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Silyl Enol Ether Prins Cyclization: Diastereoselective Formation of Substituted Tetrahydropyran-4-ones

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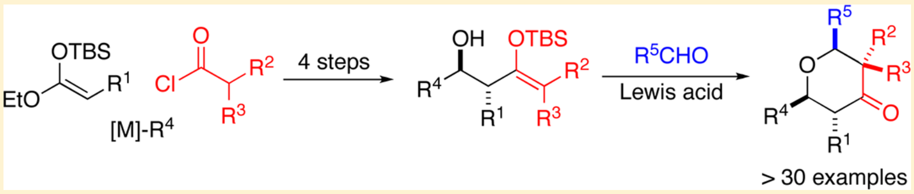
Ⓢ *Supporting Information*



ABSTRACT: A diastereoselective synthesis of *cis*-2,6-disubstituted tetrahydropyran-4-ones was developed. The key step of this methodology, a silyl enol ether Prins cyclization, was promoted by a condensation reaction between a hydroxy silyl enol ether and an aldehyde to afford substituted tetrahydropyran-4-ones. The cyclization was tolerant of many functional groups, and the modular synthesis of the hydroxy silyl enol ether allowed for the formation of more than 30 new tetrahydropyran-4-ones with up to 97% yield and >95:5 dr. The cyclization step forms new carbon−carbon and carbon−oxygen bonds, as well as a quaternary center with good diastereoselectivity. The method provides a versatile route for the synthesis of substituted tetrahydropyrans.

■ INTRODUCTION

Substituted tetrahydropyrans and tetrahydropyranones are a common motif in numerous biologically active natural products (Figure 1).[1] Synthesis of tetrahydropyran-4-ones (THPOs), followed by reduction of the ketone, has been used to form 4-hydroxytetrahydropyran rings.[2] Tetrahydropyranones are commonly prepared with carbon−carbon or carbon−oxygen bond forming reactions by aldol-type cyclization,[3] hetero-Diels−Alder cycloaddition,[4] Japp−Maitland reaction,[5] oxa-Michael condensation,[6] and Petasis−Ferrier rearrangement[7] (Figure 2).[8] These various methods have their strengths and limitations.

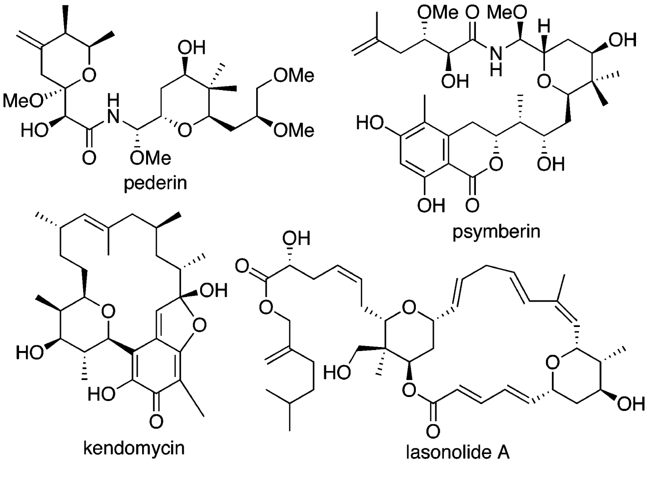


Figure 1. Biologically active natural products containing highly substituted tetrahydropyran rings, such as pederin,[10] psymberin,[11] kendomycin,[12] and lasonolide A.[13]

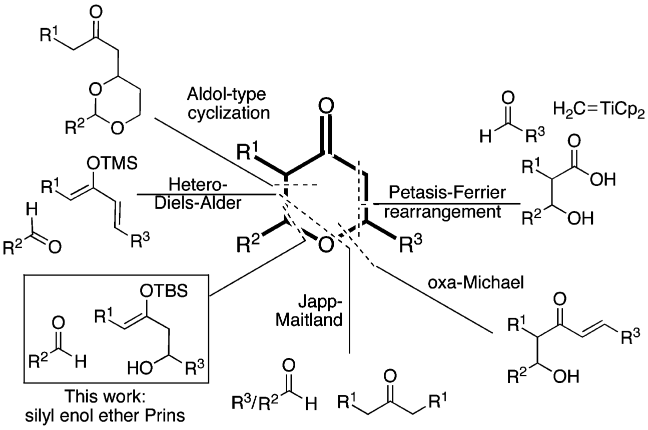


Figure 2. Common methods for forming tetrahydropyran-4-ones and the silyl enol ether Prins cyclization method discussed in this paper.

For example, the hetero-Diels−Alder cycloaddition requires electronic matching of the diene and dienophile.[4] The Petasis−Ferrier rearrangement precursor is often obtained through olefination of an ester; this route would be incompatible with other unprotected carbonyl groups in the substrate. Because tetrahydropyrans are prevalent in natural products, the development of flexible new routes for their synthesis is an important goal. We present a full account of the silyl enol ether Prins cyclization for the synthesis of tetrahydropyranones.[9]

Synthetic methods focused on the preparation of tetrahydropyran-4-ones with an enol ether and oxocarbenium ion have

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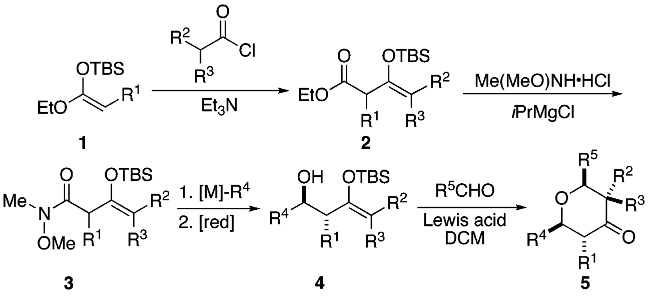
been reported.[14,15] Recently, we reported the diastereoselective synthesis of 2,6-*cis*-tetrahydropyran-4-ones through cyclization between a hydroxy silyl enol ether and an aldehyde.[9] This method was used in the total synthesis of cyanolide A.[16] Intrigued by the diastereoselectivity and functional group tolerance of this silyl enol ether Prins cyclization,[17] we decided to develop the method further by exploring the scope with different substitution patterns. An overview of the tetrahydropyran-4-one synthesis is shown in Scheme 1. The synthesis began with deprotonation of an acid chloride using triethylamine to form a ketene in situ that, when reacted with silyl ketene acetal **1**,[18] produced ester **2**. Ester **2** was transformed to Weinreb amide **3**.[19] Addition of a nucleophilic organometallic reagent and subsequent reduction of the resulting ketone afforded alcohol **4**. Silyl enol ether Prins cyclization of alcohol **4** with a Lewis acid activated aldehyde produced the desired THPO **5** with high diastereoselectivity. The thermodynamically favored cyclization is very effective for introducing quaternary centers at the C-3 position of the THPO. This method allows for the formation of highly functionalized tetrahydropyran-4-ones with substituents at each carbon atom of the THPO core.

Scheme 1. General Overview of This Method for Diastereoselective THPO Synthesis[20]

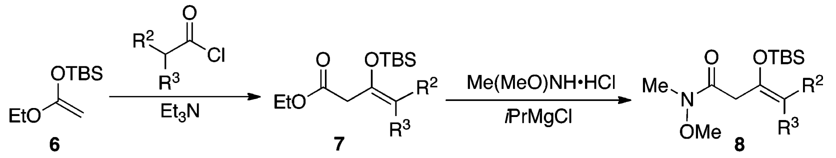


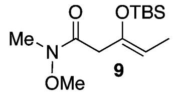
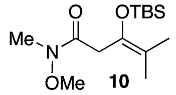
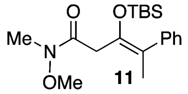
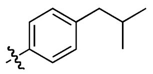
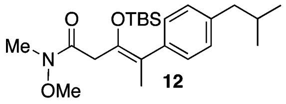
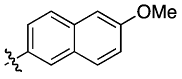
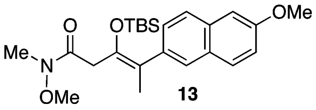
RESULTS

The syntheses of a variety of Weinreb amides are presented in Table 1. The formation of ester **7** occurred in satisfactory yields by reacting the ketene, prepared in situ by deprotonation of the acid chloride, with silyl ketene acetal **6**.[21] Dimethyl ketene (entry 2), which comes from the least acidic acid chloride, was prepared by zinc reduction of 2-bromo-2-methylpropionyl bromide.[22] In entry 3, no desired ester was observed due to the instability of the unsubstituted silyl enol ether product. The acid chloride precursors from entries 5 and 6 were prepared from the nonsteroidal anti-inflammatory drugs, ibuprofen and naproxen, respectively, demonstrating that motifs present in biologically active molecules can be incorporated into the THPO using this method. Acid chlorides with an aryl group for R^2 and a proton for R^3 generally led to low yields of ester **7** (entry 7); these esters were not taken further in the sequence. The transformation to ester **7** was highly diastereoselective; ketene acetal **6** underwent nucleophilic addition at the less hindered face of the ketene. Only a single alkene isomer of Weinreb amide **8** was isolated. The configuration with the larger R^2 substituent *cis* to the −OTBS group was favored in each case.

Weinreb amide **10** underwent nucleophilic addition with a variety of Grignard and organolithium reagents to yield ketone **14** (Table 2). Direct reduction of the crude allylic ketone

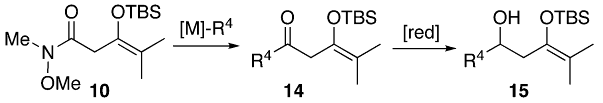
Table 1. Preparation of Weinreb Amides 9−13

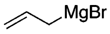
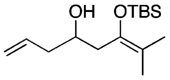
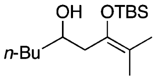
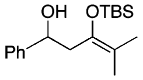
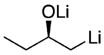
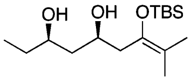
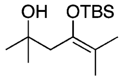
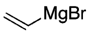
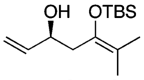
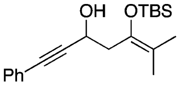


entry	R^2	R^3	yield (%) ketene addition	yield (%) amide formation	product
1	Me	H	77%	84%	 **9**
2[a]	Me	Me	60%[a]	83%	 **10**
3	H	H	decomp.	—	—
4	Ph	Me	81%	83%	 **11**
5		Me	70%	76%	 **12**
6		Me	87%	90%	 **13**
7	Ph	H	31%	—	—

[a] The dimethylketene reagent was prepared in situ by zinc reduction of 2-bromo-2-methylpropionyl bromide.

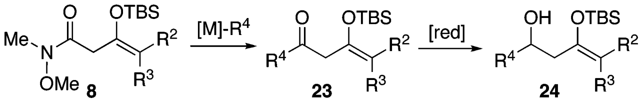
Table 2. Preparation of Hydroxy Silyl Enol Ether from Amide 10

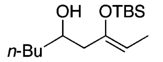
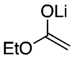
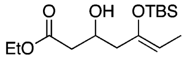
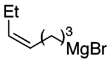
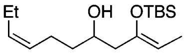
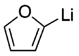
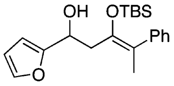
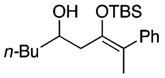
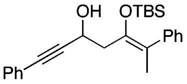
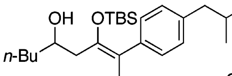
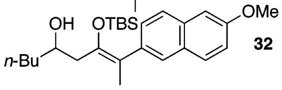


entry	[M]-R^4	yield (%) 1,2 addition	yield (%) reduction	product
1		–	47%^{a}	 **16**
2	*n*-BuLi	82%	92%^{b}	 **17**
3	PhMgBr	73%	85%^{b}	 **18**
4		82%	80%^{c} (9.8:0.2 *e.r.*)	 **19**
5	MeMgBr	66%^{d}	–	 **20**
6		67%	94%^{e} 60%^{f} (9.0:1.0 *e.r.*)	 **21**
7	Ph—≡—Li	39%	87%^{b}	 **22**

[a]Crude ketone was directly reduced with DIBAL-H. The alcohol was obtained through a: [b]$NaBH_4$ reduction, [c]$NaBH_4$ reduction with $Et_2B(OMe)$ additive, [d]double addition to ester **7**, [e]Luche reduction, [f]CBS reduction.

Table 3. Preparation of the Hydroxy Silyl Enol Ether with Varying R^2 and R^3 Substituents



entry	amide	[M]-R^4	yield (%) 1,2 addition	yield (%) reduction^a	product
1	**9**	*n*-BuLi	66%	91%	 **25**
2	**9**		59%	96%	 **26**
3	**9**		75%	95%	 **27**
3	**11**		87%	quant.	 **28**
4	**11**	*n*-BuLi	78%	84%	 **29**
5	**11**	Ph—≡—Li	58%	63%	 **30**
6	**12**	*n*-BuLi	73%	97%	 **31**
7	**13**	*n*-BuLi	60%	79%	 **32**

[a]$NaBH_4$ reduction.

(entry 1) was necessary to prevent isomerization of the double bond into conjugation with the ketone. Reduction of a vinyl ketone (entry 6) could be achieved in high yields with a Luche reduction or enantioselectively with a CBS reduction.[23] The *β*-oxy-alkyllithium reagent[24] from entry 4 was enantioenriched and *syn*-selective reduction[25] of the ketone resulted in diol **19** as a single diastereomer. Tertiary alcohol **20** was obtained by double addition of methylmagnesium bromide into ester **7** (R^2 and R^3 = Me). Modest yields were observed with smaller nucleophiles (entry 7), possibly due to deprotection of the product by nucleophilic attack on the silyl group.[26] A wide variety of hydroxy silyl enol ethers were prepared by this sequence.

Transformation of Weinreb amides with varying R^2 and R^3 substituents to the corresponding alcohols is shown in Table 3. Addition of Grignard or organolithium reagents to Weinreb amide **8** gave the desired ketone **23**. When treated with organolithium reagents, isomerization of less substituted silyl enol ether **9** to form the conjugated silyl enol ether was observed as a side reaction. Reduction of ketone **23** with sodium borohydride occurred in good yield to give racemic hydroxyl silyl enol ethers **25**–**32**.

In our previous publication, cyclization of hydroxyl silyl enol ethers with aromatic and conjugated aldehydes was shown to be most effective with $BF_3 \cdot OEt_2$, while TMSOTf was necessary for aliphatic aldehydes.[9] A new optimization of the THPO cyclization reaction was performed with hydroxyl silyl enol ether **17**, benzaldehyde, and $BF_3 \cdot OEt_2$ (Table 4). It was determined that a polar solvent was necessary for reactivity (entries 1–3). No product was observed when the reaction was run in toluene (entry 2). Dichloromethane (DCM) or acetonitrile (MeCN) as the solvent resulted in similar yields, 66% and 65%, respectively, after 4 h. Dichloromethane was selected as the solvent of choice due to its ease of removal after the cyclization. Reaction concentrations were also examined, with concentrations of 0.1, 0.4, and 1.0 M of alcohol **17** evaluated (entries 4–6). It was found that the most concentrated mixture, 1.0 M, gave the highest yield of 69%. Optimization of temperature, equivalents of the aldehyde, and equivalents of Lewis acid were conducted using design of experiments (DoE).[27] Yields were improved at lower temperatures: reactions at −95 °C gave the slightly higher yields but were much slower. Cyclization reactions shown herein were conducted at −78 °C for ease of operation. Excess $BF_3 \cdot OEt_2$ relative to the aldehyde lowered yields (entry 10), and a 1:1 molar ratio was found to be optimal. It was found that a large excess of both $BF_3 \cdot OEt_2$ and aldehyde minimally affected the yields (entry 9). Dropwise addition of hydroxyl silyl enol ether **17** to a solution of aldehyde and Lewis acid lowered yields (entry 16). In the optimized conditions for the cyclization reaction, it was run at −78 °C in 1.0 M dichloromethane with 1.5 equiv of both the Lewis acid and the aldehyde relative to the alcohol.

The tetrahydropyran-4-one synthesis with aromatic aldehydes is shown in Table 5. Electron-rich aldehydes gave higher yields than electron-poor aldehydes (entries 1–4), possibly due to enhanced stabilization of oxocarbenium ion intermediate **33**. This cyclization reaction is compatible with heterocycles such as furans (entry 6) and benzothiophenes (entry 7), but no reaction occurred with sulfonate-protected indole carboxaldehyde[28] (entry 5). Indole carboxaldehyde[29] and 2-pyridinecarboxaldehyde were also tested as the aldehyde partner in the

Table 4. Optimization of the THPO Cyclization Reaction

entry	temp (°C)	equiv of PhCHO	equiv of $BF_3·OEt_2$	solvent	conc (M)	% yield[a]
1	−78	3.0	3.0	DCM	0.4	66
2	−78	3.0	3.0	toluene	0.4	no rxn
3	−78	3.0	3.0	MeCN	0.4	65
4	−95	3.0	2.0	DCM	1.0	69
5	−95	3.0	2.0	DCM	0.5	46
6	−95	3.0	2.0	DCM	0.1	48
7	−95	4.5	1.5	DCM	0.4	71
8	−95	1.5	1.5	DCM	0.4	71
9	−95	4.5	4.5	DCM	0.4	74
10	−95	1.5	4.5	DCM	0.4	63
11	−40	4.5	1.5	DCM	0.4	51
12	−40	1.5	1.5	DCM	0.4	49
13	−40	4.5	4.5	DCM	0.4	50
14	−40	1.5	4.5	DCM	0.4	62
15	−78	1.5	1.5	DCM	1.0	69
16[b]	−78	1.5	1.5	DCM	0.5	48

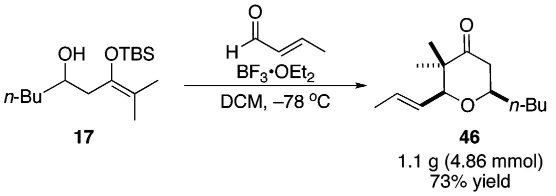
[a] Yields were determined by ^1H NMR spectroscopy with respect to mesitylene internal standard. [b] A diluted solution of silyl enol ether was added dropwise to a solution of aldehyde and $BF_3·OEt_2$ at −78 °C.

cyclization, but only starting material was recovered. Irreversible binding of the Lewis acid to the nitrogen atom may cause the lack of reactivity. The reaction conditions are tolerant of free aliphatic and aromatic alcohols (entries 8 and 9), esters (entry 4), and aryl halides (entry 3). Only the THPO 2,6-*cis* diastereomer was observed when starting with hydroxyl silyl enol ether **15**.

The cyclization reaction also was compatible with aliphatic and conjugated aldehydes (Table 6). Conjugated aldehydes are especially good substrates and generated clean products in high yields (entries 3 and 6). These aldehydes are expected to form resonance stabilized oxocarbenium ion intermediates, which appear to facilitate the cyclization. The difference between aliphatic and conjugated aldehydes is especially apparent when comparing entries 5 and 6. The reaction is tolerant of Boc-protected amines (entry 2). Tertiary alcohol **20** resulted in THPO **50** with two tetrasubstituted carbons (entry 8). A silyl-protected alcohol (entry 1) was partially deprotected under the cyclization reaction conditions. Optimized procedures were found to allow for deprotection or retention of the silyl-protected alcohols. Full deprotection of the silyl group was achieved by removing the reaction mixture from its −78 °C bath and stirring for a few minutes before quenching with sodium bicarbonate. Retention of the silyl group was achieved by adding a bulky base additive, 2,6-di-*tert*-butyl-4-methylpyridine, to neutralize the triflic acid formed during the reaction. Cyclization of hydroxy silyl enol ether **22** with crotonaldehyde led to a 4.1:1.0 ratio of the 2,6-*cis* and 2,6-*trans* THPO product. Cyclizations with a variety of aldehydes and alcohols **16**−**21** resulted in only a single diastereomer. The origin of the diastereoselectivity in the cyclization with hydroxy silyl enol ether **22** will be considered in the Discussion section.

Enantiomerically enriched THPOs can be synthesized using this route (Scheme 2).[9] THPO **48** was synthesized from enantiomerically enriched alcohol precursor **19**. The enantiomeric ratio of thioether **53**, obtained from epoxide opening with thiophenol, was 98.0:2.0. The enantiomeric ratio of THPO **48** was 97.9:2.1, and the enantiospecificity of the reaction was >99%, demonstrating that essentially no optical activity was lost during the cyclization reaction.[30]

The scalability of the cyclization reaction was explored with alcohol **17** (eq 1). Reacting crotonaldehyde with 1.9 g (6.7 mmol) of alcohol **17** produced THPO **46** in 73% yield as a single diastereomer. The reaction was completed after 4 h at −78 °C. This result indicates that no significant loss in yield was observed at a scale useful in multistep syntheses.

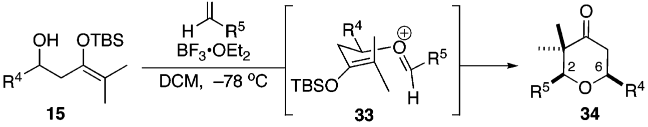


(1)

The tetrahydropyran-4-ones described to this point have been dimethyl substituted at the C-3 position. Table 7 shows examples with a variety of different substituents on the silyl enol ether. These silyl enol ethers often resulted in a mixture of 2,6-*cis* and 2,6-*trans* diastereomers; when the C-3 was dimethyl substituted, usually only a single diastereomer was observed by ^1H NMR. The cyclization reactions with unsymmetric silyl enol ethers form two new stereocenters during the cyclizations, one of them at a quaternary carbon. Substituents R^3 = methyl and R^2 = hydrogen (entries 1−4) were examined because many THP(O) natural products contain a single methyl group at the C-3 position.[1] Lower THPO yields were obtained with hydroxy silyl enol ether **25** because this monosubstituted silyl enol ether underwent the competitive intermolecular Mukaiyama aldol addition, presumably because **25** is less sterically hindered at the enol ether moiety than other hydroxy silyl enol ether cyclization partners. The cyclization was compatible with ester groups (entry 3). Alkene geometries were unchanged under the cyclization reaction conditions even though a conjugated oxocarbenium ion was formed. THPO **62** was synthesized with a 5:1 *Z*:*E* mixture of the aldehyde,[31] and the same *Z*:*E* ratio was obtained after the reaction. Similar to THPO **52** (Table 6, entry 10), the small alkyne substituent on the alcohol led to a loss of *cis*/*trans* diastereoselectivity (Table 7, entry 9). Hydroxy silyl enol ethers with substituted aromatic rings underwent cyclization successfully (entries 10 and 11).

The stereoselective outcome of the THPO cyclization reaction was further examined with substitution at C-5. The

Table 5. Scope of the Tetrahydropyran-4-one Synthesis with Hydroxyl Silyl Enol Ether 15 and Aromatic Aldehydes[20]



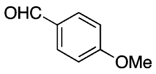
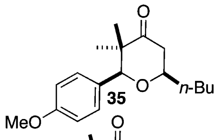
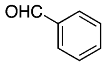
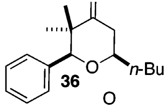
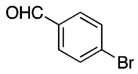
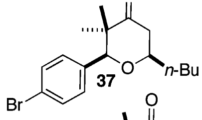
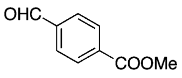
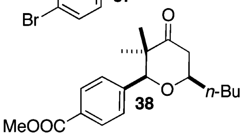
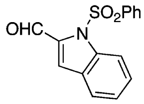
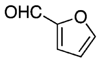
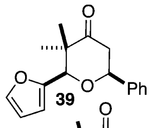
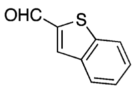
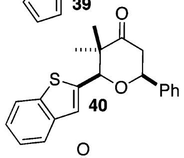
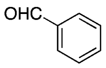
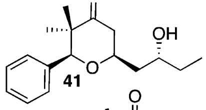
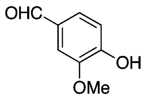
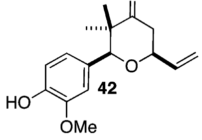
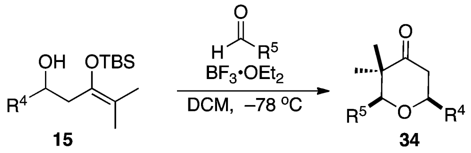
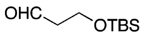
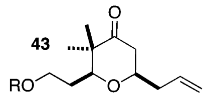
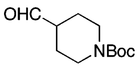
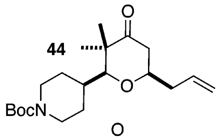
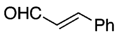
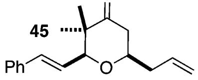
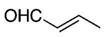
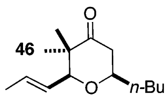
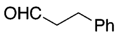
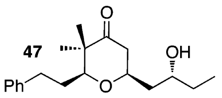
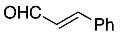
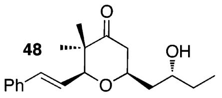
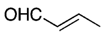
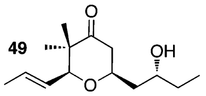
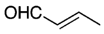
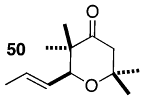
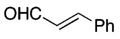
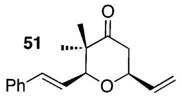
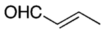
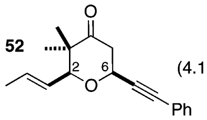
entry	alcohol	aldehyde	product	yield (%)
1	**17**		 **35**	69%
2	**17**		 **36**	47%
3	**17**		 **37**	43%
4	**17**		 **38**	35%
5	**17**		–	no rxn
6	**18**		 **39**	63%
7	**18**		 **40**	38% (95% BRSM)
8	**19**		 **41**	52%
9	**21**		 **42**	30%

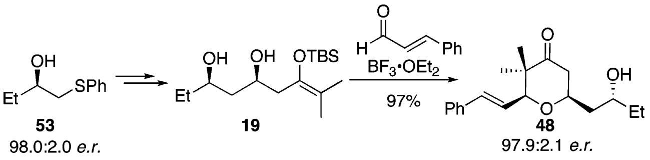
Table 6. Scope of the Tetrahydropyran-4-one Synthesis with Hydroxy Silyl Enol Ether 15 and Conjugated and Aliphatic Aldehydes[20]



entry	alcohol	aldehyde	product	yield (%)
1[a]	**16**		 **43**	76% R = TBS:H 1:1.7
2[a]	**16**		 **44**	42%
3	**16**		 **45**	91%
4	**17**		 **46**	77%
5[a]	**19**		 **47**	37%
6	**19**		 **48**	97%
7	**19**		 **49**	65%
8	**20**		 **50**	80%
9	**21**		 **51**	62%
10	**22**		 **52**	71% (4.1: 1.0 *cis:trans*)

[a]TMSOTf was used as the Lewis acid instead of $BF_3 \cdot OEt_2$.

Scheme 2. Enantiomeric Ratio Is Retained Throughout the Cyclization



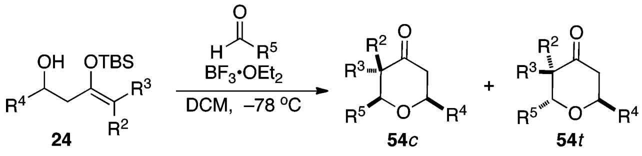
hydroxy silyl enol ether synthesis is shown in Scheme 3. The synthesis began with zinc reduction of 2-bromo-2-methylpropionyl bromide to form dimethyl ketene in situ.[22] Dimethyl ketene added to silyl ketene acetal **66** to afford ester **67**, which was transformed to Weinreb amide **68**. Addition of *n*-butyllithium resulted in ketone **69**, and diastereoselective reduction of **69** with L-selectride produced a mixture of *anti*-alcohol **70** (major) and *syn*-alcohol **71** (minor). The two diastereomers were isolated and used in separate THPO forming reactions.

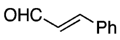
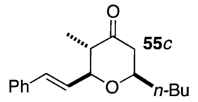
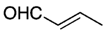
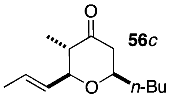
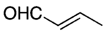
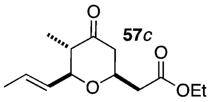
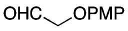
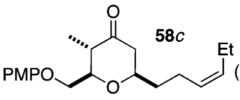
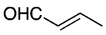
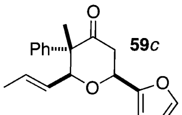
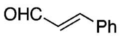
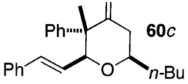
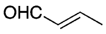
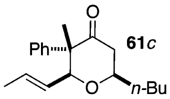
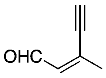
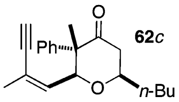
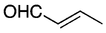
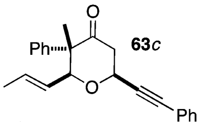
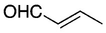
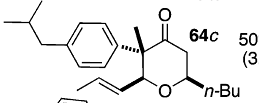
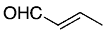
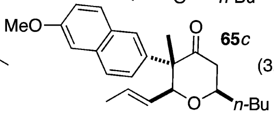
Alcohol **70** underwent cyclization with crotonaldehyde to afford THPO **72** as a single diastereomer in 50% yield. All four substituents on the six-membered ring occupied pseudo-equatorial positions in THPO **72** (Scheme 4). Cyclization of *cis*-alcohol **71** with crotonaldehyde resulted in a mixture of diastereomers, THPO **73*c*** and **73*t***. This cyclization was the first in which the 2,6-*trans* THPO was the major product and the 2,6-*cis* THPO was the minor product. An explanation for this reversal of selectivity is presented in the Discussion section.

■ DISCUSSION

The proposed mechanism for the silyl enol ether cyclization is outlined in Scheme 5. The reaction begins with formation of

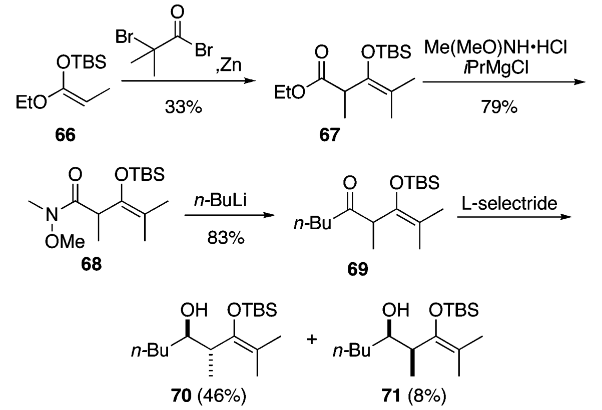
Table 7. Scope of the Tetrahydropyran-4-one Synthesis with Different Aldehydes and Alcohols, with Varying Substituents at the C-3 Position



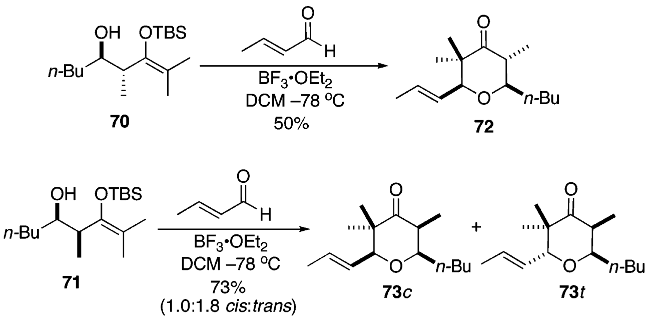
entry	alcohol	aldehyde	product	yield (%)
1	**25**		 **55*c***	40% (8.3:1:0 *cis*:*trans*)
2	**25**		 **56*c***	30% (7.0:1.0 *cis*:*trans*)
3	**26**		 **57*c***	49% (5.6:1.0 *cis*:*trans*)
4[a]	**27**		 **58*c***	72% (3.3:1.0 *cis*:*trans*)
5	**28**		 **59*c***	62% (6.0:1:0 *cis*:*trans*)
6	**29**		 **60*c***	69% (8.2:1:0 *cis*:*trans*)
7	**29**		 **61*c***	82% (2.8:1.0 *cis*:*trans*)
8	**29**	 (5:1 *Z*:*E*)	 **62*c***	48% (5:1 *Z*:*E*)
9	**30**		 **63*c***	94% (1.7:1:0 *cis*:*trans*)
10	**31**		 **64*c***	50% (76% BRSM) (3.0:1.0 *cis*:*trans*)
11	**32**		 **65*c***	94% (3.1:1.0 *cis*:*trans*)

[a] TMSOTf was used as the Lewis acid instead of BF$_3$·OEt$_2$. Abbreviation: PMP = *p*-methoxyphenyl.

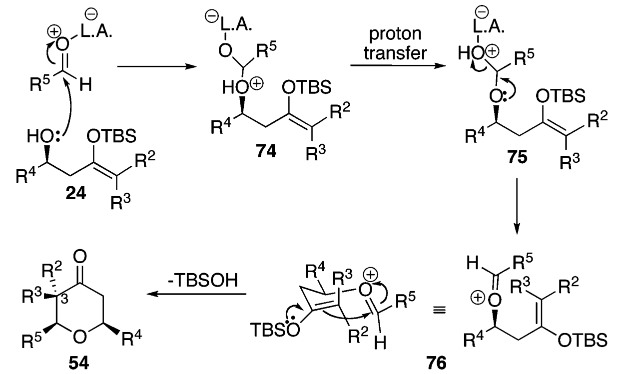
Scheme 3. Formation of the Hydroxy Silyl Enol Ether with R^1 = Methyl for Substitution at C-5 in the Resulting Tetrahydropyran-4-one



Scheme 4. Tetrahydropyran-4-one Synthesis with Substitution at C-5



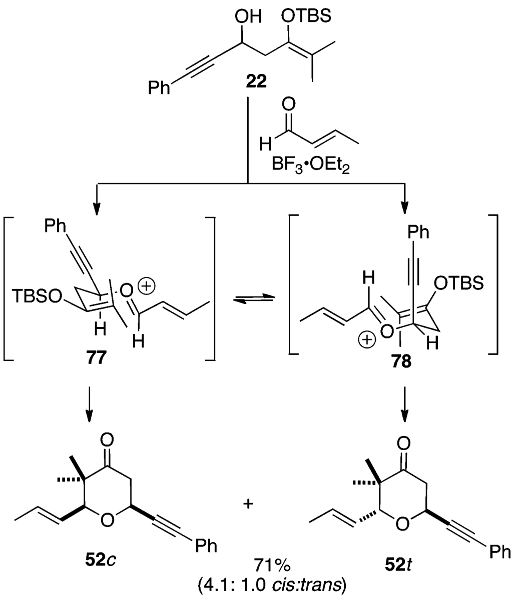
Scheme 5. Proposed Mechanism for the Silyl Enol Ether Prins Cyclization



the hemiacetal **74** from the alcohol and the aldehyde, followed by expulsion of the leaving group, to generate the key oxocarbenium ion intermediate **76**. These steps are presumably promoted by the Lewis acid. Irreversible[32] nucleophilic attack of the silyl enol ether onto the oxocarbenium ion forms the desired THPO **54**. A chairlike conformation with *E*-configuration at the oxocarbenium[33] is expected in the cyclization transition state. The configuration of the major product is consistent with this transition state geometry. Placement of the R^4 groups in the pseudo-equatorial position favors one of the two possible chairlike transitions states. The quaternary stereocenter at C-3 arises from the *Z*-configuration of the enol ether in the chairlike transition state. The sterically biased ketene addition (Table 3) results in the less bulky substituent at R^3 in enol ether **24**; the cyclization reactions place this substituent in the axial position at C-3 in the new tetrahydropyran-4-one ring. The stereochemical outcome of the silyl enol ether Prins cyclization is consistent with the expected chairlike transition state.

Silyl enol ether **22** (Table 6, entry 10) leads to a large amount of the 2,6-*trans* THPO product in the cyclization with crotonaldehyde. The diastereoselectivity of the major product in the cyclization results from the alkyne and crotonaldehyde alkene being placed in the lower energy pseudo-equatorial position in the chairlike reactive conformer 77 (Scheme 6). When the R^4 substituent is sterically small, in this case an alkyne, the energetic cost for it to occupy a pseudo-axial position in the reactive conformation 78 is modest, and the cyclization results in a significant amount of the 2,6-*trans* diastereomer **52*t***. For relative size comparison, an alkyne group has an *A* value of 0.41 kcal/mol and a methyl group has an *A* value of 1.7 kcal/mol in a cyclohexane ring.[34] The 2,6-*trans* diastereomer was obtained when the small alkyne substituent occupied a pseudo-axial position in the chairlike transition state.

Scheme 6. Small R^4 Groups Resulted in Diminished Diastereoselectivity during Cyclization



The 2,6-*cis*/*trans* selectivity was influenced by the substituents on the C-3 position. The data are summarized in Figure 3. When the substituents on C-3 are identical, THPO **46** was observed as a single diastereomer with a 2,6-*cis* configuration. When there was a methyl group and proton on C-3, a 7.0:1.0 *cis*:*trans* diastereomeric ratio was obtained. With aryl and methyl substitution on C-3, diastereoselectivity further diminished to about a 3:1 ratio of *cis*:*trans* diastereomers. Note that, in all of these examples, the larger group occupied the equatorial position at C-3 in the 2,6-*cis* product. Interestingly, the minor diastereomer in this cyclization reaction is not the same one reported for similar cyclizations, an oxonia-cope Prins reaction.[35] Dalgard and Rychnovsky reported[14] the C-3 epimer of the 2,6-*cis* product as the minor diastereomer in their systems and suggest that the minor product could arise from *E*/*Z* isomerization of the starting silyl enol ether[36] or a competing chair−boat cyclization.[1a] Our minor diastereomer had a different relative stereochemical relationship between C-2 and C-6 and retained relative stereochemistry between C-2 and C-3; we proposed that the minor diastereomer would arise through the diastereomeric chairlike transition state **80** (Figure 3). One would expect that, as the size of the R^2 group increases, the steric interactions between the R^2 substituent and the −OTBS and crotyl groups in TS **79** would increase. TS **80** places the R^2 substituent axial, relieving steric interactions between the crotyl group, and becomes more favorable as the size of the R^2 substituent relative to the R^3 substituent increases. Thus, increasing the difference in size between the large R^2 and small R^3 subsitutents would lead to more of the 2,6-*trans* diastereomer, which is the observed outcome in this series.

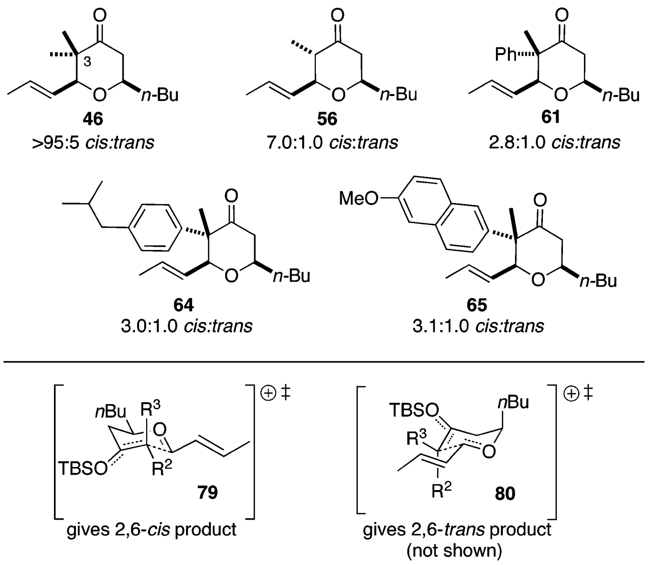


Figure 3. Diastereoselective trend caused by varying the substituents at C-3 is shown with the major 2,6-*cis* isomer drawn. The minor diastereomer has a 2,6-*trans* relationship. The relative stereochemistry between C-2 and C-3 remained the same for both diastereomers.

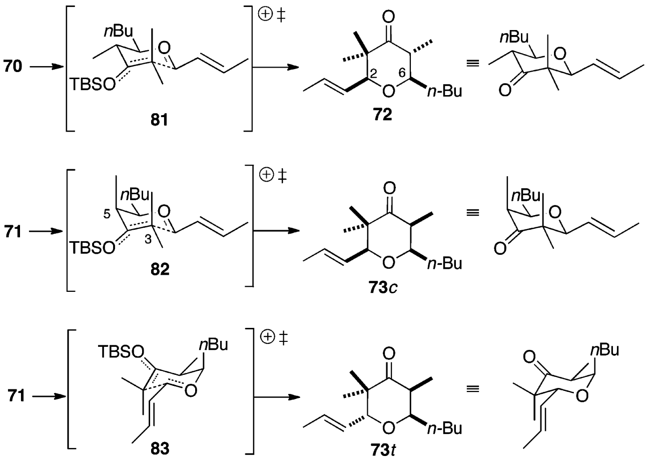


Figure 4. Proposed chairlike transition states to explain the diastereoselectivity of THPO **72**, **73*c***, and **73*t***. Full reaction conditions are shown in Scheme 4.

Introducing a new stereogenic center at C-5 influenced the selectivity of the cyclization (Scheme 4 and Figure 4). When alcohol **70** reacted with crotonaldehyde, it likely proceeded through chairlike transition state **81** where all possible substituents adopted pseudo-equatorial positions (Figure 4). In contrast, the cyclization geometry from the reaction of alcohol **71** and crotonaldehyde must have at least one substituent axial. Disfavored transition state **82** has the C-5 methyl group in an axial configuration with a 1,3-diaxial orientation to a C-3 methyl group. In the preferred transition state **83**, the *n*-butyl group at C-6 occupies an axial position. Both of these transition states have destabilizing interactions, and the result is modest selectivity in the cyclization for **73*t***. Apparently, placing the *n*-butyl group axial is preferable to the diaxial interaction between the methyl groups in the transition state, leading to 73*c*. The lowest energy chair conformer for each is product shown in Figure 4.[37]

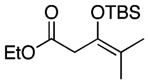
■ CONCLUSION

The silyl enol ether Prins reaction is highly diastereoselective with most substrates, and the major products are consistent with cyclizations through chairlike transition states. The reaction is tolerant of a variety of functional groups and can form a quaternary center on the THPO with good diastereoselectivity. This method allows for the synthesis of substituted THPOs with substitution demonstrated at every carbon atom in the ring. The flexibility of this silyl enol ether Prins method makes it a useful tool for synthesizing diverse THPO cores found in natural products or medicinal chemistry targets.

■ EXPERIMENTAL SECTION

General Information. All air- and moisture-sensitive reactions were carried out in flame- or oven-dried flasks equipped with a magnetic stir bar under an argon atmosphere. All commercially available reagents were used as received unless stated otherwise. Zinc dust was activated by sequential washing with 1 M HCl, water, and ethanol and was then dried under reduced pressure. $BF_3·OEt_2$ was distilled neat under an argon atmosphere. TMSOTf was distilled over CaH_2 under reduced pressure. Thin-layer chromatography (TLC) was performed on 250 μm layer silica gel plates, and developed plates were visualized by UV light, *p*-anisaldehyde, potassium permanganate, or vanillin.

^1H NMR spectra were recorded at 500 MHz, and ^{13}C NMR spectra were recorded at 126 MHz. Chemical shifts (δ) were referenced to either TMS or the residual solvent peak. The ^1H NMR spectra data are presented as follows: chemical shift, multiplicity (s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet, app. = apparent, br. = broad), coupling constant(s) in hertz (Hz), and integration. Infrared spectra were recorded on NaCl plates. High-resolution mass spectrometry was performed using ESI-TOF. Structures not numbered in the article were numbered consecutively starting with **101**. Compounds **101**−**104**, **10**, **16**−**20**, **35**−**39**, **41**, **44**, **47**, **48**, **50**, and **53** were formed using known procedures.[9]



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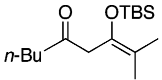
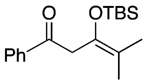
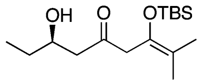


102

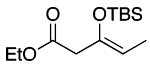


103



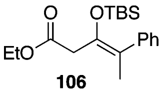
104

General Procedures to Form Ester 7. Triethylamine (1.7 equiv) was added dropwise to a solution of acid chloride (1.7 equiv) in dry THF (0.6 M relative to **6**) at 0 °C. The mixture turned into a white sludge due to the formation of Et_3NCl salt. Silyl ketene acetal **6** (1.0 equiv) was added to the mixture, and the solution was stirred overnight, slowly warming from 0 °C to room temperature. The reaction was quenched with saturated aqueous $NaHCO_3$, and the mixture was extracted with Et_2O (3×). The organic layer was dried over anhydrous $MgSO_4$, filtered, and concentrated in vacuo. Purification by column chromatography of the crude residue produced ethyl ester **7**.



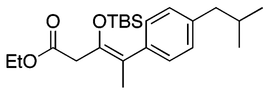
105

(*Z*)-Ethyl 3-(*tert*-Butyldimethylsilyloxy)pent-3-enoate (105). A sample of silyl ketene acetal **6** (2.50 g, 12.4 mmol) and propanoyl chloride (1.95 g, 21.1 mmol) was converted to **105** following the general procedures for ester **7** formation. Purification by column chromatography (5:1:94 Et_2O:Et_3N:hexanes) of the crude residue afforded **105** as a clear colorless oil (2.5 g, 77%): R_f = 0.49 (10% Et_2O/hexanes); ^1H NMR (500 MHz, $CDCl_3$) δ 4.66 (q, *J* = 6.6 Hz, 1H), 4.15 (q, *J* = 7.1 Hz, 2H), 3.02 (s 1H), 1.56 (d, *J* = 6.7 Hz, 3H), 1.26 (t, *J* = 7.1 Hz, 3H), 0.94 (s, 9H), 0.14 (s, 6H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 170.8, 144.4, 106.4, 60.9, 43.0, 25.9, 18.4, 14.3, 11.19, −3.9; IR (thin film) 2958, 2931, 2859, 1742, 1682 cm^{-1}; HRMS (ES/MeOH) *m*/*z* calcd for $C_{13}H_{26}O_3SiNa$ [M + Na]$^+$ 281.1549, found 281.1542



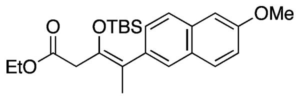
106

(*Z*)-Ethyl 3-(*tert*-Butyldimethylsilyloxy)-4-phenylpent-3-enoate (106). A sample of silyl ketene acetal **6** (300 mg, 1.48 mmol) and 2-phenylpropanoyl (424 mg, 2.52 mmol) was converted to **106** following the general procedures for ester **7** formation. Purification by column chromatography (5:1:94 Et_2O:Et_3N:hexanes) of the crude residue afforded **106** as a clear colorless oil (400 mg, 81%): R_f = 0.43 (5% Et_2O/hexanes); ^1H NMR (500 MHz, $CDCl_3$) δ 7.31−7.25 (m, 4H), 7.15 (t, *J* = 7.5 Hz, 1H), 4.20 (q, *J* = 7.1 Hz, 2H), 3.29 (s, 2H), 1.96 (s, 3H), 1.30 (t, *J* = 7.2 Hz, 3H), 0.73 (s, 9H), −0.25 (s, 6H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 170.5, 141.9, 139.8, 129.4, 127.9, 126.1, 118.1, 60.9, 39.8, 25.7, 19.6, 18.1, 14.4, −4.5; IR (thin film) 2956, 2930, 2896, 2858, 1738, 1660 cm^{-1}; HRMS (ES/MeOH) *m*/*z* calcd for $C_{19}H_{30}O_3SiNa$ [M + Na]$^+$ 357.1862, found 357.1863.



107

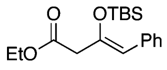
(*Z*)-Ethyl 3-(*tert*-Butyldimethylsilyloxy)-4-(4-isobutylphenyl)-pent-3-enoate (107). A sample of silyl ketene acetal **6** (267 mg, 1.32 mmol) and 2-(4-isobutylphenyl)propanoyl chloride (504 mg, 2.24 mmol) was converted to **107** following the general procedures for ester **7** formation. Purification by column chromatography (15:1:84 EtOAc:Et_3N:hexanes) of the crude residue afforded **107** as a clear colorless oil (362 mg, 70%): R_f = 0.67 (15% EtOAc/hexanes); ^1H NMR (500 MHz, $CDCl_3$) δ 7.20 (d, *J* = 8.0 Hz, 2H), 7.04 (d, *J* = 10.5 Hz, 2H), 4.20 (q, *J* = 7.2 Hz, 2H), 3.28 (s, 2H), 2.44 (d, *J* = 7.5 Hz, 2H), 1.95 (s, 3H), 1.84 (app. septet, *J* = 6.8 Hz, 1H), 1.30 (t, *J* = 7.2 Hz, 3H), 0.89 (d, *J* = 7.0 Hz, 6H), 0.73 (s, 9H), −0.25 (s, 6H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 170.9, 139.8, 139.7, 139.4, 129.3, 128.9, 118.3, 61.1, 45.6, 40.1, 30.7, 26.0, 22.7, 19.9, 18.4, 14.6, −4.2; IR (thin film) 2955, 2929, 2093, 2858, 1741, 1658 cm^{-1}; HRMS (ES/MeOH) *m*/*z* calcd for $C_{23}H_{38}O_3SiNa$ [M + Na]$^+$ 413.2488, found 413.2486.



108

(*Z*)-Ethyl 3-(*tert*-Butyldimethylsilyloxy)-4-(6-methoxynaphthalen-2-yl)pent-3-enoate (108). Triethylamine (0.31 mL, 2.22 mmol, 1.70 equiv) was added dropwise to a solution of 2-(6-methoxynaphthalen-2-yl)propanoyl chloride (552 mg, 2.22 mmol, 1.70 equiv) in dry THF (0.6 M relative to **6**) at 0 °C. The mixture turned into a white sludge due to the formation of $Et_3N·HCl$ salt. Silyl ketene acetal **6** (264 mg, 1.30 mmol, 1.00 equiv) was added to the mixture, and the solution was stirred overnight slowly, warming from 0 °C to room temperature. A second portion of triethylamine (0.31 mL, 2.22 mmol, 1.70 equiv) was added dropwise to the solution at rt. The reaction was monitored by TLC, and once starting material was consumed, the reaction was quenched with saturated aqueous $NaHCO_3$ (10 mL). The mixture was extracted with Et_2O (3 × 10 mL). The organic layers were combined, dried over anhydrous $MgSO_4$, and filtered, and the resulting solution was concentrated in vacuo. Purification by column chromatography (10:1:89 EtOAc:Et_3N:hexanes) of the crude residue afforded **108** as a clear colorless oil (471 mg. 87%): R_f = 0.7 (10% EtOAc/hexanes); ^1H NMR (500 MHz, $CDCl_3$) δ 7.70 (br. s, 1H), 7.65 (dd, *J* = 9.0, 7.0 Hz, 2H), 7.44

(dd, *J* = 8.5, 1.5 Hz, 1H), 7.11−7.09 (m, 2H), 4.23 (q, *J* = 7.2 Hz, 2H), 3.92 (s, 3H), 3.34 (s, 2H), 2.04 (s, 3H), 1.32 (t, *J* = 7.25 Hz, 3H), 0.71 (s, 9H), −0.30 (s, 6H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 170.8, 157.7, 140.3, 137.3, 133.4, 129.7, 129.1, 128.8, 127.9, 126.3, 118.8, 118.1, 105.9, 61.2, 55.6, 40.2, 26.0, 19.8, 18.3, 14.7, −4.2; IR (thin film) 2931, 2956, 2897, 2857, 1739, 1605 cm^{-1}; HRMS (ES/MeOH) *m*/*z* calcd for $C_{24}H_{34}O_4SiNa$ [M + Na]$^+$ 437.2124, found 437.2112.



109

(*Z*)-Ethyl 3-(*tert*-Butyldimethylsilyloxy)-4-phenylbut-3-enoate (109). A sample of silyl ketene acetal **6** (200 mg, 1.00 mmol) and phenylacetyl chloride (260 mg, 1.68 mmol) was converted to **109** following the general procedures for ester **7** formation. Purification by column chromatography (20:1:79 EtOAc:Et_3N:hexanes) of the crude residue afforded **109** as a clear colorless oil (98 mg, 31%): R_f = 0.65 (20% EtOAc/hexanes); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.48 (d, *J* = 7.5 Hz, 2H), 7.25 (app. t, *J* = 7.8 Hz, 2H), 7.13 (app. t, *J* = 7.5 Hz, 1H), 5.58 (s, 1H), 4.20 (q, *J* = 7.2 Hz, 2H), 3.2 (s, 2H), 1.29 (t, *J* = 7.0 Hz, 3H), 0.92 (s, 9H), 0.06 (s, 6H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 170.2, 145.5, 136.0, 128.7, 127.9, 126.0, 111.6, 61.0, 43.8, 25.8, 18.3, 14.3, −3.8; IR (thin film) 2931, 2858, 1740, 1654 cm^{-1}; HRMS (ES/MeOH) *m*/*z* calcd for $C_{18}H_{28}O_3SiNa$ [M + Na]$^+$ 343.1705, found 343.1712.

General Procedures To Form Weinreb Amide 8.[19] A solution of 2.0 M *i*-PrMgCl (2.4 equiv) in dry THF was added dropwise to a solution of ethyl ester **7** (1.0 equiv) and Me(MeO)NH·HCl (1.2 equiv) in dry THF (0.12 M relative to **7**) at −20 °C. The mixture was stirred at −20 °C for 2 h, and the reaction was then quenched with saturated aqueous NH_4Cl. The mixture was extracted with Et_2O (3×). The organic layers were combined, dried over anhydrous $MgSO_4$, and filtered, and the resulting solution was concentrated in vacuo. Purification by column chromatography of the crude residue afforded Weinreb amide **8**.

(*Z*)-3-(*tert*-Butyldimethylsilyloxy)-*N*-methoxy-*N*-methylpent-3-enamide (9). A sample of 258 mg of ester **105** (1.0 mmol) was converted to **9** following the general procedures for Weinreb amide **8** formation; the combined organic layers were dried over anhydrous Na_2SO_4 instead of $MgSO_4$. Purification by column chromatography (20:1:79 EtOAc:Et_3N:hexanes) of the crude residue afforded **9** as a clear colorless oil (230 mg, 84%): R_f = 0.47 (20% EtOAc/hexanes); ^{1}H NMR (500 MHz, $CDCl_3$) δ 4.52 (q, *J* = 6.8 Hz, 1H), 3.61 (s, 3H), 3.11 (app. s, 5H), 1.49 (d, *J* = 6.7 Hz, 3H), 0.88 (s, 9H), 0.08 (s, 6H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 171.2, 144.7, 105.0, 61.2, 40.3, 32.2, 25.7, 18.18, 10.9, −4.1; IR (thin film) 2957, 2931, 2896, 2858, 1682 cm^{-1}; HRMS (ES/MeOH) *m*/*z* calcd for $C_{13}H_{27}NO_3SiNa$ [M + Na]$^+$ 296.1658, found 296.1663.

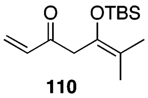
(*Z*)-3-(*tert*-Butyldimethylsilyloxy)-*N*-methoxy-*N*-methyl-4-phenylpent-3-enamide (11). A sample of 843 mg of ester **106** (2.50 mmol) was converted to **11** following the general procedures for Weinreb amide **8** formation. The amount of the 2.0 M *i*-PrMgCl solution added was increased from 2.4 equiv to 3.0 equiv. The amount of Me(MeO)NH·HCl added was increased from 1.2 equiv to 1.5 equiv. Purification by column chromatography (20:1:79 EtOAc:Et_3N:hexanes) of the crude residue afforded **11** as a clear colorless oil (733 mg, 83%): R_f = 0.42 (20% EtOAc/hexanes); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.33 (d, *J* = 7.3 Hz, 2H), 7.26 (t, *J* = 7.6 Hz, 2H), 7.14 (t, *J* = 7.3 Hz, 1H), 3.75 (s, 3H), 3.44 (s, 2H), 3.22 (s, 3H), 1.96 (s, 3H), 0.73 (s, 9H), −0.24 (s, 6H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 171.4, 142.1, 140.3, 129.4, 127.8, 126.0, 117.8, 61.4, 38.2, 32.6, 25.8, 19.4, 18.1, −4.4; IR (thin film) 2955, 2930, 2895, 2857, 1682 cm^{-1}; HRMS (ES/MeOH) *m*/*z* calcd for $C_{19}H_{31}NO_3SiNa$ [M + Na]$^+$ 372.1971, found 372.1963.

(*Z*)-3-(*tert*-Butyldimethylsilyloxy)-4-(4-isobutylphenyl)-*N*-methoxy-*N*-methylpent-3-enamide (12). A solution of 2.0 M *i*-PrMgCl (0.30 mL, 0.60 mmol, 2.0 equiv) in dry THF was added dropwise to a two-neck flask containing ethyl ester **107** (116 mg, 0.30 mmol, 1.0 equiv) and Me(MeO)NH·HCl (29 mg, 0.30 mmol, 1.0 equiv) in dry THF (1.25 mL) and dry toluene (1.25 mL) at rt. The mixture was stirred for 6 h at rt. Four portions of 2.0 M *i*-PrMgCl (each portion: 0.30 mL, 0.60 mmol, 2.0 equiv) in dry THF and Me(MeO)NH·HCl (each portion: 29 mg, 0.30 mmol, 1.0 equiv) were added to the solution at rt in 6 h intervals. The reaction was monitored by TLC, and once starting material was consumed, the reaction was quenched with saturated aqueous NH_4Cl (3 mL). The mixture was extracted with Et_2O (3 × 5 mL). The organic layers were combined, dried over anhydrous $MgSO_4$, and filtered, and the resulting solution was concentrated in vacuo. Purification by column chromatography (15:1:84 EtOAc:Et_3N:hexanes) of the crude residue afforded Weinreb amide **12** as a clear colorless oil (92 mg. 76%): R_f = 0.17 (15% EtOAc/hexanes); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.23 (d, *J* = 8.0 Hz, 2H), 7.04 (d, *J* = 8.0 Hz, 2H), 3.74 (s, 3H), 3.43 (s, 2H), 3.22 (s, 3H), 2.43 (d, *J* = 7.2 Hz, 2H), 1.94 (s, 3H), 1.83 (app. septet, *J* = 6.7 Hz, 1H), 0.89 (d, *J* = 6.6 Hz, 6H), 0.73 (s, 9H), −0.24 (s, 6H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 171.5, 140.0, 139.4 (2), 129.1, 128.6, 117.7, 61.4, 45.3, 38.3, 32.6, 30.4, 25.9, 22.4, 19.5, 18.1, −4.4; IR (thin film) 2954, 2930, 2857, 1677 cm^{-1}; HRMS (ES/MeOH) *m*/*z* calcd for $C_{23}H_{39}NO_3SiNa$ [M + Na]$^+$ 428.2597, found 428.2599.

(*Z*)-3-(*tert*-Butyldimethylsilyloxy)-*N*-methoxy-4-(6-methoxynaphthalen-2-yl)-*N*-methylpent-3-enamide (13). A solution of 2.0 M *i*-PrMgCl (0.48 mL, 0.96 mmol, 2.0 equiv) in dry THF was added dropwise to a two-neck flask containing ethyl ester **108** (200 mg, 0.48 mmol, 1.0 equiv) and Me(MeO)NH·HCl (47 mg, 0.48 mmol, 1.0 equiv) in dry THF (2 mL) and dry toluene (2 mL) at 0 °C. The mixture was stirred for 7 h, slowly warming to rt. A second portion of 2.0 M *i*-PrMgCl (0.48 mL, 0.96 mmol, 2.0 equiv) in dry THF and Me(MeO)NH·HCl (47 mg, 0.48 mmol, 1.0 equiv) was added to the solution and stirred overnight at rt. A third portion of 2.0 M *i*-PrMgCl (0.48 mL, 0.96 mmol, 2.0 equiv) in dry THF and Me(MeO)NH·HCl (47 mg, 0.48 mmol, 1.0 equiv) was added to the solution. The reaction was monitored by TLC, and once starting material was consumed, the reaction was quenched with saturated aqueous NH_4Cl (20 mL). The mixture was extracted with EtOAc (5 × 20 mL). The organic layers were combined, dried over anhydrous $MgSO_4$, and filtered, and the resulting solution was concentrated in vacuo. Purification by column chromatography (20:1:79 EtOAc:Et_3N:hexanes) of the crude residue afforded Weinreb amide **13** as a clear colorless oil (183 mg. 90%): R_f = 0.55 (20% EtOAc/hexanes); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.74 (br. s, 1H), 7.65 (app. dd, *J* = 8.8, 6.1 Hz, 2H), 7.5 (app. d, *J* = 8.5 Hz, 1H), 7.12−7.07 (m, 2H), 3.91 (s, 3H), 3.77 (s, 3H), 3.49 (s, 2H), 3.24 (s, 3H), 2.04 (s, 3H), 0.72 (s, 9H), 0.29 (s, 6H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 171.1, 157.3, 140.5, 137.2, 133.0, 129.4, 128.8, 128.6, 127.7, 126.0, 118.5, 117.6, 105.6, 77.4, 61.4, 55.3, 38.2, 25.8, 19.4, 18.1, −4.3; IR (thin film) 2954, 2932, 2856, 2896, 1674, 1604 cm^{-1}; HRMS (ES/MeOH) *m*/*z* calcd for $C_{24}H_{35}NO_4SiNa$ [M + Na]$^+$ 452.2233, found 452.2219.

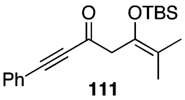
General Procedures to Form Ketone 14/23 with an Organolithium Reagent. To a flask containing Weinreb amide **8**/**10** (1.0 equiv) and dry THF (0.3 M) was added an organolithium reagent (1.5 equiv) dropwise at −78 °C. The mixture was stirred for 5 h at −78 °C, and the reaction was quenched with saturated aqueous NH_4Cl. The solution was extracted with DCM (4×). The organic layers were combined, dried with anhydrous $MgSO_4$, filtered, and concentrated in vacuo. Purification by column chromatography of the crude residue afforded ketone **14**/**23**.

General Procedures to Form Ketone 14/23 with a Grignard Reagent. A Grignard reagent (1.5 equiv) was added dropwise to a solution of Weinreb amide **8**/**10** (1.0 equiv) in dry THF (0.3 M) at 0 °C. The mixture was stirred overnight, slowly warming to room temperature. The reaction was quenched with saturated aqueous NH_4Cl. The mixture was extracted with EtOAc (4×). The organic layers were combined and dried over anhydrous Na_2SO_4, filtered, and concentrated in vacuo. Purification by column chromatography of the crude residue afforded ketone **14**/**23**.



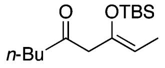
110

5-(*tert*-Butyldimethylsilyloxy)-6-methylhepta-1,5-dien-3-one (110). Vinylmagnesium bromide (0.87 M in THF, 1.7 mL) and Weinreb amide **10** (100 mg, 0.348 mmol) were converted to ketone **110** following the general procedures for ketone **14** formation with a Grignard reagent. The solution was stirred for 3 h, slowly warming to room temperature. The mixture was extracted with DCM (3 × 5 mL) instead of EtOAc. Purification by column chromatography (100% hexanes on florisil instead of Si_2O) of the crude residue afforded ketone **110** as a yellow oil (60 mg, 67%): R_f = 0.43 (100% hexanes); ^{1}H NMR (500 MHz, $CDCl_3$) δ 6.48 (dd, J = 17.5, 10.5 Hz, 1H), 6.27 (dd, J = 17.5, 1.4 Hz, 1H), 5.73 (dd, J = 10.6, 1.4 Hz, 1H), 3.34, (s, 2H), 1.65 (s, 3H), 1.60 (s, 3H), 0.91 (s, 9H), 0.10 (s, 6H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 197.1, 137.6, 135.0, 128.3, 114.2, 45.8, 25.9, 19.2, 18.3, 18.2, −3.8; IR (thin film) 2957, 2930, 2858, 1698, 1678, 1617 cm^{-1}; HRMS (ES/MeOH) m/z calcd for $C_{14}H_{26}O_2SiNa$ $[M + Na]^+$ 277.1600, found 277.1607.



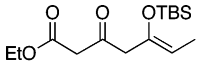
111

5-(*tert*-Butyldimethylsilyloxy)-6-methyl-1-phenylhept-5-en-1-yn-3-one (111). *n*-BuLi (2.27 M in hexanes, 0.22 mL) was added to a solution of phenyl acetylene (57 μL, 0.52 mmol) in dry THF (1.2 mL) at −78 °C. The mixture was stirred for 1 h; then Weinreb amide **10** (100 mg, 0.35 mmol) was added. The solution was stirred for 4 h, slowly warming to rt. The reaction was quenched with saturated aqueous NH_4Cl (2 mL), and the mixture was extracted with EtOAc (3 × 5 mL). The organic layers were combined, dried with anhydrous $MgSO_4$, filtered, and concentrated in vacuo. Purification by column chromatography (5% EtOAc/hexanes) of the crude residue afforded ketone **111** as a yellow oil (45 mg, 39%): R_f = 0.62 (10% EtOAc/hexanes); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.56−7.54 (m, 2H), 7.45−7.43 (m, 1H), 7.40−7.36 (m, 2H), 3.46 (s, 2H), 1.72 (s, 3H), 1.71 (s, 3H), 0.94 (s, 9H), 0.14 (s, 6H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 184.8, 137.1, 133.3, 130.8, 128.7, 120.3, 115.0, 91.2, 88.0, 49.5, 30.0, 19.6, 18.4, 18.3, −3.7; IR (thin film) 2957, 2929, 2858, 1667 cm^{-1}; HRMS (ES/MeOH) m/z calcd for $C_{20}H_{28}O_2SiNa$ $[M + Na]^+$ 351.1756, found 351.1754.



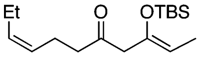
112

(*Z*)-3-(*tert*-Butyldimethylsilyloxy)non-2-en-5-one (112). Weinreb amide **9** (200 mg, 0.82 mmol) and *n*-BuLi (2.27 M in hexanes, 0.38 mL) were converted to ketone **112** following the general procedures for ketone **23** formation with an organolithium reagent. Purification by column chromatography (10% EtOAc/hexanes) of the crude residue afforded ketone **112** as a clear colorless oil (130 mg, 66%): R_f = 0.66 (10% EtOAc/hexanes); ^{1}H NMR (500 MHz, $CDCl_3$) δ 4.64 (q, J = 6.7 Hz, 1H), 3.03 (s, 2H), 2.50 (t, J = 7.4 Hz, 2H), 1.56 (d, J = 6.7 Hz, 3H), 1.56−1.51 (m, 2H), 1.26 (app. sextet, J = 7.4 Hz, 2H), 0.93 (s, 9H), 0.89 (t, J = 7.4 Hz, 3H), 0.12 (s, 6H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 208.8, 145.3, 107.0, 51.7, 40.9, 25.89, 25.86, 22.4, 18.3, 14.0, 11.2, −3.9; IR (thin film) 2958, 2932, 2860, 1716, 1674 cm^{-1}; HRMS (ES/MeOH) m/z calcd for $C_{15}H_{30}O_2SiNa$ $[M + Na]^+$ 293.1913, found 293.1909.



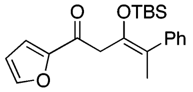
113

(*Z*)-Ethyl 5-(*tert*-Butyldimethylsilyloxy)-3-oxohept-5-enoate (113). Ethyl acetate (0.09 mL, 0.88 mmol) was added dropwise to a freshly made solution of LDA (0.5 M in THF, 1.8 mL) over 5 min at −78 °C. The mixture was stirred for 1 h. DMPU (0.13 mL, 1.10 mmol) and Weinreb amide **9** (200 mg, 0.82 mmol) were added to the solution, and the mixture was stirred for 28 h at −78 °C. The reaction was quenched with saturated aqueous NH_4Cl (2 mL), and the mixture was extracted with EtOAc (3 × 10 mL). The organic layers were combined, dried with anhydrous $MgSO_4$, filtered, and concentrated in vacuo. Purification by column chromatography (10% EtOAc:hexanes) of the crude residue afforded ketone **113** as a clear colorless oil (129 mg, 59%): R_f = 0.44 (10% EtOAc:hexanes); ^{1}H NMR (500 MHz, $CDCl_3$) δ 4.71 (q, J = 6.7 Hz, 1H), 4.18 (q, J = 7.1 Hz, 2H), 3.54 (s, 2H), 3.18 (s, 2H), 1.57 (d, J = 6.8 Hz, 3H), 1.27 (t, J = 7.2 Hz, 3H), 0.93 (s, 9H), 0.13 (s, 6H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 201.0, 167.6, 144.4, 108.3, 61.4, 51.8, 47.5, 25.8, 18.3, 14.2, 11.3, −3.9; IR (thin film) 2932, 2957, 2859, 2897, 1748, 1721, 1676 cm^{-1}; HRMS (ES/MeOH) m/z calcd for $C_{15}H_{28}O_4SiNa$ $[M + Na]^+$ 323.1655, found 323.1652.



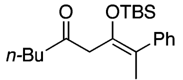
114

(2*Z*,8*Z*)-3-(*tert*-Butyldimethylsilyloxy)undeca-2,8-dien-5-one (114). Freshly formed (*Z*)-hex-3-enylmagnesium bromide (1.0 M in THF, 2.0 mL) was added dropwise to a solution of amide **9** (365 mg, 1.30 mmol) in dry THF (4.3 mL) at 0 °C. The mixture was stirred for 6 h at 0 °C, and the reaction was quenched with saturated aqueous NH_4Cl (10 mL). The mixture was extracted with EtOAc (3 × 10 mL). The organic layers were combined, dried over anhydrous $MgSO_4$, and filtered, and the resulting solution was concentrated in vacuo. Purification by column chromatography (10:1:89 EtOAc:Et_3N:hexanes) of the crude residue afforded ketone **114** as a colorless oil (289 mg, 75%): R_f = 0.68 (10% EtOAc/hexanes); ^{1}H NMR (500 MHz, $CDCl_3$) δ 5.40−5.36 (m, 1H), 5.30−5.25 (m, 1H), 4.65 (q, J = 6.7 Hz, 1H), 3.04 (s, 2H), 2.55 (t, J = 7.5 Hz, 2H), 2.28 (q, J = 7.4 Hz, 2H), 2.04 (quintet, J = 7.3 Hz, 2H), 1.57 (d, J = 6.7 Hz, 3H), 0.95 (t, J = 1.0 Hz, 3H), 0.93 (s, 9H), 0.12 (s, 6H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 208.2, 145.2, 132.8, 127.5, 107.2, 51.8, 41.2, 25.9, 21.6, 20.6, 18.3, 14.4, 11.2, −3.8; IR (thin film) 3007, 2988, 2959, 2859, 2896, 1718, 1675 cm^{-1}; HRMS (ES/MeOH) m/z calcd for $C_{17}H_{32}O_2SiNa$ $[M + Na]^+$ 319.2069, found 319.2063.



115

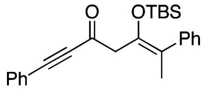
(*Z*)-3-(*tert*-Butyldimethylsilyloxy)-1-(furan-2-yl)-4-phenylpent-3-en-1-one (115). *n*-BuLi (2.27 M in hexanes, 0.18 mL) was added to a solution of furan (30 μL, 0.40 mmol) and TMEDA (60 μL, 0.40 mmol) in dry THF (0.95 mL) at 0 °C. The mixture was stirred for 1 h, followed by addition of Weinreb amide **11** (100 mg, 0.29 mmol). The solution was stirred for 1 h, and then the reaction was quenched with saturated aqueous $NaHCO_3$ (3 mL). The mixture was extracted with EtOAc (3 × 10 mL). The organic layers were combined, dried with anhydrous $MgSO_4$, filtered, and concentrated in vacuo. Purification by column chromatography (15% EtOAc/hexanes) of the crude residue afforded ketone **115** as a yellow oil (89 mg, 87%): R_f = 0.52 (15% EtOAc/hexanes); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.61 (dd, J = 1.65, 0.69 Hz, 1H), 7.33 (dd, J = 3.5, 0.7 Hz, 1H), 7.31−7.24 (m, 4H), 7.15 (tt, J = 7.1, 2.2 Hz, 1H), 6.56 (dd, J = 3.6, 1.7 Hz, 1H), 3.78 (s, 2H), 1.99 (s, 3H), 0.70 (s, 9H), −0.26 (s, 6H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 185.3, 152.6, 146.4, 141.8, 140.0, 129.4, 127.9, 126.2, 118.7, 117.4, 112.4, 44.7, 25.8, 19.6, 18.1, −4.4; IR (thin film) 3022, 2954, 2928, 2894, 2856, 1682 cm^{-1}; HRMS (ES/MeOH) m/z calcd for $C_{21}H_{28}O_3SiNa$ $[M + Na]^+$ 379.1705, found 379.1696.



116

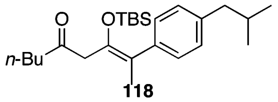
(*Z*)-3-(*tert*-Butyldimethylsilyloxy)-2-phenylnon-2-en-5-one (116). Weinreb amide **11** (438 mg, 1.25 mmol) and *n*-BuLi (2.27 M in hexanes, 0.83 mL) were converted to ketone **116** following the general procedures for ketone **23** formation with an organolithium reagent. Purification by column chromatography (10% EtOAc/hexanes) of the crude residue afforded ketone **116** as a light yellow oil (337 mg, 78%): R_f = 0.68 (10% EtOAc/hexanes); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.30−7.25 (m, 4H), 7.19−7.15 (m, 1H), 3.29 (s, 2H), 2.61 (t, J = 7.4 Hz, 2H), 1.96 (s, 3H), 1.64−1.58 (m, 2H), 1.39−1.32 (m, 2H), 0.93 (t, J = 7.4 Hz, 3H), 0.72 (s, 9H), −0.27 (s, 6H); ^{13}C NMR (126 MHz,

$CDCl_3$) δ 208.0, 141.8, 140.6, 129.2, 128.0, 126.2, 118.5, 48.8, 40.9, 25.9, 25.7, 22.5, 19.6, 18.0, 14.0, −4.4; IR (thin film) 2956, 2930, 2858, 1716, 1652 cm^{-1}; HRMS (ES/MeOH) *m*/*z* calcd for $C_{21}H_{34}O_2SiNa$ $[M + Na]^+$ 369.2226, found 369.2233.



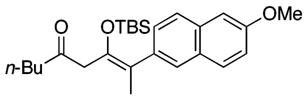
117

(*Z*)-5-(*tert*-Butyldimethylsilyloxy)-1,6-diphenylhept-5-en-1-yn-3-one (117). *n*-BuLi (2.27 M in hexanes, 0.28 mL) was added to a solution of phenyl acetylene (70 μL, 0.63 mmol) in dry THF (1.9 mL) at −78 °C. The mixture was stirred for 1.5 h; then Weinreb amide **11** (200 mg, 0.57 mmol) was added. The solution was stirred for 2.5 h at −78 °C, warmed to 0 °C, and stirred for an additional 2 h. The reaction was quenched with saturated aqueous $NaHCO_3$ (3 mL), and the mixture was extracted with EtOAc (3 × 10 mL). The organic layers were combined, dried with anhydrous $MgSO_4$, filtered, and concentrated in vacuo. Purification by column chromatography (15% EtOAc/hexanes) of the crude residue afforded ketone **117** as a yellow oil (130 mg, 58%): R_f = 0.76 (15% EtOAc/hexanes); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.58 (dd, *J* = 8.2, 1.1 Hz, 2H), 7.47−7.44 (m, 1H), 7.39−7.34 (m, 4H), 7.28 (app. t, *J* = 8.3 Hz, 2H), 7.19−7.16 (m, 1H), 3.56 (s, 2H), 2.07 (s, 3H), 0.73 (s, 9H), −0.23 (s, 6H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 184.4, 141.8, 139.5, 133.3, 130.9, 129.3, 128.8, 128.0, 126.3, 120.2, 120.0, 91.4, 87.9, 50.3, 25.7, 19.9, 18.1, −4.4; IR (thin film) 2954, 2928, 2856, 1673 cm^{-1}; HRMS (ES/MeOH) *m*/*z* calcd for $C_{25}H_{30}O_2SiNa$ $[M + Na]^+$ 413.1913, found 413.1923.



118

(*Z*)-3-(*tert*-Butyldimethylsilyloxy)-2-(4-isobutylphenyl)non-2-en-5-one (118). Weinreb amide **12** (176 mg, 0.43 mmol) and *n*-BuLi (2.49 M in hexanes, 0.36 mL) were converted to ketone **118** following the general procedures for ketone **23** formation with an organolithium reagent. The mixture was stirred overnight, slowly warming from −78 to 0 °C. The solution was extracted with EtOAc instead of DCM. Purification by column chromatography (20% EtOAc/hexanes) of the crude residue afforded ketone **118** as a clear colorless oil (126 mg, 73%): R_f = 0.86 (20% EtOAc/hexanes); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.20 (d, *J* = 8.0 Hz, 2H), 7.06 (d, *J* = 8.0 Hz, 2H), 3.28 (s, 2H), 2.61 (t, *J* = 7.4 Hz, 2H), 2.44 (d, *J* = 7.1 Hz, 2H), 1.96 (s, 3H), 1.84 (app. septet, *J* = 6.9 Hz, 1H), 1.61 (app. quintet, *J* = 7.4 Hz, 2H), 1.35 (app. sextet, *J* = 7.4 Hz, 2H), 0.93 (t, *J* = 7.4 Hz, 3H), 0.89 (d, *J* = 6.6 Hz, 6 H), 0.72 (s, 9H), 0.27 (s, 6H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 208.2, 140.3, 139.6, 139.0, 128.9, 128.7, 118.4, 48.8, 45.3, 40.8, 30.4, 25.9, 25.8, 22.5, 22.4, 19.7, 18.0, 14.0, −4.4; IR (thin film) 2957, 2930, 2859, 1717, 1653 cm^{-1}; HRMS (ES/MeOH) *m*/*z* calcd for $C_{25}H_{42}O_2SiNa$ $[M + Na]^+$ 425.2852, found 425.2842.



119

(*Z*)-3-(*tert*-Butyldimethylsilyloxy)-2-(6-methoxynaphthalen-2-yl)non-2-en-5-one (119). Weinreb amide **13** (50 mg, 0.12 mmol) and *n*-BuLi (2.37 M in hexanes, 0.16 mL) were converted to ketone **119** following the general procedures for ketone **23** formation with an organolithium reagent. *n*-BuLi was added in two equal portions; the second portion was added after 5 h. The mixture was stirred for an additional 1 h. The solution was extracted with EtOAc instead of DCM. Purification by column chromatography (10% EtOAc/hexanes) of the crude residue afforded ketone **119** as a clear colorless oil (30 mg, 60%): R_f = 0.63 (10% EtOAc/hexanes); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.69 (d, *J* = 7.4 Hz, 1H), 7.66 (dd, *J* = 9.0, 2.7 Hz, 2H), 7.44 (dd, *J* = 8.5, 1.7 Hz, 1H), 7.13−7.09 (m, 2H), 3.92 (s, 3H), 3.35 (s, 2H), 2.65 (t, *J* = 7.4 Hz, 2H), 2.04 (s, 3H), 1.65 (app. quintet, *J* = 7.5 Hz, 2H), 1.39 (app. sextet, *J* = 7.4 Hz, 2H), 0.96 (t, *J* = 3H), 0.70 (s, 9H), −0.32 (s, 6H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 207.9, 157.5, 140.8, 136.9, 133.2, 129.4, 128.9, 128.4, 127.6, 126.2, 118.7, 118.3, 105.7, 55.4, 49.0, 41.0, 26.0, 25.8, 22.6, 19.7, 18.0, 14.0, −4.3; IR (thin film) 2956, 2931, 2858, 1717, 1633, 1605 cm^{-1}; HRMS (ES/MeOH) *m*/*z* calcd for $C_{26}H_{38}O_3SiNa$ $[M + Na]^+$ 449.2488, found 449.2477.

General Procedures to Form Alcohol 15/24. Sodium borohydride (1.1 equiv) was added to a vial containing ketone **14**/**23** (1.0 equiv) in MeOH (0.2 M relative to the ketone) at −20 °C. The reaction was monitored by TLC, and when starting material was consumed, the reaction was quenched with saturated aqueous NH_4Cl. The solution was extracted with EtOAc (3×), and the organic layers were combined, dried with anhydrous $MgSO_4$, filtered, and concentrated in vacuo. Purification by column chromatography of the crude residue afforded alcohol **15**/**24**.

(*S*)-5-(*tert*-Butyldimethylsilyloxy)-6-methylhepta-1,5-dien-3-ol (21). Enantioselective Reduction. A solution of $BH_3 \cdot SMe_2$ (1.0 M in DCM, 0.23 mL), (*R*)-(+)-2-methyl-CBS-oxazaborolidine (1.0 M in toluene, 0.04 mL) and 3.6 mL of dry toluene was stirred for 10 min at rt, cooled to −40 °C, and stirred for an additional 10 min. A solution of enone **110** (91 mg, 0.36 mmol) in 0.8 mL dry toluene was added dropwise over 5 min. The mixture was stirred overnight, warming to 0 °C. The solution was cooled back down to −40 °C, and an additional portion of $BH_3 \cdot SMe_2$ (1.0 M in DCM, 0.23 mL) was added. The mixture was stirred for 4.5 h, slowly warming to −20 °C. The reaction was quenched with H_2O (1 mL), and the solution was extracted with EtOAc (3 × 2 mL). The combined organic layers were washed with saturated aqueous NaCl (2 mL), dried with anhydrous $MgSO_4$, filtered, and concentrated in vacuo. Purification of the crude residue by column chromatography (10% EtOAc:hexanes) afforded enantioenriched alcohol **21** (9.0:1.0 *e.r.*) as a clear colorless oil (50 mg, 60%). Racemic reduction: $CeCl_3 \cdot 7H_2O$ (160 mg, 0.43 mmol) was added to a vial containing enone **110** (100 mg, 0.39 mmol) and MeOH (1.95 mL) at −78 °C. The mixture was stirred for 10 min. Then $NaBH_4$ (16 mg, 0.43 mmol) was added, and the solution was stirred for an additional 20 min. The reaction was quenched with saturated aqueous NH_4Cl (10 mL) and diluted with 10 mL of saturated aqueous NaCl. The solution was extracted with EtOAc (3 × 15 mL), and the organic layers were combined, dried with anhydrous Na_2SO_4, filtered, and concentrated in vacuo. Purification by column chromatography (10% EtOAc:hexanes) of the crude residue afforded racemic alcohol **21** as a clear colorless oil (94 mg, 94%): R_f = 0.46 (10% EtOAc/hexanes); $[\alpha]_D^{24}$ = 7.5 (*c* 1.97, acetone); ^{1}H NMR (500 MHz, $CDCl_3$) δ 5.89 (ddd, *J* = 17.0, 10.7, 6.0 Hz, 1H), 5.26 (d, *J* = 17.2 Hz, 1H), 5.10 (d, *J* = 10.5 Hz, 1H), 4.35−4.31 (m, 1H), 2.41 (dd, *J* = 14.1, 8.8 Hz, 1H), 2.27 (dd, *J* = 14.1, 4.1 Hz, 1H), 1.64 (app. s, 6H), 0.95 (s, 9H), 0.12 (s, 3H), 0.11 (s, 3H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 140.8, 140.5, 114.4, 113.6, 71.3, 40.1, 26.0, 19.3, 18.4, 18.3, −3.67, −3.74; IR (thin film) 3417, 2958, 2930, 2859, 1681 cm^{-1}; HRMS (ES/MeOH) *m*/*z* calcd for $C_{14}H_{28}O_2SiNa$ $[M + Na]^+$ 279.1756, found 279.1762.

5-(*tert*-Butyldimethylsilyloxy)-6-methyl-1-phenylhept-5-en-1-yn-3-ol (22). Ketone **111** (207 mg, 0.63 mmol) was converted to alcohol **22** following the general procedures for alcohol **15** formation. The mixture was stirred for 1.5 h at −20 °C and extracted with DCM instead of EtOAc. Purification by column chromatography (20% EtOAc/hexanes) of the crude residue afforded alcohol **22** as a clear light yellow oil (182 mg, 87%): R_f = 0.55 (20% EtOAc/hexanes); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.44−7.42 (m, 2H), 7.30−7.29 (m, 3H), 4.82 (dd, *J* = 7.7, 5.2 Hz, 1H), 2.73 (dd, *J* = 14.1, 7.7 Hz, 1H), 2.62 (dd, *J* = 14.0, 5.1 Hz, 1H), 2.55 (br. s, 1H), 1.72 (s, 3H), 1.67 (s, 3H), 0.97 (s, 9H), 0.15 (s, 6H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 140.0, 131.8, 128.34, 128.30, 122.9, 114.5, 89.9, 84.6, 61.6, 40.5, 26.0, 19.4, 18.4, 18.3, −3.7, −3.8; IR (thin film) 3390, 2956, 2929, 2858, 1682 cm^{-1}; HRMS (ES/MeOH) *m*/*z* calcd for $C_{20}H_{30}O_2SiNa$ $[M + Na]^+$ 353.1913, found 353.1920.

(*Z*)-3-(*tert*-Butyldimethylsilyloxy)non-2-en-5-ol (25). Ketone **112** (120 mg, 0.44 mmol) was converted to alcohol **25** following the general procedures for alcohol **24** formation. The mixture was stirred for 1 h at −20 °C. The reaction was quenched with H_2O instead of saturated aqueous NH_4Cl and dried with Na_2SO_4 instead of $MgSO_4$. Purification by column chromatography (10% EtOAc/hexanes) of the crude residue afforded alcohol **25** as a clear colorless oil (109 mg, 91%): R_f = 0.44 (10% EtOAc/hexanes); ^{1}H NMR (500 MHz, $CDCl_3$) δ 4.61 (q, *J* = 6.7 Hz, 1H), 3.80−3.73 (m, 1H), 2.19−2.18 (m, 1H), 2.03 (d, *J* = 2.5 Hz, 1H), 2.00 (dd, *J* = 13.8, 8.8 Hz, 1H), 1.54 (dd, *J* = 6.7, 0.5 Hz, 3H), 1.43−1.32 (m, 6H), 0.96 (s, 9H), 0.90 (t, *J* = 7.2 Hz, 3H), 0.15 (s, 3H), 0.13 (s, 3H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 148.5, 105.6, 69.2, 45.0, 36.6, 28.0, 25.9, 22.9, 18.4, 14.2, 11.1, −3.8; IR (thin film) 3340, 2957, 2931, 2860, 1678 cm^{-1}; HRMS (ES/MeOH) *m/z* calcd for $C_{15}H_{32}O_2SiNa$ [M + Na]$^+$ 295.2069, found 295.2075.

(*Z*)-Ethyl 5-(*tert*-Butyldimethylsilyloxy)-3-hydroxyhept-5-enoate (26). Ketone **113** (50 mg, 0.17 mmol) was converted to alcohol **26** following the general procedures for alcohol **24** formation. EtOH was used as the solvent instead of MeOH, in case transesterification occurred. The mixture was stirred for 2 h at −40 °C. Purification by column chromatography (10% EtOAc/hexanes) of the crude residue afforded alcohol **26** as a clear yellow oil (47 mg, 96%): R_f = 0.32 (10% EtOAc/hexanes); ^{1}H NMR (500 MHz, $CDCl_3$) δ 4.60 (q, *J* = 6.9 Hz, 1H), 4.24−4.18 (m, 1H), 4.16 (q, *J* = 7.2 Hz, 2H), 2.88 (d, *J* = 2.9 Hz, 1H), 2.53 (dd, *J* = 16.2, 3.9 Hz, 1H), 2.42 (dd, *J* = 16.2, 8.4 Hz, 1H), 2.25 (dd, *J* = 14.0, 7.2 Hz, 1H), 2.16 (dd, *J* = 14.0, 6.0 Hz, 1H), 1.52 (d, *J* = 6.6 Hz, 3H), 1.26 (t, *J* = 7.2 Hz, 3H), 0.95 (s, 9H), 0.14 (s, 3H), 0.13 (s, 3H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 172.7, 147.5, 105.9, 66.1, 60.7, 44.0, 40.9, 25.9, 18.4, 14.3, 11.1, −3.8, −3.9; IR (thin film) 3461, 2956, 2931, 2859, 1736, 1677 cm^{-1}; HRMS (ES/MeOH) *m/z* calcd for $C_{15}H_{30}O_4SiNa$ [M + Na]$^+$ 325.1811, found 325.1803.

(2*Z*,8*Z*)-3-(*tert*-Butyldimethylsilyloxy)undeca-2,8-dien-5-ol (27). Ketone **114** (50 mg, 0.17 mmol) was converted to alcohol **27** following the general procedures for alcohol **24** formation. The mixture was stirred for 1 h at −20 °C. Purification by column chromatography (10:1:89 EtOAc:Et_3N,hexanes) of the crude residue afforded alcohol **28** (43 mg, 85%): R_f = 0.48 (10% EtOAc/hexanes); ^{1}H NMR (500 MHz, $CDCl_3$) δ 5.41−5.31 (m, 2H), 4.61 (q, *J* = 6.5 Hz, 1H), 3.86−3.76 (m, 1H), 2.20−2.01 (m, 3H), 2.09−2.01 (m, 4H), 1.54 (d, *J* = 6.6 Hz, 3H), 1.53−1.43 (m, 2H), 0.97−0.92 (m, 3H), 0.95 (s, 9H), 0.14 (s, 3H), 0.13 (s, 3H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 148.4, 132.4, 128.7, 105.6, 68.8, 45.0, 36.9, 26.0, 23.6, 20.7, 18.4, 14.5, 11.1, −3.8; IR (thin film) 3375, 3006, 2961, 2932, 2859, 1676 cm^{-1}; HRMS (ES/MeOH) *m/z* calcd for $C_{17}H_{34}O_2SiNa$ [M + Na]$^+$ 321.2226, found 321.2223.

(*Z*)-3-(*tert*-Butyldimethylsilyloxy)-1-(furan-2-yl)-4-phenylpent-3-en-1-ol (28). Ketone **115** (58 mg, 0.16 mmol) was converted to alcohol **28** following the general procedures for alcohol **24** formation. The mixture was stirred for 3 h at −20 °C. Purification by column chromatography (15% EtOAc/hexanes) of the crude residue afforded alcohol **28** as a clear colorless oil (58 mg, quant.): R_f = 0.40 (15% EtOAc/hexanes); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.46−7.45 (m, 1H), 7.34−7.28 (m, 4H), 7.26−7.20 (m, 1H), 6.42−6.38 (m, 2H), 5.15 (dd, *J* = 7.4, 5.7 Hz, 1H), 2.92 (dd, *J* = 13.8, 8.0 Hz, 1H), 2.82 (dd, *J* = 13.9, 5.3 Hz, 1H), 2.70 (br. s, 1H), 1.97 (s, 3H), 0.82 (s, 9H), −0.17 (s, 3H), −0.19 (s, 3H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 156.0, 142.5, 142.1, 142.0, 129.4, 127.9, 126.1, 118.9, 110.4, 106.2, 66.9, 39.4, 25.8, 19.4, 18.1, −4.4, −4.5; IR (thin film) 3396, 2954, 2928, 2857, 1659, 1600 cm^{-1}; HRMS (ES/MeOH) *m/z* calcd for $C_{21}H_{30}O_3SiNa$ [M + Na]$^+$ 381.1862, found 381.1870.

(*Z*)-3-(*tert*-Butyldimethylsilyloxy)-2-phenylnon-2-en-5-ol (29). Ketone **116** (325 mg, 0.94 mmol) was converted to alcohol **29** following the general procedures for alcohol **24** formation. The mixture was stirred for 1 h at −20 °C. Purification by column chromatography (10% EtOAc/hexanes) of the crude residue afforded alcohol **29** as a clear yellow oil (277 mg, 84%): R_f = 0.56 (10% EtOAc/hexanes); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.30−7.22 (m, 4H), 7.15 (app. sextet, *J* = 4.3 Hz, 1H), 4.00−3.94 (m, 1H), 2.45−2.36 (m, 2H), 1.98 (s, 3H), 1.58−1.52 (m, 2H), 1.50−1.45 (m, 1H), 1.43−1.33 (m, 3H), 0.93 (t, *J* = 7.0 Hz, 3H), 0.74 (s, 9H), −0.25 (s, 3H), −0.30 (s, 3H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 144.1, 142.2, 129.4, 127.9, 126.1, 118.0, 70.8, 40.7, 36.8, 28.1, 25.8, 22.9, 19.6, 18.1, 14.2, −4.3, −4.4; IR (thin film) 3388, 2930, 2856, 2858, 1651 cm^{-1}; HRMS (ES/MeOH) *m/z* calcd for $C_{21}H_{36}O_2SiNa$ [M + Na]$^+$ 371.2382, found 371.2379.

(*Z*)-5-(*tert*-Butyldimethylsilyloxy)-1,6-diphenylhept-5-en-1-yn-3-ol (30). Ketone **117** (130 mg, 0.33 mmol) was converted to alcohol **30** following the general procedures for alcohol **24** formation. The mixture was stirred for 2 h at −20 °C. Purification by column chromatography (15% EtOAc/hexanes) of the crude residue afforded alcohol **30** as a clear yellow oil (82 mg, 63%): R_f = 0.44 (15% EtOAc/hexanes); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.44−7.41 (m, 2H), 7.31−7.24 (m, 7H), 7.18−7.14 (m, 1H), 4.98−4.94 (m, 1H), 2.83 (dd, *J* = 13.7, 6.9 Hz, 1H), 2.76 (dd, *J* = 13.7, 5.9 Hz, 1H), 2.62 (br. s, 1H), 2.06 (s, 3H), 0.75 (s, 9H), −0.22 (s, 3H), −0.27 (s, 3H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 142.3, 142.1, 131.8, 129.4, 128.45, 128.38, 128.0, 126.2, 122.8, 119.3, 89.6, 85.0, 62.1, 41.1, 25.8, 19.9, 18.1, −4.4, −4.5; IR (thin film) 3350, 2954, 2928, 2894, 2857, 1655 cm^{-1}; HRMS (ES/MeOH) *m/z* calcd for $C_{25}H_{32}O_2SiNa$ [M + Na]$^+$ 415.2069, found 415.2067.

(*Z*)-3-(*tert*-Butyldimethylsilyloxy)-2-(4-isobutylphenyl)non-2-en-5-ol (31). Ketone **118** (126 mg, 0.31 mmol) was converted to alcohol **31** following the general procedures for alcohol **24** formation. The mixture was stirred for 4 h at −20 °C and extracted with DCM instead of EtOAc. Purification by column chromatography (10% EtOAc/hexanes) of the crude residue afforded alcohol **31** as a clear light yellow oil (122 mg, 97%): R_f = 0.46 (10% EtOAc/hexanes); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.18 (d, *J* = 8.1 Hz, 2H), 7.05 (d, *J* = 8.0 Hz, 2H), 4.00−3.95 (m, 1H), 2.44 (d, *J* = 7.2 Hz, 2H), 2.42−2.36 (m, 2H), 2.32 (br. s, 1H), 1.98 (s, 3H), 1.84 (app. septet, *J* = 6.7 Hz, 1H), 1.60−1.36 (m, 6H), 0.94 (t, *J* = 7.1 Hz, 3H), 0.90 (d, *J* = 6.8 Hz, 6H), 0.75 (s, 9H), −0.24 (s, 3H), −0.28 (s, 3H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 143.8, 139.5, 139.4, 129.1, 128.7, 118.0, 70.8, 45.3, 40.8, 36.8, 30.4, 28.1, 25.9, 22.9, 22.4, 19.6, 18.1, 14.2, −4.3, −4.4; IR (thin film) 3400, 2955, 2929, 2859, 1652 cm^{-1}; HRMS (ES/MeOH) *m/z* calcd for $C_{25}H_{44}O_2SiNa$ [M + Na]$^+$427.3008, found 427.3010.

(*Z*)-3-(*tert*-Butyldimethylsilyloxy)-2-(6-methoxynaphthalen-2-yl)non-2-en-5-ol (32). Ketone **119** (51 mg, 0.12 mmol) was converted to alcohol **32** following the general procedures for alcohol **24** formation. The mixture was stirred for 4 h at −20 °C and extracted with DCM instead of EtOAc. Purification by column chromatography (10% EtOAc/hexanes) of the crude residue afforded alcohol **32** as a clear light yellow oil (40 mg, 79%): R_f = 0.30 (10% EtOAc/hexanes); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.67−7.64 (m, 3H), 7.41 (dd, *J* = 8.5, 1.5 Hz, 1H), 7.12−7.10 (m, 2H), 4.05−3.99 (m, 1H), 3.92 (s, 3H), 2.50−2.42 (m, 2H), 2.32 (br. s, 1H), 2.07 (s, 3H), 1.63−1.36 (m, 6H), 0.95 (t, *J* = 7.1 Hz, 3H), 0.72 (s, 9H), −0.29 (s, 3H), −0.35 (s, 3H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 157.4, 144.4, 137.4, 133.1, 129.4, 128.9, 128.6, 127.7, 126.1, 118.6, 117.8, 105.6, 70.9, 55.4, 40.9, 36.9, 28.1, 25.9, 22.9, 19.6, 18.1, 14.2, −4.2, −4.3; IR (thin film) 3444, 2956, 2929, 2858, 1604 cm^{-1}; HRMS (ES/MeOH) *m/z* calcd for $C_{26}H_{40}O_3SiNa$ [M + Na]$^+$ 451.2644, found 451.2645.

General Procedures for THPO Formation. $BF_3{\cdot}OEt_2$ (1.5 equiv) was added dropwise to a solution of aldehyde (1.5 equiv) and hydroxy silyl enol ether (1.0 equiv) in DCM (1.0 M relative to the silyl enol ether) at −78 °C. The mixture was stirred for 4 h, and the reaction was quenched with saturated aqueous $NaHCO_3$. The solution was extracted with DCM (3×), and the organic layers were combined, dried with anhydrous $MgSO_4$, filtered, and concentrated in vacuo. Purification by column chromatography of the crude residue afforded the desired THP.

(2*R*,6*S*)-2-(Benzo[*b*]thiophen-2-yl)-3,3-dimethyl-6-phenyldihydro-2*H*-pyran-4(3*H*)-one (40). Alcohol **18** (50 mg, 0.16 mmol) and 1-(1-benzothien-3-yl)ethanone (41 mg, 0.25 mmol) were converted to **40** following the general procedures for THPO formation. Purification by column chromatography (10% EtOAc/hexanes) of the crude residue afforded THPO **40** as a clear colorless oil (21 mg, 38%) and recovered alcohol **18** (34 mg): R_f = 0.36 (10% EtOAc/hexanes); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.90−7.86 (m, 2H), 7.57 (s, 1H), 7.48−7.46 (m, 2H), 7.41−7.38 (m, 3H), 7.36−7.31 (m, 2H), 5.06 (s, 1H), 4.87 (dd, *J* = 12.0, 2.8 Hz, 1H), 3.08 (dd, *J* = 14.5, 12.1 Hz, 1H), 2.71 (dd, *J* = 14.4, 2.9 Hz, 1H), 1.31 (s, 3H), 1.03 (s, 3H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 211.1, 141.0, 140.1, 138.3, 132.5, 128.8, 128.3, 125.7, 124.4, 124.2, 122.93, 122.88, 81.9, 79.8, 51.3, 46.3, 20.7, 19.9; IR (thin film) 2972, 1710 cm^{-1}; HRMS (ES/MeOH) *m*/*z* calcd for $C_{21}H_{24}O_2SN$ $[M + NH_4]^+$ 354.1528, found 354.1535.

(2*S*,6*S*)-2-(4-Hydroxy-3-methoxyphenyl)-3,3-dimethyl-6-vinyldihydro-2*H*-pyran-4(3*H*)-one (42). Alcohol **21** (43 mg, 0.16 mmol) and vanillin (38 mg, 0.25 mmol) were converted to **42** following the general procedures for THPO formation. Purification by column chromatography (gradient: 10% to 50% EtOAc/hexanes) of the crude residue afforded THPO **42** as a clear colorless oil (13 mg, 30%): R_f = 0.78 (50% EtOAc/hexanes); ^{1}H NMR (500 MHz, $CDCl_3$) δ 6.88 (dd, *J* = 5.0, 3.2 Hz, 2H), 6.81 (dd, *J* = 8.2, 1.8 Hz, 1H), 6.00 (ddd, *J* = 17.3, 10.6, 5.4 Hz, 1H), 5.59 (s, 1H), 5.35 (app. dt, *J* = 9.3, 5.8 Hz, 1H), 5.22 (app. dt, *J* = 5.9, 3.5 Hz, 1H), 4.34 (s, 1H), 4.28−4.24 (m, 1H), 3.91 (s, 3H), 2.79 (dd, *J* = 14.3, 12.0 Hz, 1H), 2.44 (dd, *J* = 14.3, 2.9 Hz, 1H), 1.06 (s, 3H), 0.94 (s, 3H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 211.4, 146.0, 145.5, 137.4, 129.1, 121.3, 116.2, 113.7, 110.7, 86.1, 78.1, 56.2, 50.7, 44.2, 20.0, 19.6; IR (thin film) 3418, 2970, 2934, 1712, 1604 cm^{-1}; HRMS (ES/MeOH) *m*/*z* calcd for $C_{16}H_{21}O_4$ $[M + H]^+$ 277.1440, found 277.1450.

THPO 43. Alcohol **16** (49 mg, 0.18 mmol) and 3-(*tert*-butyldimethylsilyloxy)propanal (53 mg, 0.28 mmol) were converted to **43** following the general procedures for THPO formation. TMSOTf was used as the Lewis acid instead of $BF_3{\cdot}OEt_2$. Purification by column chromatography (gradient: 10% EtOAc/hexanes to 100% EtOAc) of the crude residue afforded THPO **43** as a clear colorless oil (Overall: 35 mg, 76%): For R = H: Isolated 18.2 mg, 48%, R_f = 0.51 (10% EtOAc/hexanes); ^{1}H NMR (500 MHz, $CDCl_3$) δ 5.85−5.76 (m, 1H), 5.16−5.12 (m, 2H), 3.82−3.78 (m, 2H), 3.75−3.70 (m, 1H), 3.48 (dd, *J* = 10.7, 2.1 Hz, 1H), 2.65 (t, *J* = 5.5 Hz, 1H), 2.56 (dd, *J* = 14.4, 11.9 Hz, 1H), 2.40−2.33 (m, 2H), 2.29 (dd, *J* = 14.4, 2.7 Hz, 1H), 1.85−1.93 (m, 1H), 1.67−1.62 (m, 1H), 1.13 (s, 3H), 1.00 (s, 3H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 211.1, 133.5, 118.6, 84.9, 77.1, 62.0, 49.2, 44.1, 40.8, 31.1, 19.5, 18.9; IR (thin film) 3416, 3078, 2969, 2934, 2875, 1712, 1642 cm^{-1}; HRMS (ES/MeOH) *m*/*z* calcd for $C_{12}H_{21}O_3$ $[M + H]^+$ 213.1491, found 213.1490. For R = TBS: Isolated 16.5 mg, 28%, R_f = 0.46 (50% EtOAc/hexanes); ^{1}H NMR (500 MHz, $CDCl_3$) δ 5.89 (tdd, *J* = 17.1, 10.2, 7.0 Hz, 1H), 5.18−5.14 (m, 2H), 3.84−3.78 (m, 2H), 3.69−3.63 (m, 1H), 3.46 (dd, *J* = 6.8, 5.3 Hz, 1H), 2.58 (dd, *J* = 14.4, 11.8 Hz, 1H), 2.48−2.43 (m, 1H), 2.38−2.32 (m, 1H), 2.32 (dd, *J* = 14.3, 2.7 Hz, 1H), 1.76−1.72 (m, 2H), 1.15 (s, 3H), 1.05 (s, 3H), 0.94 (s, 9H), 0.10 (s, 6H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 212.3, 133.7, 117.8, 80.2, 76.8, 59.9, 49.0, 44.2, 40.7, 32.7, 26.1, 19.4, 18.9, 18.4, −5.2, −5.3; IR (thin film) 2958, 2930, 2857, 1714, 1643 cm^{-1}; HRMS (ES/MeOH) *m*/*z* calcd for $C_{18}H_{34}O_3SiNa$ $[M + Na]^+$ 349.2175, found 349.2173.

(2*S*,6*R*)-6-Allyl-3,3-dimethyl-2-styryldihydro-2*H*-pyran-4(3*H*)-one (45). Alcohol **16** (49 mg, 0.18 mmol) and cinnamaldehyde (37 mg, 0.28 mmol) were converted to **45** following the general procedures for THPO formation. Purification by column chromatography (10% EtOAc/hexanes) of the crude residue afforded THPO **45** as a clear colorless oil (44 mg, 91%): R_f = 0.50 (10% EtOAc/hexanes); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.47 (d, *J* = 7.3 Hz, 2H), 7.40 (t, *J* = 7.6 Hz, 2H), 7.32 (app. t, *J* = 7.3 Hz, 1H), 6.73 (d, *J* = 15.9 Hz, 1H), 6.29 (dd, *J* = 16.0, 6.6 Hz, 1H), 5.94 (ddt, *J* = 17.1, 10.2, 7.0 Hz, 1H), 5.23−5.19 (m, 2H), 4.00 (d, *J* = 6.6 Hz, 1H), 3.83 (dtd, *J* = 11.8, 9.2, 4.3 Hz, 1H), 2.70 (dd, *J* = 14.4, 11.9 Hz, 1H), 2.58−2.43 (m, 2H), 2.38 (dd, *J* = 14.4, 2.7 Hz, 1H), 1.23 (s, 3H), 1.11 (s, 3H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 211.7, 136.7, 133.6, 133.4, 128.7, 128.0, 126.7, 124.3, 118.3, 85.0, 76.8, 49.7, 43.9, 40.7, 19.9, 19.2; IR (thin film) 3080, 3026, 2976, 2933, 2850, 1713 cm^{-1}; HRMS (ES/MeOH) *m*/*z* calcd for $C_{18}H_{23}O_2$ $[M + H]^+$ 271.1698, found 271.1690.

(2*S*,6*R*)-6-Butyl-3,3-dimethyl-2-((*E*)-prop-1-enyl)dihydro-2*H*-pyran-4(3*H*)-one (46). Alcohol **17** (1.92 g, 6.70 mmol) and crotonaldehyde (0.70 g, 10 mmol) were converted to **46** following the general procedures for THPO formation. Purification by column chromatography (10% EtOAc/hexanes) of the crude residue afforded THPO **46** as a clear light yellow oil (1.09 g, 73%): R_f = 0.51 (10% EtOAc/hexanes); ^{1}H NMR (500 MHz, $CDCl_3$) δ 5.78−5.72 (m, 1H), 5.53 (dq, *J* = 15.3, 2.9 Hz, 1H), 3.67 (d, *J* = 7.2 Hz, 1H), 3.61−3.58 (m, 1H), 2.53 (dd, *J* = 14.2, 11.8 Hz, 1H), 2.26 (dd, *J* = 14.2, 2.6 Hz, 1H), 1.75−1.74 (m, 3H), 1.73−1.66 (m, 1H), 1.58−1.50 (m, 1H), 1.44−1.37 (m, 1H), 1.36−1.28 (m, 3H), 1.11 (s, 3H), 0.94 (s, 3H), 0.90 (t, *J* = 7.0 Hz, 3H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 212.4, 130.7, 126.1, 85.3, 77.5, 49.5, 44.6, 36.3, 27.4, 22.8, 19.8, 19.2, 18.2, 14.1; IR (thin film) 2961, 2933, 2860, 1713 cm^{-1}; HRMS (ES/MeOH) *m*/*z* calcd for $C_{14}H_{25}O_2$ $[M + H]^+$ 225.1855, found 225.1857.

(2*S*,6*R*)-6-((*R*)-2-Hydroxybutyl)-3,3-dimethyl-2-((*E*)-prop-1-enyl)dihydro-2*H*-pyran-4(3*H*)-one (49). Alcohol **19** (50 mg, 0.17 mmol) and crotonaldehyde (18 mg, 0.26 mmol) were converted to **49** following the general procedures for THPO formation. Purification by column chromatography (30% EtOAc/hexanes) of the crude residue afforded THPO **49** as a clear colorless oil (26 mg, 65%): R_f = 0.42 (30% EtOAc/hexanes); $[\alpha]_D^{24} = -24.5$ (*c* 1.30, $CHCl_3$), ^{1}H NMR (500 MHz, $CDCl_3$) δ 5.76−5.67 (m, 1H), 5.49 (ddq, *J* = 15.4, 7.1, 1.8 Hz, 1H), 3.89 (ddt, *J* = 12.1, 9.4, 4.7 Hz, 1H), 3.79−3.72 (m, 2H), 3.52 (br. s, 1H), 2.61 (dd, *J* = 14.4, 11.9 Hz, 1H), 2.28 (dd, *J* = 14.4, 2.7 Hz, 1H), 1.73−1.71 (m, 3H), 1.66−1.62 (m, 2H), 1.54−1.43 (m, 2H), 1.11 (s, 3H), 0.95 (s, 3H), 0.94 (t, *J* = 7.4 Hz, 3H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 211.0, 131.1, 125.4, 85.4, 78.5, 72.9, 49.6, 44.9, 42.6, 30.4, 19.7, 19.1, 18.1, 9.9; IR (thin film) 3468, 2967, 2936, 2875, 1712 cm^{-1}; HRMS (ES/MeOH) *m*/*z* calcd for $C_{14}H_{25}O_3$ $[M + H]^+$ 241.1804, found 241.1812.

(2*S*,6*S*)-3,3-Dimethyl-2-styryl-6-vinyldihydro-2*H*-pyran-4(3*H*)-one (51). Alcohol **21** (47 mg, 0.18 mmol) and cinnamaldehyde (36 mg, 0.27 mmol) were converted to **51** following the general procedures for THPO formation. Purification by column chromatography (10% EtOAc/hexanes) of the crude residue afforded THPO **51** as a clear colorless oil (29 mg, 62%): R_f = 0.43 (10% EtOAc/hexanes); $[\alpha]_D^{24} = -24.7$ (*c* 0.28, $CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.41 (d, *J* = 7.4 Hz, 2H), 7.33 (t, *J* = 7.5 Hz, 2H), 7.26 (app. t, *J* = 7.3 Hz, 1H), 6.68 (d, *J* = 15.9 Hz, 1H), 6.24 (dd, *J* = 16.0, 6.7 Hz, 1H), 5.98 (ddd, *J* = 17.2, 10.6, 5.6 Hz, 1H), 5.35 (d, *J* = 17.2 Hz, 1H), 5.24 (d, *J* = 10.6 Hz, 1H), 4.24−4.20 (m, 1H), 4.00 (dd, *J* = 6.7, 0.6 Hz, 1H), 2.72 (dd, *J* = 14.3, 12.0 Hz, 1H), 2.40 (dd, *J* = 14.4, 2.8 Hz, 1H), 1.19 (s, 3H), 1.06 (s, 3H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 211.0, 137.3, 136.6, 133.8, 128.7, 128.0, 126.7, 124.1, 116.5, 85.0, 76.9, 49.9, 44.2, 19.9, 19.2; IR (thin film) 3026, 2972, 2933, 2843, 1713 cm^{-1}; HRMS (ES/MeOH) *m*/*z* calcd for $C_{17}H_{24}O_2N$ $[M + NH_4]^+$ 274.1807, found 274.1821.

3,3-Dimethyl-6-(phenylethynyl)-2-((*E*)-prop-1-enyl)dihydro-2*H*-pyran-4(3*H*)-one (52). Alcohol **22** (90 mg, 0.27 mmol) and crotonaldehyde (29 mg, 0.41 mmol) were converted to **52** following the general procedures for THPO formation. Purification by column chromatography (10% EtOAc/hexanes) of the crude residue afforded THPO **52** as a clear colorless oil (51 mg, 71%) in a 4.1:1.0 *cis*:*trans* ratio. A small amount of THPO **52*c*** and THPO **52*t*** was separated for characterization, but most of it was recovered as a mixture of the two diastereomers: **THPO 52*c***: R_f = 0.57 (10% EtOAc/hexanes); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.46 (dd, *J* = 7.6, 1.8 Hz, 2H), 7.33−7.26 (m, 3H), 5.84−5.77 (m, 1H), 5.59 (app. ddq, *J* = 15.4, 7.6, 1.6 Hz, 1H), 4.63 (dd, *J* = 12.2, 3.0 Hz, 1H), 3.77 (d, *J* = 7.6 Hz, 1H), 3.06 (dd, *J* = 14.6, 12.2 Hz, 1H), 2.59 (dd, *J* = 14.7, 3.0 Hz, 1H), 1.76 (dd, *J* = 15.7, 8.7 Hz, 3H), 1.20 (s, 3H), 0.98 (s, 3H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 209.9, 132.0, 131.9, 128.9, 128.4, 125.3, 122.2, 86.3, 86.2, 85.6, 67.8, 49.7, 44.8, 19.7, 19.1, 18.1; IR (thin film) 2971, 2934, 2854, 2232, 1715 cm^{-1}; HRMS (ES/MeOH) *m*/*z* calcd for $C_{18}H_{24}O_2N$ $[M + NH_4]^+$ 286.1807, found 286.1796. **THPO 52*t***: R_f = 0.46 (10% EtOAc/hexanes); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.42−7.40 (m, 2H), 7.33−7.26 (m, 3H), 5.83 (dq, *J* = 15.3, 3.0 Hz, 1H), 5.56 (ddq, *J* = 15.3, 7.4, 1.8 Hz, 1H), 5.29 (dd, *J* = 7.2, 1.8 Hz, 1H), 4.42 (d, *J* = 7.4 Hz, 1H), 3.14 (dd, *J* = 14.3, 7.2 Hz, 1H), 2.52 (dd, *J* = 14.2, 1.8 Hz, 1H), 1.76 (dd, *J* = 6.5, 1.1 Hz, 3H), 1.15 (s, 3H), 1.04 (s, 3H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 209.9, 132.0, 131.7. 128.9, 128.4, 125.6, 122.1, 88.6, 85.6, 80.7, 65.8, 50.1, 43.7, 19.9, 19.7, 18.2; IR (thin film) 2970, 2932, 2872, 1714 cm^{-1}; HRMS (ES/MeOH) *m*/*z* calcd for $C_{18}H_{24}O_2N$ $[M + NH_4]^+$ 286.1807, found 286.1793.

(2*S*,3*S*,6*R*)-6-Butyl-3-methyl-2-styryldihydro-2*H*-pyran-4(3*H*)-one (55*c*). Alcohol **25** (40 mg, 0.15 mmol) and cinnamaldehyde (29 mg, 0.22 mmol) were converted to **55*c*** following the general procedures for THPO formation. Purification by column chromatography (10% EtOAc/hexanes) of the crude residue afforded THPO **55** as a clear colorless oil in a 8.3:1.0 *cis*:*trans* ratio (16 mg, 40%): R_f = 0.43 (10% EtOAc/hexanes); ^{1}H NMR (500 MHz, CDCl$_3$) δ 7.42−7.40 (m, 2H), 7.33 (t, *J* = 7.5 Hz, 2H), 7.28−7.25 (m, 1H), 6.64 (d, *J* = 15.9 Hz, 1H), 6.23 (dd, *J* = 15.9, 7.4 Hz, 1H), 3.83 (dd, *J* = 10.0, 7.6 Hz, 1H), 3.71−3.66 (m, 1H), 2.49−2.37 (m, 3H), 1.75−1.72 (m 1H), 1.59−1.54 (m, 1H), 1.46−1.32 (m, 4H), 1.01 (d, *J* = 6.7 Hz, 3H), 0.91 (t, *J* = 3H); ^{13}C NMR (126 MHz, CDCl$_3$) δ 208.5, 136.4, 133.5, 128.7, 128.2, 127.7, 126.8, 84.4, 76.9, 50.3, 48.2, 36.3, 27.5, 22.7, 14.1, 9.6; IR (thin film) 3026, 2957, 2932, 2860, 1715 cm^{-1}; HRMS (ES/MeOH) *m*/*z* calcd for $C_{18}H_{25}O_2$ [M + H]$^+$ 273.1855, found 273.1857.

(2*S*,3*S*,6*R*)-6-Butyl-3-methyl-2-((*E*)-prop-1-enyl)dihydro-2*H*-pyran-4(3*H*)-one (56*c*). Alcohol **25** (69 mg, 0.25 mmol) and crotonaldehyde (26 mg, 0.37 mmol) were converted to **56*c*** following the general procedures for THPO formation. Purification by column chromatography (10% EtOAc/hexanes) of the crude residue afforded THPO **56** as a clear colorless oil in a 7.0:1.0 *cis*:*trans* ratio (16 mg, 30%): R_f = 0.51 (10% EtOAc/hexanes); ^{1}H NMR (500 MHz, CDCl$_3$) δ 5.75 (dq, *J* = 17.4, 6.5 Hz, 1H), 5.51 (app. dqd, *J* = 15.2, 7.8, 1.8 Hz, 1H), 3.63−3.58 (m, 2H), 2.41 (dd, *J* = 13.6, 2.4 Hz, 1H), 2.37−2.28 (m, 2H), 1.74 (dd, *J* = 6.5, 1.6 Hz, 3H), 1.73−1.66 (m, 1H), 1.56−1.49 (m, 1H), 1.44−1.37 (m, 1H), 1.36−1.28 (m, 3H), 0.93 (d, *J* = 6.7 Hz, 3H), 0.90 (t, *J* = 7.0 Hz, 3H); ^{13}C NMR (126 MHz, CDCl$_3$) δ 209.0, 130.6, 130.0, 84.5, 77.6, 50.1, 48.2, 36.3, 27.5, 22.7, 18.0, 14.1, 9.6; IR (thin film) 2959, 2934, 2860, 1717 cm^{-1}; HRMS (ES/MeOH) *m*/*z* calcd for $C_{13}H_{26}O_2N$ [M + NH$_4$]$^+$ 228.1964, found 228.1964.

Ethyl 2-((2*S*,5*S*,6*S*)-5-Methyl-4-oxo-6-((*E*)-prop-1-enyl)tetrahydro-2*H*-pyran-2-yl)acetate (57*c*). Alcohol **26** (46 mg, 0.15 mmol) and crotonaldehyde (16 mg, 0.23 mmol) were converted to **57*c*** following the general procedures for THPO formation. TMSOTf was used as the Lewis acid instead of BF$_3$·OEt$_2$. Purification by column chromatography (20% EtOAc/hexanes) of the crude residue afforded THPO **57** as a clear colorless oil in a 5.6:1.0 *cis*:*trans* ratio (18 mg, 49%): R_f = 0.45 (10% EtOAc/hexanes); ^{1}H NMR (500 MHz, CDCl$_3$) δ 5.78−5.68 (m, 1H), 5.48 (app. ddq, *J* = 14.8, 7.3, 1.8 Hz, 1H), 4.17−4.06 (m, 3H), 3.66 (dd, *J* = 10.2, 7.8 Hz, 1H), 2.72 (dd, *J* = 15.4, 6.8 Hz, 1H), 2.53−2.48 (m, 2H), 2.42 (dd, *J* = 11.6, 1.1 Hz, 1H), 2.33−2.26 (m, 1H), 1.73 (dd, *J* = 6.5, 1.6 Hz, 3H), 1.25 (t, *J* = 7.2 Hz, 3H), 0.94 (d, *J* = 6.7 Hz, 3H); ^{13}C NMR (126 MHz, CDCl$_3$) δ 207.5, 170.2, 131.0, 129.6, 84.3, 73.6, 60.9, 49.8, 47.4, 41.4, 17.9, 14.3, 9.6; IR (thin film) 2977, 2935, 2877, 1736, 1717 cm^{-1}; HRMS (ES/MeOH) *m*/*z* calcd for $C_{13}H_{20}O_4Na$ [M + Na]$^+$ 263.1259, found 263.1258.

6-((*Z*)-Hex-3-enyl)-2-((4-methoxyphenoxy)methyl)-3-methyldihydro-2*H*-pyran-4(3*H*)-one (58). Alcohol **27** (46 mg, 0.15 mmol) and 2-(4-methoxyphenoxy)acetaldehyde (38 mg, 0.23 mmol) were converted to **58** following the general procedures for THPO formation using TMSOTf instead of BF$_3$·OEt$_2$. Purification by column chromatography (20% EtOAc/hexanes) of the crude residue afforded THPO **58*c*** (28 mg, 55%) and **58*t*** (8 mg, 17%) as a clear colorless oil: **THPO 58*c***: R_f = 0.42 (20% EtOAc/hexanes); ^{1}H NMR (500 MHz, CDCl$_3$) δ 6.83−6.78 (m, 4H), 5.54−5.47 (m, 1H), 5.22 (ddd, *J* = 15.3, 8.7, 1.5 Hz, 1H), 4.02 (dd, *J* = 10.4, 2.0 Hz, 1H), 3.85 (dd, *J* = 10.4, 6.1 Hz, 1H), 3.82−3.77 (m, 1H), 3.76 (s, 3H), 3.42 (ddd, *J* = 10.2, 6.1, 2.0 Hz, 1H), 2.75 (dd, *J* = 15.5, 7.3 Hz, 1H), 2.54−2.40 (m, 3H), 2.19−2.12 (m, 1H), 1.82 (dq, *J* = 13.2, 3.5 Hz, 1H), 1.69 (dq, *J* = 12.7, 4.3 Hz, 1H), 1.62 (dd, *J* = 6.4, 1.5 Hz, 3H), 1.46 (m, 1H), 1.37−1.29 (m, 1H), 1.02 (t, *J* = 7.3 Hz, 3H); ^{13}C NMR (126 MHz, CDCl$_3$) δ 210.3, 153.9, 153.5, 131.6, 127.2, 116.0, 114.6, 80.2, 74.4, 70.8, 55.8, 49.0, 41.0, 37.2, 31.2, 30.8, 18.2, 7.7; IR (thin film) 2935, 2918, 2876, 2854, 1714, 1508 cm^{-1}; HRMS (ES/MeOH) *m*/*z* calcd for $C_{20}H_{28}O_4Na$ [M + Na]$^+$ 355.1885, found 355.1878. **THPO 58*t***: R_f = 0.53 (20% EtOAc/hexanes); ^{1}H NMR (500 MHz, CDCl$_3$) δ 6.91−6.89 (m, 2H), 6.84−82 (m, 2H), 5.42−5.37 (m, 1H), 5.31−5.26 (m, 1H), 4.22 (ddd, *J* = 10.6, 2.0 Hz, 1H), 4.06 (ddd, *J* = 10.6, 4.4 Hz, 1H), 3.77 (s, 3H), 3.66−3.61 (m, 1H), 3.53 (ddd, *J* = 10.5, 4.3, 2.0 Hz, 1H), 2.78−2.72 (m, 1H), 2.50−2.36 (m, 2H), 2.22 (app. sextet, *J* = 7.7 Hz, 1H), 2.14 (app. sextet, *J* = 7.2 Hz, 1H), 2.06 (quintet, *J* = 7.8 Hz, 2H), 1.84−1.76 (m, 1H), 1.56−1.50 (m, 1H), 1.05 (d, *J* = 6.6 Hz, 3H), 0.95 (t, *J* = 7.5 Hz, 3H); ^{13}C NMR (126 MHz, CDCl$_3$) δ 208.8, 154.3, 153.2, 132.8, 127.9, 116.1, 114.7, 81.5, 77.0, 70.0, 55.9, 48.0, 46.5, 36.2, 23.0, 20.6, 14.5, 9.3; IR (thin film) 3000, 2960, 2932, 2873, 2852, 1716, 1508 cm^{-1}; HRMS (ES/MeOH) *m*/*z* calcd for $C_{20}H_{28}O_4Na$ [M + Na]$^+$ 355.1885, found 355.1884.

(2*S*,3*S*,6*S*)-6-(Furan-2-yl)-3-methyl-3-phenyl-2-((*E*)-prop-1-enyl)dihydro-2*H*-pyran-4(3*H*)-one (59*c*). Alcohol **28** (58 mg, 0.16 mmol) and crotonaldehyde (17 mg, 0.24 mmol) were converted to **59*c*** following the general procedures for THPO formation. Purification of the crude residue on a preparative TLC plate (10% EtOAc/hexanes) afforded THPO **59** as a white film in a 6.0:1.0 *cis*:*trans* ratio (29 mg, 62%): R_f = 0.44 (10% EtOAc/hexanes); ^{1}H NMR (500 MHz, CDCl$_3$) δ 7.46 (app. d, *J* = 1.0 Hz, 1H), 7.37−7.32 (m, 2H), 7.31−7.27 (m, 1H), 7.20−7.18 (m, 2H), 6.40−6.39 (m, 2H), 5.50−5.43 (m, 1H), 5.17 (ddt, *J* = 15.4, 5.6, 4.9 Hz, 1H), 5.02 (dd, *J* = 12.4, 3.0 Hz, 1H), 4.59 (d, *J* = 5.5 Hz, 1H), 3.28 (dd, *J* = 15.8, 12.4 Hz, 1H), 2.71 (dd, *J* = 15.8, 3.1 Hz, 1H), 1.62 (s, 3H), 1.53 (dd, *J* = 6.5, 1.1 Hz, 3H); ^{13}C NMR (126 MHz, CDCl$_3$) δ 209.8, 152.7, 143.1, 139.5, 130.0, 128.4, 128.3, 127.3, 124.8, 110.5, 108.0, 84.4, 72.0, 58.8, 42.0, 18.0, 16.7; IR (thin film) 3031, 2989, 2916, 2854, 1714 cm^{-1}; HRMS (ES/MeOH) *m*/*z* calcd for $C_{19}H_{20}O_3Na$ [M + Na]$^+$ 319.1310, found 319.1305.

6-Butyl-3-methyl-3-phenyl-2-styryldihydro-2*H*-pyran-4(3*H*)-one (60). Alcohol **29** (36 mg, 0.10 mmol) and cinnamaldehyde (20 mg, 0.15 mmol) were converted to **60** following the general procedures for THPO formation. Purification by column chromatography (10% EtOAc/hexanes) of the crude residue afforded THPO **60** as a clear colorless oil in a 8.2:1.0 *cis*:*trans* ratio (24 mg, 69%). A small amount of THPO **60*c*** and THPO **60*t*** was separated for characterization, but most of it was recovered as a mixture of the two diastereomers; R_f = 0.28 (10% EtOAc/hexanes): **THPO 60*c***: ^{1}H NMR (500 MHz, CDCl$_3$) δ 7.37 (app. t, *J* = 7.5 Hz, 2H), 7.31−7.17 (m, 8H), 6.46 (dd, *J* = 16.1, 1.4 Hz, 1H), 5.74 (dd, *J* = 16.1, 4.4 Hz, 1H), 4.64 (dd, *J* = 4.4, 1.6 Hz, 1H), 3.99−3.93 (m, 1H), 2.71 (dd, *J* = 15.6, 11.9 Hz, 1H), 2.52 (dd, *J* = 15.6, 2.9 Hz, 1H), 1.87−1.81 (m, 1H), 1.69−1.63 (m, 1H), 1.58−1.55 (m, 1H), 1.56 (s, 3H), 1.48−1.37 (m, 3H), 0.96 (t, *J* = 7.2 Hz, 3H); ^{13}C NMR (126 MHz, CDCl$_3$) δ 210.9, 139.6, 136.9, 131.9, 128.6, 128.43, 128.41, 127.7, 127.4, 126.5, 124.4, 83.9, 76.9, 58.7, 44.4, 36.3, 27.6, 22.8, 16.8, 14.2; IR (thin film) 3057, 3026, 2956, 2930, 2859, 1714 cm^{-1}; HRMS (ES/MeOH) *m*/*z* calcd for $C_{24}H_{28}O_2Na$ [M + Na]$^+$ 371.1987, found 371.1986. **THPO 60*t***: ^{1}H NMR (500 MHz, CDCl$_3$) δ 7.39−7.37 (m, 6H), 7.33 (app. t, *J* = 7.4 Hz, 2H), 7.29−7.26 (m, 2H), 6.76 (d, *J* = 15.6 Hz, 1H), 6.27 (dd, *J* = 15.6, 8.4 Hz, 1H), 5.22 (d, *J* = 8.4 Hz, 1H), 4.16 (quintet, *J* = 6.5 Hz, 1H), 2.41−2.39 (m, 2H), 1.61−1.53 (m, 1H), 1.46−1.37 (m, 1H), 1.30−1.17 (m, 7H), 0.84 (t, *J* = 3H); ^{13}C NMR (126 MHz, CDCl$_3$) δ 210.4, 142.4, 136.4, 136.2, 129.0, 128.8, 128.4, 127.1, 127.0, 126.9, 124.3, 80.7, 72.7, 58.2, 45.1, 35.9, 27.2, 22.7, 22.2, 14.1; IR (thin film) 3058, 3026, 2956, 2928, 2860, 1711 cm^{-1}; HRMS (ES/MeOH) *m*/*z* calcd for $C_{24}H_{28}O_2Na$ [M + Na]$^+$ 371.1987, found 371.1995.

6-Butyl-3-methyl-3-phenyl-2-((*E*)-prop-1-enyl)dihydro-2*H*-pyran-4(3*H*)-one (61). Alcohol **29** (79 mg, 0.23 mmol) and crotonaldehyde (30 mg, 0.43 mmol) were converted to **61** following the general procedures for THPO formation. Purification by column chromatography (10% EtOAc/hexanes) of the crude residue afforded THPO **61*c*** (39 mg, 60%) and **61*t*** (14 mg, 22%) as a clear colorless oil. **THPO 61*c***: R_f = 0.35 (10% EtOAc/hexanes); ^{1}H NMR (500 MHz, CDCl$_3$) δ 7.26 (app. t, *J* = 7.5 Hz, 1H), 7.20−7.17 (m, 2H), 7.09 (dd, *J* = 8.3, 1.1 Hz, 2H), 5.44 (dqd, *J* = 15.4, 6.6, 1.4 Hz, 1H), 5.03 (dd, *J* = 15.5, 2.2 Hz, 1H), 4.34 (dd, *J* = 3.7, 1.2 Hz, 1H), 3.81 (ddq, *J* = 12.6, 6.6, 1.8 Hz, 1H), 2.58 (dd, *J* = 15.6, 11.9 Hz, 1H), 2.39 (dd, *J* = 15.5, 2.9 Hz, 1H), 1.73−1.67 (m, 1H), 1.57−1.51 (m, 1H), 1.49 (app. dt, *J* = 6.6, 1.4 Hz, 3H), 1.46 (s, 3H), 1.44−1.41 (m, 1H), 1.37−1.27 (m, 3H), 0.87 (t, *J* = 7.1 Hz, 3H); ^{13}C NMR (126 MHz, CDCl$_3$) δ 211.2, 139.8, 129.0, 128.4, 128.2, 127.1, 125.4, 84.0, 76.9, 58.6, 44.4, 36.3, 27.5, 22.8, 18.0, 16.6, 14.2; IR (thin film) 3031, 2957, 2932, 2859, 1714 cm^{-1}; HRMS (ES/MeOH) *m*/*z* calcd for $C_{19}H_{26}O_2Na$ [M + Na]$^+$ 309.1830, found 309.1820. **THPO 61*t***: R_f = 0.35 (10% EtOAc/hexanes); ^{1}H NMR (500 MHz, CDCl$_3$) δ 7.35−7.32 (m, 4H), 7.25−7.22 (m, 1H), 5.88 (dq, *J* = 17.2, 5.0 Hz, 1H), 5.60 (ddq, *J* = 14.9, 8.9, 1.9 Hz, 1H), 5.02 (d, *J* = 8.9 Hz, 1H), 4.09−

4.04 (m, 1H), 2.33 (dd, J = 13.7, 9.8 Hz, 1H), 2.28 (dd, J = 13.7, 4.2 Hz, 1H), 1.75 (dd, J = 6.5, 1.6 Hz, 3H), 1.54−1.49 (m, 1H), 1.41−1.33 (m, 1H), 1.28−1.21 (m, 4H), 1.19 (s, 3H), 0.85 (t, J = 7.0 Hz, 3H); ^{13}C NMR (126 MHz, CDCl$_3$) δ 210.5, 142.8, 133.2, 128.9, 126.98, 126.95, 126.2, 81.0, 72.3, 58.0, 45.2, 36.0, 27.1, 22.7, 22.6, 18.2, 14.1; IR (thin film) 2956, 2930, 2860, 1713 cm^{-1}; HRMS (ES/MeOH) m/z calcd for $C_{19}H_{26}O_2Na$ $[M + Na]^+$ 309.1830, found 309.1826.

(2*S*,3*S*,6*R*)-6-Butyl-3-methyl-2-((*Z*)-2-methylbut-1-en-3-ynyl)-3-phenyldihydro-2*H*-pyran-4(3*H*)-one (62*c*). Alcohol **29** (33 mg, 0.10 mmol) and 3-methylpent-2-en-4-ynal (5:1 *Z*:*E* ratio, 14 mg, 0.15 mmol) were converted to **62*c*** following the general procedures for THPO formation. Purification by column chromatography (10% EtOAc/hexanes) of the crude residue afforded THPO **62*c*** as a clear colorless oil with a 5:1 *Z*:*E* ratio (14 mg, 48%); R_f = 0.35 (10% EtOAc/hexanes): ^{1}H NMR (500 MHz, CDCl$_3$) δ 7.32−7.28 (m, 2H), 7.26−7.22 (m, 1H), 7.19−7.14 (m, 2H), 5.69 (dd, J = 8.7, 0.6 Hz, 1H), 4.91 (d, J = 8.7 Hz, 1H), 3.97−3.91 (m, 1H), 2.92 (s, 1H), 2.65 (dd, J = 15.8, 11.8 Hz, 1H), 2.50 (dd, J = 15.8, 3.2 Hz, 1H), 1.74 (d, J = 1.4 Hz, 3H), 1.62 (s, 3H), 1.61−1.56 (m, 1H), 1.48−1.46 (m, 1H), 1.41−1.33 (m, 4H), 0.93 (t, J = 7.0 Hz, 3H); ^{13}C NMR (126 MHz, CDCl$_3$) δ 210.6, 139.0, 132.1, 128.6, 128.1, 127.2, 123.4, 82.1, 81.9, 81.8, 76.9, 58.2, 44.5, 36.3, 27.4, 23.5, 22.8, 17.1, 14.2; IR (thin film) 3286, 2955, 2929, 2862, 1715 cm^{-1}; HRMS (ES/MeOH) m/z calcd for $C_{21}H_{26}O_2Na$ $[M + Na]^+$ 333.1830, found 333.1825.

3-Methyl-3-phenyl-6-(phenylethynyl)-2-((*E*)-prop-1-enyl)dihydro-2*H*-pyran-4(3*H*)-one (63). Alcohol **30** (41 mg, 0.10 mmol) and crotonaldehyde (11 mg, 0.16 mmol) were converted to **63** following the general procedures for THPO formation. Purification by column chromatography (10% EtOAc/hexanes) of the crude residue afforded THPO **63** as a mixture of diastereomers (1.7:1.0 *cis*:*trans*) that was a clear light yellow oil (31 mg, 94%). Some of THPO **63*c*** and THPO **63*t*** was separated for characterization, but some of it was recovered as a mixture of the two diastereomers: **THPO 63*c***: R_f = 0.44 (10% EtOAc/hexanes); ^{1}H NMR (500 MHz, CDCl$_3$) δ 7.50−7.48 (m, 2H), 7.37−7.33 (m, 5H), 7.30−7.28 (m, 1H), 7.16 (d, J = 7.3 Hz, 2H), 5.56−5.49 (m, 1H), 5.20 (dq, J = 15.4, 2.4 Hz, 1H), 4.92 (dd, J = 12.1, 3.2 Hz, 1H), 4.49 (d, J = 5.5 Hz, 1H), 3.17 (dd, J = 15.9, 12.1 Hz, 1H), 2.79 (dd, J = 15.9, 3.2 Hz, 1H), 1.56 (s, 3H), 1.56 (d, J = 3H); ^{13}C NMR (126 MHz, CDCl$_3$) δ 209.0, 139.3, 132.1, 130.4, 129.0, 128.4, 128.3, 128.3, 127.4, 124.6, 122.1, 86.5, 86.3, 84.6, 67.6, 58.8, 44.6, 18.0, 16.7; IR (thin film) 2915, 1715 cm^{-1}; HRMS (ES/MeOH) m/z calcd for $C_{23}H_{22}O_2Na$ $[M + Na]^+$ 353.1518, found 353.1519. **THPO 63*t***: R_f = 0.46 (10% EtOAc/hexanes); ^{1}H NMR (500 MHz, CDCl$_3$) δ 7.48−7.46 (m, 2H), 7.36−7.32 (m, 5H), 7.28−7.25 (m, 3H), 5.65−5.58 (m, 1H), 5.36 (dd, J = 6.5, 3.3 Hz, 1H), 5.29 (ddq, J = 14.0, 5.4, 1.4 Hz, 1H), 5.19 (d, J = 6.0 Hz, 1H), 3.14 (dd, J = 15.0, 6.5 Hz, 1H), 2.71 (dd, J = 15.0, 3.4 Hz, 1H), 1.62 (d, J = 6.6 Hz, 3H), 1.50 (s, 3H); ^{13}C NMR (126 MHz, CDCl$_3$) δ 209.0, 140.3, 132.0, 130.6, 129.1, 128.6, 128.5, 128.1, 127.2, 125.1, 122.0, 88.9, 86.0, 79.8, 65.2, 58.9, 43.9, 18.1, 18.0; IR (thin film) 2927, 2854, 1711 cm^{-1}; HRMS (ES/MeOH) m/z calcd for $C_{23}H_{22}O_2Na$ $[M + Na]^+$ 353.1518, found 353.1512.

6-Butyl-3-(6-methoxynaphthalen-2-yl)-3-methyl-2-((*E*)-prop-1-enyl)dihydro-2*H*-pyran-4(3*H*)-one (64). Alcohol **31** (48 mg, 0.12 mmol) and crotonaldehyde (13 mg, 0.18 mmol) were converted to **64** following the general procedures for THPO formation. Purification by column chromatography (10% EtOAc/hexanes) of the crude residue afforded THPO **64** as a mixture of diastereomers (3.0:1.0 *cis*:*trans*) that was a clear light yellow oil (20 mg, 50%). Some of THPO **64*c*** and THPO **64*t*** was separated for characterization, but some of it was recovered as a mixture of the two diastereomers: **THPO 64*c***: R_f = 0.60 (10% EtOAc/hexanes); ^{1}H NMR (500 MHz, CDCl$_3$) δ 7.10 (d, J = 8.1 Hz, 2H), 7.05 (d, J = 8.2 Hz, 2H), 5.52−5.45 (m, 1H), 5.12−5.08 (m, 1H), 4.38 (d, J = 4.8 Hz, 1H), 3.90−3.85 (m, 1H), 2.64 (dd, J = 15.5, 11.8 Hz, 1H), 2.48−2.44 (m, 3H), 1.86 (app. septet, J = 6.7 Hz, 1H), 1.81−1.74 (m, 1H), 1.63−1.57 (m, 1H), 1.55 (d, J = 6.8 Hz, 3H), 1.51 (s, 3H), 1.51−1.35 (m, 4H), 0.93 (t, J = 7.1 Hz, 3H), 0.90 (dd, J = 6.6, 1.7 Hz, 6H); ^{13}C NMR (126 MHz, CDCl$_3$) δ 211.4, 140.4, 137.0, 128.9, 128.8, 128.0, 125.6, 84.1, 76.9, 58.3, 45.2, 44.5, 36.3, 30.2, 27.5, 22.8, 22.6, 22.5, 18.0, 16.7, 14.2; IR (thin film) 2955, 2929, 2867, 1714 cm^{-1}; HRMS (ES/MeOH) m/z calcd for $C_{23}H_{34}O_2Na$ $[M + Na]^+$ 365.2456, found 365.2453. **THPO 64*t***: R_f = 0.70 (10% EtOAc/hexanes); ^{1}H NMR (500 MHz, CDCl$_3$) δ 7.23 (d, J = 8.1 Hz, 2H), 7.10 (d, J = 8.1 Hz, 2H), 5.86 (dq, J = 14.0, 4.3 Hz, 1H), 5.59 (app. ddd, J = 15.1, 8.8, 1.1 Hz, 1H), 5.00 (d, J = 8.8 Hz, 1H), 4.08−4.03 (m, 1H), 2.44 (d, J = 7.2 Hz, 2H), 2.35 (dd, J = 13.6, 10.4 Hz, 1H), 2.26 (dd, J = 13.7, 3.5 Hz, 1H), 1.85 (app. septet, J = 6.7 Hz, 1H), 1.74 (d, J = 6.4 Hz, 3H), 1.54−1.49 (m, 1H), 1.41−1.33 (m, 2H), 1.31−1.20 (m, 3H), 1.18 (s, 3H), 0.89 (d, J = 6.6 Hz, 6H), 0.84 (t, J = 6.8 Hz, 3H); ^{13}C NMR (126 MHz, CDCl$_3$) δ 210.8, 140.4, 140.1, 133.0, 129.6, 126.6, 126.3, 81.2, 72.2, 57.6, 45.1, 45.0, 36.0, 30.3, 27.1, 22.6. 22.54, 22.52, 18.2, 14.1; IR (thin film) 2955, 2927, 2868, 1713 cm^{-1}; HRMS (ES/MeOH) m/z calcd for $C_{23}H_{34}O_2Na$ $[M + Na]^+$ 365.2456, found 365.2447.

6-Butyl-3-(4-isobutylphenyl)-3-methyl-2-((*E*)-prop-1-enyl)dihydro-2*H*-pyran-4(3*H*)-one (65). Alcohol **32** (36 mg, 0.08 mmol) and crotonaldehyde (9 mg, 0.13 mmol) were converted to **65** following the general procedures for THPO formation. Purification by column chromatography (10% EtOAc/hexanes) of the crude residue afforded THPO **65*c*** (21 mg, 68%) and THPO **65*t*** (8 mg, 26%) as a clear light yellow oil: **THPO 65*c***: R_f = 0.28 (10% EtOAc/hexanes); ^{1}H NMR (500 MHz, CDCl$_3$) δ 7.70 (d, J = 8.4 Hz, 2H), 7.57 (d, J = 1.6 Hz, 1H), 7.21 (dd, J = 8.6, 1.9 Hz, 1H), 7.14−7.12 (m, 2H), 5.53 (dqd, J = 15.6, 6.6, 1.4 Hz, 1H), 5.12 (ddq, J = 15.4, 4.9, 1.7 Hz, 1H), 4.52 (dt, J = 3.1, 1.6 Hz, 1H), 3.96−3.90 (m, 1H), 3.92 (s, 3H), 2.69 (dd, J = 15.5, 11.9 Hz, 1H), 2.50 (dd, J = 15.6, 2.9 Hz, 1H), 1.83−1.77 (m, 1H), 1.67−1.60 (m, 1H), 1.63 (s, 3H), 1.52 (app. dt, J = 6.6, 1.4 Hz, 3H), 1.52−1.36 (m, 4H), 0.95 (t, J = 7.2 Hz, 3H); ^{13}C NMR (126 MHz, CDCl$_3$) δ 211.4, 157.9, 135.1, 133.7, 129.7, 129.0, 128.9, 127.3, 127.0, 126.5, 125.5, 118.8, 105.6, 83.7, 77.2, 58.5, 55.5, 44.6, 36.3, 27.5, 22.8, 18.0, 16.8, 14.2; IR (thin film) 3058, 2956, 2933, 2858, 1710, 1606 cm^{-1}; HRMS (ES/MeOH) m/z calcd for $C_{24}H_{30}O_3Na$ $[M + Na]^+$ 389.2093, found 389.2079. **THPO 65*t***: R_f = 0.45 (10% EtOAc/hexanes); ^{1}H NMR (500 MHz, CDCl$_3$) δ 7.80 (s, 1H), 7.72 (app. t, J = 8.1 Hz, 2H), 7.37 (dd, J = 8.6, 1.2 Hz, 1H), 7.15 (dd, J = 8.8, 2.3 Hz, 1H), 7.11 (d, J = 2.1 Hz, 1H), 5.92 (dq, J = 18.2, 4.3 Hz, 1H), 5.64 (dd, J = 14.9, 8.9 Hz, 1H), 5.14 (d, J = 8.9 Hz, 1H), 4.12−4.07 (m, 1H), 3.92 (s, 3H), 2.38−2.28 (m, 2H), 1.76 (d, J = 6.4 Hz, 3H), 1.55−1.48 (m, 1H), 1.39−1.30 (m, 1H), 1.26−1.18 (m, 6H), 0.93−0.87 (m, 1H), 0.84−0.81 (m, 3H); ^{13}C NMR (126 MHz, CDCl$_3$) δ 210.7, 157.9, 137.9, 133.5, 133.2, 129.8, 129.2, 127.4, 126.3, 125.7, 125.6, 119.1, 105.5, 81.2, 72.3, 57.9, 55.5, 45.2, 36.0, 27.1, 22.7, 22.6, 18.2, 14.1; IR (thin film) 2956, 2930, 2858, 1711, 1605 cm^{-1}; HRMS (ES/MeOH) m/z calcd for $C_{24}H_{30}O_3Na$ $[M + Na]^+$ 389.2093, found 389.2086.

Ethyl 3-(*tert*-Butyldimethylsilyloxy)-2,4-dimethylpent-3-enoate (67). 2-Bromo-2-methylpropionyl bromide (1.6 g, 6.9 mmol) was added dropwise to a suspension of activated zinc dust (0.91 g, 13.9 mmol) in dry THF (12 mL) at 0 °C. The reaction mixture was stirred for 1 h at 0 °C and then transferred via cannula to a solution of silyl ketene acetal **66** (0.5 g, 2.3 mmol) in dry THF (12 mL) at 0 °C. The gray-green mixture was stirred overnight, slowly warming to room temperature. The reaction mixture was then diluted with Et$_2$O (25 mL) and washed with H$_2$O (15 mL). The aqueous layer was extracted with Et$_2$O (20 mL × 6). The organic layers were combined, dried over anhydrous MgSO$_4$, filtered, and concentrated in vacuo. Purification by column chromatography (10:1:89 Et$_2$O:Et$_3$N:hexanes) of the crude residue produced ethyl ester **67** as a colorless oil (0.22 g, 33%): R_f = 0.57 (10% Et$_2$O/hexanes); ^{1}H NMR (500 MHz, CDCl$_3$) δ 4.15−4.03 (m, 2H), 3.53 (q, J = 7.3 Hz, 1H), 1.59 (s, 3H), 1.57 (s, 3H), 1.24 (d, J = 7.2 Hz, 3H), 1.21 (t, J = 7.1 Hz, 3H), 0.91 (s, 9H), 0.10 (s, 3H), 0.05 (s, 3H); ^{13}C NMR (126 MHz, CDCl$_3$) δ 173.9, 142.8, 111.3, 60.7, 42.6, 26.2, 19.0, 18.9, 18.8, 14.4, 14.4, −3.5, −3.8; IR (thin film) 2956, 2932, 2905, 2859, 1736, 1675 cm^{-1}; HRMS (ES/MeOH) m/z calcd for $C_{15}H_{30}O_3SiNa$ $[M + Na]^+$ 309.1862, found 309.1864.

3-(*tert*-Butyldimethylsilyloxy)-*N*-methoxy-*N*,2,4-trimethylpent-3-enamide (68). A solution of 2.0 M *i*-PrMgCl (0.92 mL, 1.8 mmol) in dry THF was added dropwise to a solution of ethyl ester **67**

(0.22 g, 0.77 mmol) and Me(MeO)NH·HCl (90 mg, 0.92 mmol) in dry THF (6.4 mL) at −78 °C. The mixture was stirred for 3.5 h at −78 °C, warmed to 0 °C, and stirred for an additional 2.5 h. A solution of 2.0 M *i*-PrMgCl (0.92 mL, 1.8 mmol) in dry THF and Me(MeO)NH·HCl (90 mg, 0.92 mmol) was added to the reaction mixture and stirred for 2.5 h at 0 °C. The reaction was then quenched with saturated aqueous NH_4Cl (5 mL). The mixture was extracted with EtOAc (3 × 10 mL). The organic layers were combined, dried over anhydrous $MgSO_4$, and filtered, and the resulting solution was concentrated in vacuo. Purification by column chromatography (15% EtOAc/hexanes) of the crude residue afforded Weinreb amide **68** as a colorless oil (183 mg, 79%): R_f = 0.54 (15% EtOAc/hexanes); ^{1}H NMR (500 MHz, $CDCl_3$) δ 3.73−3.62 (m, 1H), 3.59 (s, 3H), 3.14 (s, 3H), 1.59 (s, 3H), 1.58 (s, 3H), 1.24 (d, *J* = 7.2 Hz, 3H), 0.93 (s, 9H), 0.14 (s, 3H), 0.12 (s, 3H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 174.8, 143.7, 109.9, 77.4, 60.7, 41.1, 26.2, 18.9, 18.7, 18.6, 14.8, −3.3, −3.4; IR (thin film) 2956, 2932, 2898, 2858, 1668 cm^{-1}; HRMS (ES/MeOH) *m*/*z* calcd for $C_{15}H_{31}NO_3SiNa$ [M + Na]$^+$ 324.1971, found 324.1979.

3-(*tert*-Butyldimethylsilyloxy)-2,4-dimethylnon-2-en-5-one (69). *n*-BuLi (2.27 M in hexanes, 0.33 mL) was added dropwise to a solution of amide **68** (150 mg, 0.50 mmol) in dry THF (1.7 mL) at −78 °C. The mixture was stirred for 2.5 h, and the reaction was quenched with saturated aqueous NH_4Cl (5 mL). The mixture was extracted with EtOAc (3 × 5 mL). The organic layers were combined, dried over anhydrous $MgSO_4$, and filtered, and the resulting solution was concentrated in vacuo. Purification by column chromatography (10% EtOAc/hexanes) of the crude residue afforded ketone **69** as a colorless oil (123 mg, 83%): R_f = 0.82 (15% EtOAc/hexanes); ^{1}H NMR (500 MHz, $CDCl_3$) δ 3.34 (q, *J* = 7.0 Hz, 1H), 2.50 (ddd, *J* = 16.6, 8.3, 6.9 Hz, 1H), 2.36 (ddd, *J* = 16.6, 8.3, 6.6 Hz, 1H), 1.61 (s, 3H), 1.58 (s, 3H), 1.56−1.45 (m, 2H), 1.27 (m, 2H), 1.16 (d, *J* = 7.0 Hz, 3H), 0.90 (s, 9H), 0.86 (t, *J* = 7.4 Hz, 3H), 0.083 (s, 3H), 0.079 (s, 3H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 210.3, 143.8, 111.7, 50.4, 40.0, 26.3, 26.2, 22.5, 19.1, 18.9, 18.7, 14.0, 13.1, −3.38, −3.42; IR (thin film) 2958, 2932, 2860, 1718, 1670 cm^{-1}; HRMS (ES/MeOH) *m*/*z* calcd for $C_{17}H_{34}O_2SiNa$ [M + Na]$^+$ 321.2226, found 321.2222.

3-(*tert*-Butyldimethylsilyloxy)-2,4-dimethylnon-2-en-5-ol (70/71). L-Selectride (1.0 M in THF, 0.53 mL) was added dropwise to a solution of ketone **69** (106 mg, 0.36 mmol) in dry THF (3.6 mL) at −78 °C. The mixture was stirred overnight, slowly warming to room temperature. The reaction was quenched with saturated aqueous NH_4Cl (10 mL), and the mixture was extracted with EtOAc (3 × 5 mL). The organic layers were combined, dried over anhydrous $MgSO_4$, and filtered, and the resulting solution was concentrated in vacuo. Purification by column chromatography (5% EtOAc/hexanes) of the crude residue afforded a mixture of alcohol **70** as a colorless oil (50 mg, 46%) and alcohol **71** as a colorless oil (8 mg, 8%): Alcohol **70**: R_f = 0.52 (5% EtOAc/hexanes); ^{1}H NMR (500 MHz, $CDCl_3$) δ 3.55−3.52 (m, 1H), 2.62 (app. dt, *J* = 15.7, 7.1 Hz, 1H), 2.22 (d, *J* = 2.1 Hz, 1H), 1.633 (s, 3H), 1.628 (s, 3H), 1.56−1.49 (m, 2H), 1.38−1.29 (m, 4H), 0.98 (d, *J* = 8.4 Hz, 3H), 0.97 (s, 9H), 0.92−0.89 (m, 3H), 0.16 (s, 6H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 145.7, 111.9, 73.2, 41.7, 34.1, 28.0, 26.5, 23.0, 19.4, 19.2, 19.1, 15.4, 14.3, −2.7, −3.2; IR (thin film) 3567, 3489, 2957, 2932, 2859, 1713, 1668 cm^{-1}; HRMS (ES/MeOH) *m*/*z* calcd for $C_{17}H_{36}O_2SiNa$ [M + Na]$^+$ 323.2382, found 323.2381. Alcohol **71**: R_f = 0.27 (5% EtOAc/hexanes); ^{1}H NMR (500 MHz, $CDCl_3$) δ 3.66−3.62 (m, 1H), 2.58 (app. quintet, *J* = 7.0 Hz, 1H), 1.91 (br. s, 1H), 1.62 (s, 3H), 1.59 (s, 3H), 1.38−1.27 (m, 6H), 1.09 (d, *J* = 7.1 Hz, 3H), 0.96 (s, 9H), 0.90 (t, *J* = 7.0 Hz, 3H), 0.16 (s, 3H), 0.14 (s, 3H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 147.3, 109.2, 75.0, 41.2, 34.8, 28.4, 26.6, 22.9, 19.5, 19.3, 19.1, 14.3, 13.7, −2.4, −3.1; IR (thin film) 3340, 2956, 2930, 2858, 1708, 1669 cm^{-1}; HRMS (ES/MeOH) *m*/*z* calcd for $C_{17}H_{37}O_2Si$ [M + H]$^+$ 301.2563, found 301.2576.

(2*S*,5*R*,6*R*)-6-Butyl-3,3,5-trimethyl-2-((*E*)-prop-1-enyl)-dihydro-2*H*-pyran-4(3*H*)-one (72). Alcohol **70** (50 mg, 0.17 mmol) and crotonaldehyde (18 mg, 0.25 mmol) were converted to **72** following the general procedures for THPO formation. Purification by column chromatography (5% EtOAc/hexanes) of the crude residue afforded THPO **72** as a clear colorless oil (20 mg, 50%): R_f = 0.43 (5% EtOAc/hexanes); ^{1}H NMR (500 MHz, $CDCl_3$) δ 5.74 (dq, *J* = 14.1, 4.4 Hz, 1H), 5.53 (app. ddd, *J* = 15.3, 6.8, 1.4 Hz, 1H), 3.64 (d, *J* = 7.0 Hz, 1H), 3.23−3.19 (m, 1H), 2.64−2.61 (m, 1H), 1.75 (d, *J* = 6.5 Hz, 3H), 1.72−1.67 (m, 1H), 1.60−1.52 (m, 1H), 1.43−1.25 (m, 4H), 1.11 (s, 3H), 0.97−0.93 (m, 6H), 0.92 (t, *J* = 7.2 Hz, 3H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 213.8, 130.3, 126.3, 85.3, 83.0, 49.3, 45.5, 33.9, 27.1, 22.9, 20.0, 19.7, 18.2, 14.2, 9.9; IR (thin film) 2959, 2934, 2859, 1710 cm^{-1}; HRMS (ES/MeOH) *m*/*z* calcd for $C_{15}H_{30}O_2N$ [M + NH_4]$^+$ 256.2277, found 256.2276.

6-Butyl-3,3,5-trimethyl-2-((*E*)-prop-1-enyl)dihydro-2*H*-pyran-4(3*H*)-one (73). Alcohol **71** (9 mg, 0.03 mmol) and crotonaldehyde (6 mg, 0.09 mmol) were converted to **73** following the general procedures for THPO formation using 3.0 equiv of aldehyde and 3.0 equiv of $BF_3 \cdot OEt_2$ instead of 1.5 equiv. The solution was run at 0.3 M instead of 1.0 M. Purification by column chromatography (5% EtOAc/hexanes) of the crude residue afforded THPO **73** as a mixture of diastereomers (1.0:1.8 *cis*:*trans*) that was a clear colorless oil (5.2 mg, 72%). Some of the THPO **73*t*** was separated for characterization, but most of it was recovered as a mixture of the two diastereomers. **THPO 73*c***: R_f = 0.49 (5% EtOAc/hexanes); ^{13}C NMR (126 MHz, $CDCl_3$) δ 219.9, 130.4, 126.5, 85.6, 79.0, 49.3, 47.5, 31.6, 27.9, 22.8, 21.1, 21.0, 18.2, 14.2, 12.6; ^{13}C chemical shifts were determined by taking a ^{13}C NMR spectra of the diastereomeric mixture and subtracting peaks that belonged to THPO **73*t***. **THPO 73*t***: R_f = 0.42 (5% EtOAc/hexanes); ^{1}H NMR (500 MHz, $CDCl_3$) δ 5.72 (dq, *J* = 18.4, 4.3 Hz, 1H), 5.54 (dd, *J* = 15.3, 7.5 Hz, 1H), 4.18−4.10 (m, 1H), 3.79 (d, *J* = 7.4 Hz, 1H), 3.23 (app. quintet, *J* = 6.8 Hz, 1H), 1.75 (d, *J* = 6.4 Hz, 3H), 1.39−1.27 (m, 4H), 1.17 (s, 3H), 0.93 (s, 3H), 0.90 (d, *J* = 7.5 Hz, 3H), 0.88−0.83 (m, 5H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 214.0, 130.6, 126.5, 79.2, 78.6, 44.5, 29.8, 27.4, 26.0, 22.6, 20.7, 19.7, 18.1, 14.2, 10.3; IR (thin film) 2959, 2932, 2859, 1709 cm^{-1}; HRMS (ES/MeOH) *m*/*z* calcd for $C_{15}H_{30}O_2N$ [M + NH_4]$^+$ 256.2277, found 256.2274.

■ ASSOCIATED CONTENT

Ⓢ Supporting Information

^{1}H and ^{13}C NMR spectra of all new compounds, as well as structure coordinates for the calculation on **72**, **73*c***, and **73*t***, and Chiracel AD HPLC traces for **48**, **51**, and **53**. This material is available free of charge via the Internet at http://pubs.acs.org.

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Notes

The authors declare no competing financial interest.

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