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Polyketide Assembly by Alkene−Alkyne Reductive Cross-Coupling: Spiroketals through the Union of Homoallylic Alcohols

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Spiroketal-containing natural products represent a rich class of complex molecules that are known to possess potent and diverse biological properties. Examples include molecules that target HIV-1 protease, tubulin polymerization, protein phosphatases, and isoleucyl tRNA synthetase among other therapeutically interesting targets.[1] As a result, the synthesis and evaluation of spiroketal-containing molecules has been a topic of considerable interest in chemistry and medicine. Recent investigations along these lines have led to the discovery of natural product-inspired spiroketals that inhibit microtubule assembly, cause apoptosis, inhibit phosphatases, modulate the tubulin cytoskeleton, and show promise as potential therapeutics for B-cell chronic lymphocytic leukemia.[2] As a result of their significant potential in defining novel medicinally relevant small molecules, it is not surprising that many chemical strategies have emerged for the synthesis of stereodefined spiroketals.[3] While recent interest has focused on methods for controlling the stereochemistry of the acetal,[4] few general and flexible strategies for accessing the carbon skeleton have been advanced beyond multistep aldol chemistry,[5] which involves processes that currently require numerous carbonyl redox and protecting-group manipulations. Here we describe a highly convergent and concise entry to substituted and stereodefined spiroketals by the union of homoallylic alcohols with trimethylsilylacetylene (TMS-acetylene) (**2** + **3** + **4** → **1**; Figure 1A). Because a variety of methods for stereoselective allyl transfer exist,[6] this spiroketal synthesis defines a simple convergent pathway that proceeds by the union of aldehydes (**5** and **6**) through a sequence that establishes four C−C bonds and up to six new stereocenters.

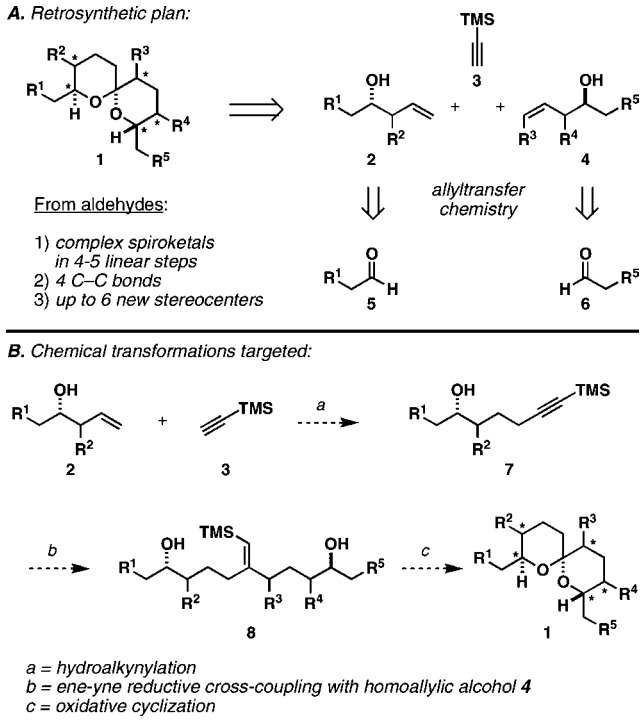

Figure 1. Convergent assembly of spiroketals by the selective union of homoallylic alcohols.

With well-established allyl transfer chemistry in place, the union of homoallylic alcohols **2** and **4** with TMS-acetylene (**3**) en route to complex spiroketals **1** was targeted through a three-step process, as depicted in Figure 1B. Initial functionalization of homoallylic alcohol **2** by regioselective formal hydroalkynylation with TMS-acetylene would deliver alkyne **7**. Subsequent site- and stereoselective reductive cross-coupling between **7** and the second homoallylic alcohol **4** would then deliver complex diol **8**. Finally, oxidative cleavage of the central alkene with subsequent dehydrative cyclization would furnish complex spiroketal **1**.

Initial attempts to accomplish formal hydroalkynylation via hydroboration of a terminal alkene followed by B−alkyl Suzuki coupling with bromo-TMS-acetylene were met with failure.[7] Turning our attention to classic alkynylborate chemistry,[8] we hypothesized that the desired bond construction could proceed by the sequence depicted in Figure 2A. Initial hydroboration of **2** was anticipated to deliver a trialkylborane intermediate that, although capable of undergoing the desired alkynylborate chemistry, was anticipated to be problematic, as selectivity in subsequent 1,2-alkyl migration is known to proceed with competitive ring expansion of the borabicyclononane system.[9] Thus, we pursued site-selective mono-oxidation of the resulting trialkylborane[10] followed by addition of Li-TMS-acetylide to deliver intermediate mixed lithium alkynylborates having the general structure **9**. Subsequent iodine-initiated group-selective 1,2-alkyl migration and base-induced elimination would then deliver **7**, the product of formal hydroalkynylation of **2**.

As illustrated in Figure 2B, this design for formal hydroalkynylation proved effective and general, providing coupled products in 72−86% yield (eqs 1−6). Overall, the required sequence of reactions was easy to perform in a one-pot process and provided products bearing a range of stereodefined alkyl substitution (**11**, **13**, **15**, **17**, **19**, and **21**).

Next, we explored the second C−C bond-forming process for the proposed spiroketal construction: *ene−yne cross-coupling between stereodefined homoallylic alcohols and a suitably functionalized TMS-alkyne* (**22**; Figure 3). Building on our earlier observations that culminated in a general method for ene−yne cross-coupling,[11] we explored titanium-mediated alkoxide-directed reductive coupling as a means to accomplish the desired bond construction. Initial formation of a Ti−alkyne complex

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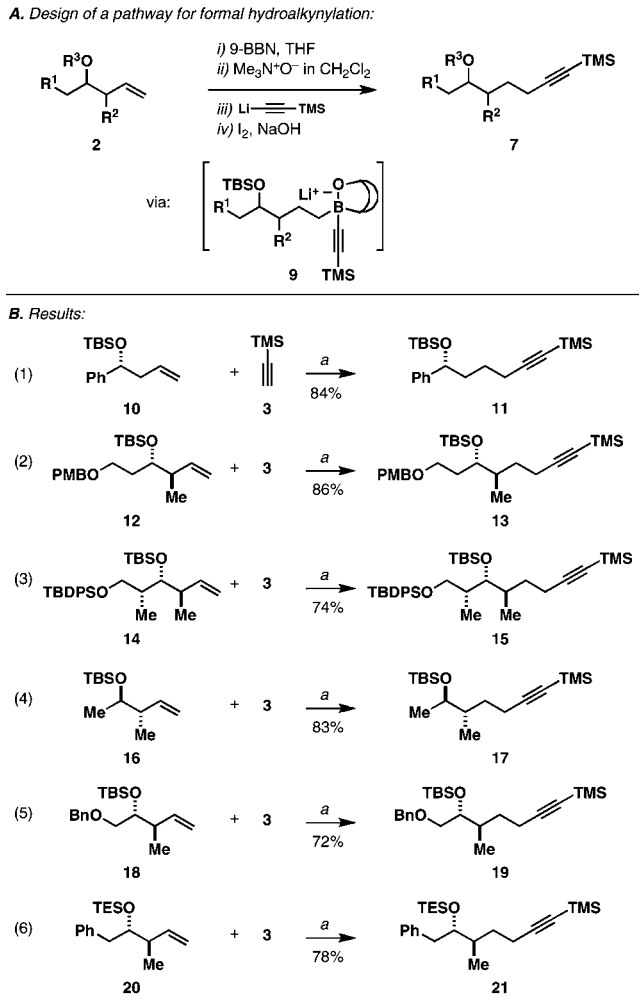


Figure 2. Formal hydroalkynylation by alkynylborate chemistry.

by exposure of **22** to the combination of Ti(O*i*-Pr)$_4$ and *c*-C_5H_9MgCl,[12] followed by addition of the lithium alkoxide of homoallylic alcohol **23**, provided the homologated product **24** in 87% yield as a single isomer (eq 7) after aqueous workup. This ene−yne reductive cross-coupling proved to be effective for a range of homoallylic alcohols (**25**, **27**, **29**, and **31**), delivering the corresponding cross-coupled products **26**, **28**, **30**, and **32** in 74−88% yield (eqs 8−11). Of these examples, eqs 10 and 11 highlight an interesting and powerful feature of this coupling process. In these cases, the deoxypropionate architecture was established in a highly stereoselective fashion through a complex metallacycle-mediated coupling reaction that proceeds with high levels of regioselectivity with respect to each unsymmetrically disubstituted π system in concert with the establishment of a new allylic stereogenic center (ds $\geq$ 20:1).[13]

While we were delighted with the apparent generality of this fragment union process, a limitation was observed in our initial study. As depicted in eq 12, reductive cross-coupling of homoallylic alcohol **33** with alkyne **22** did proceed, but product **34** could be isolated in only 22% yield. This limitation appears to be associated with the use of a homoallylic alcohol substrate containing both a disubstituted alkene and a sterically hindered directing group.

With methods for regioselective hydroalkynylation and ene−yne cross-coupling in hand, we turned our attention to the assembly of

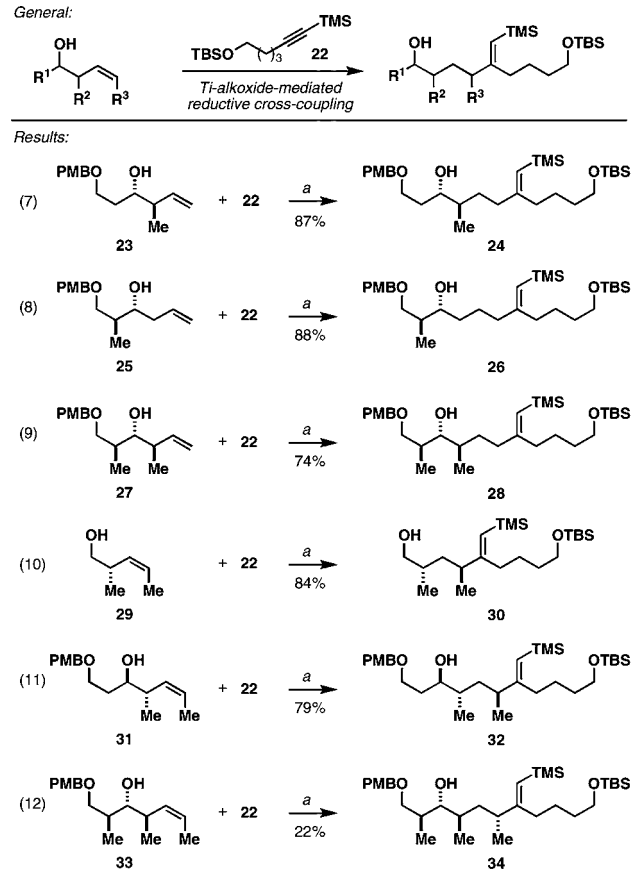
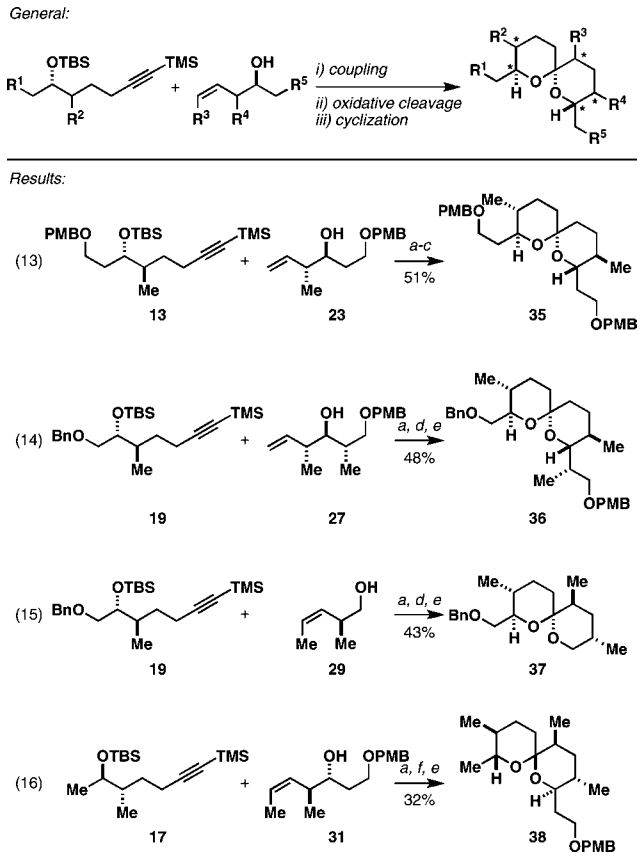


Figure 3. Titanium-mediated reductive cross-coupling.

spiroketals. As illustrated in Figure 4, a three-step sequence composed of reductive cross-coupling, oxidative cleavage, and acid-promoted dehydration[14] was pursued as a general strategy for the synthesis of stereodefined spiroketals. Overall, complex and diverse polysubstituted spiroketals **35**−**38** were generated with very high levels of stereoselection from the union of a range of stereochemically defined homoallylic alcohols (**23**, **27**, **29** and **31**) with the products of formal hydroalkynylation (**13**, **17** and **19**), as shown in eqs 13−16.[15] While the overall yields for this three-step process define an area for future improvement, the current efficiencies derive from sequences of reactions with average yields per step ranging from 68−80%.

In summary, we have developed a strategy for the convergent assembly of highly substituted and stereodefined spiroketals that proceeds through the union of two chiral homoallylic alcohols. The chemical process defined here is based on merging well-established stereoselective allyl transfer chemistry with (1) a regioselective formal hydroalkynylation and (2) a metallacycle-mediated reductive cross-coupling reaction between functionalized homoallylic alcohols and TMS-alkynes (the product that results from the hydroalkynylation reaction). While defining a synthetic pathway to spiroketals that can accommodate substitution patterns not easily attained by other convergent methods (based on aldol technology, allylmetal chemistry, cross-metathesis, and dithiane alkylation processes), these studies demonstrate the potential utility of ene−yne reductive cross-coupling reactions in the synthesis of complex molecules. We look forward to advances that follow from these initial studies.



Reaction conditions: [a] alkyne (2.5 eq), $Ti(O\textit{i}\text{-}Pr)_4$ (2.5 eq), $c\text{-}C_5H_9MgCl$ (2.5 eq), Et_2O, −78 °C to −30 °C, then add homoallylic alkoxide (−30 °C to 0 °C), then 1N HCl. [b] OsO_4, $NaIO_4$, *t*-BuOH, pyr. [c] PPTS, CH_2Cl_2, CH_3OH. [d] TsOH, acetone. [e] O_3, CH_2Cl_2, then Me_2S, then TsOH. [f] HCl (1N), THF (1:1).

Figure 4. Spiroketal synthesis by the convergent union of homoallylic alcohols.

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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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(14) On the basis of a reviewer's suggestion, we add that these conditions are typical for thermodynamic control in the stereoselective generation of the spiroacetal. See the Supporting Information for additional details.

(15) In each case (eqs 13−16), no evidence was found for the production of stereoisomeric spiroketals. This observation is in accord with the well-established thermodynamic preference for the generation of spiroketals that are stabilized by a double anomeric effect. See the Supporting Information for additional details.

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