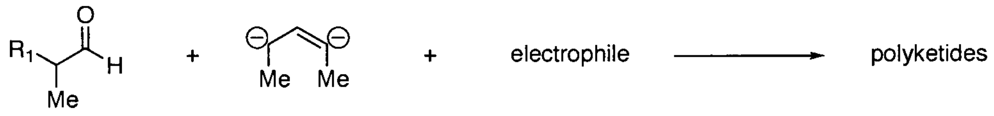
Group 4 Metals in Polyketide Synthesis: A convergent strategy for the synthesis of polypropionate-derived (*E*,*E*)-trisubstituted 1,3-dienes.

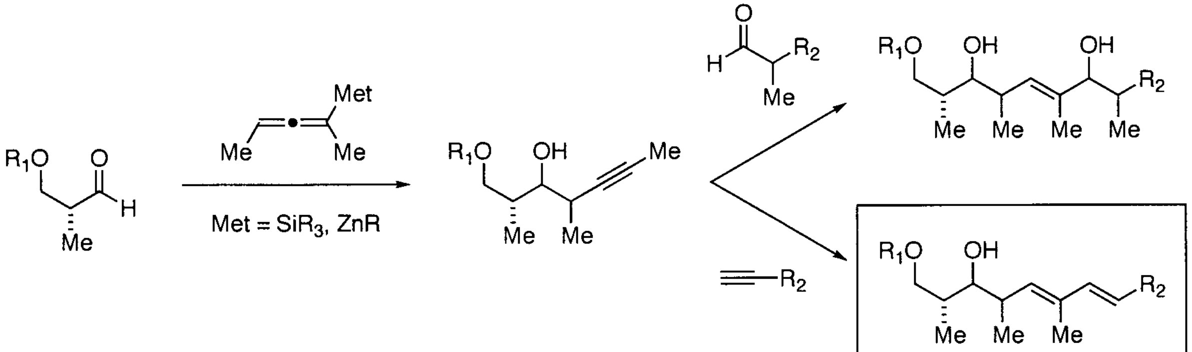
Heidi L. Shimp and Glenn C. Micalizio
Organic Letters **2005**, *7*, 5111.

The Strategy

General Strategy:

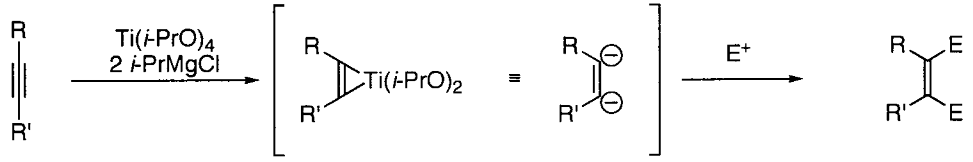


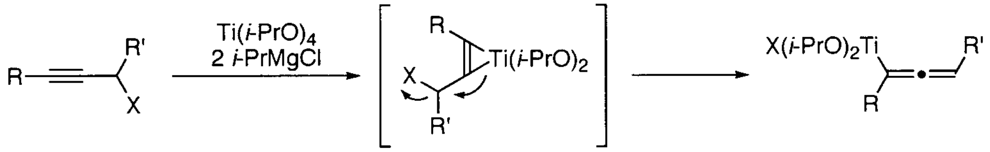
Synthetic approach:

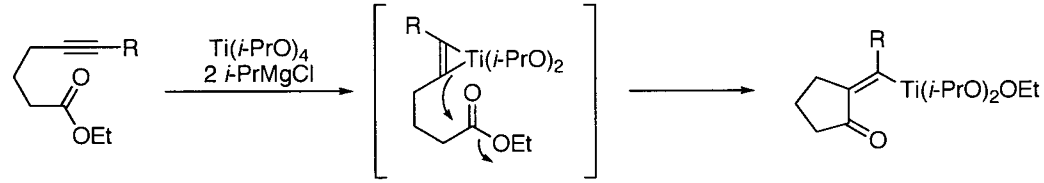


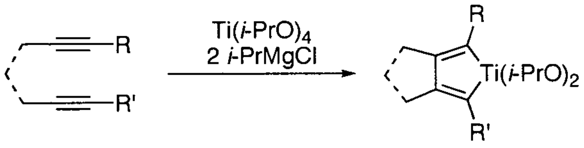
- 2 steps
- 2 C-C bonds
- 2 stereogenic centers
- 2 stereodefined double bonds

Reactions Mediated by $Ti(i\text{-}PrO)_4$/ 2 i-PrMgCl









Review: Sato, F.; Okamoto, S. *Adv. Synth. Catal.* **2001**, *343*, 759-784.

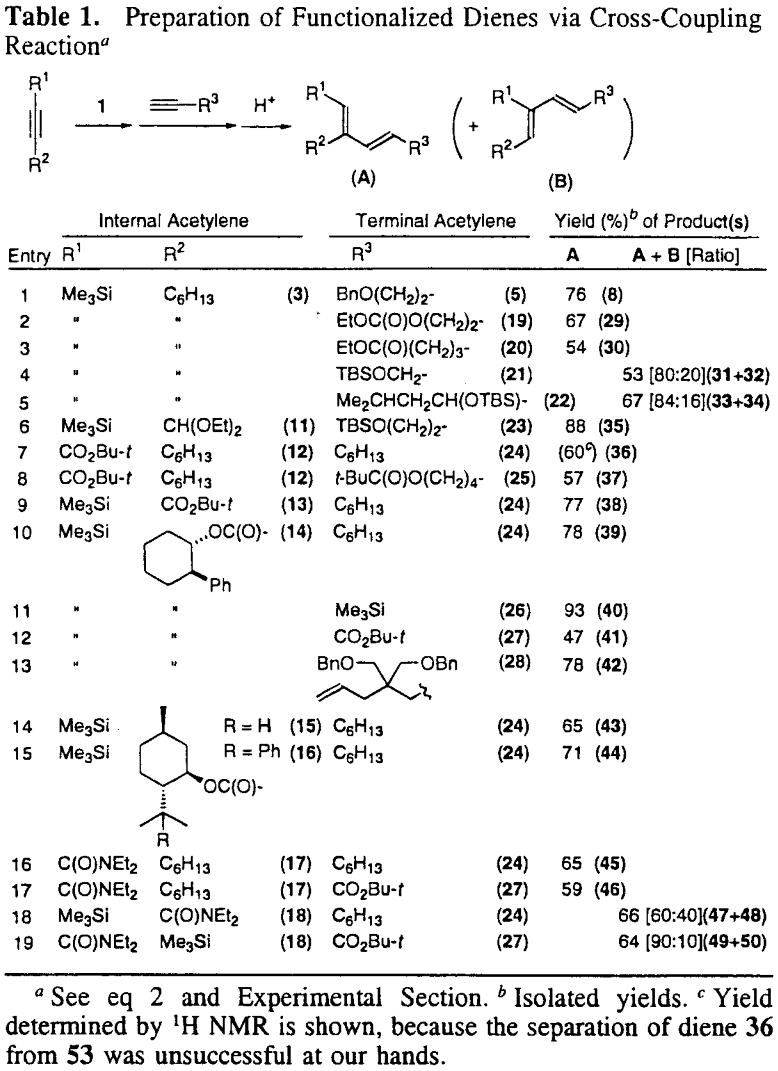


Table 1. Preparation of Functionalized Dienes via Cross-Coupling Reaction[a]

Entry	Internal Acetylene R^1	Internal Acetylene R^2		Terminal Acetylene R^3		Yield (%)[b] of Product(s) A	A + B [Ratio]
1	Me_3Si	C_6H_{13}	**(3)**	$BnO(CH_2)_2$-	**(5)**	76 **(8)**	
2	"	"		$EtOC(O)O(CH_2)_2$-	**(19)**	67 **(29)**	
3	"	"		$EtOC(O)(CH_2)_3$-	**(20)**	54 **(30)**	
4	"	"		$TBSOCH_2$-	**(21)**		53 [80:20]**(31+32)**
5	"	"		$Me_2CHCH_2CH(OTBS)$-	**(22)**		67 [84:16]**(33+34)**
6	Me_3Si	$CH(OEt)_2$	**(11)**	$TBSO(CH_2)_2$-	**(23)**	88 **(35)**	
7	CO_2Bu-*t*	C_6H_{13}	**(12)**	C_6H_{13}	**(24)**	(60^c) **(36)**	
8	CO_2Bu-*t*	C_6H_{13}	**(12)**	*t*-$BuC(O)O(CH_2)_4$-	**(25)**	57 **(37)**	
9	Me_3Si	CO_2Bu-*t*	**(13)**	C_6H_{13}	**(24)**	77 **(38)**	
10	Me_3Si	...OC(O)- Ph	**(14)**	C_6H_{13}	**(24)**	78 **(39)**	
11	"	"		Me_3Si	**(26)**	93 **(40)**	
12	"	"		CO_2Bu-*t*	**(27)**	47 **(41)**	
13	"	"		BnO—, —OBn	**(28)**	78 **(42)**	
14	Me_3Si	R = H OC(O)- R	**(15)**	C_6H_{13}	**(24)**	65 **(43)**	
15	Me_3Si	R = Ph	**(16)**	C_6H_{13}	**(24)**	71 **(44)**	
16	$C(O)NEt_2$	C_6H_{13}	**(17)**	C_6H_{13}	**(24)**	65 **(45)**	
17	$C(O)NEt_2$	C_6H_{13}	**(17)**	CO_2Bu-*t*	**(27)**	59 **(46)**	
18	Me_3Si	$C(O)NEt_2$	**(18)**	C_6H_{13}	**(24)**		66 [60:40]**(47+48)**
19	$C(O)NEt_2$	Me_3Si	**(18)**	CO_2Bu-*t*	**(27)**		64 [90:10]**(49+50)**

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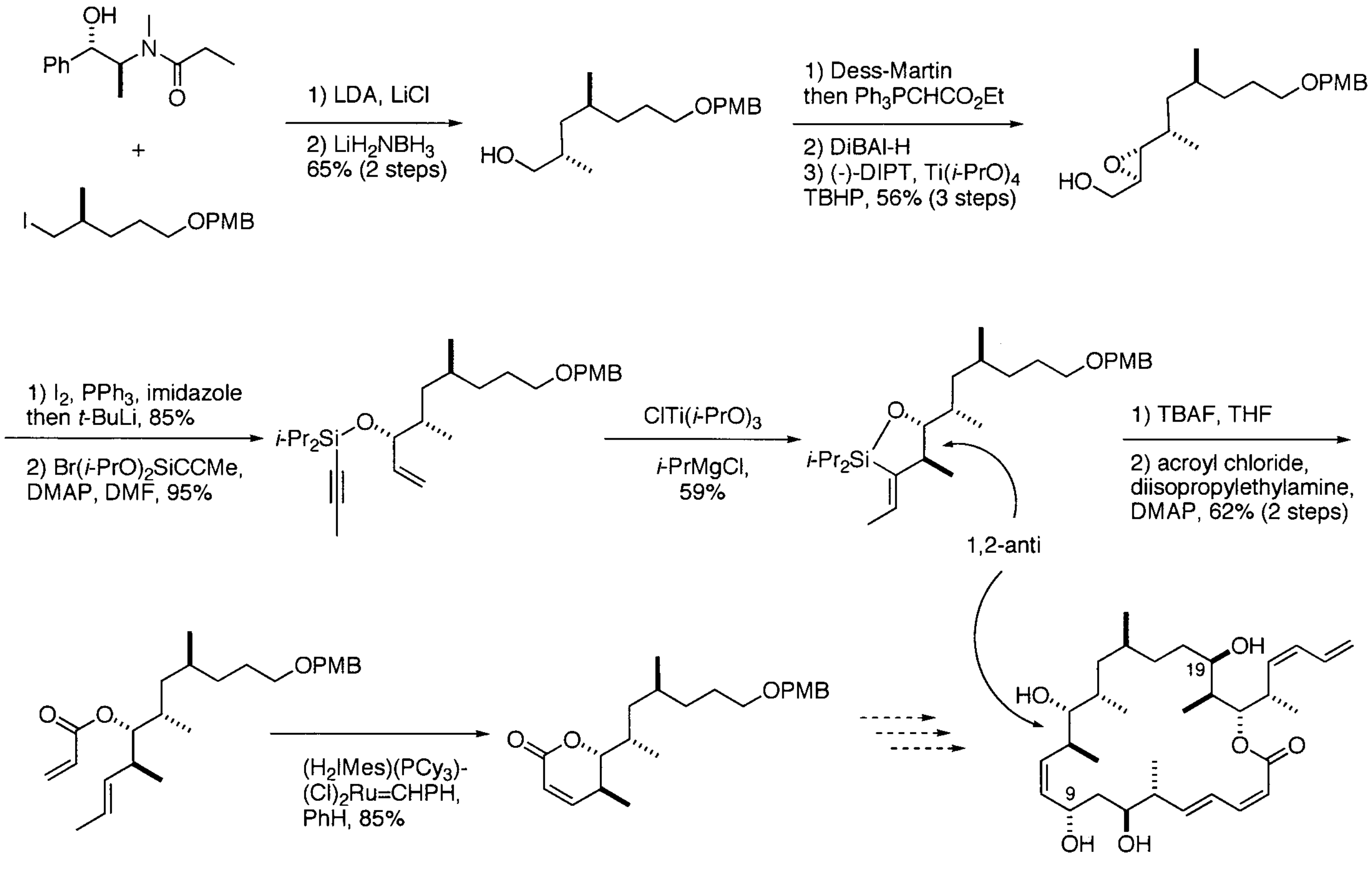
[a] See eq 2 and Experimental Section. [b] Isolated yields. [c] Yield determined by ^1H NMR is shown, because the separation of diene **36** from **53** was unsuccessful at our hands.

Hamada, T.; Suzuki, D.; Urabe, H.; Sato, F. *J. Am. Chem. Soc.* **1999**, *121*, 7342.

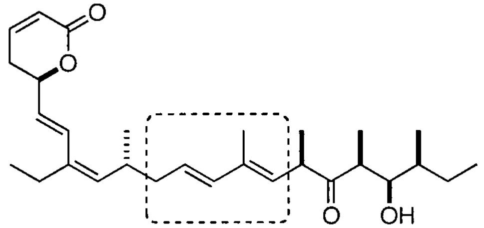
Ti(II)-mediated reductive cyclizations



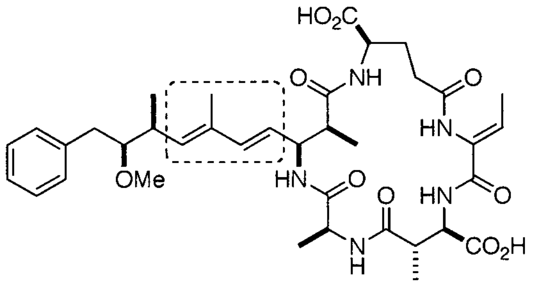
Dictyostatin-1

O'Neil, G. W.; Phillips, A. J. *Tetrahedron Lett.* **2004**, *45*, 4253.

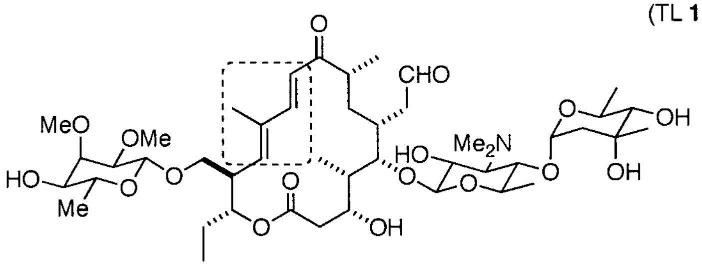
Trisubstituted (*E*,*E*)-1,3-dienes



(-)-callystatin A
(TL **1997**, *38*, 2859)

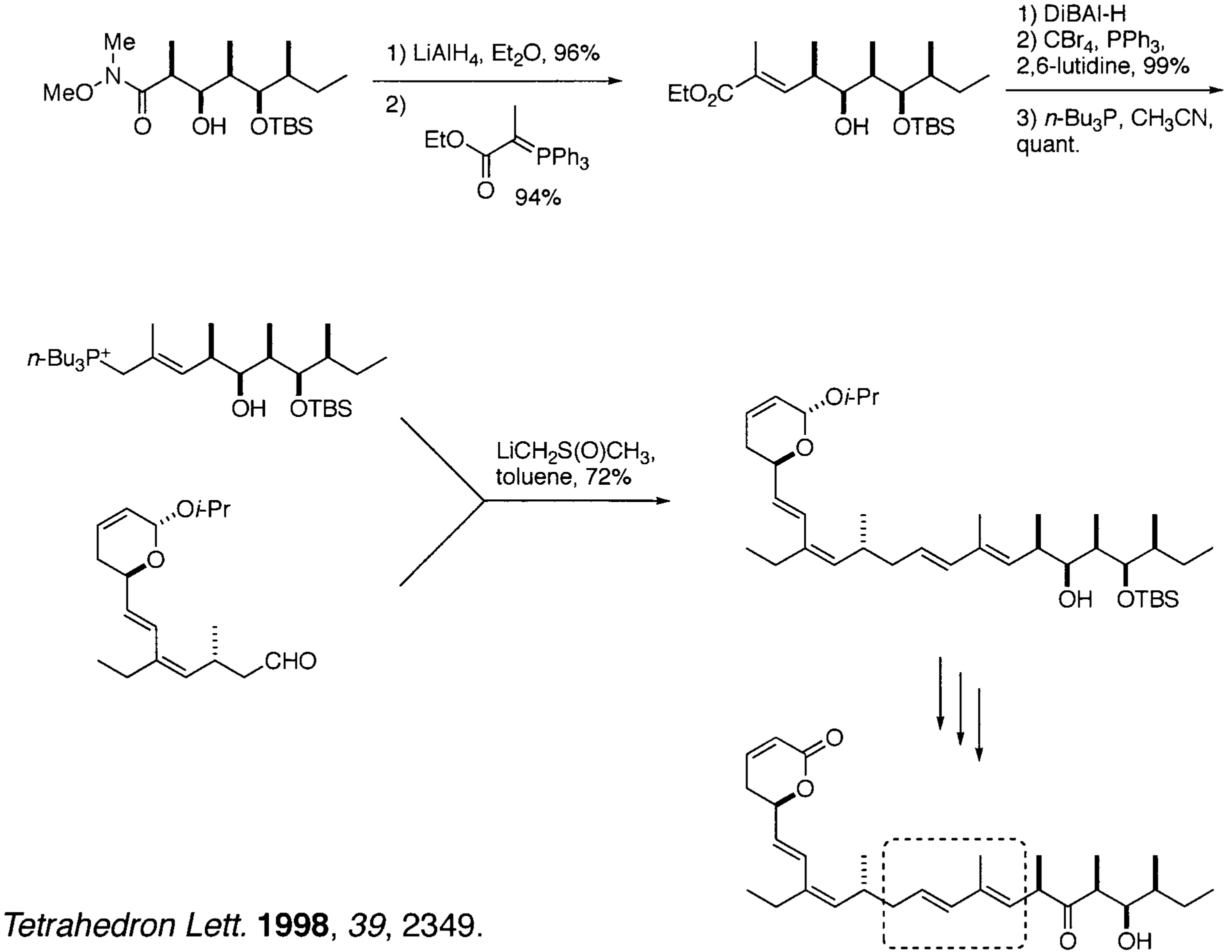


motuporin
(TL **1992**, *33*, 1561)



tylosin
(*Antibiot. Chemother.* **1961**, *11*, 328)

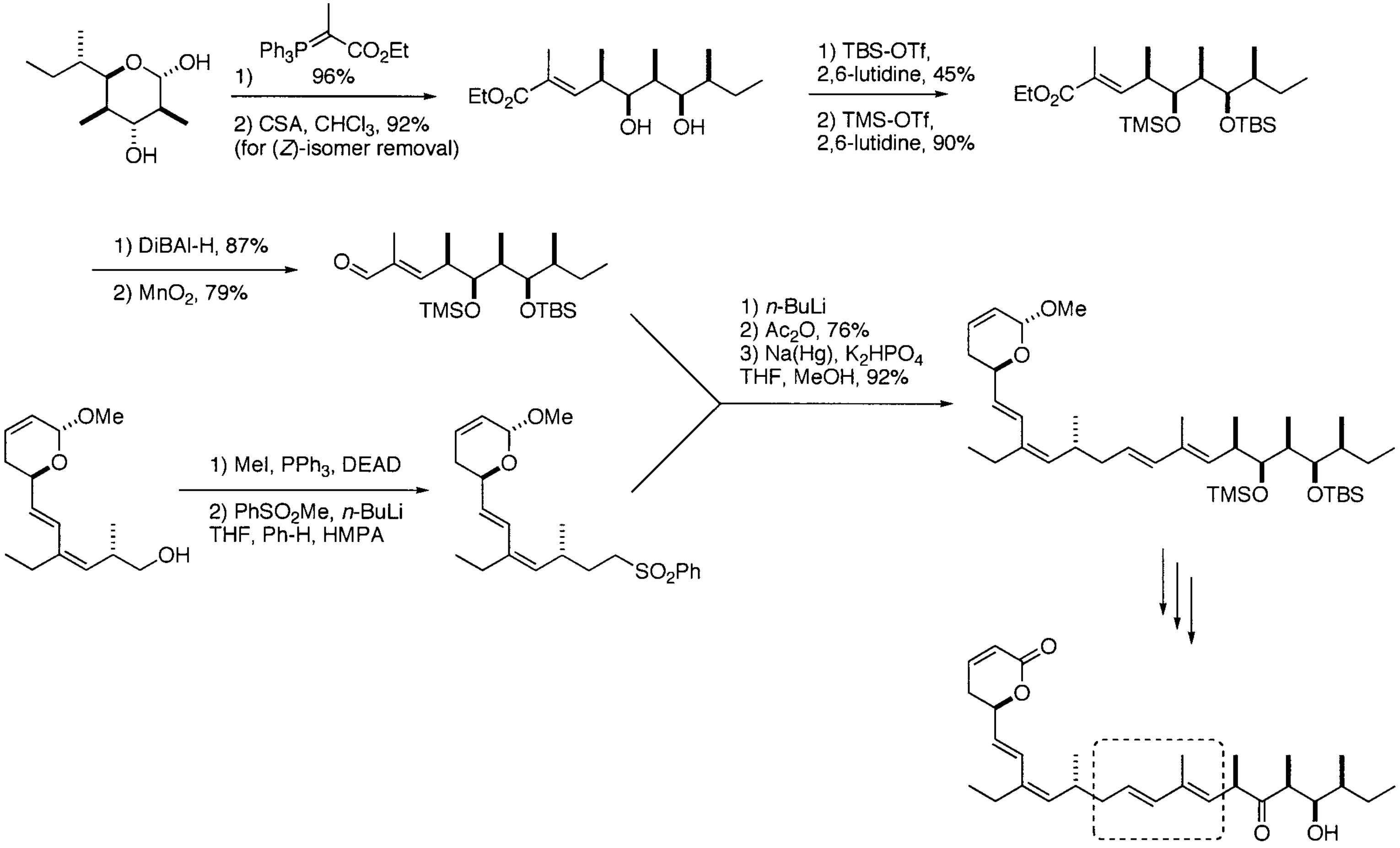
Kobayashi's Synthesis



(-)-callystatin A

Murakami *et. al. Tetrahedron Lett.* **1998**, *39*, 2349.
Similar Wittig approaches:
Crimmins, M. T.; King, B. W. *J. Am. Chem. Soc.* **1998**, *120*, 9084
Lautens, M.; Stammers, T. A. *Synthesis* **2002**, 1993.
Enders, D. *et. al Chem. Eur. J.* **2002**, *8*, 4272.

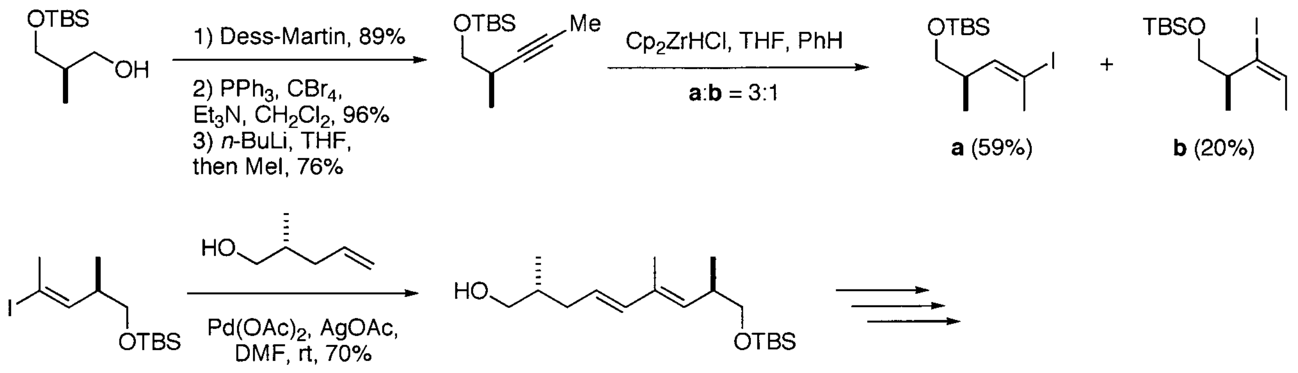
Smith's Synthesis

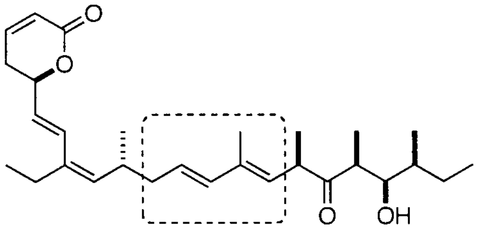


(-)-callystatin A

Smith, A. B.; Brandt, B. M. *Org. Lett.* **2001**, *3*, 1685.

Kalesse's Synthesis

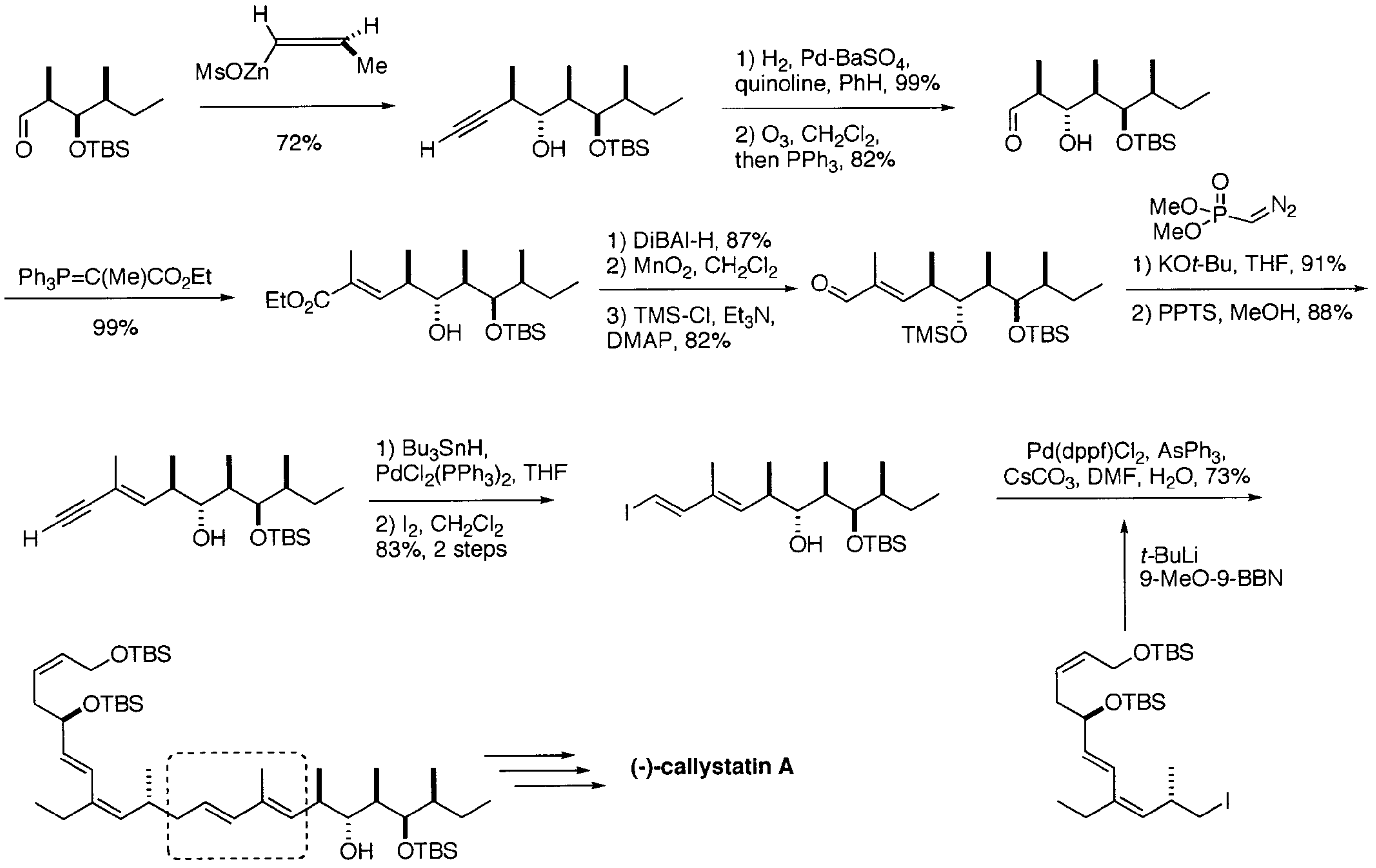




(-)-callystatin A

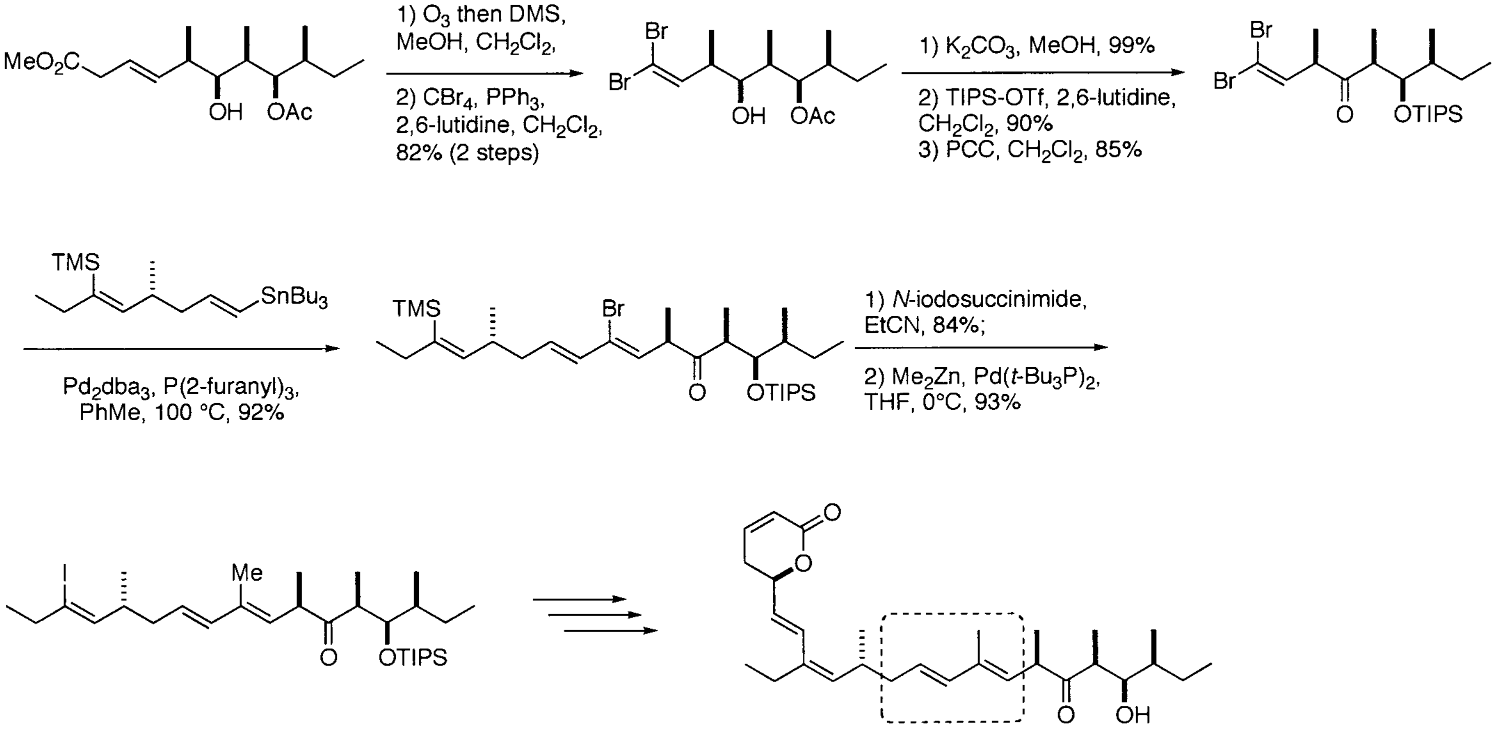
Kalesse et. al. *Chem. Eur. J.* **2003**, *9*, 1129.
Kalesse et. al. *Org. Lett.* **2001**, *3*, 3107.

Marshall's Synthesis



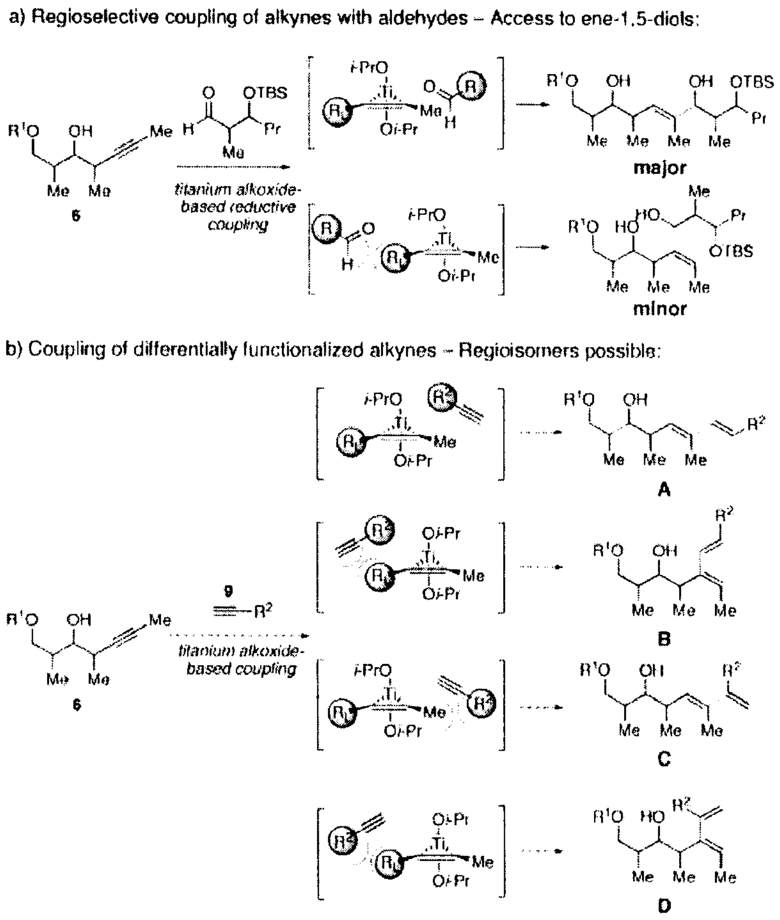
Marshall, J. A.; Bourbeau, M. P. *J. Org. Chem.* **2002**, *67*, 2751.
2nd generation synthesis: Marshall, J. A.; Bourbeau, M. P. *Org. Lett.* **2002**, *4*, 3931.
for a similar Suzuki coupling: Dias, L. C.; Meira, P. R. R. *J. Org. Chem.* **2005**, *70*, 4762.

Panek's Synthesis



(-)-callystatin A

Langille, N. F.; Panek, J. S. *Org. Lett.* **2004**, *6*, 3203.

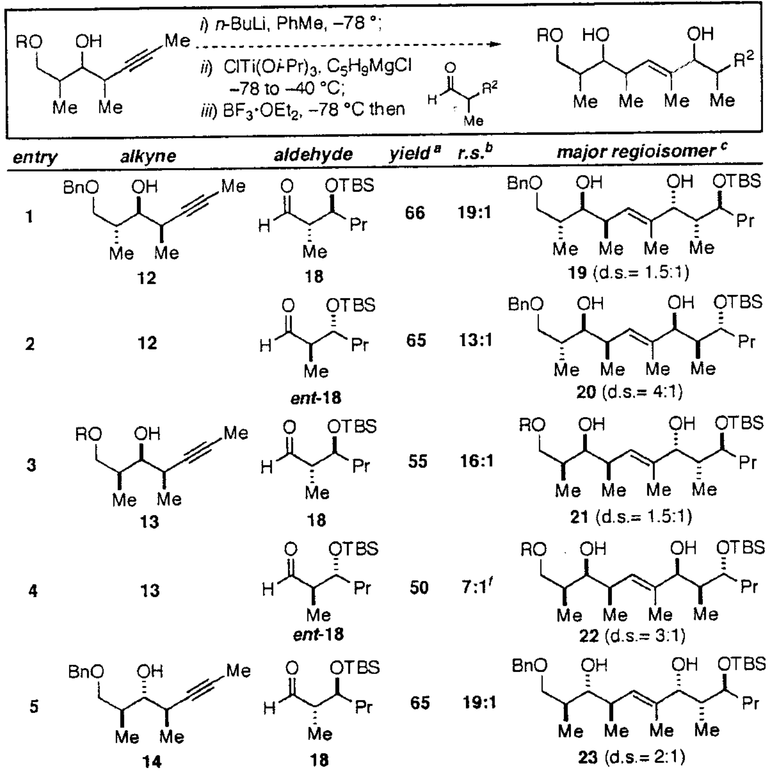

a) Regioselective coupling of alkynes with aldehydes – Access to ene-1,5-diols:

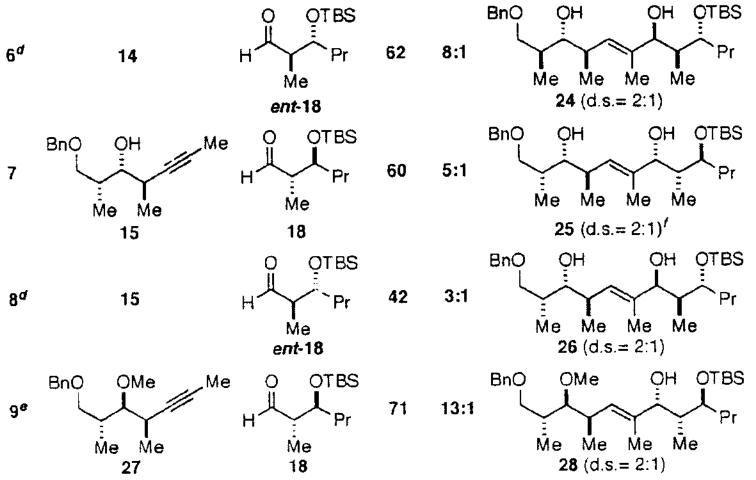
b) Coupling of differentially functionalized alkynes – Regioisomers possible:

Figure 3. Concerning regioselection.

Shimp H. L.; Micalizio G. C. *Org. Lett.* **2005**, *7*, 5111.

Table 1. Application to the Synthesis of Complex Polypropionates





entry	*alkyne*	*aldehyde*	*yield*[a]	*r.s.*[b]	*major regioisomer*[c]
1	**12**	**18**	66	19:1	**19** (d.s.= 1.5:1)
2	**12**	***ent*-18**	65	13:1	**20** (d.s.= 4:1)
3	**13**	**18**	55	16:1	**21** (d.s.= 1.5:1)
4	**13**	***ent*-18**	50	7:1[f]	**22** (d.s.= 3:1)
5	**14**	**18**	65	19:1	**23** (d.s.= 2:1)
6[d]	**14**	***ent*-18**	62	8:1	**24** (d.s.= 2:1)
7	**15**	**18**	60	5:1	**25** (d.s.= 2:1)[f]
8[d]	**15**	***ent*-18**	42	3:1	**26** (d.s.= 2:1)
9[e]	**27**	**18**	71	13:1	**28** (d.s.= 2:1)

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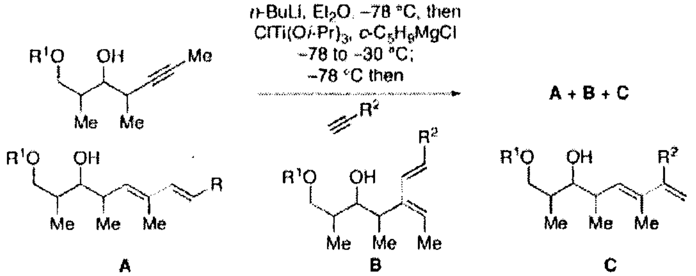
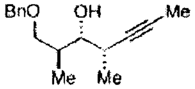
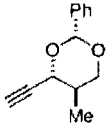
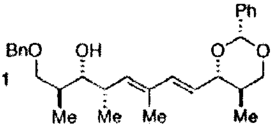
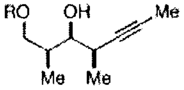
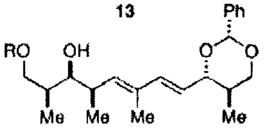
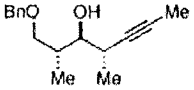
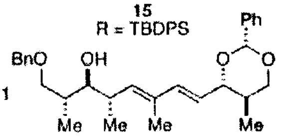
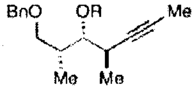
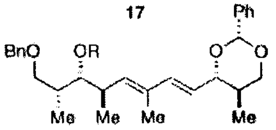
[a] Yield reported for major regioisomer. [b] Regioselectivity determined by ^{1}H NMR of the crude reaction mixture. [c] Major diastereomer is depicted. [d] Addition of RCHO at −100 °C. [e] Deprotonation step not performed. [f] Selectivity determined after isolation.

Bahadoor, A. B.; Flyer, A.; Micalizio, G. C. *J. Am. Chem. Soc.* **2005**, *127*, 3694.

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(Oi-Pr)$_3$, c-C$_5$H$_9$MgCl, −78 to −30 °C, then −78 °C and addition of terminal alkyne.

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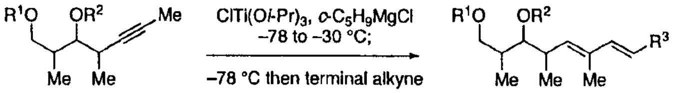
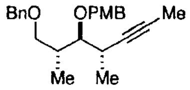
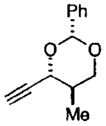
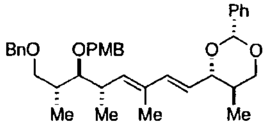
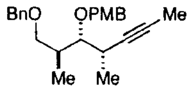
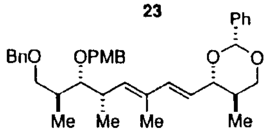
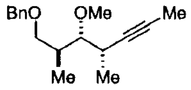
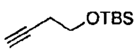
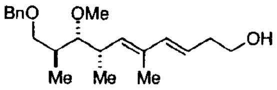
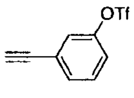
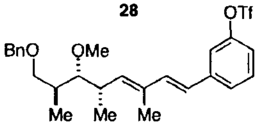
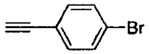
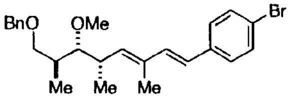
Table 2. Flexible Convergent Method for Assembly of (*E*,*E*)-Trisubstituted 1,3-Dienes



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 ¹H 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).

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Summary

- a method for the convergent assembly of alkynes was demonstrated
- methodology affords (*E*,*E*)-trisubstituted 1,3-dienes with good regioselectivity
- does not require pre-functionalization of the alkynes
- Ti and Mg are more acceptable than Pd, Rh, Ni, Sn, etc.