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Tandem Silylformylation−Crotylsilylation/Tamao Oxidation of Internal Alkynes: A Remarkable Example of Generating Complexity from Simplicity

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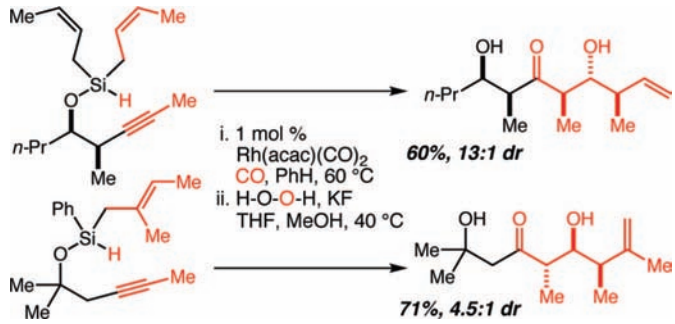
ABSTRACT



The rhodium-catalyzed tandem silylformylation−crotylsilylation reaction has been extended to include internal alkynes. Tamao oxidation of the initial product leads to the production of a substituted enol, which undergoes highly diastereoselective tautomerization. The resulting one-pot procedure fashions three new stereocenters, a ketone, and a terminal alkene from a butenyl group, a propynyl group, a silyl hydride, H_2O_2, and CO.

As part of a program devoted to the development of efficient tandem reaction strategies for polyketide natural product synthesis we have reported the tandem intramolecular silylformylation−allyl(crotyl)silylation of alkynes which, following Tamao oxidation, provides access to β,β'-dihydroxyketones with good levels of 1,5-diastereoselection (Scheme 1).[1] In an effort to expand the scope of this methodology to include more heavily propionate-derived polyketide fragments the use of internal alkynes presented itself as an intriguing possibility. Assuming the rhodium-catalyzed silylformylation would tolerate such substrates,[2] the tandem crotylsilylation event would produce intermediates such as **1**. Tamao oxidation[3] would then presumably generate an enol that upon tautomerization would generate an additional methyl-bearing stereocenter.[4] The ultimate utility of this method would of course depend on the levels of diastereoselectivity that could be achieved in the Tamao oxidation/tautomerization process. If successful, reactions of this type would represent a remarkable example of a complexity-generating reaction, as a butenyl fragment, a

(1) (a) O'Malley, S. J.; Leighton, J. L. *Angew. Chem., Int. Ed.* **2001**, *40*, 2915. (b) Zacuto, M. J.; O'Malley, S. J.; Leighton, J. L. *J. Am. Chem. Soc.* **2002**, *124*, 7890. (c) Zacuto, M. J.; O'Malley, S. J.; Leighton, J. L. *Tetrahedron* **2003**, *59*, 8889. (d) Schmidt, D. R.; Park, P. K.; Leighton, J. L. *Org. Lett.* **2003**, *5*, 3535. (e) Park, P. K.; O'Malley, S. J.; Schmidt, D. R.; Leighton, J. L. *J. Am. Chem. Soc.* **2006**, *128*, 2796.

(2) For seminal early examples of silylformylation of internal alkynes, see: (a) Matsuda, I.; Ogiso, A.; Sato, S.; Izumi, Y. *J. Am. Chem. Soc.* **1989**, *111*, 2332. (b) Doyle, M. P.; Shanklin, M. S. *Organometallics* **1994**, *13*, 1081. (c) Monteil, F.; Matsuda, I.; Alper, H. *J. Am. Chem. Soc.* **1995**, *117*, 4419. (d) Ojima, I.; Vidal, E.; Tzamarioudaki, M.; Matsuda, I. *J. Am. Chem. Soc.* **1995**, *117*, 6797.

(3) (a) Tamao, K.; Kumada, H. *Tetrahedron Lett.* **1984**, *25*, 321. (b) Jones, G. R.; Landais, Y. *Tetrahedron* **1996**, *52*, 7599.

(4) For an example of a Tamao oxidation of a vinylsilane that generates a *prochiral* enol that undergoes a diastereoselective tautomerization, see: Suginome, M.; Matsunaga, S.-I.; Ito, Y. *Synlett* **1995**, 941.

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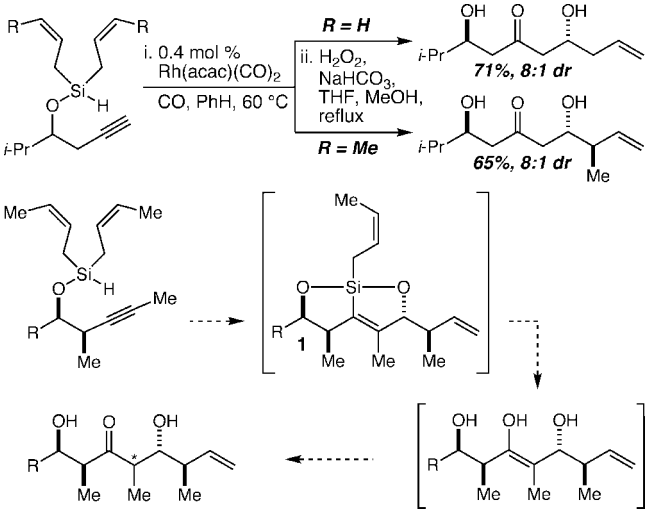
propynyl fragment, and CO would be transformed in a one-pot process into stereochemically and functionally complex polypropionate arrays.

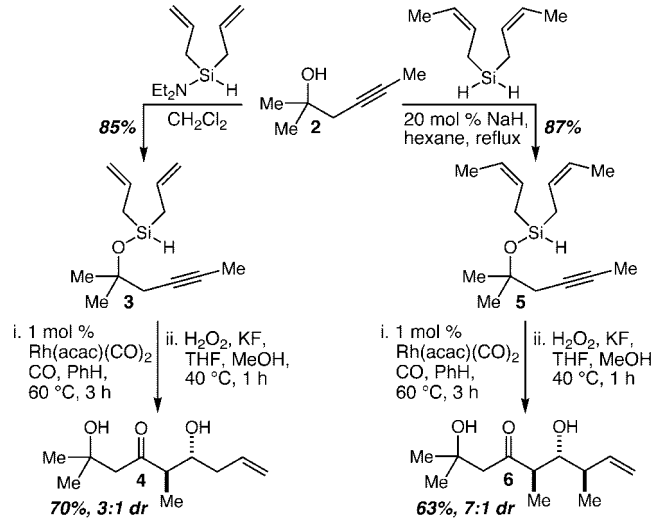
Scheme 1



The investigation commenced with achiral alcohol **2** in order to isolate the diastereoselectivity of the tautomerization event relative to the neighboring stereocenter(s). Silylation of **2** with 1,1-diallyl-*N*,*N*-diethylsilanamine[5] gave silane **3** in 85% yield (Scheme 2). When **3** was subjected to tandem silylformylation−allylsilylation/Tamao oxidation, keto diol **4** was indeed produced, with promising (4:1) diastereoselectivity albeit in only 46% yield. Examination of the reaction mixture revealed substantial amounts of an enone byproduct suggesting elimination during the Tamao oxidation. Use of KF in place of $NaHCO_3$ solved this problem and led to the isolation of **4** in 70% yield and 3:1 dr. When di-*cis*-crotylsilane **5** was prepared and subjected to the tandem reaction conditions, **6** was isolated in 63% yield and 7:1 dr.

Having established (1) that internal alkynes are well tolerated in the tandem silylformylation−allylsilylation reaction and (2) that useful levels of diastereoselectivity may be attained in the Tamao oxidation/tautomerization, we turned next to an examination of chiral homopropargylic alcohol starting materials. Silanes **7**, **8**, and **9** were prepared and subjected to the reaction conditions (Scheme 3). As shown, these substrates led to ketodiols **10**, **11**, and **12** with 6:1, 13:1, and 15:1 dr respectively (major/all minor diastereomers). Assuming that the 1,5-diastereoselectivity is 8:1 for

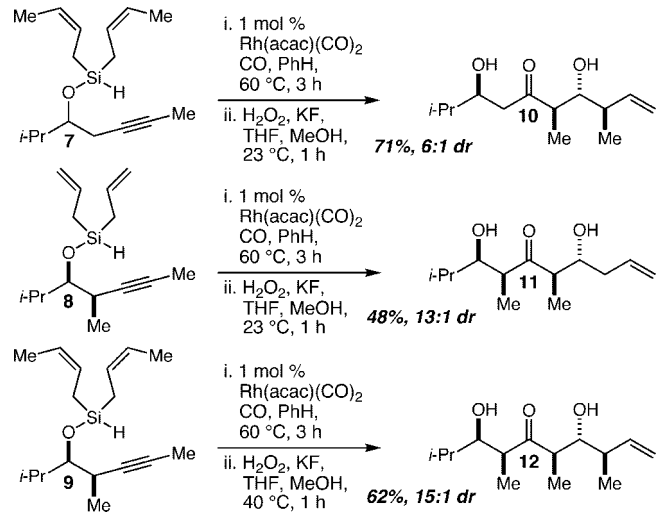
Scheme 2



7 and 23:1 for **8** and **9**,[6] the diastereoselectivity of the tautomerization event may be estimated to be ≥20:1 in all three cases.

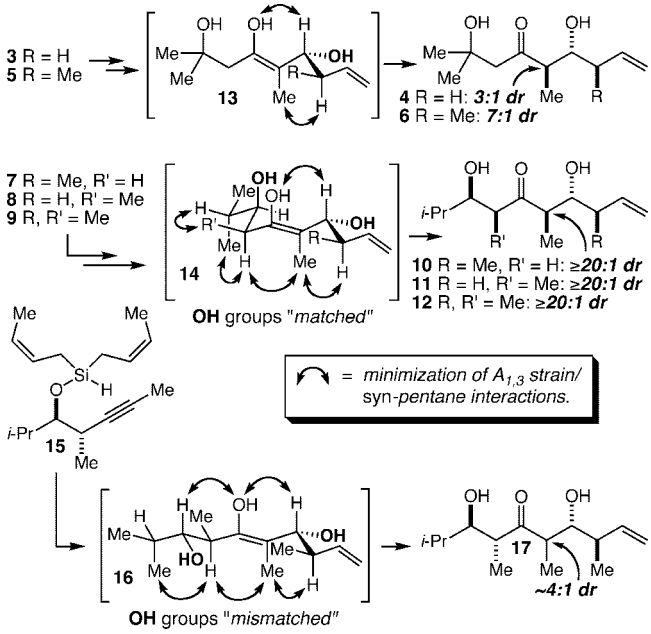
In constructing a model to rationalize these results it was assumed that in the protic environment of the Tamao oxidation internal hydrogen bonding would not be relevant and the dictates of allylic 1,3-strain[7] and minimization of *syn*-pentane interactions would prevail. Thus, the enols formed during the reactions of silanes **3** and **5** may assume the conformation depicted in structure **13** (Scheme 4). Protonation of the enol from the back face is expected on steric grounds (the higher selectivity for **6** is consistent with this proposal), and perhaps more importantly, the **OH** group likely plays a role in delivering the proton to the enol through hydrogen bonding. Substrates **7**, **8**, and **9** all display significantly higher diastereoselectivity (≥20:1 dr) in the tautomerization, clearly indicating a direct role for the

Scheme 3



(5) Bolshakov, S.; Leighton, J. L. *Org. Lett.* **2005**, *7*, 3809.
(6) These diastereoselectivities are the reported values for the reactions of the corresponding terminal (desmethyl) alkynes. See ref 1a.
(7) Hoffmann, R. W. *Chem. Rev.* **1989**, *89*, 1841.
(8) Bareille, L.; Becht, S.; Cui, J. L.; Le Gendre, P.; Moïse, C. *Organometallics* **2005**, *24*, 5802.
(9) Total syntheses of the spongistatins have been reviewed. See: Yeung, K.-S.; Paterson, I. *Chem. Rev.* **2005**, *105*, 4237.
(10) Schmidt, D. R.; O'Malley, S. J.; Leighton, J. L. *J. Am. Chem. Soc.* **2003**, *125*, 1190.

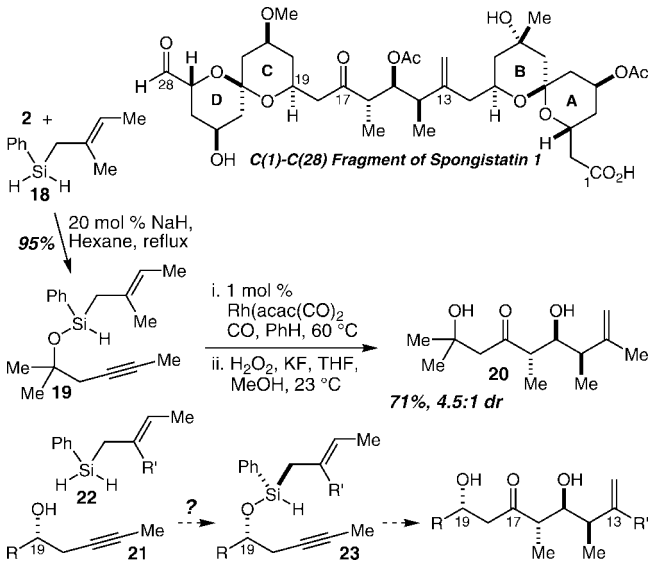
Scheme 4



original homopropargylic alcohol stereocenter. These reactions may proceed by way of enol **14**, wherein *both* **OH** groups are well positioned to assist in the delivery of the proton to the back face of the enol resulting in a "matched" case. Based on this model, it was straightforward to predict that substrate **15** should represent a "mismatched" case, proceeding by way of enol **16** wherein the two **OH** groups are positioned on opposite faces of the enol. Indeed, reaction of **15** produced **17** with only moderate (unassigned) diastereoselectivity for the tautomerization event.

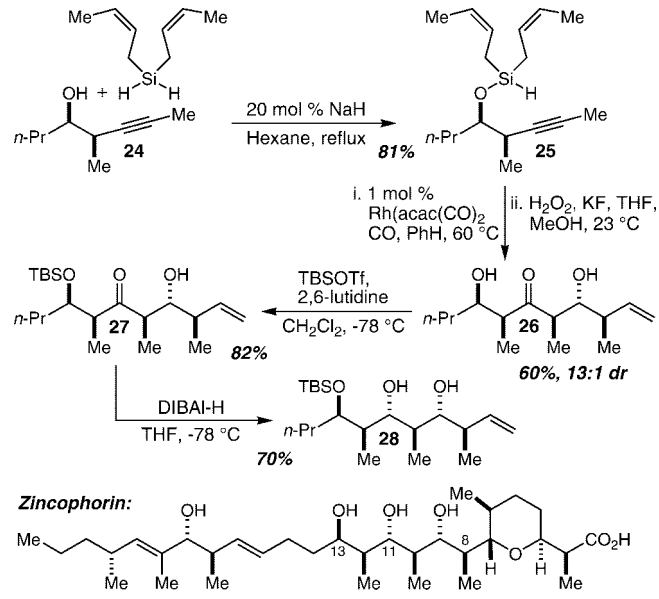
Two examples will demonstrate the potential of this method to deliver complex polyketide natural product

Scheme 5



fragments in a highly efficient manner. In the first, NaH-catalyzed alcoholysis of silane **18**[8] with **2** gave **19** in 95% yield (Scheme 5). Subjection of **19** to the tandem reaction conditions followed by the Tamao oxidation led to (racemic) ketodiol **20** in 71% yield and 4.5:1 dr. This fragment corresponds to the C(19)−C(12) fragment of spongistatin 1, a polyketide natural product with extraordinary anticancer activity.[9] While application of this method to an asymmetric synthesis of spongistatin 1 will require an asymmetric silane alcoholysis (**21** + **22** → **23**),[10] it is nevertheless remarkable that the C(17) ketone, the C(13) 1,1-disubstituted alkene, and the three stereocenters in between may all be installed in a one-pot process from what is largely a simple hydrocarbon (**19**). We note as well that the moderate diastereoselectivity (4.5:1) in this case need not be of concern: in the projected application of this method to a synthesis of spongistatin 1 the C(19) alcohol stereochemistry will represent a "matched" case (see Scheme 4, above), and the diastereoselectivity may reasonably be expected to be significantly higher than 4.5:1.

Scheme 6



In the second example, we have developed a brief synthesis of the stereochemical array presented in the C(8)−C(13) fragment of the antibiotic zincophorin (Scheme 6).[11] Homopropargylic alcohol **24** was silylated with di-*cis*-crotylsilane as above to give silane **25** in 81% yield. Subjection of **25** to the tandem silylformylation-crotylsilylation/Tamao oxidation gave **26** in 60% yield and 13:1 dr. Selective protection of the less hindered alcohol as its *tert*-butyldimethylsilyl (TBS) ether gave **27** in 82% yield. Finally, ketone reduction with diisobutylaluminum hydride (DIBAL)

(11) (a) Gräfe, U.; Schade, W.; Roth, M.; Radics, L.; Incze, M.; Ujszaszy, K. *J. Antibiot.* **1984**, *37*, 836. (b) Brooks, H. A.; Gardner, D.; Poyser, J. P.; King, T. J. *J. Antibiot.* **1984**, *37*, 1501.

proceeded sterospecifically (≥98:2 dr) to give **28** in 70% yield.[12] The four step conversion of **24** to **28** is a particularly straightforward way to address the all-*anti* stereotetrad (C(8)−C(11)) a challenge that has elicted significant interest from synthetic chemists.[13]

We have extended the tandem silylformylation−crotylsilylation/Tamao oxidation reaction to internal alkynes. High levels of diastereoselectivity may be realized in the tautomerization of the resulting enols, and the potential of this tandem reaction may therefore be more fully realized. The application of this method to the synthesis of polyketide natural products is being pursued.

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

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(12) Kiyooka, S.-I.; Kuroda, H.; Shimasaki, Y. *Tetrahedron Lett.* **1986**, *27*, 3009.

(13) (a) Danishefsky, S. J.; Selnick, H. G.; Zelle, R. E.; DeNinno, M. P. *J. Am. Chem. Soc.* **1988**, *110*, 4368. (b) Cywin, C. L.; Kallmerten, J. *Tetrahedron Lett.* **1993**, *34*, 1103. (c) Marshall, J. A.; Palovich, M. R. *J. Org. Chem.* **1998**, *63*, 3701. (d) Chemler, S. R.; Roush, W. R. *J. Org. Chem.* **1998**, *63*, 3800. (e) Guindon, Y.; Murtagh, L.; Caron, V.; Landry, S. R.; Jung, G.; Bencheqroun, M.; Faucher, A.-M.; Guérin, B. *J. Org. Chem.* **2001**, *66*, 5427. (f) Defosseux, M.; Blanchard, N.; Meyer, C.; Cossy, J. *J. Org. Chem.* **2004**, *69*, 4626. (g) Komatsu, K.; Tanino, K.; Miyashita, M. *Angew. Chem., Int. Ed.* **2004**, *43*, 4341. (h) Mulzer, J.; Sieg, A.; Brücher, C.; Müller, D.; Martin, H. J. *Synlett* **2005**, 685. (i) Song, Z.; Hsung, R. P.; Lu, T.; Lohse, A. G. *J. Org. Chem.* **2007**, *72*, 9722.