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The allenic Alder-ene reaction: constitutional group selectivity and its application to the synthesis of ovalicin

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Abstract—The scope of the novel allenic Alder-ene reaction using Rh(I) and Ir(I) catalysts has been extended to differentially substituted 1,1,3-trisubstituted allenes. This allenyl substitution pattern can give three possible cross-conjugated triene products. The selectivity of this transformation can be controlled by varying reaction temperature, solvent, and catalyst. Progress toward the synthesis of ovalicin using this triene forming protocol is described.

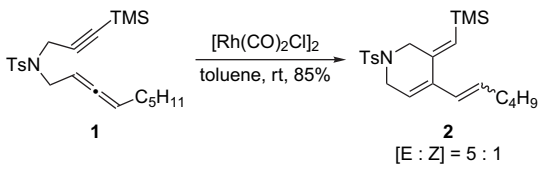
1. Introduction

Transition metal-catalyzed carbon–carbon bond formation is an efficient method to rapidly increase molecular complexity via skeletal reorganization and/or cycloaddition processes.[1] The mild conditions, functional group compatibility, and high regio- and stereoselectivities of these transition metal-catalyzed reactions are just a few reasons for their prominence in natural product synthesis. Transition metal-catalyzed cycloisomerizations such as the formal Alder-ene reaction utilize functionalized enynes or allenynes to access a unique array of cyclic structures.[2] For example, Trost[3] has worked extensively on the intramolecular Alder-ene reaction of 1,6-enynes using palladium or ruthenium to obtain 1,3- or 1,4-dienes, respectively. Ruthenium gives exclusively the 1,4-diene regioisomer while palladium gives regioisomeric ratios dependent on the substrate structure. Trost has also used ruthenium to effect an intermolecular Alder-ene allene–ene coupling to give diene substrates.[4] Buchwald[5] and Takacs[6] formed 1,4-dienes from enynes selectivity using either titanium or iron catalysts, respectively.

Intramolecular Alder-ene reactions of allene–ynes are not as widely studied and only a few examples are known. Both Malacria[7] and Livinghouse[8] used cobalt to effect an intramolecular allenic Alder-ene reaction. Malacria used this cycloisomerization reaction in a synthesis of steroidal analogs,[9] while the triene was obtained as a by-product in 33% yield by Livinghouse. Sato[10] demonstrated an allenic Alder-ene reaction using stoichiometric amounts of titanium.

Recently, rhodium has stepped into the limelight and proven itself as a useful and powerful transition metal catalyst for the Alder-ene reaction.[11] In 2000, Zhang demonstrated the first Rh(I)-catalyzed Alder-ene reaction with 1,6-enynes, yielding 1,4-dienes.[12] Rhodium was beneficial over ruthenium, cobalt, or iron because reactions could be performed at room temperature and the ligands on the catalyst could be easily tuned to accommodate steric or electronic factors in the substrates.[13]

We have previously reported the reaction of Rh(I) with allenynes to produce cross-conjugated trienes. One example is shown in Scheme 1, where allenyne **1** affords an 85% yield of triene **2**.[14] This formal allenic Alder-ene reaction is unique from others because the reaction conditions are used to direct which double bond of the allene reacts. For example, Malacria[7] and Sato[10] reported the same reactivity pattern using cobalt and titanium, respectively; however, π-bond selectivity was obtained using substrate control (sterics and ring strain).[15] Rhodium, unlike other transition metals, was found to give selective cyclization with the distal double bond of the allene regardless of the substitution pattern on the allene or tether length.[16]



1 **2**
[E : Z] = 5 : 1

Scheme 1. Rh(I)-catalyzed allenic Alder-ene reaction.

Cross-conjugated trienes are seldom found in the literature, which may be attributed to a lack of general procedures for

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the formation of these highly unsaturated systems.[17] Brummond et al. have shown that the formal Alder-ene reaction gives high yields of trienes with moderate *E*/*Z* selectivity for a variety of substrates and that rhodium biscarbonyl chloride dimer is a general catalyst. The *E*/*Z* selectivity was increased by changing the neutral Rh(I) catalyst to a cationic Rh(I) or Ir(I) catalyst; altering selectivity from 5:1 to 13:1 or 99:1, respectively.[14]

The high yields and mild conditions of the Rh(I)-catalyzed allenic Alder-ene reaction motivated us to examine its value in natural product synthesis. The application of this carbocyclization process to the ovalicin/fumagillol class of sesquiterpenoids was the most exciting, due in part to the potentially rapid access to the entire carbocyclic skeleton and the interesting biological activity associated with these compounds (Fig. 1).

Fumagillin (**5**), ovalicin (**4**), and analogs of these compounds have been shown to inhibit angiogenesis in vivo.[18] Angiogenesis is essential for tumor growth and by suppressing this process the tumor does not grow beyond a few cubic millimeters, nor does it metastasize.[19] Fumagillol (**3**) and the analog TNP-470 (**6**) have been found to have an inhibitory effect on the growth and metastasis of various cancers including breast, colon, gastric, renal, ovarian, and prostate.[20] It is known that endothelial cells play a necessary role in angiogenesis, and both ovalicin and TNP-470 were found to inhibit endothelial cell proliferation. However, the mechanism of action for this inhibition is still unclear. Clardy[21] illustrated that fumagillin, ovalicin, and TNP-470 covalently bind to a cobalt-containing enzyme called methionine amino peptidase (MetAP-2), but do not bind to the closely related MetAP-1. It is significant that this binding is selective since inhibition of both MetAP-1 and MetAP-2 is lethal.[22] Methionine amino peptidase-2 removes methionine residues from the N-termini of proteins in a critical co-translational processing event and there is a strong correlation between inhibition of endothelial cell proliferation and inhibition of MetAP-2.[23] However, the significance of the binding is still under great debate since recently it was reported that MetAP-2 function is independent of endothelial cell production.[24] Despite the enigmatic mechanisms of action for these natural products, they are still under investigation in the biological and clinical sector and are synthetically popular targets.[25]

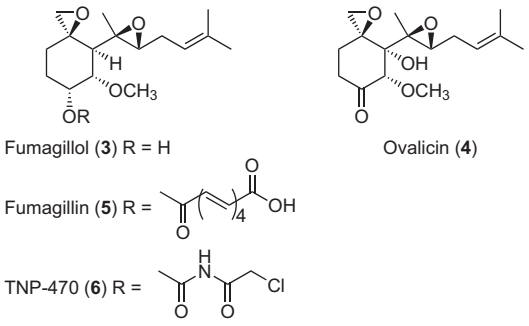


Figure 1. Structure of fumagillol, fumagillin, TNP-470, and ovalicin.

Corey was the first to synthesize (±)-ovalicin in 1985 in 12 steps. After the novel formation of an epoxy ketone, he stereoselectively added the lithiated diene to give the desired carbocyclic skeleton (Fig. 2).[26] Subsequently, Corey published an asymmetric synthesis of ovalicin by preparing the epoxy ketone via an asymmetric dihydroxylation reaction.[27] Bath[28] and Barco[29] gain access to (−)-ovalicin by manipulating naturally occurring optically pure building blocks L-quebrachitol and (−)-quinic acid, respectively. The most recent syntheses of (−)-ovalicin were reported by Takahashi who starts with a simple sugar, D-mannose, while also featuring ring closing metathesis and Hayashi whose approach is similar to that of Corey.[30]

Our retrosynthetic analysis of ovalicin (**4**) is outlined in Scheme 2. Conversion of **7** to ovalicin will be accomplished by a stereoselective hydroxyl directed epoxidation of the double bond, and conversion of the primary hydroxyl group into the terminally trisubstituted double bond via an oxidation and homologation sequence similar to the strategy used by Taber in his synthesis of fumagillin.[31] The highly functionalized cyclohexanone **7**, in turn, can be prepared via a series of selective oxidations carried out on triene **8**.

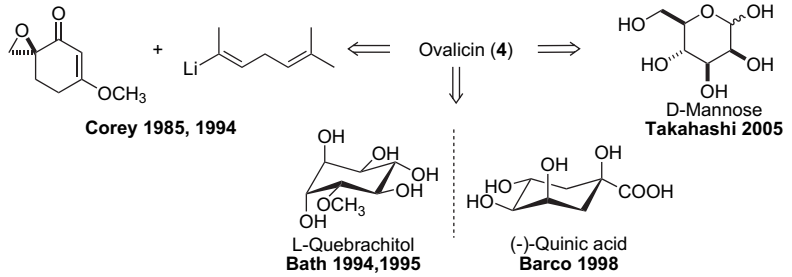
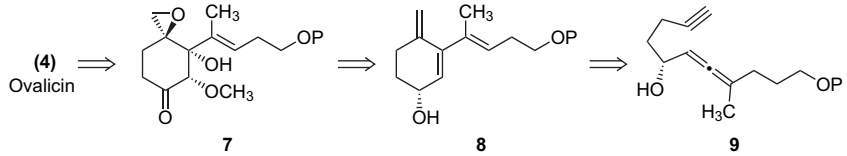
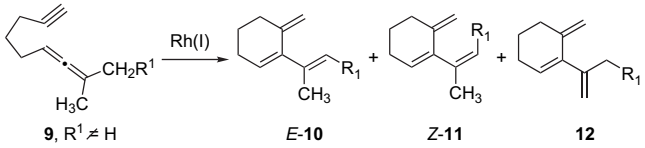


Figure 2. Previous synthetic strategies.



Scheme 2. Retrosynthetic analysis of ovalicin (**7**).

We plan to use the secondary hydroxyl group to direct the regio- and stereoselectivities of the oxidation reactions. The successful conversion of allene **9** to the desired triene **8** will require a regio- and stereoselective β-hydride elimination step. For example, when 1,1,3-trisubstituted allene **9** is used, β-hydride elimination can occur to give *E*-**10**, *Z*-**11**, and the constitutional isomer **12** (Scheme 3). Selective transformations of this type have not been previously addressed in our group[32] and to the best of our knowledge, little is known about the selectivity of these elimination reactions.

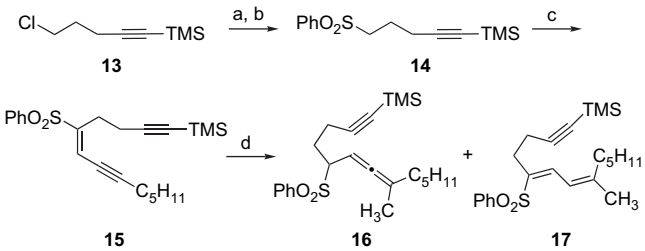


Scheme 3. Rh(I)-catalyzed Alder-ene reaction.

Trost observed competing β-hydride eliminations in a Pd-catalyzed cycloisomerization of 1,6-enynes; however, these cases were different because the elimination reactions gave either 1,3-diene or 1,4-diene products. Trost was able to alter the product distribution by changing the functional groups on the substrates.[33] Bäckvall's[34] Pd-catalyzed carbocyclization of ene–allenes gave constitutional isomers resulting from β-hydride elimination of differentially substituted allenes, which produced 1,4-dienes in a 1:1 ratio. Altering the functional groups on the starting material gave complete constitutional group selectivity. Because so little is known about the selectivity of this reaction, we initiated our synthesis of ovalicin by first examining the selectivity of the key Alder-ene reaction on a readily available precursor. Moreover, since we have previously demonstrated that *E*/*Z* isomeric ratios can be significantly increased by altering the catalyst,[13] we planned on first taking advantage of reagent control and then if necessary substrate control.

2. Results and discussion

With an eye toward the synthesis of ovalicin, model sulfonyl allenyne **16** was prepared to explore the constitutional group selectivity of the β-hydride elimination in the Alder-ene reaction. Reaction of commercially available 5-chloro-1-(trimethylsilyl)-1-pentyne (**13**) with NaI/acetone gave 5-iodo-1-(trimethylsilyl)-1-pentyne in a 99% yield (Scheme 4).



Scheme 4. Preparation of allenyne **16**. Reagents and conditions: (a) NaI, acetone, reflux, 99%; (b) benzenesulfinic acid sodium salt, DMF, 50 °C, 76%; (c) 2-octynal, *n*-BuLi, THF, −78 °C, quench Ac_2O; DBU, THF, 0 °C, 60% (three steps); (d) CuI, MeLi, TMSOTf, ether, −30 °C, 67% [**16**:**17**=7:1].

Treatment of the resulting iodide with benzenesulfinic acid sodium salt formed sulfone **14** in 2 h in 76% yield.[35] Addition of α-sulfonyl anion to 2-octynal followed by quenching with acetic anhydride gave the crude acetate as a 1:1 mixture of diastereomers. This diastereomeric mixture was reacted with DBU to give enyne *E*-**15** selectively in 60% yield in three steps. Then a conjugate 1,6-addition of lithium dimethylcuprate to enyne **15** gave a mixture of allene **16** and diene **17** in 67% yield.[36] Unfortunately, compounds **16** and **17** were only separable via HPLC; therefore, they were taken on as a mixture to the next step. Treatment of sulfonyl allene **16** and diene **17** with 5 mol% of $[Rh(CO)_2Cl]_2$ gave trienes *E*-**18**, *Z*-**18**, **19**, and unreacted **17** in a 90% yield as a 3:5:1 ratio of trienes, respectively. This is a rare example of the *Z*-isomer **18** predominating in any transition metal-catalyzed Alder-ene reaction (entry 1, Table 1).[37]

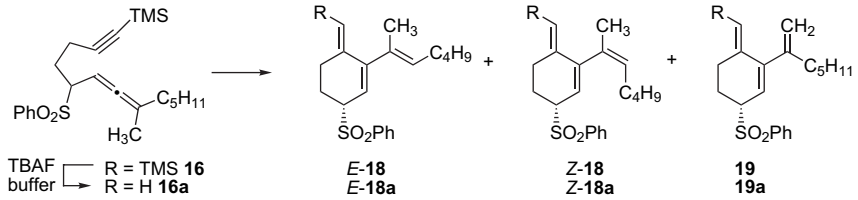
This seemingly anomalous result can be understood by considering the metallocycle intermediates **I** and **II** (Fig. 3). In order for β-hydride elimination to occur the dihedral angle of the Rh–C–C–H_a arrangement must be almost syn periplanar. Two competing conformations are depicted in **I** and **II**, leading to the *E*-**18** and *Z*-**18** isomers, respectively. Conformation **I** reveals an eclipsing interaction between the methyl and butyl groups as well as possible steric interference between the butyl group and the ligands on the rhodium. Conformation **II** alleviates these steric and eclipsing interactions but possesses $A^{1,3}$ strain. Thus, it is postulated that the *Z*-isomer is formed preferentially via the selective reaction of conformation **II**. Interestingly, removal of the TMS moiety from the terminus of the alkyne caused a reversal in the *E*/*Z* selectivity (compare entries 2 and 12, Table 1).

Triene *E*-**18** is the desired isomer for the synthesis of ovalicin; therefore, a systematic study to obtain *E*-**18** selectively was initiated and the results are summarized in Table 1. Reaction of allenyne **16** with $[Rh(CO)_2Cl]_2$ gave *Z*-**18** as the major product at 50 °C and room temperature (entries 1 and 2, Table 1). Because cationic Rh(I) or Ir(I) catalysts give *E*-isomers preferentially,[13] allene **16** was subjected to $[Rh(COD)Cl]_2$/$AgBF_4$. This afforded *E*-**18** in preference to *Z*-**18**, but significant quantities of the constitutional isomer **19** were also formed (*E*-**18**:**19**=1:1) (entry 3, Table 1). Exposure of **16** to the cationic iridium conditions ($[Ir(COD)Cl]_2$/$AgBF_4$) gave a 9:1:5 ratio of trienes *E*-**18**:*Z*-**18**:**19**, respectively (entry 4, Table 1). The use of cationic Rh(I) and Ir(I) catalysts reversed the *E*/*Z* selectivity (1:2 to 9:1), as expected, yet decreased the constitutional group selectivity (8:1 to 2:1) (entries 1–4, Table 1). We do not have an explanation for these results at this time.

Next, a series of reactions were performed on allene **16** using $[Ir(COD)Cl]_2$/$AgBF_4$ as the catalyst (entries 4–7, Table 1) and varying only the temperature. These experiments revealed an increase in selectivity at lower reaction temperature. At −30 °C a 6:1 *E*/*Z* isomeric ratio and a 7:1 constitutional isomeric ratio were obtained (entry 7, Table 1). This produced a 3:1 ratio (*E*-**18** to *Z*-**18**+**19**) and confirms that the regio- and stereoselectivity can be governed by the reaction conditions.

The Alder-ene reactions summarized in Table 1 illustrate that one constitutional isomer (*E*/*Z*-**18**) is preferred over the other (**19**). The selectivity between the constitutional

Table 1. Results of rhodium-catalyzed Alder-ene reaction with sulfonyl allenynes **16** and **16a**[a]



Entry	Substrate	Catalyst[b]	Solvent	*t* (°C)	*E*-**18**:*Z*-**18**:**19**	**18**:**19**	*E*-**18**:*Z*-**18**	Yield (%)
1	**16**	A	Toluene	50	3:5:1	8:1	3:5	73[d]
2	**16**	A	Toluene	rt	2:4:1	6:1	1:2	93
3	**16**	B	DCE	rt	1:0:1	1:1	1:0	97
4[c]	**16**	C	DCE	rt	9:1:5	2:1	9:1	44[d]
5	**16**	C	DCE	0	4:1:1	5:1	4:1	80
6	**16**	C	DCE	−10	5:1:2	3:1	5:1	
7	**16**	C	DCE	−30	6:1:1	7:1	6:1	80
8[c]	**16**	D	Acetone/DCE	rt	4:1:2	3:1	4:1	85
9	**16**	D	Acetone/DCE	−30	4:1:1	5:1	4:1	80
10	**16**	D	Toluene	−40	NR			
11	**16**	D	Toluene	−60	NR			
12	**16a**	A	Toluene	rt	2:1:1	3:1	2:1	87

[a] For reaction conditions see Section 4. Product ratios were determined by integration of olefin peaks in the ^{1}H NMR.
[b] A: 3–5 mol % $[Rh(CO)_2Cl]_2$; B: 5 mol % $[Rh(COD)Cl]_2$, 10 mol % $AgBF_4$; C: 10 mol % $[Ir(COD)Cl]_2$, 20 mol % $AgBF_4$; D: 5 mol % $[Ir(COD)Cl]_2$, 10 mol % $In(OTf)_3$.
[c] Desilylated trienes *E*/*Z*-**18a** and **19a** were obtained.
[d] Nonpolar impurity was seen during reaction.

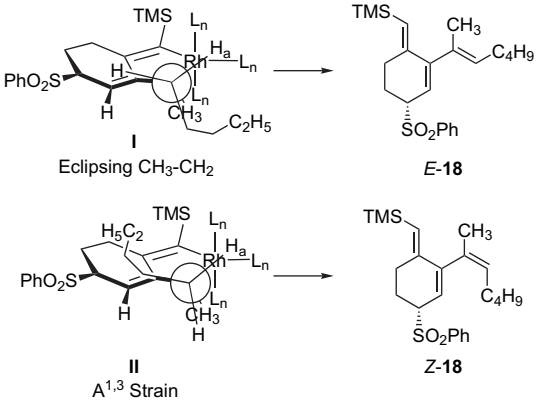


Figure 3. Explanation of *E*/*Z* selectivity.

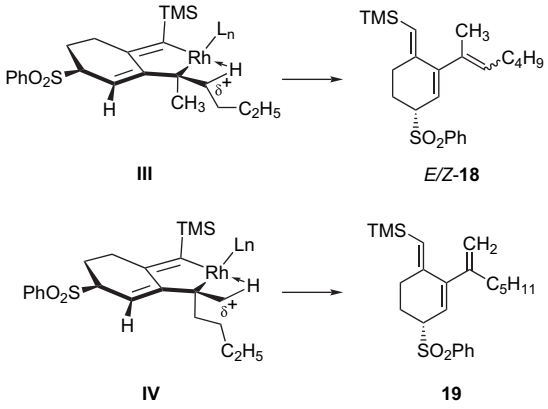
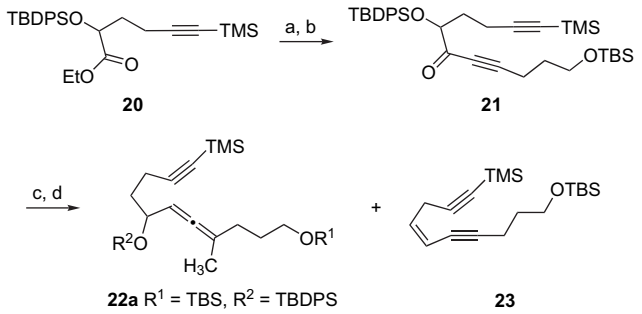


Figure 4. Explanation of constitutional group selectivity.

isomers is rationalized by the ability of either group (methylene (**18**) or methyl (**19**)) to stabilize the partial positive charge developing in the β-hydride elimination step of the reaction. Consequently, the β-hydride elimination is more favorable from the methylene group in **III** rather than the methyl group in **IV**; ultimately favoring elimination from intermediate **III** to give *E*/*Z*-**18**, predominately (Fig. 4).

These studies suggested that we could not obtain the desired selectivity by only altering the reaction conditions, and needed some assistance from the substrate. With this in mind we turned our focus on the preparation of allenyne **22**, which is particularly advantageous due to the changes that can be made to R^1 and R^2, in addition to being a well-suited substrate for the synthesis of ovalicin/fumagillol. Allene **22** is obtained by the addition of 4-magnesium-bromo-1-(trimethylsilyl)-1-butyne to ethyl glyoxylate followed by protection of the newly formed α-hydroxy group to give silyl ether **20** in a 65% combined yield (Scheme 5).[38] Ester **20** was transformed into the Weinreb amide in an 80% yield with MeNHOMe·HCl and *i*-PrMgCl. Addition of the lithium anion of silyl protected 4-pentyn-1-ol[39] to the Weinreb amide gave alkynyl ketone **21**.[40] Exposure of ketone **21** to the Luche reduction conditions gave the desired propargylic alcohol in a 58% yield (over two steps) as a single diastereomer by ^{1}H NMR. The propargylic alcohol was converted to a mesylate with Et_3N and MsCl. After workup the crude mesylate was subjected to lithium dimethylcuprate at −78 °C forming allenyne **22a** and enyne **23** in 80% yield in a 23:1 ratio, respectively.[41] Treatment of allenyne **22a** with $[Rh(CO)_2Cl]_2$ gave an 83% yield of trienes *E*-**24a**, *Z*-**24a**, and **25a** in a 13:5:2 ratio, respectively (entry 1, Table 2).[42] These *E*/*Z* ratios were similar to those observed previously, but are interesting considering that the *E*/*Z* ratios were reversed for the sulfone system (*E*/*Z*-**18**) (entries 1 and 2, Table 1). It is possible that this reversal is due to the differing electronic natures of the sulfone group of **16** and the disilyl ether groups of **22**. This is evidenced by the difference in the reaction rates for **16** and **22** (30 min vs 24 h at rt, respectively). Hence, the slower reaction revealed an increase in the amount of the thermodynamic product, *E*-**24a**.



Scheme 5. Preparation of allenyne **22**. Reagents and conditions: (a) MeNHOMe·HCl, *i*-PrMgCl, THF, 0 °C, 80%; (b) *n*-BuLi, *tert*-butyldimethyl(pent-4-ynyloxy)silane, −78 to 0 °C; (c) $CeCl_3 \cdot 7H_2O$, $NaBH_4$, −20 to 0 °C, 58% (two steps); (d) MsCl, TEA, CH_2Cl_2, 0 °C; CuI, MeLi, THF, −78 °C, 80% [**22a**:**23**=23:1].

Allenyne **22a** was subjected to the optimized reaction conditions worked out for sulfone **16** $[Ir(COD)Cl]_2/AgBF_4$, which led to complete decomposition of the starting material (entry 4). Switching the additive from $AgBF_4$ to $In(OTf)_3$ in DCE gave good selectivity but only a trace amount of product formation and mostly starting material were observed by ^1H NMR. The insolubility of indium triflate in DCE is a likely reason for the reaction inhibition; however, changing from DCE to acetone, a solvent that indium triflate is soluble in, resulted in complete decomposition of the starting material.

Since the cationic iridium conditions were not applicable to this system, only moderate variations in rhodium-catalyzed reaction conditions could be made. Changing the solvent in the reaction conditions from toluene to DCE showed a rate enhancement, (12 h at 55 °C to 30 min at rt) and a reversal in *E*/*Z* selectivity (7:3 to 4:6; see entries 10 vs 11 and 13 vs 14). More polar solvents are known to increase the reaction rates in Pd-catalyzed Alder-ene reactions[43] and Rh-catalyzed cycloadditions[44] due to their ability to stabilize charge separation. Also, changing the solvent from toluene to DCE gave isomeric ratios closer to that seen for the sulfone system (3:5:1 vs 4:5:1; compare entry 1, Table 1 to entry 11, Table 2). Altering the temperature had no effect on the *E*/*Z* selectivity or constitutional selectivity when toluene was used as the solvent (compare entries 1 vs 2, 5 vs 6, and 9 vs 10, Table 2); however, decreasing the reaction temperature when using DCE as the solvent further increased the amount of kinetic product shifting the *E*/*Z* ratio from 1:1 to 1:4 (entry 15 vs 16, Table 2).

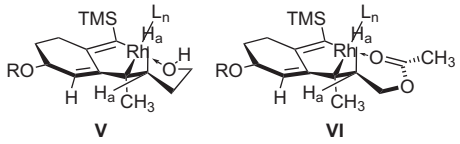
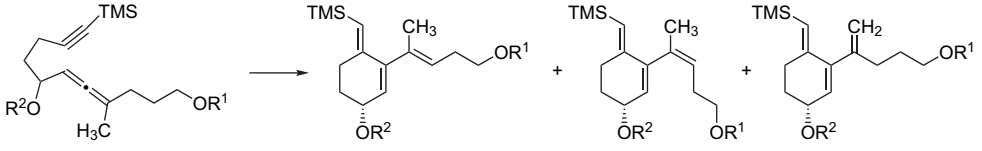


Figure 5. Explanation of changes in constitutional group selectivity.

Further attempts were made to increase the formation of the desired *E*-**24** by modifying R^1 of **22**. Changing R^1 from silyl ether to ester functionality revealed a slight decrease in constitutional group selectivity (9:1 to 4:1) and *E*/*Z* selectivity (7:3 to 6:4; compare entries 1 and 5). The free hydroxyl group had a similar, yet more enhanced effect decreasing the constitutional group selectivity from approximately 9:1 to 3:1 ratio, and it did not effect on the *E*/*Z* selectivity (compare entries 3 vs 8 and 11 vs 15). This increase in the amount of isomer **25** is believed to result from coordination of the free hydroxyl **V** and ester group **VI** to the rhodium metallocycle (Fig. 5). Syn periplanar alignment of the Rh–C–C–H_a

Table 2. Results of rhodium-catalyzed Alder-ene reaction with sulfonyl allenynes **22a–f**[a]



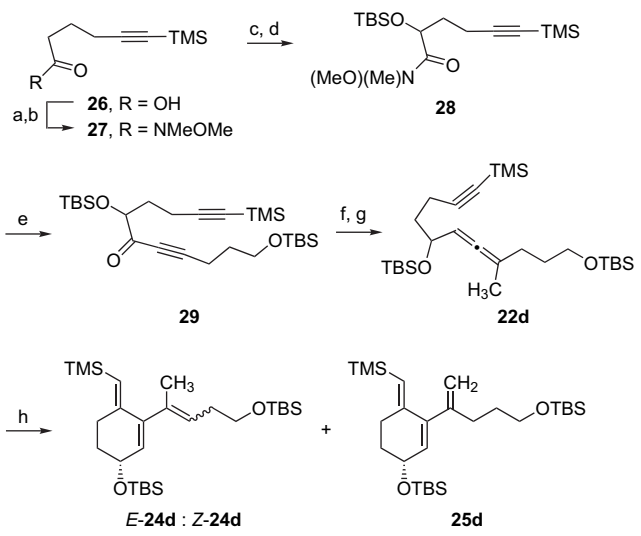
Entry	Substrate	R^1	R^2	Catalyst[b]	Solvent	*t* (°C)	*E*-**24**:*Z*-**24**:**25**	**24**:**25**	*E*-**24**:*Z*-**24**	Yield (%)
1	**22a**	TBS	TBDPS	A	Toluene	55	13:5:2	18:2	7:3	83
2	**22a**			A[c]	Toluene-d_8	rt	11:6:3	17:3	6:4	
3	**22a**			A	DCE	rt	9:8:3	17:3	5:5	55
4[d]	**22a**			B	DCE	rt	13:0:7	13:7	10:0	NA
5	**22b**	Ac	TBDPS	A	Toluene	55	10:6:4	16:4	6:4	87
6	**22b**			A	Toluene	rt	11:6:3	17:3	6:4	85
7	**22b**			C	DCE	rt	12:3:5	15:5	8:2	67[e]
8	**22c**	H	TBDPS	A	DCE	rt	5:7:8	12:8	4:6	50
9	**22d**	TBS	TBS	A	Toluene	80	12:6:2	18:2	7:3	**85**
10	**22d**			A	Toluene	55	12:5:3	17:3	7:3	95
11[f]	**22d**			A	DCE	55	8:10:2	18:2	4:6	
12[d]	**22d**			B	DCE	55				NA
13[f]	**22e**	Ac	TBS	A	Toluene	rt	11:6:3	17:3	6:4	
14	**22e**			A	DCE	rt	8:9:3	17:3	5:5	60
15	**22f**	H	TBS	A	DCE	rt	7:8:5	15:5	5:5	66
16	**22f**			A	DCE	0	3:10:7	13:7	2:8	60

[a] For reaction conditions see Section 4. Product ratios were determined by integration of olefin peaks in the ^1H NMR.
[b] A: 5–10 mol % $[Rh(CO)_2Cl]_2$; B: 10 mol % $[Ir(COD)Cl]_2$, 20 mol % $In(OTf)_3$; C: 10 mol % $[Ir(COD)Cl]_2$, 20 mol % $AgBF_4$.
[c] Catalyst (1 equiv) was used; no yield was calculated.
[d] Starting materials were recovered and experiments were irreproducible.
[e] Yield includes a mixture of inseparable by-products.
[f] Large amount of product was obtained; exact yield was not calculated.

during the β-hydride elimination step is conformationally hindered by this coordination, leading to an increase in the formation of triene **25**.[45]

Allenynes **22b** and **22c** were subjected to the iridium conditions ($[Ir(COD)Cl]_2/AgBF_4$) in hopes that they would tolerate these conditions better than the bis-silylated allenyne **22a**. Trienes *E*/*Z*-**24b** and **25b** were obtained in a 67% yield; however, the yield included a mixture of inseparable by-products and the reaction was irreproducible (entry 7, Table 2). Subjection of allenyne **22c** to $[Ir(COD)Cl]_2/AgBF_4$ led to complete decomposition of the starting material.

After finding the best isomeric ratios with the bis-silylated allenyne systems (**22a** and **22d**) we decided to separate our desired *E*-**24** isomer and turned our attention to the functionalization of the triene systems toward the synthesis of ovalicin. Diverging from the initial route, esterification of carboxylic acid **19** with MeI and $KHCO_3$ gave a 76% yield of ester **26** (Scheme 6). Reaction of **26** with MeNHOMe·HCl and *i*-PrMgCl generates amide **27** in a 91% yield. Subjection of amide **27** to 1.5 equiv of sodium hexamethyldisilazide and 1.5 equiv of 2-(phenylsulfonyl)-3-phenyloxaziridine gave a 86% yield of the α-hydroxy amide. The α-hydroxyl group was protected as a *tert*-butyldimethylsilyl ether using Et_3N and TBSOTf to give amide **28**, which in turn was subjected to the lithium anion of *tert*-butyldimethyl(pent-4-ynyloxy)-silane to give a 77% yield of alkynone **29**.



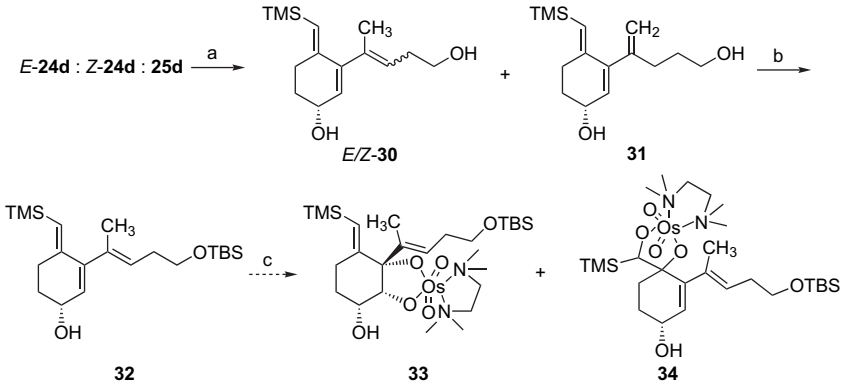
Scheme 6. Alternative preparation of trienes *E*/*Z*-**24** and **25**. Reagents and conditions: (a) $KHCO_3$, MeI, DMF, 76%; (b) MeNHOMe·HCl, *i*-PrMgCl, THF, 0 °C, 91%; (c) NaHMDS, PhNOCHPh, THF, 86%; (d)TEA, TBSOTf, CH_2Cl_2, 94%; (e) *n*-BuLi, *tert*-butyldimethyl(pent-4-ynyloxy)silane, −78 to 0 °C, 77%; (f) $CeCl_3·7H_2O$, $NaBH_4$, −20 to 0 °C, 88%; (g) MsCl, TEA, CH_2Cl_2, 0 °C; CuI, MeLi, THF, −30 °C, 86% [**22d**:**23**=7:1]; (h) $[Rh(CO)_2Cl]_2$, toluene, 80 °C, 95% [*E*-**24d**:*Z*-**24d**:**25d**=6:3:1].

Ketone **29** was reduced using Luche conditions to yield a propargylic alcohol in a 7:1 diastereomeric ratio. The diastereomers were not separated but taken on to the next step. The propargylic alcohol was converted to its mesylate using Et_3N and MsCl, then after workup the crude mesylate was subjected to lithium dimethylcuprate. Allenyne **22d** was obtained in an 86% yield as a 7:1 diastereomeric ratio as seen by ^1H NMR. Treatment of allenyne **22d** with $[Rh(CO)_2Cl]_2$ and heating to 80 °C gave trienes *E*-**24d**/*Z*-**24d**/**25d** in a 6:3:1 ratio, respectively, and in 95% yield.[46]

Separation of these trienes required removal of both of the silyl ether protecting groups (Scheme 7).[47] Buffering this deprotection reaction was essential, since decomposition of the trienes occurred in the absence of NH_4Cl. After 12 h at 50 °C, complete bis-desilylation was observed, giving trienes *E*/*Z*-**30** and **31** in 92% yield. The trienes were separated using silica gel chromatography; eluting with isopropanol/pentanes. The primary hydroxyl group on *E*-**30** was selectively protected using Et_3N and TBDMSCl giving a 75% yield of triene **32**. Next, a selective dihydroxylation of the endocyclic double bond of **32** was tested via a hydroxyl directed dihydroxylation protocol developed by Donohoe.[48] When triene **32** was subjected to TMEDA and 1 equiv of OsO_4 in CH_2Cl_2 at −78 °C, osmylation to occured forming the stable osmate esters **33** and a by-product **34** in a 6:1 ratio. Unfortunately, a small discrepancy in the ^1H NMR prevents us from knowing conclusively whether we formed our desired product **33**. Future work entails complete determination of the dihydroxylation product followed by further steps to complete the synthesis of ovalicin (**7**).

3. Conclusion

In summary, Rh(I)-catalyzed allenic Alder-ene reaction of **16** and **22a–f** leads to the formation of trienes *E*/*Z*-**18**,



Scheme 7. Attempted dihydroxylation of triene *E*-**30**. Reagents and conditions: (a) TBAF, NH_4Cl, THF, 50 °C, 92%; (b) TBDMSCl, TEA, CH_2Cl_2, 75%; (c) TMEDA, OsO_4, CH_2Cl_2, −78 °C, 90%, (**33**:**34**=6:1).

E/*Z*-**24a–f**, **19**, and **25** in good yields and moderate regioselectivities (Tables 1 and 2). The regioselectivities of the Alder-ene reaction are found to be dependent on a number of factors: temperature, solvent, catalyst (cationic vs neutral), and the ability of the substrate to coordinate with the catalyst. Furthermore, the products from the allenic Alder-ene reaction are useful substrates for further functionalization; and in turn will be a synthetically useful intermediate for the synthesis of ovalicin (**4**).

4. Experimental

4.1. General

All reactions were performed using syringe–septum cap techniques under a nitrogen atmosphere and glassware was flame dried prior to use. All commercially available compounds were purchased from Aldrich Chemical Co., GFS Chemicals, Strem Chemicals, and Acros Organics and used as received, unless otherwise specified. Tetrahydrofuran (THF), diethyl ether (Et_2O), and dichloromethane (DCM) were purified with alumina using the Sol-Tek ST-002 solvent purification system. Toluene, *N*,*N*,*N*′,*N*′-tetramethylethylenediamine (TMEDA), and triethylamine (Et_3N) were freshly distilled from CaH_2 prior to use. Trimethylsilyl trifluoromethanesulfonate (TMSOTf) was distilled from phosphorus pentoxide (P_2O_5) and stored in a septum sealed flask in the freezer. Copper iodide (CuI) was purified by following the procedure in Ref. 49.

Purification of the products by flash chromatography was performed using silica gel (32–63 μm particle size, 60 Å pore size) purchased from SAI. TLC analyses were performed on EM Science Silica Gel 60 F_{254} plates (250 μm thickness). HPLC purification was performed on a Varian-Prostar 210 instrument using a Varian Microsorb Dynamax 100-5 Si column (5 μm packing, 250 mm×10 mm) or Varian Pursuit C8 column (5 μm packing, 250 mm×10 mm).

Melting points were determined using a Laboratory Devices Mel-Temp II apparatus. All ^1H and ^{13}C spectra were obtained on either Bruker Avance 300 MHz or Bruker Avance DRX 500 MHz instrument, and chemical shifts (δ) were reported relative to residual peak $CHCl_3$ or toluene. All NMR spectra were obtained at room temperature unless otherwise specified and are tabulated as follows: chemical shift, multiplicity (s = singlet, d = doublet, t = triplet, q = quartet, qn = quintet, m = multiplet), coupling constant(s), number of protons. IR spectra were obtained using a Nicolet Avatar E.S.P. 360 FT-IR. EI mass spectrometry was performed on a Micromass Autospec high-resolution mass spectrometer. ES low-resolution mass spectrometry was performed on an HPMSD 1100 LC/MS and high-resolution was performed on ESI Biosystem time of flight mass spectrometer.

4.2. Preparation of compounds 14–32

4.2.1. 1-Phenylsulfonyl-5-(trimethylsilyl)-4-pentyne (14). To a solution of 5-chloro-1-(trimethylsilyl)-1-pentyne (4.47 mL, 22.9 mmol) in 8 mL of acetone was added NaI (5.15 g, 34.4 mmol). The mixture was brought to reflux and the progress of the reaction was monitored by ^1H NMR spectroscopy. After 24 h the mixture was quenched by addition of water and the aqueous layer was extracted with Et_2O (3×). The combined organic layers were dried over $MgSO_4$, filtered, and concentrated under reduced pressure. The residue was purified by silica gel chromatography eluting with hexanes to afford the iodide (6.06 g, 99%) as a colorless liquid. To a solution of 5-iodo-1-(trimethylsilyl)-1-pentyne (11.3 g, 42.3 mmol) in 50 mL of DMF was added anhydrous benzenesulfinic acid sodium salt (8.34 g, 50.7 mmol). The mixture was warmed to 50 °C and after 1.5 h complete consumption of starting material was observed by TLC. The mixture was poured into an Et_2O/water mixture. The aqueous layer was separated and extracted with Et_2O (3×). The combined organic layers were washed with brine, dried over $MgSO_4$, filtered, and concentrated under reduced pressure. The residue was purified by silica gel chromatography eluting with 10% EtOAc/hexanes to afford sulfone **14** (9.08 g, 76%) as a white solid. R_f 0.2 (20% EtOAc/hexanes); mp=33 °C; ^1H NMR (300 MHz, $CDCl_3$): δ 0.12 (s, 9H), 1.78–1.87 (m, 2H), 2.26 (t, J=6.8 Hz, 2H), 3.15–3.20 (m, 2H), 7.48–7.64 (m, 3H), 7.82–7.86 (m, 2H); ^{13}C NMR (75 MHz, $CDCl_3$): δ −0.18 (3C), 18.4, 21.7, 54.8, 86.3, 104.2, 127.7 (2C), 129.1 (2C), 133.5, 138.9; IR (neat) 2958, 2175, 1447, 1307 cm^{-1}; MS (GC/MS) *m*/*e* (relative intensity) 280 ($[M-CH_3]^+$, 0.4), 265 (50), 135 (100), 77 (51), 73 (63); HRMS calcd for $C_{13}H_{17}O_2SiS$: 265.0719 $[M-CH_3]^+$; found: 265.0721 $[M-CH_3]^+$.

4.2.2. (5-Benzenesulfonyltridec-5-ene-1,7-diynyl)trimethylsilane (15). To a solution of sulfone **14** (1.00 g, 3.57 mmol) in 15 mL of THF at −78 °C was added *n*-butyllithium (2.70 mL of a 1.6 M hexanes solution, 4.28 mmol) dropwise over 10 min. After 1 h at −78 °C, a solution of 2-octynal (0.53 g, 4.28 mmol) in 3 mL of THF was added via cannula and the mixture was kept at −78 °C for 1 h and then allowed to warm to 10 °C at which time complete consumption of starting material was observed by TLC. The mixture was then cooled to −78 °C and acetic anhydride (1.47 g, 14.4 mmol) was added. The mixture was quenched at ambient temperature with $NH_4Cl_{(aq)}$, and the aqueous layer was separated and washed with Et_2O (3×). The combined organic layers were washed with brine, dried over $MgSO_4$, filtered, and concentrated under reduced pressure. The crude mixture was purified by silica gel chromatography eluting with 10% EtOAc/hexanes. The mixture of diastereomers was collected (1.40 g, 3.14 mmol) and azeotroped in vacuo with benzene (3×), diluted with 8 mL of THF, and cooled to 0 °C. DBU (0.52 g, 3.45 mmol) was added to the solution and after 30 min a 10% HCl/ether solution was added to the reaction. The aqueous layer was separated and extracted with Et_2O (3×). The combined organic layers were washed with brine, dried over Na_2SO_4, filtered, and concentrated under reduced pressure. The residue was purified by silica gel chromatography eluting with 10% EtOAc/hexanes to afford enyne **15** (738 mg, 60% over two steps) as a colorless oil. ^1H NMR (300 MHz, $CDCl_3$): δ 0.13 (s, 9H), 0.92 (t, J=7.0 Hz, 3H), 1.28–1.45 (m, 4H), 1.59 (qn, J=7.1 Hz, 2H), 2.35–2.47 (m, 4H), 2.59–2.65 (m, 2H), 6.84 (t, J=2.2 Hz, 1H), 7.52–7.67 (m, 3H), 7.87–7.90 (m, 2H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 0.0 (3C), 13.8, 19.0, 19.8, 22.0, 27.8, 28.0, 30.9, 75.0, 85.2, 105.0, 106.7, 122.3, 128.0 (2C), 129.2 (2C), 133.5, 139.1, 148.5; IR (neat) 2958, 2932, 2860, 2213, 2177, 1446 cm^{-1}; MS

(GC/MS) *m/e* (relative intensity) 386 ([M]$^+$, 2), 371 (3), 135 (45), 73 (100); HRMS calcd for $C_{22}H_{30}O_2SiS$: 386.1736; found: 386. 1739.

4.2.3. (5-Benzenesulfonyl-8-methyltrideca-6,7-dien-1-yne)-trimethylsilane (16). To a suspension of CuI (1.51 g, 7.94 mmol) in 40 mL of ether at −30 °C was added MeLi (12.4 mL of a 1.3 M diethyl ether solution, 15.8 mmol) dropwise. The mixture was allowed to warm to 0 °C over a 30 min period and it changed from cloudy yellow to a clear solution. The flask was cooled to −50 °C and a solution of enyne **15** (1.53 g, 3.97 mmol) and TMSOTf (0.77 mL, 3.97 mmol) in 20 mL of ether was added dropwise with a cannula. The mixture was kept at −50 to −30 °C for 3 h and then was warmed to −15 °C and kept at that temperature for 7 h before $NH_4Cl_{(aq)}$ and ether were added. The biphasic solution was stirred vigorously until the aqueous layer turned deep blue. The solution was then filtered through a sintered glass funnel of medium porosity packed with Celite to remove the copper salts and aqueous layer. The Celite was rinsed with ether to assure complete filtration of products. The organic layer was concentrated under reduced pressure and the residue was purified by silica gel chromatography eluting with 3% EtOAc/hexanes to afford 1.08 g of a mixture of allene **16** and diene **17** in a 7:1 ratio (by ^{1}H NMR) for a 67% yield. The mixture was taken on to the next step. However, pure allene **16** was obtained by HPLC for spectroscopic purposes (Varian Microsorb Dynamax 100-5 Si column, 23 °C, EtOAc/hexanes=5%, flow rate=3 mL/min). ^{1}H NMR (300 MHz, $CDCl_3$): δ 0.14 (s, 9H), 0.88 (t, J=6.3 Hz, 3H), 1.19–1.35 (m, 4H), 1.30 (d, J=2.3 Hz, 3H), 1.75–1.90 (m, 4H), 2.18–2.52 (m, 4H), 3.68 (ddd, J=2.8, 8.5, 11.1 Hz, 1H), 4.88–4.97 (m, 1H), 7.53–7.70 (m, 3H), 7.87–7.92 (m, 2H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 0.5 (3C), 14.4, 17.8, 18.2, 22.8, 26.5, 27.3, 31.9, 33.9, 66.1, 84.0, 86.7, 103.2, 105.3, 129.2 (2C), 129.7 (2C), 133.8, 138.4, 206.0; IR (neat) 2957, 2858, 2175, 1950, 1447, 1307 cm^{-1}; MS (GC/MS) *m/e* (relative intensity) 402 ([M]$^+$, 0.6), 387 (0.6), 277 (12), 125 (12), 73 (100); HRMS calcd for $C_{23}H_{34}O_2Si_1S_1$: 402.2049; found: 402.2047. Only crude ^{1}H NMR spectra were obtained for diene **17** after desilylation. ^{1}H NMR (300 MHz, $CDCl_3$): δ 0.93 (t, J=6.7 Hz, 3H), 1.27–1.51 (m, 6H), 1.94 (m, 4H), 2.28–2.37 (m, 4H), 2.52–2.57 (m, 2H), 6.07 (d, J=11.8 Hz, 1H), 7.52–7.66 (m, 4H), 7.86–7.90 (m, 2H).

4.2.4. (5-Benzenesulfonyl-8-methyltrideca-6,7-dien-1-yne) (16a). To a solution of allenyne **16** (0.11 g, 0.26 mmol) in 1.3 mL of THF at 0 °C was added a mixture of TBAF (0.26 mL of a 1 M THF solution, 0.26 mmol) and 0.02 mL of pH 7.38 phosphate buffer solution dropwise via syringe. After 1 h the reaction was quenched at room temperature with $NH_4Cl_{(aq)}$, and the aqueous layer was separated and washed with EtOAc (3×). The combined organic layers were washed with brine, dried over $NaSO_4$, filtered, and concentrated under reduced pressure. The residue was purified by silica gel chromatography eluting with 5% EtOAc/hexanes to afford 81 mg of allenyne **16a** in 94% yield as a colorless oil (3:1, allene **16a**/diene **17a**). ^{1}H NMR (300 MHz, $CDCl_3$) allene **16a**: δ 0.87 (t, J=7.2 Hz, 3H), 1.12–1.29 (m, 7H), 1.76–1.90 (m, 4H), 1.07 (t, J=2.4 Hz, 1H), 2.18–2.48 (m, 4H), 3.69 (ddd, J=2.9, 8.6, 11.0 Hz, 1H), 4.90–4.96 (m, 1H), 7.53–7.67 (m, 3H), 7.88–7.91 (m, 2H); diene **17a**: δ 0.93 (t, J=6.7 Hz, 3H), 1.27–1.51 (m, 6H), 1.94 (m, 3H), 2.28–2.37 (m, 4H), 2.52–2.57 (m, 2H), 6.07 (d, J=11.8 Hz, 1H), 7.52–7.66 (m, 4H), 7.86–7.90 (m, 2H).

4.3. General procedure for allenic Alder-ene reaction (Table 1)

4.3.1. [4-Benzenesulfonyl-2-(1-methylhept-1*E*-enyl)-cyclohex-2-enylidenemethyl]trimethylsilane (*E*-18), [4-methylene-3-(1-methylhept-1*Z*-enyl)-cyclohex-2-enesulfonylbenzene]trimethylsilane (*Z*-18), and [4-methylene-3-(1-methyleneheptyl)-cyclohex-2-enesulfonylbenzene]-trimethylsilane (19). *Method A*: (entries 1, 2, and 12) to a flame dried test tube was added a mixture of allene **16** and diene **17**, which was then azeotroped under vacuum with benzene and charged with N_2 (3×). Toluene (0.2 M) was added and the test tube was evacuated under vacuum and charged with N_2 three times. Then, 5 mol % $[Rh(CO)_2Cl]_2$ was added at ambient temperature and the system was evacuated and charged with N_2 once more. The reaction was monitored by GC and quenched by addition to a silica gel plug eluting with 5% EtOAc/hexanes to afford trienes *E*-**18**, *Z*-**18**, and **19** and recovered **17** or *E*-**18a**, *Z*-**18a**, and **19a**. The crude mixture was analyzed by ^{1}H NMR and the ratios were determined by integration of distinct olefinic peaks from each isomer. Attempted separation of the isomers by chromatography was unsuccessful.

Method B: (entries 3–11) to a flame dried test tube was added a mixture of allene **16** and diene **17**, which was azeotroped under vacuum with benzene (3×). Dichloroethane (0.2 M) was added and the test tube was evacuated under vacuum and charged with N_2 (3×). Then, 10 mol % $[Ir(COD)Cl]_2$ or $[Rh(COD)Cl]_2$ was added followed by 20 mol % $AgBF_4$ (0.05 M dichloroethane solution) or $In(OTf)_3$ (0.05 M acetone solution) and the system was evacuated and charged with N_2 once more. The mixture was monitored by GC and quenched by addition to a silica gel plug eluting with 5% EtOAc/hexanes to afford a mixture of trienes *E*-**18**, *Z*-**18**, and **19**, and recovered **17** or *E*-**18a**, *Z*-**18a**, and **19a** depending on conditions (see Table 1). The crude mixture was analyzed by ^{1}H NMR and the ratios were determined by integration of distinct olefinic peaks from each isomer; however, pure trienes *E*-**18a**, *Z*-**18a**, and **19a** were obtained by HPLC for spectroscopic purposes (Varian Microsorb Dynamax 100-5 Si column, 23 °C, EtOAc/hexanes=5%, flow rate=3 mL/min [*E*-**18a** and **19a**], Varian Pursuit C8, 5 μm, 23 °C, H_2O/MeCN=25%, flow rate=5 mL/min [*Z*-**18a**]). ^{1}H NMR (300 MHz, $CDCl_3$) *E*-**18a**: δ 0.93 (t, J=7.0 Hz, 3H), 1.30–1.44 (m, 4H), 1.70 (s, 3H), 1.85–1.98 (m, 1H), 2.00–2.31 (m, 4H), 2.32–2.45 (m, 1H), 3.86–3.98 (m, 1H), 4.89 (s, 1H), 4.92 (s, 1H), 5.27 (t, J=7.2 Hz, 1H), 5.67 (d, J=2.7 Hz, 1H), 7.50–7.70 (m, 3H), 7.85–7.92 (m, 2H); ^{13}C NMR (75 MHz, $CDCl_3$): 14.2, 16.9, 22.6, 23.8, 27.9, 29.5, 31.8, 63.2, 114.3, 116.2, 129.1 (2C), 129.5 (2C), 130.6, 134.0, 134.5, 137.3, 140.0, 150.2; ^{1}H NMR (300 MHz, $CDCl_3$) *Z*-**18a**: δ 0.80–0.90 (m, 3H), 1.18–1.28 (m, 6H), 1.74 (s, 3H), 1.90–2.05 (m, 1H), 2.05–2.20 (m, 1H), 2.21–2.35 (m, 1H), 2.40–2.53 (m, 1H), 3.90–3.98 (m, 1H), 4.88 (s, 1H), 4.94 (s, 1H), 5.30–5.38 (m, 1H), 5.56–5.60 (m, 1H), 7.52–7.69 (m, 3H), 7.86–7.91 (m, 2H); ^{13}C NMR (75 MHz, $CDCl_3$): 14.0, 22.3, 23.3, 24.3, 28.9, 29.7, 32.0, 63.0, 113.4, 117.1, 128.9, 129.0 (2C), 129.2 (2C),

133.7, 133.9, 137.5, 138.8, 146.5; IR (neat) 2956, 2927, 1447, 1306 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) constitutional isomer **19a**: δ 0.89 (t, J=6.6 Hz, 3H), 1.00–1.42 (m, 6H), 1.88–2.30 (m, 5H), 2.38–2.49 (m, 1H), 3.88–3.96 (m, 1H), 4.80 (d, J=2.2 Hz, 1H), 4.90–4.99 (m, 3H), 5.67 (d, J=2.8 Hz, 1H), 7.52–7.69 (m, 3H), 7.86–7.92 (m, 2H); ^{13}C NMR (75 MHz, $CDCl_3$): 14.2, 22.6, 23.6, 27.9, 29.3, 31.5, 36.1, 63.0, 114.3, 114.5, 117.0, 129.1 (2C), 129.4 (2C), 133.9, 137.2, 139.8, 147.6, 148.9.

4.3.2. 11-(*tert*-Butyldimethylsilyloxy)-5-(*tert*-butyldiphenylsilyloxy)-1-trimethylsilylundeca-1,7-diyn-6-one (21). To a solution of ester **20** (1.20 g, 2.57 mmol) in 5 mL of THF was added MeNHOMe·HCl (0.38 g, 3.86 mmol) and the flask was cooled to 0 °C. Then *i*-PrMgCl (2.60 mL of a 2.0 M THF solution, 5.15 mmol) was added dropwise and after addition was finished complete consumption of starting material was observed by TLC. The mixture was quenched with $NH_4Cl_{(aq)}$, and the aqueous layer was separated and washed with CH_2Cl_2 (3×). The combined organic layers were dried over $MgSO_4$, filtered, and concentrated under reduced pressure. The residue was purified by silica gel chromatography eluting with 10–15% EtOAc/hexanes to afford amide (1.01 g, 80%) as a colorless oil. R_f 0.4 (20% EtOAc/hexanes); ^1H NMR (300 MHz, $CDCl_3$): δ 0.12 (s, 9H), 1.10 (s, 9H), 1.91–1.98 (m, 2H), 2.36 (dt, J=6.6, 17.1 Hz, 1H), 2.49 (dt, J=7.8, 17.1 Hz, 1H), 2.90 (s, 3H), 3.11 (s, 3H), 4.66 (t, J=5.8 Hz, 1H), 7.33–7.45 (m, 6H), 7.68–7.75 (m, 4H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 0.1 (3C), 15.9, 19.5, 27.0 (3C), 32.2, 33.7, 60.7, 68.9, 84.8, 106.7, 127.3 (2C), 127.5 (2C), 129.5, 129.6, 133.5 (2C), 133.6 (2C), 136.0, 136.2, 173.1; IR (neat) 2959, 2933, 2857, 2174, 1681 cm^{-1}; MS (GC/MS) *m/e* (relative intensity) 466 ($[M-CH_3]^+$, 7), 424 (100): HRMS calcd for $C_{26}H_{36}N_1O_3Si_2$: 466.2234 $[M-CH_3]^+$; found: 466.2244 $[M-CH_3]^+$. To a solution of *tert*-butyldimethyl(pent-4-ynyloxy)silane (0.82 g, 4.15 mmol) in 14 mL of THF at −78 °C was added *n*-butyllithium (1.74 mL of a 2.5 M hexane solution, 4.36 mmol) dropwise. The flask was kept at −78 °C for 10 min and then placed in a bath at −20 °C for 20 min. It was then cooled to −78 °C and added to a solution of 2-(*tert*-butyldiphenylsilyloxy)-6-trimethylsilylhex-5-ynoic acid methoxy methyl amide (1.00 g, 2.08 mmol) in 5 mL of THF at −78 °C via cannula. The mixture was then allowed to slowly warm over 2 h to 0 °C at which time complete consumption of starting material was observed by TLC. The reaction mixture was quenched with $NH_4Cl_{(aq)}$, and the aqueous layer was separated and extracted with Et_2O (3×). The combined organic layers were dried over $MgSO_4$, filtered, and concentrated under reduced pressure. The residue was purified by silica gel chromatography eluting with 5% EtOAc/hexanes to afford ketone **21** and *tert*-butyldimethyl(pent-4-ynyloxy)silane. The mixture was not separated at this point but pure ketone **21** was obtained for spectroscopic purposes. R_f 0.7 (20% EtOAc/hexanes); ^1H NMR (300 MHz, $CDCl_3$): δ 0.05 (s, 6H), 0.13 (s, 9H), 0.90 (s, 9H), 1.12 (s, 9H), 1.66–1.75 (m, 2H), 1.85–2.06 (m, 2H), 2.21–2.41 (m, 4H), 3.65 (t, J=6.5 Hz, 2H), 4.30 (t, J=5.6 Hz, 1H), 7.33–7.47 (m, 6H), 7.64–7.68 (m, 4H); ^{13}C NMR (75 MHz, $CDCl_3$): δ −5.4 (2C), 0.1 (3C), 15.3, 15.7, 18.3, 19.5, 25.9 (3C), 27.0 (3C), 30.7, 33.7, 61.3, 78.2, 79.4, 85.2, 97.7, 106.1, 127.6 (2C), 127.7 (2C), 129.8, 129.9, 133.1 (2C), 133.3 (2C), 135.8, 136.0, 188.3; IR (neat) 2956, 2857, 2211, 2176, 1675 cm^{-1}; MS (GC/MS) *m/e* (relative intensity) 603 ($[M-CH_3]^+$, 1.6), 516 (60), 197 (60), 135 (100); HRMS calcd for $C_{35}H_{51}O_3Si_3$: 603.3146 $[M-CH_3]^+$; found: 603.3120 $[M-CH_3]^+$.

4.3.3. 11-(*tert*-Butyldimethylsilyloxy)-5-(*tert*-butyldiphenylsilyloxy)-8-methyl-1-trimethylsilylundeca-6,7-dien-1-yne (22a). Ketone **21** and *tert*-butyldimethyl(pent-4-ynyloxy)silane (≈2.1 mmol) were diluted with $CeCl_3\cdot 7H_2O$ (6.83 mL of a 0.4 M methanol solution, 2.73 mmol), cooled to −20 °C, and $NaBH_4$ (0.10 g, 2.73 mmol) was added in one portion. The mixture was allowed to warm to 0 °C and after 30 min complete consumption of starting material was observed by TLC. The reaction was quenched with slow addition of H_2O, and the aqueous layer was separated and washed with Et_2O (3×). The combined organic layers were dried over $MgSO_4$, filtered, and concentrated under reduced pressure. The residue was purified by silica gel chromatography eluting with 3–10% EtOAc/hexanes to afford the alcohol (772 mg, 58%) over two steps. R_f 0.6 (20% EtOAc/hexanes); ^1H NMR (300 MHz, $CDCl_3$): δ 0.06 (s, 6H), 0.12 (s, 9H), 0.90 (s, 9H), 1.10 (s, 9H), 1.65–1.91 (m, 3H), 2.12–2.32 (m, 5H), 3.66 (t, J=6.1 Hz, 2H), 3.88 (q, J=5.3 Hz, 1H), 4.30 (m, 1H), 7.37–7.49 (m, 6H), 7.72 (t, J=6.8 Hz, 4H); ^{13}C NMR (75 MHz, $CDCl_3$): δ −5.3 (2C), 0.1 (3C), 15.2, 15.8, 18.3, 19.5, 25.9 (3C), 27.1 (3C), 31.6, 31.9, 61.6, 65.3, 75.5, 79.0, 84.7, 86.2, 106.5, 127.6 (2C), 127.7 (2C), 129.8 (2C), 133.4 (2C), 133.6 (2C), 135.87 (2C); IR (neat) 3451, 2956, 2858, 2175 cm^{-1}; MS (GC/MS) *m/e* (relative intensity) 620 ($[M]^+$, 0.3), 563 (10), 199 (97), 135 (100); HRMS calcd for $C_{32}H_{47}O_3Si_3$: 563.2833 $[M-C(CH_3)_3]^+$; found: 563.2830 $[M-C(CH_3)_3]^+$. To a solution of 11-(*tert*-butyldimethylsilyloxy)-5-(*tert*-butyldiphenylsilyloxy)-1-trimethylsilyl-1-undeca-1,7-diyn-6-ol (0.33 g, 0.51 mmol) in 1.7 mL of CH_2Cl_2 was added Et_3N (96.0 μL, 0.69 mmol) and the solution was cooled to 0 °C. Then MsCl (48.0 μL, 0.62 mmol) was added and after 30 min at 0 °C the reaction mixture was diluted with pentanes. The solution was then filtered through a sintered glass funnel of medium porosity packed with Celite and the resulting solution was washed with $NaHCO_{3(aq)}$ and brine. The organic layer was dried over $MgSO_4$, filtered, and concentrated under reduced pressure. To a suspension of CuI (0.12 g, 0.62 mmol) in 2 mL of THF at −30 °C was added MeLi (0.64 mL of a 1.6 M diethyl ether solution, 1.03 mmol) dropwise. The reaction mixture was allowed to warm to 0 °C over a 30 min period while it changed from a cloudy yellow to clear solution. It was cooled to −78 °C and a solution of the mesylate in 1.7 mL of THF was added dropwise with a cannula. The reaction mixture was kept at that temperature for 1 h before $NH_4Cl_{(aq)}$ and Et_2O were added. The biphasic solution was stirred vigorously until the aqueous layer turned deep blue. The solution was then filtered through a sintered glass funnel of medium porosity packed with Celite to remove the copper salts and aqueous layer. The organic layer was concentrated under reduced pressure and the residue was purified by silica gel chromatography eluting with 3% EtOAc/hexanes to afford allene **22a** (256 mg, 80%) as a colorless oil (23:1, allene **22a**/enyne **23**, ratio based upon integration of peaks in the ^1H NMR). R_f 0.8 (20% EtOAc/hexanes); ^1H NMR (300 MHz, $CDCl_3$): δ 0.04 (s, 6H), 0.12 (s, 9H), 0.98 (s, 9H), 1.06 (s, 9H), 1.42–1.52 (m, 2H), 1.60 (d,

J=2.8 Hz, 3H), 1.65–1.90 (m, 4H), 2.25–2.34 (m, 2H), 3.51 (t, J=6.4 Hz, 2H), 4.27–4.38 (m, 1H), 4.95–5.02 (m, 1H), 7.33–7.45 (m, 6H), 7.67–7.71 (m, 4H); IR (neat) 2956, 2858, 2175, 1966 cm^{-1}; MS (GC/MS) *m/e* (relative intensity) 618 ([M]$^+$, 5), 561 (100), 199 (94); HRMS calcd for $C_{37}H_{58}O_2Si_3$: 618.3745; found: 618.3751.

4.4. Procedures for data in Table 2

For entries 1–3, 5–11, and 13–16 general procedure for allenic Alder-ene reaction using method A was followed. The crude mixture of products was analyzed by ^{1}H NMR and the ratios were determined by integration of distinct olefinic peaks from each isomer.

For entries 4 and 12 general procedure for allenic Alder-ene reaction using method B was followed. The crude mixture of products was analyzed by ^{1}H NMR and the ratios were determined by integration of distinct olefinic peaks from each isomer.

4.4.1. 4-[3-(*tert*-Butyldiphenylsilyloxy)-6-trimethylsilylmethylenecyclohex-1-enyl]-pent-3*E*-en-1-ol (*E*-24c), 4-[3-(*tert*-butyldiphenylsilyloxy)-6-trimethylsilylmethylenecyclohex-1-enyl]-pent-3*Z*-en-1-ol (*Z*-24c), and 4-[3-(*tert*-butyldiphenylsilyloxy)-6-trimethylsilylmethylenecyclohex-1-enyl]-pent-4-en-1-ol (25c). To a flame dried test tube was added allene **22c** (0.01 g, 0.02 mmol), which was azeotroped under vacuum with benzene (3×). Dichloroethane (0.3 mL) was added and the test tube was evacuated under vacuum and charged with N_2 (3×). Then, $[Ir(COD)Cl]_2$ (2.00 mg, 2.00 μmol) was added followed by $AgBF_4$ (85.0 μL of a 0.05 M dichloroethane solution, 4.00 μmol) and the system was evacuated and charged with N_2 once more. The solution was quenched after 1.75 h by addition to a silica gel plug eluting with 5% EtOAc/hexanes to afford 9 mg of a mixture of products. This mixture of products was diluted with 1.6 mL of wet MeOH and one drop of water. Then the solution was cooled to 0 °C and K_2CO_3 (0.02 g, 0.11 mmol) was added. It was then allowed to warm to ambient temperature and after 2 h a complete consumption of the starting material was seen by TLC. The mixture was filtered and concentrated under reduced pressure. The residue was purified by silica gel chromatography eluting with 10% EtOAc/hexanes to afford 5 mg of trienes *E*-**24c**, *Z*-**24c**, and **25c** in 60% yield. Pure trienes could be obtained when a larger scale reaction was performed. The minor isomer was separated with silica gel chromatography and the other two isomers were separated on HPLC for spectroscopic purposes (Varian Microsorb Dynamax 100-5 Si column, 23 °C, EtOAc/hexanes=5%, flow rate=4 mL/min). R_f 0.3 (10% EtOAc/hexanes); ^{1}H NMR (300 MHz, $CDCl_3$) major isomer *E*-**24c**: δ 0.10 (s, 9H), 1.07 (s, 9H), 1.71 (s, 3H), 1.74–1.83 (m, 2H), 2.15–2.24 (m, 1H), 2.35 (q, J=6.8 Hz, 2H), 2.54–2.62 (m, 1H), 3.67 (dd, J=6.3, 11.9 Hz, 2H), 4.32–4.37 (m, 1H), 5.23 (dt, J=1.3, 7.3 Hz, 1H), 5.31 (s, 1H), 5.50 (d, J=3.2 Hz, 1H), 7.35–7.47 (m, 6H), 7.68–7.73 (m, 4H). ^{13}C NMR (75 MHz, $CDCl_3$) (one extra peak); IR (neat) 3374, 2957, 2929, 2856, 1472, 1428 cm^{-1}; MS (GC/MS) *m/e* (relative intensity) 504 ([M]$^+$, 4), 199 (94), 73 (100): HRMS calcd for $C_{31}H_{44}O_2Si_2$: 504.2880; found: 504.2903; minor isomer at 343 K with unknown TBDPS impurity from prior reaction. * Designates product *Z*-**24c** where peaks were resolved. ^{1}H NMR (300 MHz, toluene-d_8): δ 0.12* (s, 9H), 1.04* (s, 18H), 1.16* (s, 9H), 1.77* (s, 3H), 1.82–1.90 (m, 4H), 2.00–2.12 (m, 2H), 2.16–2.30 (m, 2H), 2.65–2.75* (m, 1H), 3.32–3.40* (m, 2H), 4.50* (dt, J=3.3, 9.5 Hz, 1H), 5.23–5.32* (m, 1H), 5.61* (s, 1H), 5.65* (d, J=3.4 Hz, 1H), 7.16–7.21 (m, 20H), 7.60–7.68* (m, 6H), 7.72–7.79* (m, 4H); IR (neat) 3383, 2957, 2857, 1427 cm^{-1}; MS (GC/MS) *m/e* (relative intensity) 504 ([M]$^+$, 55), 199 (85), 73 (100); HRMS calcd for $C_{31}H_{44}O_2Si_2$: 504.2880; found: 504.2899; ^{1}H NMR (300 MHz, $CDCl_3$) constitutional isomer **25c**: δ 0.10 (s, 9H), 1.07 (s, 9H), 1.56–1.64 (m, 3H), 1.75–1.85 (m, 2H), 2.16–2.26 (m, 3H), 2.55–2.64 (m, 1H), 3.60 (dd, J=11.6, 6.3 Hz, 2H), 4.34 (m, 1H), 4.82 (d, J=2.3 Hz, 1H), 4.96 (m, 1H), 5.41 (s, 1H), 5.51 (d, J=3.3 Hz, 1H), 7.34–7.47 (m, 6H), 7.68–7.71 (m, 4H); IR (neat) 3373, 2926, 2855, 1463, 1428 cm^{-1}; MS (GC/MS) *m/e* (relative intensity) 504 ([M]$^+$, 18), 199 (100), 73 (89); HRMS calcd for $C_{31}H_{44}O_2Si_2$: 504.2880; found: 504.2882.

4.4.2. 6-Trimethylsilylhex-5-ynoic acid methoxy methyl amide (27). To a solution of acid **26** (0.60 g, 3.26 mmol) in 2 mL of DMF were added $KHCO_3$ (0.82 g, 8.15 mmol) and MeI (1.16 g, 8.15 mmol). The mixture changed from clear to yellow to orange/brown color and was left at ambient temperature. After 24 h complete consumption of the starting material was seen by TLC and the mixture was poured into EtOAc/water solution. The aqueous layer was separated and extracted with EtOAc (3×). The combined organic layers were washed with H_2O, dried over $MgSO_4$, filtered, and concentrated under reduced pressure. The residue was purified by silica gel chromatography eluting with 5% EtOAc/hexanes to afford the ester (499 mg, 76%) as a yellow oil. R_f 0.4 (20% EtOAc/hexanes); ^{1}H NMR (300 MHz, $CDCl_3$): δ 0.15 (s, 9H), 1.85 (qn, J=7.2 Hz, 2H), 2.30 (t, J=6.9 Hz, 2H), 2.45 (t, J=7.4 Hz, 2H), 3.69 (s, 3H). To a solution of 6-trimethylsilylhex-5-ynoic acid methyl ester (0.50 g, 2.52 mmol) in 5 mL of THF was added MeNHOMe·HCl (0.37 g, 3.78 mmol) and the flask was cooled to −25 °C. Then *i*-PrMgCl (3.78 mL of a 2.0 M THF solution, 7.56 mmol) was added dropwise and after addition was finished complete consumption of starting material was observed by TLC. The mixture was quenched with $NH_4Cl_{(aq)}$, and the aqueous layer was separated and washed with Et_2O (3×). The combined organic layers were dried over $MgSO_4$, filtered, and concentrated under reduced pressure. The residue was purified by silica gel chromatography eluting with 20% EtOAc/hexanes to afford amide **27** (520 mg, 91%) as a colorless oil. R_f 0.2 (20% EtOAc/hexanes); ^{1}H NMR (300 MHz, $CDCl_3$): δ 0.12 (s, 9H), 1.77–1.86 (m, 2H), 2.29 (t, J=6.8 Hz, 2H), 2.54 (t, J=7.4 Hz, 2H), 3.16 (s, 3H), 3.67 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 0.0 (3C), 19.3, 23.2, 30.4, 32.1, 61.1, 85.1, 106.5, 173.8; IR (neat) 3483, 2959, 2901, 2174, 1667 cm^{-1}; MS (GC/MS) *m/e* (relative intensity) 227 ([M]$^+$, 10), 212 (18), 167 (65), 73 (100); HRMS calcd for $C_{11}H_{21}N_1O_2Si_1$: 227.1342; found: 227.1341.

4.4.3. 2-(*tert*-Butyldimethylsilyloxy)-6-trimethylsilylhex-5-ynoic acid methoxy methyl amide (28). To a flame dried round bottom flask was added 20 mL of THF and the flask was cooled to −78 °C. NaHMDS (8.58 mL of a 1 M THF solution, 8.58 mmol) was first added and then a solution of amide **27** (1.30 g, 5.72 mmol) in 40 mL of THF was

added. The solution was left at −78 °C for 30 min and then a solution of $PhSO_2NOCHPh$ (2.24 g, 8.58 mmol) in 30 mL of THF was added via cannula. After 30 min complete consumption of the starting material was seen by TLC. The mixture was quenched with $NH_4Cl_{(aq)}$ and allowed to warm to ambient temperature. The stir bar was removed and the organic layer was removed under reduced pressure. The mixture was diluted with Et_2O and the aqueous layer was separated and washed with Et_2O (3×). The combined organic layers were dried over Na_2SO_4, filtered, and concentrated under reduced pressure. The resulting solids were diluted with 3:1 hexane/chloroform solution and filtered via gravity filtration. After removal of solvent, the residue was purified by silica gel chromatography eluting with 20% EtOAc/hexanes to afford α-hydroxy amide (1.20 g, 86%). R_f 0.2 (30% EtOAc/hexanes); ^{1}H NMR (300 MHz, $CDCl_3$): δ 0.13 (s, 9H), 1.57–1.70 (m, 1H), 1.89–2.06 (m, 1H), 2.37–2.54 (m, 2H), 3.25 (s, 3H), 3.24 (br d, J=4.9 Hz, 1H), 3.72 (s, 3H), 4.49 (t, J=6.9 Hz, 1H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 0.1 (3C), 16.0, 32.4, 33.7, 61.4, 67.3, 84.8, 106.2, 174.5; IR (neat) 3445, 2960, 2174, 1660 cm^{-1}; MS (GC/MS) *m/e* (relative intensity) 228 ($[M-CH_3]^+$, 40), 155 (30), 73 (100), 61 (91); HRMS calcd for $C_{10}H_{18}N_1O_3Si_1$: 228.1056 $[M-CH_3]^+$; found: 228.1052 $[M-CH_3]^+$. To a solution of 2-hydroxy-6-trimethylsilylhex-5-ynoic acid methoxy methyl amide (1.20 g, 4.93 mmol) in 15 mL of CH_2Cl_2 at 0 °C was added Et_3N (1.37 mL, 9.86 mmol) and then TBSOTf (1.70 mL, 7.40 mmol). After 20 min at 0 °C a complete loss of the starting material was seen by TLC. The solution was quenched with $NH_4Cl_{(aq)}$ and Et_2O, and the aqueous layer was separated and washed with Et_2O (3×). The combined organic layers were dried over $MgSO_4$, filtered, and concentrated under reduced pressure. The residue was purified by silica gel chromatography eluting with 10% EtOAc/hexanes to afford **28** (1.65 g, 94%) as a colorless oil. R_f 0.5 (20% EtOAc/hexanes); ^{1}H NMR (300 MHz, $CDCl_3$): δ 0.09 (s, 3H), 0.10 (s, 3H), 0.14 (s, 9H), 0.91 (s, 9H), 1.72–1.91 (m, 2H), 2.28–2.51 (m, 2H), 3.19 (s, 3H), 3.72 (s, 3H), 4.72–4.83 (m, 1H). ^{13}C NMR (75 MHz, $CDCl_3$): δ −5.3, −4.7, 0.1 (3C), 16.0, 18.3, 25.8 (3C), 32.7, 33.1, 61.4, 68.0, 85.2, 106.3, 174.5; IR (neat) 3445, 2960, 2174, 1660 cm^{-1}; MS (GC/MS) *m/e* (relative intensity) 342 ($[M-CH_3]^+$, 0.1), 300 (80), 73 (100); HRMS calcd for $C_{13}H_{26}NO_3Si_2$: 300.1451 $[M-C(CH_3)_3]^+$; found: 300.1445 $[M-C(CH_3)_3]^+$.

4.4.4. 5,11-Bis-(*tert*-butyldimethylsilyloxy)-1-trimethylsilylundeca-1,7-diyn-6-one (29). To a solution of *tert*-butyldimethyl(pent-4-ynyloxy)silane (1.30 g, 6.51 mmol) in 18 mL of THF at −78 °C was added *n*-butyllithium (4.07 mL of a 1.6 M hexane solution, 6.51 mmol) dropwise. The flask was left at −78 °C for 10 min and then placed in a −20 °C bath for 20 min and then cooled to −78 °C and added to a solution of amide **28** (1.55 g, 4.34 mmol) in 9 mL of THF at −78 °C via cannula. The mixture was then allowed to slowly warm over 2 h to −10 °C and the temperature was kept at −10 °C for 30 min at which time complete consumption of starting material was observed by TLC. The solution was quenched with $NH_4Cl_{(aq)}$, the stir bar was removed, and the organic layer was removed under reduced pressure. The mixture was diluted with Et_2O and the aqueous layer was separated and washed with Et_2O (3×). The combined organic layers were dried over $MgSO_4$, filtered, and concentrated under reduced pressure. The residue was purified by silica gel chromatography eluting with 1–5% EtOAc/hexanes to afford ketone **29** (1.66 mg, 77%). R_f 0.8 (20% EtOAc/hexanes); ^{1}H NMR (300 MHz, $CDCl_3$): δ 0.03 (s, 6H), 0.06 (s, 3H), 0.08 (s, 3H), 0.12 (s, 9H), 0.87 (s, 9H), 0.91 (s, 9H), 1.70–1.86 (m, 3H), 1.87–2.01 (m, 1H), 2.34 (t, J=6.6 Hz, 2H), 2.47 (t, J=7.1 Hz, 2H), 3.67 (t, J=5.8 Hz, 2H), 4.24 (dd, J=3.8, 8.7 Hz, 1H); ^{13}C NMR (75 MHz, $CDCl_3$): δ −5.4 (2C), −5.2, −4.6, 0.1 (3C), 15.7, 15.8, 18.2 (2C), 25.8 (3C), 25.9 (3C), 30.8, 33.3, 61.2, 77.5, 79.3, 85.7, 97.5, 105.9, 189.3; IR (neat) 2956, 2930, 2858, 2211, 2176, 1676 cm^{-1}; MS (GC/MS) *m/e* (relative intensity) 479 ($[M-CH_3]^+$, 2), 269 (58), 73 (100); HRMS calcd for $C_{25}H_{47}O_3Si_3$: 479.2833 $[M-CH_3]^+$; found: 479.2844 $[M-CH_3]^+$.

4.4.5. 5,11-Bis-(*tert*-butyldimethylsilyloxy)-8-methyl-1-trimethylsilylundeca-6,7-dien-1-yne (22d). The ketone **29** (0.44, 0.89 mmol) was diluted with a solution of $CeCl_3\cdot 7H_2O$ (2.89 mL of a 0.4 M solution in methanol, 1.16 mmol), cooled to −20 °C, and $NaBH_4$ (0.04 g, 1.16 mmol) was added in one portion. The mixture was allowed to warm to 0 °C and after 30 min complete consumption of the starting material was observed by TLC. The solution was quenched with slow addition of H_2O, and the aqueous layer was separated and washed with Et_2O (3×). The combined organic layers were dried over $MgSO_4$, filtered, and concentrated under reduced pressure. The residue was purified by silica gel chromatography eluting with 5% EtOAc/hexanes to afford alcohol (388 mg, 88%) as a 7:1 diastereomeric ratio (based upon integration of peaks in the ^{1}H NMR). * Designates major diastereomer where peaks were resolved. R_f 0.6 (20% EtOAc/hexanes); ^{1}H NMR (300 MHz, $CDCl_3$): δ 0.03 (s, 6H), 0.12 (s, 15H), 0.87 (s, 9H), 0.90 (s, 9H), 1.63–1.91 (m, 4H), 2.23–2.32 (m, 4H), 2.38 (d, J=6.7 Hz, 1H), 3.65 (t, J=6.0 Hz, 2H), 3.81–3.91 (m, 1H), 4.15–4.22* (m, 1H), 4.32–4.36 (m, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) (major diastereomer): δ −5.4 (2C), −4.50, −4.47, 0.0 (3C), 15.2, 15.9, 18.1, 18.2, 25.9 (6C), 31.6, 32.2, 61.6, 65.3, 74.2, 79.5, 85.1, 85.7, 106.6; IR (neat) 3456, 2956, 2857, 2175 cm^{-1}; MS (GC/MS) *m/e* (relative intensity) 496 ($[M]^+$, 0.2), 307 (4), 73 (100); HRMS calcd for $C_{22}H_{43}O_3Si_3$: 439.2520 $[M-C(CH_3)_3]^+$; found: 439.2526 $[M-C(CH_3)_3]^+$. To a solution of 5,11-bis-(*tert*-butyldimethylsilyloxy)-1-trimethylsilylundeca-1,7-diyn-6-ol (0.39 g, 0.78 mmol) in 2.6 mL of CH_2Cl_2 was added Et_3N (140 μL, 1.0 mmol) and the solution was cooled to 0 °C. Then MsCl (73 μL, 0.94 mmol) was added and after 30 min at 0 °C the mixture was diluted with pentanes. The mixture was then filtered through a sintered glass funnel of medium porosity packed with Celite and the resulting solution was washed with $NaHCO_{3(aq)}$ and brine. The organic layer was dried over $MgSO_4$, filtered, and concentrated under reduced pressure. To a suspension of CuI (0.18 g, 0.94 mmol) in 3.1 mL of THF at −30 °C was added MeLi (977 μL of a 1.6 M diethyl ether solution, 1.56 mmol) dropwise. The mixture was allowed to warm to 0 °C over a 30 min period while it changed from a cloudy yellow to clear solution. It was then cooled to −78 °C and a solution of mesylate in 2.6 mL of THF was added dropwise with a cannula. The mixture was kept at that temperature for 45 min before $NH_4Cl_{(aq)}$ and Et_2O were added. The biphasic solution was stirred vigorously until the aqueous layer turned deep blue.

The solution was then filtered through a sintered glass funnel of medium porosity packed with Celite to remove the copper salts and aqueous layer. The organic layer was concentrated under reduced pressure and the residue was purified by silica gel chromatography eluting with 1% EtOAc/hexanes to afford allene **22d** (330 mg, 86%) as a 7:1 allene **22d**/Ene-yne **23** ratio (based upon integration of peaks in the ^{1}H NMR). Pure allene **22d** was obtained by HPLC for spectroscopic purposes (Varian Microsorb Dynamax 100-5 Si column, 23 °C, EtOAc/hexanes=1%, flow rate=3 mL/min). R_f 0.8 (10% EtOAc/hexanes); ^{1}H NMR (300 MHz, $CDCl_3$): δ 0.05 (s, 6H), 0.07 (s, 3H), 0.08 (s, 3H), 0.15 (s, 9H), 1.59–1.82 (m, 7H), 1.90–2.10 (m, 2H), 2.29 (t, J=7.3 Hz, 2H), 3.63 (t, J=6.4 Hz, 2H), 4.16–4.26 (m, 1H), 4.95–5.03 (m, 1H); ^{13}C NMR (75 MHz, $CDCl_3$): δ −5.3 (2C), −4.9, −4.3, 0.1 (3C), 16.1, 18.2, 18.3, 19.3, 25.9 (3C), 26.0 (3C), 30.2, 31.0, 37.4, 62.8, 70.5, 84.5, 94.7, 100.9, 107.3, 199.7; IR (neat) 2956, 2857, 2176, 1965 cm^{-1}; MS (GC/MS) *m/e* (relative intensity) 494 ([M]$^+$, 1.2), 479 (1.5), 269 (45), 73 (100); HRMS calcd for $C_{27}H_{54}O_2Si_3$: 494.432; found: 494.3442.

4.4.6. 7-(*tert*-Butyldimethylsilyloxy)-4-methyl-11-trimethylsilyl-1-undeca-4,5-dien-10-ynyl acetate (22e). ^{1}H NMR (500 MHz, $CDCl_3$): δ 0.06 (s, 3H), 0.07 (s, 3H), 0.14 (s, 9H), 0.89 (s, 9H), 1.60–1.81 (m, 7H), 1.95–2.05 (m, 5H), 2.25–2.31 (m, 2H), 4.08 (t, J=6.6 Hz, 2H), 4.22 (q, J=6.2 Hz, 1H), 4.98–5.05 (m, 1H); ^{13}C NMR (125 MHz, $CDCl_3$): δ −4.9, −4.4, 0.1 (3C), 16.1, 18.1, 18.2, 20.9, 25.8 (3C), 26.7, 30.1, 37.4, 64.0, 70.2, 84.6, 95.2, 100.2, 107.2, 171.1, 199.7; IR (neat) 2956, 2929, 2174, 1744 cm^{-1}; MS (GC/MS) *m/e* (relative intensity) 422 ([M]$^+$, 38), 365 (45), 269 (60), 73 (100); HRMS calcd for $C_{23}H_{42}O_3Si_2$: 422.2673; found: 422.2664.

4.4.7. 7-(*tert*-Butyldimethylsilyloxy)-4-methyl-11-trimethylsilyl-1-undeca-4,5-dien-10-ynyl-1-ol (22f). ^{1}H NMR (500 MHz, $CDCl_3$): δ 0.05 (s, 3H), 0.06 (s, 3H), 0.12 (s, 9H), 0.87 (s, 9H), 1.62–1.78 (m, 7H), 1.95–2.08 (m, 2H), 2.20–2.31 (m, 2H), 3.64 (t, J=6.4 Hz, 2H), 4.22 (q, J=6.3 Hz, 1H), 4.95–5.02 (m, 1H); ^{13}C NMR (125 MHz, $CDCl_3$): δ −5.0, −4.4, 0.1 (3C), 16.0, 18.1, 19.1, 25.8 (3C), 30.2, 30.4, 37.3, 62.3, 70.2, 84.6, 94.8, 100.7, 107.2, 199.7; IR (neat) 3347, 2955, 2929, 2175, 1250 cm^{-1}; MS (GC/MS) *m/e* (relative intensity) 380 ([M]$^+$, 30), 323 (20), 269 (60), 75 (100); HRMS calcd for $C_{21}H_{40}O_2Si_2$: 380.2567; found: 380.2558.

4.4.8. 3-(*tert*-Butyldimethylsilyloxy)-1-[4-(*tert*-butyldimethylsilyloxy)-1-methylbut-1*E*-enyl]-6-trimethylsilylmethylenecyclohexene (*E*-24d), 3-(*tert*-butyldimethylsilyloxy)-1-[4-(*tert*-butyldimethylsilyloxy)-1-methyl-but-1*Z*-enyl]-6-trimethylsilylmethylenecyclohexene (*Z*-24d), and 3-(*tert*-butyldimethylsilyloxy)-1-[4-(*tert*-butyldimethylsilyloxy)-1-methylenebutyl]-6-trimethylsilylmethylenecyclohexene (25d). To a flame dried test tube was added allene **22d** (1.66 g, 3.36 mmol), which was azeotroped under vacuum with benzene (3×). Toluene (17 mL) was added and the test tube was evacuated under vacuum and charged with N_2 (3×). Then, $[Rh(CO)_2Cl]_2$ (0.04 g, 0.09 mmol) was added at ambient temperature and the system was evacuated and charged with N_2 once more. The mixture was heated to 80 °C and followed by GC analysis. The mixture was quenched after 1 h by running through a silica gel plug eluting with 5% EtOAc/hexanes to afford 1.57 g of trienes *E*-**24d**, *Z*-**24d**, and **25d** in 6:2:1 ratio, respectively, and a 95% crude yield.

4.4.9. 3-(4-Hydroxy-1-methylbut-1*E*-enyl)-4-trimethylsilylmethylenecyclohex-2-enol (*E*-30), 3-(4-hydroxy-1-methylbut-1*Z*-enyl)-4-trimethylsilylmethylenecyclohex-2-enol (*Z*-30), and 3-(4-hydroxy-1-methylenebutyl)-4-trimethylsilylmethylenecyclohex-2-enol (31). To a solution of trienes *E*-**24d**, *Z*-**24d**, and **25d** (0.16 g, 0.32 mmol) in 8 mL of THF was added $NH_4Cl_{(s)}$ (0.1 g, 1.86 mmol) and then TBAF (1.3 mL of a 1 M THF solution, 1.3 mmol). The mixture was heated to 50 °C and after 12 h was quenched by addition of water. The stir bar was removed and the organic layer was evaporated under reduced pressure. The mixture was diluted with Et_2O and the aqueous layer was separated and washed with Et_2O (3×). The combined organic layers were dried over $MgSO_4$, filtered, and concentrated under reduced pressure. The residue was purified by silica gel chromatography eluting with 30% EtOAc/hexanes to afford trienes *E*-**30**, *Z*-**30**, and **31** (78 mg, 92%). R_f 0.1 (30% EtOAc/hexanes); R_f 0.42, 0.6, 0.45 (*E*-**30**, *Z*-**30**, **31**) (10% isopropanol/pentanes); ^{1}H NMR (300 MHz, $CDCl_3$) *E*-**30**: δ 0.11 (s, 9H), 1.58–1.70 (m, 1H), 1.72 (d, J=0.5 Hz, 3H), 2.00 (ddd, J=4.2, 8.1, 16.5 Hz, 1H), 2.10 (br s, 1H), 2.25–2.40 (m, 3H), 2.55 (ddd, J=3.7, 7.8, 14.6 Hz, 1H), 3.66 (t, J=6.6 Hz, 2H), 4.27–4.35 (m, 1H), 5.31 (dt, J=1.3, 7.2 Hz, 1H), 5.37 (s, 1H), 5.63 (d, J=3.3 Hz, 1H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 0.0 (3C), 17.2, 28.1, 31.6, 32.8, 62.1, 66.2, 124.7, 127.0, 128.4, 138.5, 147.5, 149.3; IR (neat) 3319, 2952, 1578, 1437 cm^{-1}; MS (GC/MS) *m/e* (relative intensity) 266 ([M]$^+$, 1), 192 (34), 145 (100); HRMS calcd for $C_{15}H_{26}O_2Si$: 266.1702; found: 266.1693; ^{1}H NMR (300 MHz, $CDCl_3$) *Z*-**30**: δ 0.12 (s, 9H), 1.60–1.75 (m, 1H), 1.81 (s, 3H), 2.00–2.19 (m, 3H), 2.29–2.41 (m, 1H), 2.62 (ddd, J=3.7, 6.8, 14.6 Hz, 1H), 3.51–3.63 (m, 2H), 4.31–4.38 (m, 1H), 5.36 (dt, J=1.0, 6.4 Hz, 1H), 5.44 (s, 1H), 5.60 (d, J=3.1 Hz, 1H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 0.0 (3C), 24.9, 27.9, 29.7, 32.7, 62.5, 66.3, 123.6, 126.0, 129.7, 138.5, 143.3, 148.5; IR (neat) 3318, 2953, 1577, 1434 cm^{-1}; MS (GC/MS) *m/e* (relative intensity) 266 ([M]$^+$, 1.4), 248 (8.4), 73 (100); HRMS calcd for $C_{15}H_{26}O_2Si$: 266.1702; found: 266.1698; ^{1}H NMR (300 MHz, $CDCl_3$) constitutional isomer **31**: δ 0.13 (s, 9H), 1.59–1.76 (m, 3H), 2.03 (ddd, J=4.3, 8.1, 16.8 Hz, 1H), 2.23 (t, J=7.6 Hz, 2H), 2.36 (dddd, J=1.3, 3.7, 9.8, 14.7 Hz, 1H), 2.57 (ddd, J=3.8, 7.9, 14.6 Hz, 1H), 3.63 (t, J=6.6 Hz, 2H), 4.32–4.37 (m, 1H), 4.89 (d, J=2.2 Hz, 1H), 5.02 (dt, J=1.3, 2.2 Hz, 1H), 5.49 (s, 1H), 5.67 (d, J=3.4 Hz, 1H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 0.0 (3C), 27.9, 31.2, 32.3, 32.8, 62.4, 66.2, 114.3, 127.5, 129.2, 144.9, 148.8, 149.1; IR (neat) 3332, 2949, 1577, 1435 cm^{-1}; MS (GC/MS) *m/e* (relative intensity) 248 ([M−H_2O]$^+$, 8), 73 (100); HRMS calcd for $C_{15}H_{24}OSi$: 248.1596 [M−H_2O]$^+$; found: 248.1588 [M−H_2O]$^+$.

4.4.10. 3-[4-(*tert*-Butyldimethylsilyloxy)-1-methylbut-1-enyl]-4-trimethylsilyl methylenecyclohex-2-enol (32). To a solution of triene *E*-**30** (0.07 g, 0.26 mmol) in 1.3 mL of CH_2Cl_2 were added Et_3N (150 μL, 1.10 mmol) and TBDMSCl (0.08 g, 0.29 mmol) at 0 °C. The solution was then warmed to ambient temperature and left overnight.

The mixture was quenched by addition of water, and the aqueous layer was separated and washed with CH_2Cl_2 (3×). The combined organic layers were dried over $MgSO_4$, filtered, and concentrated under reduced pressure. The residue was purified by silica gel chromatography eluting with 5% EtOAc/hexanes to afford **32** (74 mg, 75%). R_f 0.6 (30% EtOAc/hexanes); ^{1}H NMR (300 MHz, $CDCl_3$): δ 0.07 (s, 6H), 0.12 (s, 9H), 0.90 (s, 9H), 1.62–1.70 (m, 1H), 1.73 (s, 3H), 1.93–2.05 (m, 1H), 2.28–2.38 (m, 3H), 2.55 (ddd, J=3.6, 7.9, 14.5 Hz, 1H), 3.65 (t, J=7.0 Hz, 2H), 4.24–4.28 (m, 1H), 5.31 (t, J=7.2 Hz, 1H) 5.41 (s, 1H), 5.62 (d, J=3.0 Hz, 1H). ^{13}C NMR (75 MHz, $CDCl_3$): δ −5.2 (2C), 0.1 (3C), 17.2, 18.3, 26.0 (3C), 28.0, 32.0, 32.9, 62.8, 66.3, 125.4, 127.1, 128.0, 137.2, 147.9, 149.3; IR (neat) 3334, 2954, 2858, 1578 cm^{-1}; MS (GC/MS) *m/e* (relative intensity) 380 ([M]$^+$, 3), 145 (40), 73 (100); HRMS calcd for $C_{21}H_{40}O_2Si_2$: 380.2567; found: 380.2567.

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