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Tandem Intramolecular Silylformylation−Crotylsilylation: Highly Efficient Synthesis of Polyketide Fragments

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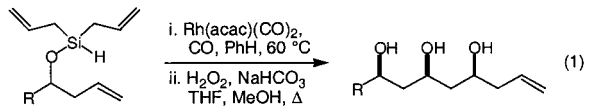
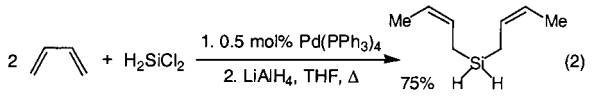
Tandem intramolecular silylformylation−allylsilylation of alkenes[1] (eq 1) and alkynes[2] allows the rapid synthesis of polyol fragments for polyketide/macrolide synthesis.[3] In an effort to expand the scope and utility of these reactions we have investigated the substitution of (*Z*)- and (*E*)-crotyl groups for the allyl groups on silicon. We report herein that such substitution leads to the stereospecific incorporation of both *anti* and *syn* propionate units into the growing polyol chain, and demonstrate the power of the methodology for the rapid assemblage of polyketide-like structures.



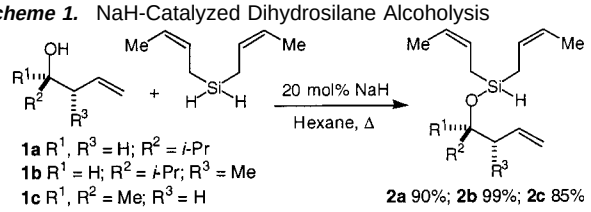
It is a unique feature of this allylsilylation chemistry that the silicon must carry two diastereotopic allyl (crotyl) groups in order to avoid the presence of an additional element of chirality at silicon. Syntheses of di-*cis*-crotylsilane and di-*trans*-crotylsilane were therefore required. Although the latter has proven surprisingly elusive (discussed in greater detail below), the former may be prepared efficiently. Double $Pd(PPh_3)_4$-catalyzed 1,4-hydrosilylation of 1,3-butadiene with dichlorosilane,[4] and reduction of the resulting dichloro-di-*cis*-crotylsilane with $LiAlH_4$ (0.56 equiv) produced di-*cis*-crotylsilane in 75% yield (eq 2).



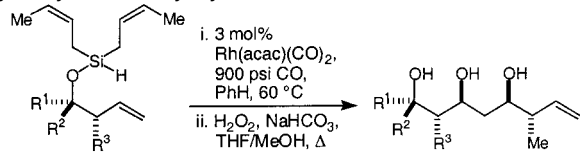
Requiring an efficient method for the silylation of the substrate alcohols, we focused on catalytic hydrosilane alcoholysis.[5] Only a few reports have described the selective monoalcoholysis of dihydrosilanes,[5m,6] and we were further constrained to catalysts that would not also catalyze hydrosilylation of the silyl ether products.[7] We therefore focused on metal alkoxides.[5a,n] Treatment of a mixture of an alcohol and di-*cis*-crotylsilane with 20 mol % NaH provided a mixture of the desired silyl ether and the dialkoxysilane that was highly dependent on the solvent, temperature, and time of reaction. Eventually, it was discovered that refluxing hexane allowed the selective monoalcoholysis reaction, and under these conditions alcohols **1a**, **1b**, and **1c**[8] could be converted to silyl ethers **2a**, **2b**, and **2c** in excellent yields (Scheme 1).

With access to the desired silyl ethers secured, we investigated their performance in the tandem intramolecular silylformylation−crotylsilylation reaction (Scheme 2). Subjection of silanes **2a**, **2b**, and **2c** to the standard reaction conditions[1] led to the isolation of triols **3a**, **3b**, and **3c**, in which three new stereocenters have been established in a single tandem reaction. In every case the yield shown is the isolated yield of purified major diastereomer. The diastereoselectivities (major diastereomer: all other diastereomers) parallel closely those observed in the corresponding diallylsilane reactions,[1] and we therefore conclude that the crotylation event is essentially stereospecific.

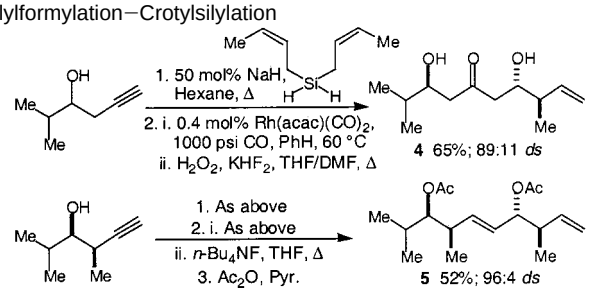
Scheme 1. NaH-Catalyzed Dihydrosilane Alcoholysis



Scheme 2. Tandem Intramolecular Silylformylation−Crotylsilylation



Scheme 3. Tandem Intramolecular Silylformylation−Crotylsilylation



Both the silylation chemistry and the tandem intramolecular silylformylation−crotylsilylation chemistry work equally well with alkyne substrates to produce ketodiol **4** and diacetate **5**[9] in 65 and 52% overall yields, respectively (Scheme 3). As above, the diastereoselectivities parallel closely those observed in the corresponding diallylsilane reactions,[2] leading to the conclusion that the crotylation event is stereospecific.

As mentioned above, our attempts to prepare di-*trans*-crotylsilane have been fruitless. The most obvious proposal was to adapt the procedure for the synthesis of *trans*-crotyl-trichlorosilane.[4b,c,10] Even under harsh conditions with many different catalysts, however, we could not induce a successful reaction between dichlorosilane and *trans*-crotyl chloride. Desiring nevertheless to establish that *trans*-crotyl groups would result in *syn* propionate units in the tandem

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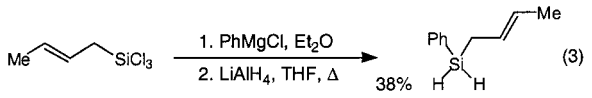
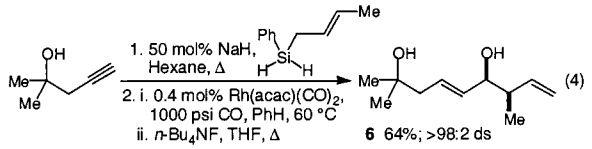
intramolecular silylformylation−allylsilylation chemistry, we synthesized *trans*-crotyl-phenylsilane as shown in eq 3.



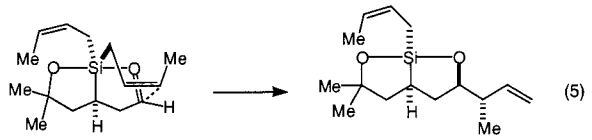
(3)

To avoid the creation of a mixture of diasteromers in the silane alcoholysis reaction, we employed an achiral alcohol (eq 4). As shown, the silylation chemistry and the tandem intramolecular silylformylation−allylsilylation chemistry work equally well with a *trans*-crotylsilane to give diol **6** in 64% overall yield. As expected, a *syn*-propionate unit was obtained stereospecifically.



(4)

We have proposed that following the silylformylation an uncatalyzed intramolecular aldehyde allylation/crotylation proceeds through a closed cyclic transition state.[1,2] The unusual observation of *anti*-propionate units from *cis*-crotyl groups and of *syn*-propionate units from *trans*-crotyl groups was predicted by, and is fully consistent with, this model. Thus, a chairlike arrangement of the six reacting atoms necessitates that the alkyl chain of the aldehyde occupy a pseudoaxial position, leading to the observed sense of induction (eq 5).

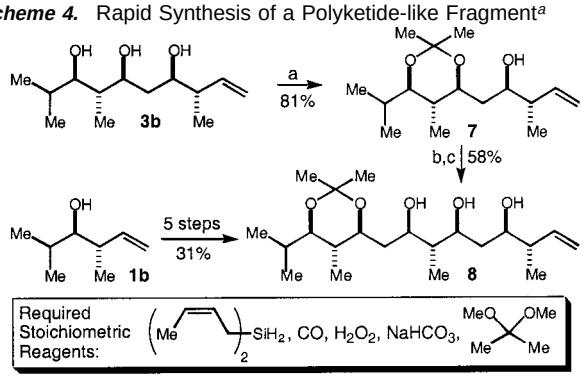


(5)

To demonstrate the power of this methodology for the iterative and rapid synthesis of polyketide-like fragments, triol **3b** (two steps and 66% yield from alcohol **1b**) was selectively (≥7:1 at equilibrium) protected to give acetonide **7** in 81% yield (Scheme 4). A second application of the tandem intramolecular silylformylation−crotylsilylation produced triol **8** (>10:1 ds) in 58% overall yield. The synthesis of **8**, which contains eight stereogenic centers, was thus achieved in five steps from alcohol **1b** in 31% overall yield, and the complete list of required stoichiometric reagents for the synthesis is: di-*cis*-crotylsilane, CO, H_2O_2, $NaHCO_3$, and 2,2-dimethoxypropane. This both indicates the power and efficiency of the tandem intramolecular silylformylation−crotylsilylation methodology and suggests the possibility not only of applying this methodology to the synthesis of natural products but also of rapidly generating several such fragments and employing them as platforms/building blocks for diversity-oriented synthesis of polyketide/macrolide-like structures.

The reactions described here significantly expand the scope of the tandem intramolecular silylformylation−allylsilylation reaction. The crotylsilanes are easily prepared, and a new, convenient, catalytic dihydrosilane alcoholysis has been developed. Further applications to the efficient synthesis of stereochemically complex targets may be readily envisioned.

Scheme 4. Rapid Synthesis of a Polyketide-like Fragment[a]



[a] (a) 2,2-Dimethoxypropane, (+)-camphorsulfonic acid, CH_2Cl_2. (b) 20 mol % NaH, di-*cis*-crotylsilane, hexane, reflux. (c) i. 3.0 mol % $Rh(acac)(CO)_2$, 900 psi CO, PhH, 60 °C; ii. H_2O_2, $NaHCO_3$, THF, MeOH, reflux.

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Supporting Information Available: Experimental procedures, characterization data, and stereochemical proofs (PDF). This material is available free of charge via the Internet at http://pubs.acs.org.

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