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Group 4 Metals in Polyketide Synthesis: A Convergent Strategy for the Synthesis of Polypropionate-derived (*E*,*E*)-Trisubstituted 1,3-Dienes

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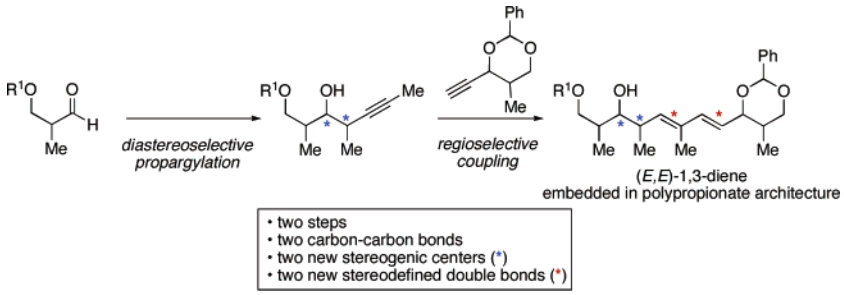
ABSTRACT



A convergent Group 4 metal-mediated coupling process is described for the synthesis of polypropionate-derived (*E*,*E*)-1,3-dienes. Both the stereochemistry of the internal alkyne and the presence/absence of a tethered alkoxide on this π-component were found to play critical roles in dictating the regiochemical course of these reactions.

Natural products of polyketide biosynthetic origin represent an important class of synthetic targets that display a range of potent and diverse biological activities.[1,2] These activities range from antibacterial and antifungal to cytotoxic and immunosuppressive. Members of this class have long served to stimulate the development of reactions designed to access their highly functionalized acyclic architectures. As such, a variety of powerful carbon−carbon bond-forming reactions have been developed that enable the synthesis of complex polypropionate-derived targets.[3−6] Trisubstituted 1,3-dienes are commonly found embedded in polypropionate regions of natural products (Figure 1).[7−9] This stereodefined functional group represents a challenge for streamlined synthesis of such targets as current methods for 1,3-diene synthesis often require either (1) multistep olefination-based processes[10] or (2) convergent cross-coupling strategies that dictate the preparation of stereodefined olefinic partners prior to coupling.[11] Either approach requires deviation from iterative aldol or allylmetal-based bond construction−*strategies that are often employed for polyketide synthesis*. To

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(5) Denmark, S. E.; Almstead, N. G. Allylation of Carbonyls: Methodology and Stereochemistry; In *Modern Carbonyl Chemistry*; Otera, J., Ed.; Wiley-VCH: Weinheim, 2000; p 299.
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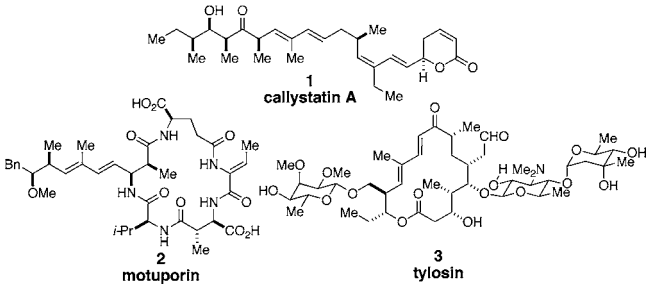

Figure 1. Trisubstituted (*E*,*E*)-1,3-dienes: Common structural motifs found in natural products of polyketide biosynthetic origin.

enable the efficient preparation of such complex polyketide-derived targets, synthetic methods are needed that provide access to this stereodefined structural motif, while remaining tolerant of a wide variety of functional groups. Herein, we report (1) a convergent approach to this synthetic problem that greatly expedites the synthesis of such molecular architecture and (2) an unprecedented interplay between stereochemistry and the presence of tethered alkoxides in the control of regioselection in Group 4 metal-mediated diyne coupling reactions.

Previously, we reported a two-step method for the convergent coupling of differentially functionalized aldehydes that enables the synthesis of ene-1,5-diols in a regio- and stereoselective manner (**4** → **6** → **8**; Figure 2).[12] In line

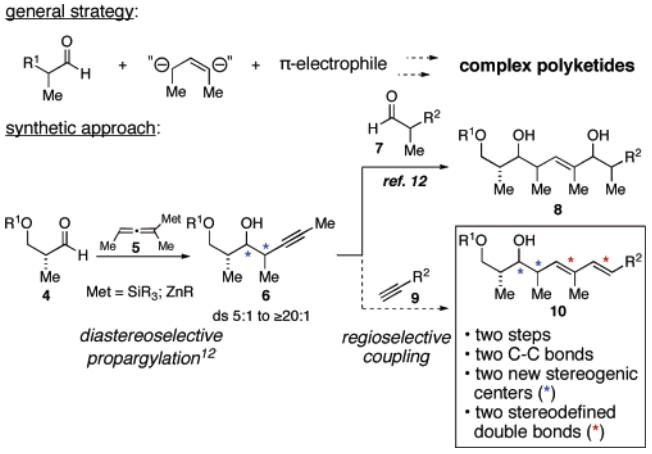

Figure 2. Group 4 metal alkoxide mediated reactions for the synthesis of complex polyketides.

with our goal of developing a *general strategy* for the efficient synthesis of *architecturally* complex and structurally diverse polypropionates, we envisioned a divergent pathway[13] whereby the homopropargylic alcohol (**6**) could be functionalized by a modified Group 4 metal-mediated coupling process with a terminal alkyne (**9**).[14] This reaction pathway would provide a direct approach to the synthesis of highly functionalized 1,3-dienes and, in combination with our earlier report,[12] greatly increase the generality of metallacycle-based bond-construction processes for polyketide assembly (**6** → **8** or **6** → **10**). Herein, we describe a regio- and stereoselective titanium-mediated coupling reaction of homopropargylic alcohols (**6**) with terminal alkynes (**9**) that provides direct access to functionalized 1,3-dienes (**10**) relevant to the synthesis of complex polyunsaturated polypropionates.

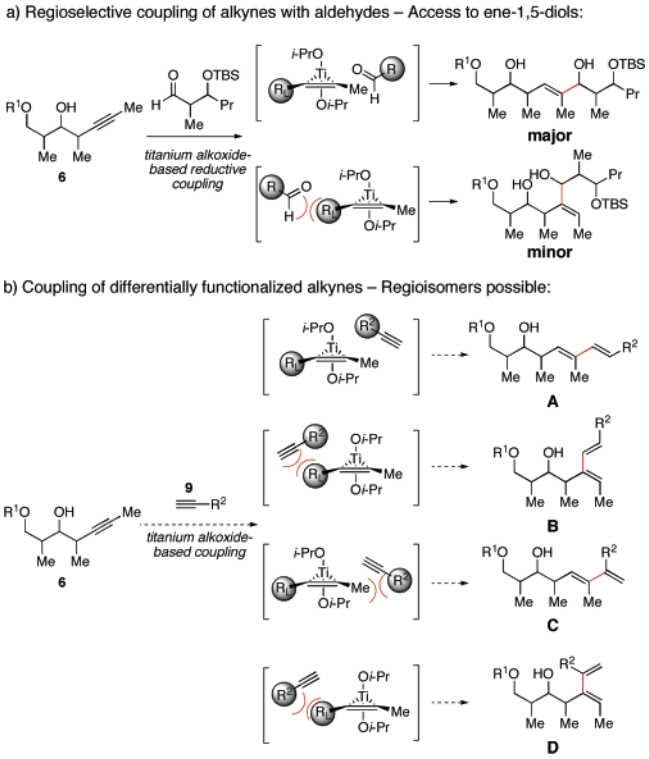

Figure 3. Concerning regioselection.

Although titanium alkoxide based coupling reactions of differentially functionalized alkynes have been reported, high regioselectivities for functionalization of the internal alkyne component have been achieved only with TMS-substituted alkynes and conjugated 2-alkynoates, requirements that prevent the broad utility of these coupling processes for polyketide assembly.[14−17] Our previous report on Group 4 metal alkoxide-mediated coupling reactions for the synthesis of ene-1,5-diols highlighted the effectiveness of highly branched polyketide architecture in dictating the regiochemical course of reductive coupling reactions of internal alkynes with branched aldehydes (Figure 3a).[12] Concerning the utility of Group 4 metal alkoxide-mediated coupling processes for

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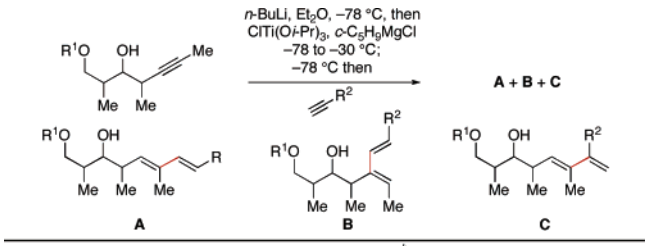
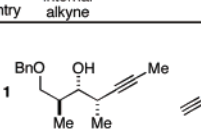
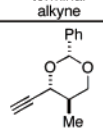
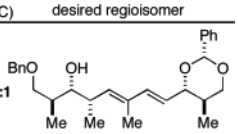
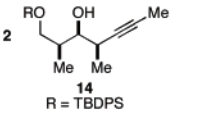
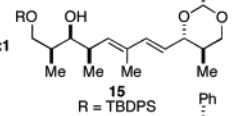
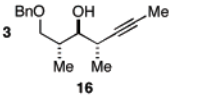
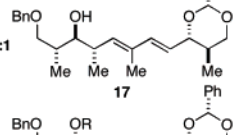
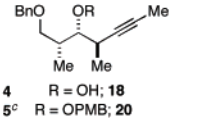
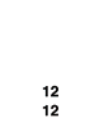
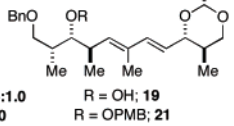
the assembly of polyunsaturated polyketides, inspection of the potential orientation of coupling partners **6** and **9** leads to the identification of four distinct pathways that have the potential to provide the regioisomeric dienes **A**−**D** (Figure 3b). At the outset, we anticipated that the branched polyketide architecture present in **6** would serve to destabilize the transition states leading to the formation of dienes **B** and **D**, hence providing a selective coupling procedure for the formation of the (*E*,*E*)-trisubstituted 1,3-diene product **A**. Additionally, because of the compatibility of this class of coupling reactions with metal alkoxides,[12,18−22] we anticipated that carbon−carbon bond formation en route to stereodefined dienes of general structure **A** would ensue without required protection of the homopropargylic alcohol, a factor that should lead to increased efficiency in polyketide synthesis.

Table 1. Construction of Complex Polyketides by Regioselective Coupling Reactions of Branched Homopropargylic Alcohols and Terminal Alkynes



entry	internal alkyne	terminal alkyne	yield [a]	rr [b] (A:B:C)	desired regioisomer
1	 **11**	 **12**	50	15:2:1	 **13**
2	 **14** R = TBDPS	**12**	70	28:1:1	 **15** R = TBDPS
3	 **16**	**12**	52	4:0:1	 **17**
4	 R = OH; **18**	 **12**	63	1.0:1.5:1.0	 R = OH; **19**
5[c]	R = OPMB; **20**	**12**	82	3:1:0	R = OPMB; **21**

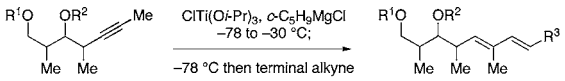
[a] Yield based on terminal alkyne. [b] Regioisomeric ratio determined by ^{1}H NMR of the product mixture after flash column chromatography (see Supporting Information for details). [c] ClTi(O*i*-Pr)$_3$, *c*-C$_5$H$_9$MgCl, −78 to −30 °C, then −78 °C and addition of terminal alkyne.

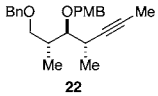
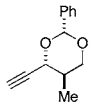
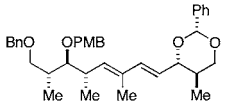
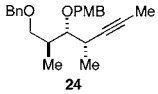
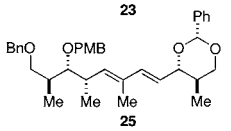
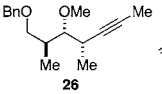
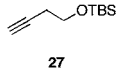
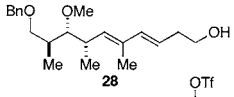
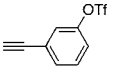
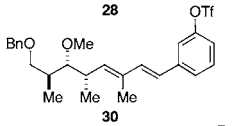
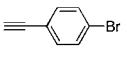
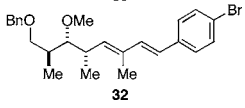
As anticipated, deprotonation of the *syn-anti* homopropargylic alcohol **11**, followed by exposure to the combination of ClTi(O*i*-Pr)$_3$ and cyclopentylmagnesium chloride, and addition of the terminal alkyne **12** provided, after aqueous workup, the 1,3-diene **13** in 50% yield (regioisomeric ratio (rr) = 15:2:1). Similarly, coupling of the diastereomeric homopropargylic alcohols **14**, **16** and **18** with terminal alkyne **12** provided the 1,3-diene products **15**, **17** and **19**. Consistent with our previous study of Group 4 metal-mediated reductive coupling reactions of polyketide-derived internal alkynes with aldehydes, the *syn-anti* and *syn-syn* stereoisomers (**11** and **14**) provided the highest levels of regioselection, while the *anti-syn* stereoisomer (**18**) exhibited the lowest levels of regioselection in this diyne-based coupling reaction. Interestingly, the stereochemistry present on the internal alkyne component was found to significantly influence the product distribution, providing variable levels of regioisomer **C**.

The production of regioisomer **C** in these coupling reactions is surprising, as this isomer is typically not observed in Group 4 metal alkoxide-mediated diyne couplings.[14−17] Interestingly, removing the tethered alkoxide in *anti-syn* stereoisomer **18** led to a significant enhancement in regioselection favoring the production of regioisomer **A**, while eliminating the production of a third regioisomer **C** (Table 1, entry 5; rr = 3:1:0). These results suggest that the combined effect of stereochemistry and the presence of a tethered alkoxide plays a significant role in regioselection, *an influence that has not previously been described in Group 4 metal-mediated* C−C *bond-forming processes*.

Following up on this interesting result, use of protected homopropargylic ethers **22** or **24**, in coupling reactions with terminal alkyne **12**, provided the functionalized dienes **23**

Table 2. Flexible Convergent Method for Assembly of (*E*,*E*)-Trisubstituted 1,3-Dienes



entry	internal alkyne	terminal alkyne	yield	rr [a, b]	major regioisomer
1	 **22**	 **12**	70	6:1	 **23**
2	 **24**	**12**	87	5:1	 **25**
3[c]	 **26**	 **27**	81	8:1	 **28**
4	**26**	 **29**	60	6:1	 **30**
5	**26**	 **31**	46	8:1	 **32**

[a] Regioisomeric ratio determined by ^{1}H NMR of the product mixture after flash column chromatography. [b] Regioisomeric ratio reported as **A**:**B** (as depicted in Table 1). [c] Yield and regioisomeric ratio reported after deprotection of the silyl ether (TBAF, THF).

and **25** in 70% and 87% yield (rr ≥ 5:1). Consistent with our earlier observation, the regioselection of each coupling process was influenced by protection of the homopropargylic

alcohol; evidence for production of a third regioisomer (**C**) was not observed in either of these cases.

Next, variation in the structure of the terminal alkyne was explored. High levels of regioselection were seen in the coupling reaction between a homopropargylic ether (**26**) and a terminal alkyne lacking α-branching (**27**; entry 3); again, only two regioisomers were observed (**A** and **B**). Coupling of the aryl-substituted alkynes **29** and **31** with the homopropargylic ether **26** were similarly effective, and provided regioselective access to the dienes **30** and **32** (entries 4 and 5). *Importantly, each of these products bears a functional group that would complicate the use of modern cross-coupling methods to install the central stereodefined diene*.[11]

Overall, we have described a general metal-mediated coupling reaction of homopropargylic alcohols and ethers with terminal alkynes that provides highly functionalized (*E*,*E*)-trisubstituted 1,3-dienes, a structural motif common to natural products of polyketide biosynthetic origin. Our preliminary studies have defined (1) a new regioselective carbon−carbon bond-forming process for the synthesis of unsaturated polypropionates that greatly expands the role of Group 4 metals in the synthesis of complex polyketides, (2) the impact of stereochemistry and the homopropargylic functional group on regioselection in these Group 4 metal-mediated diyne coupling reactions, and (3) a coupling process for the synthesis of 1,3-dienes that is tolerant of aromatic halides and triflates. As such, this method is anticipated to greatly facilitate the efficient synthesis of complex polyketide-derived targets. Progress along these lines, as well as exploration of the role of tethered alkoxides in Group 4 metal-mediated C−C bond-forming processes, will be reported in due course.

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Supporting Information Available: Experimental procedures and tabulated spectroscopic data for new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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