide cycloadduct **6** as shown in Figure 2.[23,24] The

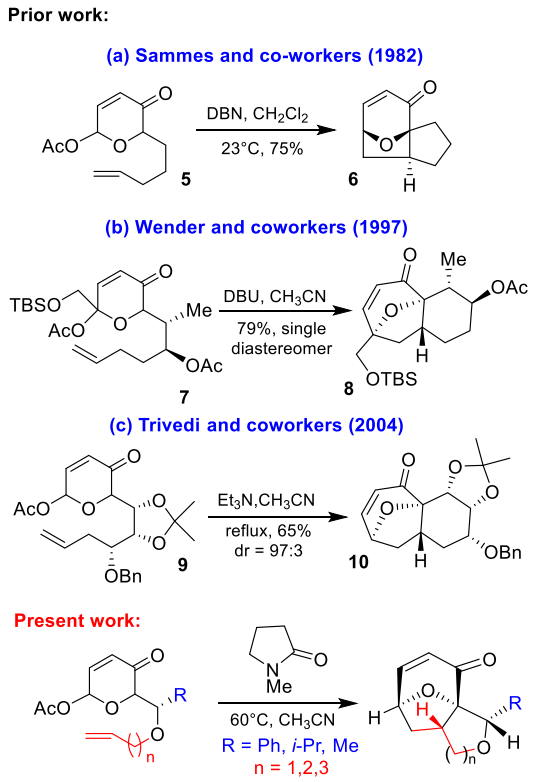


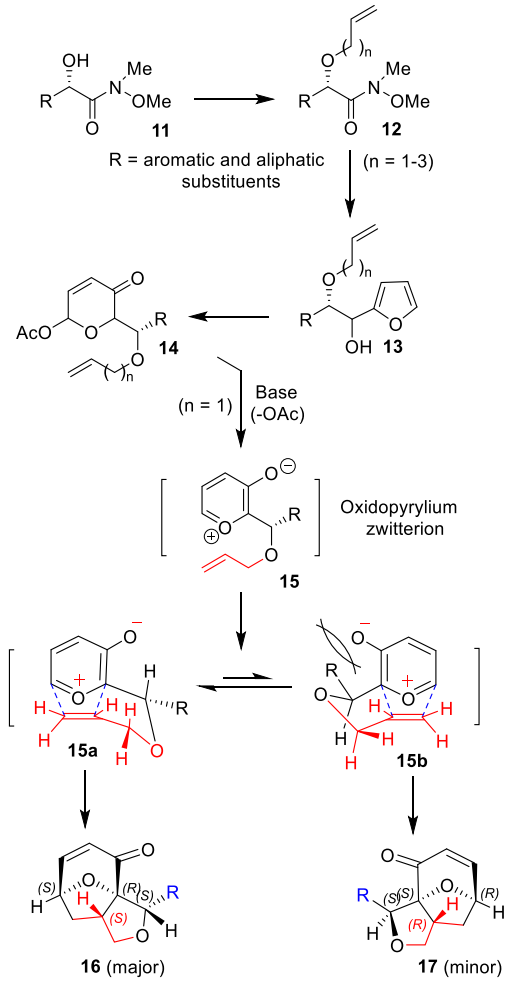

**Figure 2.** Prior works on intramolecular and asymmetric oxidopyrylium-alkene [5 + 2] cycloaddition of substrates containing an $\alpha$-chiral center.

oxidopyrylium-alkene cycloaddition can incorporate multiple stereogenic centers in the cycloadducts. A number of reports of asymmetric catalytic oxidopyrylium cycloaddition reactions using organocatalysts have appeared in the literature.[25−28] Prior to that, a number of asymmetric intramolecular oxidopyrylium-alkene cycloadditions have been reported where the oxidopyrylium ylide possessed at least an $\alpha$-chiral center. The stereochemical outcome of the cycloadduct was dictated by the substituent in the existing $\alpha$-chiral center. During the synthesis of (+)-phorbol (**1**), Wender and coworkers carried out an asymmetric cycloaddition of acetate derivative **7** to provide cycloadduct **8** as a single diastereomer in 79% yield.[16] Trivedi and co-workers reported an asymmetric cycloaddition of acetate derivative **9** to provide cycloadduct **10** with very high diastereoselectivity (dr 97%).[29] Several other oxidopyrylium-alkene cycloadditions have been reported with high selectivity in the literature.[30−34] We became interested in the oxidopyrylium-alkene cycloaddition reaction to provide access to structurally intriguing oxabicyclo[3.2.1]octane heterocyclic ring systems. We recently incorporated a variety of similar stereochemically defined cyclic ether-derived ligands and structural templates in the design of exceptionally potent HIV-1 protease inhibitors.[35−37] Herein, we report our studies on an asymmetric intramolecular cycloaddition reaction of the oxidopyrylium ylide bearing an $\alpha$-chiral center and a number of alkoxy-alkene tethers for construction of five- to seven-membered ring systems. We have examined the effect of different alkyl groups and alkene tether lengths of the alkoxy substituents on diastereoselectivity. Various cycloaddition substrates and stereochemically defined tricyclic cycloadducts were synthesized efficiently in optically active form.

## RESULTS AND DISCUSSION

Our tentative plan for the asymmetric oxidopyrylium-alkene [5 + 2] cycloadditions for substrates containing an $\alpha$-chiral center is shown in Scheme 1. We planned to synthesize various *O*-alkylated optically active Weinreb amides (**12**) from optically active $\alpha$-hydroxy amides (**11**). Reaction of furyllithium is expected to provide the corresponding ketone, which, upon reduction, would provide alcohol **13** with some degree of diastereoselectivity. The stereochemistry and diastereomeric ratio are inconsequential, as the stereocenter will be destroyed

**Scheme 1. Asymmetric Oxidopyrylium-alkene [5 + 2] Cycloaddition of Substrates Containing an $\alpha$-Alkoxy Stereocenter**



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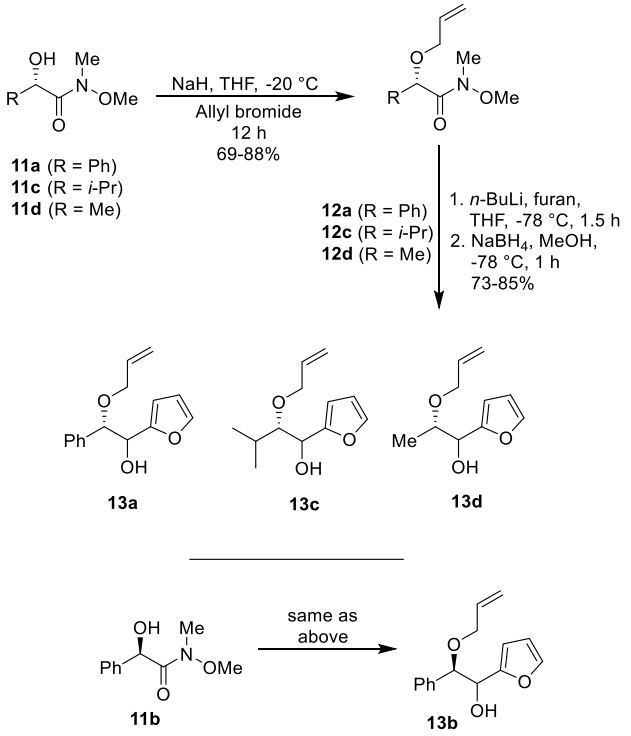
during the formation of pyrylium ylide. The alcohol mixture will be converted to acetoxy dihydropyranone derivative **14**, the oxidopyrylium precursors. Base catalyzed elimination of acetate from **14** would generate the oxidopyrylium ylide which would undergo intramolecular [5 + 2]-cycloaddition with a tethered alkene substituent to provide cycloadducts diastereoselectively. Presumably, cycloaddition would proceed through the transition states shown in **15a** and **15b**. Transition state **15a** is preferred over **15b** due to competing nonbonded interactions between the alkyl group and the alkoxy group of the pyrylium ylide in the transition-state **15b**. Tricyclic diastereomer **16** with depicted stereochemistry would be expected as the major product, and diastereomer **17** would be the minor product. In this case, the new five-membered ring will place the alkyl substituent in a pseudoequatorial orientation as shown in Scheme 1. The size of the alkyl substituents is expected to influence the degree of diastereoselectivity. Also, varying the size of the alkene tethers would enable the reaction to proceed through six- and seven-membered ring systems. The stereochemical outcome is expected to be similar, as the reaction will proceed through a similar transition state as **15a**. We planned to examine the effect of the *R*-substituents and alkoxy tether length on diastereoselectivity.

Our synthesis of variously substituted furan derivatives **13a–d** is shown in Scheme 2. Weinreb amides **11a–d** were

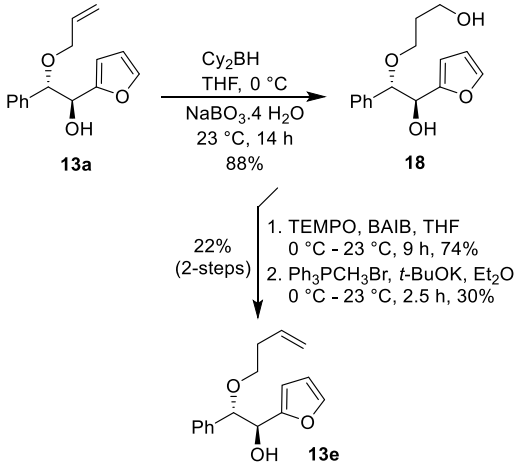
**Scheme 2. Synthesis of Furan Derivatives 13a–d**




prepared from the optically active ester as described previously.[38] Treatment of alcohols **11a–d** with NaH in THF at −20 °C for 30 min followed by reaction with allylbromide for 12−14 h provided *O*-alkylated products **12a** (87%), **12b** (87%), **12c** (88%), and **12d** (69%) in good yields.[39] Reaction of Weinreb amides **12a–d** with 2-lithiofuran, generated *in situ* with furan and *n*-BuLi at −78 °C, afforded the corresponding ketone derivatives. Reduction of the resulting ketones with sodium borohydride in MeOH at −78 °C for 1 h afforded the furfuryl alcohols **13a** (7:1, 84%), **13b** (9:1, 85%), **13c** (3:1, 83%), and **13d** (1.2:1, 73%) over two steps as a mixture of diastereomers. The diastereomers were not separable by flash column chromatography and were carried forward as a mixture for the subsequent reactions. The diastereomeric ratio and stereochemistry of the new chiral center are not important, as the chiral center will eventually be destroyed during the formation of oxidopyrylium ylide. The depicted *anti*-stereochemistry of the major isomer is based upon the chelation control model reported for the reduction of $\alpha$-alkoxy ketones.[40]

Initially, the one-carbon homologue of the *O*-allyl tether was synthesized using the furfuryl alcohol **13a** as outlined in Scheme 3. Hydroboration of alkene **13a** with dicyclohexyl

**Scheme 3. Synthesis of Furan Derivative 13e**




borane at 0 °C in THF for 2 h followed by oxidation of the resulting borane with $NaBO_3{\cdot}4H_2O$ at 23 °C for 12 h afforded the diol **18** in 88% yield.[41] Diol **18** was obtained as a mixture (1:5, *syn*/*anti*) of diastereomers, which were separated by flash column chromatography over silica gel. The major isomer was carried forward for the next reaction. Selective oxidation of the primary alcohol of diol **18** was carried out by treatment with 0.1 equiv of TEMPO and 1.2 equiv of *bis*(acetoxy)-iodobenzene (BAIB) in THF at 0° to 23 °C for 9 h to give the aldehyde in 74% yield.[42] Incorporation of the terminal olefin was achieved by Wittig reaction of the aldehyde with the methyltriphenylphosphonium ylide generated by treating 5 equiv of methyltriphenylphosphonium bromide with 4.5 equiv of *t*-BuOK to provide alkene derivative **13e** in 30% yield.[43] Overall, this route was less than satisfactory and resulted in a poor yield of the desired *O*-homoallyl furfuryl alcohol **13e**. Therefore, we examined an alternative and more convergent approach to synthesize *O*-homoallyl furfuryl alcohols via direct alkylation of the $\alpha$-hydroxy esters.

Direct O-alkylation of Weinreb amides with homoallyl bromides or iodides under various O-alkylation conditions did not provide satisfactory yield of the alkylated products. Therefore, we utilized a modified procedure using alkenyl triflates.[44] As shown in Scheme 4, reaction of $\alpha$-hydroxy esters **19a–b** with *t*-BuOK and 3-butenyl triflate in THF at −20 °C for 30 min provided *O*-alkylated products **20a** and **20b** in 47% and 54% yields, respectively. Similarly, O-alkylation of **19b** with 4-pentenyl triflate afforded alkylated product **20c** in 84%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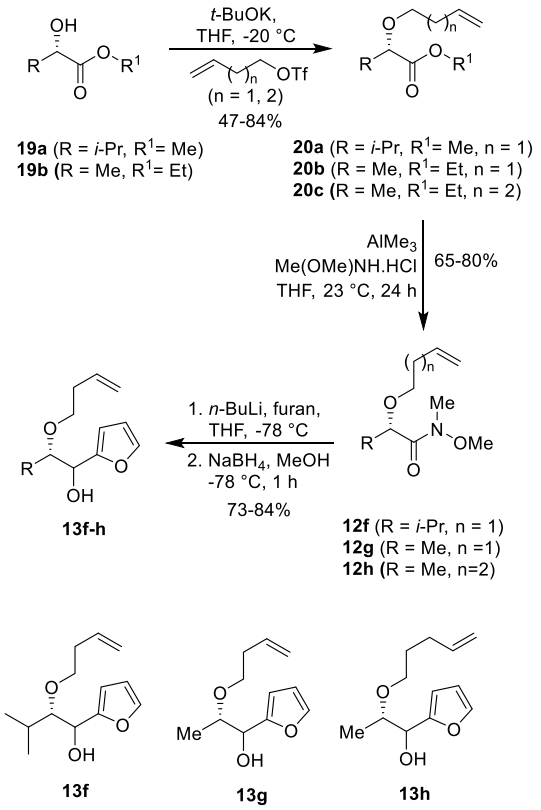
**Scheme 4. Synthesis of Furan Derivatives 13f–h**

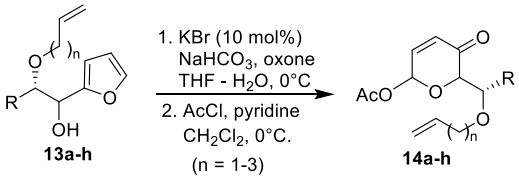


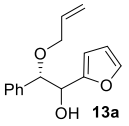
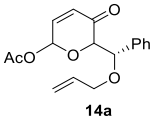
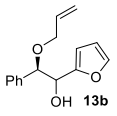
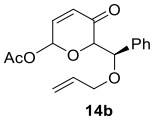
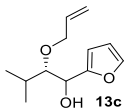
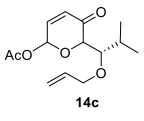
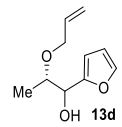
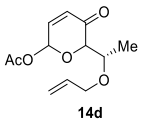
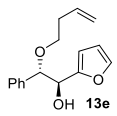
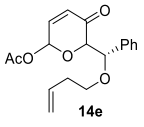
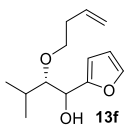
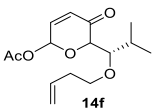
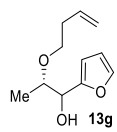
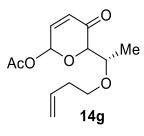
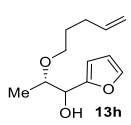
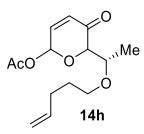

yield. Various alkylated ester derivatives **20a–c** were converted to the corresponding Weinreb amide derivatives **12f–h** by treatment with 4.0 equiv of $AlMe_3$ and 4.0 equiv of methoxymethylamine hydrochloride in THF at 23 °C for 24 h in good yields (**12f**, 75%; **12g**, 65%; **12h**, 80%). Reaction of these Weinreb amides **12f–h** with 2-lithiofuran as described in Scheme 4 resulted in the corresponding ketones, which upon reduction with $NaBH_4$ in MeOH at −78 °C for 1 h as described before, furnished alcohols **13f** (3:1 mixture, 84%), **13g** (1:1 mixture, 80%), and **13h** (1.8:1 mixture, 73%) in good yields over two steps. These diastereomeric alcohols were not separated, and the mixtures were carried forward for the subsequent reactions.

Various furfuryl alcohols **13a–h** were then converted to acetoxy-pyranone derivatives **14a–h**, and the results are shown in Table 1. Achmatowicz rearrangement of the furfuryl alcohols **13a–h** were carried out by treatment of alcohols with a catalytic amount of KBr (0.1 equiv), $NaHCO_3$ (0.5 equiv), and oxone (1.5 equiv) at 0 °C in a mixture (4:1) of THF and water to provide the corresponding lactol.[45,46] Reactions of the resulting lactols with acetyl chloride in the presence of pyridine in $CH_2Cl_2$ at 0 °C for 30 min afforded acetoxypyranone derivatives **14a–h** in good yields after silica gel chromatography (55–92%).

Following the synthesis of acetoxypyranone derivatives, we carried out the cycloaddition reaction with a mixture of diastereomers of (*S*)-phenyl acetoxypyranone **14a** under various reaction conditions (Table 2). Initially, we attempted the [5 + 2]-cycloaddition reaction without any base under thermal conditions in acetonitrile at 80 °C and in toluene at 110 °C, respectively. However, no cycloadduct was formed when $CH_3CN$ was used as a solvent (entry 1) and a complex mixture of unidentified products was obtained when

**Table 1. Synthesis of Cycloaddition Precursors, Acetoxypyranone**[a,b]




| Entry | Substrate | Product | Yield (%) |
|---|---|---|---|
| 1 |  |  | 92 |
| 2 |  |  | 55 |
| 3 |  |  | 78 |
| 4 |  |  | 60 |
| 5 |  |  | 60 |
| 6 |  |  | 65 |
| 7 |  |  | 75 |
| 8 |  |  | 64 |

[a]Reactions were carried out on 0.2 to 3 mmol scale. [b]Yields are calculated for two steps.

acetoxypyranone **14a** was heated in toluene (entry 2). We then screened different amine bases with varying equivalents in



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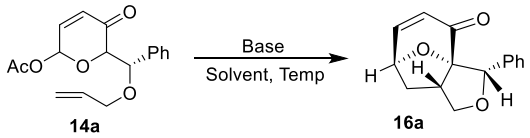
**Table 2. Initial Optimization of [5 + 2]-Cycloaddition Reaction Conditions of Acetoxypyranone 14a**




14a 16a

| Entry | Base | Equivalents | Solvent | Temp (°C) | Time (h) | Diastereomeric ratio[a] | Yield (%) **16a** |
|---|---|---|---|---|---|---|---|
| **1** | No base | – | $CH_3CN$ | 80 | 22 | – | 0 |
| **2** | No base | – | PhMe | 110 | 22 | – | complex mix |
| **3** | DABCO[b] | 2.0 | $CH_3CN$ | 60 | 12 | 9:1 | 56 |
| **4** | DABCO[b] | 4.0 | $CH_3CN$ | 60 | 12 | 9:1 | 69 |
| **5** | NMP[c] | 4.0 | $CH_3CN$ | 60 | 12 | 10:1 | 89 |
| **6** | DBU[d] | 4.0 | $CH_3CN$ | 60 | 11 | – | complex mix |
| **7** | Pyridine[e] | 4.0 | $CH_3CN$ | 60 | 12 | – | 0 |
| **8** | DBN[f] | 4.0 | $CH_3CN$ | 60 | 12 | – | 0 |
| **9** | $SiO_2$ | – | $CH_3CN$ | 80 | 24 | 10:1 | 44 |

[a]Diastereomeric ratios were determined via $^1$H NMR. [b]DABCO = 1,4-Diazabicyclo-[2.2.2]octane. [c]NMP = *N*-Methylpyrrolidine. [d]DBU = 1,8-Diazabicyclo[5.4.0]undec-7-ene, [e]Recovered **14a** (78%). [f]DBN = 1,5-Diazabicyclo[4.3.0]non-5-ene.

$CH_3CN$ at 60 °C under an argon atmosphere. Treatment of acetoxypyranone **14a** with 2.0 equiv of 1,4-diazabicyclo-[2.2.2]octane (DABCO) in acetonitrile at 60 °C for 12 h afforded the cycloadduct **16a** (CCDC 2025567) as the major diastereomer in 56% yield (entry 3). Interestingly, increasing the equivalents of base to 4.0 improved the yield to 69%, but the diastereomeric ratio remained the same (entry 4). *N*-Methylpyrrolidine (NMP) afforded the best yield and diastereomeric ratio of the cycloadduct **16a** (entry 5). DBN, DBU, and pyridine mediated cycloaddition reactions were inefficient (entries 6–8). To our surprise, heating the slurry of acetoxypyranone **14a** in silica gel (8x wt) provided the cycloadduct in moderate yield and excellent diastereoselectivity (entry 9).

We then conducted cycloadditions of various other substrates using 4 equiv of NMP as shown in entry 5, Table 2, and the results are shown in Table 3. We first investigated *O*-allyl tethered alkenes on the acetoxypyranone derivatives to examine the scope of chirality transfer from the substrates. Cycloaddition of acetoxy-pyranone **14a** provided cycloadduct **16a** in 89% yield. The diastereofacial selectivity was very high, and the diastereomeric ratio (10:1) was determined using $^1$H NMR analysis. Separation of the diastereomers via column chromatography proved to be difficult due to the similar $R_f$ values of the two diastereomers in many different solvent systems.

We have also prepared (*R*)-phenyl acetoxypyranone **14b** from (*R*)-mandelic acid and subjected it to [5 + 2] cycloaddition under similar conditions. This resulted in cycloadduct **16b** in 74% yield and showed a similar diastereomeric ratio (10:1). The relative stereochemistry of the major diastereomer of **16b** was initially established by $^1$H NMR NOESY and COSY experiments. Since the absolute stereochemistry of proton $H_c$ comes from the chiral starting material, (*R*)-mandelic acid, we can assign the relative stereochemistry of protons $H_f$ and $H_i$ from $H_c$. A COSY experiment was done first to assign the protons coupled to $H_f$ and $H_i$ respectively. The results of the observed COSY and NOESY correlation are summarized in Figure 3. The strong NOESY correlations between $H_c$–$H_e$, $H_e$–$H_f$, and $H_f$–$H_h$ provided evidence for the assigned stereochemistry of $H_f$. Similarly, the observed NOESY correlations between $H_d$–$H_g$ and $H_g$–$H_i$ supports the assigned stereochemistry of $H_i$. The cycloadduct **16b** was later crystallized in hexanes/EtOAc (4/1) solution, and the absolute stereochemistry was unambiguously determined by X-ray crystallography (CCDC 2025568).[47] The 2-D NMR correlations are consistent with the X-ray crystal structure of **16b**. More detailed NMR and X-ray studies including the ORTEP diagram of **16b** and other structures are shown in the Supporting Information. This result shows that the stereochemical outcome of [5 + 2] cycloaddition reaction can be influenced by the existing chirality of the substrate.

We investigated the effect of the alkyl groups on the stereoselectivity. The cycloaddition reaction proceeded well with acetoxypyranones **14c** and **14d** containing the isopropyl and methyl substituents, respectively. The diastereoselectivity and yield of the cycloadduct were reduced as compared to the phenyl derivative (entries 3 and 4). Surprisingly, the presence of a methyl group on the alkene tether gave a slightly better diastereoselectivity compared to the bulkier isopropyl group. To confirm the stereochemistry of the minor isomer, we separated both isomers **16c** (major) and **16c** (minor) by HPLC using a chiral column (CHIRALPAK-IC). As shown in Scheme 5, Luche reduction of **16c** (minor) using $NaBH_4$ and $CeCl_3$ at 0 °C for 1 h furnished allylic alcohol **21** as a single isomer in 75% yield (Scheme 5).

We also carried out stereochemical assignment of the alcohol **21** by 2D-NMR experiments (Figure 4). The complete assignment of all protons and carbons was achieved by proton–proton (NOESY and COSY) and proton–carbon (HMQC) correlation experiments (please see Supporting Information). Our structural assignment was not conclusive due to the lack of correlation between protons $H_c$–$H_d$. However, the X-ray crystallography of compound **21** showed that protons $H_c$ and $H_d$ are not in proximity and supported the correlation between proton $H_c$ and $H_e$. The absolute stereochemistry of alcohol **21** was assigned by X-ray crystallography (CCDC 2064460; please see Supporting Information).[47]

We further investigated the stereochemical effect of increasing the tether length to form six- and seven-membered rings containing alkyl substituents. The reaction of *O*-homoallyl acetoxypyranone **14e** with a phenyl substituent in the presence of 4 equiv of NMP for 4 h resulted in cycloadduct **16e** in 60% yield and diastereoselectivity was excellent (>19:1 by $^1$H NMR analysis of the crude reaction products).


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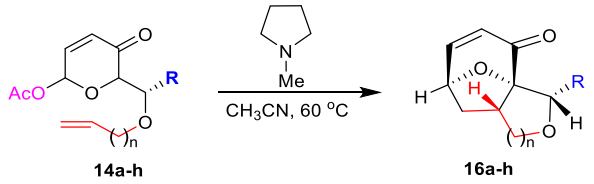
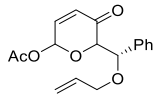
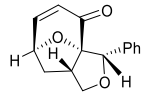
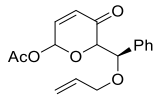
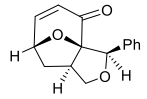
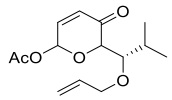
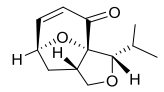
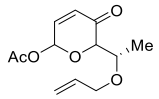
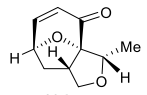
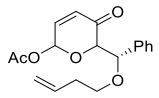
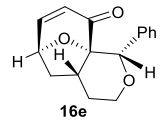
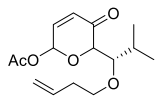
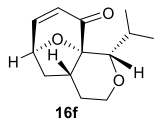
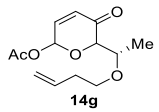
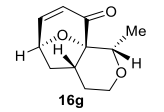
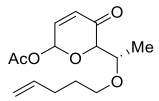
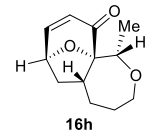
Table 3. Intramolecular [5 + 2] Cycloaddition with Oxidopyrylium Ion and the Terminal Alkene




| Entry | Acetoxypyranone | Cycloadduct[a] | Time (h) | %Yield | dr[b] |
|---|---|---|---|---|---|
| 1 |  14a |  16a | 12 h | 89% | 10:1 |
| 2 |  14b |  16b | 12 h | 74% | 10:1 |
| 3 |  14c |  16c | 12 h | 88% | 2:1 |
| 4 |  14d |  16d | 12 h | 45% | 4:1 |
| 5 |  14e |  16e | 4 h | 60% | >19:1 |
| 6 |  14f |  16f | 24 h | 84% | >19:1 |
| 7 |  14g |  16g | 18 h | 79% | >19:1 |
| 8 |  14h |  16h | 3 h | 59%[c] | >19:1 |

[a]Reactions were carried out using *N*-methylpyrrolidine, NMP (4.0 equiv), in $CH_3CN$ (0.02 M) at 60 °C. [b]The diastereomeric ratios were determined by $^1H$ NMR. [c]Reaction was carried out at 150 °C with 1.5 equiv of *N*-methyl pyrrolidine as base.

Cycloaddition reaction of homoallyl derivative **14f** with an isopropyl substituent proceeded well to provide cycloadduct **16f** in 84% yield and excellent diastereoselectivity (>19:1). Similarly, homoallyl derivative **14g** with a methyl substituent afforded cycloadduct **16g** in 79% yield with similar diastereoselectivity as the other homoallyl derivatives (entries 5−7).

We then investigated the cycloaddition of acetoxypyranone **14h** with a five carbon alkenyloxy tether containing a methyl substituent. The results are shown in Table 4. Initial cycloaddition attempt with 1.5 equiv of NMP in $CH_3CN$ at 23 °C for 24 h, resulted in no cycloaddition product (entry 1). We then carried out the cycloaddition in the presence of 4 equiv of NMP in $CH_3CN$ at 60 °C for 4 h (entry 2). These conditions resulted in a complex mixture of products (entry 2).



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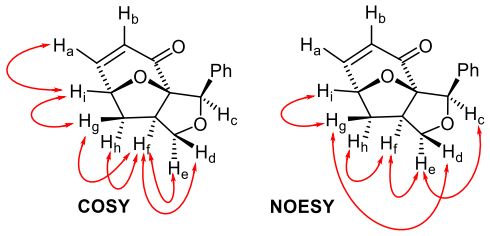
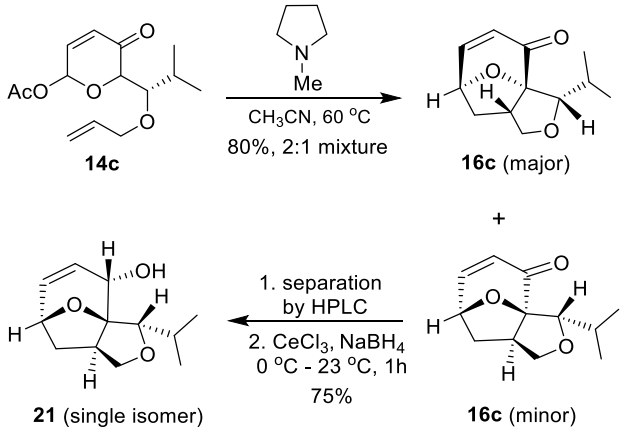



**Figure 3.** Representative $^1$H NMR COSY and NOESY correlations of compound **16b**.

**Scheme 5. Synthesis of Allylic Alcohol 21**



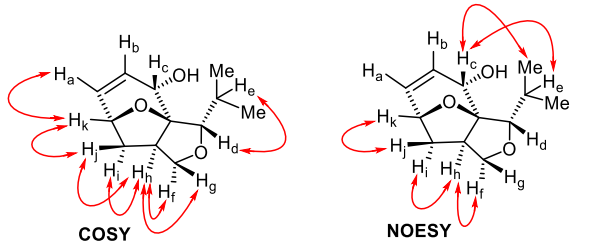
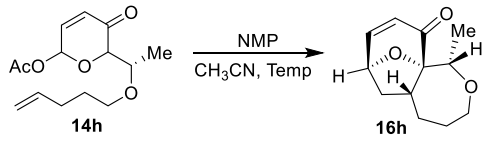




**Figure 4.** Representative $^1$H NMR COSY and NOESY correlations of alcohol **21**.

**Table 4. Temperature Screening for [5 + 2]-Cycloaddition Reaction of Acetoxypyranone 14h**




| Entry | Base (equiv) | Temp (°C) | Time (h) | Yield (%)[a,b] **16h** |
|---|---|---|---|---|
| 1 | NMP (1.5) | 23 | 24 | No product |
| 2 | NMP (4.0) | 60 | 4 | complex |
| 3 | NMP (4.0) | 80 | 6 | 26 |
| 4 | NMP (1.5) | 120 | 4 | 49 |
| 5 | NMP (2.0) | 120 | 4 | 45 |
| 6 | NMP (2.0) | 150 | 4 | 47 |
| 7 | TMP (1.5) | 150 | 19 | 58 |
| 8 | NMP (1.5) | 150 | 3 | 59 |

[a]Product **16h** shows excellent diastereoselectivity (>19:1 by $^1$H NMR analysis). Yields refer to isolated product after chromatography. [b]$CH_3CN$ was used as solvent. NMP, *N*-Methylpyrrolidine; TMP, 2,2,6,6-tetramethylpiperidine.

The reaction temperature was increased to 80 °C, and after 6 h, cycloadduct **16h** was obtained in 26% yield and 10% of the starting material **14h** was recovered (entry 3). The $^1$H NMR analysis revealed that **16h** was formed in a highly diastereoselective manner (>19:1 by $^1$H NMR analysis). Intramolecular cycloaddition reactions that form seven-membered rings are in general less reactive due to unfavorable entropy. To overcome the entropic factors, we decided to carry out the cycloaddition reaction at higher temperatures (entries 4−8). Reaction of **14h** at 120 °C in the presence of 1.5 equiv of NMP in $CH_3CN$ in a sealed tube provided the cycloadduct **16h** in 49% yield and excellent diastereoselectivity (>19:1 by $^1$H NMR) (entry 4). The corresponding reaction in the presence of 2.0 equiv of NMP resulted in a slight decrease in the yield of the cycloadduct (entry 5). A further increase of reaction temperature to 150 °C in a sealed tube for 4 h provided cycloadduct **16h** in 47% yield (entry 6). The cycloaddition proceeded a bit more efficiently in the presence of 1.5 equiv of NMP at 150 °C for 3 h which resulted in complete consumption of starting material and yielded **16h** in 59% yield (entry 8). We also examined the cycloaddition reaction of **14h** with 1.5 equiv of 2,2,6,6-tetramethylpiperidine in $CH_3CN$ at 150 °C (entry 7), as reported by Mei and co-workers.[48] This condition resulted in the formation of cycloadduct **16h** in 58% isolated yield.

To explain the stereochemical outcome of the [5 + 2]-cycloaddition of chiral substrate containing an alkoxy olefin tether, we proposed stereochemical models shown in Figure 5.

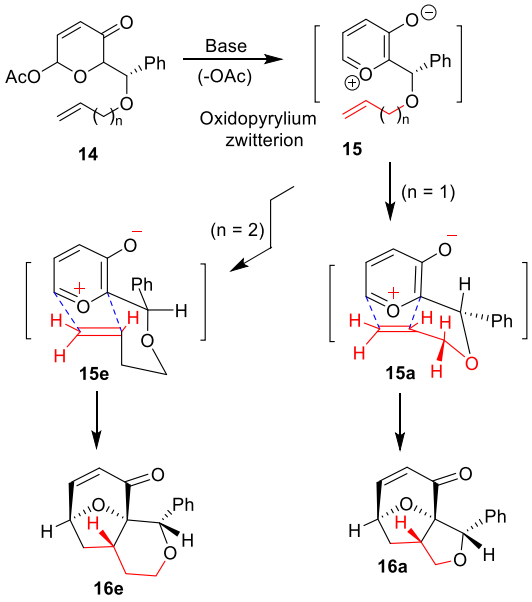



**Figure 5.** Representations of transition states of five-membered and six-membered fused cycloadducts.

Treatment of acetoxyhydropyranones **14** with base will lead to the formation of the aromatic oxidopyrylium ion **15** containing an *α*-chiral center bearing an alkyl substituent and an alkoxy tether with a terminal alkene. The *O*-allyl chain with the phenyl group will adopt a transition-state **15a** where the bulky phenyl group would occupy a pseudoequatorial position in the envelope conformation of the developing five-membered ring.[49,50] The alkyl groups on the tether act as a stereochemical handle to orient the pyranone ring at the bottom so that the terminal alkene can approach from the top face. As the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bulkiness of the alkyl substituent (R-group) on the side chain decreases, the preference of **15a** over the alternative diastereomeric transition state would also decrease and that would lead to lower diastereoselectivity for the cycloadducts. For [5 + 2] cycloaddition with a homoallyl side chain, the stereochemical outcome can be rationalized using a six-membered chair transition-state **15e** similar to that suggested by Wender and co-workers.[16] The phenyl group will be in the equatorial position and will block the bottom face, so that the approach of the alkene will occur from the top face as shown in transition state **15e**. The formation of a six-membered transition state **15e** is dominant in controlling the stereochemistry and therefore gives rise to formation of cycloadducts with high diastereoselectivity. The observed high diastereoselectivity for cycloadduct **16h** with a seven-membered ring may be due to the formation of a similar dominant pseudo chairlike transition state as **15e** for the six-membered ring as shown.

## CONCLUSION

In summary, we investigated [5 + 2] intramolecular oxidopyrylium-alkene cycloaddition reactions containing an $\alpha$-chiral center on the alkene tether. The presence of the $\alpha$-chiral center directed the formation of three new chiral centers in the 8-oxabicyclo[3.2.1]octane core containing five- to seven-membered fused oxacyclic rings with high diastereoselectivity. These cycloadditions proceeded with good to excellent yields. The degree of diastereoselectivity for the allyloxy tether is dependent upon the size of the alkyl group for the formation of the 6−5−5 tricyclic ring systems. The phenyl substituent showed very good diastereoselectivity; however, both methyl and isopropyl groups showed lower diastereoselectivity. For cycloaddition substrates containing a homoallyloxy tether, the reaction proceeded with very good yields and excellent diastereoselectivity for methyl, isopropyl, and phenyl substituents. The stereochemical outcome of the cycloaddition reaction was rationalized using stereochemical models. The product stereochemistry was assigned by extensive $^1$H NMR and X-ray crystallographic studies. For allyloxy derivatives, the cycloaddition reaction presumably proceeded through an envelope conformation with substituents oriented in a pseudoequatorial position. For the cycloaddition with homoallyloxy tethers, the reaction presumably proceeded with a chairlike transition state with the substituent on the $\alpha$-chiral center oriented equatorially, avoiding competing nonbonded interactions. Various cycloaddition substrates were synthesized efficiently from optically active starting materials. Further utilization of this asymmetric cycloaddition reaction in the synthesis of bioactive compounds in medicinal chemistry is being explored.

## EXPERIMENTAL SECTION

All chemicals were purchased from commercial suppliers and were used as received unless otherwise stated. Anhydrous solvents were obtained as follows: anhydrous tetrahydrofuran and diethyl ether were distilled from sodium metal under argon, anhydrous dichloromethane was dried via distillation from calcium hydride, DMF was dried overnight over barium oxide followed by vacuum distillation, and anhydrous methanol was distilled from activated magnesium under argon. All other solvents were reagent grade. All moisture-sensitive reactions were carried out under an argon atmosphere in either flame or oven-dried (120 °C) glassware. Stainless steel syringes and cannula were used to transfer air- or moisture-sensitive liquids. TLC analysis was conducted using glass-backed thin-layer silica gel chromatography plates (60 Å, 250 $\mu$m thickness, F254 indicator). Column chromatography was performed using silica gel, 230−400 mesh, 60 Å pore diameter. Isolated yields and yields based on the recovered starting material (brsm) were determined following purification. Proton Nuclear Magnetic Resonance NMR ($^1$H NMR) spectra and carbon nuclear magnetic resonance ($^{13}$C NMR) spectra were recorded on Bruker AV-III-400HD and Bruker AVIII-800 spectrometers. Chemical shifts for protons are reported in parts per million and are references to the NMR solvent peak ($CDCl_3$: $\delta$ 7.26). Chemical shifts for carbons are reported in parts per million and are referenced to the carbon resonances of the NMR solvent ($CDCl_3$: $\delta$77.16). Data are reported as follows: s = singlet, d = doublet, t = triplet, q = quartet, quint = quintet, sep = septet, m = multiplet, dd = doublet of doublets, ddd = doublet of doublet of doublets, dddd = doublet of doublet of doublets of doublets, td = triplet of doublets, dq = doublet of quartets, qd = quartet of doublets, dt = doublet of triplets, brs = broad singlet. All coupling constants are measured in hertz (Hz). Optical rotations were measured on a Rudolph'sAUTOPOL-III automatic digital polarimeter with a sodium lamp and are reported as follows: $[\alpha]\lambda$ $T$ °C ($c$ = g/100 mL, solvent). High-resolution mass spectrometry (HRMS) spectra were recorded under positive electron spray ionization (ESI+) and positive atmospheric pressure chemical ionization (APCI+) conditions using an LTQ Orbitrap Mass Spectrometer at the Purdue University Department of Chemistry Mass Spectrometry Center and an Agilent 6550 Q-TOF LC/MS instrument at the Purdue University Analytical Mass Spectrometry Facility.

**General Procedure A: Synthesis of Weinreb Amides 11a−d.** To a solution of the indicated $\alpha$-hydroxy ester (1.0 equiv) and *N*-methyl-*O*-methyl hydroxylamine hydrochloride (1.5 equiv) in THF (0.3 M) at −20 °C was added isopropylmagnesium chloride (2.0 M solution in THF, 4.0 equiv). The reaction mixture was warmed to 0 °C and stirred for 2−5 h at the same temperature. A solution of satd $NH_4Cl$ was added, and the layers were separated. The aqueous phase was extracted with $CH_2Cl_2$ (3×), and the combined organic extracts were dried over $Na_2SO_4$ and concentrated in vacuo. Purification by silica gel column chromatography afforded the desired Weinreb amide.

*(S)-2-Hydroxy-N-methoxy-N-methyl-2-phenylacetamide (**11a**).* The reaction was conducted according to the general procedure A with methyl (*S*)-(+)-mandelate (4.86 g, 29.30 mmol), *N*-methyl-*O*-methyl hydroxylamine hydrochloride (4.30 g, 44.0 mmol), and isopropylmagnesium chloride (59.0 mL, 2.0 M solution in THF, 117.20 mmol) in THF (100 mL) for 2 h. Purification by silica gel column chromatography (10% EtOAc/hexanes) afforded the Weinreb amide **11a** (4.96 g, 87% yield) as a colorless oil. Experimental data are consistent with the data reported in the literature.[51]

*(R)-2-Hydroxy-N-methoxy-N-methyl-2-phenylacetamide (**11b**).* The reaction was conducted according to the general procedure A with methyl (*R*)-(−)-mandelate (5.30 g, 31.90 mmol), *N*-methyl-*O*-methyl hydroxylamine hydrochloride (4.60 g, 47.85 mmol), and isopropylmagnesium chloride (63.80 mL, 2.0 M solution in THF, 127.60 mmol) in THF (100 mL) for 2 h. Purification by silica gel column chromatography (10% EtOAc/hexanes) afforded the Weinreb amide **11b** (5.60 g, 90% yield) as a colorless oil. Experimental data are consistent with the data reported in the literature.[52]

*(S)-2-Hydroxy-N-methoxy-3-methyl-N-methylbutanamide (**11c**).* The reaction was conducted according to the general procedure A with (*S*)-methyl 2-hydroxy-3-methylbutanoate[53] (1.80 g, 13.64 mmol), *N*-methyl-*O*-methyl hydroxylamine hydrochloride (2.0 g, 20.46 mmol), and isopropylmagnesium chloride (27.30 mL, 2.0 M solution in THF, 54.56 mmol) in THF (50 mL) for 4 h. Purification by silica gel column chromatography (20% EtOAc/hexanes) afforded the Weinreb amide **11c** (1.47 g, 67% yield) as a yellow oil. Experimental data are consistent with the data reported in the literature.[39]

*(S)-2-Hydroxy-N-methoxy-N-methylpropanamide (**11d**).* The reaction was conducted according to the general procedure A with (*S*)-(−)-ethyl lactate (1.0 g, 8.50 mmol), *N*-methyl-*O*-methyl hydroxylamine hydrochloride (1.24 g, 12.75 mmol), and isopropylmagnesium chloride (17.0 mL, 2.0 M solution in THF, 34 mmol) in


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THF (28 mL) for 5 h. Purification by silica gel column chromatography (30% EtOAc/hexanes) afforded the Weinreb amide **11d** (1.0 g, 89% yield) as a colorless oil. Experimental data are consistent with the data reported in the literature.[54]

**General Procedure B: *O*-Allylation of α-Hydroxy Amides 12a−d.** To a suspension of sodium hydride (60% dispersion in oil, 1.5 equiv) in dry DMF (0.6 M) at −20 °C was added a 0.3 M solution of the Weinreb amide (1.0 equiv) in dry DMF dropwise via cannula. The reaction mixture was stirred for an additional 30 min, followed by addition of allyl bromide (1.5 equiv) in one portion. The resulting yellow suspension was then warmed to −10 °C and stirred for 12−14 h. The reaction was quenched by the addition of satd $NH_4Cl$ and allowed to warm to 23 °C. The thick white suspension was then diluted with EtOAc and washed with cold $H_2O$ (5×). The combined aqueous layers were back extracted with EtOAc (2×). The combined organic layers were washed with brine, dried over $Na_2SO_4$, and concentrated under reduced pressure. Purification by silica gel column chromatography afforded the *O*-allylated product.

*(S)-2-(Allyloxy)-N-methoxy-N-methyl-2-phenylacetamide (**12a**).* The reaction was conducted according to the general procedure B with NaH (60% dispersion in oil, 308 mg, 7.60 mmol), Weinreb amide **11a** (1.0 g, 5.10 mmol), and allyl bromide (660 μL, 7.70 mmol). Purification by silica gel column chromatography (20% EtOAc/hexanes) afforded compound **12a** (1.04 g, 87% yield) as a white amorphous solid. $[\alpha]_D^{24}$ +82.3 (*c* 1.5, $CHCl_3$). $^1H$ NMR (400 MHz, $CDCl_3$) δ 7.44−7.37 (m, 2H), 7.33−7.23 (m, 3H), 5.91 (ddt, *J* = 17.3, 10.4, 5.8 Hz, 1H), 5.29−5.14 (m, 3H), 4.08−3.95 (m, 2H), 3.39 (s, 3H), 3.10 (s, 3H). $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$) δ 171.0, 136.6, 134.2, 128.4, 128.4, 128.0, 117.7, 77.6, 70.1, 60.9, 32.3. HRMS (ESI/Q-TOF) *m*/*z*: $[M + H]^+$ calcd for $C_{13}H_{18}O_3N$ 236.1281; found 236.1283.

*(R)-2-(Allyloxy)-N-methoxy-N-methyl-2-phenylacetamide (**12b**).* The reaction was conducted according to the general procedure B with NaH (60% dispersion in oil, 1.60 g, 40.77 mmol), Weinreb amide **11b** (5.30 g, 28.18 mmol), and allyl bromide (3.50 mL, 40.77 mmol). Purification by silica gel column chromatography (20% EtOAc/hexanes) afforded compound **12b** (5.60 g, 87% yield) as a white amorphous solid. $[\alpha]_D^{24}$ −83.5 (*c* 1.3, $CHCl_3$). $^1H$ NMR (400 MHz, $CDCl_3$) δ 7.42−7.36 (m, 2H), 7.31−7.21 (m, 3H), 5.89 (ddt, *J* = 17.2, 10.3, 5.8 Hz, 1H), 5.28−5.11 (m, 3H), 4.07−3.92 (m, 2H), 3.37 (s, 3H), 3.08 (s, 3H). $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$) δ 171.0, 136.6, 134.2, 128.4, 128.3, 128.0, 117.7, 77.5, 70.1, 60.9, 32.2. HRMS (ESI/Q-TOF) *m*/*z*: $[M + H]^+$ calcd for $C_{13}H_{18}O_3N$ 236.1282; found 236.1281.

*(S)-2-(Allyloxy)-N-methoxy-N,3-dimethylbutanamide (**12c**).* The reaction was conducted according to the general procedure B with NaH (60% dispersion in oil, 893 mg, 22.32 mmol), Weinreb amide **11c** (2.40 g, 14.88 mmol), and allyl bromide (2.0 mL, 22.32 mmol). Purification by silica gel column chromatography (20% EtOAc/hexanes) afforded compound **12c** (2.62 g, 88% yield) as a colorless oil. $[\alpha]_D^{24}$ −30.5 (*c* 1.0, $CHCl_3$). $^1H$ NMR (400 MHz, $CDCl_3$) δ 5.94−5.75 (m, 1H), 5.20 (dq, *J* = 17.3, 1.7 Hz, 1H), 5.10 (dq, *J* = 10.4, 1.5 Hz, 1H), 4.04 (ddt, *J* = 12.8, 5.2, 1.6 Hz, 1H), 4.00−3.87 (m, 1H), 3.79 (ddt, *J* = 12.8, 6.1, 1.4 Hz, 1H), 3.62 (s, 3H), 3.15 (s, 3H), 2.08−1.89 (m, 1H), 0.93 (d, *J* = 6.8 Hz, 3H), 0.86 (d, *J* = 6.9 Hz, 3H). $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$) δ 173.2, 134.6, 116.9, 80.4, 70.8, 61.1, 32.1, 30.8, 18.8, 18.0. HRMS (ESI/Q-TOF) *m*/*z*: $[M + H]^+$ calcd for $C_{10}H_{20}O_3N$ 202.1438; found 202.1438.

*(S)-2-(Allyloxy)-N-methoxy-N-methylpropanamide (**12d**).* The reaction was conducted according to the general procedure B with NaH (60% dispersion in oil, 680 mg, 16.90 mmol), Weinreb amide **11d** (1.50 g, 11.27 mmol), and allyl bromide (1.50 mL, 16.90 mmol). Purification by silica gel column chromatography (20% EtOAc/hexanes) afforded compound **12d** (1.33g, 69% yield) as a colorless oil. $[\alpha]_D^{24}$ −69.8 (*c* 0.8, $CHCl_3$). $^1H$ NMR (400 MHz, $CDCl_3$) δ 6.02−5.83 (m, 1H), 5.26 (ddq, *J* = 17.2, 4.8, 1.6 Hz, 1H), 5.17 (ddq, *J* = 10.3, 4.2, 1.5 Hz, 1H), 4.38 (q, *J* = 6.4 Hz, 1H), 4.17−4.03 (m, 1H), 3.95−3.83 (m, 1H), 3.68 (d, *J* = 5.3 Hz, 3H), 3.19 (d, *J* = 5.2 Hz, 3H), 1.45−1.30 (m, 3H). $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$) δ 173.7, 134.5, 117.4, 70.4, 61.3, 32.5, 17.8. HRMS (ESI/Q-TOF) *m*/*z*: $[M + H]^+$ calcd for $C_8H_{16}O_3N$ 174.1125; found 174.1126.

**General Procedure C: *O*-Alkylation of α-Hydroxy Esters 20a−c.** A flame-dried round-bottom flask was charged with 18-crown-6 (0.1 equiv) and potassium *tert*-butoxide (1.0 M solution in THF, 1.1 equiv) in freshly distilled THF (0.3 M) at −20 °C. To this mixture, a solution of the α-hydroxy ester (1.0 equiv) in freshly distilled THF (1.0 M) was added dropwise. The reaction mixture was stirred for 10 min followed by addition of but-3-en-1-yl trifluoromethanesulfonate or pent-4-en-1-yl trifluoromethanesulfonate (1.3−1.5 equiv) in one portion at −20 °C. After 20 min, the reaction was quenched with a satd solution of $NH_4Cl$ and extracted with EtOAc (3×). The combined organic layers were dried over $Na_2SO_4$, filtered, and concentrated under reduced pressure. Purification of crude by silica gel column chromatography afforded the *O*-alkylated product.

*Methyl (S)-2-(But-3-en-1-yloxy)-3-methylbutanoate (**20a**).* The reaction was conducted according to the general procedure C with (*S*)-methyl 2-hydroxy-3-methylbutanoate[53] **19a** (2.0 g, 15.15 mmol), 18-crown-6 (400 mg, 1.52 mmol), potassium *tert*-butoxide (1.0 M solution in THF, 23.0 mL, 22.70 mmol, 1.5 equiv), and but-3-en-1-yl trifluoromethanesulfonate[55] (4.60 g, 22.70 mmol). Purification by silica gel column chromatography (5% EtOAc/hexanes) afforded compound **20a** in 47% isolated yield (1.32 g, 61% brsm) as a colorless oil. $[\alpha]_D^{24}$ −45.3 (*c* 0.5, $CHCl_3$). $^1H$ NMR (400 MHz, $CDCl_3$) δ 5.81 (ddt, *J* = 17.0, 10.2, 6.7 Hz, 1H), 5.12−4.99 (m, 2H), 3.73 (s, 3H), 3.63 (dt, *J* = 9.2, 6.6 Hz, 1H), 3.57 (d, *J* = 5.8 Hz, 1H), 3.32 (dt, *J* = 9.1, 6.9 Hz, 1H), 2.34 (dtd, *J* = 8.7, 6.8, 5.3 Hz, 2H), 2.10−1.96 (m, 1H), 0.94 (d, *J* = 2.0 Hz, 3H), 0.93 (d, *J* = 2.0 Hz, 3H). $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$) δ 173.0, 134.8, 116.3, 84.4, 70.2, 51.5, 33.9, 31.5, 18.6, 17.7. HRMS (ESI/Q-TOF) *m*/*z*: $[M + Na]^+$ calcd for $C_{10}H_{18}O_3Na$ 209.1148; found 209.1152.

*Ethyl (S)-2-(But-3-en-1-yloxy)propanoate (**20b**).* The reaction was conducted according to the general procedure C with (*S*)-(−)-ethyl lactate **19b** (2.0 g, 16.94 mmol), 18-crown-6 (450 mg, 1.69 mmol), potassium *tert*-butoxide (1.0 M solution in THF, 18.60 mL, 18.60 mmol), and but-3-en-1-yl trifluoromethanesulfonate[55] (4.49 g, 22.02 mmol). Purification by silica gel column chromatography (10% EtOAc/hexanes) afforded compound **20b** in 54% isolated yield (1.55 g, 75% brsm) as a colorless oil. $[\alpha]_D^{24}$ −37.9 (*c* 0.9, $CHCl_3$). $^1H$ NMR (400 MHz, $CDCl_3$ δ 5.82 (ddt, *J* = 17.0, 10.3, 6.7 Hz, 1H), 5.18−4.97 (m, 2H), 4.25−4.14 (m, 2H), 3.95 (q, *J* = 6.8 Hz, 1H), 3.63 (dt, *J* = 9.0, 6.8 Hz, 1H), 3.41 (dt, *J* = 8.9, 6.9 Hz, 1H), 2.44−2.27 (m, 2H), 1.39 (d, *J* = 6.9 Hz, 3H), 1.28 (t, *J* = 7.1 Hz, 3H). $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$) δ 173.3, 134.7, 116.4, 74.9, 69.4, 60.7, 34.0, 18.5, 14.1. HRMS (ESI/Q-TOF) *m*/*z*: $[M + H]^+$ calcd for $C_9H_{17}O_3$ 173.1172; found 173.1171.

*Ethyl (S)-2-(Pent-4-en-1-yloxy)propanoate (**20c**).* The reaction was conducted according to the general procedure C with (*S*)-(−)-ethyl lactate **19b** (2.50 g, 21.19 mmol), 18-crown-6 (560 mg, 2.12 mmol), potassium *tert*-butoxide (1.0 M solution in THF, 23.30 mL, 23.50 mmol), and pent-4-en-1-yl trifluoromethanesulfonate[56] (6.90 g, 31.77 mmol). Purification by silica gel column chromatography (5% EtOAc/hexanes) afforded compound **20c** in 84% isolated yield (3.32 g, 92% brsm) as a colorless oil. $[\alpha]_D^{24}$ −28.7 (*c* 1.2, $CHCl_3$). $^1H$ NMR (400 MHz, $CDCl_3$) δ 5.91−5.72 (m, 1H), 5.09−4.89 (m, 2H), 4.29−4.10 (m, 2H), 4.01−3.86 (m, 1H), 3.63−3.48 (m, 1H), 3.44−3.31 (m, 1H), 2.26−2.06 (m, 2H), 1.80−1.62 (m, 2H), 1.39 (dd, *J* = 6.8, 1.2 Hz, 3H), 1.28 (td, *J* = 7.1, 1.1 Hz, 3H). $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$) δ 173.4, 138.1, 114.7, 74.9, 69.5, 60.7, 30.1, 28.8, 18.6, 14.1. HRMS (ESI/Q-TOF) *m*/*z*: $[M + Na]^+$ calcd for $C_{10}H_{18}O_3Na$ 209.1147; found 209.1149.

**General Procedure D: Synthesis of Weinreb Amides 12f−h.** To a solution of *N*-methyl-*O*-methyl hydroxylamine hydrochloride (4.0 equiv mmol) in $CH_2Cl_2$ (0.1 M) was added trimethylaluminum (2.0 M solution in *n*-hexane, 4.0 equiv) at −10 °C. The resulting clear solution was stirred for 1 h at 23 °C and then cooled to −10 °C. To the reaction mixture was cannulated a solution of *O*-alkylated ester (1.0 equiv) in $CH_2Cl_2$ (1.0 M), and the reaction mixture was slowly warmed to 23 °C over 1 h. After 24 h, the reaction was quenched by adding a satd potassium sodium tartrate solution at 0 °C, and the


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resulting mixture was warmed to 23 °C. After 1 h, the mixture was filtered through a pad of Celite and washed with $CH_2Cl_2$. The filtrate was extracted with $CH_2Cl_2$ (2×). The combined organic layers were dried over $Na_2SO_4$, filtered, and concentrated in vacuo. Purification by silica gel column chromatography afforded the desired Weinreb amide.

*(S)-2-(But-3-en-1-yloxy)-N-methoxy-N,3-dimethylbutanamide (**12f**).* The reaction was conducted according to the general procedure D with methyl (*S*)-2-(but-3-en-1-yloxy)-3-methylbutanoate **20a** (500 mg, 2.69 mmol), *N*-methyl-*O*-methyl hydroxylamine hydrochloride (1.05 g, 10.76 mmol), and trimethylaluminum (2.0 M solution in *n*-hexane, 5.40 mL, 10.76 mmol) for 24 h. Purification by silica gel column chromatography (15% EtOAc/hexanes) afforded the Weinreb amide **12f** (435 mg, 75% yield) as a colorless oil. $[\alpha]_D^{24}$ −25.3 (*c* 0.7, $CHCl_3$). $^1$H NMR (400 MHz, $CDCl_3$) $\delta$ 5.80 (ddt, *J* = 17.0, 10.2, 6.7 Hz, 1H), 5.10−4.96 (m, 2H), 3.89 (brs, 1H), 3.68 (s, 3H), 3.61−3.53 (m, 1H), 3.34−3.26 (m, 1H), 3.20 (s, 3H), 2.42−2.25 (m, 2H), 2.11−1.97 (m, 1H), 0.97 (d, *J* = 6.7 Hz, 3H), 0.89 (d, *J* = 6.9 Hz, 3H). $^{13}$C{$^1$H} NMR (100 MHz, $CDCl_3$) $\delta$ 173.4, 135.0, 116.2, 81.7, 69.4, 61.2, 34.0, 32.2, 30.9, 18.7, 18.2. HRMS (ESI/Q-TOF) *m*/*z*: $[M + H]^+$ calcd for $C_{11}H_{22}O_3N$ 216.1594; found 216.1594.

*(S)-2-(But-3-en-1-yloxy)-N-methoxy-N-methylpropanamide (**12g**).* The reaction was conducted according to the general procedure D with a slight modification using ethyl (*S*)-2-(but-3-en-1-yloxy)propanoate **20b** (820 mg, 4.76 mmol), *N*-methyl-*O*-methyl hydroxylamine hydrochloride (980 mg, 10.01 mmol), and trimethylaluminum (2.0 M solution in *n*-hexane, 5.0 mL, 10.01 mmol) for 24 h. Purification by silica gel column chromatography (20% EtOAc/hexanes) afforded Weinreb amide **12g** (575 mg, 65% yield) as a colorless oil. $[\alpha]_D^{24}$ −27.9 (*c* 0.4, $CHCl_3$). $^1$H NMR (400 MHz, $CDCl_3$) $\delta$ 5.89−5.72 (m, 1H), 5.16−4.94 (m, 2H), 4.33 (q, *J* = 6.8 Hz, 1H), 3.69 (s, 3H), 3.60−3.50 (m, 1H), 3.42−3.30 (m, 1H), 3.20 (s, 3H), 2.43−2.29 (m, 2H), 1.35 (dd, *J* = 6.7, 1.6 Hz, 3H). $^{13}$C{$^1$H} NMR (100 MHz, $CDCl_3$) $\delta$ 173.7, 134.8, 116.3, 72.5, 68.8, 61.3, 34.1, 32.2, 17.7. HRMS (ESI/Q-TOF) *m*/*z*: $[M + H]^+$ calcd for $C_9H_{18}O_3N$ 188.1281; found 188.1280.

*(S)-N-Methoxy-N-methyl-2-(pent-4-en-1-yloxy)propanamide (**12h**).* The reaction was conducted according to the general procedure D with ethyl (*S*)-2-(pent-4-en-1-yloxy)propanoate **20c** (3.25 g, 17.47 mmol), *N*-methyl-*O*-methyl hydroxylamine hydrochloride (6.80 g, 69.89 mmol), and trimethylaluminum (2.0 M solution in *n*-hexane, 35.0 mL, 69.89 mmol) for 24 h. Purification by silica gel column chromatography (15% EtOAc/hexanes) afforded the Weinreb amide **12h** (2.80 g, 80% yield) as a colorless oil. $[\alpha]_D^{24}$ −15.6 (*c* 1.0, $CHCl_3$). $^1$H NMR (400 MHz, $CDCl_3$) $\delta$ 5.84−5.68 (m, 1H), 5.02−4.85 (m, 2H), 4.27 (q, *J* = 7.1, 6.7 Hz, 1H), 3.66 (t, *J* = 2.1 Hz, 3H), 3.52−3.40 (m, 1H), 3.35−3.23 (m, 1H), 3.16 (s, 3H), 2.13−2.01 (m, 2H), 1.73−1.59 (m, 2H), 1.35−1.27 (m, 3H). $^{13}$C{$^1$H} NMR (100 MHz, $CDCl_3$) $\delta$ 173.8, 138.1, 114.5, 72.4, 68.8, 61.3, 32.2, 30.1, 28.8, 17.7. HRMS (ESI/Q-TOF) *m*/*z*: $[M + H]^+$ calcd for $C_{10}H_{20}O_3N$ 202.1437; found 202.1437.

**General Procedure E: Synthesis of Furfuryl Alcohols 13a−h.** A flame-dried round-bottom flask was charged with furan (2.0 equiv) and dry THF (0.2 M) under argon. The reaction flask was then cooled to 0 °C, and a solution of *n*-BuLi (1.6 M solution in hexane, 1.8 equiv) was added dropwise. The resulting mixture was stirred at this temperature for 30 min and then cooled to −78 °C, followed by a dropwise addition of the *O*-alkylated Weinreb amide (1.0 equiv) solution in THF. After 1 h, the reaction was quenched with satd $NH_4Cl$ and extracted with EtOAc (2×). The organic phase was washed with brine, dried over $Na_2SO_4$, and concentrated under reduced pressure. The crude product was purified by silica gel column chromatography.

The above furyl ketone (1.0 equiv) was dissolved in dry MeOH at −78 °C followed by portionwise addition of $NaBH_4$ (3.0 equiv). After 1 h, the reaction was quenched by water, the residue was diluted with $CH_2Cl_2$, and the aqueous layer was extracted with $CH_2Cl_2$ (3×). The combined organic layers were dried over $Na_2SO_4$, filtered, and concentrated under reduced pressure. The crude product was purified by silica gel column chromatography.

*(2S)-2-(Allyloxy)-1-(furan-2-yl)-2-phenylethan-1-ol (**13a**).* The reaction was conducted according to the general procedure E with furan (2.0 mL, 27.24 mmol), *n*-BuLi (1.6 M solution in hexane, 15.30 mL, 24.51 mmol), and (*S*)-2-(allyloxy)-*N*-methoxy-*N*-methyl-2-phenylacetamide **12a** (3.20 g, 13.62 mmol). Purification by silica gel column chromatography (20% EtOAc/hexanes) afforded the furyl ketone (2.90 g, 88% yield) as an amorphous white solid. $[\alpha]_D^{24}$ +25.3 (*c* 0.3, $CHCl_3$). $^1$H NMR (400 MHz, $CDCl_3$) $\delta$ 7.57 (d, *J* = 1.7 Hz, 1H), 7.50 (d, *J* = 7.3 Hz, 2H), 7.39 (d, *J* = 3.6 Hz, 1H), 7.32 (dt, *J* = 13.8, 7.0 Hz, 3H), 6.54−6.44 (m, 1H), 5.95 (ddt, *J* = 16.1, 10.6, 5.7 Hz, 1H), 5.47 (s, 1H), 5.34−5.16 (m, 2H), 4.14−4.03 (m, 2H). $^{13}$C{$^1$H} NMR (100 MHz, $CDCl_3$) $\delta$ 186.1, 150.4, 146.8, 136.0, 133.8, 128.6, 128.4, 127.4, 119.7, 118.0, 112.2, 83.6, 70.5. HRMS (ESI/Q-TOF) *m*/*z*: $[M + H]^+$ calcd for $C_{15}H_{15}O_3$ 243.1016; found 243.1018.

The above furyl ketone (2.80 g, 11.86 mmol) was reduced with $NaBH_4$ (1.35 g, 35.58 mmol) in dry MeOH (60 mL) following the general procedure E. Purification by silica gel column chromatography (10% EtOAc/hexanes) afforded the furfuryl alcohol **13a** (2.82 g, 95% yield) as a colorless oil in a 7:1 diastereomeric ratio. $^1$H NMR (400 MHz, $CDCl_3$) $\delta$ 7.37 (dd, *J* = 1.8, 0.9 Hz, 1H), 7.34−7.29 (m, 3H), 7.27−7.23 (m, 2H), 6.30 (dd, *J* = 3.3, 1.8 Hz, 1H), 6.22−6.16 (m, 1H), 5.88−5.77 (m, 1H), 5.22−5.12 (m, 2H), 4.87 (d, *J* = 5.9 Hz, 1H), 4.71−4.67 (m, 1H), 4.00 (ddt, *J* = 13.0, 5.0, 1.6 Hz, 1H), 3.80 (ddt, *J* = 12.9, 6.1, 1.4 Hz, 1H), 2.32 (brs, 1H). $^{13}$C{$^1$H} NMR (100 MHz, $CDCl_3$) $\delta$ 153.3, 141.6, 137.6, 134.3, 128.2, 128.1, 127.6, 117.0, 110.2, 107.8, 82.7, 71.2, 69.9. HRMS (ESI/Q-TOF) *m*/*z*: $[M + Na]^+$ calcd for $C_{15}H_{16}O_3Na$ 267.0992; found 267.0992.

*(2R)-2-(Allyloxy)-1-(furan-2-yl)-2-phenylethan-1-ol (**13b**).* The reaction was conducted according to the general procedure E with furan (810 μL, 11.06 mmol), *n*-BuLi (1.6 M solution in hexane, 6.20 mL, 9.95 mmol), and (*R*)-2-(allyloxy)-*N*-methoxy-*N*-methyl-2-phenylacetamide **12b** (1.30 g, 5.53 mmol). Purification by silica gel column chromatography (20% EtOAc/hexanes) afforded the furyl ketone (1.16 g, 89% yield) as an amorphous white solid. $[\alpha]_D^{24}$ −27.0 (*c* 1.8, $CHCl_3$). $^1$H NMR (400 MHz, $CDCl_3$) $\delta$ 7.59−7.51 (m, 1H), 7.53−7.44 (m, 2H), 7.41−7.34 (m, 1H), 7.36−7.23 (m, 3H), 6.52−6.41 (m, 1H), 6.03−5.86 (m, 1H), 5.47 (s, 1H), 5.36−5.23 (m, 1H), 5.25−5.16 (m, 1H), 4.17−4.04 (m, 2H). $^{13}$C{$^1$H} NMR (100 MHz, $CDCl_3$) $\delta$ 186.0, 150.4, 146.8, 136.0, 133.8, 128.6, 128.4, 127.4, 119.7, 118.0, 112.2, 83.6, 70.5. HRMS (ESI/Q-TOF) *m*/*z*: $[M + H]^+$ calcd for $C_{15}H_{15}O_3$ 243.1016; found 243.1016.

The above furyl ketone (630 mg, 2.60 mmol) was reduced with $NaBH_4$ (300 mg, 7.80 mmol) in dry MeOH (13 mL) following the general procedure E. Purification by silica gel column chromatography (10% EtOAc/hexanes) afforded the furfuryl alcohol **13b** (610 mg, 95% yield) as a colorless oil in a 9:1 diastereomeric ratio. $^1$H NMR (400 MHz, $CDCl_3$) $\delta$ 7.37 (dd, *J* = 1.8, 0.9 Hz, 1H), 7.36−7.29 (m, 3H), 7.27−7.23 (m, 2H), 6.30 (dd, *J* = 3.2, 1.8 Hz, 1H), 6.23−6.15 (m, 1H), 5.83 (dddd, *J* = 17.2, 10.4, 6.1, 5.0 Hz, 1H), 5.26−5.10 (m, 2H), 4.88 (t, *J* = 5.9 Hz, 1H), 4.69 (d, *J* = 5.9 Hz, 1H), 4.00 (ddt, *J* = 13.0, 5.0, 1.6 Hz, 1H), 3.80 (ddt, *J* = 12.9, 6.1, 1.4 Hz, 1H), 2.40−2.28 (m, 1H). $^{13}$C{$^1$H} NMR (100 MHz, $CDCl_3$) $\delta$ 153.2, 141.7, 137.6, 134.2, 128.2, 128.1, 127.6, 117.0, 110.2, 107.8, 82.7, 71.2, 69.9. HRMS (ESI/Q-TOF) *m*/*z*: $[M + Na]^+$ calcd for $C_{15}H_{16}O_3Na$ 267.0992; found 267.0993.

*(2S)-2-(Allyloxy)-1-(furan-2-yl)-3-methylbutan-1-ol (**13c**).* The reaction was conducted according to the general procedure E with furan (1.80 mL, 24.88 mmol), *n*-BuLi (1.6 M solution in hexane, 14.0 mL, 22.39 mmol), and (*S*)-2-(allyloxy)-*N*-methoxy-*N*,3-dimethylbutanamide **12c** (2.39 g, 11.89 mmol). Purification by silica gel column chromatography (20% EtOAc/hexanes) afforded the furyl ketone (2.16 g, 87% yield) as a colorless oil. $[\alpha]_D^{24}$ −19.4 (*c* 0.4, $CHCl_3$). $^1$H NMR (400 MHz, $CDCl_3$) $\delta$ 7.62 (d, *J* = 1.7 Hz, 1H), 7.43 (d, *J* = 3.6 Hz, 1H), 6.57−6.49 (m, 1H), 5.95−5.80 (m, 1H), 5.25 (dq, *J* = 17.2, 1.6 Hz, 1H), 5.17 (dq, *J* = 10.3, 1.3 Hz, 1H), 4.09 (ddt, *J* = 12.7, 5.3, 1.5 Hz, 1H), 4.00 (d, *J* = 6.6 Hz, 1H), 3.88 (ddt, *J* = 12.7, 6.0, 1.3 Hz, 1H), 2.22−2.06 (m, 1H), 1.01 (d, *J* = 6.8 Hz, 3H), 0.94 (d, *J* = 6.8 Hz, 3H). $^{13}$C{$^1$H} NMR (100 MHz, $CDCl_3$) $\delta$ 190.3, 151.3, 146.7,


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134.1, 119.4, 117.4, 112.0, 87.9, 71.5, 32.1, 18.9, 18.2.HRMS (ESI/Q-TOF) $m/z$: $[M + H]^+$ calcd for $C_{12}H_{17}O_3$ 209.1172; found 209.1173.

The above furyl ketone(2.10 g, 10.09 mmol) was reduced with $NaBH_4$ (1.15 g, 30.29 mmol) in dry MeOH (50 mL) following the general procedure E. Purification by silica gel column chromatography (10% EtOAc/hexanes) afforded the furfuryl alcohol **13c** (2.0 g, 95% yield) as a colorless oil in a 3:1 diastereomeric ratio. $^1$H NMR (400 MHz, $CDCl_3$) $\delta$ 7.37 (d, $J$ = 3.9 Hz, 1H), 6.33 (d, $J$ = 2.9 Hz, 2H), 5.80 (ddt, $J$ = 16.5, 10.8, 5.4 Hz, 1H), 5.25−5.14 (m, 1H), 5.16−5.05 (m, 1H), 4.70 (d, $J$ = 6.3 Hz, 1H), 4.04−3.85 (m, 1H), 3.82 (dd, $J$ = 12.5, 5.6 Hz, 1H), 3.46−3.35 (m, 1H), 2.39 (brs, 1H), 1.98−1.83 (m, 1H), 0.97 (dd, $J$ = 6.9, 1.9 Hz, 3H), 0.96−0.89 (m, 3H). $^{13}$C{$^1$H} NMR (100 MHz, $CDCl_3$) $\delta$ 154.6, 141.6, 134.9, 116.5, 110.3, 107.6, 86.1, 73.7, 68.3, 29.6, 19.7, 17.0. HRMS (ESI/Q-TOF) $m/z$: $[M + Na]^+$ calcd for $C_{12}H_{18}O_3Na$ 233.1148; found 233.1149.

*(2S)-2-(Allyloxy)-1-(furan-2-yl)propan-1-ol (**13d**).* The reaction was conducted according to the general procedure E with furan (1.10 mL, 15.03 mmol), *n*-BuLi (1.6 M solution in hexane, 8.50 mL, 13.52 mmol), and (*S*)-2-(allyloxy)-*N*-methoxy-*N*-methylpropanamide **12d** (1.30 g, 7.51 mmol). Purification by silica gel column chromatography (20% EtOAc/hexanes) afforded the furyl ketone (1.20 g, 89% yield) as a colorless oil. $[\alpha]_D^{24}$ −68.7 ($c$ 0.9, $CHCl_3$). $^1$H NMR (400 MHz, $CDCl_3$) $\delta$ 7.62 (dd, $J$ = 1.7, 0.7 Hz, 1H), 7.44 (dd, $J$ = 3.6, 0.7 Hz, 1H), 6.55 (dd, $J$ = 3.6, 1.7 Hz, 1H), 5.91 (ddt, $J$ = 17.2, 10.4, 5.7 Hz, 1H), 5.27 (dq, $J$ = 17.2, 1.6 Hz, 1H), 5.19 (dq, $J$ = 10.4, 1.3 Hz, 1H), 4.49 (q, $J$ = 6.9 Hz, 1H), 4.09 (ddt, $J$ = 12.6, 5.4, 1.4 Hz, 1H), 3.96 (ddt, $J$ = 12.6, 5.9, 1.3 Hz, 1H), 1.48 (d, $J$ = 6.9 Hz, 3H). $^{13}$C{$^1$H} NMR (100 MHz, $CDCl_3$) $\delta$ 190.0, 150.3, 146.8, 134.0, 119.3, 117.6, 112.1, 78.3, 70.8, 18.9. HRMS (ESI/Q-TOF) $m/z$: $[M + H]^+$ calcd for $C_{10}H_{13}O_3$ 181.0858; found 181.0859.

The above furyl ketone (1.10 g, 6.10 mmol) was reduced with $NaBH_4$ (700 mg, 18.30 mmol) in dry MeOH (30 mL) following the general procedure E. Purification by silica gel column chromatography (10% EtOAc/hexanes) afforded the furfuryl alcohol **13d** (900 mg, 82% yield) as a colorless oil in a 1:1 diastereomeric ratio. $^1$H NMR (400 MHz, $CDCl_3$) $\delta$ 7.40−7.37 (m, 1H), 6.35−6.32 (m, 2H), 5.93−5.86 (m, 1H), 5.33−5.22 (m, 2H), 4.81−4.72 (m, 1H), 4.48 (dd, $J$ = 7.5, 3.1 Hz, 1H), 3.99−3.93 (m, 1H), 3.78 (d, $J$ = 6.4 Hz, 1H), 2.57−2.49 (m, 1H), 1.14 (d, $J$ = 6.3 Hz, 3H). $^{13}$C{$^1$H} NMR (100 MHz, $CDCl_3$) $\delta$ 153.7, 141.7, 134.7, 116.9, 110.1, 107.0, 76.5, 70.3, 70.1, 14.5. HRMS (ESI/Q-TOF) $m/z$: $[M + Na]^+$ calcd for $C_{10}H_{14}O_3Na$ 205.0835; found 205.0835.

*3-((1S)-2-(Furan-2-yl)-2-hydroxy-1-phenylethoxy)propan-1-ol (**18**).* To a flame-dried flask flushed with argon was added cyclohexene (4.0 g, 48.77 mmol) in 35 mL of THF at 0 °C followed by the addition of borane dimethyl sulfide complex (2.30 mL, 24.37 mmol). The resulting white slurry was stirred at 0 °C for 3 h before the addition of a solution of furfuryl alcohol **13a** (1.72 g, 7.17 mmol) in 8.0 mL of THF. The reaction mixture was slowly warmed to 23 °C and stirred for 2 h. Oxidation of the resulting dicyclohexylborinate was achieved by adding 0.3 M water and sodium perborate tetrahydrate (11.03 g, 71.70 mmol) at 0 °C. The resulting mixture was stirred for 12 h at 23 °C and then extracted with ethyl acetate (3×). The combined organic layers were dried over $Na_2SO_4$, filtered, and concentrated under reduced pressure. Purification by silica gel column chromatography (1% MeOH/$CH_2Cl_2$) afforded the diol **18** (1.60 g, 88% yield) as a white amorphous solid in a 5.4:1 diastereomeric ratio. The diastereomers were separated via column chromatography. *Anti*-diol: $[\alpha]_D^{24}$ +62.2 ($c$ 0.9, $CHCl_3$). $^1$H NMR (400 MHz, $CDCl_3$) $\delta$ 7.43−7.37 (m, 1H), 7.39−7.28 (m, 3H), 7.25 (dt, $J$ = 7.5, 1.4 Hz, 2H), 6.32 (dd, $J$ = 3.3, 1.8 Hz, 1H), 6.18 (d, $J$ = 3.2 Hz, 1H), 4.78 (d, $J$ = 6.2 Hz, 1H), 4.61 (d, $J$ = 6.2 Hz, 1H), 3.69 (td, $J$ = 5.7, 2.2 Hz, 2H), 3.64−3.54 (m, 1H), 3.52−3.41 (m, 1H), 2.16 (brs, 2H), 1.83−1.72 (m, 2H). $^{13}$C{$^1$H} NMR (100 MHz, $CDCl_3$) $\delta$ 153.0, 142.0, 137.7, 128.4, 128.2, 127.3, 110.2, 108.1, 84.5, 71.1, 68.8, 61.8, 31.8. HRMS (ESI/Q-TOF) $m/z$: $[M + Na]^+$ calcd for $C_{15}H_{18}O_4Na$ 285.1097; found 285.1097.

*(1S,2S)-2-(But-3-en-1-yloxy)-1-(furan-2-yl)-2-phenylethan-1-ol (**13e**).* To a solution of the above *anti*-diol **18** (600 mg, 2.29 mmol) in anhydrous $CH_2Cl_2$ (10 mL) were added TEMPO (36 mg, 0.23 mmol) and *bis*(acetoxy)iodobenzene (885 mg, 2.75 mmol) at 0 °C. The reaction mixture was warmed to 23 °C over 1 h and continued to stir at 23 °C. After 8 h, the reaction mixture was quenched with satd $Na_2S_2O_3$ and extracted with $CH_2Cl_2$ (3×). The combined organic layers were dried over $Na_2SO_4$, filtered, and concentrated under reduced pressure. Purification by silica gel column chromatography (5% EtOAc/$CH_2Cl_2$) afforded the aldehyde (440 mg, 74% yield) as a yellow oil.

To a suspension of methyltriphenylphosphonium bromide (2.50 g, 6.92 mmol) in $Et_2O$ (25 mL) was added potassium *tert*-butoxide (1.0 M solution in THF, 6.20 mL, 6.21 mmol) at 0 °C. The resulting yellow suspension was then warmed to 23 °C and stirred for 30 min. The reaction mixture was cooled to −20 °C followed by addition of the solution of the above aldehyde (360 mg, 1.38 mmol) in 15 mL of $Et_2O$. After stirring at −20 °C for 2 h, the reaction was quenched with satd $NH_4Cl$ and extracted with $Et_2O$ (3×). The combined organic layers were dried over $Na_2SO_4$, filtered, and concentrated under reduced pressure. Purification by silica gel column chromatography (10% EtOAc/hexanes) afforded the furfuryl alcohol **13e** (105 mg, 30% yield) as a colorless oil. $[\alpha]_D^{24}$ +43.3 ($c$ 0.3, $CHCl_3$). $^1$H NMR (400 MHz, $CDCl_3$) $\delta$ 7.38−7.28 (m, 4H), 7.27−7.19 (m, 2H), 6.30 (dd, $J$ = 3.3, 1.9 Hz, 1H), 6.18 (d, $J$ = 3.3 Hz, 1H), 5.74 (ddt, $J$ = 17.0, 10.2, 6.7 Hz, 1H), 5.09−4.95 (m, 2H), 4.84 (t, $J$ = 5.6 Hz, 1H), 4.62 (d, $J$ = 5.8 Hz, 1H), 3.50 (dt, $J$ = 9.4, 6.6 Hz, 1H), 3.35 (dt, $J$ = 9.4, 6.6 Hz, 1H), 2.38 (d, $J$ = 6.0 Hz, 1H), 2.30 (qt, $J$ = 6.6, 1.5 Hz, 2H). $^{13}$C{$^1$H} NMR (100 MHz, $CDCl_3$) $\delta$ 153.3, 141.6, 137.8, 135.0, 128.1, 128.0, 127.4, 116.3, 110.1, 107.7, 83.7, 71.2, 68.7, 34.0. HRMS (ESI/Q-TOF) $m/z$: $[M + Na]^+$ calcd for $C_{16}H_{18}O_3Na$ 281.1148; found 281.1147.

*(2S)-2-(But-3-en-1-yloxy)-1-(furan-2-yl)-3-methylbutan-1-ol (**13f**).* The reaction was conducted according to the general procedure E with furan (605 μL, 8.26 mmol), *n*-BuLi (1.6 M solution in hexane, 7.50 mL, 7.45 mmol), and (*S*)-2-(but-3-en-1-yloxy)-*N*-methoxy-*N*,3-dimethylbutanamide **12f** (890 mg, 4.13 mmol). Purification by silica gel column chromatography (5% EtOAc/hexanes) afforded the furyl ketone (800 mg, 87% yield) as a yellow oil. $[\alpha]_D^{24}$ −81.4 ($c$ 0.6, $CHCl_3$). $^1$H NMR (400 MHz, $CDCl_3$) $\delta$ 7.61 (dd, $J$ = 1.7, 0.8 Hz, 1H), 7.43 (dt, $J$ = 3.6, 0.7 Hz, 1H), 6.53 (dd, $J$ = 3.6, 1.7 Hz, 1H), 5.77 (ddt, $J$ = 16.9, 10.0, 6.7 Hz, 1H), 5.12−4.94 (m, 2H), 3.88 (d, $J$ = 6.9 Hz, 1H), 3.64−3.52 (m, 1H), 3.43−3.32 (m, 1H), 2.40−2.24 (m, 2H), 2.17−2.03 (m, 1H), 1.00 (d, $J$ = 6.7 Hz, 3H), 0.91 (d, $J$ = 6.8 Hz, 3H). $^{13}$C{$^1$H} NMR (100 MHz, $CDCl_3$) $\delta$ 190.4, 151.2, 146.7, 134.8, 119.4, 116.4, 112.0, 89.2, 70.1, 34.1, 32.1, 18.8, 18.4. HRMS (ESI/Q-TOF) $m/z$: $[M + H]^+$ calcd for $C_{13}H_{19}O_3$ 223.1329; found 223.1329.

The above furyl ketone (665 mg, 2.99 mmol) was reduced with $NaBH_4$ (500 mg, 11.98 mmol) in dry MeOH (15 mL) following the general procedure E. Purification by silica gel column chromatography (10% EtOAc/hexanes) afforded the furfuryl alcohol **13f** (645 mg, 96% yield) as a yellow oil in a 3:1 diastereomeric ratio. $^1$H NMR (400 MHz, $CDCl_3$) $\delta$ 7.37 (dd, $J$ = 1.8, 0.9 Hz, 1H), 6.36−6.31 (m, 2H), 5.85−5.72 (m, 1H), 5.13−4.98 (m, 2H), 4.72 (d, $J$ = 5.9 Hz, 1H), 3.66−3.53 (m, 1H), 3.42−3.29 (m, 2H), 2.33−2.20 (m, 2H), 1.91−1.72 (m, 1H), 0.97 (dd, $J$ = 6.9, 1.3 Hz, 3H), 0.93−0.89 (m, 3H). $^{13}$C{$^1$H} NMR (100 MHz, $CDCl_3$) $\delta$ 154.6, 141.5, 135.4, 116.5, 110.3, 107.5, 86.9, 72.3, 68.5, 34.6, 29.8, 19.6, 17.4. HRMS (ESI/Q-TOF) $m/z$: $[M + Na]^+$ calcd for $C_{13}H_{20}O_3Na$ 247.1304; found 247.1306.

*(2S)-2-(But-3-en-1-yloxy)-1-(furan-2-yl)propan-1-ol (**13g**).* The reaction was conducted according to the general procedure E with furan (630 μL, 8.64 mmol), *n*-BuLi (1.6 M solution in hexane, 5.0 mL, 8.08 mmol), and (*S*)-2-(but-3-en-1-yloxy)-*N*-methoxy-*N*-methylpropanamide **12g** (540 mg, 2.88 mmol). Purification by silica gel column chromatography (8% EtOAc/hexanes) afforded the furyl ketone (465 mg, 83% yield) as a yellow oil. $[\alpha]_D^{24}$ −20.8 ($c$ 1.1, $CHCl_3$). $^1$H NMR (400 MHz, $CDCl_3$) $\delta$ 7.60 (d, $J$ = 1.7 Hz, 1H), 7.41 (d, $J$ = 3.6 Hz, 1H), 6.52 (dd, $J$ = 3.6, 1.7 Hz, 1H), 5.76 (ddt, $J$ = 17.1, 10.3, 6.7 Hz, 1H), 5.14−4.93 (m, 2H), 4.40 (q, $J$ = 6.9 Hz, 1H), 3.54 (dt, $J$ = 9.0, 6.8 Hz, 1H), 3.44 (dt, $J$ = 9.0, 6.8 Hz, 1H), 2.41−2.26 (m, 2H), 1.43 (d, $J$ = 6.9 Hz, 3H). $^{13}$C{$^1$H} NMR (100 MHz,


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$CDCl_3$) $\delta$ 190.1, 150.3, 146.7, 134.7, 119.4, 116.5, 112.1, 79.3, 69.3, 34.1, 18.8. HRMS (ESI/Q-TOF) $m/z$: $[M + H]^+$ calcd for $C_{11}H_{15}O_3$ 195.1015; found 195.1016.

The above furyl ketone (400 mg, 2.0 mmol) was reduced with $NaBH_4$ (230 mg, 6.0 mmol) in dry MeOH (10 mL) following the general procedure E. Purification by silica gel column chromatography (10% EtOAc/hexanes) afforded the furfuryl alcohol **13g** (375 mg, 96% yield) as a yellow oil in a 1:1 diastereomeric ratio. $^1H$ NMR (400 MHz, $CDCl_3$) $\delta$ 7.41−7.33 (m, 1H), 6.38−6.26 (m, 2H), 5.89−5.73 (m, 1H), 5.17−5.01 (m, 2H), 4.44 (d, $J$ = 7.8 Hz, 1H), 3.80−3.59 (m, 2H, superimposed by peak corresponding to the minor isomer), 3.44 (dq, $J$ = 9.2, 6.7 Hz, 1H), 3.17 (brs, 1H), 2.40−2.28 (m, 2H), 1.05 (d, $J$ = 6.2 Hz, 3H). $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$) $\delta$ 153.8, 142.1, 135.1, 116.8, 110.1, 108.0, 77.7, 71.7, 68.5, 34.3, 15.6. HRMS (ESI/Q-TOF) $m/z$: $[M + Na]^+$ calcd for $C_{11}H_{16}O_3Na$ 219.0992; found 219.0993.

*(2S)-1-(Furan-2-yl)-2-(pent-4-en-1-yloxy)propan-1-ol (**13h**).* The reaction was conducted according to the general procedure E with furan (1.73 mL, 23.88 mmol), *n*-BuLi (1.6 M solution in hexane, 13.50 mL, 21.49 mmol), and (*S*)-*N*-methoxy-*N*-methyl-2-(pent-4-en-1-yloxy)propanamide **12h** (2.40 g, 11.94 mmol). Purification by silica gel column chromatography (5% EtOAc/hexanes) afforded the furyl ketone (2.0 g, 81% yield) as a yellow oil. $[\alpha]_D^{24}$ −14.9 ($c$ 0.6, $CHCl_3$). $^1H$ NMR (400 MHz, $CDCl_3$) $\delta$ 7.58 (dd, $J$ = 1.7, 0.7 Hz, 1H), 7.37 (dd, $J$ = 3.6, 0.8 Hz, 1H), 6.50 (dd, $J$ = 3.6, 1.7 Hz, 1H), 5.72 (ddt, $J$ = 16.9, 10.2, 6.6 Hz, 1H), 5.01−4.80 (m, 2H), 4.35 (q, $J$ = 6.9 Hz, 1H), 3.46 (dt, $J$ = 9.1, 6.5 Hz, 1H), 3.36 (dt, $J$ = 9.1, 6.6 Hz, 1H), 2.05 (tdt, $J$ = 8.0, 6.4, 1.4 Hz, 2H), 1.74−1.56 (m, 2H), 1.40 (d, $J$ = 6.9 Hz, 3H). $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$) $\delta$ 190.1, 150.3, 146.7, 137.9, 119.2, 114.7, 112.0, 79.2, 69.3, 30.0, 28.8, 18.8. HRMS (ESI/Q-TOF) $m/z$: $[M + H]^+$ calcd for $C_{12}H_{17}O_3$ 209.1171; found 209.1172.

The above furyl ketone (175 mg, 0.84 mmol) was reduced with $NaBH_4$ (96 mg, 2.52 mmol) in dry MeOH (4.2 mL) following the general procedure E. Purification by silica gel column chromatography (10% EtOAc/hexanes) afforded the furfuryl alcohol **13h** (160 mg, 90% yield) as a yellow oil in a 2:1 diastereomeric ratio. $^1H$ NMR (400 MHz, $CDCl_3$) $\delta$ 7.35 (dd, $J$ = 6.2, 1.7 Hz, 1H), 6.39−6.22 (m, 2H), 5.88−5.70 (m, 1H), 5.10−4.87 (m, 2H), 4.43 (d, $J$ = 7.5 Hz, 1H), 3.77−3.47 (m, 2H), 3.38 (dt, $J$ = 9.1, 6.5 Hz, 1H), 3.19 (brs, 1H), 2.09 (dq, $J$ = 15.1, 6.7 Hz, 2H), 1.76−1.49 (m, 2H), 1.03 (d, $J$ = 6.2 Hz, 3H). $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$) $\delta$ 153.4, 142.0, 138.1, 114.8, 110.1, 107.8, 77.4, 71.6, 68.5, 30.3, 29.0, 15.6. HRMS (ESI/Q-TOF) $m/z$: $[M + Na]^+$ calcd for $C_{12}H_{18}O_3Na$ 233.1149; found 233.1148.

**General Procedure F: Synthesis of Acetoxypyranone via Achmatowicz Rearrangement 14a−h.** To a stirring solution of furfuryl alcohol (1.0 equiv) in a 4:1 mixture of THF/$H_2O$ (0.1 M) at 0 °C were added KBr (0.1 equiv), $NaHCO_3$ (0.5 equiv), and oxone (1.5 equiv). After the reaction mixture was stirred at 0 °C for 1−4 h, the reaction was quenched by addition of satd $NaHCO_3$ solution. The mixture was extracted with EtOAc (3×), washed with brine, dried over anhydrous $Na_2SO_4$, filtered, and concentrated under reduced pressure. The crude hydoxypyranone was used directly for the subsequent reaction without purification. To a solution of the crude hydroxypyranone (1.0 equiv) in $CH_2Cl_2$ at 0 °C were added pyridine (2.0 equiv) and acetyl chloride (1.5 equiv). The resulting solution was stirred for 30 min, and then the reaction was quenched by water and extracted with $CH_2Cl_2$ (3×). The combined organic layers were washed with brine, dried over $Na_2SO_4$, filtered, and concentrated under reduced pressure. Purification by silica gel column chromatography afforded the desired acetoxypyranone.

*6-((S)-(Allyloxy)(phenyl)methyl)-5-oxo-5,6-dihydro-2H-pyran-2-yl Acetate (**14a**).* The reaction was conducted according to the general procedure F with furfuryl alcohol **13a** (300 mg, 1.23 mmol), KBr (15 mg, 0.12 mmol), $NaHCO_3$ (52 mg, 0.62 mmol), and oxone (1.1 g, 0.1.85 mmol) to afford the desired hydroxypyranone. The acetylation reaction was conducted according to the general procedure using the crude hydroxypyranone (320 mg, 1.23 mmol), pyridine (216 $\mu$L, 2.46 mmol), and acetyl chloride (132 $\mu$L, 1.85 mmol) in $CH_2Cl_2$(4 mL) for 30 min. Purification by silica gel column chromatography (10% EtOAc/hexanes) afforded an inseparable mixture of diastereomers of acetoxypyranone **14a** (340 mg, 92% yield over 2 steps) as a cream color amorphous solid. $^1H$ NMR (400 MHz, $CDCl_3$) $\delta$ 7.35−7.25 (m, 5H, superimposed by peak corresponding to the minor isomer), 6.79 (dd, $J$ = 10.3, 3.6 Hz, 1H), 6.47 (d, $J$ = 3.7 Hz, 1H), 6.07−6.01 (m, 1H), 5.90 (dddd, $J$ = 17.0, 10.4, 6.4, 5.1 Hz, 1H), 5.26−5.09 (m, 2H), 5.08 (d, $J$ = 2.8 Hz, 1H), 4.95 (d, $J$ = 2.8 Hz, 1H), 4.07−3.91 (m, 1H), 3.87−3.70 (m, 1H), 2.10 (d, $J$ = 2.4 Hz, 3H). $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$)) $\delta$ 192.6, 169.2, 141.9, 136.0, 134.2, 128.6, 128.2, 128.0, 127.8, 117.4, 87.2, 79.4, 79.3, 69.9, 20.9. HRMS (ESI/LTQ) $m/z$: $[M + Na]^+$ calcd for $C_{17}H_{18}O_5Na$ 325.1046; found 325.1050.

*6-((R)-(Allyloxy)(phenyl)methyl)-5-oxo-5,6-dihydro-2H-pyran-2-yl Acetate (**14b**).* The reaction was conducted according to the general procedure F with furfuryl alcohol **13b** (600 mg, 2.45 mmol), KBr (30 mg, 0.25 mmol), $NaHCO_3$ (103 mg, 1.23 mmol), and oxone (2.95 g, 1.8 mmol) to afford the desired hydroxypyranone. The acetylation reaction was conducted according to the general procedure using crude hydroxypyranone (637 mg, 2.45 mmol), pyridine (431 $\mu$L, 4.90 mmol), and acetyl chloride (265 $\mu$L, 3.67 mmol) in $CH_2Cl_2$(8 mL). Purification by silica gel column chromatography (10% EtOAc/hexanes) afforded an inseparable mixture of diastereomers of acetoxypyranone **14b** (405 mg, 55% yield over 2 steps) as a cream color amorphous solid. $^1H$ NMR (400 MHz, $CDCl_3$) $\delta$ 7.46−7.19 (m, 5H, superimposed by peak corresponding to the minor isomer), 6.78 (dd, $J$ = 10.3, 3.7 Hz, 1H), 6.47 (d, $J$ = 3.6 Hz, 1H), 6.03 (d, $J$ = 10.3 Hz, 1H), 5.89 (dddd, $J$ = 17.0, 10.3, 6.4, 5.0 Hz, 1H), 5.27−5.12 (m, 2H), 5.12−5.04 (m, 1H), 4.95 (d, $J$ = 2.8 Hz, 1H), 4.07−3.93 (m, 1H), 3.82 (ddt, $J$ = 12.9, 6.4, 1.3 Hz, 1H), 2.09 (s, 3H). $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$) $\delta$ 192.7, 169.3, 141.9, 135.9, 134.1, 128.6, 128.2, 128.0, 127.8, 117.5, 87.2, 79.3, 79.2, 69.9, 20.85. HRMS (ESI/LTQ) $m/z$: $[M + Na]^+$ calcd for $C_{17}H_{18}O_5Na$ 325.1046; found 325.1049.

*6-((S)-1-(Allyloxy)-2-methylpropyl)-5-oxo-5,6-dihydro-2H-pyran-2-yl Acetate (**14c**).* The reaction was conducted according to the general procedure F with furfuryl alcohol **13c** (200 mg, 0.95 mmol), KBr (12 mg, 0.1 mmol), $NaHCO_3$ (40 mg, 0.48 mmol), and oxone (877 mg, 1.43 mmol) to afford the desired hydroxypyranone. The acetylation reaction was conducted according to the general procedure using the crude hydroxypyranone (215 mg, 0.95 mmol), pyridine (167 $\mu$L, 1.90 mmol), and acetyl chloride (102 $\mu$L, 1.43 mmol) in $CH_2Cl_2$ (1.5 mL) for 30 min. Purification by silica gel column chromatography (10% EtOAc/hexanes) afforded an inseparable mixture of diastereomers of acetoxypyranone **14c** (198 mg, 78% over 2 steps) as a yellow oil. $^1H$ NMR (400 MHz, $CDCl_3$) $\delta$ 6.89 (dd, $J$ = 3.6, 2.0 Hz, 1H), 6.54 (d, $J$ = 3.8 Hz, 1H), 6.22−6.17 (m, 1H), 5.95−5.83 (m, 1H), 5.30−5.19 (m, 1H), 5.16−5.07 (m, 2H), 4.68 (d, $J$ = 2.3 Hz, 1H), 4.16 (ddt, $J$ = 12.7, 5.4, 1.4 Hz, 1H), 4.01 (ddt, $J$ = 13.7, 6.8, 1.3 Hz, 1H, superimposed by peak corresponding to the minor isomer), 3.57 (dd, $J$ = 8.5, 2.3 Hz, 1H), 2.09 (s, 3H), 1.04−0.99 (m, 1H), 0.99−0.94 (m, 3H). $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$) $\delta$ 193.8, 169.3, 140.9, 134.8, 128.8, 116.7, 87.0, 84.4, 77.0, 72.2, 29.4, 20.8, 19.5, 19.2. HRMS (ESI/Q-TOF) $m/z$: $[M + Na]^+$ calcd for $C_{14}H_{20}O_5Na$ 291.1203; found 291.1202.

*6-((S)-1-(Allyloxy)ethyl)-5-oxo-5,6-dihydro-2H-pyran-2-yl Acetate (**14d**).* The reaction was conducted according to the general procedure F with furfuryl alcohol **13d** (330 mg, 1.81 mmol), KBr (27 mg, 0.22 mmol), $NaHCO_3$ (76 mg, 0.90 mmol), and oxone (1.85 g, 3.01 mmol) to afford the desired hydroxypyranone. The acetylation reaction was conducted according to the general procedure using the crude hydroxypyranone (360 mg, 1.81 mmol), pyridine (318 $\mu$L, 3.62 mmol), and acetyl chloride (195 $\mu$L, 2.71 mmol) in $CH_2Cl_2$ (5 mL) for 30 min. Purification by silica gel column chromatography (10% EtOAc/hexanes) afforded an inseparable mixture of diastereomers of acetoxypyranone **14d** (260 mg, 60% over 2 steps) as a yellow oil. $^1H$ NMR (400 MHz, $CDCl_3$) $\delta$ 6.90 (td, $J$ = 10.1, 3.5 Hz, 1H), 6.54 (d, $J$ = 3.5 Hz, 1H), 6.16 (d, $J$ = 10.3 Hz, 1H), 5.93−5.81 (m, 1H), 5.16−5.03 (m, 2H), 4.66 (d, $J$ = 2.1 Hz, 1H), 4.14−3.91 (m, 3H, superimposed by peak corresponding to the minor isomer), 2.07 (s, 3H), 1.14 (d, $J$ = 6.5 Hz, 3H). $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$) $\delta$


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193.7, 169.2, 142.0, 134.7, 128.7, 116.9, 87.2, 77.7, 73.9, 70.0, 20.8, 14.3. HRMS (ESI/LTQ) $m/z$: $[M + Na]^+$ calcd for $C_{12}H_{16}O_5Na$ 263.0890; found 263.0892.

*6-((S)-(But-3-en-1-yloxy)(phenyl)methyl)-5-oxo-5,6-dihydro-2H-pyran-2-yl Acetate (**14e**).* The reaction was conducted according to the general procedure G with furfuryl alcohol **13e** (50 mg, 0.19 mmol), KBr (2.5 mg, 0.02 mmol), $NaHCO_3$ (8.2 mg, 0.1 mmol), and oxone (145 mg, 0.23 mmol) to afford the desired hydroxypyranone. The acetylation reaction was conducted according to the general procedure using the crude hydroxypyranone(53 mg, 0.19 mmol), pyridine (25 μL, 0.29 mmol), and acetyl chloride (20 μL, 0.29 mmol) in $CH_2Cl_2$ (1.0 mL) for 3 h. Purification by silica gel column chromatography (15% EtOAc/hexanes) afforded a separable mixture of *anti*/*syn*-acetoxypyranone **14e** (36 mg, 60% yield over 2 steps) as a colorless oil in 3:1 diastereomeric ratio. *anti*-Acetoxypyranone **14e**: $^1H$ NMR (400 MHz, $CDCl_3$) $\delta$ 7.36−7.21 (m, 5H), 6.79 (dd, $J$ = 10.3, 3.6 Hz, 1H), 6.48 (dd, $J$ = 3.6, 0.6 Hz, 1H), 6.06 (dd, $J$ = 10.3, 0.7 Hz, 1H), 5.79 (ddt, $J$ = 17.0, 10.2, 6.7 Hz, 1H), 5.10−4.97 (m, 3H), 4.92 (d, $J$ = 2.8 Hz, 1H), 3.45 (ddt, $J$ = 32.7, 9.3, 6.8 Hz, 2H), 2.35 (dq, $J$ = 7.0, 1.5 Hz, 2H), 2.11 (s, 3H). $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$) $\delta$ 192.8, 169.3, 141.9, 136.3, 134.9, 128.6, 128.3, 127.9, 127.8, 116.4, 87.3, 80.5, 79.4, 68.8, 34.0, 20.9. HRMS (ESI/LTQ) $m/z$: $[M + Na]^+$ calcd for $C_{18}H_{20}O_5Na$ 339.1203; found 339.1208.

*6-((S)-1-(But-3-en-1-yloxy)-2-methylpropyl)-5-oxo-5,6-dihydro-2H-pyran-2-yl Acetate (**14f**).* The reaction was conducted according to the general procedure G with furfuryl alcohol **13f** (100 mg, 0.45 mmol), KBr (5.0 mg, 0.04 mmol), $NaHCO_3$ (19.0 mg, 0.22 mmol), and oxone (330 mg, 0.54 mmol) to afford the desired hydroxypyranone. The acetylation reaction was conducted according to the general procedure using the crude hydroxypyranone (107 mg, 0.45 mmol), pyridine (78 μL, 0.89 mmol), and acetyl chloride (48 μL, 0.67 mmol) in $CH_2Cl_2$ (1.5 mL) for 30 min. Purification by silica gel column chromatography (15% EtOAc/hexanes) afforded a mixture of diastereomers of acetoxypyranone **14f** (82 mg, 65% yield over 2 steps) as a yellow oil. $^1H$ NMR (400 MHz, $CDCl_3$) $\delta$ 6.91 (d, $J$ = 3.7 Hz, 1H), 6.58−6.52 (m, 1H), 6.28−6.18 (m, 1H), 5.88−5.75 (m, 1H), 5.14−5.01 (m, 2H), 4.69 (d, $J$ = 2.1 Hz, 1H), 3.72−3.64 (m, 1H), 3.48−3.40 (m, 2H), 2.34−2.28 (m, 2H), 2.24−2.19 (m, 1H), 2.14 (s, 3H), 1.10−0.86 (m, 6H, superimposed by peak corresponding to the minor isomer). $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$) $\delta$ 193.7, 169.2, 140.9, 135.2, 128.8, 116.1, 87.7, 84.9, 79.0, 70.6, 34.3, 29.4, 20.7, 19.7, 19.2. HRMS (ESI/Q-TOF) $m/z$: $[M + Na]^+$ calcd for $C_{15}H_{22}O_5Na$ 305.1360; found 305.1357.

*6-((S)-1-(But-3-en-1-yloxy)ethyl)-5-oxo-5,6-dihydro-2H-pyran-2-yl Acetate (**14g**).* The reaction was conducted according to the general procedure G with furfuryl alcohol **13g** (55 mg, 0.28 mmol), KBr (4 mg, 0.03 mmol), $NaHCO_3$ (12 mg, 0.14 mmol), and oxone (210 mg, 0.34 mmol) to afford the desired hydroxypyranone. The acetylation reaction was conducted according to the general procedure using the crude hydroxypyranone (59 mg, 0.28 mmol), pyridine (50 μL, 0.55 mmol), and acetyl chloride (30 μL, 0.41 mmol) in $CH_2Cl_2$ (1.0 mL) for 40 min. Purification by silica gel column chromatography (10% EtOAc/hexanes) afforded a mixture of diastereomers of acetoxypyranone **14g** (53 mg, 75% yield over 2 steps) as a yellow oil. $^1H$ NMR (400 MHz, $CDCl_3$) $\delta$ 6.94−6.88 (m, 1H), 6.63 (dd, $J$ = 3.4, 0.7 Hz, 1H), 6.22−6.15 (m, 1H), 5.86−5.72 (m, 1H), 5.11−4.91 (m, 2H), 4.29−4.26 (m, 1H), 4.14−4.09 (m, 1H), 3.58−3.50 (m, 2H), 2.24−2.18 (m, 2H), 2.09 (s, 3H), 1.28 (d, $J$ = 6.5 Hz, 3H). $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$) $\delta$ 193.8, 169.1, 142.3, 134.9, 129.2, 116.2, 87.3, 79.8, 74.4, 69.3, 34.1, 20.8, 15.2. HRMS (ESI/LTQ) $m/z$: $[M + Na]^+$ calcd for $C_{13}H_{18}O_5Na$ 277.1046; found 277.1050.

*5-Oxo-6-((S)-1-(pent-4-en-1-yloxy)ethyl)-5,6-dihydro-2H-pyran-2-yl Acetate (**14h**).* The reaction was conducted according to the general procedure G with furfuryl alcohol **13h** (200 mg, 0.95 mmol), KBr (11.0 mg, 0.1 mmol), $NaHCO_3$ (40.0 mg, 0.48 mmol), and oxone (700 mg, 1.14 mmol) to afford the desired hydroxypyranone. The acetylation reaction was conducted according to the general procedure using the crude hydroxypyranone (215 mg, 0.95 mmol), pyridine (170 μL, 1.90 mmol), and acetyl chloride (100 μL, 1.43 mmol) in $CH_2Cl_2$ (3.0 mL) for 50 min. Purification by silica gel column chromatography (10% EtOAc/hexanes) afforded a mixture of diastereomers of acetoxypyranone **14h** (163 mg, 64% yield over 2 steps) as a yellow oil. $^1H$ NMR (400 MHz, $CDCl_3$) $\delta$ 6.94−6.86 (m, 1H), 6.53 (d, $J$ = 3.7 Hz, 1H), 6.21−6.13 (m, 1H), 5.83−5.65 (m, 1H), 4.94−4.85 (m, 2H), 4.29−4.23 (m, 1H), 4.08 (dd, $J$ = 7.0, 2.8 Hz, 1H), 3.56−3.38 (m, 2H), 2.07 (d, $J$ = 1.3 Hz, 3H), 2.03−1.93 (m, 2H), 1.66−1.58 (m, 2H), 1.24 (d, $J$ = 6.5 Hz, 3H). $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$) $\delta$ 193.8, 169.1, 142.3, 138.1, 129. 1, 114.6, 87.2, 79.7, 74.2, 68.4, 30.1, 28.8, 20.8, 15.2. HRMS (ESI/LTQ) $m/z$: $[M + Na]^+$ calcd for $C_{14}H_{20}O_5Na$ 291.0203; found 291.0207.

**General Procedure G: Synthesis of the Cycloadducts 16a−h.** To a stirred solution of the acetoxypyranone (1.0 equiv) in $CH_3CN$ (0.02 M) at 23 °C was added *N*-methylpyrrolidine (4.0 equiv), and the resulting mixture was heated to 60−150 °C in an oil bath. After 3−24 h, the mixture was concentrated, and the residue was purified by silica gel column chromatography afforded the desired cycloadduct.

*(3S,3aS,7S,8aS)-3-Phenyl-1,7,8,8a-tetrahydro-3H,4H-3a,7-epoxycyclohepta[c]furan-4-one (**16a**).* The reaction was conducted according to the general procedure G with acetoxypyranone **14a** (100 mg, 0.33 mmol) and *N*-methylpyrrolidine (138 μL, 1.32 mmol) in $CH_3CN$ (12.7 mL) at 60 °C for 12 h. Purification by silica gel column chromatography (20% EtOAc/hexanes) afforded the cycloadduct **16a** (71 mg, 89% yield, dr = 10:1) as a crystalline white solid. The purified compound was dissolved in ethyl acetate and hexanes and was allowed to crystallize at 23 °C for 5 days. $^1H$ NMR (800 MHz, $CDCl_3$) $\delta$ 7.47 (d, $J$ = 7.4 Hz, 2H), 7.37−7.26 (m, 3H), 7.15 (dd, $J$ = 9.7, 4.3 Hz, 1H), 6.01 (d, $J$ = 9.7 Hz, 1H), 5.56 (s, 1H), 5.05−4.98 (m, 1H), 4.22 (t, $J$ = 8.6 Hz, 1H), 4.08 (dd, $J$ = 9.3, 3.4 Hz, 1H), 2.97−2.89 (m, 1H), 2.33 (dd, $J$ = 12.1, 8.9 Hz, 1H), 2.16 (dt, $J$ = 12.0, 6.1 Hz, 1H). $^{13}C\{^1H\}$ NMR (200 MHz, $CDCl_3$) $\delta$ 194.9, 151.8, 135.6, 127.8, 127.8, 126.7, 126.7, 97.7, 80.0, 76.7, 71.9, 46.5, 36.4. HRMS (APCI/LTQ) $m/z$: $[M + H]^+$ calcd for $C_{15}H_{15}O_3$ 243.1016; found 243.1014.

*(3R,3aR,7R,8aR)-3-Phenyl-1,7,8,8a-tetrahydro-3H,4H-3a,7-epoxycyclohepta[c]furan-4-one (**16b**).* The reaction was conducted according to the general procedure G with acetoxypyranone **14b** (170 mg, 0.56 mmol) and *N*-methylpyrrolidine (235 μL, 2.25 mmol) in $CH_3CN$ (22 mL) at 60 °C for 12 h. Purification by silica gel column chromatography (20% EtOAc/hexanes) afforded the cycloadduct **16b** (100 mg, 74% yield, dr = 10:1) as a crystalline white solid. The purified compound was dissolved in ethyl acetate and hexanes and was allowed to crystallize at 23 °C for 5 days. $^1H$ NMR (800 MHz, $CDCl_3$) $\delta$ 7.47 (d, $J$ = 7.6 Hz, 2H), 7.36−7.26 (m, 3H), 7.15 (dd, $J$ = 9.7, 4.3 Hz, 1H), 6.01 (d, $J$ = 9.7 Hz, 1H), 5.56 (s, 1H), 5.02 (dd, $J$ = 6.7, 4.2 Hz, 1H), 4.22 (t, $J$ = 8.7 Hz, 1H), 4.08 (dd, $J$ = 9.2, 3.4 Hz, 1H), 2.96−2.90 (m, 1H), 2.33 (dd, $J$ = 12.0, 8.9 Hz, 1H), 2.16 (dt, $J$ = 12.3, 6.3 Hz, 1H). $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$) $\delta$ 194.9, 151.8, 135.6, 127.8, 127.8, 126.7, 126.7, 97.7, 80.0, 76.7, 71.9, 46.5, 36.4. HRMS (APCI/LTQ) $m/z$: $[M + H]^+$ calcd for $C_{15}H_{15}O_3$ 243.1016; found 243.1018.

*(3S,3aS,7S,8aS)-3-isopropyl-1,7,8,8a-tetrahydro-3H,4H-3a,7-epoxycyclohepta[c]furan-4-one (**16c**).* The reaction was conducted according to the general procedure G with acetoxypyranone **14c** (190 mg, 0.71 mmol) and *N*-methylpyrrolidine (295 μL, 1.41 mmol) in $CH_3CN$ (27 mL) at 60 °C for 12 h. Purification by silica gel column chromatography (15% EtOAc/hexanes) afforded the cycloadduct **16c** (129 mg, 88% yield, dr = 2:1) as a yellow oil. **16c** (major): $[\alpha]_D^{24}$ +38.6 (*c* 0.3, $CHCl_3$). $^1H$ NMR (400 MHz, $CDCl_3$) $\delta$ 7.17 (dd, $J$ = 9.8, 4.3 Hz, 1H), 5.98 (d, $J$ = 9.8 Hz, 1H), 5.01 (dd, $J$ = 6.6, 4.3 Hz, 1H), 4.01−3.93 (m, 2H), 3.84 (dd, $J$ = 9.2, 3.2 Hz, 1H), 2.74−2.66 (m, 1H), 2.22 (dd, $J$ = 12.0, 8.9 Hz, 1H), 2.05−1.90 (m, 2H), 1.06 (d, $J$ = 6.6 Hz, 3H), 0.84 (d, $J$ = 6.8 Hz, 3H). $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$) $\delta$ 195.4, 151.6, 126.7, 96.8, 84.6, 76.4, 71.4, 47.2, 36.2, 28.0, 20.3, 19.1. **16c** (minor): $[\alpha]_D^{24}$ −116.4 (*c* 0.2, $CHCl_3$). $^1H$ NMR (400 MHz, $CDCl_3$) $\delta$ 7.16 (dd, $J$ = 9.7, 4.4 Hz, 1H), 6.00 (d, $J$ = 9.5 Hz, 1H), 5.11 (d, $J$ = 4.9 Hz, 1H), 4.29 (t, $J$ = 8.2 Hz, 1H), 3.44 (t, $J$ = 9.1 Hz, 1H), 3.28 (d, $J$ = 10.4 Hz, 1H), 2.82 (dp, $J$ = 9.6, 6.4 Hz, 1H), 2.66 (p, $J$ = 7.8 Hz, 1H), 1.93 (t, $J$ = 5.4 Hz, 2H), 1.01 (d, $J$ = 6.6 Hz,


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3H), 0.81 (d, $J$ = 6.5 Hz, 3H). $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$) $\delta$ 195.7, 150.8, 128.0, 97.0, 93.1, 79.5, 72.7, 49.8, 31.9, 26.5, 20.3, 19.2.HRMS (APCI/LTQ) $m/z$: $[M + H]^+$ calcd for $C_{12}H_{17}O_3$ 209.1172; found 209.1174.

*(3S,3aS,7S,8aS)-3-Methyl-1,7,8,8a-tetrahydro-3H,4H-3a,7-epoxycyclohepta[c]furan-4-one (**16d**).* The reaction was conducted according to the general procedure G with acetoxypyranone **14d** (75 mg, 0.31 mmol) and *N*-methylpyrrolidine (130 $\mu$L, 1.25 mmol) in $CH_3CN$ (12 mL) at 60 °C for 12 h. Purification by silica gel column chromatography (20% EtOAc/hexanes) afforded the cycloadduct **16d** (25 mg, 45% yield, dr = 4:1) as a colorless oil. $^1H$ NMR (400 MHz, $CDCl_3$) $\delta$ 7.17 (dd, $J$ = 9.8, 4.3 Hz, 1H), 5.97 (d, $J$ = 9.7 Hz, 1H), 5.01 (dd, $J$ = 6.4, 4.4 Hz, 1H), 4.43 (q, $J$ = 6.4 Hz, 1H), 3.98 (dd, $J$ = 9.2, 8.0 Hz, 1H), 3.84 (dd, $J$ = 9.3, 3.0 Hz, 1H), 2.81−2.69 (m, 1H), 2.27 (dd, $J$ = 12.0, 8.9 Hz, 1H), 2.05 (dt, $J$ = 12.2, 6.2 Hz, 1H), 1.28 (d, $J$ = 6.4 Hz, 3H). $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$) $\delta$ 195.0, 151.9, 126.6, 96.7, 76.4, 74.9, 71.8, 46.0, 36.5, 12.8. HRMS (APCI/LTQ) $m/z$: $[M + H]^+$ calcd for $C_{10}H_{13}O_3$ 181.0859; found 181.0860.

*(1S,4aR,6S,9aS)-1-Phenyl-4,4a,5,6-tetrahydro-1H-6,9a-epoxycyclohepta[c]pyran-9(3H)-one (**16e**).* The reaction was conducted according to the general procedure G with acetoxypyranone **14e** (25 mg, 0.08 mmol) and *N*-methylpyrrolidine (33 $\mu$L, 0.32 mmol) in $CH_3CN$ (4.0 mL) at 60 °C for 4 h. Purification by silica gel column chromatography (20% EtOAc/hexanes) afforded the cycloadduct **16e** (12 mg, 60% yield, dr >19:1) as a white amorphous solid. $^1H$ NMR (400 MHz, $CDCl_3$) $\delta$ 7.43−7.36 (m, 2H), 7.36−7.19 (m, 4H), 5.91 (dd, $J$ = 9.8, 1.2 Hz, 1H), 5.50 (s, 1H), 4.86−4.77 (m, 1H), 4.10 (ddd, $J$ = 11.7, 4.6, 2.3 Hz, 1H), 3.65 (td, $J$ = 11.9, 1.7 Hz, 1H), 2.24 (qd, $J$ = 9.0, 7.4, 5.2 Hz, 1H), 2.13 (dd, $J$ = 12.3, 8.1 Hz, 1H), 2.00 (ddt, $J$ = 12.3, 7.2, 4.1 Hz, 2H), 1.80−1.65 (m, 1H). $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$) $\delta$ 197.1, 155.3, 138.3, 127.9, 127.7, 127.6, 126.7, 87.7, 77.2, 71.3, 66.4, 39.8, 35.1, 30.4. HRMS (APCI/LTQ) $m/z$: $[M + H]^+$ calcd for $C_{16}H_{17}O_3$ 257.1172; found 257.1173.

*(1S,4aR,6S,9aS)-1-Isopropyl-4,4a,5,6-tetrahydro-1H-6,9a-epoxycyclohepta[c]pyran-9(3H)-one (**16f**).* The reaction was conducted according to the general procedure G with acetoxypyranone **14f** (50 mg, 0.18 mmol) and *N*-methylpyrrolidine (75 $\mu$L, 0.71 mmol) in $CH_3CN$ (9.0 mL) at 60 °C for 24 h. The reaction mixture was concentrated, and the residue was washed with 1 N HCl. The mixture was extracted with EtOAc (3×), washed with brine, dried over anhydrous $Na_2SO_4$, filtered, and concentrated. Purification by silica gel column chromatography (15% EtOAc/hexanes) afforded the cycloadduct **16f** (33 mg, 84% yield, dr >19:1) as a white amorphous solid. $^1H$ NMR (400 MHz, $CDCl_3$) $\delta$ 7.37 (dd, $J$ = 9.8, 4.8 Hz, 1H), 6.02 (d, $J$ = 9.8 Hz, 1H), 4.82 (dd, $J$ = 7.6, 4.8 Hz, 1H), 4.01 (d, $J$ = 7.9 Hz, 1H), 3.97−3.84 (m, 1H), 3.47−3.29 (m, 1H), 2.16−1.96 (m, 2H), 1.96−1.77 (m, 3H), 1.58−1.41 (m, 1H), 1.01 (d, $J$ = 6.7 Hz, 3H), 0.79 (d, $J$ = 6.9 Hz, 3H). $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$) $\delta$ 197.9, 154.3, 126.7, 86.8, 80.5, 71.0, 65.7, 39.5, 35.7, 30. 9, 30.6, 20.2, 19.5. HRMS (APCI/LTQ) $m/z$: $[M + H]^+$ calcd for $C_{13}H_{19}O_3$ 223.1329; found 223.1331.

*(1S,4aR,6S,9aS)-1-Methyl-4,4a,5,6-tetrahydro-1H-6,9a-epoxycyclohepta[c]pyran-9(3H)-one (**16g**).* The reaction was conducted according to the general procedure G with acetoxypyranone **14g** (50 mg, 0.20 mmol) and *N*-methylpyrrolidine (82 $\mu$L, 0.79 mmol) in $CH_3CN$ (10 mL) at 60 °C for 18 h. Purification by silica gel column chromatography (20% EtOAc/hexanes) afforded the cycloadduct **16g** (30 mg, 79% yield, dr >19:1) as a white amorphous solid. $^1H$ NMR(400 MHz, $CDCl_3$) $\delta$ 7.43 (dd, $J$ = 9.7, 4.8 Hz, 1H), 5.98 (d, $J$ = 9.7 Hz, 1H), 4.87−4.79 (m, 1H), 4.40 (q, $J$ = 6.5 Hz, 1H), 3.89 (ddd, $J$ = 11.6, 4.6, 2.3 Hz, 1H), 3.50−3.38 (m, 1H), 2.17−2.01 (m, 2H), 1.99−1.85 (m, 2H), 1.61−1.46 (m, 1H), 1.19 (d, $J$ = 6.5 Hz, 3H). $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$) $\delta$ 197.4, 155.7, 126.6, 87.3, 71.3, 71.2, 65.8, 39.7, 34.1, 30.5, 16.8. HRMS (APCI/LTQ) $m/z$: $[M + H]^+$ calcd for $C_{11}H_{15}O_3$ 195.1016; found 195.1017.

*(1S,5aR,7S,10aS)-1-Methyl-3,4,5,5a,6,7-hexahydro-1H,10H-7,10a-epoxycyclohepta[c]oxepin −10-one (**16h**).* The reaction was conducted according to the general procedure G with acetoxypyranone **14h** (100 mg, 0.37 mmol) and *N*-methylpyrrolidine (58 $\mu$L, 0.56 mmol) in $CH_3CN$ (19 mL) in a sealed tube for 3 h at 150 °C. Purification by silica gel column chromatography (20% EtOAc/hexanes) afforded the cycloadduct **16h** (46 mg, 59% yield, dr >19:1) as a white amorphous solid. $^1H$ NMR(400 MHz, $CDCl_3$) $\delta$ 7.28−7.20 (m, 1H), 5.89 (dd, $J$ = 9.8, 0.8 Hz, 1H), 4.85 (q, $J$ = 4.2 Hz, 1H), 4.25 (q, $J$ = 6.5 Hz, 1H), 3.90 (dd, $J$ = 11.5, 5.9 Hz, 1H), 3.65−3.49 (m, 1H), 2.33−2.18 (m, 1H), 2.03−1.92 (m, 3H), 1.90−1.77 (m, 2H), 1.69 (q, $J$ = 9.1, 6.9 Hz, 1H), 1.23 (dd, $J$ = 6.4, 0.8 Hz, 3H). $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$) $\delta$ 198.4, 153.0, 125.8, 92.7, 73.7, 71.6, 40.8, 35.6, 29.0, 26.3, 18.3. HRMS (APCI/LTQ) $m/z$: $[M + H]^+$ calcd for $C_{12}H_{17}O_3$ 209.1172; found 209.1174.

*(3S,3aS,4S,7R,8aR)-3-Isopropyl-4,7,8,8a-tetrahydro-1H,3H-3a,7-epoxycyclohepta[c]furan-4-ol (**21**).* To a solution of the cycloadduct **16c** (minor) (20 mg, 0.10 mmol) in a 4:1 mixture of $MeOH/CH_2Cl_2$ (5 mL) at 23 °C was added $CeCl_3{\cdot}7H_2O$ (54 mg, 0.14 mmol). After stirring for 30 min the reaction mixture was cooled to 0 °C and sodium borohydride (4.0 mg, 0.10 mmol) was added. After 1 h, the reaction was quenched with $H_2O$ and extracted with ethyl acetate (3×). The combined organic layers were washed with brine, dried over $Na_2SO_4$, filtered, and concentrated under reduced pressure. Purification by silica gel column chromatography (25% EtOAc/hexanes) afforded the allylic alcohol **21** (15.0 mg, 75% yield, dr >19:1) as a white amorphous solid. $[\alpha]_D^{24}$ +25.3 ($c$ 0.1, $CHCl_3$). $^1H$ NMR(400 MHz, $CDCl_3$) $\delta$ 5.99 (dd, $J$ = 9.7, 3.9 Hz, 1H), 5.49 (dd, $J$ = 9.7, 2.0 Hz, 1H), 4.86 (s, 1H), 4.74 (t, $J$ = 5.0 Hz, 1H), 4.18 (t, $J$ = 8.4 Hz, 1H), 3.39 (t, $J$ = 8.7 Hz, 1H), 3.26 (p, $J$ = 7.4 Hz, 2H), 2.10 (dq, $J$ = 12.6, 6.4 Hz, 1H), 2.01 (dd, $J$ = 11.6, 8.1 Hz, 1H), 1.76 (dt, $J$ = 12.0, 6.3 Hz, 1H), 1.68 (s, 1H), 1.03 (t, $J$ = 6.9 Hz, 6H). $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$) $\delta$ 133.0, 127.7, 94.2, 91.1, 80.1, 72.4, 68.2, 43.8, 36.6, 27.3, 20.1, 19.8. HRMS (APCI/LTQ) $m/z$: $[M + H]^+$ calcd for $C_{12}H_{19}O_3$ 211.1329; found 211.1328.

## ■ ASSOCIATED CONTENT

### Supporting Information

The Supporting Information is available free of charge at https://pubs.acs.org/doi/10.1021/acs.joc.1c00600.

$^1H$ and $^{13}C$ NMR spectra for all new compounds, HPLC data, and X-ray crystallographic data (PDF)

### Accession Codes

CCDC 2025567−2025568 and 2064460 contain the supplementary crystallographic data for this paper. These data can be obtained free of charge via www.ccdc.cam.ac.uk/data_request/cif, or by emailing data_request@ccdc.cam.ac.uk, or by contacting The Cambridge Crystallographic Data Centre, 12 Union Road, Cambridge CB2 1EZ, UK; fax: +44 1223 336033.

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### Notes

The authors declare no competing financial interest.

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