Chemoselective Reductive Cross-Coupling of 1,5-Diene-3-ols with Alkynes: A Facile Entry to Stereodefined Skipped Trienes

Peter S. Diez and Glenn C. Micalizio*

Department of Chemistry, The Scripps Research Institute, Scripps Florida, Jupiter, Florida 33458

Received May 5, 2010; E-mail: micalizio@scripps.edu

Abstract: A convergent synthesis of highly substituted and stereo-defined skipped polyenes is described from the reductive cross-coupling of substituted 1,5-diene-3-ols with alkynes. The control of site selectivity in functionalization of the substituted diene is a central feature of this complex fragment union reaction.

Skipped polyenes are structural motifs that are present in a vast array of natural products of biological significance. While stereochemically homogeneous skipped polyenes are a central feature of a variety of natural polyunsaturated fatty acids,[1] skipped polyenes of diverse stereochemistry and substitution are also abundant, with examples including natural products that are of potential value as antibiotic, antifungal, and anticancer agents (Figure 1).[2] Despite their frequent occurrence in natural products, and potential utility in organic chemistry, there remains a great dearth of efficient methods for the synthesis of stereodefined skipped polyenes.[3] We describe here a highly selective convergent pathway to skipped trienes via chemo-, regio-, and stereoselective reductive cross-coupling of substituted 1,5-dienes and alkynes.
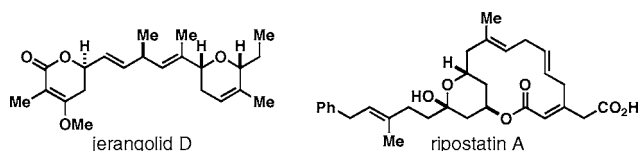

Figure 1. Natural products housing skipped polyenes.

In efforts aimed at providing a solution to problems associated with the synthesis of stereochemically heterogeneous skipped polyenes, we previously described a reductive cross-coupling of substituted vinylcyclopropanes with alkynes.[4] This reaction, depicted in Figure 2A, furnishes skipped trienes bearing a central (E)-alkene, with the potential to install a flanking (E)- or (Z)-disubstituted alkene. We hypothesized that a related reductive cross-coupling of 1,5-dienes with alkynes may define a more convenient and stereochemically complementary pathway to related skipped trienes (Figure 2B). That said, such a process would require control of chemoselectivity defined by the competition between reaction paths depicted in Figure 2C: (1) Site selective reductive cross-coupling at the allylic alcohol (Path A),[5] (2) site selective reductive cross-coupling via the homoallylic alcohol (Path B),[6] or (3) reaction at both alkenes of the 1,5-diene.

Our initial investigations were focused on determining whether structural features on the 1,5-diene could be used to control site selective C–C bond formation. As depicted in entry 1 of Table 1, coupling of the parent unsubstituted diene **2** with symmetrical alkyne **1** (by treatment of the alkyne with the combination of Ti(O*i*-Pr)$_4$ and *c*-C$_5$H$_9$MgCl,[7] followed by addition of the lithium alkoxide of **2** and subsequent hydrolysis with a saturated aqueous solution
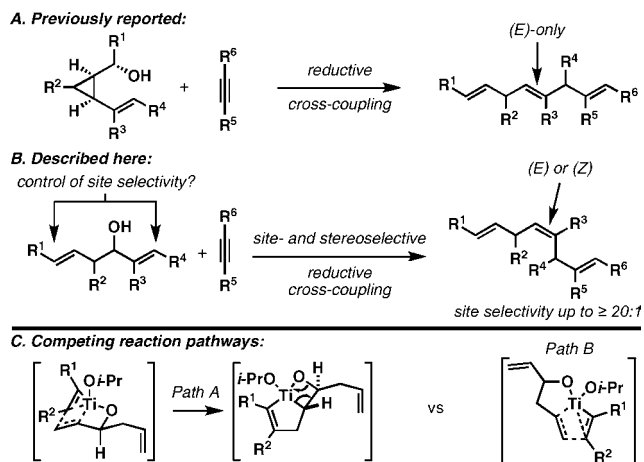

Figure 2. Convergent coupling reactions for skipped triene synthesis.

of NH$_4$Cl) led to the formation of the skipped triene **3**. While we were delighted to isolate a skipped triene from this coupling reaction, both the site selectivity and stereoselectivity for this process were poor (1.4:1 and 1:1, respectively). Moving on, reaction of the Me-substituted 1,5-diene **4** with alkyne **1** delivered the 1,7-diene **5** in 50% yield, with no trace of a skipped triene being produced (entry 2).

To our delight, when both alkenes of the 1,5-diene are substituted, reductive cross-coupling reactions uniformly proceed with high selectivity for the formation of stereodefined skipped trienes. The generality of this process can be seen in entries 3–6, where skipped trienes bearing two or three stereodefined alkenes (**7**, **9**, **11**, and **13**) are produced with ≥20:1 selectivity for C–C bond formation at the allylic alcohol terminus of the 1,5-diene. Notably, these coupling reactions proceed with very high levels of stereoselectivity, do not disturb the preset stereochemistry of the 1,5-diene starting material, and provide a foundation of evidence that supports the ability to control site selectivity in reductive cross-coupling reactions of dienes with alkynes.

Advancing beyond a simple exploration of the 1,5-diene partner, we shifted our attention to employing this bond construction for regioselective coupling of unsymmetrical alkynes.[8] While TMS-alkynes were expected to behave in a predictable manner, with C–C bond formation occurring distal to the TMS group, we were delighted to see that TMS-substituted *enynes* (**14** and **16**) were compatible substrates in this chemoselective reductive cross-coupling reaction (Table 2, entries 1–2). Here, selective activation of the alkyne of **14** and **16** is followed by chemo- and stereoselective C–C bond formation with substituted 1,5-dienes. Even alkynes that boast a modest level of steric differentiation (Me- vs TIPSOEt-) result in regioselective cross-coupling (entry 3); here, the stereodefined triene **19** is produced in 54% yield (rs = 9:1). Use of a more sterically differentiated internal alkyne results in skipped

Table 1

entry	1,5-diene	yield[a] (%)	path selectivity[b]	stereoselectivity	major product[d]
1	**2**	–	1.4:1	1:1	**3**
2	**4**	50	≥20:1	–	**5**
3	**6**	57	≥20:1	≥20:1[c]	**7**
4	**8**	57	≥20:1	≥20:1[c]	**9**
5	**10**	76	≥20:1	≥20:1[c]	**11**
6	**12**	53[e]	≥20:1	≥20:1[c]	**13**

[a] Reaction conditions: **1** (2−3 equiv), Ti(Oi-Pr)$_4$, c-C$_5$H$_9$MgCl, PhMe (−78 to −35 °C), then cool to −78 °C and add Li alkoxide of the allylic alcohol as a solution in THF (warm to 0 °C). [b] In cases where selectivity is reported as ≥20:1, no evidence was found for products derived from C−C bond formation by a different path. [c] In cases where selectivity is reported as ≥20:1, no evidence was found for the formation of stereoisomeric products. [d] Olefin geometry of the major products was assigned by analogy to previous examples. [e] Yield reported is after HPLC purification.

Table 2

entry	alkyne	1,5-diene	yield (%)[a]	skipped triene product
1	**14**	**8**	60[b]	**15**
2	**16**	**10**	51[b]	**17**
3	**18**	**10**	54[b]	**19**
4	**20**	**10**	65	**21**
5	**18**	**22**	58[b]	**23**

[a] Reaction conditions: alkyne (2−3 equiv), Ti(Oi-Pr)$_4$ or ClTi(Oi-Pr), c-C$_5$H$_9$MgCl, PhMe (−78 to −35 °C), then cool to −78 °C and add Li alkoxide of the allylic alcohol as a solution in THF (warm to 0 °C). [b] Yield reported is over two steps: chemoselective reductive cross-coupling and silyl deprotection with TBAF in THF.

unexpected and points to a potentially powerful aspect of the present reductive cross-coupling reaction. We look forward to advances that follow from these initial findings.

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.

trienes with even higher levels of regioselection. As depicted in entry 4, union of alkyne **20** with diene **10** produces triene **21** in 65% yield with ≥20:1 rs. Substitution is also tolerated in the 1,5-diene partner. As illustrated in entry 5, union of alkyne **18** with diene **22** results in the formation of triene **23**, a stereodefined skipped polyene possessing one (E)-trisubstituted, one (Z)-trisubstituted, and one (Z)-disubstituted alkene, while also establishing a 1,4-diene bearing a central stereodefined alkyl substituent.

In conclusion, we have described a convenient synthetic pathway to a range of stereochemically defined skipped trienes by the union of 1,5-dienes with disubstituted alkynes. This achievement documents the ability to control chemoselectivity in reductive cross-coupling reactions of dienes, where alkene substitution and location of a pendant alkoxide combine to dictate the course of C−C bond formation.[9] A mechanistic feature that has been revealed in the course of these studies is the increased sensitivity of homoallylic alcohol-alkyne reductive cross-coupling reactions to alkene substitution in comparison to allylic alcohol-alkyne coupling processes. In all cases explored, where each alkene of a 1,5-diene is disubstituted, chemoselective reductive cross-coupling proceeds by a pathway that exploits the enhanced reactivity of an allylic alcohol in preference to a homoallylic alcohol; a mechanistic rationale for this divergent reactivity awaits further experimentation. Finally, we have demonstrated that this coupling reaction is useful for the selective union of unsymmetrical coupling partners, including substrates that display only minor steric differences (i.e., **18**); this observation was

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