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# A Practical Method for the Synthesis of 2-Alkynylpropenals

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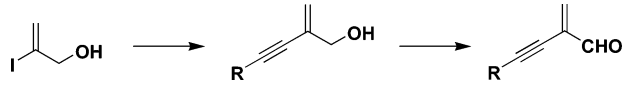
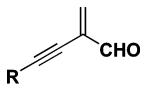


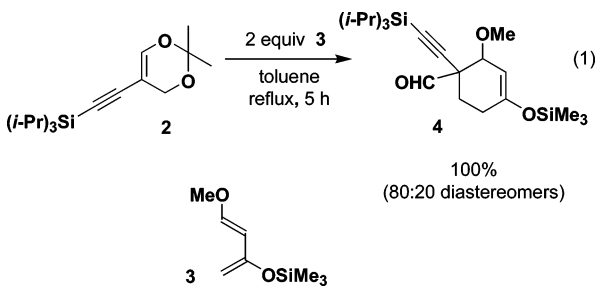

A general method for the preparation of 2-alkynyl acroleins is described beginning with vinyl iodide **5** and involving a combination of Sonogashira coupling and Dess−Martin oxidation. Critical to the success of this approach is the use of a special workup procedure for the oxidation step. The resultant enynals participate in a variety of addition reactions including aldol condensations and reactions with organolithium compounds.

In connection with our studies on the total synthesis of glycinoeclepin A, we required a practical and efficient method for the preparation of α,β-unsaturated aldehydes of type **1** bearing alkynyl substituents at the C-2 position ("α-alkynyl acroleins"). Remarkably, only one example of the isolation and characterization of an aldehyde of this class has previously been reported in the literature.[1] Acrolein derivatives of this type are expected to undergo facile dimerization via hetero-Diels−Alder [4+2] cycloaddition,[2,3] and also should be exceptionally prone to polymerization via radical pathways and in the presence of nucleophiles. On the other hand, the multiple functional groups incorporated in these compounds suggest that they should serve as valuable synthetic building blocks in a number of applications. Unfortunately, the anticipated sensitivity of these enynals limits the range of methods potentially applicable for their preparation, and to date the synthetic utility of this class of aldehydes remains unrealized.[4]




**1**

In 2000, Funk and co-workers described an ingenious method for the in situ generation of sensitive 2-substituted acroleins involving the thermal [4+2] cycloreversion of 5-substituted 4*H*-1,3-dioxins.[5] Attempted application of this protocol to the preparation of a 2-alkynyl acrolein derivative led only to the isolation of the corresponding hetero-Diels−Alder dimer, but the unstable enynal could be trapped in situ by carrying out the thermolysis in the presence of excess Danishefsky's diene (eq 1).[5] Unfortunately, these conditions are not compatible with our projected use of 2-alkynylpropenals, which involves aldol condensation of the aldehydes at low temperature with lithium enolates. The elevated temperatures required in the Funk protocol, as well as the fact that 1 equiv of acetone is generated as a byproduct of the retro-Diels−Alder reaction, obviously set severe constraints on the range of applications possible for 2-alkynyl acroleins produced under these conditions. We therefore undertook an investigation of alternative methods for the preparation of these α,β-unsaturated aldehydes that would be compatible with a broader range of subsequent transformations.




(1)

Scheme 1 outlines our approach to the synthesis of 2-alkynylpropenals. Sonogashira coupling[6] of 2-iodo-2-propenol[7] (**5**) with a wide range of acetylenes was expected to provide convenient access to enynyl alcohols of type **7**,[8] which would then be oxidized to furnish the desired aldehydes. In the event, standard oxidation protocols provided the unstable acroleins in poor yield due to the propensity of these α,β-unsaturated aldehydes to undergo Diels−Alder dimerization and polymerization. Success was finally achieved by employing a modified Dess−Martin oxidation[9,10] protocol, which avoids an

(1) Dreiding has reported that vapor phase pyrolysis of propargyl propiolate at 500 °C affords a complex mixture of products from which 2-ethynylpropenal was isolated in 12% yield. See: Bilinski, V.; Dreiding, A. S.; Hollenstein, H. *Helv. Chim. Acta* **1983**, *66*, 2322.

(2) For reviews of the hetero-Diels−Alder reaction, see: (a) Tietze, L. F.; Kettschau, G. *Top. Curr. Chem.* **1997**, *189*, 1. (b) Boger, D. L.; Weinreb, S. M. *Hetero Diels−Alder Methodology in Organic Synthesis*; Academic Press: San Diego, CA, 1987.

(3) For examples, see: (a) Schulz, H.; Wagner, H. *Angew. Chem.* **1950**, *29*, 105. (b) Laitalainen, T.; Kuronen, P.; Hesso, A. *Org. Prep. Proced. Int.* **1993**, *25*, 597.

(4) For a review of methods for the synthesis of acrolein and its α-substituted derivatives, see: Keiko, N. A.; Voronkov, M. G. *Russ. Chem. Rev*. **1993**, *62*, 751.

(5) Fearnley, S. P.; Funk, R. L.; Gregg, R. J. *Tetrahedron* **2000**, *56*, 10275.

(6) For recent reviews on palladium-catalyzed alkynylation, see: (a) Sonogashira, K. Sonogashira Alkyne Synthesis. In *Handbook of Organopalladium Chemistry for Organic Synthesis*; Negishi, E., de Meijere, A., Eds.; Wiley-Interscience: New York, 2002; Vol. I, p 493. (b) Negishi, E.; Xu, C. Palladium-Catalyzed Alkynylation with Alkynylmetals and Alkynyl Electrophiles. In *Handbook of Organopalladium Chemistry for Organic Synthesis*; Negishi, E., de Meijere, A., Eds.; Wiley-Interscience: New York, 2002; Vol. I, p 531. (c) Negishi, E.; Anastasia, L. *Chem. Rev.* **2003**, *103*, 1979.

(7) Available by reaction of propargyl alcohol with chlorotrimethylsilane and sodium iodide according to the procedure of: Kamiya, N.; Chikami, Y.; Ishii, Y. *Synlett* **1990**, 675.

(8) Nicolaou has reported that Sonogashira coupling of (trimethylsilyl)acetylene with **5** furnishes 7**a** in near quantitative yield. See: Nicolaou, K. C.; Koide, K. *Tetrahedron Lett.* **1997**, *38*, 3667.

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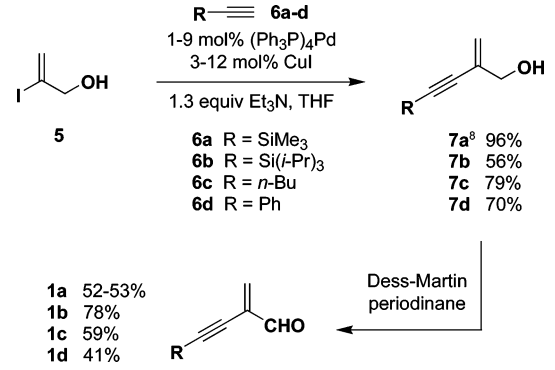
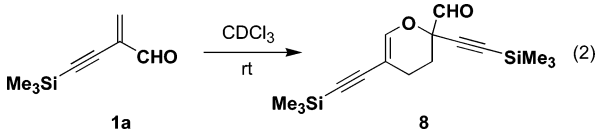
**SCHEME 1**

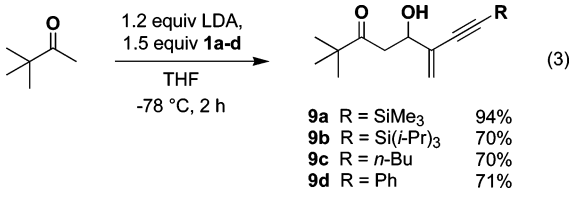



aqueous workup procedure. A stratagem for precipitating iodinane byproducts by diluting with pentane was introduced recently by Wavrin and Viala,[11] and we found that with some modification this protocol can be employed for the efficient formation of highly sensitive 2-alkynylpropenals. Specifically, oxidation is first carried out using 1.1−1.3 equiv of Dess−Martin periodinane in $CH_2Cl_2$ at 0 °C. The reaction mixture is then cooled to −78 °C and diluted with an equal volume of pentane, and then excess poly(4-vinylpyridine) is added to sequester the acetic acid generated in the reaction. The reaction mixture is filtered under a positive pressure of argon through a jacketed plug of silica gel cooled at −78 °C, and then concentrated with the aid of toluene to remove remaining traces of acetic acid via azeotropic distillation. Final concentration to dryness is conducted at 0.05 mmHg and −78 °C. The desired aldehydes **1a**−**d** are obtained in 41−78% overall yield and in greater than 95% purity as determined by IR and $^1$H NMR analysis.

As expected, 2-alkynylpropenals **1a**−**d** readily undergo dimerization via hetero-Diels−Alder cycloaddition. For example, NMR analysis of a solution of aldehyde **1a** in $CDCl_3$ (0.4 M) showed traces of dimer formation within minutes at room temperature, and after standing overnight, more than half of the starting material was converted to the hetero-Diels−Alder cycloadduct **8**. On

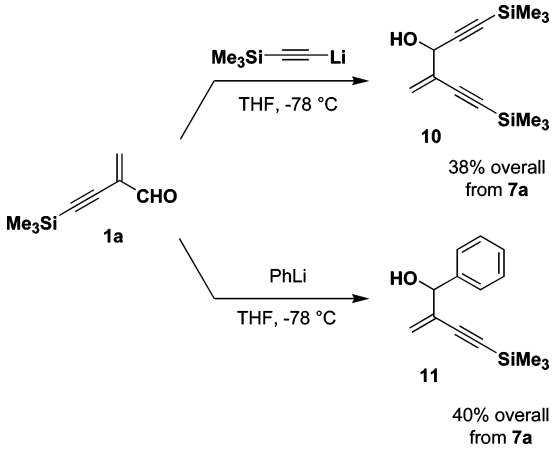



the other hand, the 2-alkynyl α,β-unsaturated aldehydes produced in this fashion can be taken up in THF and employed in a number of subsequent useful synthetic transformations. For example, aldol condensation with the lithium enolate derivative of pinacolone provides the desired β-hydroxy ketones **9a**−**d** in good to excellent yield (eq 3).

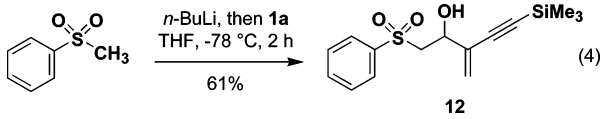



In a similar fashion, addition of organo- and alkynyllithium compounds proceeds smoothly as outlined in

**SCHEME 2**




Scheme 2 to furnish the expected enynyl alcohols **10** and **11** in good overall yield from **7a**, the precursor to the alkynyl acrolein. Moderately stabilized organolithium compounds react in a like manner. For example, addition of the lithium derivative of methyl phenyl sulfone to enynal **1a** occurs smoothly to afford the expected β-hydroxy sulfone **12** in 61% yield (eq 4).




In summary, the combination of Sonogashira coupling and Dess−Martin oxidation provides a convenient method for the preparation of a wide range of 2-alkynyl acroleins. Critical to the success of this approach is the use of a modified workup procedure for the oxidation step, in which byproducts are separated by precipitation with pentane, trapping with poly(4-vinylpyridine), and azeotropic distillation with toluene.

## Experimental Section

**General Procedure for the Preparation of Enynyl Alcohols: 2-Methylene-4-(triisopropylsilyl)but-3-yn-1-ol (7b).** A 50-mL, one-necked, round-bottomed flask fitted with a rubber septum and argon inlet needle was charged with $(Ph_3P)_4Pd$ (0.089 g, 0.077 mmol), CuI (0.042 g, 0.22 mmol), and 10 mL of THF. A solution of the vinyl iodide **5** (0.464 g, 2.52 mmol) in 3 mL of THF was added via cannula over 2 min (the flask was rinsed with 2 mL of THF) and triethylamine (0.46 mL, 0.33 g, 3.28 mmol) was then added via syringe over 30 s. The resulting yellow mixture was stirred at room temperature for 3 min, and then (triisopropylsilyl)acetylene (0.74 mL, 0.60 g, 3.28 mmol) was added via syringe over 2 min. The reaction mixture was stirred at room temperature for 11.5 h and then heated at reflux for 9 h. The reaction mixture was allowed to cool to room temperature and then filtered through 10 g of silica gel with the aid of three 15-mL portions of $Et_2O$. Concentration of the filtrate afforded 0.689 g of a brown oil. Column chromatography on 35 g of silica gel (gradient elution with 0−10% EtOAc−hexane) provided 0.336 g (56%) of enyne **7b** as a yellow oil: IR

(9) (a) Dess, D. B.; Martin, J. C. *J. Org. Chem.* **1983**, *48*, 4155. (b) Dess, D. B.; Martin, J. C. *J. Am. Chem. Soc.* **1991**, *113*, 7277.

(10) For reviews of oxidations using the Dess−Martin periodinane, see: (a) Boeckman, R. K.; Shao, P.; Mullins, J. J. In *Organic Syntheses*; Wiley & Sons: New York, 2004; Collect. Vol. X, p 696. (b) Tohma, H.; Kita, Y. *Adv. Synth. Catal.* **2004**, *346*, 111.

(11) Wavrin, L.; Viala, J. *Synthesis* **2002**, 326.

(film) 3356, 2942, 2865, 2145, and 1617 $cm^{-1}$; $^1H$ NMR (500 MHz, $CDCl_3$) $\delta$ 5.54 (dd, $J$ = 1.5, 10.5 Hz, 2H), 4.12 (td, $J$ = 1.5, 7.0 Hz, 2H), 1.68 (dt, $J$ = 1.5, 7.0 Hz, 1H), and 1.09 (app s, 21H); $^{13}C$ NMR (125 MHz, $CDCl_3$) $\delta$ 131.7, 120.8, 104.7, 93.0, 65.5, 18.8, and 11.4; HRMS-EI $m/z$ $[M]^+$ calcd for $C_{14}H_{26}OSi$ 238.1747, found 238.1741.

**General Procedure for the Oxidation of Allylic Alcohols to Enynyl Aldehydes: 2-Methylene-4-(trimethylsilyl)but-3-ynal (1a).** A 50-mL, two-necked, pear-shaped flask fitted with an argon inlet adapter and a rubber septum was charged with a solution of the allylic alcohol **7a** (0.942 g, 6.11 mmol) in 30 mL of dichloromethane and cooled at 0 °C while Dess−Martin periodinane (2.856 g, 6.73 mmol) was added in one portion. The heterogeneous reaction mixture was stirred at 0 °C for 5 min and then allowed to warm to room temperature. After 20 min, the reaction mixture was cooled to −78 °C and diluted with 30 mL of pentane, poly(4-vinylpyridine) (3.227 g, 30.69 mmol) was added in one portion, and the resulting mixture was stirred at −78 °C for 25 min. A 2.5-cm diameter jacketed column fitted with a rubber septum at the top and a short needle at the bottom was charged with a 6-cm plug of silica gel, which was cooled at −78 °C by filling the jacket with dry ice−acetone. The reaction mixture was transferred into the column by cannula and filtered through the silica gel under a positive pressure of argon into a 200-mL recovery flask fitted with a rubber septum with a short needle as vent. The reaction flask and the column were rinsed with four 15-mL portions of 4:1 pentane−ether. The filtrate was concentrated by rotary evaporation at 25 °C (20 mmHg) to a volume of ca. 3 mL and this solution was then cooled to −78 °C and diluted with 5 mL of toluene. The resulting solution was concentrated by rotary evaporation at 25 °C to a volume of ca. 3 mL and the resulting pale yellow solution was cooled to −78 °C and further concentrated at 0.05 mmHg (ca. 15 min) to furnish aldehyde **1a** as a yellow oil. For spectroscopic analysis, this material was dissolved in ca. 1 mL of $CDCl_3$ and 4-isopropylbenzaldehyde (0.92 mL, 0.90 g, 6.1 mmol) was added as an internal standard. The resulting solution was transferred to an NMR tube via cannula under a positive pressure of argon. The yield of aldehyde **1a** was determined by $^1H$ NMR analysis to be 52%: IR (film) 2960, 2928, 2144, 1749, and 1624 $cm^{-1}$; $^1H$ NMR (500 MHz, $CDCl_3$) $\delta$ 9.48 (s, 1H), 6.63 (d, $J$ = 1.5 Hz, 1H), 6.40 (d, $J$ = 1.5 Hz, 1H), and 0.25 (s, 1H); $^{13}C$ NMR (125 MHz, $CDCl_3$) $\delta$ 190.0, 139.6, 133.1, 101.8, 97.5, and −0.1.

**General Procedure for the Aldol Reaction of Enynyl Aldehydes: 5-Hydroxy-2,2-dimethyl-6-methylene-8-(trimethylsilyl)oct-7-yn-3-one (9a).** A 25-mL, two-necked, round-bottomed flask fitted with an argon inlet adapter and a rubber septum was charged with 12 mL of THF and diisopropylamine (0.19 mL, 0.13 g, 1.3 mmol) and cooled at 0 °C while 0.50 mL of $n$-BuLi solution (2.41 M in hexane, 1.2 mmol) was added dropwise via syringe over 30 s. The resulting yellow solution was stirred at 0 °C for 15 min and then cooled to −78 °C.

A 10-mL, one-necked, pear-shaped flask was charged with 1.5 mL of THF and pinacolone (0.12 mL, 0.10 g, 1.0 mmol) and cooled to −78 °C. The resulting solution was transferred to the solution of LDA via cannula over 3 min (the flask was rinsed with 0.5 mL of THF) and the resulting cloudy pale-yellow mixture was stirred at −78 °C for 2 h.

Oxidation of allylic alcohol **7a** (0.423 g, 2.74 mmol) with Dess−Martin periodinane (1.284 g, 3.027 mmol) in 27 mL of $CH_2Cl_2$ was carried out according to the General Procedure to furnish aldehyde **1a** (estimated yield of 1.5 mmol based on previous experiments). This material (not allowed to warm above −78 °C once solvent was removed) was dissolved in 3 mL of THF and then transferred via cannula over 2 min into the solution of lithium enolate prepared as described above. The resulting clear, yellow solution was stirred at −78 °C for 2 h and then treated dropwise with 1 mL of half-saturated aq $NH_4Cl$ solution (pre-cooled at 0 °C). The resulting mixture was diluted with 15 mL of $Et_2O$ and 10 mL of water, and the aqueous phase was separated and extracted with three 7-mL portions of $Et_2O$. The combined organic phases were washed with 20 mL of saturated NaCl solution, dried over $MgSO_4$, filtered, and concentrated to afford 0.406 g of a yellow oil. Column chromatography on 20 g of silica gel (gradient elution with 0−10% EtOAc−hexane) afforded 0.242 g (94%) of **9a** as a pale yellow oil: IR (film) 3473, 2964, 2906, 2873, 2143, 1705, and 1625 $cm^{-1}$; $^1H$ NMR (500 MHz, $CDCl_3$) $\delta$ 5.69 (t, $J$ = 1.5 Hz, 1H), 5.55 (t, $J$ = 1.5 Hz, 1H), 4.50−4.52 (m, 1H), 3.51 (d, $J$ = 5.0 Hz, 1H), 3.02 (dd, $J$ = 3.0, 17.5 Hz, 1H), 2.79 (dd, $J$ = 8.5, 17.5 Hz, 1H), 1.16 (s, 9H), and 0.20 (s, 9H); $^{13}C$ NMR (125 MHz, $CDCl_3$) $\delta$ 217.3, 132.8, 122.1, 103.0, 96.9, 70.0, 44.7, 41.9, 26.3, and 0.1; HRMS-ESI $m/z$ $[M + H]^+$ calcd for $C_{14}H_{24}O_2Si$ 253.1618, found 253.1625.

**1,6-Bis(trimethylsilyl)-3-hydroxy-4-methylenehexa-1,5-diyne (10).** A 50-mL, two-necked, round-bottomed flask fitted with an argon inlet adapter and rubber septum was charged with 12 mL of THF and trimethylsilylacetylene (0.26 mL, 0.182 g, 1.85 mmol) and cooled at −78 °C while 0.67 mL of $n$-BuLi solution (2.50 M in hexane, 1.68 mmol) was added dropwise via syringe over 30 s. The resulting pale yellow solution was stirred at −78 °C for 1 h.

Oxidation of allylic alcohol **7a** (0.129 g, 0.84 mmol) with Dess−Martin periodinane (0.394 g, 0.92 mmol) in 4 mL of $CH_2Cl_2$ was carried out according to the General Procedure to furnish aldehyde **1a** (estimated yield of 0.44 mmol based on previous experiments). This material (not allowed to warm above −78 °C once solvent was removed) was dissolved in 3 mL of THF, and then transferred via cannula over 3 min into the solution of lithium (trimethylsilyl)acetylide prepared as described above. The resulting clear yellow solution was allowed to stir at −78 °C for 15 min and then treated with 5 mL of saturated aq $NH_4Cl$ solution. The resulting mixture was diluted with 10 mL of $Et_2O$ and 5 mL of water, and the aqueous phase was separated and extracted with three 10-mL portions of $Et_2O$. The combined organic phases were washed with 20 mL of saturated NaCl solution, dried over $MgSO_4$, filtered, and concentrated to afford 0.118 g of yellow oil. Column chromatography on 15 g of silica gel (gradient elution with 0−5% EtOAc−hexane) afforded 0.081 g (38% overall from **7a**) of alcohol **10** as a pale yellow oil: IR (film) 3356, 2961, 2178, 2149, and 1616 $cm^{-1}$; $^1H$ NMR (500 MHz, $CDCl_3$) $\delta$ 5.74 (t, $J$ = 1.5 Hz, 1H), 5.59 (t, $J$ = 1.5 Hz, 1H), 4.84 (dt, $J$ = 1.0, 7.5 Hz, 1H), 2.23 (d, $J$ = 2.0 Hz, 1H), 0.22 (s, 9H), and 0.20 (s, 9H); $^{13}C$ NMR (125 MHz, $CDCl_3$) $\delta$ 131.4, 123.1, 103.1, 101.6, 97.7, 91.9, 65.3, 0.05, and −0.04; HRMS-ESI $m/z$ $[M + Na]^+$ calcd for $C_{13}H_{22}OSi_2$ 273.1101, found 273.1107.

**1-Phenyl-1-hydroxy-2-methylene-4-(trimethylsilyl)-3-butyne (11).** A 50-mL, two-necked, round-bottomed flask fitted with an argon inlet adapter and a rubber septum was charged with 30 mL of THF and 1.24 mL of PhLi solution (1.80 M in hexane, 2.23 mmol) and cooled at −78 °C.

Oxidation of allylic alcohol **7a** (0.149 g, 0.97 mmol) with Dess−Martin periodinane (0.459 g, 1.07 mmol) in 5 mL of $CH_2Cl_2$ was carried out according to the General Procedure to furnish aldehyde **1a** (estimated yield of 1.0 mmol based on previous experiments). This material (not allowed to warm above −78 °C once solvent was removed) was dissolved in 3 mL of THF, and then transferred via cannula over 3 min into the solution of PhLi described above. The resulting clear yellow solution was allowed to stir at −78 °C for 1 h and then treated dropwise with 5 mL of saturated aq $NH_4Cl$ solution. The resulting mixture was diluted with 10 mL of $Et_2O$ and 5 mL of water, and the aqueous phase was separated and extracted with three 10-mL portions of $Et_2O$. The combined organic phases were washed with 20 mL of saturated NaCl solution, dried over $MgSO_4$, filtered, and concentrated to afford 0.249 g of yellow oil. Column chromatography on 25 g of silica gel (gradient elution with 0−5% EtOAc−hexane) afforded 0.089 g (40% overall from **7a**) of alcohol **11** as a pale yellow oil: IR (film) 3385, 3088, 3065, 3031, and 2146 $cm^{-1}$; $^1H$ NMR (500 MHz, $CDCl_3$) $\delta$ 7.41−7.43 (m, 2H), 7.34−7.38 (m, 2H), 7.31 (tt, $J$ = 2.5, 7.0 Hz, 1H), 5.63 (t, $J$ = 1.5 Hz, 1H), 5.57 (dd, $J$ = 1.0, 1.5 Hz, 1H), 5.22 (d, $J$ = 5.0 Hz, 1H), 2.29 (d, $J$ = 5.0 Hz, 1H), and 0.14 (s, 9H); $^{13}C$ NMR (125 MHz, $CDCl_3$) $\delta$ 141.4, 134.4, 128.5, 128.1, 126.8, 121.9, 102.6, 98.0, 76.4, and −0.04; HRMS-ESI $m/z$ $[M + Na]^+$ calcd for $C_{14}H_{18}OSi$ 253.1019, found 253.1024.

**1-Phenylsulfonyl-2-hydroxy-3-methylene-5-(trimethylsilyl)-4-pentyne (12).** A 25-mL, two-necked, round-bottomed flask fitted with an argon inlet adapter and a rubber septum

was charged with phenyl methyl sulfone (0.095 g, 0.60 mmol) and 5 mL of THF and cooled at −78 °C while 0.28 mL of *n*-BuLi solution (2.40 M in hexane, 0.67 mmol) was added dropwise via syringe over 30 s. The resulting yellow solution was stirred at −78 °C for 1 h.

Oxidation of allylic alcohol **7a** (0.198 g, 1.28 mmol) with Dess−Martin periodinane (0.659 g, 1.54 mmol) in 5 mL of $CH_2Cl_2$ was carried out according to the General Procedure to furnish aldehyde **1a** (estimated yield of 0.7 mmol based on previous experiments). This material (not allowed to warm above −78 °C once solvent was removed) was dissolved in 3 mL of THF, and then transferred via cannula over 5 min into the solution of lithiated sulfone prepared as described above. The resulting clear yellow solution was allowed to stir at −78 °C for 1.7 h and then treated dropwise with 10 mL of half-saturated aq $NH_4Cl$ solution (pre-cooled at 0 °C). The resulting mixture was allowed to warm to room temperature over 15 min and then diluted with 15 mL of $Et_2O$ and 10 mL of water. The aqueous phase was separated and extracted with four 10-mL portions of $Et_2O$, and the combined organic phases were washed with 30 mL of saturated NaCl solution, dried over $MgSO_4$, filtered, and concentrated to afford 0.248 g of an orange-yellow oil. Column chromatography on 13 g of silica gel (gradient elution with 10−40% EtOAc−hexane) afforded 0.114 g (61%) of alcohol **12** as a white solid: mp 122−123 °C; IR (film) 3492, 3067, 2960, 2147, and 1307 $cm^{-1}$; $^1H$ NMR (500 MHz, $CDCl_3$) $\delta$ 7.95−7.98 (m, 2H), 7.71 (tt, $J$ = 1.5, 8.0 Hz, 1H), 7.60−7.63 (m, 2H), 5.72 (t, $J$ = 1.5 Hz, 1H), 5.56 (t, $J$ = 1.0 Hz, 1H), 4.54−4.58 (m, 1H), 3.61 (dd, $J$ = 2.0, 14.5 Hz, 1H), 3.46 (d, $J$ = 3.0 Hz, 1H), 3.31 (dd, $J$ = 9.5, 15.0 Hz, 1H), and 0.14 (s, 9H); $^{13}C$ NMR (125 MHz, $CDCl_3$) $\delta$ 139.1, 134.3, 130.5, 129.6, 128.2, 123.2, 101.4, 97.9, 68.4, 61.2, and −0.07; HRMS-ESI $m/z$ $[M + Na]^+$ calcd for $C_{15}H_{20}O_3SSi$ 331.0795, found 331.0801.

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**Supporting Information Available:** Experimental procedures and characterization data for compounds **7c**,**d**, **1b**−**d**, and **9b**−**d** and $^1H$ NMR spectra for compounds **1a**−**d**, **7b**−**d**, **9a**−**d**, and **10**−**12**. This material is available free of charge via the Internet at http://pubs.acs.org.

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