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Stereoselective Synthesis of Trisubstituted (*E*,*E*)-1,3-Dienes by the Site-Selective Reductive Cross-Coupling of Internal Alkynes with Terminal Alkynes: A Fragment Coupling Reaction for Natural Product Synthesis

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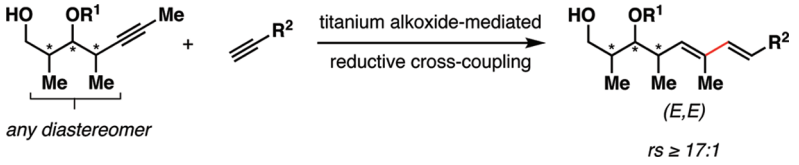

A highly selective convergent coupling reaction is described between alkynes for the synthesis of stereodefined trisubstituted (*E*,*E*)-1,3-dienes—structural motifs commonly found embedded in the skeletons of bioactive polyketide-derived natural products. While numerous multistep processes for the synthesis of this stereodefined functional group exist, the current method represents a significant advance as it does not require stereodefined olefinic coupling partners (vinyl halide or vinyl organometallic); it proceeds by a single convergent C−C bond-forming event (avoiding multistep methods based on carbonyl olefination) and is tolerant of a diverse array of functional groups including free hydroxyls. Through a systematic study of titanium-mediated reductive cross-coupling reactions of internal alkynes with terminal alkynes, a fragment coupling reaction of great utility in natural product synthesis has emerged. Here, use of a proximal hydroxy group to control regioselection in the functionalization of a preformed titanacyclopropene has led to the establishment of a highly selective bimolecular coupling process, where C−C bond formation occurs in concert with the establishment of two stereodefined alkenes. Compared to the body of literature known for related metal-mediated coupling reactions, the current work defines a powerful advance, achieving site-selective bimolecular C−C bond formation without the need for using TMS-alkynes or conjugated alkynes. Overall, complex 1,3-dienes relevant for the synthesis of polyketide-derived natural products of varying stereochemistry were prepared with typically ≥20:1 selectivity, defining the important role of an alkoxide directing group located δ to preformed titanacyclopropenes.

Introduction

Since the discovery of the Diels−Alder reaction, substituted 1,3-dienes have played an important role in organic chemistry.[1] In addition to their utility in cycloaddition processes, substituted and stereodefined 1,3-dienes are a structural motif found in a variety of complex bioactive natural products (Figure 1).[2] Not surprisingly, many synthetic methods have appeared that provide access to this structural motif, and countless examples highlight the utility of these methods in natural product synthesis. Nevertheless, challenges remain in the area of organic chemistry focused on their synthesis, as commonly encountered subsets of 1,3-dienes often dictate the use of numerous chemical transformations to establish their stereodefined architectures.

(1) (a) Diels, O.; Alder, K. *Liebigs Ann. Chem.* **1928**, *460*, 98–122. For recent reviews, see: (b) Fringuelli, F.; Taticchi, A., *The Diels-Alder Reaction: Selected Practical Methods*. 2002, West Sussex, England: John Wiley & Sons. 340. (c) Reymond, S.; Cossy, J. *Chem. Rev.* **2008**, *108*, 5359–5406. (d) Sauer, J.; Sustmann, R. *Angew. Chem., Int. Ed. Engl.* **1980**, *19*, 779–807.

(2) For piericidin C7, see: (a) Hayakawa, Y.; Shirasaki, S.; Shiba, S.; Kawasaki, T.; Matsuo, Y.; Adachi, K.; Shizuri, Y. *J. Antibiot.* **2007**, *60*, 196–200. (b) Hayakawa, Y.; Shirasaki, S.; Kawasaki, T.; Matsuo, Y.; Adachi, K.; Shizuri, Y. *J. Antibiot.* **2007**, *60*, 201–203. For a review of the leptomycins (including callystatin), see: (c) Kalesse, M.; Christmann, M. *Synthesis* **2002**, 981–1003. For the isolation and structure elucidation of arenicolide C, see: (d) Williams, P. G.; Miller, E. D.; Asolkar, R. N.; Jensen, P. R.; Fenical, W. *J. Org. Chem.* **2007**, *72*, 5025–5034. For the isolation and structure elucidation of lycogalinoside A, see: (e) Rezanka, T.; Dvorakova, R. *Phytochem* **2003**, *63*, 945–952. For the isolation and structure elucidation of pectenotoxin II, see: (f) Yasumoto, T.; Murata, M.; Oshima, Y.; Sano, M.; Matumoto, G. K.; Clardy, J. *Tetrahedron* **1985**, *41*, 1019–1025.

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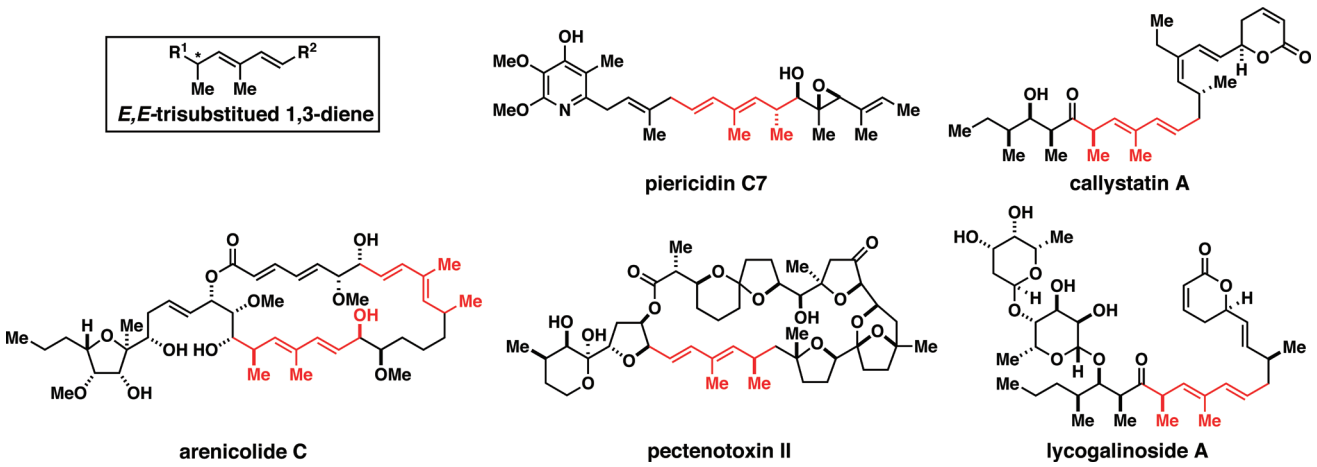

FIGURE 1. Stereodefined *E*,*E*-trisubstituted alkenes are structural motifs found embedded in the carbon skeleton of a variety of architecturally complex natural products.

For example, the stereodefined (*E*,*E*)-trisubstituted 1,3-diene substructure found in many complex natural products (Figure 1) poses an underappreciated problem in stereoselective synthesis. Sequential carbonyl olefination reactions have been established to provide a means of accessing such architecture, yet they typically require several functional group manipulations and redox processes that are not associated with C−C bond formation.[3] Alternatively, while modern palladium-catalyzed coupling reactions define unique convergent processes for the synthesis of 1,3-dienes,[4] these catalytic reactions typically require the use of two stereodefined coupling partners (the vinylhalide and vinylorganometallic reagents), the syntheses of which require the use of numerous stoichiometric transformations prior to the catalytic C−C bond-forming event.

An alternative to these established methods, for the stereoselective synthesis of a subset of geometrically defined trisubstituted 1,3-dienes, could derive from the reductive cross-coupling of an appropriately functionalized internal alkyne **1** with a terminal alkyne **2** (Figure 2). Such a process would represent a potentially powerful fragment coupling reaction for natural product synthesis (i.e., Figure 1). Here, nonstereogenic functional groups (alkynes) define the sites of

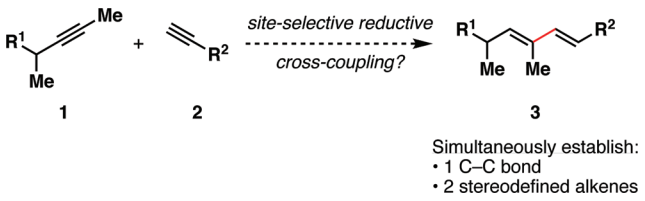

FIGURE 2. Reductive cross-coupling as a potential strategy for the synthesis of stereodefined *E*,*E*-trisubstituted alkenes.

reactivity for each coupling partner, and during the course of the C−C bond-forming process, two stereodefined alkenes are established, one of which is trisubstituted (**3**, Figure 2). To further enhance the merit of such a bond construction, alkynes possess orthogonal reactivity to a large array of functional groups and can be installed by a variety of well-established methods. Despite the significant potential of this class of coupling reactions, barriers related to the control of reactivity and selectivity have stood in the way of advancing useful methods for broad application in natural product synthesis.

Background Associated with Regioselectivity in the Reductive Cross-Coupling of Alkynes. Over the last five decades,

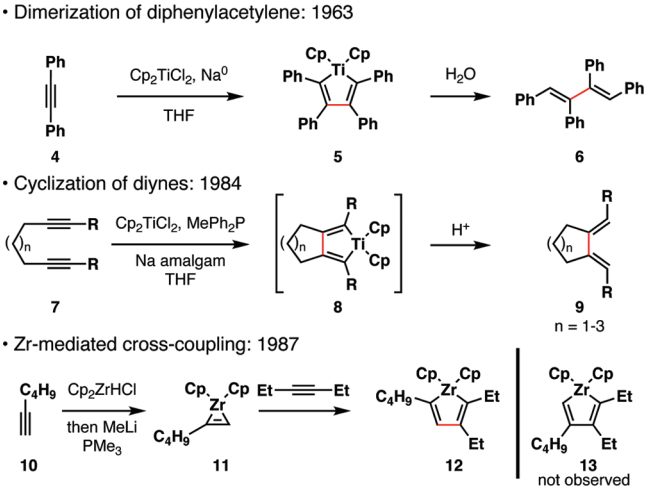

FIGURE 3. Development of alkyne−alkyne reductive coupling chemistry.

(3) For a review of carbonyl olefination methods, see: (a) Takeda, T., ed. *Modern Carbonyl Olefination: Methods and Applications*. 2004, Wiley-VCH. 365. (b) Maryanoff, B. E.; Reitz, A. B. *Chem. Rev*. **1989**, *89*, 863–927. For selected examples of carbonyl olefination for the stereoselective generation of 1,3-dienes in the context of natural product total synthesis, see: (c) Bonazzi, S.; Güttinger, S.; Zemp, I.; Kutay, U.; Gademann, K. *Angew. Chem., Int. Ed*. **2007**, *46*, 8707–8710. (d) Arai, N.; Chikaraishi, N.; Omura, S.; Kuwajima, I. *Org. Lett*. **2004**, *6*, 2845–2848. (e) Marshall, J. A.; Bourbeau, M. P. *J. Org. Chem*. **2002**, *67*, 2751–2754. (f) Lautens, M.; Stammers, T. A. *Synthesis* **2002**, 1993–2012. (g) Smith, A. B.; Brandt, B. M. *Org. Lett*. **2001**, *3*, 1685–1688. (h) Kobayashi, M.; Wang, W.; Tsutsui, Y.; Sugimoto, M.; Murakami, N. *Tetrahedron Lett*. **1998**, *39*, 8291–8294. (i) Schnermann, M. J.; Romero, F. A.; Hwang, I.; Nakamaru-Ogiso, E.; Yagi, T.; Boger, D. L. *J. Am. Chem. Soc*. **2006**, *128*, 11799–11807. (j) Evans, D. A.; Rajapakse, H. A.; Chiu, A.; Stenkamp, D. *Angew. Chem., Int. Ed*. **2002**, *41*, 4573–4576.

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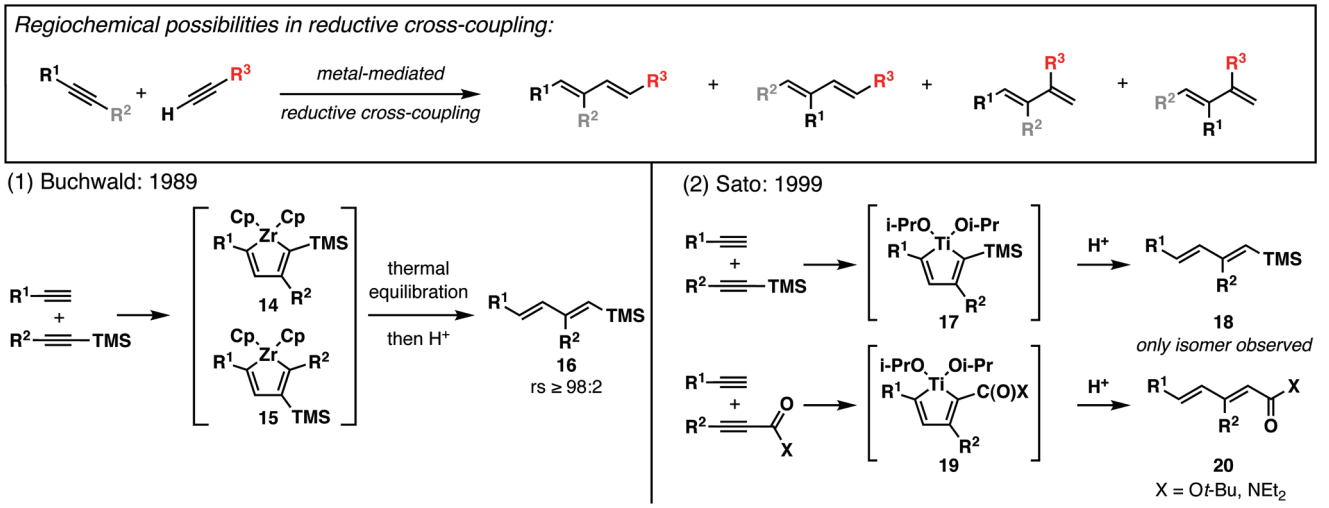

FIGURE 4. Challenges with selective reductive cross-coupling of disubstituted alkynes and terminal alkynes, along with the methods known for control.

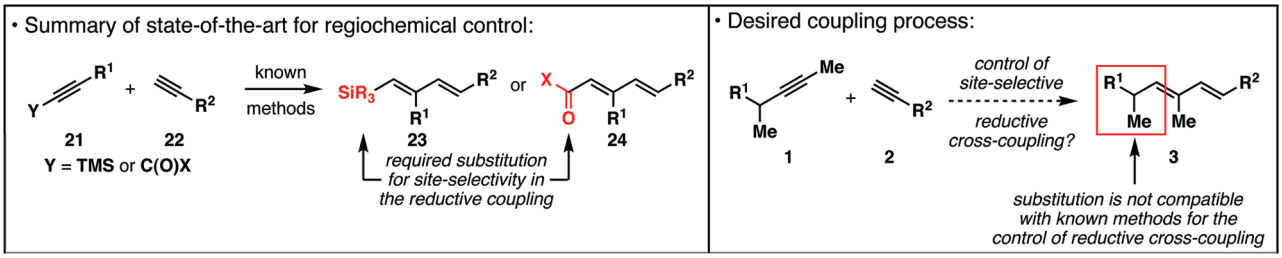

FIGURE 5. Reductive cross-coupling methods known are not suitable for the bond construction of interest.

significant progress has been made in the reductive coupling chemistry of alkynes. As illustrated in Figure 3, early observations of the dimerization of diphenylacetylene (**4** → **5**)[5] have been followed by diyne cyclization (**7** → **8** → **9**)[6] and, most recently, cross-coupling (**10** → **11** → **12**).[7] Here, selective "crossed" reductive coupling was made possible by the preformation of complex **11** followed by exposure to 3-hexyne. A notable feature of this reaction was the high regioselectivity with which the terminal alkyne was functionalized: C−C bond formation was observed at the terminal position of the alkyne.

Following these ground-breaking accomplishments, more advanced cross-coupling reactions between alkynes began to appear. Specifically, convergent assembly of trisubstituted dienes was achieved through the regioselective coupling of unsymmetrical internal alkynes with terminal alkynes (Figure 4).[8] In Zr-mediated processes, coupling produces a mixture of isomeric metallacyclopentadienes (**14** and **15**), the equilibration and subsequent protonation of which provide asymmetrically substituted dienes (**16**) with very high levels of selectivity (rs ≥98:2). Distinct from previously described reductive cross-coupling processes between alkynes, in this convergent coupling regiochemical control was achieved in the functionalization of *both* alkynes.[8,9] In related Ti-mediated processes, TMS alkynes and conjugated internal alkynes represent the most general substrate classes known to react in a regioselective fashion with terminal alkynes and provide a means of accessing dienes of general structures **18** and **20**.[10]

While reductive coupling of alkynes has been known for nearly 50 years, the use of this mode of reactivity for the cross-coupling of unsymmetrically substituted alkynes remains significantly limited. As summarized in Figure 5, high levels of regioselection can be obtained with only a small subset of internal alkynes (**21**). The requirement of silyl substitution or the use of a polarized conjugated alkyne restricts this bimolecular bond construction to the synthesis of stereodefined dienes of the substitution depicted in **23** and **24**. In desiring a reductive cross-coupling process to provide access to the branched (*E*,*E*)-trisubstituted 1,3-diene substructure shared by a variety of complex natural products, we set out to design a means by which to control regioselection in alkyne−alkyne reductive cross-coupling that would be amenable to the selective formation of dienes **3** from alkynes **1** and **2** (Figure 5).

Results and Discussion

A common strategy for the design of regio- and stereoselective bond forming reactions in organic chemistry targets

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(7) Buchwald, S. L.; Watson, B. T.; Huffman, J. C. *J. Am. Chem. Soc.* **1987**, *109*, 2544–2546.
(8) Buchwald, S. L.; Nielsen, R. B. *J. Am. Chem. Soc.* **1989**, *111*, 2870–2874.
(9) For an example of regioselective reductive cross-coupling between a 1-methylthioalkyne and a symmetrical internal alkyne, see: Van Wagenen, B. C.; Livinghouse, T. *Tetrahedron Lett.* **1989**, *30*, 3495–3498.
(10) Hamada, T.; Suzuki, D.; Urabe, H.; Sato, F. *J. Am. Chem. Soc.* **1999**, *121*, 7342–7344.

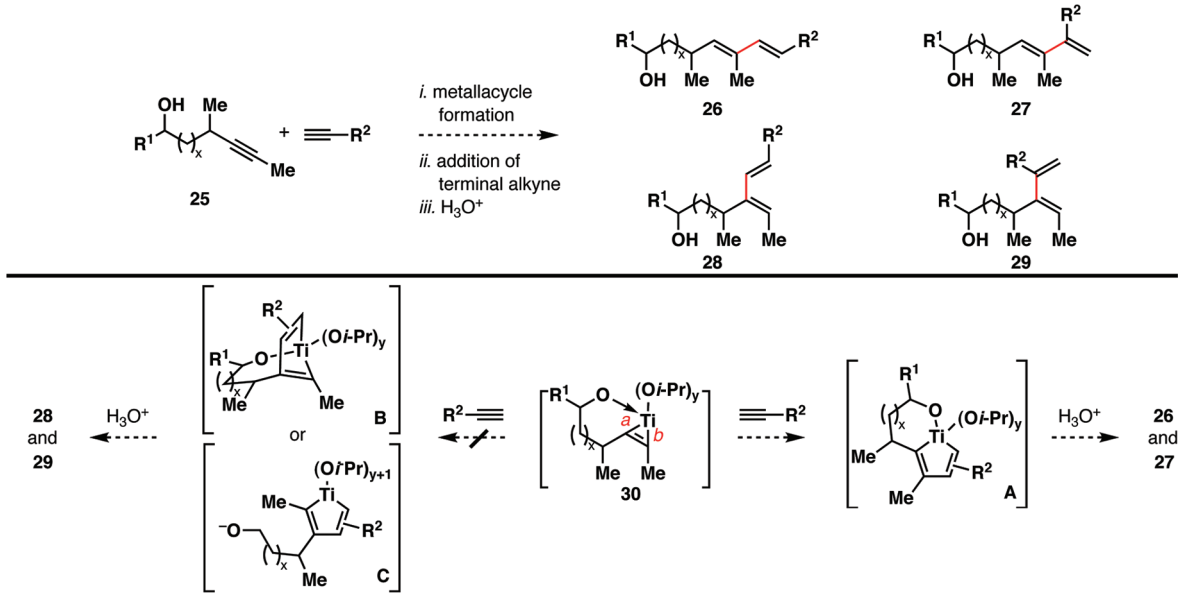

FIGURE 6. Design of a directed alkyne−alkyne reductive cross-coupling.

preassociation of a reagent with a substrate as a means to render a reaction intramolecular.[11] Reactions that proceed by such preorganization often provide products with exquisite levels of regio- and stereoselection as a function of the highly ordered transition state geometries through which they proceed. As such, we aimed to develop a directed version of a reductive cross-coupling reaction between alkynes.[12]

Due to the density of heteroatom functionality typically present in stereochemically complex natural products that possess the trisubstituted 1,3-diene substructure of interest (Figure 1),[13] we sought a reductive coupling process capable of being directed by neighboring hydroxy substituents.[14,15] While a number of metals are known to participate in metallacycle-mediated C−C bond formation, our selection of a reaction system suitable for the synthetic problem at hand was based on (1) the ability of metal alkoxides to undergo rapid and reversible ligand exchange[16] and (2) the previously demonstrated reactivity of titanium alkoxide reagents in metallacycle-mediated C−C bond forming reactions.[17]

Our initial reaction design is outlined in Figure 6. We speculated that an alkoxide proximal to the preformed titanium−alkyne complex of an internal alkyne may associate with the neighboring metal center in the transition state for C−C bond formation.[18] If so, we would anticipate that the

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(14) For examples of hydroxyl-directed carbometalation reactions based on titanium, see: (a) Coleman, R. A.; O'Doherty, C. M.; Tweedy, H. E.; Harris, T. V.; Thompson, D. W. *J. Organomet. Chem.* **1976**, *107*, C15–C17. (b) Brown, D. C.; Nichols, S. A.; Gilpin, A. B.; Thompson, D. W. *J. Org. Chem.* **1979**, *44*, 3457–3461. (c) Ewing, J. C.; Ferguson, G. S.; Moore, D. W.; Schultz, F. W.; Thompson, D. W. *J. Org. Chem.* **1985**, *50*, 2124–2128. For hydroxyl-directed carbometalation based on magnesium, see: (d) Eisch, J. J.; Merkley, J. H. *J. Organomet. Chem.* **1969**, *20*, P27–P31. (e) Eisch, J. J. *J. Organomet. Chem.* **1980**, *200*, 101–117. (f) Richey, H. G.; Von Rein, F. W. *J. Organomet. Chem.* **1969**, *20*, P32–P35. (g) Hoveyda, A. H.; Xu, Z. *J. Am. Chem. Soc.* **1991**, *113*, 5079–5080. (h) Hoveyda, A. H.; Xu, Z.; Morken, J. P.; Houri, A. F. *J. Am. Chem. Soc.* **1991**, *113*, 8950–8952. (i) Itami, K.; Mitsudo, K.; Yoshida, J. *Angew. Chem., Int. Ed.* **2001**, *40*, 2337–2339. (j) Itami, K.; Kamei, T.; Yoshida, J. *J. Am. Chem. Soc.* **2003**, *125*, 14670–14671. For directed carbometalation based on tantalum, see: (k) Takai, K.; Yamada, M.; Odaka, H.; Utimoto, K. *J. Org. Chem.* **1994**, *59*, 5852–5853. For directed carbometalation based on aluminum/zirconium, see: (l) Ma, S.; Negishi, E.-I. *J. Org. Chem.* **1997**, *62*, 784–785.

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(17) For reviews of titanium alkoxide-mediated C−C bond formation, see: (a) Kulinkovich, O. G.; de Meijere, A. *Chem. Rev.* **2000**, *100*, 2789–2834. (b) Sato, F.; Urabe, H.; Okamoto, S. *Chem. Rev.* **2000**, *100*, 2835–2886.

(18) This design was constrained by the requirement of pregenerating a Ti−alkyne complex of the internal alkyne (rather than the terminal alkyne). Attempted reductive coupling of terminal alkynes with aldehydes has been reported to be unsuccessful: (a) Harada, K.; Urabe, H.; Sato, F. *Tetrahedron Lett.* **1995**, *36*, 3203–3206. Surprisingly, some examples have reported that related coupling reactions with terminal alkynes, that likely proceed by formation of a titanium−alkyne complex are successful: (b) Yamaguchi, S.; Jin, R.-Z.; Tamao, K.; Sato, F. *J. Org. Chem.* **1998**, *63*, 10060–10062. For the generation of metallated titanacyclopropenes from terminal alkynes, see: (c) Averbuj, C.; Kaftanov, J.; Marek, I. *Synlett* **1999**, 1939–1941.

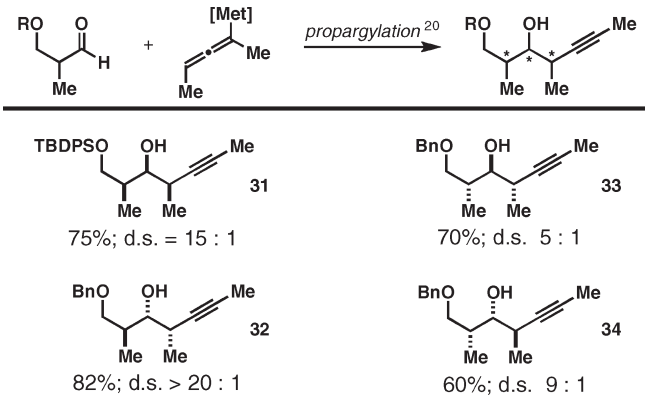


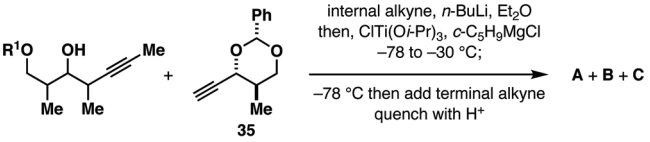
FIGURE 7. Generation of stereodefined coupling partners.

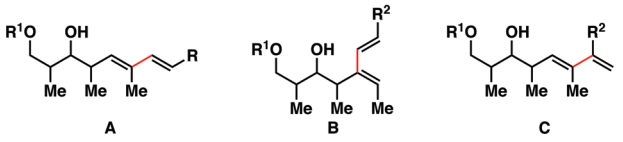
two metal−carbon bonds (*a* and *b*) of the asymmetrically substituted metallacyclopropene **30** would differ in their levels of reactivity in bimolecular carbometalation. Of the products that would be reasonably expected from such a process (**26**−**29**), we anticipated that isomers **27** and **29** were unlikely, as others have demonstrated that functionalization of the terminal alkyne component generally occurs at the terminal carbon of the alkyne.[10] Of the remaining isomeric products (**26** and **28**), we expected that the transition state leading to the metallacyclic precursor of **28** (**B** or **C**) would be destabilized due to the significant strain associated with the formation of a bridgehead alkene (via a carbometalation process that engaged bond "*a*" of **30**; see **B**) or require interruption of the tethering interaction (σ_{Ti-O}; *en route* to **C**).

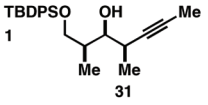
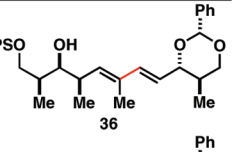
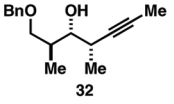
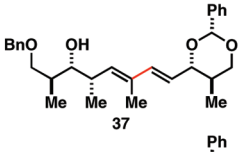
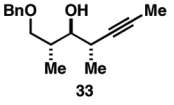
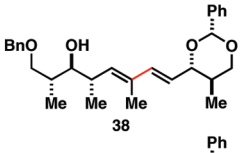
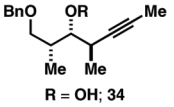
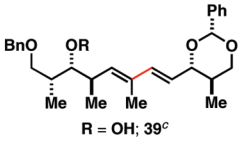
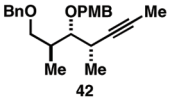
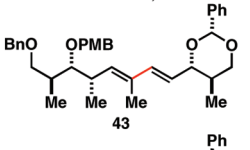
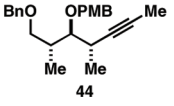
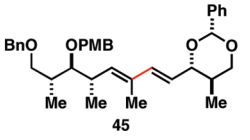
Based on this design, and the desire to define a synthetically straightforward coupling process, it was essential that the coupling partners be readily available, without the requirement of numerous orthogonal functionalization reactions to C−C bond formation. A variety of methods are available for the synthesis of substituted alkynes, and most of these install the alkyne through a process that occurs with simultaneous chain extension (C−C bond formation).[19] Among the known methods, Marshall's propargylation chemistry was particularly attractive, as C−C bond formation occurs in concert with the establishment of two stereogenic centers.[20] Additionally, Marshall's thorough study of this process has led to stereodivergent methods that allow for the synthesis of all possible stereoisomers of simple homopropargylic alcohols. As illustrated in Figure 7, pentynylation of readily available chiral aldehydes provides direct and stereoselective access to all diastereomers of a model substrate suitable for interrogation of the proposed alkoxide-directed reductive cross-coupling reaction.[21]

Consistent with our goal of defining a general method that was useful for the synthesis of a range of stereochemically complex targets, we began investigating the coupling reaction of each stereodefined homopropargylic alcohol (**31**−**34**) with a second chiral coupling partner (**35**) to deliver complex products of potential utility in natural product synthesis (Table 1).[22] The coupling reactions were conducted by initial deprotonation of the homopropargylic alcohol, followed by exposure to the combination of ClTi(O-*i*-Pr)$_3$ and cyclopentylmagnesium chloride (to form a presumed intermediate metallacyclopropene), addition of the terminal alkyne, and aqueous workup. As illustrated in entries 1−4, the factors that contribute to selectivity in this reductive cross-coupling process appeared more complex than initially expected. In most cases, high to moderate levels of regioselection were observed for the production of the desired isomer (entries 1−3). Surprisingly, coupling of

TABLE 1. Initial Study of Alkoxide-Directed Reductive Cross-Coupling of Internal Alkynes with Terminal Alkynes[22]





entry	internal alkyne	yield[a]	rr[b] (A:B:C)	major regioisomer
1		70	28:1:1	
2		50	15:2:1	
3		52	4:0:1	
4	 R = OH; 34	63	1.0:1.5:1.0	 R = OH; 39[c]
5[d]	R = OPMB; 40	82	3:1:0	R = OPMB; 41
6		87	5:1:0	
7		70	6:1:0	

[a]Yield based on terminal alkyne. [b]Regioisomeric ratio determined by ^{1}H NMR of the product mixture after flash column chromatography (see the Supporting Information for details). [c]Compound **39** is not the major isomer from this coupling reaction. [d]ClTi(O*i*-Pr)$_3$, *c*-C$_5$H$_9$MgCl, −78 to −30 °C, then −78 °C and addition of terminal alkyne.

(19) For general reviews of acetylene chemistry, see: (a) Stang, P. J.; Diederich, F., eds. *Modern Acetylene Chemistry*. 1995, Wiley-VCH. 527. (b) Diederich, F.; Stang, P. J.; Tykwinski, R. R., eds. *Acetylene Chemistry: Chemistry, Biology, and Material Science*. 2005, Wiley-VCH. 2005.

(20) For recent reviews, see: (a) Marshall, J. A. *J. Org. Chem.* **2007**, *72*, 8153–8166. (b) Marshall, J. A. *Chem. Rev.* **2000**, *100*, 3163–3185.

(21) Bahadoor, A. B.; Flyer, A.; Micalizio, G. C. *J. Am. Chem. Soc.* **2005**, *127*, 3694–3695.

(22) Shimp, H. L.; Micalizio, G. C. *Org. Lett.* **2005**, *7*, 5111–5114.

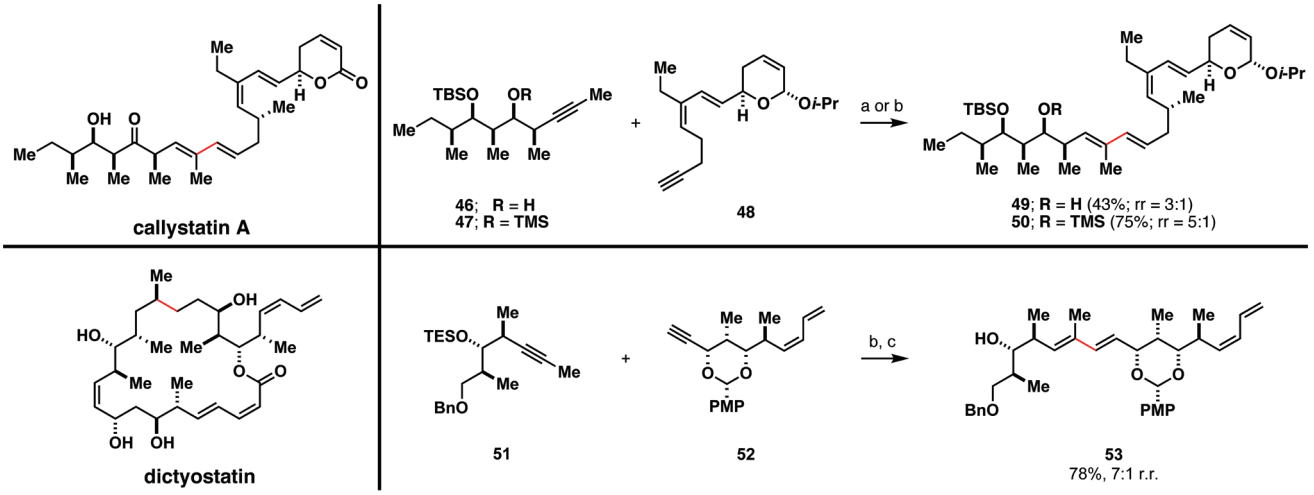


FIGURE 8. Demonstration in the context of natural product synthesis.

the *anti-syn* isomer **34** was unselective, providing a nearly equal distribution of isomers A−C.

These initial results demonstrated that relative stereochemistry of the internal alkyne component plays a significant role in site-selectivity for the reductive coupling reaction. Interestingly, this stereochemical dependence on regiochemistry applies not only to the functionalization of the internal alkyne, but also to the terminal alkyne coupling partner **35** (as demonstrated by the varying levels of isomer C observed in entries 1−4 as a function of the stereochemistry of the internal alkyne).[22] While highlighting a unique interplay between stereochemical pairing and site-selective C−C bond formation, the observation of isomer C in all of these reactions was surprising, as previous studies of reductive cross-coupling reactions of simple TMS-alkynes and polarized alkynes with terminal alkynes did not lead to the formation of noticeable quantities of this isomer.[10]

To explore the impact of the tethered hydroxy substituent on regioselection, several experiments were conducted with the corresponding PMB ethers. While coordination of the ethereal oxygen of the PMB ether might still be expected to play a role in the transition state for reductive cross-coupling, we observed a significant change in selectivity for these reactions. As illustrated in entry 5, use of the PMB-protected *anti-syn* isomer **40** results in an enhancement of regioselection, providing the desired trisubstituted 1,3-diene **41** in 82% yield (rr 3:1). Unfortunately, this enhancement of regioselection with the use of the fully protected internal alkyne is not uniform throughout the stereoisomeric series. Coupling of the PMB-protected *syn-anti* isomer **42** leads to a slight decrease in regioselection compared to the homopropargylic alcohol (entry 6 vs entry 2), while coupling of the PMB-protected *anti-anti* isomer **44** leads to a modest increase in regioselection (entry 7 vs entry 3).

Overall, these preliminary results suggested that the factors that govern site-selectivity in this reductive cross-coupling reaction are complex, affected by both the stereochemistry of the internal alkyne component and the nature of the substituents present on the tether (PMB vs alkoxide). Nevertheless, the bond construction defined by these initial studies proved to be of utility in complex molecule synthesis. For example, initial studies toward a convergent total synthesis of callystatin explored the reductive cross-coupling of the homopropargylic alcohol **46** with terminal alkyne **48** (Figure 8).[23] While the desired product **49** was produced in moderate yield and selectivity, we found in subsequent studies that both yield and selectivity were increased in the coupling reaction of the TMS-protected substrate **47** (75%, rr = 5:1). In a related campaign in total synthesis targeting dictyostatin, reductive cross-coupling between **51** and **52** provided the stereodefined tetraene **53** in 78% yield (rr = 7:1).[24] In each case, the application of the alkyne−alkyne reductive cross-coupling reaction proved quite useful, defining a highly convergent method for the assembly of natural products of polyketide biosynthetic origin, while demonstrating an impressive functional group compatibility profile and substantial chemoselectivity.

Observing a glimpse of the potential power of this cross-coupling reaction in natural product synthesis, we aimed to achieve higher levels of control in this fragment coupling process. In considering the complexity associated with the trends in regioselectivity illustrated in Table 1, the uncertainty regarding the nature of the transition state for these processes guided our next series of experiments. The initial design for the alkoxide-directed reductive cross-coupling was based on the proposition that a bicyclic metallacyclopropene plays a role in the transition state for C−C bond formation. With this mechanistic picture in mind, the homopropargylic alcohol substrates explored may not represent ideal substrates to probe the merit of the design. As depicted in Figure 9, we anticipated that the proposed intermediate bicyclic metallacyclopropene **54** would be destabilized by ring strain. As such, we recognized that monocyclic (**55**) or oligomeric (**56**) species may play a significant role in these cross-coupling reactions. To further complicate understanding the trends in selectivity observed, we expected that partitioning between **54**, **55**, and

(23) Reichard, H. A.; Rieger, J. C.; Micalizio, G. C. *Angew. Chem., Int. Ed.* **2008**, *47*, 7837–7840.
(24) Shimp, H. L.; Micalizio, G. C. *Tetrahedron* **2009**, *65*, 5908–5915.

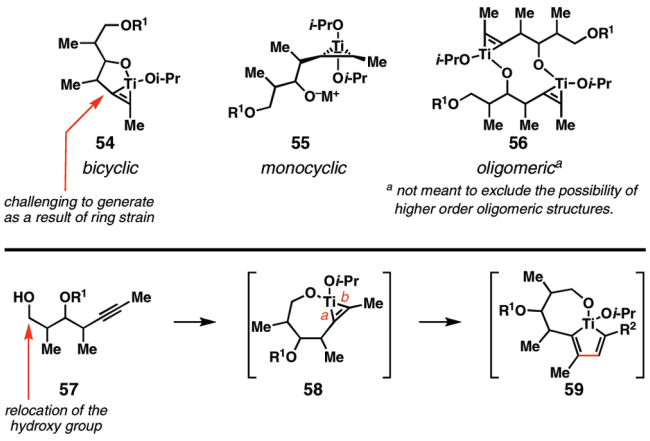


FIGURE 9. Uncertainty regarding the nature of the titanium−alkyne complex in the transition state for carbometalation and proposed perturbation.

56 may also contribute to the complex structure−selectivity relationships observed in these reductive cross-coupling reactions.

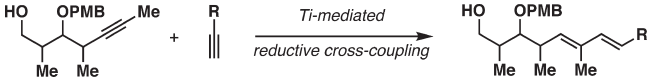
While the precise nature of the reactive metallacycle in the transition state for C−C bond formation is unknown, we speculated that relocating the "directing" functional group to a position further removed from the alkyne (as in **57**) may alleviate some of the anticipated ring strain in the formation of a proposed bicyclic metallacyclopropene (i.e **58** vs **54**). If such a structural modification led to the preferential participation of a structure like **58** in the transition state for coupling, we would anticipate selective carbometalation with a terminal alkyne to deliver metallacyclopentadienes of general structure **59**. As before, this expectation is in accord with a transition-state geometry that leads to the formation of a fused bicyclic metallacyclopentadiene (via cleavage of bond "*b*") in preference to a bridged bicyclic isomer (via cleavage of bond "*a*").

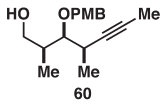
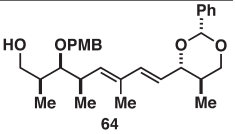
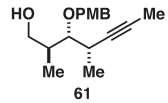
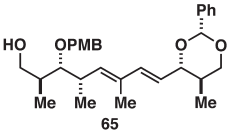
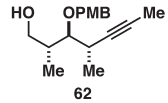
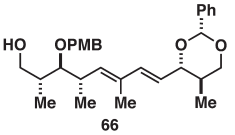
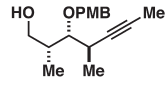
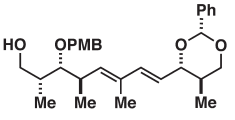
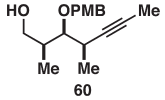
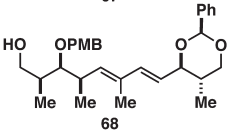
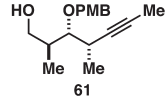
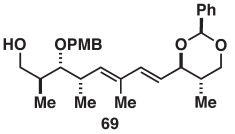
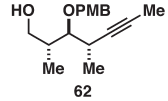
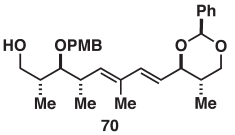
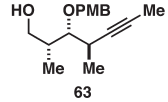
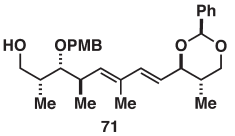
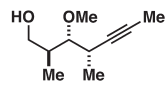
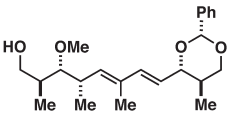
To our delight, we found that stereodefined internal alkynes of general structure **57** were superb substrates for reductive cross-coupling with terminal alkyne **35** (Table 2). In most cases, regioselection was ≥20:1 in favor of the desired (*E*,*E*)-trisubstituted 1,3-diene product (entries 1−4). Furthermore, we observed that double-asymmetric relationships do little to affect the regioselection of this cross-coupling process. As illustrated in entries 5−8, coupling with ***ent*-35** is similarly effective with all stereoisomers of the internal alkyne (rs ≥20:1 in all cases).

While each stereoisomer **60**−**63** demonstrated high levels of regioselection in reductive cross-coupling reactions with alkynes **35** and ***ent*-35**, the origins of regioselection remain a complex function of alkyne structure. As demonstrated in entry 9, replacing the PMB ether of **61** with a methyl ether results in a modest decrease in regioselection in reductive cross-coupling of alkyne **72** with **35**, yet still delivers the stereodefined (*E*,*E*)-trisubstituted 1,3-diene **73** in 78% as a 10:1 mixture of regioisomers.[25]

(25) Perez, L. J.; Micalizio, G. C. *Synthesis* **2008**, 627–648. Similarly, removal of branching between the tethered alkoxide and the internal alkyne also leads to significant decreases in regioselection. The quantitative effect of each branched substituent on regioselection has not been determined.

TABLE 2. Highly Regioselective Alkoxide-Directed Reductive Cross-Coupling Reactions of Internal Alkynes with Terminal Alkynes



entry	internal alkyne	terminal alkyne	yield [a]	rr [b]	major regioisomer
1	 **60**	**35**	60	17:1	 **64**
2	 **61**	**35**	57	≥ 20:1	 **65**
3	 **62**	**35**	47	≥ 20:1	 **66**
4	 **63**	**35**	53	≥ 20:1	 **67**
5	 **60**	***ent*-35**	64	≥ 20:1	 **68**
6	 **61**	***ent*-35**	63	≥ 20:1	 **69**
7	 **62**	***ent*-35**	64	≥ 20:1	 **70**
8	 **63**	***ent*-35**	68	≥ 20:1	 **71**
9	 **72**	**35**	78	10:1	 **73**

[a] Yield based on terminal alkyne. [b] Regioisomeric ratio with respect to functionalization of the internal alkyne (A/B) determined by ^{1}H NMR of the product mixture after a simple filtration column (see the Supporting Information for details). In a few cases, observable quantities of the minor regioisomer "C" (as defined in Table 1) were observed (entry 4 = 12:1, entry 6 = 14:1, entry 7 = 17:1).

With a highly selective reductive cross-coupling reaction in hand for the synthesis of stereochemically complex 1,3-dienes, we began to explore the basic functional group compatibility and selectivity of the process (Figure 10). In the cross-coupling of an array of differentially functionalized terminal alkynes with a propionate-inspired internal alkyne, uniformly high levels of regioselection were observed (**74**−**81**). Among the observations made, terminal alkynes

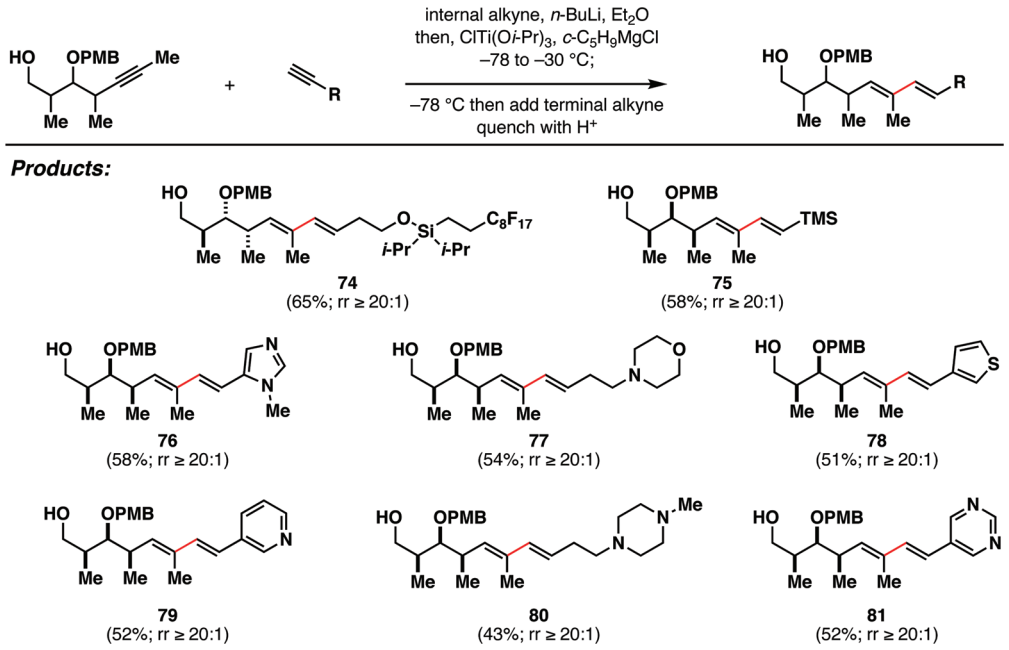


FIGURE 10. Structurally diverse terminal alkynes are compatible with the alkoxide-directed cross-coupling.

that lack α-branching are suitable substrates, the coupling is compatible with fluorous technology (**74**),[26] and a diverse array of saturated and aromatic heterocycles are compatible with this metal-mediated C−C bond-forming process (**76**−**81**). In all cases, the diene products were produced with very high levels of regioselection and as single stereoisomers.

Conclusion

Branched (*E*,*E*)-trisubstituted 1,3-dienes are structural motifs found in a range of complex bioactive natural products. While stereoselective methods exist for their preparation, these methods typically require numerous sequential transformations to (1) enable stepwise carbonyl olefination or (2) prepare the stereodefined coupling partners required for catalytic cross-coupling methodology (vinyl halides and vinyl organometallic reagents). With a goal of defining chemical methods to increase the efficiency with which complex natural products can be prepared, we were guided by the substitution pattern of a collection of polyunsaturated natural products (Figure 1). We targeted the development of a reductive cross-coupling reaction between suitably substituted alkynes to define a process that forges a C−C bond in concert with establishing the stereochemistry of two substituted alkenes. Overall, attempting to define a convergent coupling reaction that would avoid the multiple functional group manipulations required in other common pathways to stereodefined 1,3-dienes.

While the basic reactivity required for this bond construction, the reductive dimerization of alkynes, was discovered nearly 50 years ago, lack of a suitable means to control selectivity in these processes has greatly limited the impact of this reductive cross-coupling in natural product synthesis. Here, we define a titanium-mediated reductive cross-coupling reaction that provides an exceptionally direct, stereo- and regioselective route to substituted 1,3-dienes that are found embedded in the skeletons of many biologically active polyketide-derived natural products. Central to this success, we have elucidated a means for the control of regioselection based on the proximity of a tethered alkoxide to the internal alkyne-containing coupling partner. While the precise mechanistic implications of our observations remain unclear, highest selectivities were observed with substrates bearing an alkoxide γ to the internal alkyne. Due to the low cost of the metal-containing reagents, ready availability of the coupling partners, benign nature of the byproducts (TiO_2 and Mg(II) salts), and substrate-controlled selectivity, the current fragment coupling process is anticipated to be of great utility in chemical synthesis.

Experimental Section

Representative Example of the Alkoxide-Directed Reductive Cross-Coupling: (2*S*,3*S*,4*R*)-(5*E*,7*E*)-3-(4-Methoxybenzyloxy)-2,4,6-trimethyl-8-((2′*R*,4′*S*,5′*R*)-5′-methyl-2′-phenyl-1′,3′-dioxan-4′-yl)octa-5,7-dien-1-ol (64). To a solution of the internal alkyne 60 (20 mg, 0.072 mmol) in Et_2O (725 μL, 0.1 M) at ambient temperature was added *n*-BuLi (30 μL, 0.072 mmol, 2.5 M in hexanes), followed by Ti(O*i*-Pr)$_4$ (32 μL, 0.109 mmol). The resultant pale yellow solution was cooled to −78 °C and treated with *c*-C_5H_9MgCl (110 μL, 0.217 mmol, 2.0 M in Et_2O). The mixture was allowed to warm to −30 °C over 1.5 h and was stirred at −30 °C for 30 min. The resulting dark brown solution was cooled to −78 °C and was treated with a solution of terminal alkyne **35** (102 μL, 0.051 mmol, 0.5 M in Et_2O). The mixture was allowed to warm to 0 °C over 2 h, diluted with Et_2O (2 mL), and quenched by the addition of 1 N HCl (1 mL). After being stirred at ambient temperature for 45 min, the biphasic mixture was transferred to a separatory funnel, extracted with Et_2O (3 × 10 mL), dried over $MgSO_4$, filtered, and concentrated in vacuo. Flash column chromatography on 10 mL of SiO_2 eluting with 10% EtOAc/hexanes to 50% EtOAc/hexanes provided the coupled product as a 17:1 mixture of regioisomers (15.8 mg, 64%). Isolation of the major regioisomer was achieved by

(26) For recent examples, see: (a) Curran, D. P. *Science* **2008**, *321*, 1645–1646. (b) Chu, Q.; Henry, C.; Curran, D. P. *Org. Lett.* **2008**, *10*, 2453–2456. (c) Jung, W.-H.; Guyenne, S.; Riesco-Fagundo, C.; Mancuso, J.; Nakamura, S.; Curran, D. P. *Angew. Chem., Int. Ed.* **2008**, *47*, 1130–1133.

normal-phase HPLC using a gradient from 20% EtOAc/hexanes to 50% EtOAc/hexanes over 25 min: $[\alpha]^{20}_{589}$ +32.4 (*c* 0.7, $CHCl_3$); ^1H NMR (500 MHz, $CDCl_3$) δ 7.51 (d, J = 6.9 Hz, 2H), 7.38−7.28 (m, 5H), 6.88 (d, J = 8.2 Hz, 2H), 6.31 (d, J = 15.8 Hz, 1H), 5.61 (dd, J = 15.8, 7.3 Hz, 1H), 5.55 (s, 1H), 5.31 (d, J = 9.8 Hz, 1H), 4.58 (A of AB, J = 10.7 Hz, 1H), 4.53 (B of AB, J = 10.7 Hz, 1H), 4.18 (dd, J = 11.4, 4.7 Hz, 1H), 3.93 (dd, J = 9.8, 8.2 Hz, 1H), 3.80 (s, 3H), 3.59−3.52 (m, 3H), 3.41 (dd, J = 8.8, 2.2 Hz, 1H), 2.85−2.77 (m, 1H), 1.99−1.90 (m, 1H), 1.90−1.82 (m, 1H), 1.77 (m, 3H), 1.08 (d, J = 6.6 Hz, 3H), 0.86 (d, J = 6.9 Hz, 3H), 0.79 (d, J = 6.6 Hz, 3H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 159.2, 138.6, 138.5, 136.7, 132.1, 130.9, 129.4, 128.8, 128.3, 126.3, 124.8, 113.8, 101.4, 84.9, 83.8, 74.7, 73.1, 66.2, 55.3, 38.6, 36.5, 34.5, 31.6, 22.6, 17.9, 14.1, 12.7, 12.6, 10.7; IR (thin film, NaCl) 3481, 2961, 2932, 2872, 2836, 1612, 1514, 1457, 1387, 1364, 1302, 1248, 1174, 1070, 1032, 967, 822, 752, 698; LRMS (EI) calcd for $C_{30}H_{40}O_5Na$ 503.3 m/z (M + Na), obsed 503.5 m/z $(M + Na)^+$; HRMS (FT-ICR) calcd for $C_{30}H_{40}O_5Na$ 503.2768 m/z (M + Na), obsd 503.2778 m/z $(M + Na)^+$.

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Supporting Information Available: Experimental procedures, compound characterization, and copies of spectral data. This material is available free of charge via the Internet at http://pubs.acs.org.