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Strategies to Control Alkoxy Radical-Initiated Relay Cyclizations for the Synthesis of Oxygenated Tetrahydrofuran Motifs

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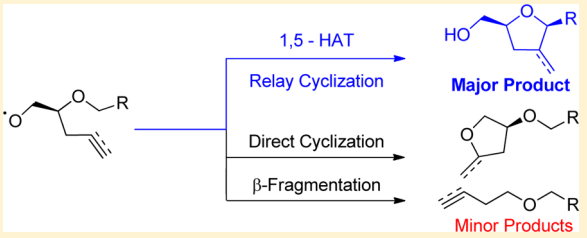
Supporting Information

ABSTRACT: Radical relay cyclizations initiated by alkoxy radicals are a powerful tool for the rapid construction of substituted tetrahydrofurans. The scope of these relay cyclizations has been dramatically increased with the development of two strategies that utilize an oxygen atom in the substrate to accelerate the desired hydrogen atom transfer (HAT) over competing pathways. This has enabled a chemoselective 1,6-HAT over a competing 1,5-HAT. Furthermore, this allows for a chemoselective 1,5-HAT over competing direct cyclizations and β-fragmentations. Oxygen atom incorporation leads to a general increase in cyclization diastereoselectivity over carbon analogues. This chemoselective relay cyclization strategy was utilized in the improved synthesis of the tetrahydrofuran fragment in (−)-amphidinolide K.



INTRODUCTION

Over the past few decades, tetrahydrofuran (THF)-containing macrolides, such as (−)-amphidinolide K (**1**)[1−4] and mandelalide A (**2**),[5,6] have emerged as an important class of bioactive macrolides (Figure 1).[7] As they are often isolated in only small amounts, the ability to synthetically access these important natural products is critical for structural elucidation, stereochemical confirmation, and additional medicinal testing. The synthesis of these polyketides has received considerable attention, and construction of the THF ring is often a key component of the overall strategy.[7]

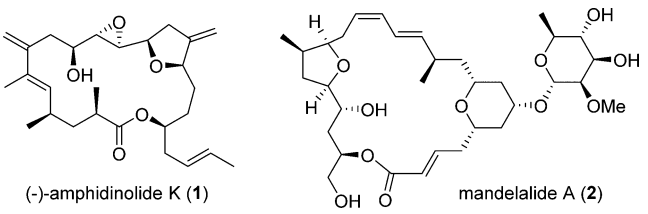


Figure 1. Representative tetrahydrofuran-containing, bioactive polyketide macrolides.

Our strategy[8] to synthesize the THF rings in these important macrolides is to utilize radical relay (or translocation) cyclization cascades[9−11] initiated by alkoxy radicals (Figure 2).[12,13] The first step of these cascade reactions involves the generation of a highly reactive alkoxy radical species (**3**) that can undergo a 1,5-hydrogen atom transfer (1,5-HAT) of an unactivated or an activated carbon−hydrogen bond to form carbon radical **4**. Once the radical has been "relayed" across the substrate, a radical cyclization cascade takes place to form the key tetrahydrofuran (**5**). This approach has two key advantages over previously developed methods: no prefunctionalization is required at C-5 (**3**), and initiating with an alkoxy radical leaves an alcohol for further synthetic manipulation. Overall, this enables the rapid conversion of simple starting compounds to the key tetrahydrofuran motif.

We have previously developed a radical relay cyclization methodology[8] in which *N*-alkoxyphthalimides were utilized as alkoxy radical precursors.[14] While this methodology focused on the formation of carbocycles, we reported that three substrates could be used for the formation of tetrahydrofurans (Scheme 1). Simple tetrahydrofuran **7** (eq 1) was formed in high yield and diastereoselectivity. Furthermore, the cyclization afforded a 2,4,5-trisubstituted tetrahydrofuran (**9**) favoring the all *cis* stereoisomer with high selectivity (eq 2). We also demonstrated that the relay methodology could be used to form the tetrahydrofuran motif in (−)-amphidinolide K (**1**) in only five steps from commercially available starting materials (eq 3).

The most significant limitation of our initial methodology was that the 1,5-HAT necessitates a three-carbon chain between the alcohol and the ring (Figure 3, **13**). This oxygenation pattern is ideal for the synthesis of tetrahydrofuran motifs like those found in (−)-amphidinolide K; however, application of this methodology to other THF-containing macrolides, such as mandelalide A, would require further redox steps to access the required oxygenation pattern. This significantly limits the applicability and utility of our initial methodology for future applications to the synthesis of most of the THF-containing macrolides.

One possible method to increase the substrate scope is to utilize the oxygen of the ether to bias the chemoselectivity of the initial hydrogen atom transfer to favor the 1,6-HAT over the standard 1,5-HAT (Figure 4, Type A). This substrate class has the advantage of allowing direct access to a homologated oxygenation pattern of the THF-containing product (**15**). It is

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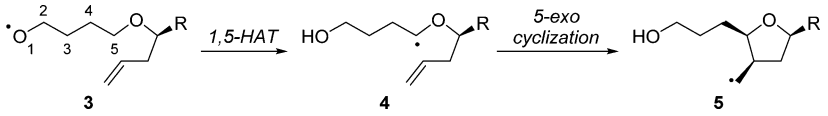
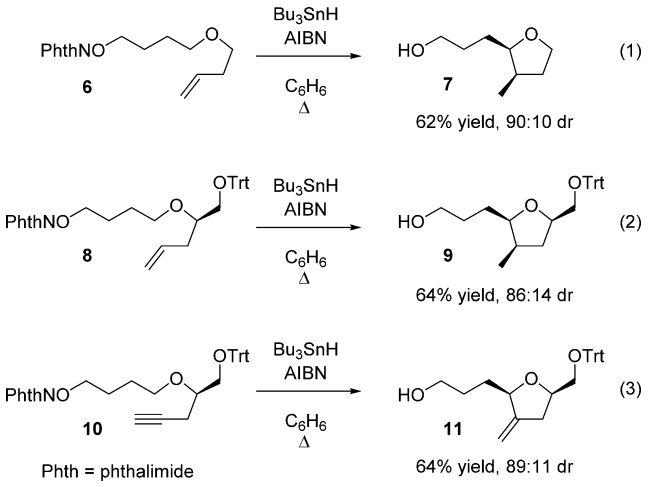


Figure 2. Radical relay cascade.

Scheme 1. Previously Demonstrated Alkoxy Radical-Initiated Relay Cyclizations for the Synthesis of THF Rings



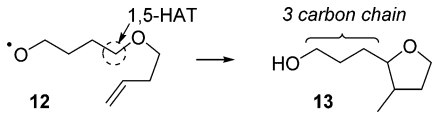


Figure 3. Substrate scope limitations in the original relay cyclization methodology.

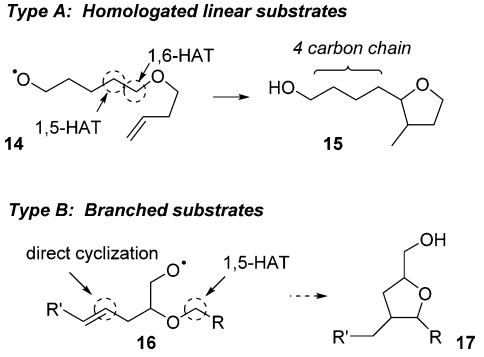


Figure 4. This work: strategies to improve the substrate scope of the radical relay cyclization.

well-known that an oxygen atom will stabilize an adjacent radical[15−20] and will lead to an increase in reaction rate. This has been utilized to control hydrogen abstraction by alkoxy radicals,[21] and to increase the rates of 1,6-HATs over competing 1,5-HATs in cyclic systems.[10b,22,23] For this strategy to be successfully employed in these linear substrates, the relative rate of the desired hydrogen abstraction pathway must increase by several orders of magnitude to compete with other very fast processes, such as 5-*exo* cyclizations.

Branched substrates (Figure 4, Type B) would significantly increase the versatility of alkoxy radical-initiated relay cyclizations if they could be utilized as viable cyclization precursors. However, these substrates present a formidable challenge as the rate of side reactions, such as the direct 5-*exo* cyclization onto an alkene,[24,25] can be faster than the desired 1,5-HAT.[26,27] While the oxygen of the ether should accelerate the desired 1,5-HAT compared to the direct cyclization, it should also accelerate other undesired reactions, such as a β-fragmentation.

In addition, it is essential to have a better understanding of the factors that are involved in cyclization diastereoselectivity for these reactions to be generally useful for the synthesis of the THF rings found in bioactive macrolides. In our initial studies, the three tetrahydrofurans (**7**, **9**, and **11**, Scheme 1) were synthesized in notably higher diastereoselectivities compared to the carbon analogues. However, more substrates need to be examined to determine the influence of oxygen on cyclization diastereoselectivity.

In this paper, we present new investigations into radical relay cyclizations initiated by alkoxy radicals. We first examined the cyclization diastereoselectivities when forming THF and THP rings. We then detail studies into the development of new relay cyclizations using substrates of Types A and B (Figure 4) that use the ether oxygen atom to direct the initial hydrogen atom transfer. Finally, we compared our new methodology to a previously reported synthesis of the THF ring of (−)-amphidinolide K.

RESULTS AND DISCUSSION

Relay Cyclization Diastereoselectivity Study. In our initial communication,[8] the diastereoselectivity for cyclization of the simplest straight-chain substrate (**6**, Scheme 1) was significantly higher compared to the carbon analogue (90:10 vs 75:25).[28] As this was the only direct comparison, additional studies are necessary to determine if this is a general trend. We focused our studies on the oxa-analogues of previously studied relay cyclization substrates.[8] Synthetic routes to the cyclization precursors are outlined in Scheme 2.

We started our investigation by examining the effect secondary *N*-alkoxyphthalimides have on reaction diastereoselectivity (Table 1, entries 1, 2). In our previous study, cyclization of **19b** provided the corresponding cyclopentane derivative in an 80:20 ratio of *cis*- to *trans*-isomers (entry 2).[8] Similar to what was previously observed, cyclization of the oxygen-containing analogue (**19a**) afforded tetrahydrofuran derivative **30a** with notably higher diastereoselectivity (entry 1).

We next examined 1,5-HATs, followed by cyclizations onto 1,2-disubstituted alkenes (Table 1, entries 3−7). Cyclization of phenyl-substituted alkene substrate **19c** afforded the corresponding tetrahydrofuran **30c** in an 83:17 mixture of *cis*- to *trans*-isomers (entry 3). This is an improvement over the carbon analogue in our previous study, which afforded the corresponding cyclopentane in a 75:25 ratio favoring the *cis*-isomer. A direct comparison of these two results may not directly reflect the influence of oxygen incorporation as the E/Z ratio between the two starting materials is notably different (80:20 for **19c** compared to 65:35 for the carbon analogue). To address this concern, we examined the cyclization of **19d**, which is more enriched in the *E* isomer. The cyclization to **30d** occurred in comparable diastereoselectivity (entry 4, 77:23 ratio of *cis*- to *trans*-isomers) to what was previously reported, which indicates

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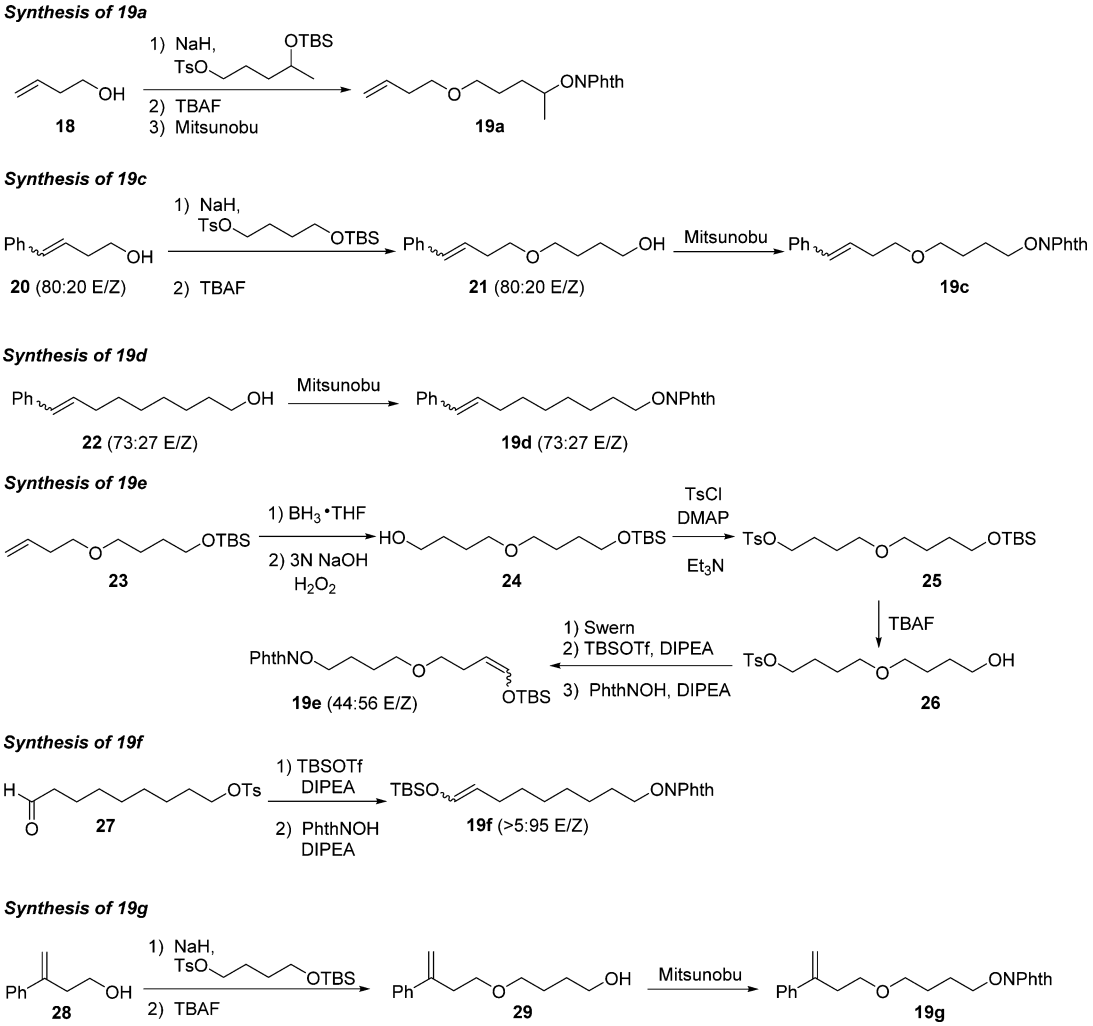
Scheme 2. Synthetic Routes for the Synthesis of Substrates 19[29]



that the increase in selectivity for the oxa-analogue was not the result of the difference in starting olefin geometry.

Cyclizations onto silyl enol ethers provide an additional handle for further synthetic manipulation. Under our standard relay cyclization conditions, silyl enol ether substrate **19e** cyclized to afford tetrahydrofuran **30e** as a 66:34 mixture of *cis*- to *trans*-isomers (entry 5). Cyclization of both E- and Z-enriched carbon analogues **19f** afforded the corresponding cyclopentane derivatives (**30f**) in similar diastereoselectivities (entries 6, 7). This again suggests that the starting alkene geometry is not the determining factor for the difference in observed cyclization diastereoselectivities between the carbon and oxa-analogues.

With encouraging improvements in selectivities for five-membered ring formation, we next examined the formation of THP rings. In our initial investigations, 6-*exo* cyclizations formed the corresponding cyclohexane or tetrahydropyran (THP) ring in moderate to poor yields with low cyclization diastereoselectivities. We, therefore, focused on comparing the selectivity of 6-*endo* cyclizations. As previously reported,[8] cyclization of the gem-disubstituted alkene **19h** afforded the corresponding cyclohexane (**31h**) in a moderate 65:35 ratio of *trans*- to *cis*-isomers (entry 9), while the oxygen-containing analogue, precursor **19g**, cyclized to form **31g** in good yield almost exclusively as the *trans*-isomer (entry 8).

The general increase in cyclization diastereoselectivity between the carbo- and the oxacycles may be explained based on the calculations of the Beckwith and Houk groups for radical 5-*exo* cyclizations.[30] According to calculations, the two lowest energy transition states for 5-*exo* radical cyclizations should be the two chairlike transition states depicted in Figure 5.[31] Transition state **34**, leading to *cis*-cyclization product **35** should be lower in energy than transition state **32** as orienting R^1 in the pseudoequatorial position minimizes 1,3-diaxial-type interactions. When an oxygen atom is incorporated in the ring, the bond lengths in both chairlike transition states (**36** and **38**) are shortened. This decreased bond length should not significantly affect transition state **38**, but should increase the 1,3-diaxial interactions in **36**. This greater steric interaction between R^1 and the pseudoaxial protons results in a greater relative energy difference between **36** and **38** and, thus, should provide higher *cis*-selectivities. Consistent with our study, secondary *N*-alkoxyphthalimides should have minimal impact on cyclization diastereoselectivity. A similar rationale can be used to explain the selectivities for the 6-*endo* cyclizations (Table 1, entries 8, 9). While this model rationalizes the trend in cyclization diastereoselectivities for the majority of oxygen-containing relay substrates, it appears to be limited when cyclizing onto electron-rich olefins (Table 1, entries 5−7).

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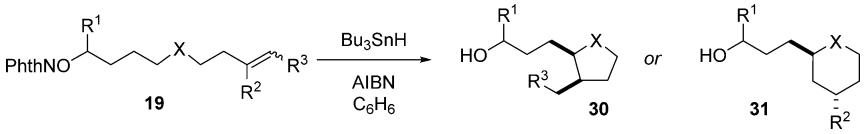
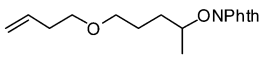
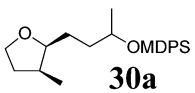
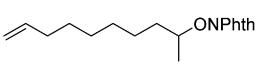
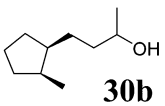
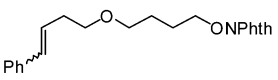
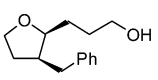
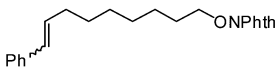
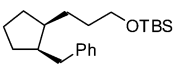
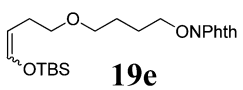
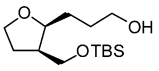
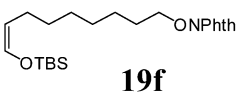
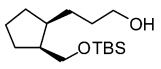
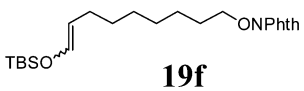
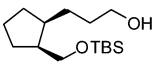
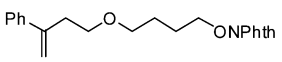
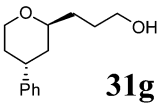
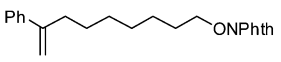
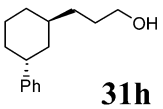
Table 1. Relay Cyclization Diastereoselectivity Study[a,b,c,d,e,f]



entry	substrate[a]	olefin geometry (E/Z)	product[b]	yield(%)[c]	dr[d] (*cis*:*trans*)
1	 **19a**	-	 **30a**	55[e]	91:9
2	 **19b**	-	 **30b**	66[e,f]	80:20[f]
3	 **19c**	80:20	 **30c**	75	83:17
4	 **19d**	73:27	 **30d**	55e	77:23
5	 **19e**	44:56	 **30e**	60	66:34
6	 **19f**	>5:95	 **30f**	62	70:30
7	 **19f**	70:30	 **30f**	62	75:25
8	 **19g**	-	 **31g**	65	>5:95
9	 **19h**	-	 **31h**	65[f]	35:65[f]

[a]Reactions were carried out on a >0.25 mmol scale. [b]The relative stereochemistry was determined by NOE experiments. [c]Isolated yields of the mixture of diastereomers after flash chromatography. [d]The diastereomeric ratio was determined by ^{1}H NMR spectroscopy. [e]The isolated yield corresponds to a two-step cyclization/silylation procedure. [f]Experimental details for this reaction can be found in ref 8.

1,6-HAT RELAY CYCLIZATIONS

With a general understanding of the influence of oxygen incorporation on cyclization diastereoselectivity, we next focused on accessing different oxygenation patterns in the THF motifs. We began by investigating homologated substrates that would allow for a longer tether between the alcohol and the THF ring (Figure 4, Type A). To accomplish this, the oxygen of the ether must direct an initial 1,6-HAT over a competing 1,5-HAT. Investigations began with the preparation of cyclization test substrates **42** and **43** (Scheme 3).

Alkoxy radical **44** (Figure 6) may first undergo a 1,5-hydrogen atom transfer, followed by a 6-*exo* cyclization, to form tetrahydropyran derivative **46** (Path A). Alternatively, the oxygen of the ether should be sufficient to bias the system to a preferential 1,6-HAT[10b,22,23,32,33] forming radical intermediate **47**, which would then cyclize to form tetrahydrofuran **48** (Path B). Using the previously optimized relay cyclization conditions,[8] precursor **42** cyclized to tetrahydrofuran **48** in 66% isolated yield as an 80:20 ratio of isomers (Scheme 4).[34]

To further examine preferential 1,6-HATs over competing 1,5-HATs, we examined cyclization of oxygen-transposed substrate **43** (Scheme 5). If the reaction proceeds exclusively through a 1,6-HAT pathway, then the resulting radical is too close to the olefin to cyclize efficiently and will simply quench with tributyltin hydride to form a linear alcohol (Path A). However, if the generated alkoxy radical undergoes a 1,5-HAT, then the resulting 5-*exo* cyclization is significantly faster than hydrogen quenching, and a cyclized product should be observed (Path B). Treatment

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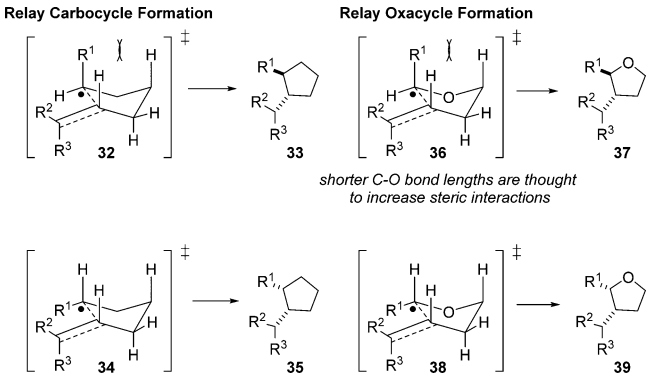
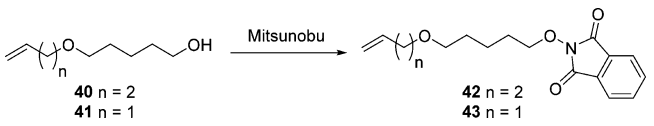


Figure 5. Chairlike transition states for the 5-*exo* cyclization step of the radical relay process.

Scheme 3. Synthesis of Substrates 42 and 43



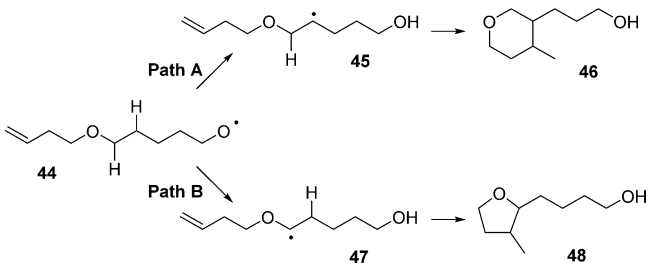
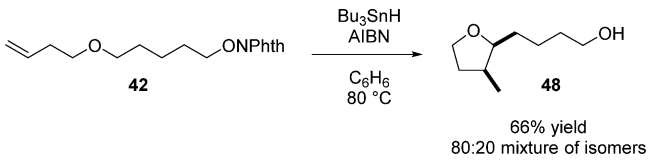


Figure 6. Competition between 1,5-HAT and 1,6-HAT.

Scheme 4. Relay Cyclization Starting with a 1,6-HAT



of **43** under the standard radical relay cyclization conditions affords exclusively the linear alcohol (**41**), confirming that, under these reaction conditions, the 1,6-HAT of a C−H bond α to an oxygen is indeed over 2 orders of magnitude faster than a 1,5-HAT of a secondary alkyl C−H, and this strategy is effective for synthesizing tetrahydrofurans with hydroxybutyl substituents.[35]

Branched Relay Cyclization Substrates. We next examined whether we could significantly alter the oxygenation pattern of the THF-containing motif by initiating the relay cyclization from a branched position (Figure 7, **53**). This is a

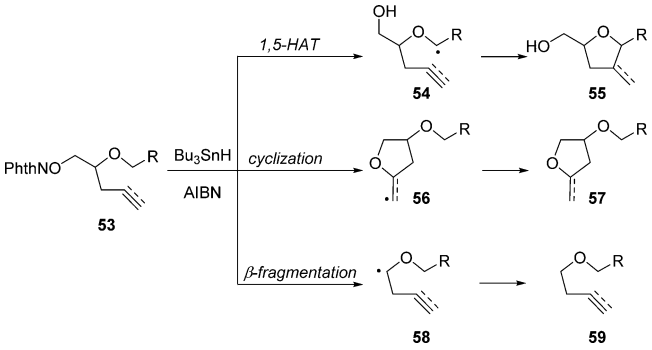
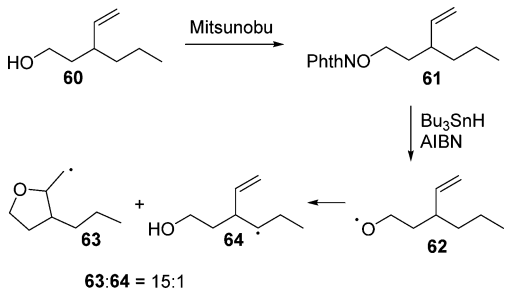


Figure 7. Competing radical pathways.

challenging substrate as there are two radical pathways that may interfere with the desired 1,5-HAT: direct 5-*exo* cyclization with the alkene[24,25] and β-fragmentation.[11a,g,36] The rate of the direct alkene cyclization is very fast, on the order of 10^8 s^{-1},[25] and should compete with the desired 1,5-HAT. In substrates where there is no oxygen adjacent to the site of hydrogen abstraction (such as **61**, Scheme 6),[37] the 5-*exo* cyclization pathway

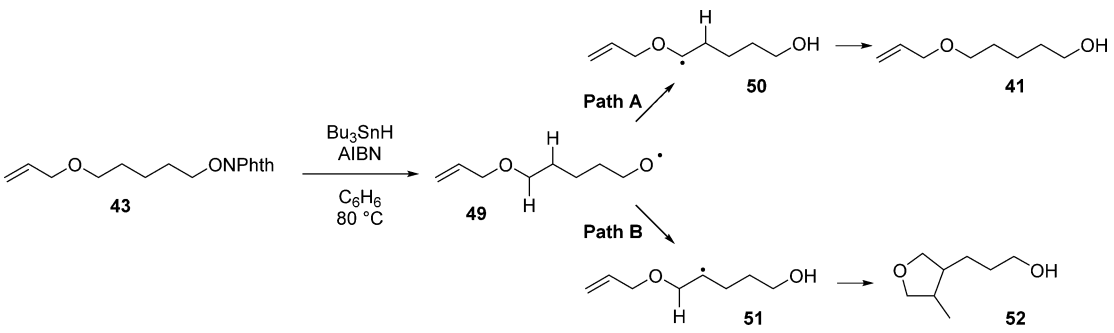
Scheme 6. Competition between 5-*exo* Cyclization and 1,5-HAT



dominates. The second competing pathway available for **53** (Figure 7) is a β-fragmentation, which should also be accelerated by the presence of an oxygen atom in the substrate.

Not only are the branched relay cyclization substrates interesting for testing chemoselectivity but also they are synthetically useful building blocks. These substrates have the advantage of being synthesized in only 3−4 synthetic steps (Schemes 7 and 8) from readily available enantioenriched

Scheme 5. Competition between 1,6-HAT and 1,5-HAT



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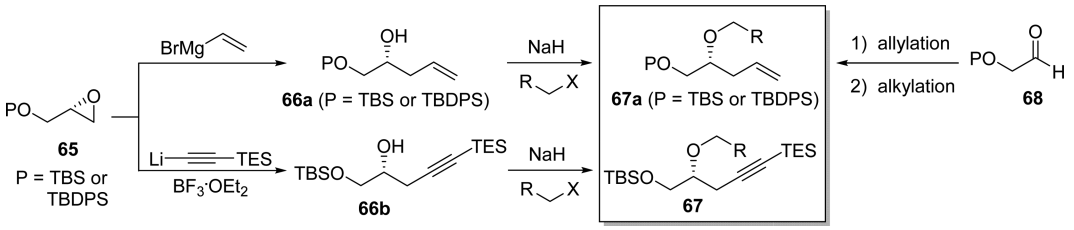
Scheme 7. Synthesis of Branched Substrate Intermediate



Scheme 8. Incorporation of an *N*-Hydroxyphthalimide into the Branched Substrate

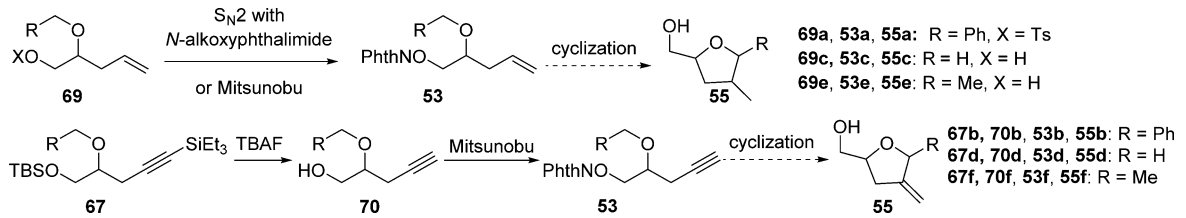
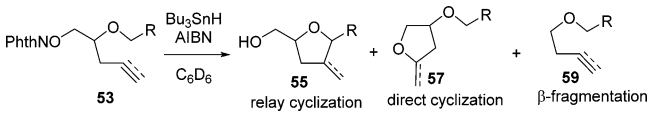
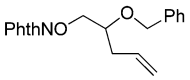
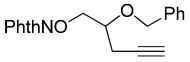
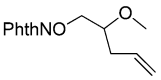
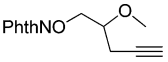
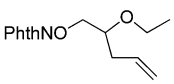
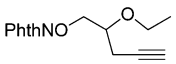


Table 2. Temperature Effects on Radical Relay Cyclizations[a,b,c,d,e]



entry	Substrate	**55**(%)[a]	**57**(%)[a,b]	**59**(%)[a]	T(°C)[c]
1	 **53a**	>95 (74)[d]	<5	<5	90
2	 **53b**	88(70)[d]	12	0	90
3	 **53c**	25 (20)[e]	44	31	90
4		25	53	22	70
5		27	53	20	60
6	 **53d**	30 (25)[e]	27	43	90
7		39	21	40	60
8	 **53e**	41 (34)[e]	32	27	90
9		60	19	21	70
10		72 (62)[e]	11	17	60
11	 **53f**	38 (25)[e]	38	24	90
12		61	22	17	60

[a]Determined by ^{1}H NMR anlaysis. [b]The direct cyclization product can undergo several subsequent radical reactions. The reported yield represents all subsequent products resulting from an initial direct cyclization. See the Supporting Information for details. [c]This number refers to the temperature of the oil bath, not the internal reaction temperature. [d]The number in brackets indicates the isolated yield after flash column chromatography. [e]The relay cyclization products are volatile, so the substrates were protected first as *tert*-butyldiphenylsilyl ethers prior to isolation. The number in brackets indicates the isolated yield after this two-step procedure.

epoxides or through allylation reactions (Scheme 7). The *N*-hydroxyphthalimide can be incorporated in the penultimate step through either an S_N2 displacement or a Mitsunobu reaction[38] (Scheme 8). This synthetic route is highly modular with respect to both the incorporation of the radical acceptor and the ether. Furthermore, the stereocenter can be used to direct the overall cyclization, providing enantioenriched cyclization product **55**.

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We first investigated a cyclization of substrates that are biased toward the desired 1,5-HAT through the use of phenyl substitution α to the proton to be abstracted (Table 2, entries 1, 2). The presence of a heteroatom and a group capable of resonance stabilization should provide additional capto-dative stabilization[17a] to allow a 1,5-HAT to compete with the direct cyclization and fragmentation pathways. Indeed, cyclization of **53a** provided exclusive formation of the radical relay product in 74% isolated yield as a 53:45:2 mixture of diastereomers,[39] with no direct cyclization or β-fragmentation products observed (entry 1). Cyclization of alkyne-containing precursor **53b** (entry 2) afforded radical relay product in 88% NMR yield (70% isolated yield as a >95:5 mixture of diastereomers favoring the all-*cis*-stereoisomer) along with 12% NMR yield of the product resulting from direct cyclization onto the alkyne.

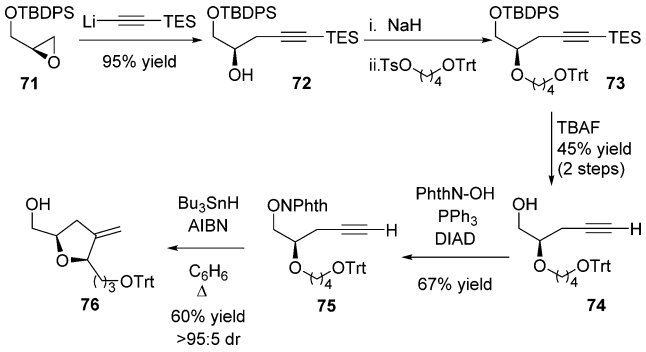
We next examined substrates containing only ether oxygen stabilization with no additional substitution α to the proton to be abstracted (**53c,d**). Cyclization of **53c** under the radical relay conditions provided radical relay cyclization product **55c** as the minor product (entry 3, Table 2) compared to direct cyclization (44%) and β-fragmentation (31%). As each of the different radical reactions should have markedly different reaction profiles to changes in temperature, we decreased the temperature to 70 °C (entry 4). The yield of radical relay cyclization product **55c** did not change. Decreasing the temperature to 60 °C only slightly improved the relative rate of radical relay cyclization compared to direct cyclization and β-fragmentation, providing cyclization product **55c** in 27% yield (entry 5).[40] A similar temperature effect was observed when the acceptor was changed to an alkyne (entries 6, 7).

The final substrates examined contained alkyl substitution α to the oxygen (R = CH_3, **53e,f**). At 90 °C, cyclized product **55e** was the major compound observed, but it was only formed in 41% NMR yield (entry 8, Table 2). Decreasing the temperature to 70 °C led to a decrease in direct cyclization product, with a concomitant small change in the amount of β-fragmentation (entry 9). At 60 °C, the reaction proceeded to the radical relay cyclization product in usable isolated yields with approximately a 93:7 isomeric mixture favoring the all *cis*-diastereoisomer (entry 10). Cyclization onto an alkyne acceptor provided a similar trend in regioselectivity (entries 11, 12). At 60 °C, the reaction afforded cyclized product **55f** in 61% yield as an 85:15 mixture of *cis*- and *trans*-isomers (entry 12).

Application to the Synthesis of the Tetrahydrofuran Fragment of (−)-Amphidinolide K. We have previously demonstrated that the tetrahydrofuran fragment of (−)-amphidinolide K can be rapidly synthesized using our alkoxy radical-initiated methodology.[8] We chose this same fragment to test our new branched relay cyclizations because it provides a good point of comparison to evaluate the efficiency of our new transformation. Furthermore, the branched relay cyclization products provide direct access to the opposite alcohol protection pattern of (−)-amphidinolide K THF fragment **11** (Scheme 1), which avoids two additional protection and deprotection steps.

The synthesis began with the opening of commercially available enantioenriched epoxide **71** with a lithiated alkyne to provide alcohol **72** in excellent yield (Scheme 9). A subsequent etherification, followed by silyl deprotection and *N*-alkoxyphthalimide installation using a Mitsunobu reaction, afforded cyclization precursor **75**. Under the cyclization conditions at 60 °C, the desired tetrahydrofuran (**76**) was isolated in 60% yield as a >95:5 mixture of *cis*- to *trans*-isomers.[41] The isolated yield closely matches the yield reported for the cyclization of similarly

Scheme 9. Synthesis of the Tetrahydrofuran Fragment within (−)-Amphidinolide K Using a Type B (Figure 4) Relay Substrate



substituted cyclization precursor **53f** (Table 2, entry 12). Overall, the desired tetrahydrofuran fragment was synthesized in only five steps from commercially available material. It is noteworthy that the yield is comparable to the original cyclization despite the potential competing pathways available to cyclization precursor **75**.

CONCLUSION

We have developed two methods that utilize the ether oxygen atom to direct the initial hydrogen atom transfer. In our first approach using homologated linear substrates, a 1,6-HAT was favored over a competing 1,5-HAT. In our second approach, branched substrates displayed preferential 1,5-HAT over the usually dominant 5-*exo* cyclization pathway. We have utilized this new cyclization approach in an alternative synthesis of the tetrahydrofuran moiety in (−)-amphidinolide K. We have also successfully demonstrated that oxygen atom incorporation generally leads to higher diastereoselectivities compared to carbon analogues. Overall, the high cyclization diastereoselectivities, coupled with the chemoselectivity of the hydrogen atom transfer, significantly increase the potential substrate scope of radical relay cyclizations and demonstrate that these relay cyclizations are effective for the rapid synthesis of functionalized tetrahydrofurans.

EXPERIMENTAL SECTION

General Methods. All reactions were performed under a nitrogen atmosphere in flame-dried glassware. Tetrahydrofuran, diethyl ether, and dichloromethane were purified by a solvent purification system. All other solvents were used without further purification. Thin-layer chromatography (TLC) was performed on UV_{254} precoated TLC plates. Chromatographic separations were effected over silica gel (230−400 mesh). Basefied silica gel has been stirred with triethylamine prior to packing. All chemicals were purchased from commercial sources and used as received. Chemical shifts are reported in parts per million (ppm) and are referenced to the centerline of deuterochloroform (7.27 ppm ^{1}H NMR; 77.0 ppm ^{13}C NMR) or deuterobenzene (7.16 ppm ^{1}H NMR; 128.4 ppm ^{13}C NMR). High-resolution mass spectra (HRMS) were measured by TOF.

Synthesis of Substrates 19. *2-((5-(But-3-en-1-yloxy)pentan-2-yl)oxy)isoindoline-1,3-dione (**19a**).* To a stirring solution of NaH (60% dispersion in mineral oil, 589 mg, 14.7 mmol) in anhydrous DMF (25 mL) was added 3-buten-1-ol (0.65 mL, 554 mg, 7.38 mmol). The solution was stirred for 10 min at ambient temperature, after which a solution of 4-((*tert*-butyldimethylsilyl)oxy)pentyl-4-methylbenzenesulfonate[42] (2.5 g, 6.70 mmol) in anhydrous DMF (2.0 mL) was added. The solution was then heated to 75 °C and stirred for 2 h, and allowed to cool to ambient temperature. The reaction was quenched via the slow addition of H_2O (40 mL), followed by saturated $NaHCO_3$ (10

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mL). The reaction was extracted with Et_2O (3 × 50 mL), and the combined organic layers were washed with H_2O (20 mL) and brine (20 mL), dried over Na_2SO_4, and concentrated by rotary evaporation to yield crude ((5-(but-3-en-1-yloxy)pentan-2-yl)oxy)(*tert*-butyl)-dimethylsilane as a colorless oil. The crude oil was dissolved in THF (20 mL), and tetrabutylammonium fluoride (1.0 M in THF, 4.55 mL, 4.55 mmol) was added. The solution was then stirred for 12 h at ambient temperature. The reaction was quenched with H_2O (20 mL) and extracted with Et_2O (3 × 20 mL). The combined organic layers were washed with H_2O (20 mL) and brine (20 mL), dried over Na_2SO_4, and concentrated by rotary evaporation. The product was semipurified using flash column chromatography (3:1 hexanes/EtOAc) to yield 5-(but-3-en-1-yloxy)pentan-2-ol as a colorless oil. To a solution of this alcohol (210 mg, 1.32 mmol) in THF (13 mL) were sequentially added triphenylphosphine (521 mg, 1.99 mmol) and *N*-hydroxyphthalimide (324 mg, 1.99 mmol). The solution was stirred until all solids were dissolved, at which point diisopropylazodicarboxylate (0.47 mL, 483 mg, 2.38 mmol) was added via syringe pump (rate = 0.8 mL/h). The resulting yellow solution was stirred for 12 h at ambient temperature, and was then quenched with H_2O (10 mL). The aqueous layer was extracted with EtOAc (3 × 20 mL), and the combined organic layers were washed with $NaHCO_3$ (3 × 20 mL) and brine (20 mL). The organic layer was dried over Na_2SO_4, concentrated using rotary evaporation, and purified by flash column chromatography (3:1 hexanes/Et_2O) to provide *N*-alkoxyphthalimide **19a** as a colorless oil (321 mg, 16% over 3 steps). **IR** (neat): 2930, 2847, 1795, 1734, 1373, 1117, 878, 695 cm^{-1}; **^{1}H NMR** (400 MHz, $CDCl_3$): δ = 7.87−7.81 (m, 2 H), 7.79−7.72 (m, 2 H), 5.82 (tdd, *J* = 6.8, 10.3, 17.0 Hz, 1 H), 5.09 (dd, *J* = 1.4, 17.4 Hz, 1 H), 5.02 (d, *J* = 10.6 Hz, 1 H), 4.46−4.37 (m, 1 H), 3.54−3.45 (m, 4 H), 2.33 (q, *J* = 6.6 Hz, 2 H), 1.89−1.64 (m, 4 H), 1.36 (d, *J* = 6.5 Hz, 3 H); **^{13}C NMR** (100 MHz, $CDCl_3$): δ = 164.3, 135.3, 134.4, 129.0, 123.4, 116.2, 84.1, 70.4, 70.0, 34.1, 31.5, 25.4, 18.8; **HRMS-ESI** (*m*/*z*): calcd. for $C_{17}H_{22}NO_4$ $[M + H]^+$: 304.1549, found 304.1547.

Synthesis of 19c. *4-((4-Phenylbut-3-en-1-yl)oxy)butan-1-ol (**21**).* To a stirring suspension of sodium hydride (60 wt % dispersion in mineral oil, 281 mg, 7.04 mmol) in anhydrous DMF (19 mL) was added **20**[43] (870 mg, 5.87 mmol). The solution was stirred for 1 h, after which a solution of 4-((*tert*-butyldimethylsilyl)oxy)butyl tosylate[22] (1.04 g, 2.89 mmol) in DMF (2.0 mL) was added. The solution was then heated to 50 °C and stirred overnight, and then allowed to cool to ambient temperature. The reaction was quenched via the slow addition of H_2O (10 mL), followed by saturated $NaHCO_3$ (10 mL). The reaction was extracted with Et_2O (3 × 20 mL), and the combined organic layers were dried over Na_2SO_4, concentrated by rotary evaporation, and purified using flash column chromatography (50:1 hexanes/Et_2O) to yield *tert*-butyldimethyl(4-((4-phenylbut-3-en-1-yl)oxy)butoxy)silane as a colorless oil (615 mg, 35%). This compound was carried forward without further purification. To a stirring solution of the silyl ether (270 mg, 0.80 mmol) in THF (3 mL) was added tetrabutylammonium fluoride (1.0 M in THF, 2.4 mL, 2.4 mmol), and the solution was stirred overnight at ambient temperature. The reaction was quenched with H_2O (5 mL) and extracted with Et_2O (3 × 10 mL). The combined organic layers were washed with H_2O (10 mL) and brine (10 mL), dried over Na_2SO_4, and concentrated by rotary evaporation. The product was purified using flash column chromatography (4:1 then 1:1 hexanes/EtOAc) to yield alcohol **21** as a colorless oil (130 mg, 80%, *E*:*Z* = 80:20). **IR** (neat): 3391, 2921, 2865, 1726, 1452, 1265, 1113, 800, 704 cm^{-1}; **^{1}HNMR** (400 MHz, $CDCl_3$): δ = 7.40−7.28 (m, 4 H), 7.26−7.18 (m, 1 H), 6.53 (d, *J* = 11.6 Hz, 0.2 H, *Z alkene*), 6.47 (d, *J* = 15.8 Hz, 0.78 H), 6.23 (td, *J* = 7.0, 15.8 Hz, 0.8 H), 5.71 (td, *J* = 7.2, 11.6 Hz, 0.2 H, *Z alkene*), 3.66−3.60 (m, 2 H), 3.59−3.53 (m, 2 H), 3.53−3.44 (m, 2 H), 2.85 (br. s., 1 H), 2.64 (dq, *J* = 1.5, 6.9 Hz, 0.43 H, *Z alkene*), 2.51 (q, *J* = 6.7 Hz, 1.6 H), 1.76−1.59 (m, 4 H); **^{13}C NMR** (100 MHz, $CDCl_3$): δ = 137.3, 137.1 (*Z alkene*), 131.5, 130.4 (*Z alkene*), 128.5 (*Z alkene*), 128.3 (*Z alkene*), 128.2, 127.9 (*Z alkene*), 126.8, 126.6, 126.5 (*Z alkene*), 125.8, 70.7, 70.6 (*Z alkene*), 70.2, 62.1, 33.2, 29.7, 29.7 (*Z alkene*), 28.9 (*Z alkene*), 26.3, 26.3 (*Z alkene*); **HRMS-ESI** (*m*/*z*): calcd. for $C_{14}H_{21}O_2$ $[M + H]^+$: 221.1542, found 221.1539.

*2-(4-((4-Phenylbut-3-en-1-yl)oxy)butoxy)isoindoline-1,3-dione (**19c**).* To a solution of alcohol **21** (130 mg, 0.59 mmol) in THF (20 mL) were sequentially added triphenylphosphine (233 mg, 0.89 mmol) and *N*-hydroxyphthalimide (145 mg, 0.89 mmol). The solution was stirred until the solids were dissolved, at which point diisopropylazodicarboxylate (0.22 mL, 222 mg, 1.1 mmol) was added via syringe pump (rate = 0.8 mL/h). The resulting yellow solution was stirred overnight at ambient temperature, and was then quenched with H_2O (10 mL). The aqueous layer was extracted with EtOAc (3 × 20 mL), and the combined organic layers were washed with $NaHCO_3$ (3 × 20 mL) and brine (20 mL) and were dried over Na_2SO_4. The organics were concentrated using rotary evaporation and purified by flash column chromatography (4:1 hexanes/EtOAc) to provide *N*-alkoxyphthalimide **19c** as a colorless oil (200 mg, 92%, *E*:*Z* = 80:20). **IR** (neat): 2921, 2865, 1791, 1730, 1478, 1378, 1265, 1178, 1108, 969, 878, 700 cm^{-1}; **^{1}H NMR** (400 MHz, $CDCl_3$): δ = 7.87−7.80 (m, 2 H), 7.78−7.71 (m, 2 H), 7.37−7.28 (m, 4 H), 7.22−7.15 (m, 1 H), 6.53−6.41 (m, 1 H), 6.24 (td, *J* = 7.0, 15.8 Hz, 0.78 H), 5.70 (td, *J* = 7.2, 11.8 Hz, 0.16 H, *Z alkene*), 4.29−4.20 (m, 2 H), 3.60−3.48 (m, 4 H), 2.62 (dq, *J* = 1.5, 6.8 Hz, 0.4 H, *Z alkene*), 2.50 (dq, *J* = 0.9, 6.7 Hz, 1.6 H), 1.95−1.77 (m, 4 H); **^{13}C NMR** (100 MHz, $CDCl_3$): δ = 163.7 (*Z alkene*), 163.5, 137.5, 137.3 (*Z alkene*), 134.3, 134.2 (*Z alkene*), 131.4, 130.3 (*Z alkene*), 128.8, 128.7 (*Z alkene*), 128.6 (*Z alkene*), 128.3, 128.0 (*Z alkene*), 127.0, 126.9, 126.5 (*Z alkene*), 125.9, 123.3, 123.3 (*Z alkene*), 108.7 (*Z alkene*), 78.1, 70.2 (*Z alkene*), 70.2, 70.1, 70.1 (*Z alkene*), 69.0 (*Z alkene*), 33.4, 30.7 (*Z alkene*), 29.1 (*Z alkene*), 25.7, 25.0, 22.4 (*Z alkene*); **HRMS-ESI** (*m*/*z*): calcd. for $C_{22}H_{24}NO_4$ $[M + H]^+$: 366.1705, found 366.1702.

*2-(9-Phenylnon-8-enyloxy)-2H-isoindoline-1,3-dione (**19d**).* To a solution of alcohol **22**[22] (640 mg, 2.93 mmol) in THF (50 mL) were sequentially added triphenylphosphine (1.15 g, 4.4 mmol) and then *N*-hydroxyphthalimide (1.06 g, 4.4 mmol). The solution was stirred until all solids were dissolved, at which point diisopropylazodicarboxylate (1.06 g, 5.27 mmol) was added via syringe pump (rate = 0.8 mL/h). The resulting yellow solution was allowed to stir overnight at ambient temperature. The reaction was quenched with H_2O (25 mL) and extracted with Et_2O (3 × 25 mL). The combined organic extracts were dried over Na_2SO_4, concentrated using rotary evaporation, and then purified by flash column chromatography (4:1 hexanes/EtOAc) to yield the title compound as a white solid (851 mg, 80%, *E*:*Z* = 73:27). The compound obtained matched literature characterization data.[22] **^{1}H NMR** (400 MHz, $CDCl_3$): δ = 7.81−7.74 (m, 2 H), 7.71−7.64 (m, 2 H), 7.31−7.18 (m, 4 H), 7.17−7.08 (m, 1 H), 6.39−6.27 (m, 1 H), 6.16 (td, *J* = 6.8, 15.7 Hz, 0.73 H), 5.60 (td, *J* = 7.3, 11.8 Hz, 0.27 H), 4.14 (q, *J* = 6.8 Hz, 2 H), 2.27 (dq, *J* = 1.5, 7.3 Hz, 0.56 H), 2.15 (q, *J* = 6.8 Hz, 1.45 H), 1.80−1.66 (m, 2 H), 1.51−1.23 (m, 8 H).

Synthesis of 19e. *4-(4-((tert-Butyldimethylsilyl)oxy)butoxy)-butan-1-ol (**24**).* To a stirring solution of alkene **23**[22] (800 mg, 3.09 mmol) in dry THF (12 mL) at 0 °C was added borane (1.0 M in THF, 5.80 mL, 5.80 mmol) dropwise, and the solution was stirred 2 h at 0 °C and then allowed to warm to ambient temperature and stirred overnight. The reaction was cooled to 0 °C, and H_2O (5 mL) was added dropwise, followed by addition of 3 N NaOH (15 mL) and H_2O_2 (15 mL). The ice bath was removed, and the resulting mixture was stirred for an additional 30 min and extracted with CH_2Cl_2 (3 × 20 mL). The organic layers were dried over Na_2SO_4, and concentrated by rotary evaporation. The product was purified using flash column chromatography (4:1 hexanes/EtOAc) to yield alcohol **24** as a colorless oil (757 mg, 88%). **IR** (neat): 3382, 2939, 2847, 1469, 1356, 1252, 1078, 839, 773, 665 cm^{-1}; **^{1}H NMR** (400 MHz, $CDCl_3$): δ = 3.60 (t, *J* = 6.2 Hz, 4 H), 3.47−3.39 (m, 4 H), 2.81 (br. s, 1 H), 1.72−1.48 (m, 8 H), 0.86 (s, 9 H), 0.02 (s, 6 H); **^{13}C NMR** (100 MHz, $CDCl_3$): δ = 70.8, 70.7, 62.8, 62.5, 30.2, 29.4, 26.8, 26.0, 25.9, 18.2, −5.4; **HRMS-ESI** (*m*/*z*): calcd. for $C_{14}H_{33}O_3Si$ $[M + H]^+$: 277.2199, found 277.2206.

*4-(4-((tert-Butyldimethylsilyl)oxy)butoxy)butyl 4-Methylbenzene-sulfonate (**25**).* To a stirring solution of **24** (645 mg, 2.33 mmol) in CH_2Cl_2(20 mL) at 0 °C were sequentially added *para*-toluenesulfonyl chloride (533 mg, 2.80 mmol) and triethylamine (0.65 mL, 4.66 mmol) and 4-(dimethylamino)pyridine (28 mg, 0.23 mmol). The resulting solution was stirred overnight. The solvent was evaporated, and the residue was diluted with Et_2O (50 mL). The resulting mixture was washed with aqueous saturated $NaHCO_3$ (10 mL) and brine (10 mL) and dried over Na_2SO_4. The organic layer was filtered and concentrated

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by rotary evaporation. The product was purified by flash column chromatography (20:1 hexanes/EtOAc) to yield the title compound (**25**) as a colorless oil (613 mg, 61%). **IR** (neat): 2923, 2854, 1264, 1215, 1191, cm^{-1}; **^{1}H NMR** (400 MHz, $CDCl_3$): δ = 7.79 (d, J = 8.2 Hz, 2 H), 7.35 (d, J = 7.9 Hz, 2 H), 4.06 (t, J = 6.5 Hz, 2 H), 3.61 (t, J = 6.1 Hz, 2 H), 3.36 (q, J = 6.1 Hz, 4 H), 2.45 (s, 3 H), 1.80−1.69 (m, 2 H), 1.61−1.49 (m, 6 H), 0.89 (s, 9 H), 0.05 (s, 6 H); **^{13}C NMR** (100 MHz, $CDCl_3$): δ = 144.6, 133.2, 129.8, 127.9, 70.8, 70.4, 69.7, 62.9, 29.5, 26.1, 25.9, 25.9, 25.7, 21.6, 18.3, −5.3; **HRMS-ESI** (m/z): calcd. for $C_{21}H_{39}O_5SSi$ $[M + H]^+$: 431.2287, found 431.2283.

*4-(4-Hydroxybutoxy)butyl-4-methylbenzenesulfonate (**26**).* To a stirred solution of **25** (570 mg, 1.33 mmol) in THF (10 mL) was added tetrabutylammonium fluoride (1.0 M in THF, 2.66 mL, 2.66 mmol). The resulting solution was stirred for 5 h before being diluted with aqueous NH_4Cl (20 mL). The aqueous layer was extracted with Et_2O (3 × 20 mL). The combined organic layers were dried over Na_2SO_4 and concentrated using rotary evaporation, and purified by column chromatography (3:2 hexanes/EtOAc) to yield the title compound (**26**) as a colorless oil (400 mg, 95%). **IR** (neat): 3411, 1215, 1191, 815 cm^{-1}; **^{1}H NMR** (400 MHz, $CDCl_3$): δ = 7.79 (d, J = 8.2 Hz, 2 H), 7.35 (d, J = 7.9 Hz, 2 H), 4.06 (t, J = 6.3 Hz, 2 H), 3.66−3.61 (m, 2 H), 3.42 (q, J = 5.9 Hz, 4 H), 2.46 (s, 3 H), 2.36 (br. s., 1 H), 1.80−1.50 (m, 8 H); **^{13}C NMR** (100 MHz, $CDCl_3$): δ =144.7, 129.8, 127.9, 126.4, 70.9, 70.3, 70.0, 62.8, 30.1, 26.8, 25.8, 25.6, 21.6; **HRMS-ESI** (m/z): calcd. for $C_{15}H_{25}O_5S$ $[M + H]^+$: 317.1423, found 317.1421.

*2-(4-((4-((tert-Butyldimethylsilyl)oxy)but-3-en-1-yl)oxy)butoxy)-isoindoline-1,3-dione (**19e**).* To a solution of oxalyl chloride (95 mg, 0.75 mmol) in dry CH_2Cl_2 (4 mL) at −78 °C was added dimethyl sulfoxide (118 mg, 1.51 mmol) dropwise over 1 min. The solution was stirred at −78 °C for 30 min, and then **26** (200 mg, 0.63 mmol) in CH_2Cl_2 (1 mL) was added dropwise over 1 min. The resulting solution was stirred for 90 min at −78 °C. Triethylamine (0.44 mL, 319 mg, 3.16 mmol) was then added, and the solution was allowed to warm to ambient temperature and stirred for 12 h. The reaction was poured into H_2O (10 mL) and extracted with CH_2Cl_2 (3 × 20 mL). The combined organic layers were washed with brine (30 mL), dried over Na_2SO_4, and concentrated using rotary evaporation to give a crude aldehyde, which was used for the next step without further purification. To a solution of crude aldehyde in CH_2Cl_2 (6 mL) at 0 °C was added *N*,*N*-diisopropylethylamine (168 mg, 1.26 mmol). To this solution was added *tert*-butyldimethyltrifluoromethanesulfonate (249 mg, 4.2 mmol) dropwise over 5 min, and the yellow solution was allowed to stir overnight at 0 °C. The reaction was quenched by addition of aqueous $NaHCO_3$ (10 mL) and extracted with CH_2Cl_2 (2 × 10 mL). The organic layers were washed with brine (10 mL), dried over Na_2SO_4, concentrated using rotary evaporation, and semipurified by column chromatography (3:2 hexanes/EtOAc) to yield a colorless oil, which was used immediately. To a stirred solution of 4-((4-((*tert*-butyldimethylsilyl)oxy)but-3-en-1-yl)oxy)butyl 4-methylbenzenesulfonate (220 mg, 0.6 mmol), *N*-hydroxyphthlamide (147 mg, 0.9 mmol) in DMF (3 mL) was added diisopropylethylamine (155 mg, 1.2 mmol). The resulting mixture then was heated to 90 °C and stirred for 2 h. The solution was cooled to room temperature and quenched with H_2O (10 mL), and extracted with Et_2O (3 × 10 mL). The combined organic layers were washed with H_2O (10 mL), aqueous $NaHCO_3$ (10 mL), and brine (10 mL) and dried over Na_2SO_4. The organic layer was filtered, concentrated by rotary evaporation, then purified by flash column chromatography (4:1 hexanes/EtOAc) to yield the title compound (**19f**) as a colorless oil (150 mg, 58% over 3 steps, *E*:*Z* = 44:56). **IR** (neat): 2925, 1995, 1737, 1261,1216, 1192 cm^{-1}; **^{1}H NMR** (400 MHz, C_6D_6): δ = 7.30 (dd, J = 3.1, 5.1 Hz, 2 H), 6.84−6.76 (m, 2 H), 6.34 (d, J = 12.3 Hz, 0.44 H, *E alkene*), 6.22 (d, J = 6.1 Hz, 0.55 H), 5.20 (td, J = 7.6, 11.9 Hz, 0.42 H, *E alkene*), 4.65 (q, J = 6.8 Hz, 0.56 H), 4.09−4.01 (m, 2 H), 3.39 (t, J = 7.0 Hz, 1.13 H, *E alkene*), 3.31 (t, J = 5.8 Hz, 1.19 H), 3.29−3.22 (m, 2 H), 2.59 (dq, J = 1.2, 7.0 Hz, 1.13 H), 2.17 (q, J = 7.1 Hz, 0.91 H, *E alkene*), 1.82−1.66 (m, 4 H), 0.95 (s, 4 H, *E alkene*), 0.93 (s, 5 H), 0.08 (s, 2.7 H, *E alkene*), 0.03 (s, 3.3 H);**^{13}C NMR** (100 MHz, C_6D_6): δ = 163.7, 142.2, 140.2, 134.1, 134.0, 129.9, 123.3, 108.6, 107.7, 78.7, 78.6, 72.0, 71.2, 70.6, 70.6, 28.9, 26.7, 26.2, 26.1, 25.9, 25.9, 25.6, 18.8, −4.8, −5.0; **HRMS-ESI** (m/z): calcd. for $C_{22}H_{34}NO_5Si$ $[M + H]^+$: 420.2206, found 420.2195.

*(Z)-2-((9-((tert-Butyldimethylsilyl)oxy)non-8-en-1-yl)oxy)isoindoline-1,3-dione (**19f**, Table 1, entry 7).* To a solution of aldehyde **27**[22] (800 mg, 2.56 mmol) and CH_2Cl_2 (14 mL) at 0 °C was added *N*,*N*-diisopropylethylamine (662 mg, 5.12 mmol). To this solution was added *tert*-butyldimethyltrifluoromethanesulfonate (1.01g, 3.84 mmol) dropwise over 5 min, and the yellow solution was allowed to warm to room temperature and stirred overnight. The reaction was quenched by addition of aqueous $NaHCO_3$ (10 mL), and extracted with CH_2Cl_2 (2 × 10 mL). The organic layers were washed with brine (10 mL), dried over Na_2SO_4, concentrated using rotary evaporation, and semipurified by column chromatography (10:1 hexanes/EtOAc) to yield a colorless oil, which was used immediately. To a solution of (*Z*)-9-((*tert*-butyldimethylsilyl)oxy)non-8-en-1-yl 4-methylbenzenesulfonate in DMF (5 mL) were added *N*-hydroxyphthalimide (248 mg, 1.51 mmol), and diisopropylethylamine (0.35 mL, 2.02 mmol). The solution was heated to 90 °C and stirred for 5 h. The reaction mixture was cooled to room temperature and quenched with H_2O (20 mL), and extracted with Et_2O (3 × 20 mL). The combined organics were washed with H_2O (20 mL) and brine (20 mL), dried over Na_2SO_4, concentrated by rotary evaporation, and purified by flash column chromatography (3:1 hexane/EtOAc) to yield *N*-alkoxyphthalimide **19f** as a colorless oil (270 mg, 33% over 2 steps, *E*:*Z* > 5:95). **IR** (neat): 2942, 2866, 1791, 1736,1654, 1466, 1398,1369, 1258, 1187, 1127, 1092 cm^{-1}; **^{1}H NMR** (400 MHz, $CDCl_3$): δ = 7.90−7.81 (m, 2 H), 7.79−7.71 (m, 2 H), 6.17 (td, J = 1.5, 5.8 Hz, 1 H), 4.44 (dt, J = 5.8, 7.2 Hz, 1 H), 4.20 (t, J = 6.8 Hz, 2 H), 2.08 (dq, J = 1.4, 7.2 Hz, 2 H), 1.85−1.74 (m, 2 H), 1.54−1.42 (m, 2 H), 1.41−1.29 (m, 6 H), 0.93 (s, 9 H), 0.12 (s, 6 H); **^{13}C NMR** (100 MHz, $CDCl_3$): δ = 163.7, 138.4, 134.4, 129.0, 123.5, 110.7, 78.7, 29.6, 29.2, 29.1, 28.1, 25.6, 25.5, 23.5, 18.3, −5.4; **HRMS-ESI** (m/z): calcd. for $C_{23}H_{35}NNaO_4Si$ $[M + Na]^+$: 440.2233, found 440.2230.

Synthesis of 19g. *4-((3-Phenylbut-3-en-1-yl)oxy)butan-1-ol (**29**).* To a dry round-bottom flask was added sodium hydride (60% wt. dispersion in mineral oil, 450 mg, 6.41 mmol), and the dispersion was washed with hexanes (3 × 5 mL). To the resulting solid was added anhydrous DMF (22 mL), and the suspension was cooled to 0 °C. **28**[44] (1.0 g, 6.75 mmol) was added dropwise over 5 min and stirred until the evolution of gas had ceased. A solution of 4-((*tert*-butyldimethylsilyl)-oxy)butyl tosylate (3.97 g, 11.07 mmol) in anhydrous DMF (2 mL) was added dropwise over 5 min. The resulting solution was heated to 75 °C, and stirred overnight. The solution was then allowed to cool to ambient temperature. The reaction was quenched with the dropwise addition of H_2O (5 mL) and extracted with Et_2O (4 × 20 mL). The combined organic layers were washed with aqueous $NaHCO_3$ (25 mL), H_2O (25 mL), and brine (25 mL) and dried over Na_2SO_4, and concentrated by rotary evaporation. The crude compound was semipurified by flash column chromatography (20:1 hexanes/Et_2O) to yield *tert*-butyl-dimethyl(4-((3-phenylbut-3-en-1-yl)oxy)butoxy)silane as a colorless oil. To a stirring solution of the silyl ether (870 mg, 2.6 mmol) in THF (5 mL) was added tetrabutylammonium fluoride (1.0 M in THF, 7.8 mL, 7.8 mmol), and the solution was stirred overnight at ambient temperature. The reaction was quenched with H_2O (5 mL) and extracted with Et_2O (3 × 15 mL). The combined organic layers were washed with H_2O (10 mL) and brine (10 mL), dried over Na_2SO_4, and concentrated by rotary evaporation. The product was purified using flash column chromatography (gradient 4:1 to 1:1 hexanes/EtOAc) to yield alcohol **29** as a colorless oil (510 mg, 39%). **IR** (neat): 3395, 2939, 2860, 1721, 1682, 1447, 1108, 1056, 700 cm^{-1}; **^{1}HNMR** (400 MHz, $CDCl_3$): δ = 7.39−7.32 (m, 2 H), 7.30−7.24 (m, 2 H), 7.23−7.18 (m, 1 H), 5.29 (d, J = 1.4 Hz, 1 H), 5.07 (q, J = 1.1 Hz, 1 H), 3.55 (t, J = 5.8 Hz, 2 H), 3.49 (t, J = 7.2 Hz, 2 H), 3.40−3.35 (m, 2 H), 2.75 (dt, J = 1.0, 7.0 Hz, 2 H), 2.71 (br. s., 1 H), 1.64−1.51 (m, 4 H); **^{13}C NMR** (100 MHz, $CDCl_3$): δ = 145.0, 140.7, 128.2, 127.3, 125.9, 113.8, 70.8, 69.5, 62.4, 35.4, 30.0, 26.5; **HRMS-ESI** (m/z): calcd. for $C_{14}H_{20}O_2Na$ $[M + Na]^+$: 243.1361, found 243.1365.

*2-(4-((3-Phenylbut-3-en-1-yl)oxy)butoxy)isoindoline-1,3-dione (**19g**).* To a solution of alcohol **29** (350 mg, 1.59 mmol) in regular THF (60 mL) were sequentially added triphenylphosphine (624 mg, 2.38 mmol) and *N*-hydroxyphthalimide (388 mg, 2.38 mmol). The solution

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was stirred until the solids were dissolved, at which point diisopropyl-azodicarboxylate (0.56 mL, 578 mg, 2.86 mmol) was added via syringe pump (0.8 mL/h). The resulting yellow solution was stirred overnight at ambient temperature, and was then quenched with H_2O (10 mL). The aqueous layer was extracted with EtOAc (3 × 30 mL), and the combined organic layers were washed with aqueous $NaHCO_3$ (3 × 25 mL), H_2O (25 mL), and brine (25 mL) and were dried over Na_2SO_4. The organic layers were concentrated using rotary evaporation and semipurified by flash column chromatography (4:1 hexanes/EtOAc) to provide the title compound (**19g**) as a colorless oil contaminated with diisopropyl 1,2-hydrazinedicarboxylate[45] (520 mg, 89%, 92% purity). which was immediately subjected to general cyclization procedure A (see details below). **^{1}H NMR** (400 MHz, $CDCl_3$): δ = 7.35 (d, J = 7.3 Hz, 2 H), 7.29 (dd, J = 3.0, 5.2 Hz, 2 H), 7.25−7.03 (m, 3 H), 6.79 (dd, J = 3.0, 5.2 Hz, 2 H), 5.32 (s, 1 H), 5.07 (s, 1 H), 4.04 (t, J = 6.2 Hz, 2 H), 3.39 (t, J = 7.0 Hz, 2 H), 3.19 (t, J = 5.9 Hz, 2 H), 2.73 (t, J = 6.9 Hz, 2 H), 1.76−1.59 (m, 4 H).

General Cyclization Procedures. *Procedure A.* To a 0.02 M solution of cyclization precursor (1 equiv) in degassed benzene at reflux was added a 0.2 M solution of tributyltin hydride (1.2 equiv) and AIBN (0.15 equiv) in degassed benzene by syringe pump (0.4 mL/h). The reaction was then stirred for an additional 1 h at reflux.

Procedure B. To a 0.02 M solution of cyclization precursor (1 equiv) in degassed d_6-benzene at 70 °C was added a 0.2 M solution of tributyltin hydride (1.8 equiv) and AIBN (0.15 equiv) in degassed d_6-benzene by syringe pump (0.3 mL/h). The reaction was then stirred for an additional 1 h at 70 °C.

Procedure C. To a 0.02 M solution of cyclization precursor (1 equiv) in degassed d_6-benzene at 60 °C was added a 0.2 M solution of tributyltin hydride (1.8 equiv) and AIBN (0.15 equiv) in degassed d_6-benzene by syringe pump (0.4 mL/h). The reaction was then stirred for an additional 1 h at 60 °C.

General Purification Procedures. The resulting solution was allowed to cool to ambient temperature, concentrated by evaporation, and semipurified by flash column chromatography to afford a mixture of cyclized products and linear alcohol as a colorless oil. The product mixture was then dissolved in CH_2Cl_2 (0.3 M) and cooled to 0 °C. *meta*-Chloroperbenzoic acid (3 equiv) was added in one portion. The resulting mixture was allowed to warm to ambient temperature and stirred overnight. The reaction was quenched with 2.0 M aq. $Na_2S_2O_3$ (10 mL), washed with saturated aqueous Na_2CO_3 (3 × 5 mL) and H_2O (5 mL), dried over Na_2SO_4, and concentrated by rotary evaporation. The cyclized products were purified by flash column chromatography. The relative stereochemistry of the cyclized products was determined using NOE experiments, and the major diastereomer is shown. Characterization for compounds **30b**, **30d**, **30**f, and **31h** have been previously reported.[8]

*Methyl((4-((2S,3S)-3-methyltetrahydrofuran-2-yl)butan-2-yl)-oxy)diphenylsilane (**30a**).* *N*-Alkoxyphthalimide **19a** (285 mg, 0.93 mmol) was subjected to general cyclization procedure A. To the crude mixture in CH_2Cl_2 (20 mL) were sequentially added triethylamine (303 mg, 3.0 mmol) and then methyldiphenylsilyl chloride (349 mg, 1.50 mmol), and the mixture was stirred overnight. The solvent was evaporated, and the residue was dissolved in Et_2O (20 mL). The organic layer was washed with aq. $NaHCO_3$ (20 mL) and brine (20 mL) and dried over Na_2SO_4, and concentrated using rotary evaporation. The crude product was purified using flash column chromatography (10:1 hexanes/EtOAc) to afford **30a** as a colorless oil (180 mg, 55%, two steps, *cis*:*trans* = 91:9). **IR** (neat): 2960, 2869, 1430, 1369, 1256, 1121, 1069, 1004, 800, 739, 700 cm^{-1}; **^{1}H NMR** (400 MHz, $CDCl_3$): δ = 7.70−7.58 (m, 4 H), 7.48−7.35 (m, 6 H), 4.11−3.86 (m, 1.92 H), 3.84−3.77 (m, 0.18 H), 3.77−3.61 (m, 1.82 H), 3.32−3.18 (m, 0.07 H), 2.28−2.00 (m, 1.92 H), 1.84−1.33 (m, 4.79 H), 1.20 (d, J = 5.8 Hz, 3 H), 1.01 (d, J = 6.8 Hz, 0.25 H), 0.94−0.83 (m, 2.72 H), 0.69 (d, J = 1.7 Hz, 3 H); **^{13}C NMR** (100 MHz, $CDCl_3$): δ = 136.8, 136.8, 134.4, 134.4, 129.6, 127.7, 81.9, 81.4, 69.7, 69.1, 65.9, 65.9, 36.7, 36.2, 35.2, 35.2, 33.8, 33.8, 27.0, 26.1, 23.8, 23.5, 14.2, 14.1, −2.3; **HRMS-ESI** (m/z): calcd. for $C_{22}H_{31}SiO_2$ [M + H]$^+$:355.2093, found 355.2102.

*3-(3-Benzyltetrahydrofuran-2-yl)propan-1-ol (**30c**).* *N*-Alkoxyphthalimide **19c** (111 mg, 0.30 mmol) was subjected to general cyclization procedure A. Purification with the general procedure and finally by flash column chromatography (4:1 hexanes/EtOAc) afforded **30c** as a colorless oil (50 mg, 75%, *cis*:*trans* = 83:17). **IR** (neat): 3381, 2934, 2869, 1608, 1500, 1460, 1386, 1352, 1256, 1065, 1021, 800, 752, 704 cm^{-1}; **^{1}H NMR** (400 MHz, $CDCl_3$): δ = 7.34−7.27 (m, 2 H), 7.24−7.15 (m, 3 H), 4.02−3.89 (m, 1.72 H), 3.87−3.81 (m, 0.28 H), 3.80−3.59 (m, 2.75 H), 3.55 (dt, J = 2.0, 8.2 Hz, 0.15 H), 2.85 (dd, J = 3.9, 12.8 Hz, 0.85 H), 2.78 (dd, J = 5.8, 13.7 Hz, 0.18 H), 2.72−2.36 (m, 2.9 H), 2.13−1.94 (m, 0.34 H), 1.94−1.82 (m, 0.96 H), 1.80−1.52 (m, 4.67 H), 1.50−1.42 (m, 0.11 H); **^{13}C NMR** (100 MHz, $CDCl_3$): δ = 140.8, 128.8, 128.7, 128.4, 126.1, 126.0, 84.1, 81.5, 66.7, 66.2, 62.9, 62.8, 46.2, 43.1, 39.0, 34.6, 32.5, 31.6, 30.5, 30.4, 29.9, 27.8; **HRMS-ESI** (m/z): calcd. for $C_{14}H_{20}O_2Na$ [M + Na]$^+$:243.1361, found 243.1363.

*(3-(2-Benzylcyclopentyl)propoxy)(tert-butyl)dimethylsilane (**30d**).* *N*-Alkoxyphthalimide **19d** (230 mg, 0.63 mmol) was subjected to general cyclization procedure A. To the crude mixture in CH_2Cl_2 (20 mL) were sequentially added triethylamine (202 mg, 2.0 mmol) and then *tert*-butyldimethylsilyl chloride (218 mg, 0.94 mmol), and the mixture was stirred overnight. The solvent was evaporated, and the residue was dissolved in Et_2O (20 mL). The organic layer was washed with aq. $NaHCO_3$ (10 mL) and brine (10 mL) and dried over Na_2SO_4, and concentrated using rotary evaporation. The crude product was purified using flash column chromatography (20:1 hexanes/EtOAc) to afford **30d** as a colorless oil (160 mg, 55%, two steps, *cis*:*trans* = 77:23). The compound obtained matched literature characterization data.[8] **^{1}H NMR** (400 MHz, $CDCl_3$):δ = 7.27 (s, 2 H), 7.22−7.13 (m, 3 H), 3.65 (t, J = 6.4 Hz, 1.52 H), 3.60 (t, J = 5.9 Hz, 0.46 H), 2.86 (dd, J = 4.4, 13.2 Hz, 0.23 H), 2.76 (dd, J = 4.6, 13.1 Hz, 0.76 H), 2.39 (dd, J = 9.1, 13.4 Hz, 0.23 H), 2.29 (dd, J = 10.4, 13.4 Hz, 0.77 H), 2.23−2.13 (m, 0.76 H), 1.95−1.83 (m, 1 H), 1.81−1.46 (m, 7 H), 1.45−1.06 (m, 3 H), 0.93 (s, 6.2 H), 0.93 (s, 2.8 H), 0.09 (s, 4.2 H), 0.08 (s, 1.8 H).

*3-(3-(((tert-Butyldimethylsilyl)oxy)methyl)tetrahydrofuran-2-yl)-propan-1-ol (**30e**).* *N*-Alkoxyphthalimide **19e** (23 mg, 0.05 mmol) was subjected to general cyclization procedure A. Purification with the general procedure and finally by flash column chromatography (3:1 hexanes/EtOAc) afforded **30e** as a solution in hexanes (8.3 mg, 60%, 3.4 M, *cis*:*trans* = 66:33). **IR** (neat): 3375, 2527, 2855, 1259, 1215, 1192, 749 cm^{-1}; **^{1}H NMR** (400 MHz, $CDCl_3$); δ = 3.79−3.43 (m, 5.76 H), 3.41−3.31 (m, 1.36 H), 2.18−2.09 (m, 0.65 H), 2.07 (t, J = 6.0 Hz, 0.34 H), 1.96 (t, J = 5.6 Hz, 0.65 H), 1.87−1.34 (m, 6.86 H), 0.96 (s, 6 H), 0.95 (s, 3 H), 0.03 (s, 4 H), 0.01 (s, 2 H); **^{13}C NMR** (100 MHz, $CDCl_3$): δ = 82.6, 81.3, 67.2, 66.5, 65.2, 63.2, 63.2, 62.9, 47.5, 44.7, 33.1, 31.7, 31.0, 29.9, 29.4, 28.0, 26.4, 18.8, 18.8, −5.0, −5.0; **HRMS-ESI** (m/z): calcd. for $C_{14}H_{30}NaO_3Si$ [M + Na]$^+$: 297.1862, found 297.1859.

*33-(2-(((tert-Butyldimethylsilyl)oxy)methyl)cyclopentyl)propan-1-ol (**30f**, Table 1, entry 6).* *N*-Alkoxyphthalimide **19f** (150 mg, 0.35 mmol) was subjected to general cyclization procedure A. Purification with the general procedure and finally by flash column chromatography (4:1 hexanes/EtOAc) afforded **30f** as a colorless oil (62 mg, 62%, *cis*:*trans* = 70:30). **IR** (neat): 3381, 2934, 2869, 1608, 1500, 1460, 1386, 1352, 1256, 1065, 1021, 800, 752, 704 cm^{-1}; **^{1}H NMR** (400 MHz, $CDCl_3$): δ = 3.68−3.57 (m, 2.73 H), 3.54 (dd, J = 5.8, 9.9 Hz, 0.34 H), 3.51−3.41 (m, 1 H), 2.13−2.00 (m, 0.75 H), 1.95−1.42 (m, 9.69 H), 1.41−1.13 (m, 3 H), 0.89 (s, 9 H), 0.04 (s, 6 H); **^{13}C NMR** (100 MHz, $CDCl_3$): δ = 66.6, 63.4, 63.3, 63.3, 47.9, 44.3, 41.9, 41.6, 32.8, 32.1, 31.8, 31.7, 31.0, 29.3, 28.1, 25.9, 25.9, 25.8, 24.4, 22.9, 18.3, 18.3, −5.3, −5.4; **HRMS-ESI** (m/z): calcd. for $C_{15}H_{32}O_2NaSi$ [M + Na]$^+$: 295.2069, found 295.2067.

*33-(2-(((tert-Butyldimethylsilyl)oxy)methyl)cyclopentyl)propan-1-ol (**30f**, Table 1, entry 7).* *N*-Alkoxyphthalimide **19f** (150 mg, 0.35 mmol) was subjected to the general cyclization procedure A. Purification with the general procedure and finally by flash column chromatography (4:1 hexanes/EtOAc) afforded **30f** as a colorless oil (62 mg, 62%, *cis*:*trans* = 75:25).

*3-(4-Phenyltetrahydro-2H-pyran-2-yl)propan-1-ol (**31g**).* *N*-Alkoxyphthalimide **19g** (212 mg, 0.58 mmol) was subjected to general cyclization procedure A. Purification with the general procedure and finally by flash column chromatography (1:1 hexanes/EtOAc) afforded **31g** as a colorless oil (126 mg, 65%, *cis*:*trans* > 5:95). **IR** (neat): 3373, 2943, 2852, 1734, 1452, 1373, 1265, 1073, 921, 800, 760,717 cm^{-1}; **^{1}H**

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NMR (400 MHz, $CDCl_3$): δ = 7.37−7.30 (m, 2 H), 7.25−7.20 (m, 3 H), 4.15 (td, J = 3.2, 11.3 Hz, 1 H), 3.73−3.56 (m, 3 H), 3.50−3.43 (m, 1 H), 2.85−2.75 (m, 1 H), 2.50 (t, J = 5.8 Hz, 1 H), 1.86−1.46 (m, 10 H); **^{13}C NMR** (100 MHz, $CDCl_3$): δ = 145.6, 128.5, 126.7, 126.3, 77.9, 68.2, 62.9, 41.7, 39.5, 33.5, 33.3, 29.3; **HRMS-ESI** (m/z): calcd. for $C_{14}H_{20}O_2Na$ $[M + Na]^+$: 243.1361, found 243.1357.

*4-(But-3-enyloxy)butan-1-ol (**40**).* To a stirring solution of sodium hydride (60% dispersion in mineral oil, 220 mg, 5.50 mmol) in anhydrous DMF (10 mL) was added 3-buten-1-ol (0.32 mL, 272 mg, 3.78 mmol). The solution was stirred for 1 h, after which a solution of 5-((*tert*-butyldimethylsilyl)oxy)pentyl 4-methylbenzenesulfonate[46] (1.03 g, 2.89 mmol) in anhydrous DMF (1.0 mL) was added. The solution was then heated to 75 °C and stirred for 1 h, and allowed to cool to ambient temperature. The reaction was quenched via the slow addition of H_2O (10 mL), followed by saturated aq. $NaHCO_3$ (10 mL). The reaction was extracted with Et_2O (3 × 20 mL), and the combined organic layers were dried over Na_2SO_4, concentrated by rotary evaporation, and semi-purified using flash column chromatography (50:1 hexanes/Et_2O) to yield ((5-(but-3-en-1-yloxy)pentyl)oxy)(*tert*-butyl)dimethylsilane as a colorless oil, which was used without further purification. To a stirring solution of ((5-(but-3-en-1-yloxy)pentyl)oxy)(*tert*-butyl)dimethylsilane (400 mg, 1.46 mmol) in THF (7 mL) was added tetrabutylammonium fluoride (1.0 M in THF, 4.4 mL, 4.4 mmol), and the solution was stirred 12 h at ambient temperature. The reaction was quenched with H_2O (10 mL) and extracted with Et_2O (3 × 10 mL). The combined organic layers were washed with H_2O (10 mL) and brine (10 mL), dried over Na_2SO_4, and concentrated by rotary evaporation. The product was purified using flash column chromatography (1:1 hexanes/EtOAc) to yield the title compound as a colorless oil (196 mg, 43% over 2 steps). **IR** (neat): 3369, 2930, 2857, 1730, 1639, 1117, 1059, 904, 791 cm^{-1}; **^{1}HNMR** (400 MHz, $CDCl_3$): δ = 5.80 (tdd, J = 6.7, 10.4, 17.2 Hz, 1 H), 5.07 (qd, J = 1.7, 17.2 Hz, 1 H), 5.03−4.99 (m, 1 H), 3.60 (t, J = 6.5 Hz, 2 H), 3.48−3.38 (m, 4 H), 2.31 (tq, J = 1.4, 6.8 Hz, 2 H), 2.07 (s, 1 H), 1.63−1.51 (m, 4 H), 1.45−1.35 (m, 2 H); **^{13}C NMR** (100 MHz, $CDCl_3$): δ = 135.4, 116.4, 70.9, 70.3, 62.8, 34.3, 32.6, 29.5, 22.6. **HRMS-ESI** (m/z): calcd. for $C_9H_{19}O_2$ $[M + H]^+$: 159.1385, found 159.1382.

*Synthesis of 2-((5-(But-3-en-1-yloxy)pentyl)oxy)isoindoline-1,3-dione (**42**).* To a solution of alcohol **40** (130 mg, 0.82 mmol) in THF (20 mL) were sequentially added triphenylphosphine (322 mg, 1.23 mmol) and then *N*-hydroxyphthalimide (200 mg, 1.23 mmol). The solution was stirred until all solids were dissolved, at which point diisopropylazodicarboxylate (0.29 mL, 297 mg, 1.47 mmol) was added via syringe pump (rate = 0.8 mL/h). The resulting yellow solution was stirred for 12 h at ambient temperature, and was then quenched with H_2O (10 mL). The aqueous layer was extracted with EtOAc (3 × 20 mL), and the combined organic layers were washed with aq. $NaHCO_3$(3 × 20 mL) and brine (20 mL) and were dried over Na_2SO_4. The organics were concentrated using rotary evaporation and purified by flash column chromatography (4:1 hexanes/EtOAc) to provide *N*-alkoxyphthalimide **42** as a colorless oil (186 mg, 69%). **IR** (neat): 2943, 2856, 1795, 1726, 1473, 1378, 1191, 1117, 982, 886, 704 cm^{-1}; **^{1}H NMR** (400 MHz, $CDCl_3$): δ = 7.83 (dd, J = 3.0, 5.2 Hz, 2 H), 7.74 (dd, J = 3.0, 5.5 Hz, 2 H), 5.82 (tdd, J = 6.7, 10.3, 17.1 Hz, 1 H), 5.08 (dd, J = 1.5, 17.1 Hz, 1 H), 5.03 (d, J = 10.1 Hz, 1 H), 4.21 (t, J = 6.7 Hz, 2 H), 3.51−3.42 (m, 4 H), 2.33 (q, J = 6.7 Hz, 2 H), 1.82 (quin, J = 7.1 Hz, 2 H), 1.72−1.51 (m, 4 H); **^{13}C NMR** (100 MHz, $CDCl_3$): δ = 163.6, 135.3, 134.4, 128.9, 123.4, 116.2, 78.4, 70.6, 70.1, 34.2, 29.3, 27.9, 22.24; **HRMS-ESI** (m/z): calcd. for $C_{17}H_{22}NO_4$ $[M + H]^+$: 304.1549, found 304.1544.

*Synthesis of 2-((5-(Allyloxy)pentyl)oxy)isoindoline-1,3-dione (**43**).* To a solution of **41**[47] (310 mg, 2.15 mmol) in THF (20 mL) were sequentially added triphenylphosphine (844 mg, 3.22 mmol) and then *N*-hydroxyphthalimide (525 mg, 3.22 mmol). The solution was stirred until all solids were dissolved, at which point diisopropylazodicarboxylate (0.76 mL, 782 mg, 3.86 mmol) was added via syringe pump (rate = 0.8 mL/h). The resulting yellow solution was stirred for 12 h at ambient temperature, and was then quenched with H_2O (10 mL). The aqueous layer was extracted with EtOAc (3 × 20 mL), and the combined organic layers were washed with $NaHCO_3$ (3 × 20 mL) and brine (20 mL) and were dried over aq. Na_2SO_4. The organics were concentrated using rotary evaporation and purified by flash column chromatography (5:1 hexanes/EtOAc) to provide *N*-alkoxyphthalimide **43** as a colorless oil (400 mg, 64%). **IR** (neat): 2943, 2860, 1791, 1730, 1465, 1365, 1191, 1126, 1078, 986, 873, 704 cm^{-1}; **^{1}H NMR** (400 MHz, $CDCl_3$): δ = 7.84−7.78 (m, 2 H), 7.76−7.70 (m, 2 H), 5.97−5.83 (m, 1 H), 5.24 (qd, J = 1.7, 17.1 Hz, 1 H), 5.17−5.10 (m, 1 H), 4.19 (t, J = 6.7 Hz, 2 H), 3.94 (td, J = 1.5, 5.5 Hz, 2 H), 3.44 (t, J = 6.3 Hz, 2 H), 1.86−1.75 (m, 2 H), 1.70−1.60 (m, 2 H), 1.60−1.50 (m, 2 H); **^{13}C NMR** (100 MHz, $CDCl_3$): δ = 163.5, 134.9, 134.3, 128.9, 123.4, 116.6, 78.3, 71.7, 70.0, 29.3, 27.9, 22.2; **HRMS-ESI** (m/z): calcd. for $C_{16}H_{20}NO_4$ $[M + H]^+$: 290.1392, found 290.1397.

*4-(3-Methyltetrahydrofuran-2-yl)butan-1-ol (**48**).* *N*-Alkoxyphthalimide **42** (100 mg, 0.30 mmol) was subjected to general cyclization procedure A. Purification with the general procedure and finally by flash column chromatography (1:1 hexanes/EtOAc) afforded **48** (major isomer) as a colorless oil (31 mg, 66%, ratio 80:20). **IR** (neat): 3385, 2934, 2870, 1709, 1458, 1375, 1055 cm^{-1}; **^{1}H NMR** (400 MHz, $CDCl_3$): δ = 3.95−3.87 (m, 1 H), 3.77−3.70 (m, 2 H), 3.67 (t, J = 6.4 Hz, 2 H), 2.30−2.17 (m, 1 H), 2.15−2.01 (m, 1 H), 1.68−1.37 (m, 8 H), 0.91 (d, J = 7.0 Hz, 3 H); **^{13}C NMR** (100 MHz, $CDCl_3$): δ = 81.6, 65.9, 62.7, 35.3, 33.9, 32.8, 30.1, 22.9, 14.2; **HRMS-ESI** (m/z): calcd. for $C_9H_{19}O_2$ $[M + H]^+$:159.1385, found 159.1382.

General Procedures for Synthesis of 53. To a 0.1 M solution of sodium hydride (60% dispersion in mineral oil, 2 equiv) in dry THF at 0 °C was added a 5 M solution of 1-((*tert*-butyldimethylsilyl)oxy)pent-4-en-2-ol (**66a**, P = TBS),[48] 1-((*tert*-butyldiphenylsilyl)oxy)pent-4-en-2-ol (**66a**, P = TBDPS),[42] or **66b** in THF dropwise over 10 min. The solution was stirred for an additional 30 min at 0 °C. Alkyl iodide or aryl iodide (2 equiv) was added dropwise over 5 min, and the solution was warmed to ambient temperature and stirred overnight. The reaction was quenched with H_2O, and the aqueous layer was extracted with EtOAc. The combined organic layers were washed with brine, dried over Na_2SO_4, and concentrated by rotary evaporation to provide ether as a colorless oil. To a stirred 0.1 M solution of ether in THF at 0 °C was added tetrabutylammonium fluoride (1.5 equiv). The mixture was allowed to warm to ambient temperature and stirred overnight. The reaction was quenched with saturated aq. NH_4Cl (10 mL) and extracted with Et_2O (3 × 20 mL). The combined organic extracts were dried over Na_2SO_4 and concentrated using rotary evaporation. Purification by flash column chromatography (3:1 hexanes/EtOAc) afforded an alcohol, which was used immediately. To 0.03 M solution of the alcohol in THF were sequentially added triphenylphosphine (1.5 equiv) and *N*-hydroxyphthalimide (1.5 equiv). The solution was stirred until the solids had dissolved, at which point diisopropylazodicarboxylate (2 equiv) was added dropwise via syringe pump (rate = 0.8 mL/h). The resulting yellow solution was stirred overnight at ambient temperature and then quenched with H_2O (20 mL). The aqueous layer was extracted with EtOAc (3 × 30 mL), and the combined organic layers were washed with $NaHCO_3$ (3 × 30 mL) and brine (30 mL) and were dried over Na_2SO_4. The organics were concentrated using rotary evaporation and purified by flash column chromatography to provide the *N*-alkoxyphthalimide.

*2-((2-(Benzyloxy)pent-4-en-1-yl)oxy)isoindoline-1,3-dione (**53a**).* Colorless oil (21% over 3 steps). **IR** (neat):3069, 2926, 2860, 1786, 1730, 1473, 1373, 1186, 1130, 1026, 991, 917, 878, 704 cm^{-1}; **^{1}H NMR** (400 MHz, $CDCl_3$): δ = 7.85−7.78 (m, 2 H), 7.77−7.70 (m, 2 H), 7.38−7.32 (m, 2 H), 7.31−7.20 (m, 3 H), 5.89 (tdd, J = 7.1, 9.9, 17.1 Hz, 1 H), 5.18 (dd, J = 1.2, 17.2 Hz, 1 H), 5.12 (d, J = 9.9 Hz, 1 H), 4.74 (d, J = 11.6 Hz, 1 H), 4.68 (d, J = 11.6 Hz, 1 H), 4.35−4.24 (m, 2 H), 3.99−3.89 (m, 1 H), 2.57−2.41 (m, 2 H); **^{13}C NMR** (100 MHz, $CDCl_3$): δ = 163.3, 138.3, 134.4, 133.6, 128.9, 128.2, 127.8, 127.5, 123.5, 118.0, 79.8, 76.5, 71.9, 35.9; **HRMS-ESI** (m/z): calcd. for $C_{20}H_{20}NO_4$ $[M + H]^+$: 338.1392, found 338.1385.

*2-((2-(Benzyloxy)pent-4-yn-1-yl)oxy)isoindoline-1,3-dione (**53b**).* Colorless oil (35% over 3 steps). **IR** (neat): 3286, 2956, 1786, 1726, 1465, 1373, 1265, 1186, 1104, 1030, 878, 804, 700 cm^{-1}; **^{1}H NMR** (400 MHz, C_6D_6): δ = 7.28 (d, J = 7.3 Hz, 2 H), 7.24 (dd, J = 3.0, 5.2 Hz, 2 H), 7.09 (t, J = 7.2 Hz, 2 H), 7.05−7.00 (m, 1 H), 6.77 (dd, J = 3.2, 5.3 Hz, 2 H), 4.51 (d, J = 11.6 Hz, 1 H), 4.45 (d, J = 11.6 Hz, 1 H), 4.38−4.24 (m, 2 H), 3.84 (quin, J = 5.4 Hz, 1 H), 2.50−2.34 (m, 2 H), 1.70 (t, J = 2.6 Hz, 1 H); **^{13}C NMR** (100 MHz, $CDCl_3$): δ = 163.4, 139.1, 134.0, 129.7,

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128.7, 128.2, 127.9, 123.4, 80.5, 79.6, 76.4, 72.4, 71.3, 21.8; **HRMS-ESI** (m/z): calcd. for $C_{20}H_{17}NaNO_4$ $[M + Na]^+$: 358.1055, found 358.1066.

*2-((2-Methoxypent-4-en-1-yl)oxy)isoindoline-1,3-dione (**53c**).* Colorless oil (13% over 3 steps). **IR** (neat): 2930, 1786, 1730, 1473, 1382, 1186, 1134, 1082, 986, 873, 717 cm^{-1}; **^{1}H NMR** (400 MHz, C_6D_6): δ = 7.29 (dd, J = 3.0, 5.2 Hz, 2 H), 6.80 (dd, J = 3.0, 5.5 Hz, 2 H), 5.78 (tdd, J = 7.0, 10.1, 17.2 Hz, 1 H), 5.06 (dd, J = 1.7, 17.5 Hz, 1 H), 5.00 (dd, J = 0.9, 10.1 Hz, 1 H), 4.22−4.14 (m, 1 H), 4.12−4.03 (m, 1 H), 3.59−3.48 (m, 1 H), 3.26 (s, 3 H), 2.30−2.22 (m, 2 H)); **^{13}C NMR** (100 MHz, $CDCl_3$): δ = 163.3, 134.4, 133.4, 128.9, 123.5, 118.0, 79.3, 78.2, 57.5, 35.2; **HRMS-ESI** (m/z): calcd. for $C_{15}H_{15}NaN_2O$ $[M + Na]^+$: 262.1082, found 262.1087.

*2-((2-Methoxypent-4-yn-1-yl)oxy)isoindoline-1,3-dione (**53d**).* Colorless oil (60%). **IR** (neat): 2982, 2926, 1791, 1734, 1473, 1382, 1269, 1182, 1108, 1030, 991, 882, 708 cm^{-1}; **^{1}H NMR** (400 MHz, C_6D_6): δ = 7.27 (dd, J = 3.0, 5.5 Hz, 2 H), 6.78 (dd, J = 3.0, 5.5 Hz, 2 H), 4.27 (d, J = 5.5 Hz, 2 H), 3.58 (quin, J = 5.5 Hz, 1 H), 3.15 (s, 3 H), 2.35−2.32 (m, 2 H), 1.68 (t, J = 2.7 Hz, 1 H); **^{13}C NMR** (100 MHz, $C_6D_6/CDCl_3$ ∼ 2/1): δ = 163.8, 134.8, 129.5, 123.9, 80.2, 79.3, 77.7, 71.2, 58.1, 21.2; **HRMS-ESI** (m/z): calcd. for $C_{14}H_{14}NO4$ $[M + H]^+$: 260.0923, found 260.0925.

*2-((2-(Ethoxy)pent-4-en-1-yl)oxy)isoindoline-1,3-dione (**53e**).* Colorless oil (35% over 3 steps). **IR** (neat): 2978, 2891, 1795, 1734, 1473, 1373, 1256, 1195, 1108, 1026, 878, 791, 704 cm^{-1}; **^{1}H NMR** (400 MHz, $CDCl_3$): δ = 7.88 (dd, J = 3.0, 5.2 Hz, 2 H), 7.79 (dd, J = 3.2, 5.3 Hz, 2 H), 5.90 (tdd, J = 7.0, 10.1, 17.2 Hz, 1 H), 5.19 (d, J = 17.1 Hz, 1 H), 5.14 (d, J = 10.1 Hz, 1 H), 4.32−4.20 (m, 2 H), 3.86−3.78 (m, 1 H), 3.75−3.60 (m, 2 H), 2.49−2.36 (m, 2 H), 1.19 (t, J = 7.0 Hz, 3 H); **^{13}C NMR** (100 MHz, C_6D_6): δ = 163.5, 134.7, 134.1, 129.8, 123.4, 118.0, 80.3, 77.4, 65.6, 36.6, 16.0; **HRMS-ESI** (m/z): calcd. for $C_{15}H_{18}NO_4$ $[M + H]^+$: 276.1234, found 276.1236.

*2-((2-Ethoxypent-4-yn-1-yl)oxy)isoindoline-1,3-dione (**53f**).* Colorless oil (35%). **IR** (neat): 2982, 2926, 1791, 1734, 1473, 1382, 1269, 1182, 1108, 1030, 991, 882, 708 cm^{-1}; **^{1}H NMR** (400 MHz, $CDCl_3$):δ = 7.90−7.82 (m, 2 H), 7.81−7.70 (m, 2 H), 4.44−4.28 (m, 2 H), 3.94−3.84 (m, 1 H), 3.75−3.58 (m, 2 H), 2.61 (dd, J = 2.7, 6.0 Hz, 2 H), 2.02 (t, J = 2.6 Hz, 1 H), 1.15 (t, J = 7.0 Hz, 3 H); **^{13}C NMR** (100 MHz, $CDCl_3$): δ =163.3, 134.5, 128.9, 123.5, 79.9, 78.9, 75.7, 70.5, 65.5, 21.1, 15.3; **HRMS-ESI** (m/z): calcd. for$C_{15}H_{15}NaNO_4$ $[M + Na]^+$: 296.0899, found 296.0897

Synthesis of 55a−g. *(4-Methyl-5-phenyltetrahydrofuran-2-yl)-methanol (**55a**).* *N*-Alkoxyphthalimide **53a** (62 mg, 0.18 mmol) was subjected to general cyclization procedure A. Purification with the general procedure and finally by flash column chromatography (4:1 hexanes/EtOAc) afforded **55a** as a colorless oil (42 mg, 74%, ratio 53:45:2). **IR** (neat): 3404, 2917, 2865, 1713, 1456, 1273, 1069, 1021, 704 cm^{-1}; **^{1}H NMR** (400 MHz, $CDCl_3$): δ = 7.31−7.15 (m, 5 H), 5.01 (d, J = 5.5 Hz, 0.02 H), 4.95 (d, J = 7.0 Hz, 0.44 H), 4.43−4.36 (m, 0.02 H), 4.36−4.29 (m, 0.09 H), 4.26 (d, J = 8.5 Hz, 0.5 H), 4.22−4.14 (m, 0.39 H), 4.12−4.03 (m, 0.4 H), 3.84−3.75 (m, 0.42 H), 3.73−3.63 (m, 1 H), 3.62−3.54 (m, 0.42 H), 3.51 (td, J = 6.0, 11.7 Hz, 0.14 H), 2.55 (spt, J = 7.2 Hz, 0.45 H), 2.21−1.89 (m, 2.45 H), 1.77−1.66 (m, 0.51 H), 1.55−1.45 (m, 0.09 H), 1.45−1.33 (m, 0.47 H), 0.95 (d, J = 6.1 Hz, 1.6 H), 0.56 (d, J = 7.0 Hz, 0.12 H), 0.54−0.49 (m, 1.33 H); **^{13}C NMR** (100 MHz, $CDCl_3$): δ = 140.7, 140.1, 128.4, 128.4, 127.9, 127.8, 127.1, 126.5, 126.4, 126.3, 88.7, 87.7, 83.9, 79.6, 79.1, 78.3, 65.8, 65.3, 65.2, 43.8, 42.0, 37.6, 36.8, 36.2, 35.4, 16.6, 16.2, 15.3; **HRMS-ESI** (m/z): calcd. for $C_{12}H_{16}NaO_2$ $[M + Na]^+$: 215.1048, found 215.1046.

*(4-Methylene-5-phenyltetrahydrofuran-2-yl)methanol (**55b**).* *N*-Alkoxyphthalimide **53b** (70 mg, 0.21 mmol) was subjected to general cyclization procedure A. Solvent was evaporated and the mixture was purified by flash column chromatography (4:1 hexanes/EtOAc) to afford **55b** as a colorless oil (28 mg, 70%, *cis*:*trans* > 95:5). **IR** (neat): 3391, 2921, 1717, 1447, 1260, 1095, 1026, 800,700 cm^{-1}; **^{1}H NMR** (400 MHz, C_6D_6): δ = 7.33−7.27 (m, J = 6.8 Hz, 2 H), 7.21−7.00 (m, 3 H), 5.11 (s, 1 H), 4.82 (q, J = 2.2 Hz, 1 H), 4.60 (q, J = 2.0 Hz, 1 H), 3.92−3.82 (m, 1 H), 3.59 (ddd, J = 3.1, 6.4, 11.7 Hz, 1 H), 3.41 (td, J = 5.9, 11.4 Hz, 1 H), 2.45−2.33 (m, 1 H), 2.21 (dd, J = 6.4, 15.6 Hz, 1 H), 1.56 (t, J = 6.5 Hz, 1 H); **^{13}C NMR** (100 MHz, $CDCl_3$): δ = 151.3, 141.0, 128.5, 128.1, 127.3, 107.6, 83.9, 78.8, 64.4, 34.5; **HRMS-ESI** (m/z): calcd. for $C_{12}H_{15}O_2$ $[M + H]^+$: 191.1072, found 191.1074.

*tert-Butyl((4-methyltetrahydrofuran-2-ol)methoxydiphenylsilane (**55c**).* *N*-Alkoxyphthalimide **53c** (88 mg, 0.33 mmol) was subjected to general cyclization procedure A. To the crude mixture were sequentially added imidazole (45 mg, 0.66 mmol) and then *tert*-butyldiphenylsilyl chloride (137 mg, 0.50 mmol), and the mixture was stirred overnight. The solvent was evaporated, and the residue was dissolved in Et_2O (50 mL). The organic layers were washed with brine (20 mL) and dried over Na_2SO4, and concentrated using rotary evaporation. The crude product was purified using flash column chromatography (4:1 hexanes/EtOAc) to afford **55c** as a colorless oil (28 mg, 20%, two steps, *cis*:*trans* > 95:5). **IR** (neat): 2969, 2921, 2856, 1739, 1478, 1434, 1117, 708 cm^{-1}; **^{1}H NMR** (300 MHz, C_6D_6): δ = 7.91−7.80 (m, 4 H), 7.27−7.20 (m, 6 H), 4.11−4.00 (m, 1 H), 3.86−3.66 (m, 3 H), 3.29 (t, J = 8.2 Hz, 1 H), 2.07−1.90 (m, 1 H), 1.82−1.70 (m, 1 H), 1.27−1.13 (m, 10 H), 0.79 (d, J = 6.6 Hz, 3 H); **^{13}C NMR** (100 MHz, $C_6D_6/CDCl_3$ ∼2/1): δ = 136.4, 134.4, 130.2, 128.3, 80.8, 77.7, 75.5, 67.3, 37.2, 35.0, 27.5, 19.9, 17.5; **HRMS-ESI** (m/z): calcd. for $C_{22}H_{30}NaSiO_2$ $[M + Na]^+$: 377.1913, found 377.1911.

*tert-Butyl((4-methylenetetrahydrofuran-2-yl)methoxy)diphenylsilane (**55d**).* *N*-Alkoxyphthalimide **53d** (160 mg, 0.61 mmol) was subjected to general cyclization procedure A. To the crude mixture were sequentially added imidazole (81 mg, 1.2 mmol), and then *tert*-butyldiphenylsilyl chloride (202 mg, 0.74 mmol), and the mixture was stirred overnight. The solvent was evaporated, and the residue was dissolved in Et_2O (50 mL). The organic layer was washed with brine (20 mL) and dried over Na_2SO_4, and concentrated using rotary evaporation. The crude product was purified using flash column chromatography (25:1 hexanes/EtOAc) to afford **55d** as a colorless oil (60 mg, 25%, two steps). **IR** (neat): 2982, 2926, 1791, 1734, 1473, 1382, 1269, 1182, 1108, 1030, 991,882, 708 cm^{-1}; **^{1}H NMR** (400 MHz, C_6D_6): δ = 7.84−7.77 (m, 4 H), 7.23 (t, J = 2.9 Hz, 6 H), 4.83 (quin, J = 2.2 Hz, 1 H), 4.70 (t, J = 2.1 Hz, 1 H), 4.36−4.28 (m, 1 H), 4.21−4.14 (m, 1 H), 4.10−4.03 (m, 1 H), 3.71 (dd, J = 2.6, 4.7 Hz, 2 H), 2.37−2.31 (m, 2 H), 1.17 (s, 9 H); **^{13}C NMR** (100 MHz, $CDCl_3$): δ = 147.9, 135.6, 133.6, 129.6, 127.6, 104.2, 79.8, 71.3, 66.0, 34.9, 26.8, 19.2; **HRMS-ESI** (m/z): calcd. for $C_{22}H_{28}NaSiO_2$ $[M + Na]^+$:375.1756, found 375.1753.

*tert-Butyl((4,5-dimethyltetrahydrofuran-2-yl)methoxy)diphenylsilane (**55e**).* *N*-Alkoxyphthalimide **53e** (250 mg, 0.91 mmol) was subjected to general cyclization procedure C. To the crude mixture were sequentially added imidazole (116 mg, 1.7 mmol) and then *tert*-butyldiphenylsilyl chloride (370 mg, 1.36 mmol), and the mixture was stirred overnight. The solvent was evaporated, and the residue was dissolved in Et_2O (50 mL). The organic layer was washed with brine (20 mL), dried over Na_2SO_4, and concentrated using rotary evaporation. The crude product was purified using flash column chromatography (30:1 hexanes/Et_2O) to afford **55e** (major isomer) as a colorless oil (200 mg, 62%, two steps, ratio 93:7 mixture of isomers). **IR** (neat): 2965, 2921, 2843, 1469, 1426, 1378, 1265, 1113, 830, 795, 739, 704 cm^{-1}; **^{1}H NMR** (400 MHz, C_6D_6): δ = 7.90−7.81 (m, 4 H), 7.26−7.21 (m, 6 H), 4.04−3.95 (m, 1 H), 3.92 (quin, J = 6.5 Hz, 1 H), 3.81−3.73 (m, 2 H), 2.01−1.89 (m, 1 H), 1.78 (td, J = 7.2, 12.3 Hz, 1 H), 1.28 (td, J = 8.0, 12.4 Hz, 1 H), 1.20 (s, 9 H), 1.03 (d, J = 6.4 Hz, 3 H), 0.73 (d, J = 7.0 Hz, 3 H); **^{13}C NMR** (100 MHz, $CDCl_3$): δ = 135.7, 135.7, 133.8, 133.7, 129.5, 127.6, 78.8, 77.6, 67.0, 36.2, 35.9, 26.8, 19.2, 16.8, 14.9; **HRMS-ESI** (m/z): calcd. for $C_{23}H_{32}NaSiO_2$ $[M + Na]^+$:391.2069, found 391.2064.

*tert-Butyl((5-methyl-4-methylenetetrahydrofuran-2-yl)methoxy)-diphenylsilane (**55f**).* *N*-Alkoxyphthalimide **53f** (100 mg, 0.36 mmol) was subjected to general cyclization procedure A. To the crude mixture were sequentially added imidazole (49 mg, 0.73 mmol) and then *tert*-butyldiphenylsilyl chloride (120 mg, 0.44 mmol), and the mixture was stirred overnight. The solvent was evaporated, and the residue was dissolved in Et_2O (30 mL). The organic layer was washed with brine (20 mL) and dried over Na_2SO_4, and concentrated using rotary evaporation. The crude product was purified using flash column chromatography (25:1 hexanes/EtOAc) to afford **55f** as a colorless oil (60 mg, 25%, two steps, *cis*:*trans* = 85:15). **IR** (neat): 2982, 2926, 1791, 1734, 1473, 1382, 1269, 1182, 1108, 1030, 991,882, 708 cm^{-1}; **^{1}H NMR** (400 MHz, C_6D_6):δ = 7.87−7.78 (m, 4 H), 7.25−7.20 (m, 6 H), 4.85−4.79 (m, 1

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H), 4.69 (q, J = 2.1 Hz, 1 H), 4.56−4.47 (m, 0.17 H), 4.32 (s, 0.80 H), 4.16 (s, 0.17 H), 3.98 (tdd, J = 4.5, 6.7, 8.7 Hz, 0.82 H), 3.80−3.72 (m, 1.67 H), 3.68 (dd, J = 3.5, 4.7 Hz, 0.31 H), 2.47−2.35 (m, 1.82 H), 2.35−2.31 (m, 0.17 H), 1.27 (d, J = 6.4 Hz, 2.55 H), 1.23 (d, J = 6.4 Hz, 0.89 H), 1.18 (s, 7.4 H), 1.17 (s, 2.1 H); **^{13}C NMR** (100 MHz, $CDCl_3$): δ = 152.7, 135.7, 135.6, 135.6, 133.7, 133.6, 129.6, 129.6, 127.6, 127.6, 104.2, 104.1, 78.1, 77.2, 77.2, 66.1, 66.1, 35.4, 34.8, 26.8, 20.8, 20.5, 19.3; **HRMS-ESI** (m/z): calcd. for$C_{15}H_{30}NaO_2Si$ $[M + Na]^+$: 293.1913, found 293.1913.

*3-Vinyl Hexanol (**60**).* To a solution of methyl 3-vinylhexanoate[49] (174 mg, 1.1 mmol, 1 equiv) in Et_2O (11 mL) cooled to 0 °C (ice/water bath) was added lithium aluminum hydride (64 mg, 1.7 mmol, 1.5 equiv) in small portions over 30 s. The gray suspension was stirred for 30 min, and then quenched with the slow addition of Na_2SO_4 decahydrate (1 g) over 3 min (violent bubbling observed during quenching). The suspension was filtered through a plug of $MgSO_4$, and the solids were washed with Et_2O (5 × 40 mL). The combined organic extracts were concentrated by rotary evaporation to yield 100 mg (70%) of alcohol **60** as a colorless oil. **IR** (neat): 3331, 3076, 2958, 2930, 1640, 1466, 1458, 1419, 1379, 1046, 995, 912 cm^{-1}; **^{1}H NMR** (400 MHz, C_6D_6): δ = 5.49−5.32 (m, 1H), 4.94 (s, 1H), 4.93−4.88 (m, 1H), 3.47−3.33 (m, 2H), 2.12−1.96 (m, 1H), 1.51−1.40 (m, 1H), 1.36−1.07 (m, 5H), 0.86 (t, J = 7.0 Hz, 3H), 0.64 (bs, 1H); **^{13}C NMR** (100 MHz, C_6D_6): δ = 143.6, 115.0, 61.2, 41.3, 38.6, 38.0, 20.9, 14.6; **HRMS-ESI** (m/z): $[M + H]^+$ calcd for $C_8H_{17}O$: 129.1279, found: 129.1277.

*Synthesis of 2-(3-Vinylhexyloxy)isoindoline-1,3-dione (**61**).* To 3-vinyl hexanol **60** (98 mg, 0.77 mmol, 1.0 equiv) were added *N*-hydroxyphthalimide (189 mg, 1.16 mmol, 1.5 equiv), triphenylphosphine (301 mg, 1.16 mmol, 1.5 equiv), and THF (7.7 mL). The solution was cooled to 0 °C (ice/water bath), and diisopropylazodicarboxylate (280 mL, 1.4 mmol, 1.8 equiv) was added dropwise over 10 min. The colorless solution turned to an orange-red solution during addition. The reaction was stirred for 18 h and allowed to warm to ambient temperature. The light-yellow solution was poured into Et_2O (75 mL), and washed with 50% saturated aq. $NaHCO_3$ (2 × 25 mL) and brine (25 mL). The yellow organic extract was dried over Na_2SO_4, filtrated, and concentrated by rotary evaporation to provide a yellow oil. Purification by flash chromatography (7:2 hexanes:Et_2O), followed by crystallization from cold pentanes (−10 °C), yielded two crops of *N*-alkoxyphthalimide **61** (156 mg combined, 74%) as fluffy white needles. **mp** 44−45.5 °C; **IR** ($CHCl_3$): 3683, 3621, 1790, 1732, 1468, 1188, 878, 703 cm^{-1}; **^{1}H NMR** (400 MHz, C_6D_6): δ = 7.30 (dd, J = 5.4, 3.0 Hz, 2H), 6.80 (dd, J = 5.4, 3.0 Hz, 2H), 5.41−5.26 (m, 1H), 5.10 (dd, J = 17.1, 1.8 Hz, 1H), 4.99 (dd, J = 10.3, 1.8 Hz, 1H), 4.29−3.90 (m, 2H), 2.41−2.13 (m, 1 H), 1.88−1.74 (m, 1H), 1.55−1.40 (m, 1H), 1.38−1.06 (m, 4H), 0.85 (t, J = 7.0 Hz, 1H); **^{13}C NMR** (100 MHz, C_6D_6): δ = 163.7, 142.5, 134.1, 129.8, 123.4, 116.0, 77.1, 40.9, 37.8, 33.9, 20.9, 14.6; **HRMS-ESI** (m/z): $[M + Na]^+$ calcd for $C_{16}H_{19}NO_3Na$: 296.1263, found: 296.1265.

*1-((tert-Butyldimethylsilyl)oxy)-5-(triethylsilyl)pent-4-yn-2-ol (**66b**).* To a solution of triethylsilylacetylene (1.11 g, 7.95 mmol) in dry THF (20 mL) at −78 °C was added a solution of butyllithium (1.6 M in hexanes, 5.0 mL, 7.95 mmol) dropwise over 10 min. The solution was stirred for an additional 30 min at −78 °C. Boron trifluoride diethyl etherate (1.0 mL, 1.13 g, 7.95 mmol) was added dropwise over 5 min, and the solution was stirred for another 20 min. A solution of *tert*-butyldimethyl(oxiran-2-ylmethoxy)silane (1.0 g, 5.3 mmol) in anhydrous THF (2.6 mL) was then added dropwise over 5 min. The resulting mixture was stirred for 1 h. The reaction was quenched with saturated aq. NH_4Cl (25 mL) and extracted with EtOAc (3 × 25 mL). The combined organic extracts were washed with brine (25 mL), dried over Na_2SO_4, concentrated by rotary evaporation, and purified by flash chromatography (20:1 hexanes/EtOAc) to afford 1-((*tert*-butyldimethylsilyl)oxy-5-(triethylsilyl)pent-4-yn-2-ol as a colorless oil (1.44 g, 83%). **IR** (neat): 3421, 2956, 2873, 2169, 1460, 1265, 1121, 1017, 852, 817, 773, 717 cm^{-1}; **^{1}H NMR** (400 MHz, $CDCl_3$): δ = 3.74−3.63 (m, 2H), 3.64−3.68 (m, 1H), 2.43−2.56 (m, 3H), 0.99 (t, J = 8.0 Hz, 9 H), 0.92 (s, 9 H), 0.59 (q, J = 8.0 Hz, 6 H), 0.09 (s, 6H); **^{13}C NMR** (100 MHz, $CDCl_3$): δ = 103.7, 84.3, 70.2, 65.4, 25.8, 24.5, 18.3, 7.45, 4.43, −5.41, −5.44; **HRMS-ESI** (m/z): calcd. for $C_{17}H_{37}Si_2O_2$ $[M + H]^+$: 329.2332, found 329.2327.

*2-(Benzyloxy)pent-4-en-1-yl-4-methylbenzenesulfonate (**69a**).* To a stirring solution of 2-(benzyloxy)pent-4-en-1-ol[50] (170 mg, 0.88 mmol) in dry CH_2Cl_2 (5 mL) were sequentially added *para*-toluenesulfonyl chloride (202 mg, 1.06 mmol) and then triethylamine (0.24 mL, 1.76 mmol). The resulting solution was stirred overnight. H_2O (5 mL) was added, and the reaction mixture was stirred for another 10 min. The organic layer was washed with aqueous saturated aq. $NaHCO_3$ (5 mL), H_2O (5 mL), and brine (5 mL) and dried over Na_2SO_4. The organic layer was filtered and concentrated by rotary evaporation. The product was purified by flash column chromatography (10:1 hexanes/EtOAc) to yield the title compound (**69a**) as a colorless oil (254 mg, 83%). **IR** (neat): 2926, 1726, 1595, 1447, 1356, 1173, 1091, 978, 913, 813 cm^{-1}; **^{1}H NMR** (400 MHz, $CDCl_3$): δ = 7.75 (d, J = 7.9 Hz, 2H), 7.31−7.22 (m, 7H), 5.75−5.65 (m, 1H), 5.05 (d, J = 5.8 Hz, 1H), 5.01 (s, 1H), 4.50 (s, 2 H), 4.07−3.97 (m, 2 H), 3.65 (quin, J = 5.5 Hz,1H), 2.41 (s, 3 H), 2.27 (t, J = 6.5 Hz,2H); **^{13}C NMR** (100 MHz, $CDCl_3$): δ = 144.8, 137.9, 133.0, 132.9, 129.8, 128.3, 127.9, 127.7, 127.7, 118.2, 75.9, 72.0, 70.9, 35.6, 21.6; **HRMS-ESI** (m/z): calcd. for $C_{19}H_{22}NaSO_4$ $[M + Na]^+$: 369.1137, found 369.1131.

*Synthesis of (R)-1-((tert-Butyldiphenylsilyl)oxy)-5-(triethylsilyl)-pent-4-yn-2-ol (**72**).* To a solution of triethylsilylacetylene (3.45 g, 24.1 mmol) in dry THF (70 mL) at −78 °C was added a solution of butyllithium (1.6 M in hexane, 15 mL, 24.1 mmol) dropwise over 10 min. The solution was stirred for an additional 10 min at −78 °C. Boron trifluoride diethyl etherate (3.0 mL, 3.43 g, 24.1 mmol) was added dropwise over 5 min, and the solution was stirred for an additional 20 min. A solution of epoxide **71**[51] (5.0 g, 16.1 mmol) in anhydrous THF (30 mL) was then added dropwise over 10 min. The resulting mixture was stirred for 2 h at −78 °C. The reaction was quenched with saturated aqueous NH_4Cl (25 mL) and extracted with EtOAc (3 × 25 mL). The combined organic extracts were washed with brine (25 mL), dried over Na_2SO_4, concentrated by rotary evaporation, and purified by flash chromatography (20:1 hexanes/EtOAc) to afford alcohol **72** (with trace amounts of EtOAc) as a colorless oil (6.47 g, 88%). $[\alpha]_D^{21}$ − 10.5 (*c* 1.56, $CHCl_3$); **IR** (neat): 3447, 3069, 3043, 2956, 2926, 2869, 2173, 1469, 1421, 1260, 1113, 1004, 821, 739, 695, 621 cm^{-1}; **^{1}H NMR** (400 MHz, $CDCl_3$): δ = 7.68 (d, J = 7.5 Hz, 4 H), 7.50−7.35 (m, 6 H), 3.90 (sxt, J = 5.6 Hz, 1 H), 3.81 (dd, J = 4.4, 10.2 Hz, 1 H), 3.72 (dd, J = 6.1, 9.9 Hz, 1 H), 2.62−2.48 (m, 3 H), 1.09 (s, 9 H), 0.95 (t, J = 7.9 Hz, 9 H), 0.55 (q, J = 7.7 Hz, 6 H); **^{13}C NMR** (100 MHz, $CDCl_3$): δ = 135.5, 135.5, 133.1, 133.1, 129.8, 127.8, 103.5, 84.4, 70.3, 66.4, 26.8, 24.7, 19.3, 7.4, 4.4; **HRMS-ESI** (m/z): calcd. for $C_{27}H_{40}NaSi_2O_2$ $[M + Na]^+$: 475.2465, found 475.2470.

*Synthesis of (R)-2-(4-(Trityloxy)butoxy)pent-4-yn-1-ol (**74**).* To a suspension of sodium hydride (60 wt % dispersion in mineral oil, 247 mg, 6.18 mmol) in anhydrous DMF (12 mL) was added **72** (1.87 g, 4.12 mmol) in anhydrous DMF (2 mL). This solution was stirred for 1 h at ambient temperature. 4-(Trityloxy)butyl-4-methylbenzenesulfonate[52] (2.06 g, 4.12 mmol) in anhydrous DMF (10 mL) was added dropwise in 60 min. The resulting solution was stirred overnight. The reaction was quenched with H_2O (25 mL), and the aqueous layer was extracted with Et_2O (3 × 30 mL). The combined organic extracts were washed with brine (15 mL), dried over Na_2SO_4, and concentrated by rotary evaporation. The crude product was used in the next step without further purification. To a solution of the resulting mixture in anhydrous THF (20 mL) was added tetrabutylammonium fluoride (1.0 M in THF, 6.8 mL, 6.8 mmol), and the reaction was stirred for 12 h. The reaction was quenched with saturated aqueous NH_4Cl (10 mL) and extracted with Et_2O (3 × 20 mL). The combined organic extracts were washed with brine (20 mL), dried over Na_2SO_4, and concentrated using rotary evaporation. Purification by flash column chromatography (5:1 hexanes/EtOAc) afforded alcohol **74** as a clear oil (440 mg, 48% over 2 steps). $[\alpha]_D^{21}$ − 4.5 (*c* 1.23, $CHCl_3$); **IR** (neat): 3430, 3295, 3086, 3052, 3021, 2921, 2860, 1491,1443, 1213, 1073, 752, 708, 634 cm^{-1}; **^{1}H NMR** (400 MHz, C_6D_6): δ = 7.56 (d, J = 7.5 Hz, 6 H), 7.14 (t, J = 7.9 Hz, 6 H), 7.08−7.00 (m, 3 H), 3.63−3.45 (m, 2 H), 3.27−3.17 (m, 2 H), 3.16−3.03 (m, 3 H), 2.18 (dd, J = 2.7, 6.5 Hz, 2 H), 1.70 (t, J = 2.7 Hz, 1 H), 1.68−1.46 (m, 5 H); **^{13}C NMR** (100 MHz, C_6D_6): δ = 145.4, 129.5,

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128.4, 127.5, 87.2, 81.3, 79.0, 70.8, 69.9, 64.1, 63.9, 27.5, 27.4, 21.1; **HRMS-ESI** (m/z): calcd. for $C_{28}H_{30}NaO_3$ $[M + Na]^+$: 437.2093, found 437.2102.

*(R)-2-((2-(4-(Trityloxy)butyoxy)pent-4-yn-1-yl)oxy)isoindoline-1,3-dione (**75**).* To the alcohol **74** (100 mg, 0.24 mmol) in dry THF (2 mL) were sequentially added triphenylphosphine (90 mg, 0.34 mmol) and *N*-hydroxyphthalimide (55 mg, 0.34 mmol). The solution was stirred until the solids were dissolved, at which point diisopropylazodicarboxylate (83 mg, 0.41 mmol) was added dropwise via syringe pump (0.8 mL/h). The resulting yellow solution was stirred overnight at ambient temperature, and was then quenched with H_2O (2 mL). The aqueous layer was extracted with EtOAc (3 × 10 mL), and the combined organic extracts were washed with aq. $NaHCO_3$ (3 × 10 mL) and brine (10 mL) and were dried over Na_2SO_4. The organics were concentrated using rotary evaporation and purified by flash column chromatography (5:1 hexanes/EtOAc) to provide *N*-alkoxyphthalimide **75** as a colorless oil (107 mg, 80%). $[\alpha]_D^{21}$ − 6.5 (*c* 2.56, $CHCl_3$); **IR** (neat): 3282, 2947, 2865, 1800, 1730, 1443, 1373, 1186, 1078, 1078, 1008, 878, 704 cm^{-1}; **^{1}H NMR** (400 MHz, $CDCl_3$): δ = 7.85−7.79 (m, 2 H), 7.73−7.69 (m, 2 H), 7.45−7.39 (m, 6 H), 7.32−7.27 (m, 5 H), 7.25−7.19 (m, 3 H), 4.39−4.26 (m, 2 H), 3.86−3.78 (m, 1 H), 3.60−3.51 (m, 2 H), 3.01 (t, *J* = 5.6 Hz, 2 H), 2.61−2.54 (m, 2 H), 1.99 (t, *J* = 2.7 Hz, 1 H), 1.61 (d, *J* = 5.8 Hz, 4 H); **^{13}C NMR** (100 MHz, $CDCl_3$): δ = 163.3, 144.4, 134.4, 128.9, 128.7, 127.7, 126.8, 123.5, 86.2, 79.9, 78.7, 75.8, 70.5, 69.9, 63.1, 26.7, 26.5, 21.0; **HRMS-ESI** (m/z): calcd. for $C_{36}H_{33}NaNO_5$ $[M + Na]^+$: 582.2256, found 582.2249.

*((2R,5R)-4-Methylene-5-(3-trityloxy)propyl)tetrahydrofuran-2-yl)-methanol (**76**).* *N*-Alkoxyphthalimide **75** (170 mg, 0.30 mmol) was subjected to general cyclization procedure C. Solvent was evaporated, and the mixture was purified by flash column chromatography (3:2 hexanes/Et_2O) afforded **76** as a colorless oil (78 mg, 60%, *cis*:*trans* > 95:5). $[\alpha]_D^{21}$ + 8.65 (*c* 10.5, $CHCl_3$); **IR** (neat): 3413, 2965, 2917, 2847, 1737, 1447, 1265, 1073 cm^{-1}; **^{1}H NMR** (400 MHz, C_6D_6): δ = 7.60−7.56 (m, 6 H), 7.12 (t, *J* = 7.5 Hz, 6 H), 7.06−7.00 (m, 3 H), 4.78 (q, *J* = 2.0 Hz, 1 H), 4.67 (q, *J* = 2.3 Hz, 1 H), 4.20−4.15 (m, 1 H), 3.74−3.67 (m, 1 H), 3.55−3.48 (m, 1 H), 3.34−3.26 (m, 1 H), 3.21 (t, *J* = 6.4 Hz, 2 H), 2.28−2.18 (m, 1 H), 2.09 (dd, *J* = 6.1, 15.8 Hz, 1 H), 1.96−1.84 (m, 1 H), 1.82−1.66 (m, 2 H), 1.62−1.44 (m, 2 H); **^{13}C NMR** (100 MHz, C_6D_6): δ = 152.3, 145.4, 129.5, 128.3, 127.5, 104.9, 87.3, 81.4, 78.9, 64.8, 64.3, 35.1, 32.7, 26.9; **HRMS-ESI** (m/z): calcd. for $C_{28}H_{30}NaO_3$ $[M + Na]^+$: 437.2093, found 437.2102.

■ ASSOCIATED CONTENT

Ⓢ Supporting Information

Complete characterization analysis and ^{1}H and ^{13}C spectral data is included in the Supporting Information. 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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