JOC The Journal of Organic Chemistry

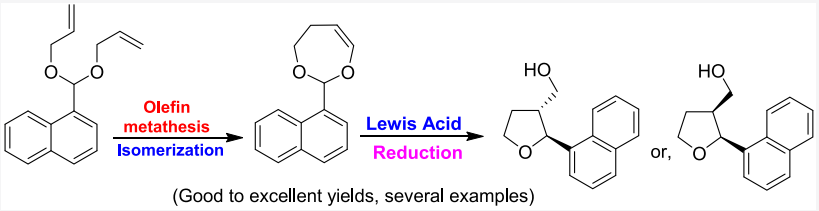
pubs.acs.org/joc Article

Lewis Acid-Catalyzed Vinyl Acetal Rearrangement of 4,5-Dihydro-1,3-dioxepines: Stereoselective Synthesis of *cis*- and *trans*-2,3-Disubstituted Tetrahydrofurans

Arun K. Ghosh* and Miranda R. Belcher

Cite This: https://dx.doi.org/10.1021/acs.joc.0c00390 Read Online

ACCESS | Metrics & More | Article Recommendations | Supporting Information



ABSTRACT: Lewis acid-catalyzed rearrangements of 4,5-dihydro-1,3-dioxepines have been investigated. Rearrangement of vinyl acetals under a variety of conditions resulted in *cis*- and *trans*-2,3-disubstituted tetrahydrofuran derivatives in a highly stereoselective manner. Rearrangements at lower temperatures typically provided the *cis*-2,3-disubstituted tetrahydrofuran carbaldehydes. At higher temperatures, the corresponding *trans*-2,3-disubstituted tetrahydrofuran carbaldehydes are formed. The requisite substrates for the vinyl acetal rearrangement were synthesized via ring-closing olefin metathesis of bis(allyoxy)methyl derivatives using Grubbs second-generation catalyst followed by olefin isomerization using a catalytic amount of $RuCl_2(PPh_3)_3$. We examined the substrate scope using substituted aromatic and aliphatic derivatives. Additionally, the rearrangement was utilized in the synthesis of a stereochemically-defined bis-tetrahydrofuran (bis-THF) derivative, which is one of the key structural elements of darunavir, an FDA-approved drug for the treatment of HIV/AIDS.

INTRODUCTION

Substituted tetrahydrofurans are important structural motifs in a variety of bioactive natural products and pharmaceutical agents.[1,2] Representative examples include anticancer agent amphidinolide T (**1**, Figure 1),[3,4] proliferation-promoting agent amphirionin-4 (**2**),[5] antifungal agent posaconazole (**3**),[6,7] and anti-HIV agent darunavir (**4**).[8,9] Over the years, numerous methods for the synthesis of disubstituted tetrahydrofurans have been developed.[10,11] However, development of efficient methods for the synthesis of 2,3-disubstituted tetrahydrofurans has not received much attention. Synthetic methods such as halocyclization, radical cyclization, and vinyl acetal rearrangements have been utilized for the synthesis of these tetrahydrofuran derivatives.[12−14] In our continuing studies toward the protein X-ray crystal structure-based design of molecular probes, we require a range of stereochemically defined cyclic ether-derived ligands and structural templates.[15,16] Of particular interest is a general synthesis of 2-(alkoxymethyl or substituted aryl)-3-tetrahydrofuranyl-methanol derivatives. As outlined in Scheme 1, Lewis acid-catalyzed vinyl acetal rearrangement of 4,5-dihydro-1,3-dioxepines (**5**) provided access to substituted tetrahydrofuranyl derivatives.[14] In particular, Scharf and coworkers, Frauenrath and coworkers, and Suzuki and coworkers investigated such Lewis acid-catalyzed vinyl acetal rearrangements to provide *cis*- and *trans*-2,3-tetrahydrofuran-3-carbaldehydes depending on the reaction conditions.[17−20]

As shown, Lewis acid activation of 4,5-dihydro-1,3-dioxepines **5** with a Lewis acid of choice would provide intermediate **8**, which rearranges to the kinetic zwitterionic oxocarbenium ion intermediate **9** at low temperatures. However, at higher temperatures, intermediate **9** can invert to the thermodynamically more stable oxocarbenium ion **10** to avoid steric hindrance between the bulky aromatic ring and the enolate substituent.[17] Oxocarbenium ion intermediates **9** and **10** would stereoselectively provide *cis*- and *trans*-aldehydes **6** and **7**, respectively.[21,22] The reaction of vinyl acetals at lower temperatures (−78 °C) under kinetically controlled conditions provided the *cis*-tetrahydrofuran derivatives as the major products.[14,17] Additionally, as speculated by Scharf and coworkers, there exists an equilibrium between aldehyde products **6** and **7** in which upon exposure of **6** to Lewis acid, the Lewis acid chelates to the aldehyde oxygen and the

Received: March 10, 2020

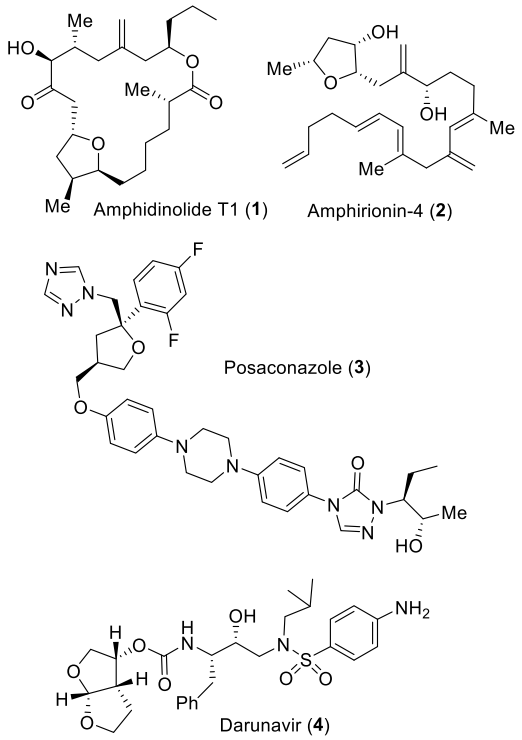
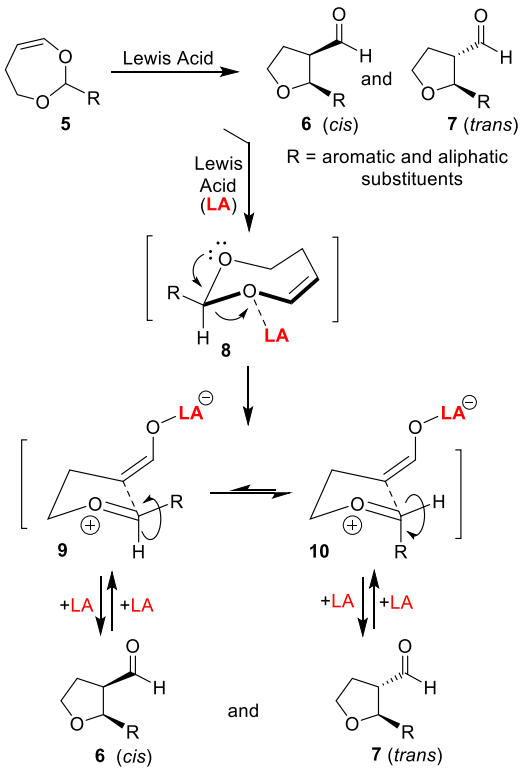


Figure 1. Representative bioactive compounds containing functionalized tetrahydrofurans.

Scheme 1. Lewis-Acid-Catalyzed Vinyl Acetal Rearrangement of 4,5-Dihydro-1,3-dioxepines to *cis*- and *trans*-Disubstituted Tetrahydrofurans



product rearranges back to intermediate **9**.[17] Following rearrangement, **9** then undergoes inversion to **10**, ultimately resulting in the thermodynamically favored aldehyde product **7**.[17] Scharf and coworkers also observed that the *trans*-derivatives prevailed as the major isomers at higher temperatures (150 °C).[17] From this work, it was concluded that at higher temperatures, the kinetic *cis*-aldehyde product is converted to the thermodynamically more stable *trans*-aldehyde. Furthermore, exposure of the aldehyde products to a deuterated acid resulted in no deuterium incorporation.[17] Therefore, it can be argued that the *cis*-aldehyde is not converted to the *trans*-aldehyde via its enol form. Rather, conversion occurs via another Lewis-acid-catalyzed rearrangement. Frauenrath and coworkers observed the *cis*-derivatives as the major isomers at lower temperature (−78 °C), which they explain occurred through cyclization that arises from oxocarbenium ion facial bias.[18,19,21,22] Additionally, they obtained the *trans*-derivatives via epimerization of the *cis*-derivatives with 10 mol % morpholine.[18,19] In a contradicting report, Suzuki and coworkers claimed that the *trans*-derivatives were obtained as the major isomers at lower temperatures (−73 °C).[20] Additionally, Rovis and coworkers reported a stereoretentive rearrangement of vinyl acetals dictated by oxocarbenium ion facial bias and tight ion-pair binding in the solvent cage.[23]

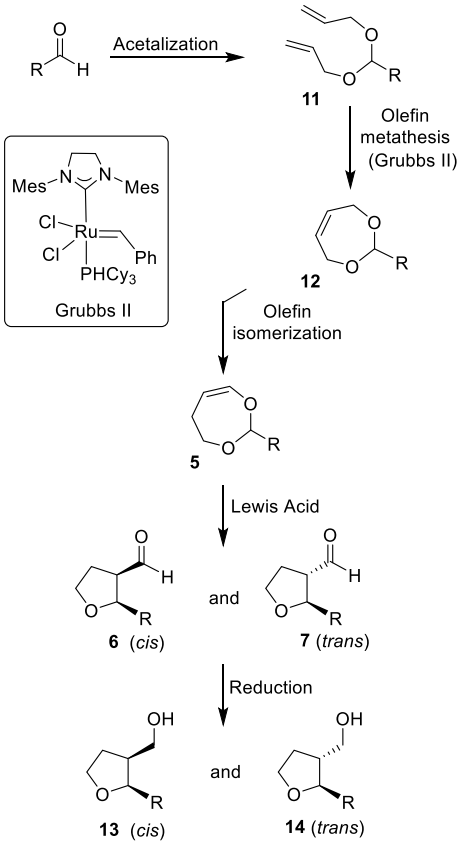
Based upon these reports, we investigated the scope and generality of these Lewis-acid-catalyzed reactions with a variety of substituted 4,5-dihydro-1,3-dioxepine derivatives under mild conditions. For efficient synthesis of 4,7-dihydro-1,3-dioxepines, we carried out ring-closing metathesis of diallyl acetals to provide the cyclic acetals in excellent yields. Subsequent double-bond isomerization using a catalytic amount of hydridic ruthenium provided the 4,5-dihydro-1,3-dioxepine substrates. We synthesized a variety of both *cis*- and *trans*-2,3-disubstituted tetrahydrofuran derivatives. Furthermore, rearrangement of the product resulting from 2-(benzyloxymethyl)-4,5-dihydro-1,3-dioxepine was converted to the bis-tetrahydrofuran derivative, a key structural component of darunavir, an FDA approved HIV-1 protease inhibitor drug for the treatment of HIV/AIDS.[15,16]

RESULTS AND DISCUSSION

Our general plans for the synthesis of *cis*- and *trans*-disubstituted tetrahydrofurans using a Lewis-acid-catalyzed vinyl acetal rearrangement are shown in Scheme 2. We planned to synthesize variously substituted 4,7-dihydro-1,3-dioxepines efficiently via olefin metathesis of the corresponding diallyl acetal. As shown, our reaction sequence begins with an aldehyde of choice, which undergoes acetalization with allyl alcohol and a catalytic amount of *p*-toluenesulfonic acid (PTSA) to form a diallyl acetal **11**. Substituted dioxepines **12** can be synthesized from diallyl acetal derivatives via olefin metathesis using Grubbs second-generation catalyst.[24,25] A ruthenium or potassium *tert*-butoxide catalyzed olefin isomerization of **12** would provide various 4,5-dihydro-1,3-dioxepine substrates **5** for our investigation of Lewis-acid-catalyzed rearrangements to substituted tetrahydrofurans. For accurate stereochemical analysis of our products, we planned to reduce aldehydes **6** and **7** and characterize the stereochemical outcome using alcohols **13** and **14**. We initially optimized reaction conditions using the phenyl dioxepine derivative **12a** (R = Ph) and utilized the conditions for other substrates. The results are shown in Table 1. The reaction of benzaldehyde with allyl alcohol in THF in the presence of a catalytic amount of PTSA and 4 Å molecular sieves at 23 °C for 24 h provided diallyl acetal **11a** in 53% yield. Similarly, variously substituted

https://dx.doi.org/10.1021/acs.joc.0c00390
J. Org. Chem. XXXX, XXX, XXX−XXX

Scheme 2. General Synthesis of 4,5-Dihydro-1,3-dioxepines and Subsequent Lewis-Acid-Catalyzed Vinyl Acetal Rearrangement

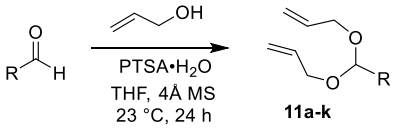


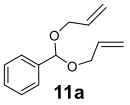
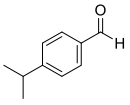
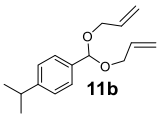
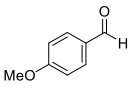
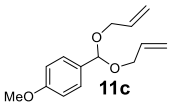
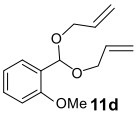
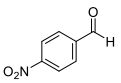
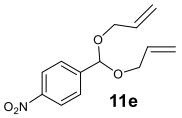
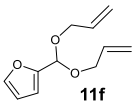
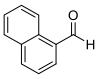
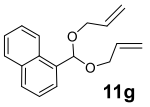
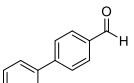
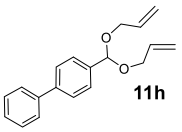
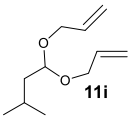
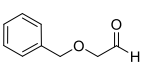
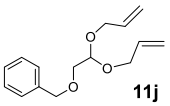
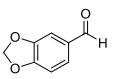
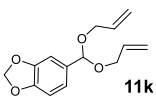
aromatic aldehydes, isovaleraldehyde, and benzyloxyacetaldehyde provided the corresponding diallyl acetals **11b**–**11k** in good to excellent yields (20–99%).

The diallyl acetals **11a**–**k** were then converted to dioxepine derivatives **12a**–**12k** using ring-closing metathesis and the results are shown in Table 2. Treatment of diallyl acetal **11a** with a catalytic amount (5 mol %) of Grubbs second-generation catalyst[24,25] in CH_2Cl_2 at reflux for 2 h afforded 2-phenyl-4,7-dihydro-1,3-dioxepine **12a** in 81% yield. Similarly, ring closing metathesis of other diallyl acetals furnished dioxepine derivatives **12b**–**k** in 61–95% yield.

Olefin isomerizations[20,26,27] of the 4,7-dihydro-1,3-dioxepines were then carried out using a catalytic amount of $RuCl_2(PPh_3)_3$ and a small amount of $NaBH_4$ in methanol at reflux. The results are shown in Table 3. Exposure of **12a** with 2 mol % $RuCl_2(PPh_3)_3$ and 5 mol % $NaBH_4$ in methanol for 3 h provided 2-phenyl-4,5-dihydro-1,3-dioxepine **5a** along with a small amount of hydrogenated product. These products were not separable by silica gel chromatography and the combined yield of both products was 67%. The ^1H NMR analysis revealed the presence of 7% hydrogenated product. Other 4,5-dihydro-1,3-dioxepines **5b**–**k** were also prepared using the conditions below in varying yields (23–96%). Saturated product yields are shown within the parentheses. The yields of these reactions vary from substrate to substrate. The hydrogenated double-bond derivative was observed as a major side-product (typically ranging from 10 to 30%; acetals containing electron-donating groups typically had larger amounts of hydrogenated byproduct). As with the case of

Table 1. Synthesis of Diallyl Acetals from Aldehydes and Allyl Alcohol[a]



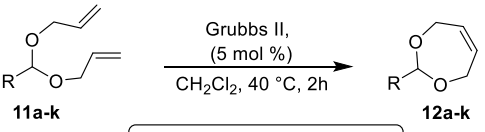
Entry	Aldehyde	Product	Yield[b] (%)
1		 **11a**	53
2		 **11b**	89
3		 **11c**	51
4		 **11d**	60
5		 **11e**	99
6		 **11f**	73
7		 **11g**	64
8		 **11h**	71
9		 **11i**	77
10		 **11j**	43[b]
11		 **11k**	20

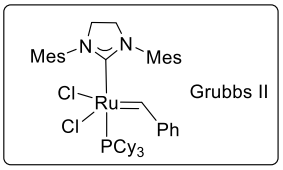
[a]Reactions were carried out typically on a 7 to 8 mmol scale at 23 °C in THF (1.5 M solution) in the presence of allyl alcohol (5 equiv), PTSA·H_2O (0.2 equiv), and 4 Å MS. [b]Yield taken over 2 steps.

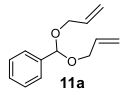
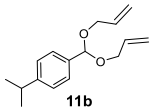
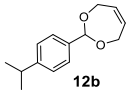
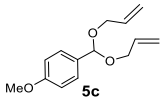
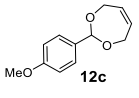
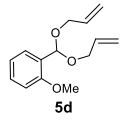
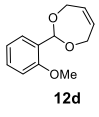
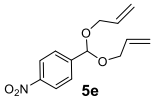
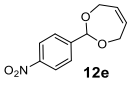
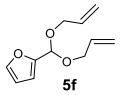
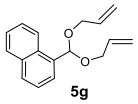
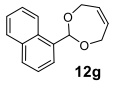
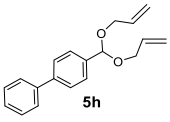
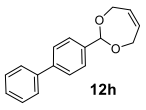
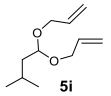
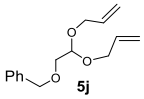
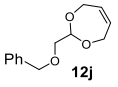
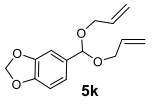
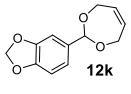
5a, the hydrogenated derivatives are inseparable from the desired 4,5-dihydro-1,3-dioxepines via silica gel column

https://dx.doi.org/10.1021/acs.joc.0c00390
J. Org. Chem. XXXX, XXX, XXX−XXX

Table 2. Synthesis of 4,7-Dihydro-1,3-dioxepines Using Ring-Closing Metathesis[a]

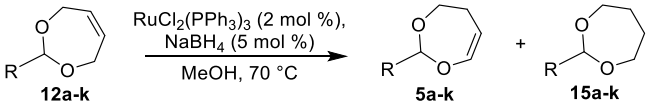


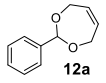
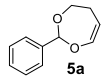
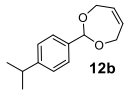
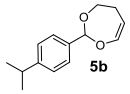
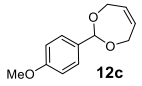
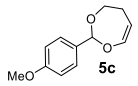
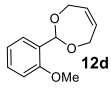
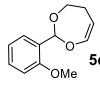
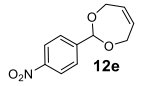
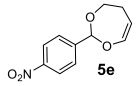
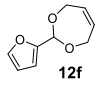
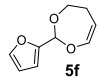
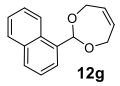
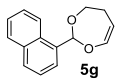
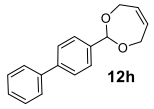


Entry	Substrate	Product	Yield (%)
1	 11a	 12a	81
2	 11b	 12b	90
3	 5c	 12c	74
4	 5d	 12d	91
5	 5e	 12e	88
6	 5f	 12f	61
7	 5g	 12g	87
8	 5h	 12h	62
9	 5i	 12i	62
10	 5j	 12j	95
11	 5k	 12k	90

[a]Reactions were carried out typically on a 0.7 mmol scale at 40 °C in CH_2Cl_2 (0.01 M solution) in the presence of Grubbs second-generation catalyst (5 mol %).

Table 3. Results and Structures from the Double Bond Isomerization Reaction[a]



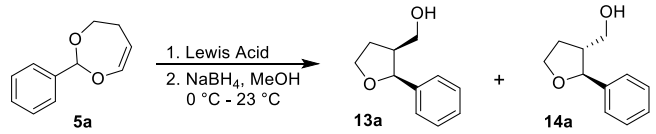
Entry	Substrate	Product	Yield[b] (%)
1	 12a	 5a	67 (7)
2	 12b	 5b	89 (21)
3	 12c	 5c	96 (30)
4	 12d	 5d	96 (0)
5	 12e	 5e	48 (3)
6	 12f	 5f	66 (16)
7	 12g	 5g	79 (13)
8	 12h	5h	23[c]
9	12i	5i	44 (15)
10	12j	5j	80 (12)
11	12k	5k	73 (4)

[a]Reactions were carried out at 70 °C in methanol (1 M solution) in the presence of $RuCl_2(PPh_3)_3$ (2 mol %) and $NaBH_4$ (5 mol %). See the Experimental Section for further information. [b]Combined yield of 4,5-dihydro-1,3-dioxepine and its hydrogenated derivative. Yield of hydrogenated derivative is in the parentheses. [c]Alternate conditions with *t*-BuOK in DMSO provided 23% yield of isomerized product 5 h (70% combined yield of product and starting material). Please see the Experimental Section for this information.

chromatography. Thus, following a short column in EtOAc/hexanes spiked with triethylamine, the combined product

https://dx.doi.org/10.1021/acs.joc.0c00390
J. Org. Chem. XXXX, XXX, XXX−XXX

Table 4. Catalyst Loading and Lewis Acid Optimization of the Vinyl Acetal Rearrangement



5a 13a 14a

entry	Lewis acid	equivalents of lewis acid	temperature (°C)	solvent	time	diastereomeric ratio (*cis*:*trans*)[a]	yield (2 steps) (%)
1	$BF_3{\cdot}OEt_2$	1	−78	CH_2Cl_2	10 min	20:1	77
2	$BF_3{\cdot}OEt_2$	0.5	−78	CH_2Cl_2	10 min	20:1	77
3	$BF_3{\cdot}OEt_2$	0.2	−78	CH_2Cl_2	10 min	20:1	77
4	$BF_3{\cdot}OEt_2$	0.2	23	CH_2Cl_2	3 h	1:6	22
5	TMSOTf	0.2	−78	CH_2Cl_2	10 min	6:1	66
6	TBSOTf	0.2	−78	CH_2Cl_2	10 min	6:1	58
7	$Sc(OTf)_3$	0.2	−78	CH_2Cl_2	6 h	14:1	52
8	$Sc(OTf)_3$	0.2	−40	CH_2Cl_2	1 h	4:1	82
9	$Cu(OTf)_2$	0.2	0	CH_2Cl_2	4 h	2:1	74
10	$FeCl_3$	0.2	−20	CH_2Cl_2	1 h	5:1	79
11	$FeCl_3$	0.2	0	CH_2Cl_2	1 h	4:1	58
12	$ZnCl_2$	0.2	23	CH_2Cl_2	2 h	2:1	76
13	$Zn(OTf)_2$	0.2	23	CH_2Cl_2	3 h	2:1	80
14	$Zn(OTf)_2$	0.2	40	CH_2Cl_2	3 h	1:1	88
15	$Zn(OTf)_2$	0.2	110	PhMe	3 h	1:4	69
16	$Zn(OTf)_2$	0.2	132	PhCl	9 h	1:17	41
17	$Zn(OTf)_2$	0.2	140	Xylenes	8.5 h	1:20	48
18	$Dy(OTf)_3$	0.2	23	CH_2Cl_2	24 h	1:2	80

[a]Diastereomeric ratios were determined via integration of the characteristic benzylic peak in the ^1H NMR spectra.

yields were reported, and the yield of the hydrogenated products (within parentheses) are calculated by ^1H NMR integration. The saturated side-products do not affect further reactions; thus, the 4,5-dihydro-1,3-dioxepines were utilized in the next reaction without further attempts at purification. In the case of substrate **12h**, the $RuCl_2(PPh_3)_3$ and $NaBH_4$-catalyzed reaction conditions provided only the corresponding saturated product in 68% yield. Therefore, we utilized alternate conditions with *t*-BuOK in DMSO at 23 °C for 24 h to provide 23% yield of isomerized product **5h** along with 47% unreacted starting material **12h**. The isomerized product **5h** could not be separated from the starting material **12h** by silica gel chromatography. The mixture of products was used directly in the rearrangement reaction.

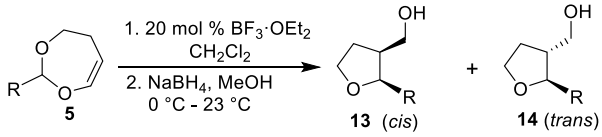
Following the synthesis of various 4,5-dihydro-1,3-dioxepines, we sought to optimize the Lewis acid-catalyzed vinyl acetal rearrangement using phenyl derivative **5**. A variety of Lewis acids, along with varying reaction conditions, were examined. As mentioned previously, diastereoselectivities were determined after reduction of the aldehydes to the corresponding alcohols using $NaBH_4$ in MeOH from 0 to 23 °C. The results are shown in Table 4. As shown, $BF_3{\cdot}OEt_2$-catalyzed reactions at −78 °C afforded the best ratio of *cis*:*trans* isomers and yields (entries 1−3). A lower catalyst loading of 20 mol %, as shown in entry 3, provided the optimized results with excellent *cis*-selectivity. Interestingly, the $BF_3{\cdot}OEt_2$-catalyzed reaction at 23 °C afforded the *trans*-isomer as the major product in 22% isolated yield (entry 4). Both TMSOTf and TBSOTf catalyzed reactions showed lower selectivity and yields (entries 5 and 6). The $Sc(OTf)_3$-catalyzed reaction at −78 °C showed excellent *cis*-selectivity; however, yield was significantly lower (entry 7). The $Zn(OTf)_2$-catalyzed reaction at 23 °C showed marginal *cis*-selectivity (2:1) and at higher temperatures showed good to excellent *trans*-selectivity (entries 13−17).

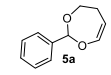
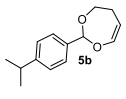
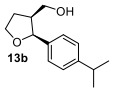
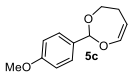
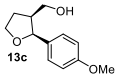
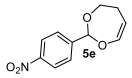
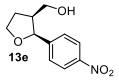
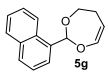
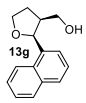
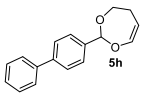
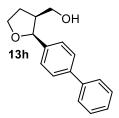
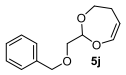
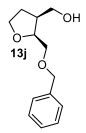
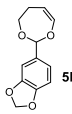
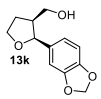
We then examined the vinyl acetal rearrangement with a variety of substrates using 20 mol % $BF_3{\cdot}OEt_2$ as shown in entry 3. The results are shown in Table 5. It should be noted that the substrate in entry 10 required a slightly higher temperature for the reaction to go to completion. Introduction of *p*-alkyl or *p*-methoxy groups affected *cis*-diastereoselectivity (entries 2 and 3). The *ortho*-methoxyphenyl, however, increased the diastereomeric ratio up to greater than 20:1 (entry 4). Interestingly, electron-withdrawing substituents at the *para*-position of the phenyl ring also decreased the *cis*-diastereoselectivity drastically (entry 5). Yields and diastereomeric ratios were calculated once again after reduction of the aldehyde to the corresponding alcohol. Separation of the *cis*- and *trans*- diastereomers via column chromatography proved to be difficult due to the similar R_f values of the two diastereomers. Thus, we decided to confirm the relative stereochemistry of the *cis*-diastereomer of alcohol **13e** by obtaining an X-ray crystal structure of the *p*-bromobenzoate derivative of the major diastereomer. As shown in Scheme 3, alcohol **13e** was reacted with *p*-bromobenzoyl chloride in the presence of Et_3N and a catalytic amount of DMAP in CH_2Cl_2 at 23 °C for 12 h to provide the benzoate ester *cis*-**16** in 80% yield. Standard recrystallization in a mixture of ethyl acetate and hexanes (23 °C, 3 days) provided crystals for X-ray analysis. The ORTEP drawing of the *p*-bromobenzoate ester *cis*-**16** is shown in the Supporting Information, and the structure supported the assignment of *cis*-stereochemistry.[28,29]

We also investigated the Lewis-acid-catalyzed vinyl acetal rearrangement under thermal conditions in an effort to obtain *trans*-2,3-disubstituted tetrahydrofuran derivatives. As shown in Table 4 (entries 13−18), $Zn(OTf)_2$-catalyzed reactions at higher temperatures resulted in the *trans*-2,3-disubstituted tetrahydrofuran derivatives as major products. Thus, with a select few substrates, reactions were carried out with $Zn(OTf)_2$ (20 mol %) in xylenes at 140 °C. For convenient isolation and

https://dx.doi.org/10.1021/acs.joc.0c00390
J. Org. Chem. XXXX, XXX, XXX−XXX

Table 5. Substrate Scope for the Vinyl Acetal Rearrangement[a]



Entry	Substrate	Major Product	Temp [° C]	Time	Diastereomeric ratio (*cis:trans*)[b]	Yield (2 steps) [%]
1			-78	10 min	20:1	70
2			-78	1 h	3:1	68
3			-78	30 min	2:1	49
4			-78	30 min	>20:1	58
5			-78	5 h	3:1	50
6			-78	30 min	3:1	54
7			-78	10 min	14:1	55
8[c]			-78	30 min	11:1	63
9			-78	10 min	2:1	55
10			-78 to -40	2 h	5:1	42
11			-78	10 min	4:1	68

[a]Reactions were carried out typically on a 0.5 mmol scale at −78 °C in CH_2Cl_2 (0.2 M solution) in the presence of $BF_3{\cdot}OEt_2$ (0.2 equiv). After the consumption of starting material was observed via TLC, the reaction was cooled to 0 °C, and methanol (0.2 M with respect to the starting material) and $NaBH_4$ (>3 equiv) were added. [b]Diastereomeric ratios were determined via integration of the characteristic peaks in the ^{1}H NMR spectra. [c]Toluene was utilized as a solvent for entry 8 due to the compound's poor solubility in CH_2Cl_2.

stereochemical analysis, the resulting aldehyde was reduced with $NaBH_4$ to provide the *trans*-alcohols as the major products with good diastereoselectivities. The results are shown in Table 6.

Support of stereochemistry for **14e** was achieved through X-ray structural analysis. As shown in Scheme 4, nitro derivative

Scheme 3. Synthesis of *p*-Bromobenzoate Ester *cis*-16

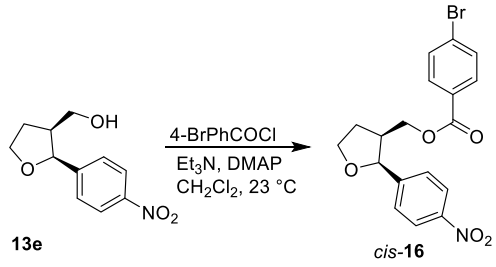
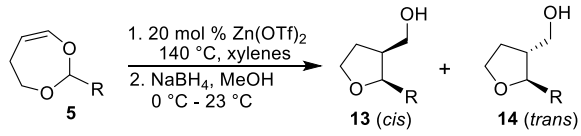
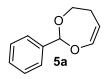
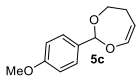
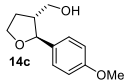
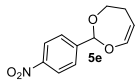
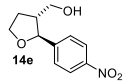
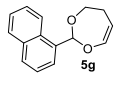
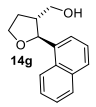
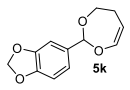
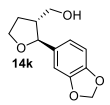


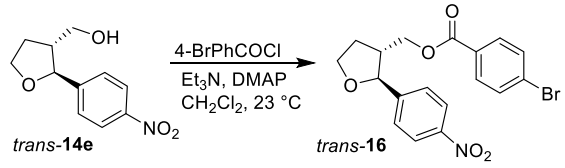
Table 6. Lewis-Acid-Catalyzed Vinyl Acetal Rearrangements under Thermal Conditions[a]



Entry	Substrate	Product	Time	Diastereomeric ratio (*cis:trans*)[b]	Yield (2 steps) [%]
1			8.5 h	1:20	48
2			4 h	1:7	32
3			4 h	1:6	49
4			3 h	1:5	45
5			4 h	1:5	67

[a]Reactions were carried out typically on a 0.5 mmol scale at 140 °C in xylenes (0.2 M solution) in the presence of $Zn(OTf)_2$ (0.2 equiv). After the specified reaction time, the reaction was cooled to 0 °C, and methanol (0.2 M with respect to the starting material) and $NaBH_4$ (>3 equiv) were added. [b]Diastereomeric ratios were determined via integration of the characteristic benzylic peak in the ^{1}H NMR spectra.

Scheme 4. Synthesis of *p*-Bromobenzoate Ester *trans*-16



14e was converted to *p*-bromobenzoyl ester derivative *trans*-**16** in 84% yield. It was recrystallized from a mixture of ethyl acetate and hexanes (23 °C, 3 days). Subsequent single crystal X-ray crystallographic analysis supported the assignment of *trans*-stereochemistry.[25,26]

We also carried out stereochemical assignment of compounds **13e** and **14e** by ^{1}H-NMR NOESY experiments. As shown in Figure 2, the observed NOESY between the 2,3-*cis* protons for compound **13e** is consistent with the assigned

https://dx.doi.org/10.1021/acs.joc.0c00390
J. Org. Chem. XXXX, XXX, XXX−XXX

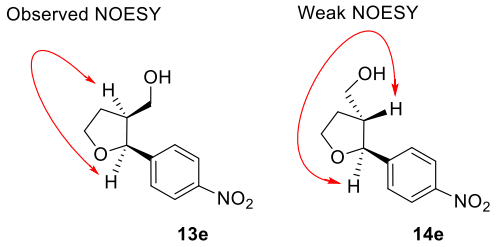


Figure 2. Representative NOESY correlation of compounds **13e** and **14e**. The ^{1}H-NOESY spectra can be found in the Supporting Information.

stereochemistry. As expected, for the *trans*-compound **14e**, a much weaker NOESY interaction was observed between the 2,3-*trans* protons. This interaction can be attributed to the fact that the five-membered tetrahydrofuran ring can adopt an envelope conformation, which puts the two protons at approximately a 120° angle.[30]

In an attempt to examine the equilibrium of products **6** to **7**, we interrupted the reaction of substrate **5a** with catalytic amount of $Zn(OTf)_2$ in xylenes at 140 °C at various time intervals. The product mixture was reduced as described previously. The *cis/trans* ratio is shown in Table 7. As shown,

Table 7. Study on the Diastereomeric Ratios of the Thermal Reaction of 5a to 14a at Various Time Intervals[a]

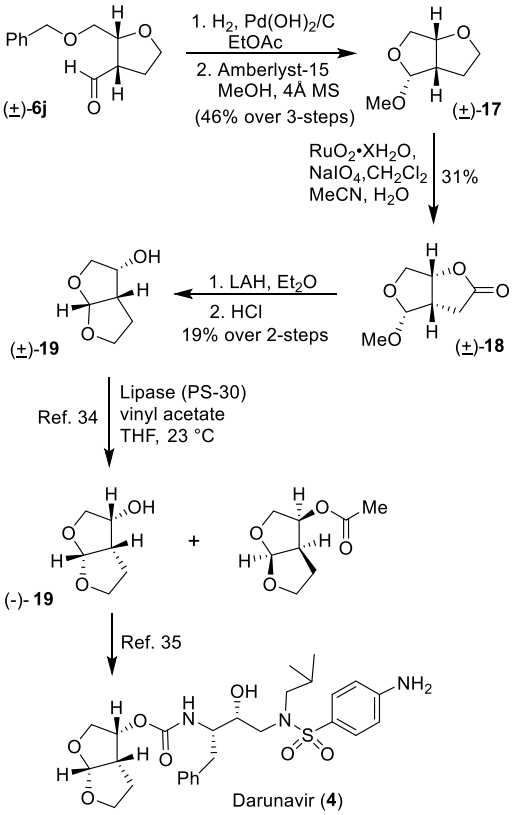
entry	time (h)	diastereomeric ratio (*cis*:*trans*)[b]	yield (2 steps) (%)
1	1	1:7	50
2	2	1:7	50
3	4	1:14	47
4	8.5	1:20	48

[a]Reactions were carried out at 140 °C in xylenes (0.2 M solution) in the presence of $Zn(OTf)_2$ (0.2 equiv). After the specified reaction time, the reaction was cooled to 0 °C, and methanol (0.2 M with respect to the starting material) and $NaBH_4$ (>3 equiv) were added. [b]Diastereomeric ratios were determined via integration of the characteristic benzylic peak in the ^{1}H NMR spectra.

over time, the amount of *trans*-product increased. Presumably, under thermal conditions, the *cis*-product **6** (Scheme 1) is converted to the thermodynamically more stable *trans*-product via Lewis-acid-catalyzed rearrangement.

We also demonstrated the utility of the vinyl acetal rearrangement in the synthesis of bis-THF, which contains three contiguous chiral centers.[16] This bis-THF ligand is an important part of the FDA approved drug darunavir.[8,9] The synthesis is shown in Scheme 5. As shown previously, vinyl acetal rearrangement of dioxepine derivative **5j** afforded *cis*-alcohol **13j** as a 5:1 mixture of *cis/trans*-diastereomers in 42% yield over 2 steps (Table 5, entry 10). Catalytic hydrogenation of its aldehyde precursor **6j** over Pearlman's catalyst in ethyl acetate under a hydrogen filled balloon removed the benzyl group and the resulting hemiacetal was treated with Amberlyst-15 in a mixture of MeOH and ether at 23 °C for 5 h to provide acetal **17** which was isolated as a single diastereomer. The depicted stereochemistry is based upon ^{1}H-NMR NOESY data.[31] We required oxidation of tetrahydrofuran to the corresponding γ-lactone derivative. For this oxidation, we utilized ruthenium-catalyzed conditions.[32] Oxidation of methyl acetal **17** with a catalytic amount of RuO_2 in the presence of $NaIO_4$ in a mixture of CH_2Cl_2, MeCN, and water (2:2:3) at 23 °C for 2 h afforded lactone **18** in 31% yield. Reduction of

Scheme 5. Synthesis of Bis-THF Ligand for Darunavir



lactone **18** with LAH and treatment with a stoichiometric amount of hydrochloric acid (33% by volume in water) in ether at −10 °C for 3 h furnished the racemic alcohol **19**.[33] Chiral resolution of the racemic alcohol has been previously carried out using Amano lipase PS-30.[34,35] Optically active bis-THF has been previously converted to darunavir.[8,9,36]

In summary, we investigated the Lewis acid-catalyzed vinyl acetal rearrangement of a wide range of substituted 4,5-dihydro-1,3-dioxepines under a variety of reaction conditions. In general, $BF_3{\cdot}OEt_2$-catalyzed reactions afforded the best results. When the reaction was carried out at low temperatures in the presence of a catalytic amount of $BF_3{\cdot}OEt_2$, *cis*-2,3-disubstituted tetrahydrofurans were obtained in a highly stereoselective manner. When the reaction was carried out at a higher temperature, around 140 °C, *trans*-2,3-disubstituted tetrahydrofurans were formed as major products. For the synthesis of the 4,7-dihydro-1,3-dioxepines, we developed an efficient synthesis using ring-closing metathesis of the corresponding diallyl acetal derivatives. Both aromatic and aliphatic aldehyde-derived substrates provided 4,7-dihydro-1,3-dioxepine derivatives in good to excellent yields. The syntheses of 4,5-dihydro-1,3-dioxepine substrates were carried out by a ruthenium-catalyzed olefin isomerization. The *cis*-tetrahydrofuran derivative obtained from benzyloxyacetaldehyde was converted to the bis-tetrahydrofuranyl alcohol, which is the P2-ligand for darunavir, a widely utilized FDA-approved drug for the treatment of HIV-1 infection and AIDS. Further applications of vinyl acetal rearrangements are in progress in our laboratories.

EXPERIMENTAL SECTION

All chemicals and reagents were purchased from commercial suppliers and used without further purification unless otherwise noted. The

https://dx.doi.org/10.1021/acs.joc.0c00390
J. Org. Chem. XXXX, XXX, XXX−XXX

following reaction solvents were distilled prior to use: CH_2Cl_2 from calcium hydride, diethyl ether and tetrahydrofuran from Na/benzophenone, and methanol from activated magnesium under argon. All reactions were carried out under an argon atmosphere in either flame- or oven-dried (120 °C) glassware. TLC analysis was conducted using glass-backed thin-layer silica gel chromatography plates (60 Å, 250 μm thickness, F-254 indicator). Column chromatography was performed using 230−400 mesh, 60 Å pore diameter silica gel. ^{1}H and ^{13}C NMR spectra were recorded at 23 °C on Varian MERCURY300, Bruker AV-400, and Bruker Avance-800 instruments. Chemical shifts (δ values) are reported in parts per million and are referenced to the deuterated residual solvent peak. NMR data are reported as δ value (chemical shift, J value (Hz), integration, where s = singlet, d = doublet, t = triplet, q = quartet, quint = quintet, sep = septet, m = multiplet, dd = doublet of doublets, ddd = doublet of doublet of doublets, td = triplet of doublets, dq = doublet of quartets, brs = broad singlet, app = apparent). LRMS and HRMS spectra were recorded at the Purdue University Department of Chemistry Mass Spectrometry Center.

Synthesis of Diallyl Acetals 11a−k: General Procedure. To an oven-dried round-bottom flask containing activated 4 Å molecular sieves was added the aldehyde of choice (1 equiv), THF (1.5 M solution), allyl alcohol (5 equiv), and PTSA·H_2O (0.2 equiv) at 23 °C. The reaction mixture was then stirred for 24 h and filtered. The solution was concentrated under reduced pressure, and the crude material was purified by column chromatography (using specified solvent systems) over silica gel to afford **11a−k**.

*(Bis(allyloxy)methyl)benzene (**11a**).*[37] Following the general procedure, the reaction of benzaldehyde (0.89 mL, 9.4 mmol), allyl alcohol (3.2 mL, 47 mmol), PTSA·H_2O (358 mg, 1.8 mmol), and tetrahydrofuran (6.3 mL) followed by filtration and column chromatography (100% hexanes−5% EtOAc/hexanes) afforded **11a** as a colorless oil (1.03 g, 5.0 mmol, 53%). ^{1}H NMR (400 MHz, $CDCl_3$, δ): 7.60−7.54 (m, 2H), 7.47−7.35 (m, 3H), 6.00 (ddt, J = 17.2, 10.7, 5.5 Hz, 2H), 5.70 (s, 1H), 5.37 (dd, J = 17.2, 1.8 Hz, 2H), 5.23 (dd, J = 10.4, 1.6 Hz, 2H), 4.12 (dt, J = 5.5, 1.6 Hz, 4H); ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$, δ): 138.2, 134.3 (2C), 128.2 (2C), 128.0 (2C), 126.6 (2C), 116.5 (2C), 100.2, 65.8 (2C); LRMS-ESI (m/z): 227.1 [M + Na]$^+$.

*1-(Bis(allyloxy)methyl)-4-isopropylbenzene (**11b**).* Following the general procedure, the reaction of cuminaldehyde (1.2 mL, 8.0 mmol), allyl alcohol (2.7 mL, 40 mmol), PTSA·H_2O (327 mg, 1.7 mmol), and tetrahydrofuran (5.3 mL) followed by filtration and column chromatography (100% hexanes−5% EtOAc/hexanes) afforded **11b** as a light-yellow oil (1.77 g, 7.2 mmol, 89%). ^{1}H NMR (400 MHz, $CDCl_3$, δ): 7.44−7.39 (m, 1H), 7.25−7.20 (m, 1H), 5.95 (ddt, J = 17.2, 10.4, 5.5 Hz, 2H), 5.61 (s, 1H), 5.32 (dq, J = 17.2, 1.7 Hz, 2H), 5.23−5.11 (m, 2H), 4.07 (dt, J = 5.6, 1.5 Hz, 4H), 2.91 (p, J = 6.9 Hz, 1H), 1.25 (d, J = 6.9 Hz, 6H); ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$, δ): 149.1, 135.8, 134.6 (2C), 126.7 (2C), 126.2 (2C), 116.7 (2C), 100.5, 66.2 (2C), 33.9, 24.0 (2C). HRMS (APCI-Orbitrap) (m/z): calcd for $C_{16}H_{22}O_2Na$ [M + Na]$^+$, 269.1512; found, 269.1514.

*1-(Bis(allyloxy)methyl)-4-methoxybenzene (**11c**).*[38] Following the general procedure, the reaction of *p*-anisaldehyde (0.90 mL, 7.4 mmol), allyl alcohol (2.5 mL, 37 mmol), PTSA·H_2O (282 mg, 1.5 mmol), and tetrahydrofuran (4.9 mL) followed by column chromatography (100% hexanes−5% EtOAc/hexanes) afforded **11c** as a light-yellow oil (885 mg, 3.8 mmol, 51%). ^{1}H NMR (400 MHz, $CDCl_3$, δ): 7.52−7.38 (m, 2H), 6.91 (d, J = 8.8 Hz, 2H), 5.96 (ddt, J = 17.3, 10.7, 5.5 Hz, 2H), 5.62 (s, 1H), 5.33 (dd, J = 17.2, 1.8 Hz, 2H), 5.18 (dd, J = 10.4, 1.6 Hz, 2H), 4.07 (dt, J = 5.6, 1.6 Hz, 4H), 3.80 (s, 3H); ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$, δ): 159.5, 134.4 (2C), 130.5, 127.8 (2C), 116.4 (2C), 113.3 (2C), 100.1, 65.8 (2C), 55.0; LRMS-ESI (m/z): 235.1 [M + H]$^+$.

*1-(Bis(allyloxy)methyl)-2-methoxybenzene (**11d**).*[39] Following the general procedure, the reaction of *o*-anisaldehyde (1.02 g, 7.5 mmol), allyl alcohol (2.5 mL, 37 mmol), PTSA·H_2O (284 mg, 1.5 mmol), and tetrahydrofuran (5.0 mL) followed by filtration and column chromatography (5−10% EtOAc/hexanes) afforded **11d** as a colorless oil (1.05 g, 4.5 mmol, 60%). ^{1}H NMR (400 MHz, $CDCl_3$, δ): 7.64 (dd, J = 7.6, 1.8 Hz, 1H), 7.31 (ddd, J = 8.3, 7.4, 1.8 Hz, 1H), 6.99 (td, J = 7.5, 1.0 Hz, 1H), 6.89 (dd, J = 8.3, 1.0 Hz, 1H), 6.03−5.89 (m, 3H), 5.31 (dq, J = 17.2, 1.7 Hz, 2H), 5.16 (dq, J = 10.4, 1.5 Hz, 2H), 4.11 (dt, J = 5.6, 1.5 Hz, 4H), 3.84 (s, 3H); ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$, δ): 157.1, 134.8 (2C), 129.7, 127.5, 126.6, 120.3, 116.6 (2C), 110.7, 96.3, 67.0 (2C), 55.5; LRMS-ESI (m/z): 257.1 [M + Na]$^+$.

*1-(Bis(allyloxy)methyl)-4-nitrobenzene (**11e**).*[40] Following the general procedure, the reaction of 4-nitrobenzaldehyde (1.07 g, 7.1 mmol), allyl alcohol (2.4 mL, 35 mmol), PTSA·H_2O (269 mg, 1.4 mmol), and tetrahydrofuran (4.7 mL) followed by filtration and column chromatography (5% EtOAc/hexanes) afforded **11e** as a light-yellow oil (1.73 g, 7.0 mmol, 99%). ^{1}H NMR (400 MHz, $CDCl_3$, δ): 8.28−8.17 (m, 2H), 7.75−7.63 (m, 2H), 5.93 (ddt, J = 17.2, 10.4, 5.5 Hz, 2H), 5.70 (s, 1H), 5.32 (dq, J = 17.2, 1.6 Hz, 2H), 5.21 (dq, J = 10.4, 1.4 Hz, 2H), 4.15−3.98 (m, 4H); ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$, δ): 148.0, 145.4, 133.8 (2C), 127.8 (2C), 123.4 (2C), 117.3 (2C), 99.1, 66.4 (2C); LRMS-ESI (m/z): 272.0 [M + Na]$^+$.

*2-(Bis(allyloxy)methyl)furan (**11f**).*[41] Following the general procedure, the reaction of furfural (0.6 mL, 7.1 mmol), allyl alcohol (2.4 mL, 36 mmol), PTSA·H_2O (271 mg, 1.4 mmol), and tetrahydrofuran (4.8 mL) followed by filtration and column chromatography (5−10% EtOAc/hexanes) afforded **11f** as an amber-colored oil (1.01 g, 5.2 mmol, 73%). ^{1}H NMR (300 MHz, $CDCl_3$, δ): 7.39 (s, 1H), 6.48−6.29 (m, 2H), 5.91 (ddt, J = 16.9, 11.2, 5.7 Hz, 2H), 5.65 (s, 1H), 5.29 (dq, J = 17.2, 1.9 Hz, 2H), 5.17 (dd, J = 10.7, 2.2 Hz, 2H), 4.08 (dd, J = 5.5, 2.1 Hz, 4H); ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$, δ): 151.1, 142.4, 134.1 (2C), 117.0 (2C), 110.0, 108.3, 95.2, 66.3 (2C); LRMS-ESI (m/z): 217.1 [M + Na]$^+$.

*(1-(Bis(allyloxy)methyl)naphthalene (**11g**).* Following the general procedure, the reaction of naphthaldehyde (1.0 mL, 7.4 mmol), allyl alcohol (2.5 mL, 37 mmol), PTSA·H_2O (280 mg, 1.5 mmol), and tetrahydrofuran (4.9 mL) followed by filtration and column chromatography (5−10% EtOAc/hexanes) afforded **11g** as a colorless oil (1.20 g, 4.7 mmol, 64%). ^{1}H NMR (400 MHz, $CDCl_3$, δ): 8.41 (dt, J = 8.7, 1.0 Hz, 1H), 7.95−7.83 (m, 1H), 7.63−7.47 (m, 4H), 6.23 (s, 1H), 6.00 (ddt, J = 17.2, 10.4, 5.6 Hz, 2H), 5.37 (dd, J = 17.2, 1.7 Hz, 2H), 5.22 (dq, J = 10.4, 1.5 Hz, 2H), 4.27−4.08 (m, 5H); ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$, δ): 134.5 (2C), 133.7, 133.3, 130.8, 129.2, 128.4, 126.1, 125.6, 124.9, 124.8, 124.2, 116.8 (2C), 99.3, 66.4 (2C); LRMS-ESI (m/z): 197.1 [M-CH_2CHCH_2O]$^+$. HRMS (APCI-Orbitrap) (m/z): calcd for $C_{14}H_{13}O$ [M-CH_2CHCH_2O]$^+$, 197.0966; found, 197.0965.

*4-(Bis(allyloxy)methyl)-1,1′-biphenyl (**11h**).* Following the general procedure, the reaction of biphenyl-4-carboxaldehyde (1.46 g, 8.0 mmol), allyl alcohol (2.7 mL, 40 mmol), PTSA·H_2O (304 mg, 1.6 mmol), and tetrahydrofuran (5.3 mL) followed by filtration and column chromatography (100% hexanes−10% EtOAc/hexanes) afforded **11h** as a colorless oil (1.60 g, 5.7 mmol, 71%). ^{1}H NMR (400 MHz, $CDCl_3$, δ): 7.72−7.57 (m, 6H), 7.47 (dd, J = 8.3, 6.8 Hz, 2H), 7.43−7.34 (m, 1H), 6.01 (ddt, J = 17.3, 10.4, 5.5 Hz, 2H), 5.73 (s, 1H), 5.38 (dd, J = 17.2, 1.7 Hz, 2H), 5.24 (dd, J = 10.4, 1.6 Hz, 2H), 4.14 (dt, J = 5.6, 1.5 Hz, 4H); ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$, δ): 141.3, 140.7, 137.4, 134.5 (2C), 128.7 (2C), 127.3, 127.1 (2C), 127.1 (2C), 126.9 (2C), 116.8 (2C), 100.3, 66.1 (2C); LRMS-ESI (m/z): 303.1 [M + Na]$^+$. HRMS (APCI-Orbitrap) (m/z): calcd for $C_{19}H_{20}O_2Na$ [M + Na]$^+$, 303.1356; found, 303.1360.

*1,1-Bis(allyloxy)-3-methylbutane (**11i**).* Following the general procedure, the reaction of isovaleraldehyde (0.9 mL, 7.9 mmol), allyl alcohol (2.7 mL, 40 mmol), PTSA·H_2O (302 mg, 1.6 mmol), and tetrahydrofuran (5.3 mL) followed by filtration and column chromatography (100% hexanes−10% EtOAc/hexanes) afforded **11i** as a colorless oil (1.12 g, 6.1 mmol, 77%), ^{1}H NMR (400 MHz, $CDCl_3$, δ): 5.95−5.77 (m, 1H), 5.24 (dq, J = 17.2, 1.8 Hz, 2H), 5.16−5.06 (m, 2H), 4.64 (t, J = 5.9 Hz, 1H), 4.11−3.89 (m, 4H), 1.71 (dp, J = 13.5, 6.7 Hz, 1H), 1.50 (dd, J = 7.0, 5.9 Hz, 2H), 0.88 (dd, J = 6.7, 0.6 Hz, 6H); ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$, δ): 134.7 (2C), 116.3 (2C), 100.7, 65.8 (2C), 42.0, 24.3, 22.6 (2C).

https://dx.doi.org/10.1021/acs.joc.0c00390
J. Org. Chem. XXXX, XXX, XXX−XXX

*((2,2-Bis(allyloxy)ethoxy)methyl)benzene (**11j**).* Following the general procedure, the reaction of benzyloxyacetaldehyde[42] (1.33 g, 8.8 mmol), allyl alcohol (3.0 mL, 44.1 mmol), PTSA·H_2O (336 mg, 1.8 mmol), and tetrahydrofuran (6.0 mL) followed by filtration and column chromatography (5% EtOAc/hexanes−20% EtOAc/hexanes) afforded **11j** as a light-yellow oil (623 mg, 2.5 mmol, 43% over 2 steps). ^{1}H NMR (400 MHz, $CDCl_3$, δ): 7.40−7.27 (m, 5H), 5.95 (ddt, J = 17.2, 10.4, 5.6 Hz, 2H), 5.32 (dd, J = 17.2, 1.7 Hz, 2H), 5.19 (dd, J = 10.4, 1.6 Hz, 2H), 4.81 (t, J = 5.2 Hz, 1H), 4.60 (s, 2H), 4.23−4.03 (m, 4H), 3.59 (d, J = 5.2 Hz, 2H); ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$, δ): 137.8, 134.3 (2C), 128.1 (2C), 127.5 (2C), 127.4, 116.7 (2C), 100.0, 73.2, 70.2, 67.1 (2C); LRMS-ESI (m/z): 266.1 [M +NH_4]$^+$. HRMS (APCI-Orbitrap) (m/z): calcd for $C_{15}H_{24}NO_3$ [M +NH_4]$^+$, 266.1756; found, 266.1760.

*(5-(Bis(allyloxy)methyl)benzo[d][1,3]dioxole (**11k**).* Following the general procedure, the reaction of piperonal (1.02 g, 6.8 mmol), allyl alcohol (2.3 mL, 34 mmol), PTSA·H_2O (259 mg, 1.4 mmol), and tetrahydrofuran (5.5 mL) followed by filtration and column chromatography (10% EtOAc/hexanes−30% EtOAc/hexanes) afforded **11k** as a colorless oil (340 mg, 1.4 mmol, 20%), NMR (400 MHz, $CDCl_3$, δ): 7.04−6.94 (m, 2H), 6.79 (d, J = 8.0 Hz, 1H), 6.01−5.86 (m, 4H), 5.53 (s, 1H), 5.30 (dq, J = 17.2, 1.7 Hz, 2H), 5.25−5.11 (m, 2H), 4.04 (dq, J = 5.7, 1.5 Hz, 4H); ^{13}C{^{1}H} 147.7, 134.6 (2C), 132.7, 120.5 (2C), 116.9 (2C), 108.0, 107.3, 101.2, 100.3, 66.2 (2C). HRMS (APCI-Orbitrap) (m/z): calcd for $C_{14}H_{16}O_4Na$ [M + Na]$^+$, 279.0941; found, 279.0943.

Synthesis of 4,7-Dihydro-1,3-dioxepines 12a−k: General Procedure. To a two-necked round-bottom flask containing the diallyl acetal of choice was added CH_2Cl_2 (0.01 M solution) and Grubbs second-generation catalyst (5 mol %). The reaction mixture was then heated at reflux for 2 h, concentrated under reduced pressure and purified via silica gel column chromatography (using the specified solvent systems) to give **12a−k**.

*2-Phenyl-4,7-dihydro-1,3-dioxepine (**12a**).*[20] Following the general procedure, the reaction of (bis(allyloxy)methyl)benzene **11a** (150 mg, 0.73 mmol), Grubbs second-generation catalyst (31 mg, 0.04 mmol), and dichloromethane (73 mL) followed by column chromatography (100% hexanes−5% EtOAc/hexanes) afforded **12a** as a golden-colored oil (104 mg, 0.59 mmol, 81%). ^{1}H NMR (400 MHz, $CDCl_3$, δ): 7.58−7.50 (m, 2H), 7.42−7.31 (m, 3H), 5.86 (s, 1H), 5.82−5.74 (m, 2H), 4.46−4.23 (m, 4H); ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$, δ): 138.8, 129.9 (2C), 128.4, 128.2 (2C), 126.4 (2C), 102.1, 64.6 (2C).

*2-(4-Isopropylphenyl)-4,7-dihydro-1,3-dioxepine (**12b**).* Following the general procedure, the reaction of 1-(bis(allyloxy)methyl)-4-isopropylbenzene **11b** (110 mg, 0.45 mmol), Grubbs second-generation catalyst (19 mg, 0.02 mmol), and dichloromethane (45 mL) followed by column chromatography (100% hexanes−5% EtOAc/hexanes) afforded **12b** as a colorless oil (88 mg, 0.40 mmol, 90%). ^{1}H NMR (400 MHz, $CDCl_3$, δ): 7.51−7.41 (m, 2H), 7.24 (dd, J = 8.9, 2.5 Hz, 2H), 5.84 (s, 1H), 5.77 (t, J = 1.8 Hz, 2H), 4.48−4.21 (m, 4H), 2.92 (p, J = 6.9 Hz, 1H), 1.26 (d, J = 6.9 Hz, 6H); ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$, δ): 149.1, 136.3, 129.9 (2C), 126.3 (2C), 126.2 (2C), 102.3, 64.6 (2C), 33.9, 24.0 (2C); LRMS-ESI (m/z): 219.1 [M + H]$^+$, 241.1 [M + Na]$^+$. HRMS (APCI-Orbitrap) (m/z): calcd for $C_{14}H_{19}O_2$ [M + H]$^+$, 219.1380; found, 219.1382.

*2-(4-Methoxyphenyl)-4,7-dihydro-1,3-dioxepine (**12c**).*[14] Following the general procedure, the reaction of 1-(bis(allyloxy)methyl)-4-methoxybenzene **11c** (194 mg, 0.83 mmol), Grubbs second-generation catalyst (35 mg, 0.04 mmol), and dichloromethane (70 mL) followed by column chromatography (100% hexanes−10% EtOAc/hexanes) afforded **12c** as a brownish oil (126 mg, 0.61 mmol, 74%). ^{1}H NMR (400 MHz, $CDCl_3$, δ): 7.50−7.41 (m, 2H), 6.90 (d, J = 8.8 Hz, 2H), 5.83 (s, 1H), 5.77 (t, J = 1.8 Hz, 2H), 4.45−4.19 (m, 4H), 3.81 (s, 3H); ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$, δ): 159.6, 131.1, 129.9 (2C), 127.6 (2C), 113.4 (2C), 102.0, 64.3 (2C), 55.2; LRMS-ESI (m/z): 207.1 [M + H]$^+$.

*2-(2-Methoxyphenyl)-4,7-dihydro-1,3-dioxepine (**12d**).* Following the general procedure, the reaction of 1-(bis(allyloxy)methyl)-2-methoxybenzene **11d** (501 mg, 2.1 mmol), Grubbs second-generation catalyst (91 mg, 0.11 mmol), and dichloromethane (220 mL) followed by column chromatography (100% hexanes−10% EtOAc/hexanes) afforded **12d** as a brownish oil (403 mg, 2.0 mmol, 91%). ^{1}H NMR (400 MHz, $CDCl_3$, δ): 7.64 (dd, J = 7.6, 1.8 Hz, 1H), 7.32 (ddd, J = 8.3, 7.4, 1.8 Hz, 1H), 7.04−6.86 (m, 2H), 6.10 (s, 1H), 5.78 (t, J = 1.8 Hz, 2H), 4.53−4.19 (m, 4H), 3.86 (s, 3H); ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$, δ): 156.9, 129.7 (2C), 129.7, 126.8, 126.7, 120.1, 110.7, 98.1, 65.2 (2C), 55.6; LRMS-ESI (m/z): 207.1 [M + H]$^+$, 229.0 [M + Na]$^+$. HRMS (APCI-Orbitrap) (m/z): calcd for $C_{12}H_{15}O_2$ [M + H]$^+$, 207.1016; found, 207.1018.

*2-(4-Nitrophenyl)-4,7-dihydro-1,3-dioxepine (**12e**).* Following the general procedure, the reaction of 1-(bis(allyloxy)methyl)-4-nitrobenzene **11e** (123 mg, 0.50 mmol), Grubbs second-generation catalyst (25 mg, 0.03 mmol), and dichloromethane (50 mL) followed by column chromatography (100% hexanes−10% EtOAc/hexanes) afforded **12e** as a light-yellow solid (96 mg, 0.43 mmol, 88%). ^{1}H NMR (400 MHz, $CDCl_3$, δ): 8.23 (dt, J = 8.8, 1.6 Hz, 2H), 7.78−7.66 (m, 2H), 5.88 (s, 1H), 5.78 (d, J = 1.6 Hz, 1H), 4.42−4.25 (m, 4H); ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$, δ): 148.0, 145.7, 129.6 (2C), 127.6 (2C), 123.4 (2C), 101.0, 64.9 (2C); HRMS (APCI-Orbitrap) (m/z): calcd for $C_{11}H_{12}NO_4$ [M + H]$^+$, 222.0761; found, 222.0760.

*2-(Furan-2-yl)-4,7-dihydro-1,3-dioxepine (**12f**).* Following the general procedure, the reaction of 2-(bis(allyloxy)methyl)furan **11f** (266 mg, 1.4 mmol), Grubbs second-generation catalyst (58 mg, 0.07 mmol), and dichloromethane (140 mL) followed by column chromatography (100% hexanes−10% EtOAc/hexanes) afforded **12f** as an amber-colored oil (139 mg, 0.84 mmol, 61%), ^{1}H NMR (400 MHz, $CDCl_3$, δ): 7.43−7.38 (m, 1H), 6.46 (dd, J = 3.3, 0.9 Hz, 1H), 6.37 (dd, J = 3.3, 1.8 Hz, 1H), 5.86 (s, 1H), 5.75 (t, J = 1.8 Hz, 2H), 4.51−4.22 (m, 5H); ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$, δ): 151.3, 142.6, 129.8 (2C), 110.1, 107.9, 97.5, 64.8 (2C); HRMS (APCI-Orbitrap) (m/z): calcd for $C_9H_{11}O_3$ [M + H]$^+$, 167.0703; found, 167.0702.

*2-(Naphthalen-1-yl)-4,7-dihydro-1,3-dioxepine (**12g**).* Following the general procedure, the reaction of (1-(bis(allyloxy)methyl)-naphthalene **11g** (135 mg, 0.53 mmol), Grubbs second-generation catalyst (23 mg, 0.03 mmol), and dichloromethane (53 mL) followed by column chromatography (100% hexanes−5% EtOAc/hexanes) afforded **12g** as a yellowish oil (104 mg, 0.46 mmol, 87%). ^{1}H NMR (400 MHz, $CDCl_3$, δ): 8.33−8.24 (m, 1H), 7.88 (dd, J = 9.6, 7.8 Hz, 3H), 7.61−7.46 (m, 3H), 6.48 (s, 1H), 5.91−5.79 (m, 2H), 4.58−4.32 (m, 4H); ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$, δ): 133.8, 133.3, 130.8, 130.0 (2C), 129.2, 128.5, 126.1, 125.5, 124.8, 124.1, 123.9, 100.4, 64.8 (2C); LRMS-ESI (m/z): 227.1 [M + H]$^+$, 249.1 [M + Na]$^+$. HRMS (APCI-Orbitrap) (m/z): calcd for $C_{15}H_{15}O_2$ [M + H]$^+$, 227.1067; found, 227.1070.

*2-([1,1′-Biphenyl]-4-yl)-4,7-dihydro-1,3-dioxepine (**12h**).* Following the general procedure, the reaction of 4-(bis(allyloxy)methyl)-1,1′-biphenyl **11h** (298 mg, 1.1 mmol), Grubbs second-generation catalyst (45 mg, 0.05 mmol), and dichloromethane (110 mL) followed by column chromatography (100% hexane-10% EtOAc/hexanes) afforded **12h** as a white solid (165 mg, 0.66 mmol, 62%). ^{1}H NMR (400 MHz, $CDCl_3$, δ): 7.66−7.57 (m, 6H), 7.49−7.40 (m, 2H), 7.40−7.31 (m, 1H), 5.91 (s, 1H), 5.80 (t, J = 1.8 Hz, 2H), 4.44 (dt, J = 15.7, 2.0 Hz, 2H), 4.37−4.25 (m, 2H); ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$, δ): 141.3, 140.8, 137.9, 129.9 (2C), 128.8 (2C), 127.4, 127.2 (2C), 127.0 (2C), 126.9 (2C), 102.1, 64.6 (2C). LRMS-ESI (m/z): 253.1 [M + H]$^+$. HRMS (APCI-Orbitrap) (m/z): calcd for $C_{17}H_{17}O_2$ [M + H]$^+$, 253.1223; found, 253.1224.

*2-Isobutyl-4,7-dihydro-1,3-dioxepine (**12i**).*[43] Following the general procedure, the reaction of 1,1-bis(allyloxy)-3-methylbutane **11i** (366 mg, 2.0 mmol), Grubbs second-generation catalyst (84 mg, 0.10 mmol), and dichloromethane (200 mL) followed by column chromatography (5−10% EtOAc/hexanes) afforded **12i** as a colorless oil (193 mg, 1.2 mmol, 62%). ^{1}H NMR (400 MHz, $CDCl_3$, δ): 5.70 (dd, J = 2.2, 1.6 Hz, 2H), 4.82 (t, J = 5.9 Hz, 1H), 4.36 (dt, J = 16.3, 2.5 Hz, 2H), 4.21−4.06 (m, 2H), 1.73 (ddt, J = 13.3, 7.3, 6.6 Hz, 1H), 1.52 (dd, J = 7.0, 5.8 Hz, 2H), 0.91 (d, J = 6.7 Hz, 6H); ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$, δ): 129.8 (2C), 103.2, 64.9 (2C), 42.1, 24.5, 22.7 (2C); LRMS-ESI (m/z): 157.1 [M + H]$^+$.

https://dx.doi.org/10.1021/acs.joc.0c00390
J. Org. Chem. XXXX, XXX, XXX−XXX

*2-((Benzyloxy)methyl)-4,7-dihydro-1,3-dioxepine (**12j**).* Following the general procedure, the reaction of ((2,2-bis(allyloxy)ethoxy)-methyl)benzene **11j** (588 mg, 2.4 mmol), Grubbs second-generation catalyst (101 mg, 0.12 mmol), and dichloromethane (240 mL) followed by column chromatography (100% hexanes−20% EtOAc/hexanes) afforded **12j** as a yellowish oil (498 mg, 2.3 mmol, 95%). ^{1}H NMR (400 MHz, $CDCl_3$, δ): 7.42−7.26 (m, 5H), 5.71 (t, J = 1.9 Hz, 2H), 4.96 (t, J = 5.1 Hz, 1H), 4.45 (dt, J = 16.3, 2.5 Hz, 2H), 4.29−4.15 (m, 2H), 3.56 (d, J = 5.1 Hz, 2H); ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$, δ): 137.8, 129.4, 128.3, 127.7, 127.6, 102.1, 73.4, 69.9, 65.9; LRMS-ESI (m/z): 221.1 [M + H]$^+$, 243.1 [M + Na]$^+$. HRMS (APCI-Orbitrap) (m/z): calcd for $C_{13}H_{17}O_3$ [M + H]$^+$, 221.1172; found, 221.1174.

*5-(4,7-Dihydro-1,3-dioxepin-2-yl)benzo[d][1,3]dioxole (**12k**).*[44] Following the general procedure, the reaction of (5-(bis(allyloxy)-methyl)benzo[d][1,3]dioxole **11k** (340 mg, 1.4 mmol), Grubbs second-generation catalyst (58 mg, 0.07 mmol), and dichloromethane (140 mL) followed by column chromatography (5% EtOAc/hexanes) afforded **12k** as a light-brownish oil (271 mg, 1.2 mmol, 90%). NMR (400 MHz, $CDCl_3$, δ): 7.01 (tdd, J = 4.2, 1.7, 0.8 Hz, 2H), 6.80 (d, J = 8.4 Hz, 1H), 5.95 (s, 2H), 5.76 (dd, J = 4.3, 2.5 Hz, 3H), 4.46−4.18 (m, 4H); ^{13}C{^{1}H} NMR 147.6, 133.1, 130.0 (2C), 120.1 (2C), 108.0, 107.2, 101.9, 101.1, 64.5 (2C); LRMS-ESI (m/z): 221.0 [M + H]$^+$, 243.0 [M + Na]$^+$.

Synthesis of 4,5-Dihydro-1,3-dioxepines 5a−g and 5i−k: General Procedure. To a single-necked round-bottom flask was added the 4,7-dihydro-1,3-dioxepine of choice (1 equiv), methanol (1 M solution), $RuCl_2(PPh_3)_3$ (2 mol %), and $NaBH_4$ (0.05 equiv or 1 spatula tip). Then, a reflux condenser was attached, and the reaction was allowed to stir at reflux for 3 h. The reaction mixture was then concentrated under reduced pressure and the crude material was passed through a short silica gel column (spiked with triethylamine) to give **5a−g** and **5i−k**, along with their corresponding hydrogenated derivatives in most cases. Since the hydrogenated derivatives do not affect the following reactions, the quantities of the desired 4,5-dihydro-1,3-dioxepines were therefore determined by the ratios of the integrated acetal protons in the ^{1}H NMR spectra and used in the next steps without further purification.

Synthesis of 4,5-Dihydro-1,3-dioxepine 5h: Alternate Procedure. To a single-necked round-bottom flask was added 4 Å molecular sieves, 2-([1,1′-biphenyl]-4-yl)-4,7-dihydro-1,3-dioxepine (1 equiv), dimethyl sulfoxide (1 M solution), and solid potassium *tert*-butoxide (1.2 equiv). The reaction was then allowed to stir at 23 °C for 24 h. At this point, the reaction mixture was diluted with diethyl ether and extracted once with deionized water. The aqueous layer was then extracted three times with diethyl ether. The combined organic layer was dried over sodium sulfate and the ethereal solution was concentrated under reduced pressure. After purification of the crude material over a short silica gel column (spiked with triethylamine), **5h** was acquired as an inseparable mixture with its 4,7-dihydro-1,3-dioxepine starting material. Because the remaining 4,7-dihydro-1,3-dioxepine does not affect reactions later in the sequence, no further purification attempts were utilized, and the quantity of desired 4,5-dihydro-1,3-dioxepine was determined by the ratios of the integrated acetal protons in the ^{1}H NMR spectrum.

Synthesis of 2,3-Disubstituted Tetrahydrofurans 13a−k under Reduced Temperature Conditions: General Procedure. To a solution of 4,5-dihydro-1,3-dioxepine **5** (1 equiv) in dichloromethane (0.2 M solution) was added $BF_3{\cdot}OEt_2$ (0.2 equiv) at −78 °C. After consumption of the starting material was observed via TLC, the reaction mixture was immediately warmed up to 0 °C and methanol (0.2 M solution) and $NaBH_4$ (>3 equiv) were added. After reduction of the aldehyde was observed on TLC (about 1 h), the reaction was quenched with deionized water and the aqueous layer was extracted 3× with EtOAc. The combined organic layer was then dried over Na_2SO_4. Column chromatography using the specified solvent systems provided the 2,3-*cis*-disubstituted tetrahydrofuran products **13a−k** as major products. Their diastereomeric ratios (*cis*:*trans*) were determined via integration of the ^{1}H NMR spectra.

*(2-Phenyltetrahydrofuran-3-yl)methanol (**13a**).*[18] Following the general procedure, the reaction of 2-phenyl-4,5-dihydro-1,3-dioxepine **5a** (1.28 g, 7.3 mmol), dichloromethane (36 mL), $BF_3{\cdot}OEt_2$ (180 μL, 206 mg, 1.5 mmol), and methanol (36 mL) and $NaBH_4$ (>3 equiv) followed by workup and column chromatography (30−50% EtOAc/hexanes) afforded **13a** as a colorless oil (905 mg, 5.1 mmol, 70% over 2 steps). ^{1}H NMR (400 MHz, $CDCl_3$, δ) (diastereomeric ratio = 20:1): 7.42−7.27 (m, 5H), 5.01 (d, J = 6.8 Hz, 1H), 4.21 (td, J = 8.3, 4.7 Hz, 1H), 3.91 (dt, J = 8.4, 7.8 Hz, 1H), 3.39−3.17 (m, 2H), 2.65 (dq, J = 7.7, 6.5 Hz, 1H), 2.18 (dtd, J = 12.5, 7.8, 4.7 Hz, 1H), 1.93 (dtd, J = 12.5, 7.9, 5.8 Hz, 1H), 1.06 (s, 1H); ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$, δ): 139.5, 128.4 (2C), 127.4, 126.0 (2C), 82.0, 67.5, 62.9, 45.6, 29.0; LRMS-ESI (m/z): 179.1 [M + H]$^+$.

*(2-(4-Isopropylphenyl)tetrahydrofuran-3-yl)methanol (**13b**).* Following the general procedure, the reaction of 2-(4-isopropylphenyl)-4,5-dihydro-1,3-dioxepine **5b** (263 mg, 1.2 mmol), dichloromethane (6.0 mL), $BF_3{\cdot}OEt_2$ (30 μL, 34 mg, 0.24 mmol), and methanol (6.0 mL) and $NaBH_4$ (>3 equiv) followed by workup and column chromatography (30−50% EtOAc/hexanes) afforded **13b** as a colorless oil (181 mg, 0.82 mmol, 68% over 2 steps). ^{1}H NMR (400 MHz, $CDCl_3$, δ) (diastereomeric ratio = 3:1): 7.30−7.15 (m, 4H, superimposed by peak corresponding to the minor isomer), 4.97 (d, J = 6.8 Hz, 1H), 4.18 (td, J = 8.3, 4.6 Hz, 1H), 3.88 (dt, J = 8.4, 7.8 Hz, 1H), 3.26 (ddd, J = 40.4, 11.2, 6.6 Hz, 2H), 2.89 (hept, J = 6.9 Hz, 1H, superimposed by peak corresponding to the minor isomer), 2.66−2.54 (m, 1H), 2.22−2.09 (m, 1H, superimposed by peak corresponding to the minor isomer), 1.89 (m, 1H, superimposed by peak corresponding to the minor isomer), 1.24 (d, J = 6.9 Hz, 6H, superimposed by peak corresponding to the *trans* isomer); ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$, δ):148.0, 136.7, 126.3 (2C), 125.8 (2C), 81.9, 67.4, 62.8, 45.5, 33.7, 28.9, 23.9 (2C); LRMS-ESI (m/z): 221.1 [M + H]$^+$, 243.1 [M + Na]$^+$. HRMS (APCI-Orbitrap) (m/z): calcd for $C_{14}H_{21}O_2$ [M + H]$^+$, 221.1536; found, 221.1537.

*(2-(4-Methoxyphenyl)tetrahydrofuran-3-yl)methanol (**13c**).* Following the general procedure, the reaction of 2-(4-methoxyphenyl)-4,5-dihydro-1,3-dioxepine **5c** (154 mg, 0.74 mmol), dichloromethane (3.7 mL), $BF_3{\cdot}OEt_2$ (18 μL, 21 mg, 0.15 mmol), and methanol (3.7 mL) and $NaBH_4$ (>3 equiv) followed by workup and column chromatography (20−50% EtOAc/hexanes) afforded **13c** as a light-yellow oil (76 mg, 0.36 mmol, 49% over 2 steps). ^{1}H NMR (400 MHz, $CDCl_3$, δ) (diastereomeric ratio = 2:1): 7.29−7.19 (m, 2H, superimposed by peak corresponding to the minor isomer), 6.87 (dd, J = 8.9, 2.8 Hz, 2H, superimposed by the peak corresponding to the minor isomer), 4.96 (d, J = 6.8 Hz, 1H), 4.18 (td, J = 8.3, 4.5 Hz, 1H), 3.87 (q, J = 8.0 Hz, 1H), 3.79 (s, 3H, superimposed by peak corresponding to the minor isomer), 3.37−3.17 (m, 2H), 2.67−2.52 (m, 1H), 2.15 (dtd, J = 12.3, 7.8, 4.6 Hz, 1H), 1.92−1.82 (m, 1H), 1.12 (s, 1H); ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$, δ): 158.9, 131.4, 127.1 (2C), 113.8 (2C), 81.7, 67.4, 62.9, 55.2, 45.5, 29.0; LRMS-ESI (m/z): 209.1 [M + H]$^+$, 231.1 [M + Na]$^+$. HRMS (APCI-Orbitrap) (m/z): calcd for $C_{12}H_{16}O_3$ [M + H]$^+$, 209.1172; found, 209.1176.

*(2-(2-Methoxyphenyl)tetrahydrofuran-3-yl)methanol (**13d**).* Following the general procedure, the reaction of 2-(2-methoxyphenyl)-4,5-dihydro-1,3-dioxepine **5d** (96 mg, 0.47 mmol), dichloromethane (2.4 mL), $BF_3{\cdot}OEt_2$ (11 μL, 13 mg, 0.09 mmol), and methanol (2.4 mL) and $NaBH_4$ (>3 equiv) followed by workup and column chromatography (20−50% EtOAc/hexanes) afforded **13d** as a colorless oil (57 mg, 0.27 mmol, 58% over 2 steps). ^{1}H NMR (400 MHz, $CDCl_3$, δ) (diastereomeric ratio = > 20:1): 7.47−7.35 (m, 1H), 7.26 (td, J = 8.0, 7.5, 1.8 Hz, 1H), 6.99 (td, J = 7.5, 1.0 Hz, 1H), 6.87 (dd, J = 8.1, 1.0 Hz, 1H), 5.25 (d, J = 6.7 Hz, 1H), 4.20 (td, J = 8.3, 4.3 Hz, 1H), 3.96−3.79 (m embedded in s, 4H), 3.31−3.14 (m, 2H), 2.80 (h, J = 6.7 Hz, 1H), 2.20−2.08 (m, 1H), 1.88 (dtd, J = 12.3, 8.1, 6.3 Hz, 1H), 1.64−1.55 (m, 1H); ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$, δ): 155.7, 128.4, 128.3, 126.6, 121.0, 110.1, 67.2, 63.3, 55.5, 44.4, 28.7; LRMS-ESI (m/z): 209.1 [M + H]$^+$, 231.1 [M + Na]$^+$. HRMS (APCI-Orbitrap) (m/z): calcd for $C_{12}H_{16}O_3$ [M + H]$^+$, 209.1172; found, 209.1173.

*(2-(4-Nitrophenyl)tetrahydrofuran-3-yl)methanol (**13e**).* Following the general procedure, the reaction of 2-(4-nitrophenyl)-4,5-

https://dx.doi.org/10.1021/acs.joc.0c00390
J. Org. Chem. XXXX, XXX, XXX−XXX

dihydro-1,3-dioxepine **5e** (80 mg, 0.36 mmol), dichloromethane (1.8 mL), $BF_3{\cdot}OEt_2$ (9 μL, 10 mg, 0.07 mmol), and methanol (1.8 mL) and $NaBH_4$ (>3 equiv) followed by workup and column chromatography (30−80% EtOAc/hexanes) afforded **13e** as a brownish oil (41 mg, 0.18 mmol, 50% over 2 steps). ^1H NMR (400 MHz, $CDCl_3$, δ) (diastereomeric ratio = 3:1): 8.22 (dd, *J* = 8.9, 2.3 Hz, 2H), 7.61−7.50 (m, 2H), 5.14 (d, *J* = 6.9 Hz, 1H), 4.28 (td, *J* = 8.3, 4.8 Hz, 1H), 4.00 (dt, *J* = 8.5, 7.7 Hz, 1H), 3.33−3.17 (m, 2H), 2.77 (h, *J* = 6.9 Hz, 1H), 2.24 (dtd, *J* = 12.5, 7.7, 4.8 Hz, 1H), 2.06−1.95 (m, 1H), 1.34 (s, 1H); $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$, δ): 147.7, 147.4, 127.3 (2C), 123.7 (2C), 81.6, 68.1, 62.6, 46.0, 29.1; LRMS-ESI (*m*/*z*): 242.1 $[M + H]^+$, 246.1 $[M + Na]^+$. HRMS (APCI-Orbitrap) (*m*/*z*): calcd for $C_{11}H_{14}NO_4$ $[M + H]^+$, 224.0917; found, 224.0920.

*(2-(Furan-2-yl)tetrahydrofuran-3-yl)methanol (**13f**).* Following the general procedure, the reaction of 2-(furan-2-yl)-4,5-dihydro-1,3-dioxepine **5f** (111 mg, 0.67 mmol), dichloromethane (3.3 mL), $BF_3{\cdot}OEt_2$ (16 μL, 19 mg, 0.13 mmol), and methanol (3.3 mL) and $NaBH_4$ (>3 equiv) followed by workup and column chromatography (20−80% EtOAc/hexanes) afforded **13f** as a light-yellow grainy oil (61 mg, 0.36 mmol, 54% over 2 steps). ^1H NMR (400 MHz, $CDCl_3$, δ) (diastereomeric ratio = 3:1): 7.39 (dd, *J* = 1.9, 0.9 Hz, 1H), 6.40−6.21 (m, 2H), 5.05 (d, *J* = 7.3 Hz, 1H), 4.18 (td, *J* = 8.3, 3.7 Hz, 1H), 3.87 (td, *J* = 8.4, 7.2 Hz, 1H), 3.55−3.31 (m, 2H), 2.77−2.58 (m, 1H), 2.12 (dtd, *J* = 12.2, 7.4, 3.7 Hz, 1H), 2.00−1.89 (m, 1H), 1.67 (s, 1H, superimposed by peak corresponding to the minor isomer); $^{13}C\{^1H\}$ NMR(100 MHz, $CDCl_3$, δ): 153.7, 142.4, 110.4, 107.9, 76.1, 68.1, 63.1, 46.1, 28.8; LRMS-ESI (*m*/*z*): 169.1 $[M + H]^+$. HRMS (APCI-Orbitrap) (*m*/*z*): calcd for $C_9H_{13}O_3$ $[M + H]^+$, 169.0859; found, 169.0858.

*(2-(Naphthalen-1-yl)tetrahydrofuran-3-yl)methanol (**13g**).* Following the general procedure, the reaction of 2-(naphthalen-1-yl)-4,5-dihydro-1,3-dioxepine **5g** (114 mg, 0.50 mmol) in dichloromethane (2.5 mL), $BF_3{\cdot}OEt_2$ (12 μL, 14 mg, 0.10 mmol), and methanol (2.5 mL) and $NaBH_4$ (>3 equiv) followed by workup and column chromatography (20% EtOAc/hexanes−50% EtOAc/hexanes) afforded **13g** as a colorless syrup (64 mg, 0.28 mmol, 55% over 2 steps), ^1H NMR (400 MHz, $CDCl_3$, δ) (diastereomeric ratio= 14:1): 7.97−7.84 (m, 2H), 7.76 (ddt, *J* = 19.2, 7.2, 1.0 Hz, 2H), 7.57−7.40 (m, 3H), 5.61 (d, *J* = 6.3 Hz, 1H), 4.27 (td, *J* = 8.3, 5.6 Hz, 1H), 3.98 (td, *J* = 8.5, 6.8 Hz, 1H), 3.15−3.00 (m, 2H), 2.93 (dddd, *J* = 12.7, 7.9, 6.4, 3.9 Hz, 1H), 2.34 (dtd, *J* = 12.6, 8.2, 5.6 Hz, 1H), 2.09 (dddd, *J* = 12.6, 8.0, 6.8, 3.9 Hz, 1H), 1.01 (br s, 1H); $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$, δ): 134.9, 133.5, 130.3, 129.1, 127.9, 126.3, 125.8, 125.6, 122.9, 122.8, 79.4, 67.0, 63.0, 44.4, 29.7; LRMS-ESI (*m*/*z*): 229.1 $[M + H]^+$. HRMS (APCI-Orbitrap) (*m*/*z*): calcd for $C_{15}H_{17}O_2$ $[M + H]^+$, 229.1223; found, 223.1225.

*(2-([1,1′-Biphenyl]-4-yl)tetrahydrofuran-3-yl)methanol (**13h**).* Following the general procedure, the reaction of 2-([1,1′-biphenyl]-4-yl)-4,5-dihydro-1,3-dioxepine **5h** (46 mg, 0.18 mmol) in toluene (0.90 mL), $BF_3{\cdot}OEt_2$ (5 μL, 6 mg, 0.04 mmol), and methanol (0.90 mL) and $NaBH_4$ (>3 equiv) followed by workup and column chromatography (20% EtOAc/hexanes−50% EtOAc/hexanes) afforded **13h** as a colorless syrup (29 mg, 0.11 mmol, 63% over 2 steps). ^1H NMR (400 MHz, $CDCl_3$, δ) (diastereomeric ratio = 11:1): 7.59 (dd, *J* = 7.9, 3.0 Hz, 4H), 7.47−7.38 (m, 4H), 7.37−7.31 (m, 1H), 5.07 (d, *J* = 6.8 Hz, 1H), 4.25 (td, *J* = 8.3, 4.6 Hz, 1H), 3.94 (q, *J* = 8.0 Hz, 1H), 3.34 (ddd, *J* = 35.3, 11.1, 6.5 Hz, 2H), 2.69 (h, *J* = 6.6 Hz, 1H), 2.21 (dtd, *J* = 12.5, 7.8, 4.6 Hz, 1H), 2.04−1.88 (m, 1H), 1.04 (s, 1H); $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$, δ): 140.7, 140.3, 138.6, 128.8 (2C), 127.3, 127.1 (2C), 127.0 (2C), 126.4 (2C), 81.9, 67.6, 62.9, 45.6, 29.1; LRMS-ESI (*m*/*z*): 255.1 $[M + H]^+$, 277.1 $[M + Na]^+$. HRMS (APCI-Orbitrap) (*m*/*z*): calcd for $C_{17}H_{17}O_2$ $[M - H]^-$, 253.1223; found, 253.1228.

*(2-Isobutyltetrahydrofuran-3-yl)methanol (**13i**).* Following the general procedure, the reaction of 2-isobutyl-4,5-dihydro-1,3-dioxepine **5i** (98 mg, 0.63 mmol), dichloromethane (3.1 mL), $BF_3{\cdot}OEt_2$ (15 μL, 24 mg, 0.13 mmol), and methanol (3.1 mL) and $NaBH_4$ (>3 equiv) followed by workup and column chromatography (20% EtOAc/hexanes−50% EtOAc/hexanes) afforded **13i** as a colorless grainy oil (54 mg, 0.34 mmol, 55% over 2 steps). ^1H NMR (400 MHz, $CDCl_3$, δ) (diastereomeric ratio = 2:1): 3.98−3.78 (m), 3.77−3.52 (m), 2.34−2.14 (m), 2.10−1.92 (m), 1.91−1.61 (m), 1.46 (m), 1.27 (m), 0.99−0.82 (m); $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$, δ): 79.0, 66.3, 62.5, 43.4, 38.9, 29.0, 25.6, 23.7, 22.1; LRMS-ESI (*m*/*z*): 159.1 $[M + H]^+$. HRMS (APCI-Orbitrap) (*m*/*z*): calcd for $C_9H_{19}O_2$ $[M + H]^+$, 159.1380; found, 159.1379.

*(2-((Benzyloxy)methyl)tetrahydrofuran-3-yl)methanol (**13j**).* The reaction of 2-((benzyloxy)methyl)-4,7-dihydro-1,3-dioxepine **5j** (60 mg, 0.27 mmol), dichloromethane (1.4 mL), $BF_3{\cdot}OEt_2$ (7 μL, 11 mg, 0.05 mmol), and methanol (1.4 mL) and $NaBH_4$ (>3 equiv) followed by workup and column chromatography (20% EtOAc/hexanes−80% EtOAc/hexanes) afforded **13j** as a light-brown oil (26 mg, 0.12 mmol, 42% over 2 steps). ^1H NMR (400 MHz, $CDCl_3$, δ) (diastereomeric ratio = 5:1): 7.33 (qd, *J* = 7.1, 3.4 Hz, 5H, superimposed by peak corresponding to the minor isomer), 4.58 (s, 2H), 4.15 (td, *J* = 7.2, 4.2 Hz, 1H), 3.95 (td, *J* = 8.3, 3.7 Hz, 1H), 3.76−3.53 (m, 3H, superimposed by peak corresponding to the minor isomer), 2.98 (t, *J* = 6.4 Hz, 1H), 2.56 (pd, *J* = 7.8, 5.6 Hz, 1H), 1.98 (dtd, *J* = 12.3, 7.6, 3.7 Hz, 1H), 1.67 (dq, *J* = 12.4, 8.4 Hz, 2H); $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$, δ): 137.3, 128.7 (2C), 128.1 (2C), 128.0, 78.5, 74.1, 69.5, 67.4, 62.3, 44.0, 28.5; LRMS-ESI (*m*/*z*): 223.1 $[M + H]^+$, 245.1 $[M + Na]^+$. HRMS (APCI-Orbitrap) (*m*/*z*): calcd for $C_{13}H_{19}O_2$ $[M + H]^+$, 223.1329; found, 223.1328.

*(2-(Benzo[d][1,3]dioxol-5-yl)tetrahydrofuran-3-yl)methanol (**13k**).* Following the general procedure, the reaction of 5-(4,5-dihydro-1,3-dioxepin-2-yl)benzo[d][1,3]dioxole **5k** (71 mg, 0.32 mmol), dichloromethane (1.6 mL), $BF_3{\cdot}OEt_2$ (8 μL, 13 mg, 0.06 mmol), and methanol (1.6 mL) and $NaBH_4$ (>3 equiv) followed by workup and column chromatography (20% EtOAc/hexanes−50% EtOAc/hexanes) afforded **13k** as a yellowish oil (49 mg, 0.22 mmol, 68% over 2 steps). ^1H NMR (400 MHz, $CDCl_3$, δ) (diastereomeric ratio = 4:1): 6.84−6.70 (m, 3H), 5.94 (s, 2H), 4.92 (d, *J* = 6.9 Hz, 1H), 4.17 (td, *J* = 8.3, 4.5 Hz, 1H), 3.86 (q, *J* = 7.9 Hz, 1H), 3.28 (ddd, *J* = 35.4, 11.0, 6.6 Hz, 2H), 2.68−2.53 (m, 1H), 2.14 (dtd, *J* = 12.3, 7.7, 4.6 Hz, 1H), 1.88 (dtd, *J* = 12.5, 8.0, 6.2 Hz, 1H), 1.25 (s, 1H); $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$, δ): 147.9, 146.9, 133.6, 119.2, 108.3, 106.8, 101.1, 81.9, 67.6, 62.9, 45.8, 29.1; LRMS-ESI (*m*/*z*): 223.0 $[M + H]^+$,245.0 $[M + Na]^+$. HRMS (APCI-Orbitrap) (*m*/*z*): calcd for $C_{12}H_{18}O_4$ $[M + H]^+$, 223.0965; found, 223.0967.

Synthesis of Select 2,3-Disubstituted Tetrahydrofurans under Thermal Conditions: General Procedure. To a solution of 4,5-dihydro-1,3-dioxepine **5** (1 equiv) in xylenes (0.2 M solution) was added $Zn(OTf)_2$ (0.2 equiv). The flask was then immediately immersed into an oil bath and heated at reflux for the time specified in Table 6. After this time, the reaction was allowed to cool to 23 °C and then to 0 °C. Then, methanol (0.2 M solution) and $NaBH_4$ (>3 equiv) were added. After reduction of the aldehyde was observed on TLC (about 1 h), the reaction was quenched with deionized water, and the aqueous layer was extracted twice with ethyl acetate. The combined organic layer was dried over sodium sulfate. Column chromatography using the specified solvent systems provided the 2,3-*trans*-disubstituted tetrahydrofuran products **14a−k** as major isomers. The diastereomeric ratios (*cis*:*trans*) were determined via integration of the ^1H NMR spectra.

*(2-Phenyltetrahydrofuran-3-yl)methanol (**14a**).*[18] Following the general procedure, the reaction of 2-phenyl-4,5-dihydro-1,3-dioxepine **5a** (56 mg, 0.32 mmol), xylenes (1.6 mL), $Zn(OTf)_2$ (23 mg, 0.07 mmol), and methanol (1.6 mL) and $NaBH_4$ (>3 equiv) followed by workup and column chromatography (30−50% EtOAc/hexanes) afforded **14a** as a colorless oil (27 mg, 0.15 mmol, 48% over 2 steps). ^1H NMR (400 MHz, $CDCl_3$, δ) (diastereomeric ratio = 1:20): 7.43−7.28 (m, 5H), 4.64 (d, *J* = 6.7 Hz, 1H), 4.18−4.07 (m, 1H), 3.98 (td, *J* = 8.2, 6.0 Hz, 1H), 3.82−3.61 (m, 2H), 2.34 (dt, *J* = 8.0, 6.4 Hz, 1H), 2.24−2.11 (m, 2H), 1.86 (dq, *J* = 12.6, 7.1 Hz, 1H); $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$, δ):142.7, 128.5 (2C), 127.6, 126.1 (2C), 83.2, 68.2, 64.0, 50.3, 29.7.

*(2-(4-Methoxyphenyl)tetrahydrofuran-3-yl)methanol (**14c**).* Following the general procedure, the reaction of 2-(4-methoxyphenyl)-4,5-dihydro-1,3-dioxepine **5c** (170 mg, 0.82 mmol), xylenes (4.1 mL),

https://dx.doi.org/10.1021/acs.joc.0c00390
J. Org. Chem. XXXX, XXX, XXX−XXX

$Zn(OTf)_2$ (60 mg, 0.16 mmol), and methanol (4.1 mL) and $NaBH_4$ (>3 equiv) followed by workup and column chromatography (20% EtOAc/hexanes−50% EtOAc/hexanes) provided **14c** as a yellowish oil (56 mg, 0.27 mmol, 32% over 2 steps). ^{1}H NMR (400 MHz, $CDCl_3$, δ) (diastereomeric ratio = 1:7): 7.36−7.29 (m, 2H), 6.96−6.81 (m, 2H), 4.59 (d, J = 7.0 Hz, 1H), 4.13 (ddd, J = 8.5, 7.5, 6.6 Hz, 1H), 3.98 (td, J = 8.2, 5.9 Hz, 1H), 3.83 (s, 3H), 3.79−3.65 (m, 2H), 2.43−2.31 (m, 1H), 2.21 (dtd, J = 12.5, 7.9, 5.8 Hz, 1H), 1.89 (ddt, J = 12.2, 8.0, 6.8 Hz, 1H); ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$, δ): 159.2, 134.5, 127.5 (2C), 114.0 (2C), 83.1, 68.0, 64.1, 55.4, 50.1, 29.8. HRMS (APCI-Orbitrap) (m/z): calcd for $C_{12}H_{16}O_3$ [M + H]$^+$, 209.1172; found, 209.1177.

*(2-(4-Nitrophenyl)tetrahydrofuran-3-yl)methanol (**14e**).* Following the general procedure, the reaction of 2-(4-nitrophenyl)-4,5-dihydro-1,3-dioxepine **5e** (243 mg, 1.10 mmol), xylenes (5.5 mL), $Zn(OTf)_2$ (80 mg, 0.22 mmol), and methanol (5.5 mL) and $NaBH_4$ (>3 equiv) followed by workup and column chromatography (30% EtOAc/hexanes−80% EtOAc/hexanes) provided **14e** as a brownish oily solid (120 mg, 0.54 mmol, 49% over 2 steps). ^{1}H NMR (400 MHz, $CDCl_3$, δ) (diastereomeric ratio = 1:6) 8.14 (d, J = 8.8 Hz, 1H), 7.58−7.42 (m, 2H), 4.81 (d, J = 6.1 Hz, 1H), 4.10 (ddd, J = 8.5, 7.5, 6.3 Hz, 1H), 4.05−3.95 (m, 1H), 3.73 (d, J = 6.4 Hz, 2H), 2.29 (dp, J = 8.3, 6.4 Hz, 1H), 2.18−2.03 (m, 2H), 1.84 (ddt, J = 12.6, 7.7, 6.4 Hz, 1H); ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$, δ): 150.9, 147.1, 126.6 (2C), 123.6 (2C), 82.2, 68.4, 63.6, 50.4, 29.3. HRMS (APCI-Orbitrap) (m/z): calcd for $C_{11}H_{14}NO_4$ [M + H]$^+$, 224.0917; found, 224.0920.

*2-(Naphthalen-1-yl)tetrahydrofuran-3-yl)methanol (**14g**).* Following the general procedure, the reaction of 2-(naphthalen-1-yl)-4,5-dihydro-1,3-dioxepine **5g** (40 mg, 0.17 mmol) in xylenes (1.0 mL), $Zn(OTf)_2$ (13 mg, 0.04 mmol), and methanol (1.0 mL) and $NaBH_4$ (>3 equiv) followed by workup and column chromatography (20% EtOAc/hexanes−50% EtOAc/hexanes) afforded **14g** as a colorless syrup (18 mg, 0.08 mmol, 45% over 2 steps), ^{1}H NMR (400 MHz, $CDCl_3$, δ) (diastereomeric ratio= 1:5): 8.20 (dd, J = 8.3, 1.4 Hz, 1H), 7.87 (dd, J = 7.5, 2.0 Hz, 1H), 7.78 (d, J = 8.2 Hz, 1H), 7.64−7.39 (m, 4H), 5.56 (d, J = 4.7 Hz, 1H), 4.32 (qd, J = 8.3, 4.9 Hz, 1H), 4.10 (q, J = 8.1 Hz, 1H), 3.83 (ddd, J = 35.7, 10.6, 6.6 Hz, 2H), 2.62 (dtd, J = 11.4, 6.9, 4.6 Hz, 1H), 2.19 (dq, J = 12.6, 8.2 Hz, 1H), 1.94 (ddt, J = 12.3, 7.7, 4.4 Hz, 1H); ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$, δ): 138.3, 134.0, 130.8, 128.9, 128.1, 126.1, 125.7, 125.5, 123.7, 123.4, 80.6, 68.2, 64.2, 48.9, 28.4. HRMS (APCI-Orbitrap) (m/z): calcd for $C_{15}H_{17}O_2$ [M + H]$^+$, 229.1223; found, 229.1226.

*(2-(Benzo[d][1,3]dioxol-5-yl)tetrahydrofuran-3-yl)methanol (**14k**).* Following the general procedure, the reaction of 5-(4,5-dihydro-1,3-dioxepin-2-yl)benzo[d][1,3]dioxole **5k** (61 mg, 0.28 mmol), xylenes (1.4 mL), $Zn(OTf)_2$ (20 mg, 0.06 mmol), and methanol (1.4 mL) and $NaBH_4$ (>3 equiv) followed by workup and column chromatography (20% EtOAc/hexanes−50% EtOAc/hexanes) afforded **14k** as a yellowish oil (42 mg, 0.19 mmol, 67% over 2 steps). ^{1}H NMR (400 MHz, $CDCl_3$, δ) (diastereomeric ratio = 1:4): 6.86 (d, J = 1.6 Hz, 1H), 6.83−6.72 (m, 2H), 5.94 (s, 2H), 4.54 (d, J = 6.9 Hz, 1H), 4.09 (ddd, J = 8.5, 7.5, 6.5 Hz, 1H), 3.95 (td, J = 8.2, 5.8 Hz, 1H), 3.78−3.62 (m, 2H), 2.29 (dddd, J = 13.1, 8.3, 6.9, 6.2 Hz, 1H), 2.24−2.10 (m, 1H), 1.93−1.78 (m, 1H); ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$, δ): 148.0, 147.1, 136.6, 119.6, 108.2, 106.7, 101.1, 83.3, 68.0, 64.0, 50.2, 29.7. HRMS (APCI-Orbitrap) (m/z): calcd for $C_{12}H_{15}O_4$ [M + H]$^+$, 223.0965; found, 223.0967.

Synthesis of *para*-Bromobenzoates *cis*- and *trans*-16e: General Procedure. To a solution of alcohol **13e** (37 mg, 0.17 mmol) or **14e** (11 mg, 0.05 mmol) in dichloromethane (1.7 mL; 0.50 mL, respectively) at 23 °C was added triethylamine (46 μL, 0.33 mmol; 14 μL, 0.10 mmol, respectively) dropwise. Then, 4-bromobenzoyl chloride (72 mg, 0.33 mmol; 22 mg, 0.10 mmol, respectively) and DMAP (1 spatula tip) were added. The reactions were then allowed to stir for 12 h at 23 °C. At this point, the reactions were quenched with saturated brine solution, and the aqueous layer was extracted twice with dichloromethane. The combined organic layer was dried over sodium sulfate. Column chromatography (20% EtOAc/hexanes−50% EtOAc/hexanes) provided the *para*-bromobenzoates (*cis*-**16**: 53 mg, 0.13 mmol, 80%; *trans*-**16**: 17 mg, 0.04 mmol, 84%). Recrystallization (EtOAc/hexanes, layering) provided the crystals suitable for X-ray crystallography.

*cis-(2-(4-Nitrophenyl)tetrahydrofuran-3-yl)methyl-4-bromobenzoate (cis-**16**).* ^{1}H NMR (400 MHz, $CDCl_3$, δ) 8.14 (d, J = 8.8 Hz, 2H), 7.71−7.63 (m, 2H), 7.58−7.45 (m, 4H), 5.13 (d, J = 6.6 Hz, 1H), 4.29 (td, J = 8.3, 5.3 Hz, 1H), 4.01 (td, J = 8.3, 7.0 Hz, 1H), 3.96−3.85 (m, 2H), 3.01 (pd, J = 7.1, 5.2 Hz, 1H), 2.33 (dtd, J = 13.0, 7.9, 5.3 Hz, 1H), 2.10−1.92 (m, 1H); ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$, δ): 165.4, 147.4, 146.8, 131.9 (2C), 131.0 (2C), 128.6, 128.5, 127.1 (2C), 123.7 (2C), 81.3, 67.6, 64.2, 42.7, 29.5. HRMS (APCI-Orbitrap) (m/z): calcd for $C_{18}H_{17}Br^{79}NO_5$ [M + H]$^+$, 406.0285; found, 406.0276.

*trans-(2-(4-Nitrophenyl)tetrahydrofuran-3-yl)methyl-4-bromobenzoate (trans-**16**).* ^{1}H NMR (400 MHz, $CDCl_3$, δ) ^{1}H 8.18 (d, J = 8.8 Hz, 2H), 7.76 (d, J = 8.6 Hz, 2H), 7.62−7.45 (m, 4H), 4.81 (d, J = 6.8 Hz, 1H), 4.55−4.35 (m, 2H), 4.21 (ddd, J = 8.6, 7.5, 6.5 Hz, 1H), 4.09 (td, J = 8.3, 6.1 Hz, 1H), 2.61 (dqd, J = 8.3, 7.0, 5.9 Hz, 1H), 2.28 (dtd, J = 12.7, 7.8, 6.0 Hz, 1H), 2.09−1.93 (m, 1H); ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$, δ): 165.7, 149.6, 147.5, 131.9 (2C), 131.1 (2C), 128.6, 128.5, 126.9 (2C), 123.8 (2C), 82.7, 68.4, 65.4, 47.4, 29.7; HRMS (APCI-Orbitrap) (m/z): calcd for $C_{18}H_{17}Br^{79}NO_5$ [M + H]$^+$, 406.0285; found, 406.0276.

Synthesis of 2-((Benzyloxy)methyl)tetrahydrofuran-3-carbaldehyde 6j. The reaction of 2-((benzyloxy)methyl)-4,7-dihydro-1,3-dioxepine **5j** (1.96 g, 8.9 mmol), dichloromethane (27 mL), and $BF_3{\cdot}OEt_2$ (220 μL, 1.8 mmol) followed by aqueous workup with saturated $NaHCO_3$ provided the crude tetrahydrofuran-3-carbaldehyde **6j**. The crude aldehyde was utilized in the next step without further purification.

Synthesis of Hexahydrofuro[3,4-*b*]furan-4-ol. To a solution of crude aldehyde **6j** in ethyl acetate (45 mL) was added Pearlman's catalyst (940 mg, 1.3 mmol). After purging the suspension three times with argon and three times once again with hydrogen gas, the reaction mixture was allowed to stir at 23 °C under a hydrogen atmosphere (balloon) for 16 h. At this point, TLC analysis indicated complete consumption of the starting material and the reaction mixture was filtered over Celite. The filtrate was concentrated under reduced pressure to provide the crude lactol. Due to suspected volatility and instability on silica gel, the crude material was utilized in the next step without further purification.

Synthesis of 4-Methoxyhexahydrofuro[3,4-*b*]furan 17. To a solution of crude lactol in diethyl ether (90 mL) was added 4 Å MS, methanol (1.1 mL, 27 mmol), and Amberlyst-15 (45 g). The reaction mixture was then allowed to stir under a blanket of argon for 5 h. At this point, TLC analysis indicated complete consumption of the starting material. The reaction mixture was then filtered and the filtrate was concentrated under reduced pressure. Column chromatography (10−30% EtOAc/hexanes) provided the methyl acetal **17** as a colorless oil (590 mg, 4.1 mmol, 46% over 3 steps). ^{1}H NMR (800 MHz, $CDCl_3$, δ) 4.81 (s, 1H), 4.63 (dd, J = 6.8, 4.0 Hz, 1H), 3.93 (d, J = 10.1 Hz, 1H), 3.88 (dd, J = 10.2, 4.1 Hz, 1H), 3.82 (dt, J = 8.5, 6.7 Hz, 1H), 3.71 (ddd, J = 8.5, 6.8, 5.9 Hz, 1H), 3.29 (s, 3H), 2.79 (ddd, J = 9.7, 6.7, 4.6 Hz, 1H), 2.10 (ddt, J = 12.5, 9.5, 6.9 Hz, 1H), 1.79 (dtd, J = 12.4, 6.3, 4.6 Hz, 1H); ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$, δ): 110.6, 82.9, 72.9, 68.9, 54.6, 50.5, 31.1. HRMS (APCI-Orbitrap) (m/z): calcd for $C_7H_{11}O_3$ [M − H]$^-$, 143.0703; found, 143.0701.

Synthesis of 4-Methoxytetrahydrofuro[3,4-*b*]furan-2(3*H*)-one 18. To a solution of methyl acetal **17** (590 mg, 4.1 mmol) in a mixture (2:2:3) of CH_2Cl_2:CH_3CN:H_2O (total of 39 mL) was added ruthenium oxide hydrate (217 mg) and $NaIO_4$ (2.62 g, 12 mmol). After 30 min of stirring under a blanket of argon at 23 °C, the reaction mixture became a greenish color. The reaction mixture was then allowed to stir for an additional 1.5 h under these same conditions. At this point, TLC analysis indicated complete consumption of the starting material. The reaction mixture was then filtered over Celite, quenched with sat. NaCl and the aqueous layer was back-extracted 3× with CH_2Cl_2. The combined organic layer was dried with Na_2SO_4. Column chromatography (10−50% EtOAc/hexanes) provided the lactone **18** as a colorless solid (200 mg,

https://dx.doi.org/10.1021/acs.joc.0c00390
J. Org. Chem. XXXX, XXX, XXX−XXX

1.3 mmol, 31%). ^{1}H NMR (400 MHz, $CDCl_3$, δ) 5.13 (dd, J = 7.1, 3.9 Hz, 1H), 4.86 (s, 1H), 4.08 (d, J = 10.9 Hz, 1H), 3.94 (dd, J = 10.9, 3.9 Hz, 1H), 3.31 (s, 3H), 3.07−2.96 (m, 1H), 2.82 (dd, J = 18.6, 11.3 Hz, 1H), 2.50 (dd, J = 18.6, 4.0 Hz, 1H); ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$, δ): 175.8, 110.0, 82.9, 70.6, 54.5, 45.1, 31.8; HRMS (APCI-Orbitrap) (m/z): calcd for $C_7H_{11}O_4$ [M + H]$^+$, 159.0652; found, 159.0649.

Synthesis of Hexahydrofuro[2,3-*b*]furan-3-ol 19.[35] To a solution of lactone **18** (200 mg, 1.3 mmol) in diethyl ether (15 mL) at 0 °C was added a solution of lithium aluminum hydride (1 M in tetrahydrofuran) (1.6 mL, 1.6 mmol) dropwise. The reaction mixture was allowed to slowly warm to 23 °C and stir for 2 h. At this point, the reaction mixture was cooled to −10 °C, and an aqueous solution of HCl (33% by volume, 0.30 mL, 2.0 mmol) was added dropwise. The reaction mixture was then allowed to stir at −10 °C for 3 h. The reaction was then quenched with triethylamine (0.42 mL, 2.3 mmol), and the resulting solution was concentrated under reduced pressure over an ice bath. Column chromatography (50% Et_2O/hexanes−100% Et_2O) provided hexahydrofuro[2,3-*b*]furan-3-ol **19** as a colorless oil (31 mg, 0.24 mmol, 19% over 2 steps). ^{1}H NMR (800 MHz, $CDCl_3$, δ) 5.69 (d, J = 5.1 Hz, 1H), 4.53−4.37 (m, 1H), 4.06−3.96 (m, 2H), 3.91 (ddd, J = 9.9, 8.7, 6.3 Hz, 1H), 3.64 (dd, J = 9.2, 6.9 Hz, 1H), 2.86 (ddd, J = 10.2, 7.9, 5.2 Hz, 1H), 2.31 (ddd, J = 12.9, 6.1, 2.9 Hz, 1H), 1.94−1.83 (m, 1H), 1.78 (s, 1H); ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$, δ): 109.5, 73.2, 71.1, 69.9, 46.6, 24.8.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge at https://pubs.acs.org/doi/10.1021/acs.joc.0c00390.

^{1}H and ^{13}C NMR spectra for all new compounds (PDF)

Crystallographic information (CIF)

Crystallographic information (CIF)

■ AUTHOR INFORMATION

Corresponding Author

Arun K. Ghosh − *Department of Chemistry and Department of Medicinal Chemistry, Purdue University, West Lafayette, Indiana 47907, United States;* orcid.org/0000-0003-2472-1841; Email: akghosh@purdue.edu

Author

Miranda R. Belcher − *Department of Chemistry and Department of Medicinal Chemistry, Purdue University, West Lafayette, Indiana 47907, United States;* orcid.org/0000-0003-4925-8638

Complete contact information is available at: https://pubs.acs.org/10.1021/acs.joc.0c00390

Notes

The authors declare no competing financial interest.

■ ACKNOWLEDGMENTS

Financial support of this work was provided by the National Institutes of Health (AI150466). NMR and mass spectrometry were all performed using shared resources which are partially supported by the Purdue Center for Cancer Research through NIH grant (P30CA023168). We would also like to thank Dr. Matthias Zeller (Purdue X-ray diffraction laboratory), Ms. Arlene Rothwell (Analytical Mass Spectrometry Facility), and Ms. Tianyun Zhang (Purdue University) for their help.

■ REFERENCES

(1) Lorente, A.; Lamariano-Merketegi, J.; Albericio, F.; Álvarez, M. Tetrahydrofuran-Containing Macrolides: A Fascinating Gift from the Deep Sea. *Chem. Rev.* **2013**, *113*, 4567−4610.

(2) Bhatnagar, I.; Kim, S.-K. Marine Antitumor Drugs: Status, Shortfalls, and Strategies. *Mar. Drugs* **2010**, *8*, 2702−2720.

(3) Tsuda, M.; Endo, T.; Kobayashi, J. Amphidinolide U, Novel 20-membered Macrolide from Marine Dinoflagellate *amphidinium* sp. *Tetrahedron* **1999**, *55*, 14565−14570.

(4) Kobayashi, J.; Kubota, T.; Endo, T.; Tsuda, M. Amphidinolides T2, T3, and T4, New 19-Membered Macrolides from the Dinoflagellate *Amphidinium* sp. and the Biosynthesis of Amphidinolide T1. *J. Org. Chem.* **2001**, *66*, 134−142.

(5) Minamida, M.; Kumagai, K.; Ulanova, D.; Akakabe, M.; Konishi, Y.; Tominaga, A.; Tanaka, H.; Tsuda, M.; Fukushi, E.; Kawabata, J.; Masuda, A.; Tsuda, M. Amphirionin-4 with Potent Proliferation-Promoting Activity on Bone Marrow Stromal Cells from a Marine Dinoflagellate Amphidinium Species. *Org. Lett.* **2014**, *16*, 4858−4861.

(6) Herbrecht, R. Posaconazole: A Potent, Extended-spectrum Triazole Anti-fungal for the Treatment of Serious Fungal Infections. *Int. J. Clin. Pract.* **2004**, *58*, 612−624.

(7) Torres, H. A.; Hachem, R. Y.; Chemaly, R. F.; Kontoyiannis, D. P.; Raad, I. I. Posaconazole: A Broad-spectrum Triazole Antifungal. *Lancet Infect. Dis.* **2005**, *5*, 775−785.

(8) Ghosh, A. K.; Dawson, Z. L.; Mitsuya, H. Darunavir, a Conceptually New HIV-1 Protease Inhibitor for the Treatment of Drug-Resistant HIV. *Bioorg. Med. Chem.* **2007**, *15*, 7576−7580.

(9) de Béthune, M. P.; Sekar, V.; Spinosa-Guzman, S.; Vanstockem, M.; De Meyer, S.; Wigerinck, P.; Lefebvre, E. Darunavir (Prezista, TMC114): From Bench to Clinic, Improving Treatment Options for HIV-Infected Patients. In *Antiviral Drugs: From Basic Discovery through Clinical Trials*; Kazmierski, W. M., Ed.; Wiley: New York, 2011; pp 31−45.

(10) Elliott, M. C.; Williams, E. Saturated Oxygen Heterocycles. *J. Chem. Soc. Perkin Trans. I* **2001**, 2303−2340.

(11) Wolfe, J. P.; Hay, M. B. Recent Advances in the Stereoselective Synthesis of Tetrahydrofurans. *Tetrahedron* **2007**, *63*, 261−290.

(12) Reitz, A. B.; Nortey, S. O.; Maryanoff, B. E.; Liotta, D.; Monahan, R. Stereoselectivity of Electrophile-Promoted Cyclizations of C-Hydroxyalkenes. An Investigation of Carbohydrate-Derived and Model Substrates. *J. Org. Chem.* **1987**, *52*, 4191−4202.

(13) Hartung, J.; Daniel, K.; Rummey, C.; Bringmann, G. On the Stereoselectivity of 4-Penten-1-oxyl Radical 5-Exo-trig Cyclizations. *Org. Biomol. Chem.* **2006**, *4*, 4089−4100.

(14) Scharf, H.-D.; Frauenrath, H. Fragmentierung Cyclischer Carboxonium-Ionen, III. 1,3-Dioxepan-4-ylium-Ionen, Schlüssel zur Synthese von Tetrahydrofuran-3-carbaldehyden. *Chem. Ber.* **1980**, *113*, 1472−1479.

(15) Ghosh, A. K.; Anderson, D. D.; Weber, I. T.; Mitsuya, H. Enhancing Protein Backbone Binding—a Fruitful Concept for Combating Drug-Resistant HIV. *Angew. Chem. Int. Ed.* **2012**, *51*, 1778−1802.

(16) Ghosh, A. K.; Sridhar, P. R.; Kumaragurubaran, N.; Koh, Y.; Weber, I. T.; Mitsuya, H. *Bis*-Tetrahydrofuran: a Privileged Ligand for Darunavir and a New Generation of HIV Protease Inhibitors That Combat Drug Resistance. *ChemMedChem* **2006**, *1*, 939−950.

(17) Frauenrath, H.; Runsink, J.; Scharf, H.-D. Carboxonium-Ionen-Reaktionen Cyclischer Acetale, VI. Der Sterische Verlauf der Säurekatalysierten Umlagerung von 4,5-Dihydro-1,3-dioxepinen zu Tetrahydrofuran-3-carbaldehyden. *Chem. Ber.* **1982**, *115*, 2728−2743.

(18) Frauenrath, H.; Philipps, T. Diastereoselektive Synthese von *cis*- oder *trans*-2,3-Substituierten Tetrahydrofuranen und 3,4-substituierten 4-Butanoliden. *Liebigs Annalen der Chemie* **1985**, *10*, 1951−1961.

(19) Frauenrath, H.; Runsink, J. Stereocontrolled Route to 2,3,5-Trisubstituted Tetrohydrofurans. Intermediates for the Total Synthesis of Polyether Antibiotics. *J. Org. Chem.* **1987**, *52*, 2707−2712.

(20) Suzuki, H.; Yashima, H.; Hirose, T.; Takahashi, M.; Moro-Oka, Y.; Ikawa, T. Stereoselective Synthesis of Tetrahydrofuran-3-carbaldehyde. *Tetrahedron Lett.* **1980**, *21*, 4927−4930.

(21) Hoppe, D. Diastereoselektive C-C-Verknüpfungen und ihre stereochemische Spezifikation. *Nachr. Chem., Tech. Lab.* **1982**, *30* (12), 1030−1033.
(22) Seebach, D.; Prelog, V. The Unambiguous Specification of the Steric Course of Asymmetric Syntheses. *Angew. Chem., Int. Ed. Engl.* **1982**, *21* (9), 654−660.
(23) Zhang, Y.; Reynolds, N. T.; Manju, K.; Rovis, T. Stereoretentive O-to-C Rearrangement of Vinyl Acetals: Solvent Cage Effects as a Stereocontrol Element. *J. Am. Chem. Soc.* **2002**, *124* (33), 9720−9721.
(24) Fu, G. C.; Nguyen, S. T.; Grubbs, R. H. Catalytic ring-closing metathesis of functionalized dienes by a ruthenium carbene complex. *J. Am. Chem. Soc.* **1993**, *115*, 9856−9857.
(25) Grubbs, R. H.; Chang, S. Recent advances in olefin metathesis and its application in organic synthesis. *Tetrahedron* **1998**, *54*, 4413−4450.
(26) Hallman, P. S.; McGarvey, B. R.; Wilkinson, G. The preparation and reactions of hydridochlorotris(triphenylphosphine)-ruthenium(II) including homogeneous catalytic hydrogenation of alk-1-enes. *J. Chem. Soc. A* **1968**, 3143−3150.
(27) Suzuki, H.; Koyama, Y.; Moro-Oka, Y.; Ikawa, T. Novel peparation of silyl enol ethers from allyl alcohols. *Tetrahedron Lett.* **1979**, *20*, 1415−1418.
(28) Single-crystal X-ray analysis was performed in-house: Zeller, M.. X-ray Crystallography Laboratory, Department of Chemistry, Purdue University: West Lafayette, Indiana.
(29) CCDC 1978315 and 1978311 contain the supplementary crystallographic data for compound *cis*-**16** and *trans*-**16** respectively. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif.
(30) Wu, A.; Cremer, D. Extension of the Karplus Relationship for NMR Spin-Spin Coupling Constants to Nonplanar Ring Systems: Pseudorotation of Tetrahydrofuran. *Int. J. Mol. Sci.* **2003**, *4*, 158−192.
(31) Please reference the Supporting Information for the corresponding ^{1}H-NOESY data.
(32) Sharma, G. V. M.; Gopinath, T. Radical cyclisation approach for the synthesis of (+)dihydrocanadensolide, (+)dihydrosporothriolide and their C-3 epimers from d-xylose. *Tetrahedron* **2003**, *59*, 6521−6530.
(33) Hikota, M.; Tone, H.; Horita, K.; Yonemitsu, O. Chiral synthesis of polyketide-derived natural products. 27. Stereoselective synthesis of erythronolide A via an extremely efficient macrolactonization by the modified Yamaguchi method. *J. Org. Chem.* **1990**, *55*, 5467−5476.
(34) Ghosh, A. K.; Martyr, C. D. In *Modern Drug Synthesis*; Li, J. J., Johnson, D. S., Eds.; John Wiley & Sons, 2010, pp 29−44.
(35) Ghosh, A. K.; Chen, Y. Synthesis and optical resolution of high affinity P_2-ligands for HIV-1 protease inhibitors. *Tetrahedron Lett.* **1995**, *36*, 505−508.
(36) Ghosh, A. K.; Leshchenko, S.; Noetzel, M. Stereoselective Photochemical 1,3-Dioxolane Addition to 5-Alkoxymethyl-2(5*H*)-furanone: Synthesis of Bis-tetrahydrofuranyl Ligand for HIV Protease Inhibitor UIC-94017 (TMC-114). *J. Org. Chem.* **2004**, *69* (23), 7822−7829.
(37) Brogan, J. B.; Richard, J. E.; Zercher, C. K. Preparation of Diallyl Ketals. *Synth. Commun.* **1995**, *25* (4), 587−593.
(38) Ho, T.-L.; Wong, C. M. Thermolytic Pathway to Ally Arenoates. *Synth. Commun.* **1975**, *5* (3), 213−216.
(39) Penkett, C. S.; Woolford, J. A.; Day, I. J.; Coles, M. P. The Double [3 + 2] Photocycloaddition Reaction. *J. Am. Chem. Soc.* **2010**, *132* (1), 4−5.
(40) Nair, V. A mild and efficient procedure for the preparation of dimethyl and diallyl acetals of aromatic aldehydes mediated by cerium(IV) ammonium nitrate. *Indian J. Chem.* **2005**, No. 1, 141−143.
(41) Matjoska, A. Synthesis and chemical properties of oxaalkylated acetals. *Lietuvos TSR Mokslu Akademijos Darbai, Serija B: Chemija, Technika, Fizine Geografija* **1988**, No. 6, 21−28.
(42) Szczesniak, P.; Staszewska-Krajewska, O.; Furman, B.łło.; Mlynarski, J. Solid supported Hayashi-Jørgensen catalyst as an efficient and recyclable organocatalyst for asymmetric Michael addition reactions. *Tetrahedron: Asymmetry* **2017**, *28* (12), 1765−1773.
(43) Fisera, L.; Oremus, V.; Timpe, H.-J.; Stibranyi, L.; Zalupsky, P. An unusual effect of exo-endo configuration of the quantum yield ϕ of photochemical rearrangement of 4-*R*-substituted 8-phenyl-3,5,10-trioxa-9-azabicyclo-[5,3,0]-8-decenes. *Collect. Czech. Chem. Commun.* **1986**, *51*, 2158−2166.
(44) Takano, S.; Samizu, K.; Ogasawara, K. Diastereodivergent Formation of 2,3-trans:3,4-cis- and 2,3-cis:3,4-trans-2,3,4-Trisubstituted Tetrahydrofurans from the Common 2,5-Disubstituted-4,5-dihydro-1,3-dioxepin: A Diastereocontrolled Route to Furofuran Lignan (±)-Asaranin. *Synlett* **1993**, *10*, 785−787.

https://dx.doi.org/10.1021/acs.joc.0c00390
J. Org. Chem. XXXX, XXX, XXX−XXX