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Studies in Macrolide Antibiotic Synthesis: The Role of Tethered Alkoxides in Titanium Alkoxide-Mediated Regioselective Reductive Coupling Reactions

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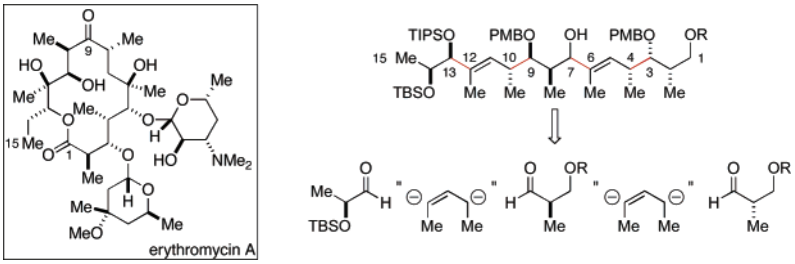
ABSTRACT



A convergent route to a C1–C15 fragment precursor for erythromycin-based macrolide antibiotics is presented. These studies define a role for tethered alkoxides in the control of site-selective carbon–carbon bond formation in titanium alkoxide-mediated coupling reactions of internal alkynes and chiral aldehydes.

Polyketides from *streptomyces* have played an important role in medicine, with members of this natural product class representing the mainstay of antibiotic therapy for the latter half of the twentieth century.[1] This medicinal value, combined with their complex architectures (Figure 1), has stimulated the development of a host of synthetic methods and strategies designed to access their highly functionalized skeletons.[2−4] Presently, the emerging problem of antibiotic resistance has reinvigorated the search for effective therapeutics. One approach to facilitate this search is to develop powerful synthetic methods to enable facile and flexible syntheses of complex polyketides.

In line with this goal, we initiated research aimed at defining a general approach to macrolide antibiotics based

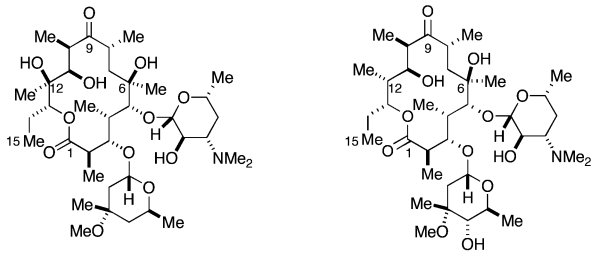


Figure 1. Macrolide antibiotics erythromycin A and B.

(1) Omura, S., Ed. *Macrolide Antibiotics. Chemistry, Biology, and Practice*, 2nd ed.; Academic Press: New York, 2002.

(2) Total synthesis of erythromycin A, see: Woodward, R. B. et al. *J. Am. Chem.* Soc. **1981**, *103*, 3215−3217. Total synthesis of erythromycin B, see: Martin, S. F.; Hida, T.; Kym, P. R.; Loft, M.; Hodgson, A. *J. Am. Chem.* Soc. **1997**, *119*, 3193−3194.

(3) For reviews on early synthetic work directed at macrolide antibiotic synthesis, see: (a) Paterson, I.; Mansuri, M. M. *Tetrahedron* **1985**, *41*, 3569−3624. (b) Mulzer, J. *Angew. Chem., Int. Ed. Engl.* **1991**, *30*, 1452−1454.

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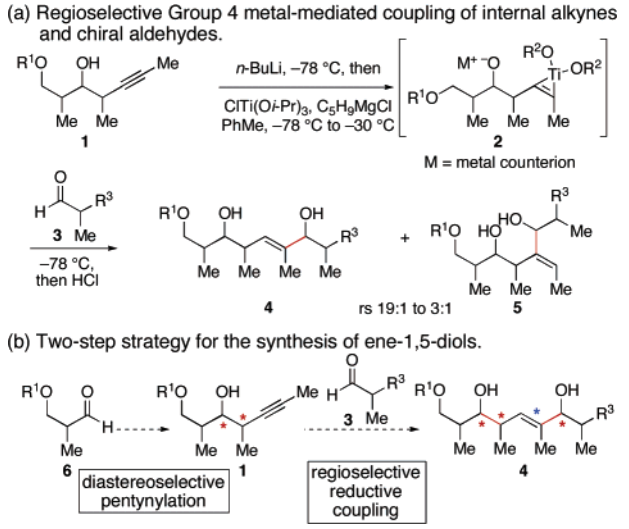
on our recently reported convergent process for polyketide construction.[5] Herein we describe the results of our initial investigations in this area that have established (1) a convergent approach to a C1−C15 fragment precursor to the erythronolides and (2) the role of tethered alkoxides in the control of site-selective C−C bond formation in titanium alkoxide-mediated coupling reactions of internal alkynes and chiral aldehydes.

Recently, we reported a two-step process for ene-1,5-diol synthesis (Scheme 1a), based on the coupling of differentially

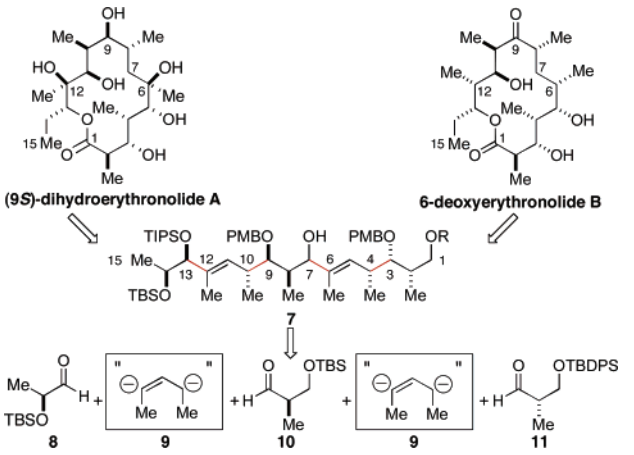
Scheme 1. Group 4 Metal Alkoxide-Mediated Coupling Reactions for Polyketide Assembly



functionalized carbonyl electrophiles with a formal pentenyl dianion equivalent (**6** → **1** → **4**; Scheme 1b).[5] Our studies revealed that a diastereoselective pentynylation (**6** → **1**), in conjunction with a group 4 metal-mediated coupling (**1** → **4**), provides general and flexible access to complex polyketides.

This basic pentenyl dianion-based coupling process serves as the foundation of our approach to the syntheses of the macrolide antibiotic aglycones (9*S*)-dihydroerythronolide A and 6-deoxyerythronolide B (Scheme 2). With the goal of accessing both targets from a common late stage intermediate (**7**),[6] we targeted the C3−C4, C6−C7, C9−C10, and C12−C13 bonds for construction with our previously described method. Such a series of C−C bond-forming reactions would represent a convergent route to the aglycons of this family of macrolide antibiotics by the stepwise coupling of lact-

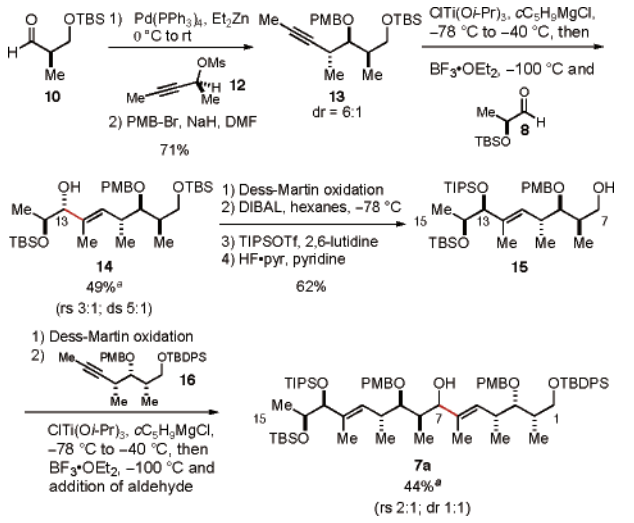
Scheme 2. Retrosynthetic Strategy for Macrolide Antibiotic Aglycone Synthesis



aldehyde **8** with 2 equiv of an α-methyl-*β*-silyloxy aldehyde (**10** and **11**).

Our initial efforts directed at realizing such a pathway to these targets are depicted in Scheme 3. Diastereoselective

Scheme 3. First-Generation Route to a C1−C15 Diene-Containing Fragment Precursor to the Erythronolides



[a] Yield reported for the isolated regioisomer.

pentynylation of the TBS-protected Roche aldehyde **10**,[5,7] followed by protection of the resulting homopropargylic alcohol furnished the homopropargylic ether **13**. Titanium alkoxide-mediated reductive coupling of this alkyne with lactaldehyde **8** provided a separable 3:1 mixture of regioisomeric products favoring the desired allylic alcohol **14**.[5,8] Oxidation to the enone, followed by diastereoselective

(4) For recent studies on the syntheses of the erythronolides and erythromycins, see: (a) Muri, D.; Lohse-Fraefel, N.; Carreira, E. M. *Angew. Chem., Int. Ed.* **2005**, *44*, 4036−4038. (b) Peng, Z.-H.; Woerpel, K. A. *J. Am. Chem. Soc.* **2003**, *125*, 6018−6019. (c) Hergenrother, P. J.; Hodgson, A.; Judd, A. S.; Lee, W.-C.; Martin, S. F. *Angew. Chem., Int. Ed.* **2003**, *42*, 3278−3281. (d) Evans, D. A.; Kim, A. S.; Metternich, R.; Novack, V. J. *J. Am. Chem. Soc.* **1998**, *120*, 5921−5942.

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

(6) For a review on allylic 1,3-strain as a control element for olefin functionalization reactions, see: Hoffman, R. W. *Chem. Rev.* **1989**, *89*, 1841−1860.

(7) Marshall, J. A.; Adams, N. D. *J. Org. Chem.* **1998**, *63*, 3812−3813.

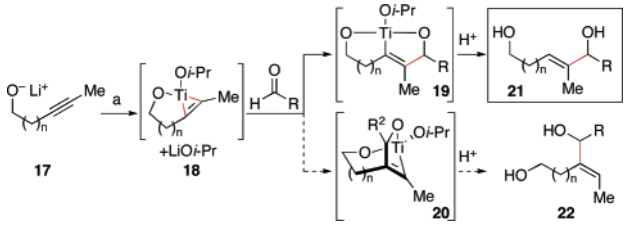
(8) Harada, K.; Urabe, H.; Sato, F. *Tetrahedron Lett.* **1995**, *36*, 3203−3206.

reduction,[9] protection of the C13 hydroxyl as the corresponding TIPS ether, and selective deprotection of the primary TBS ether afforded the C7−C15-containing fragment **15**. Oxidation to the corresponding aldehyde[10] followed by a second titanium alkoxide-mediated reductive coupling with the homopropargylic ether **16** (derived from diastereoselective pentynylation of Roche aldehyde **11**)[12] provided the fully functionalized C1−C15 diene **7a** in 44% yield, isolated from a 2:1 mixture of regioisomeric allylic alcohols. Importantly, the lack of diastereoselection in this coupling process is anticipated to be of little consequence in macrolide antibiotic synthesis, as C7 of the natural aglycons lacks substitution (Scheme 2).

Although we were successful in realizing our goal of assembling the C1−C15-containing diene **7a**, the levels of regioselection observed in the metal-mediated reductive coupling reactions with homopropargylic ethers **13** and **16** were unsatisfactory (≤3:1, Scheme 3). On the basis of our previous studies of group 4 metal-mediated coupling reactions of *homopropargylic alcohols* and chiral aldehydes,[5] we anticipated that the relative stereochemistry of the internal alkyne component would play an important role in influencing levels of regioselection. The similar levels of regioselection observed in the coupling reactions of the anti,syn and syn,syn stereoisomers of the *homopropargylic ethers* **13** and **16** stand in sharp contrast to this expectation. On the basis of these observations, and related perturbations of regioselection observed in group 4 metal-mediated coupling reactions of homopropargylic alcohols/ethers and terminal alkynes,[11] we began investigating the role of a tethered hydroxyl in these coupling reactions.

We speculated that a tethered alkoxide may influence site selective carbon−carbon bond formation in reductive coupling reactions based on the potential for interaction of the alkoxide with the titanium center. As depicted in Scheme 4,

Scheme 4. A Potential Role of Tethered Alkoxides in Regioselective C−C Bond Formation



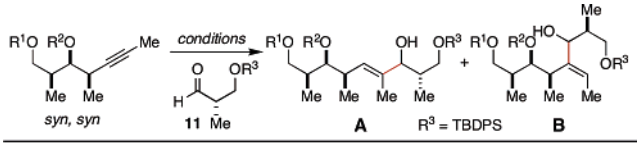
[a] Reagents: $ClTi(Oi\text{-}Pr)_3$, $c\text{-}C_5H_9MgCl$.

if the tethered alkoxide coordinates to the metal center to form a bicyclic metallacyclopropene (**18**), and this structure is retained in the transition state for reductive coupling, then C−C bond formation should preferentially afford the bicyclic metallacycle **19** over the bridged bicyclic isomer **20**. Protonation of **19** would then afford the allylic alcohol **21** as the predominant product.

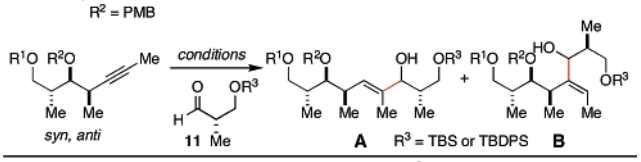
On the basis of this speculation, we explored the effect of tethered alkoxides on regioselection in titanium alkoxide-mediated reductive coupling reactions of functionalized internal alkynes and chiral aldehydes relevant for polyketide assembly. The alkynes containing syn,syn, syn,anti, anti,anti, and anti,syn stereochemical motifs were examined in coupling reactions with the Roche aldehyde **11** to probe the combined effect of stereochemistry and the position of a tethered alkoxide in the control of site-selective C−C bond formation.[13]

As depicted in Table 1, within each stereochemical series, the substrates bearing a tris-homopropargylic alcohol (**23**,

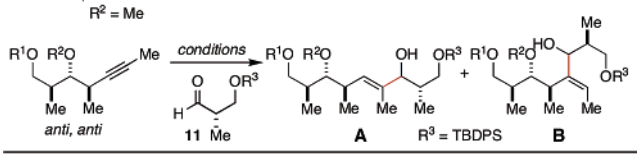
Table 1. Site-Selective C−C Bond Formation Based on the Presence and Position of a Tethered Alkoxide[a]



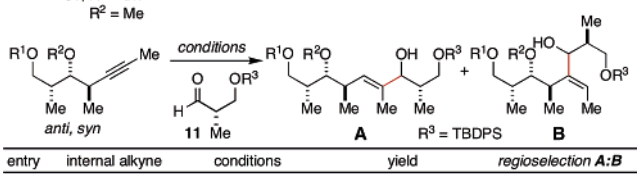
entry	internal alkyne	conditions	yield	regioselection A:B
1	**23**; R^1 = H, R^2 = PMB	a	65[a]	8:1
2	**24**; R^1 = TBDPS, R^2 = H	a	68[a]	4:1
3	**25**; R^1 = TBDPS, R^2 = PMB	b	42	1.3:1



entry	internal alkyne	conditions	yield[a]	regioselection A:B
4[c,d]	**26**; R^1 = H, R^2 = Bn	a	78	18:1
5[e]	**27**; R^1 = Bn, R^2 = H	a	58	10:1
6[e]	**28**; R^1 = Bn, R^2 = Me	b	59	4:1



entry	internal alkyne	conditions	yield	regioselection A:B
7	**29**; R^1 = H, R^2 = Bn	a	68	16:1
8	**30**; R^1 = Bn, R^2 = H	a	68	12:1
9	**31**; R^1 = Bn, R^2 = Me	b	64	12:1



entry	internal alkyne	conditions	yield	regioselection A:B
10	**32**; R^1 = H, R^2 = PMB	a	69	20:1
11	**33**; R^1 = TBS, R^2 = H	a	61	4:1
12	**34**; R^1 = TBS, R^2 = PMB	b	61	2:1

[a] yield reported is for regioisomer **A**.

[a] Reagents and conditions: (a) *n*-BuLi, PhMe, −78 °C; then $ClTi(O\text{-}i\text{-}Pr)_3$, C_5H_9MgCl, −78 to −40 °C; then $BF_3{\cdot}OEt_2$, −78 °C and aldehyde. (b) $ClTi(O\text{-}i\text{-}Pr)_3$, C_5H_9MgCl, −78 to −40 °C; then $BF_3{\cdot}OEt_2$, −78 °C and aldehyde. (c) This experiment was performed with the enantiomeric alkyne and aldehyde. (d) R^3 = TBDPS. (e) R^3 = TBS.

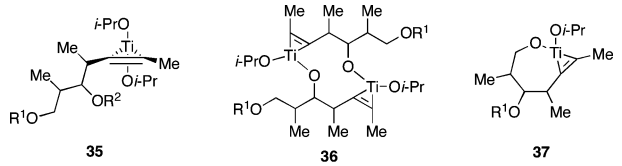
(9) Overman, L. E.; McCready, J. *Tetrahedron Lett.* **1982**, *23*, 2355−2358.
(10) Dess, D. B.; Martin, J. C. *J. Org. Chem.* **1983**, *48*, 4155−4156.
(11) Shimp, H. L.; Micalizio, G. C. *Org. Lett.* **2005**, *7*, 5111−5114.
(12) See the Supporting Information for experimental details.

26, **29**, and **32**, highlighted in red) provided the highest levels of regioselection in these coupling reactions (rs ≥ 8:1) (see entries 1, 4, 7, and 10). Uniformly, the substrates bearing a homopropargylic alcohol provided products with lower levels of regioselection (rs = 4:1 to 12:1; entries 2, 5, 8, and 11), while the fully protected substrates were generally least selective in coupling reactions with aldehyde **11** (entries 3, 6, 9, and 12).

These data indicate that the presence of a tethered alkoxide in the polyketide chain can have a dramatic influence on regioselection in these titanium alkoxide-promoted coupling reactions. To the best of our knowledge, this is the first observation of such an alkoxide-directing effect in reductive coupling reactions between internal alkynes and aldehydes.[14]

As depicted in Scheme 5, the presence of a tethered alkoxide has the potential to modulate the structure of the reactive metallacycles (monocyclic, oligomeric, or bicyclic). In the competing transition states for reductive coupling with carbonyl electrophiles that lead to the observed regioisomeric products, each of these metallacycles are expected to experience unique nonbonded steric interactions as a result of their distinct topographies.

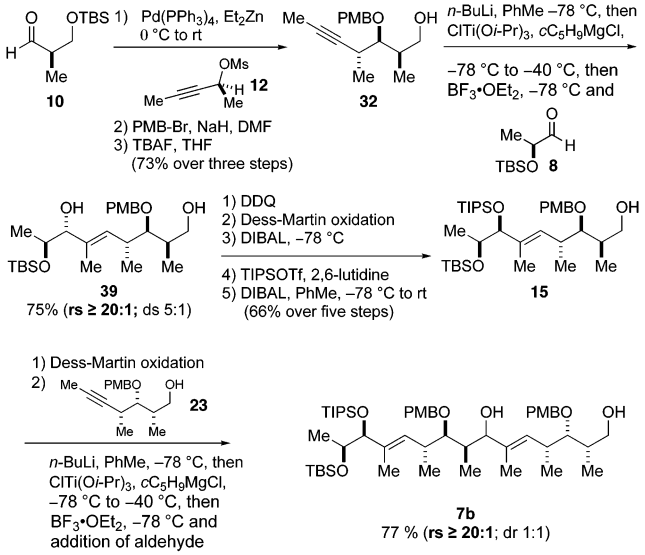
Scheme 5. Potential Variation in the Structure of the Reactive Metallacycle Based on the Presence and Position of a Tethered Alkoxide



[a] Not meant to exclude the possibility of higher order oligomeric structures. [b]The possibility of a dimer or higher order oligomer may also contribute to the changes in regioselection observed, as we realize that **37** should be destabilized by ring strain associated with the proposed [5.1.0] unsaturated ring system.

Armed with the knowledge that a tris-homopropargylic alkoxide, in a polyketide-derived internal alkyne (**23**, **26**, **29**, and **32**), maximizes regioselection in coupling reactions with the Roche aldehyde **11**, we re-examined our approach to the synthesis of a C1−C15 diene precursor to the erythronolides. As illustrated in Scheme 6, pentynylation of the TBS-protected Roche aldehyde **10**, followed by protection of the resulting homopropargylic alcohol and deprotection of the

Scheme 6. Second-Generation Route to a C1−C15 Diene



primary TBS ether provided the tris-homopropargylic alcohol **32**. Deprotonation, followed by titanium alkoxide-mediated reductive coupling with the TBS-protected lactaldehyde **8** provided the allylic alcohol **39** in 75% yield with ≥20:1 regioselection. Oxidative formation of the PMP acetal, followed by oxidation of the allylic alcohol, diastereoselective reduction (ds 6:1), protection as the corresponding TIPS ether, and reductive opening of the PMP acetal provided the primary alcohol **15** in 66% yield. Oxidation to the corresponding aldehyde, followed by a second titanium alkoxide-mediated coupling with the alkoxide derived from **23** provided the fully functionalized C1−C15 diene **7b** in 77% yield; this coupling reaction also proceeded with ≥20:1 regioselection.

Overall, we have described a highly convergent route to the synthesis of a C1−C15 functionalized diene of potential value for macrolide antibiotic synthesis. In the course of our studies we have defined an important role of tethered alkoxides in the control of site-selective C−C bond formation in titanium alkoxide-mediated reductive coupling reactions of internal alkynes and chiral aldehydes. Future work targeting the syntheses of macrolide antibiotics with these highly regioselective 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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(13) For the preparation of compounds **23**−**34**, see the Supporting Information.

(14) For an example of a magnesium alkoxide-directed zirconium-catalyzed carbomagnesiation see: (a) Hoveyda, A. H.; Morken, J. P.; Houri, A. F.; Xu, Z. *J. Am. Chem. Soc.* **1992**, *114*, 6692−6697. For olefin-directed regioselective nickel-catalyzed reductive coupling reactions of alkynes with aldehydes, see: (b) Mahandru, G. M.; Liu, G.; Montgomery, J. *J. Am.* Chem. Soc. **2004**, *126*, 3698−3699. (c) Miller, K. M.; Luanphaisarnnont, T.; Molinaro, C.; Jamison, T. F. *J. Am. Chem. Soc.* **2004**, *126*, 4130−4131. (d) Miller, K. M.; Jamison, T. F. *J. Am. Chem. Soc.* **2004**, *126*, 15342−15343.