

Synthesis of β -Hydroxy Ketones and Vinylsilanes from Homopropargylic Alcohols by Intramolecular Hydrosilation

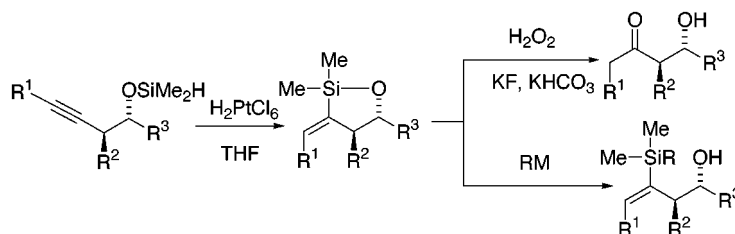
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Received May 27, 2000

ABSTRACT



Catalytic intramolecular hydrosilation of nonracemic homopropargylic alcohols affords the corresponding five-membered cyclic siloxanes regioselectively. Oxidation or alkylmetal addition converts these intermediates into β -hydroxy ketones or vinylsilanes under mild conditions.

Recently we disclosed a conversion of homopropargylic alcohols to β -hydroxy ketones through iodolactonization.¹ After the completion of our work, we discovered a preliminary report by Tamao which effected a like conversion of homopropargylic alcohols to ketones through intramolecular hydrosilation and oxidation of the resulting cyclic siloxane.² While the concept had been demonstrated with three simple examples, no further studies or applications of this conversion have appeared. With the aim of improving upon our merger of allenylmetal with aldol methodology for polyketide synthesis, we decided that further investigation was warranted.

The addition of nonracemic allenylmetal reagents **I** to aldehydes affords *syn* or *anti* homopropargylic adducts **II** with high levels of diastereoselectivity, particularly with α -branched aldehydes (Figure 1).³ This methodology pro-

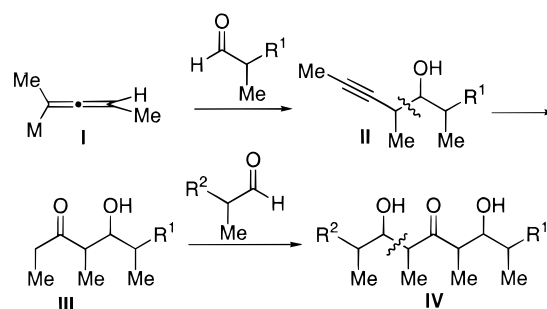


Figure 1. Merged allenylmetal/aldol approach to polyketide synthesis.

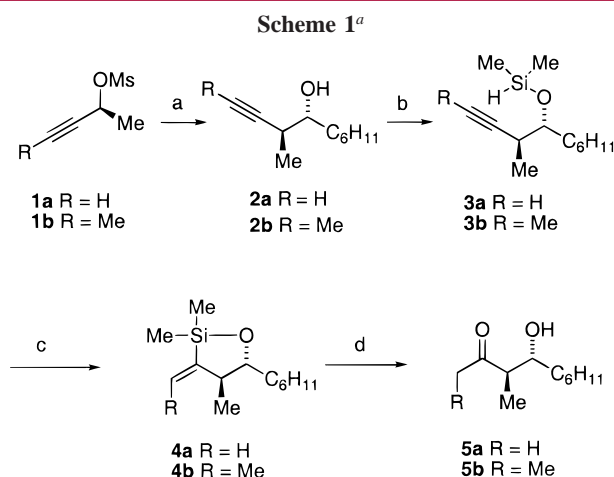
vides ready access to any of the eight possible stereotriads of general structure **II**. Subsequent regioisomeric hydration would afford the derived β -hydroxy ketones **III** whose utility in highly stereoselective aldol condensations has been convincingly demonstrated by Paterson and co-workers.⁴

The hydrosilation approach was felt to offer certain advantages over the aforementioned iodolactonization¹ se-

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(3) (a) Marshall, J. A.; Perkins, J. F.; Wolf, M. A. *J. Org. Chem.* **1995**, 60, 5556. (b) Marshall, J. A.; Palovich, M. R. *J. Org. Chem.* **1997**, 62, 6001.
(c) Marshall, J. A.; Adams, N. D. *J. Org. Chem.* **1999**, 64, 5201. (d) Marshall, J. A.; Grant, C. M. *J. Org. Chem.* **1999**, 64, 696. (e) Marshall, J. A.; Maxson, K. *J. Org. Chem.* **2000**, 65, 630.

quence by virtue of milder reaction conditions and the potential for utilizing the intermediate siloxanes as masked ketones or as precursors to vinylsilanes. The present investigation was designed to test the overall feasibility of the approach and to determine the effect of triad stereochemistry on the efficiency of the process.

Initial studies were conducted with racemic *anti* homopropargylic alcohols **2a** and **2b**, prepared by addition of the transient allenylzinc reagents, generated in situ from racemic propargylic mesylates **1a** and **1b**, to cyclohexanecarboxaldehyde (Scheme 1). Conversion of alcohols **2a** and **2b** to



^a (a) 5 mol % of Pd(OAc)₂·PPh₃, Et₂Zn, C₆H₁₁CHO, THF, 76%; (b) (Me₂SiH)₂NH, 60 °C, 100%; (c) 0.5 mol % of H₂PtCl₆, THF, 50 °C, 92%; (d) MeOH, THF, H₂O₂, KF, KHCO₃, 85%.

hydrodimethylsilyl ethers **3a** and **3b** occurred quantitatively in neat tetramethyldisilazane. Excess silazane was found to poison the catalyst in the ensuing hydrosilylation step so its complete removal under high vacuum was essential to success.

Intramolecular hydrosilylation with 0.5 mol % of chloroplatinic acid afforded cyclic siloxane intermediates **4a** and **4b**. Initially this reaction was performed in toluene at concentrations ranging from 2 to 6 M. An induction period ranging from several minutes to only a few seconds was noted prior to initiation of a highly exothermic reaction under these conditions. This observation is consistent with the formation of a Pt(0) colloidal suspension from the catalyst precursor.⁵ The subsequent uncontrolled exotherms resulted in the formation of variable amounts of intractable polymers. Changing the solvent to THF and lowering the concentration to 0.5 M moderated the rate of the reaction and suppressed polymerization. The progress of the hydrosilylation could conveniently be monitored by infrared spectral analysis (Si—H 2121 cm⁻¹). The siloxane intermediates were isolated by distillation as all attempts to purify these compounds by chromatography on silica gel, Et₃N deactivated silica gel,

or alumina resulted in decomposition. Compounds not amenable to distillation were carried on without purification. Surprisingly the siloxanes proved stable to both strong acid (6.0 M HCl/THF, 3 h) and aqueous base (1 N KOH/MeOH, reflux, 2 h).

Oxidation of siloxanes **4a** and **4b** was best achieved by a modification of Tamao's conditions.⁶ Several aspects deserve comment. Use of a large quantity of hydrogen peroxide (20–40 equiv) was required to minimize side reactions. In the absence of KF only a trace of product was formed after 24 h. Substitution of LiOH for KHCO₃ accelerated the rate but caused epimerization of the α' stereocenter prior to complete oxidation (24 h). With KHCO₃ as the base, in the presence of 3 equiv of KF and excess H₂O₂, smooth conversion to ketone product took place. Additional studies with racemic homopropargylic adducts are summarized in Table 1.

Table 1. Hydrosilylation–oxidation of Racemic Homopropargylic Alcohols

series	R ¹	R ²	R ³	yield 4 , %	yield 5 , %
a	H	Me	<i>c</i> -C ₆ H ₁₁	92	85
b	Me	Me	<i>c</i> -C ₆ H ₁₁	90	82
c	H	H	Ph	88	77
d	Me	H	Ph	75	74

We next turned our attention to the stereotriads **6**, **8**, **10**, and **12** prepared as outlined in Scheme 2.³

Silylation of hindered homopropargylic alcohols **6**, **8**, **10**, and **12** required more vigorous conditions (90 °C, 14 h) but was quantitative in all cases. Subsequent hydrosilylation of **7**, **9**, **11**, and **13** in THF also proceeded smoothly (Scheme 3).⁷ The reaction mixtures were filtered to remove the catalyst

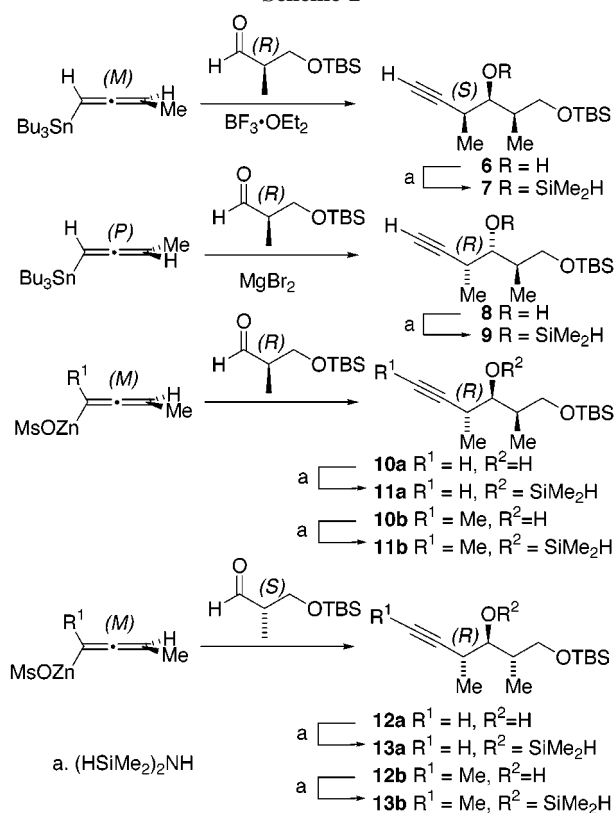
(6) (a) Tamao, K.; Kumada, M.; Maeda, K. *Tetrahedron Lett.* **1984**, 25, 321. (b) Review: Jones, G. R.; Landais, Y. *Tetrahedron* **1996**, 52, 7599.

(7) **Typical procedure for the conversion of homopropargylic alcohol (10b) to ketone (16b):** A dry flask was charged with alcohol **10b** (520 mg, 1.89 mmol) and tetramethyldisilazane (0.66 mL, 3.79 mmol), and the mixture was heated to 90 °C for 15 h. After cooling to 40 °C, excess silazane was removed in vacuo (0.05 mmHg, 2 h), affording silyl ether **11b** as a light yellow oil. The oil was diluted with THF (4 mL), and H₂PtCl₆ (0.056 M in THF, 60 μL, 0.0044 mmol) was added at rt. The mixture was heated to 55 °C for 4 h, diluted with ether (25 mL), filtered through Celite, and concentrated, affording the cyclic siloxane as a yellow oil which was used without further purification. A solution of this oil in THF/MeOH (1:1, 8 mL) was treated with KHCO₃ (600 mg, 6.00 mmol), KF (111 mg, 1.90 mmol), and 30% H₂O₂ (8 mL, ca. 70 mmol). After 3 h, excess peroxide was quenched with solid Na₂S₂O₃ (**Caution: exothermic, induction period**). The mixture was extracted with ether, dried over MgSO₄, concentrated, and purified by chromatography on silica gel (5–20% EtOAc/hexanes), affording 372 mg (68%) of ketone **16b** as a colorless oil. *R*_f = 0.50 (20% EtOAc/hexanes); [α]_D +11.8 (c 1.0, CHCl₃); IR 3501, 2960, 2864, 1710 cm⁻¹; ¹H NMR δ 0.05 (s, 6H), 0.87 (s, 9H), 0.95 (t, *J* = 7.2 Hz, 6H), 1.04 (d, *J* = 7.2 Hz, 3H), 1.70 (m, 1H), 2.51 (q, *J* = 7.2 Hz, 2H), 2.66 (dq, *J* = 7.2, 9.3 Hz, 1H), 3.21 (br, 1H), 3.65 (dd, *J* = 4.8, 9.9 Hz, 1H), 3.75 (dd, *J* = 3.9, 9.9 Hz, 1H), 3.97 (dd, *J* = 1.8, 9.3 Hz, 1H); ¹³C NMR δ -5.6, 7.4, 9.2, 13.6, 18.2, 25.8, 35.6, 36.2, 48.8, 68.6, 76.2, 215.8. Anal. Calcd for C₁₅H₃₂O₃Si: C, 62.45; H, 11.18. Found: C, 62.73; H, 11.28.

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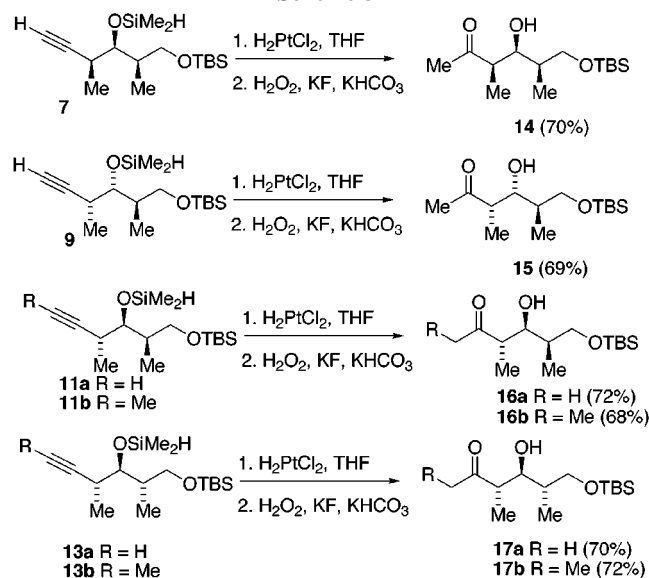
Scheme 2



and then subjected to oxidation directly, affording ketones **14**, **15**, **16**, and **17**. If the catalyst was not removed prior to the oxidation step, the peroxide was rapidly decomposed and incomplete oxidation resulted.

Use of the standard oxidation conditions led to cleavage of the primary TBS ethers. However, cleavage was negligible when only 1 equiv of KF was employed. The decreased amount of KF did not appreciably affect the rate of oxidation.

Scheme 3



Representative siloxanes **4b** and **4d** were converted to the corresponding γ -hydroxy vinylsilanes **18a–e** upon treatment with organolithium or Grignard reagents as summarized in Table 2. These vinylsilanes are easily purified by

Table 2. Conversion of Cyclic Siloxanes to Hydroxy Silanes

substrate	R ¹	R ²	R ³ M	product	yield, %
4b	<i>n</i> -C ₆ H ₁₁	Me	MeLi	18a	95
4b	<i>n</i> -C ₆ H ₁₁	Me	PhMgBr	18b	92
4d	Ph	H	MeLi	18c	68
4d	Ph	H	PhMgBr	18d	72
4d	Ph	H	BnMgCl	18e	84

chromatography. The three-step protocol affords the Markovnikov hydrosilation product with terminal alkynes, opposite in regiochemistry to that of an intermolecular hydrosilation.⁸ This aspect could prove useful for the synthesis of substituted olefins since such vinylsilanes can be converted to vinyl halides with either retention or inversion of configuration.⁹ Additionally, vinylsilanes can be employed in Pd-catalyzed cross-coupling reactions.¹⁰

Conversion to phenyl- and benzyl-substituted vinylsilanes leads to intermediates with increased stability relative to their siloxane precursors. These silanes can also serve as umpolung equivalents to ketones.¹¹ For example, the oxidation¹² of benzylsilane **18e** afforded the corresponding ketone **5d** in 84% yield.

The present methodology provides a convenient and efficient route to enantioenriched β -hydroxy ketones from readily available homopropargylic alcohols of any desired stereochemical configuration. The methodology also provides access to stable vinylsilanes for use as masked ketones in multistep transformations.

Acknowledgment. This research was supported by Research Grant CHE9901319 from the National Science Foundation. M.M.Y. thanks Nick Adams for preparing compounds **8** and **10a**.

Supporting Information Available: Experimental procedures and spectral data for all new compounds. This material is available free of charge via the Internet at <http://pubs.acs.org>.

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