Notes

Synthesis of Competent Nucleophiles for Delivering the A Ring of Taxol

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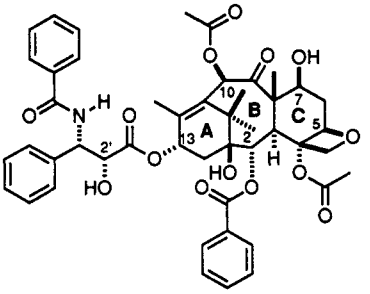
We have been pursuing a synthetic program aimed at the anticancer diterpene taxol (1). This drug was recently approved by the FDA for the treatment of refractory cases of ovarian cancer.[1] Certainly there is much need for new fully synthetic sources of taxol. Moreover, serious issues of strategy and practice must be confronted if any total synthesis is to succeed and therefore, the goal of total synthesis is both formidable and worthy. However, the most realistic prospect by which synthesis is likely to contribute in a practical sense in the taxol area lies in the generation of analogs. Such structures might carry with them useful or even improved therapeutic margins, while being more accessible than the parent drug. We are pursuing such possibilities.



1
Taxol

Our previous work had focused mainly on the synthesis of the CD-segment of taxol.[2] In this Note we wish to report two options for delivering the A ring substructure of taxol for either total synthesis or for analog construction. One route utilizes the vinyl iodides **4** and **6b**, which upon treatment with tBuLi are converted to the vinyllithium reagents corresponding to C–11 (taxol numbering). These vinyllithium reagents have been added to appropriate aldehydes to form a carbon–carbon bond corresponding to the C10–C11 bond of a taxol-like structure. Another route employs the triisopropylsulfonyl hydrazones **13** and **15** as precursors to vinyllithium reagents at C-1. These lithium reagents react with representative aldehydes to give products corresponding to the formation of the C1–C2 bond of taxol.

We had previously reported the synthesis of diketone **2** as well as its mono ethylene glycol ketal **3**.[3] The requisite vinyl idodide **4** was then prepared from this useful intermediate via its hydrazone following Barton's protocol.[4] Metalation of **4** with tBuLi followed by the addition of the aldehydes **10** listed below gave the pure alcohols **11** (eq 1) in the indicated yields following SiO_2 chromatography (Table I).

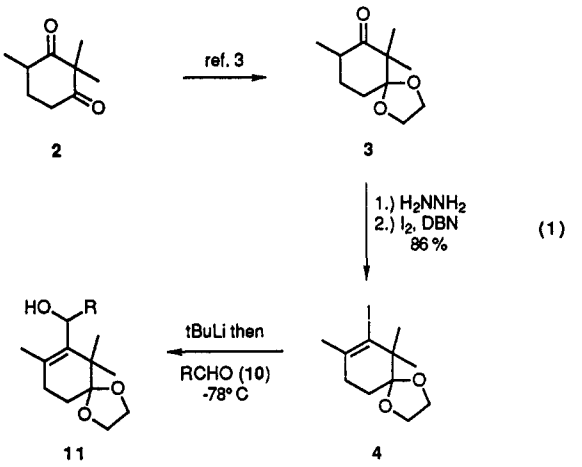


Table I. The Addition of Vinyllithium Reagent Derived from Iodide 4 to Various Aldehydes

entry	aldehyde 10	% yield of 11
1	**10a**, R = C_6H_5	**11a**, 77
2	**10b**, R = 4-H_3CO-C_6H_4	**11b**, 81
3	**10c**, RCHO = piperonal	**11c**, 92
4	**10d**, R = $C_6H_5CH_2$	**11d**, 77
5	**10e**, R = $(C_2H_5)_2CH$	**11e**, 82

Earlier research in our laboratories[3] and by others[5] suggested that the C-13 oxygen function of taxol might be introduced by allylic oxidation of various C-13 deoxy precursors. Moreover, enantioselective reduction of C-13 keto compounds was also demonstrated.[3,5] We wondered whether it would be possible to generate a vinyllithium reagent with this C-13 oxygen already in place. Our first goal was the oxygenation of **4**. This was accomplished, albeit at this writing in only 46% yield, by oxidation with CrO_3 and 3,5-dimethylpyrazole (eq 2). Reduction of the resulting enone **5** under either of two sets of conditions provided racemic **6a** (*via* $NaBH_4/CeCl_3$)[6] or **9** (*via* Corey's *R*-(+)-chiral oxazaborolidine, BH_3),[7] the latter in >98% ee.[8] Direct conversion of **6a** to a functionalized vinyllithium reagent proved problematic. Therefore **6a** was converted to its silyl derivative **6b**. Lithiation of this

(1) Chabner, B. A. *Princ. Pract. Oncol.* **1991**, *5*, 1–10. Kingston, D. G. I. *Pharmac. Ther.* **1991**, *52*, 1–34.
(2) Magee, T. V.; Bornmann, W. G.; Isaacs, R. C. A.; Danishefsky, S. J. *J. Org. Chem.* **1992**, *57*, 3274–3276. Isaacs, R. C. A.; Di Grandi, M. J.; Danishefsky, S. J. *J. Org. Chem.* **1993**, *58*, 3938–3941.
(3) Queneau, Y.; Krol, W. J.; Bornmann, W. G.; Danishefsky, S. J. *J. Org. Chem.* **1992**, *57*, 4043–4047.
(4) Barton, D. H. R.; Bashiardes, G.; Fourrey, J.-L. *Tetrahedron* **1988**, *44*, 147–162. This protocol required some modification; see Experimental Section.
(5) Nicolaou, K. C.; Hwang, C.-K.; Sorensen, E. J.; Clairborne, C. F. *J. Chem. Soc., Chem. Commun.* **1992**, 1117–1118.
(6) Gemal, A. L.; Luche, J.-L. *J. Am. Chem. Soc.* **1981**, *103*, 5454–5455.
(7) Corey, E. J.; Bakshi, R. K.; Shibata, S. *J. Am. Chem. Soc.* **1987**, *109*, 5551–5553. Corey, E. J.; Bakshi, R. K.; Shibata, S.; Chen, C.-P.; Singh, V. K. *J. Am. Chem. Soc.* **1987**, *109*, 7926–7927.
(8) The %ee was determined by NMR study of the mixture using (+)-Eu(hfc)$_3$ as chiral shift reagent.

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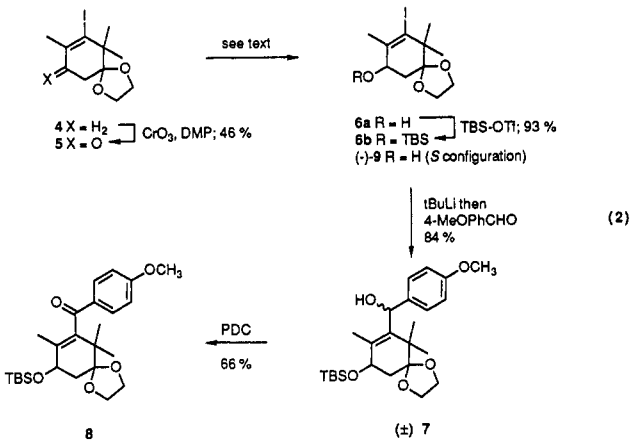
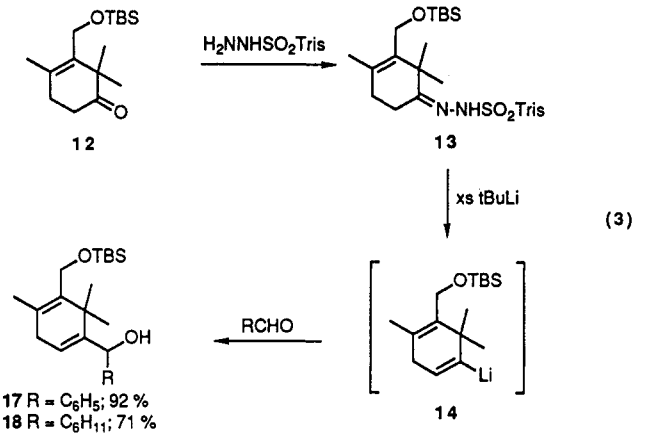


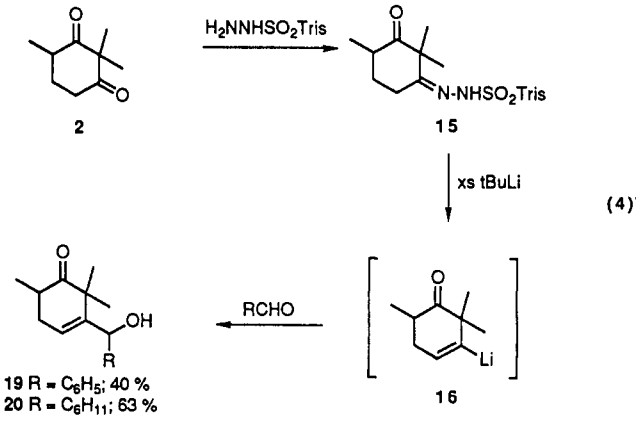
compound as before proceeded smoothly. Condensation with 4-methoxybenzaldehyde afforded a mixture of diastereomers in 84% yield, which, upon oxidation, provided ketone 8 as a single entity (racemic) in 66% yield.

We next turned our attention toward developing a route by which the A-ring of the type found in taxol could be appended at the C-1 carbon. We envisioned a vinyllithium species derived from a 2,4,6-triisopropylsulfonyl hydrazone (trisyl hydrazone) such as 13. Thus, treatment of the ketone 12[9] with 1.5 equiv of 2,4,6-triisopropylsulfonyl hydrazide[10] resulted in the formation of the trisyl hydrazone 13 (eq 3). Exposure of this hydrazone to excess tBuLi



provided the corresponding vinyllithium reagent 14, which was added to benzaldehyde and cyclohexanecarboxaldehyde to provide alcohols 17 and 18 in 92 and 71% yield, respectively.

We also considered the possibility of formation of a vinyllithium species at C-1 with a ketone in place at C-11. Of course here the concern was the potential self-destruction of the lithium reagent in a molecule which contains a ketone. On the other hand, given the steric hindrance of the C-11 ketone there seemed to be a possibility of success. The trisyl hydrazone 15 was prepared in the usual way from diketone 2 (eq 4). Remarkably, reaction of 15 with excess tBuLi provided the vinyllithium reagent 16, which was added to benzaldehyde and cyclohexanecarboxaldehyde to give alcohols 19 and 20 in 40 and 63% yields, respectively.



In summary, we have developed straightforward routes by which the entire A-ring substructure of taxol, including the oxygen function and the required chirality at C-13, can be presented as one of several possible vinyllithium reagents. Research which builds on these findings continues and will be reported in due course.

Experimental Section

General. Air and/or moisture-sensitive reactions were conducted under an atmosphere of dry nitrogen or argon using flame-dried glassware and standard syringe/septa techniques. Methylene chloride was distilled from calcium hydride immediately prior to use. Likewise THF was distilled from sodium benzophenone ketyl. Anhydrous DMF in Sure Seal bottles was purchased from Aldrich. All other reagents are commercial reagent grade, and were purchased from their suppliers and used without further purification. Melting points were measured using an Electrothermal IA 9100 digital melting point apparatus and are uncorrected. Infrared (IR) spectra were recorded with a Perkin-Elmer 1600 Series Fourier-Transform (FT) spectrometer. NMR spectra were recorded using a Bruker AMX-400 spectrometer. Flash chromatography was performed using EM Science silica gel 60 (230–400 mesh).

Vinyl Iodide 4. Monoketal ketone 3[3] (2.8 g, 14 mmol) was taken into absolute ethanol (10 mL) and treated with neat hydrazine (8 mL, 0.25 mol) and triethylamine (3 mL, 0.021 mol). The reaction was then heated at 100 °C until the starting material was consumed (approximately 2–3 days) whereupon the solvent and excess reagents were removed *in vacuo*. Chromatography of the resulting residue (99:1 ether–triethylamine) gave pure hydrazone (2.5 g, 84%).

A solution of I_2 (1.48 g, 5.8 mmol) in ether (10 mL) was added dropwise to an ethereal solution (10 mL) of the hydrazone derived from ketone 3 (0.565 g, 2.7 mmol) and excess DBN (6.6 mL, 53 mmol). As the reaction progressed the reaction mixture became turbid and by the end of the addition, a gummy brown layer had separated. After 15 min of additional stirring, the reaction was partitioned between ether and saturated $NaHCO_3$.[11] The organic layer was collected over K_2CO_3, filtered, and concentrated *in vacuo*. The resulting dark red oil was then dissolved in benzene and refluxed in the presence of DBN for 2.5 h whereupon, after cooling to rt, the mixture was poured into ether and washed with 1 N $Na_2S_2O_3$. The organic layer was dried over K_2CO_3, filtered, and concentrated *in vacuo* to give a red oil which was chromatographed (19:1 hexanes–ether) to afford pure vinyl iodide 4 (0.6 g, 84%): IR (neat, cm^{-1}) 2980, 2879, 1350, 1138, 1102, 890; ^1H NMR (400 MHz, $CDCl_3$) δ 3.98 (s, 4H), 2.29–2.32 (t, 2H), 1.89 (s, 3H), 1.75–1.79 (t, 2H), 1.40 (s, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 136.8, 113.9, 110.1, 65.1, 47.7, 31.5, 30.6, 27.0, 26.3, 24.8, 23.1; HRMS calcd for $C_{11}H_{18}O_2I$ 309.0352, found 309.0359.

(9) Prepared from monoketal 3; see ref 3. A similar compound was also reported recently; see ref 5.

(10) Cusack, N. J.; Reese, C. B.; Risius, A. C.; Roozpeikar, B. *Tetrahedron* **1976**, *32*, 2157–2162.

(11) This represents the best procedure for the synthesis of this iodide. Previous experiments had demonstrated that an initial thiosulfate workup led to a substantial amount of reduction product (H instead of I) after treatment with DBN in refluxing benzene.

Enone 5. Solid CrO_3 (12.8 g, 128 mmol) was suspended in anhydrous CH_2Cl_2 (100 mL) and cooled to −23 °C. After 10 min, 3,5-dimethylpyrazole (12.3 g, 128 mmol) was added in one portion. The suspension then became a red-brown solution. After 20 min of stirring at −23 °C, a solution of the vinyl iodide **4** (1.0 g, 3.2 mmol) in CH_2Cl_2 (20 mL) was added, and the mixture stirred for 3 h at −23 °C. Sodium hydroxide (6 N, 50 mL) was added, and the mixture stirred for 30 min at 0 °C. After dilution with water and CH_2Cl_2, the aqueous phase was extracted with a second portion of CH_2Cl_2 (100 mL), and the combined organic layers were washed with 1 N HCl and brine and dried ($MgSO_4$). Filtration, concentration and radial chromatography (9:1 hexanes–EtOAc) gave 0.40 g (41%) of enone **5** as a white solid, and 0.11 g of **4**. The recovered starting material was resubjected to the above conditions to provide additional **5** (total 0.45 g, 46%) mp 104–105 °C: IR (neat, cm^{-1}) 2942, 2874, 1666, 1576, 1206, 1034, 996; ^1H NMR (400 MHz, $CDCl_3$) δ 4.00 (m, 4H), 2.75 (s, 2H), 2.07 (s, 3H), 1.30 (s, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 191.3, 144.9, 140.6, 109.3, 65.4; 50.8, 44.2, 25.9, 23.2; HRMS calcd for $C_{11}H_{15}O_3I$ ($M^+ + 1$) 323.0156, found 323.0144.

Allylic Alcohol 6a. To a solution of enone **5** (10 mg, 0.03 mmol) and a $CeCl_3 \cdot 7H_2O$ (13 mg, 0.033 mmol) in methanol (2 mL) was added solid $NaBH_4$ (1.2 mg, 0.33 mmol) at 0 °C. After 20 min TLC indicated all of the enone had been converted to product. The solvent was removed *in vacuo* and the residue filtered through a short column of silica gel (4:1 hexanes–EtOAc) to give **6a** (10.3 mg, quant): IR (neat, cm^{-1}) 3509 (br), 2980, 2886, 1712, 1626; ^1H NMR (400 MHz, $CDCl_3$) δ 4.05 (m, 4H), 3.92 (m, 1H), 3.30 (d, 1H, J = 11.08 Hz), 2.16 (dd, 1H, J = 14.2, 5.2 Hz), 2.06 (s, 3H), 1.94 (dd, 1H, J = 14.2, 2.2 Hz), 1.17 (s, 3H), 1.13 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 139.4, 119.4, 110.5, 70.0, 65.1, 48.3, 34.7, 28.6, 26.1, 25.4; HRMS calcd for $C_{11}H_{17}O_3I$ 324.0222, found 324.0222.

***S*-(−)-Allylic Alcohol 9.** To a solution of iodo enone **5** (10.5 mg, 0.03 mmol) and (*R*)-5,5-diphenyl-2-methyl-3,4-propano-1,3,2-oxazaborolidine (4.5 mg, 0.02 mmol) in dry THF (1 mL) was added BH_3·THF complex (Aldrich 1.0 M, 1.1 equiv, 30 μL, 0.03 mmol) at rt. After 1 h the solvent was removed *in vacuo* and the residue purified by flash chromatography to give **9** (6.5 mg, 0.02 mmol, 70%) $[\alpha]_D$ = −78 °C (c = 0.5, CH_2Cl_2). All other spectral properties were identical to those of the racemic material. The ee was determined to be >98% by NMR study of the mixture (+)-Eu(hfc)$_3$ as a chiral shift reagent.

Protocol for Determination of ee. The iodo alcohol, either **6a** or **9** (2–2.5 mg), was dissolved in $CDCl_3$ (400 μL) in a 5-mm NMR tube. Tris[3-[(heptafluoropropyl)hydroxymethylene]-(−)-camphorato]europium(III) (11.7 mg, 0.01 mmol) was dissolved in $CDCl_3$ to give a 0.05 M solution. After obtaining a spectra, 1–3-μL aliquots of the shift reagent were added to the NMR tube and a new spectrum was obtained. The *gem*-methyl protons were sufficiently resolved after the addition of 25–30 μL of the shift reagent solution.

Silyl Ether 6b. Allylic alcohol **6a** was dissolved in dry CH_2Cl_2 (10 mL) and cooled to 0 °C under Ar. To this was added 2,6-lutidine (0.18 mL, 1.5 mmol) and then TBS-OTf (72 μL, 0.38 mmol). After stirring for 30 min a second portion of TBS-OTf (20 uL, 0.11 mmol) was added. Thirty minutes later the reaction was quenched with water (5 mL) and extracted with ether (2 × 20 mL). The organic layers were pooled together and washed successively with 10% $CuSO_4$ (3 × 15 mL), water (1 × 10 mL), and brine (1 × 10 mL), dried ($MgSO_4$), filtered, and concentrated *in vacuo*. The residue was purified by flash chromatography (19:1 petroleum ether–ether) to give silyl ether **6b** as a white solid (0.127 g; 92% yield): IR (neat, cm^{-1}) 2954, 2856, 1462, 1078 (s); ^1H NMR (400 MHz, $CDCl_3$) δ 4.32–4.35 (t, 1H), 3.93–4.02 (m, 5H), 1.94–1.97 (m, 5H), 1.20 (s, 3H), 1.10 (s, 3H), 0.88 (s, 9H), 0.094 (s, 3H), 0.075 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 140.3, 117.5, 109.7, 70.7, 65.3, 64.9, 48.3, 37.5, 27.2, 26.5, 26.1, 25.7, 18.1, −4.2, −4.8; HRMS calcd for $C_{17}H_{31}O_3SiI$ 438.1087, found 438.1085.

General Protocol for the Preparation of Alcohols 11a–e. Vinyl iodide **4** (1 equiv) was dissolved in dry THF (0.1 M) and cooled to −78 °C under a blanket of Ar. To this was added excess tBuLi (1.7M in pentane, 2.3 equiv) and after 10 min the resulting vinyl lithium reagent was quenched with the appropriate aldehyde (**10**, neat, 1.2 equiv). Ten minutes later the reaction was diluted with either brine or saturated NH_4Cl and the product was extracted into ether. Flash chromatography gave the pure allylic alcohols in the indicated yields.

Alcohol 11a: IR (neat, cm^{-1}) 3462 (br, s), 2884, 1132; ^1H NMR (400 MHz, $CDCl_3$) δ 7.44–7.46 (d, 2H), 7.30–7.34 (t, 2H), 7.19–7.23 (t, 1H), 5.42 (s, 1H), 3.98–4.04 (m, 4H), 2.15–2.19 (t, 2H), 1.98 (br s, 1H), 1.80–1.84 (t, 2H), 1.42 (s, 3H), 1.23 (s, 3H), 1.14 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 144.5, 139.4, 132.6, 128.0, 126.2, 125.9, 112.0, 70.7, 64.9, 43.2, 26.6, 23.0, 22.8, 21.2; HRMS calcd for $C_{18}H_{24}O_3$ 288.1725, found 288.1729.

Alcohol 11b: IR (neat, cm^{-1}) 3470 (br s), 2955, 2885, 1610, 1510, 1246; ^1H NMR (400 MHz, $CDCl_3$) δ 7.33–7.36 (d, 2H), 6.84–6.86 (d, 2H), 5.36 (s, 1H), 3.95–4.03 (m, 4H), 3.79 (s, 3H), 2.14–2.18 (t, 2H), 1.79–1.82 (t, 2H), 1.59 (br s, 1H), 1.45 (s, 3H), 1.21 (s, 3H), 1.08 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 158.1, 139.2, 136.4, 132.3, 127.3, 113.4, 112.1, 70.4, 64.9, 64.8, 55.2, 43.1, 31.3, 26.6, 23.1, 22.4, 21.2; HRMS calcd for $C_{19}H_{26}O_4$ 318.1831, found 318.1831.

Alcohol 11c: IR (neat, cm^{-1}) 3462 (br s), 2960, 2885, 1510, 1237, 1093; ^1H NMR (400 MHz, $CDCl_3$) δ 6.96 (s, 1H), 6.89–6.91 (d, 1H), 6.75–6.77 (d, 2H), 5.93 (s, 2H), 5.31–5.32 (d, 1H), 3.96–4.03 (m, 4H), 2.14–2.18 (t, 2H), 1.78–1.81 (t, 2H), 1.47 (s, 3H), 1.21 (s, 3H), 1.08 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 147.5, 145.92, 139.2, 138.5, 132.6, 119.2, 111.9, 107.8, 107.0, 100.8, 70.6, 64.9, 64.8, 43.1, 31.3, 26.6, 23.1, 22.5, 21.2; HRMS calcd for $C_{19}H_{24}O_5$ 332.1624, found 332.1603.

Alcohol 11d: IR (neat, cm^{-1}) 3477 (br s), 2933, 1207, 1135; ^1H NMR (400 MHz, $CDCl_3$) δ 7.22–7.35 (m, 5H), 4.43–4.47 (dd, 1H, J = 2.6, 10.5 Hz), 3.96–4.03 (m, 4H), 3.12–3.19 (dd, 1H, J = 10.5, 14 Hz), 2.87–2.91 (dd, 1H, J = 2.6, 14 Hz), 1.99–2.28 (m, 2H), 2.00 (s, 3H), 1.68–1.85 (m, 2H), 1.51 (br s, 1H), 1.20 (s, 3H), 1.09 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 139.8, 138.2, 130.5, 129.3, 128.6, 126.4, 111.9, 72.3, 64.9, 64.8, 43.1, 31.7, 26.5, 23.6, 21.2, 20.9; HRMS calcd for $C_{19}H_{26}O_3$ 302.1882, found 302.1863.

Alcohol 11e: IR (neat, cm^{-1}) 3491 (br s), 1460, 11337, 1058; ^1H NMR (400 MHz, $CDCl_3$) δ 4.10–4.12 (d, 1H), 3.91–3.99 (m, 4H), 2.11–2.15 (t, 2H), 1.90–2.00 (m, 1H), 1.80 (s 3H), 1.71–1.75 (t, 2H), 1.55–1.70 (m, 4H), 1.38 (br s, 1H), 1.25–1.35 (m, 1H), 1.14 (s, 3H), 1.04 (s, 3H), 0.83–0.90 (m, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 138.4, 131.1, 112.2, 72.6, 64.9, 64.8, 44.7, 43.4, 31.8, 26.5, 23.5, 22.6, 21.9, 21.0, 20.9, 12.2, 8.7; HRMS calcd for $C_{17}H_{30}O_3$ 282.2195, found 282.2187.

Enone 8. Vinyl iodide **6b** (24.5 mg, 0.056 mmol) was dissolved in dry THF (1 mL) and cooled to −78 °C under an Ar atmosphere. To this solution was added excess tBuLi (77 μL, 1.7 M in pentane, 1.3 mmol) and the resulting bright yellow solution was stirred for 10 min. At this point, neat 4-methoxybenzaldehyde (10 μL, 0.081 mmol) was added causing the color to discharge. After 10 min the reaction was quenched with brine (3 mL) and allowed to warm to rt. The mixture was extracted with ether (3 × 10 mL) and the organic layers were combined over $MgSO_4$, filtered, and concentrated *in vacuo*. Purification by flash chromatography (gradient elution, 19:1 to 4:1 petroleum ether–ether) then gave alcohols **7** (21 mg, 85%) as a mixture of diastereomers.

The purified alcohols were dissolved in CH_2Cl_2 (1 mL) and powdered 4-Å molecular sieves and excess PDC were added. The reaction was stirred under Ar for 3 days (not checked by TLC prior to this). The reaction mixture was diluted with ether (30 mL) and filtered through a Celite pad. Chromatography on SiO_2 (9:1 petroleum ether–ether) gave pure ketone **8** (14 mg, 66%) and some overoxidized product (3 mg, 17%), believed to result from desilylation followed by oxidation: IR (neat, cm^{-1}) 2950, 1680, 1250; ^1H NMR (400 MHz, $CDCl_3$) δ 7.95–7.97 (d, 2H), 6.93–6.95 (d, 2H), 4.36–4.40 (t, 1H), 3.93–4.08 (m, 4H), 3.87 (s, 3H), 2.09–2.11 (m, 2H), 1.46–2.00 (s, 3H), 0.90 (s, 15H), 0.10 (s, 3H), 0.09 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 198.0, 163.6, 139.2, 132.8, 132.5, 130.9, 113.8, 70.5, 65.8, 65.3, 65.2, 55.4, 37.6, 25.8, 25.7, 18.0, 17.2, 15.3, 15.2, −4.2, −4.8; HRMS calcd for $C_{25}H_{38}O_5Si$ 446.2489, found 446.2482.

General Protocol for the Preparation of Trisyl Hydrazones 13 and 15. The requisite ketone (1 equiv) was dissolved in dry THF (0.5 M) at room temperature. To this was added solid 2,4,6-triisopropylsulfonyl hydrazide (1.5 equiv), and the resulting solution was stirred for 24 h. The solvent was removed *in vacuo* and the concentrate was recrystallized from hexane or pentane. The mother liquor was concentrated, repurified by

flash chromatography through silica gel, and recrystallized as before. Yields of 75–90% were obtained.

Trisyl Hydrazone 13 (mp 118–120 °C): IR (neat, cm^{-1}) 3240-(br), 2958, 1600, 1462, 1255, 1164, 1057, 837, 774; ^1H NMR (400 MHz, $CDCl_3$) δ 7.15 (s, 2H), 7.10 (s, 1H), 4.18 (sept., 2H, J = 6.8 Hz), 4.09 (s, 2H), 2.90 (sept., 1H, J = 6.9 Hz), 2.34 (t, 2H, J = 6.9 Hz), 2.18 (t, 2H, J = 6.9 Hz), 1.71 (s, 3H), 1.26 (d, 12H, J = 6.8 Hz), 1.25 (d, 6H, J = 6.9 Hz), 1.08 (s, 6H), 0.87 (s, 9H), 0.03 (s, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 164.6, 153.0, 151.1, 136.0, 131.4, 124.0, 123.6, 59.0, 42.2, 34.1, 31.8, 30.5, 29.8, 25.8, 24.7, 23.5, 21.5, 19.5, 18.3, –5.4; HRMS ($M^+ + 1$) calcd for $C_{31}H_{54}N_2O_3SSi$ 563.3702, found 563.3718.

Trisyl Hydrazone 15 (mp 130–131 °C): IR (neat, cm^{-1}) 3242 (br), 2962, 2870, 1715, 1600, 1461, 1327, 1165, 1025, 737; ^1H NMR (400 MHz, $CDCl_3$) δ 7.36 (s, 1H), 7.16 (s, 2H), 4.18 (sept, 2H, J = 6.8 Hz), 2.90 (sept, 1H, J = 6.9 Hz), 2.3–2.6 (m, 3H), 2.05 (m, 1H), 1.55 (m, 1H), 1.29 (d, 6H, J = 6.9 Hz), 1.27 (d, 12H, J = 6.8 Hz), 1.16 (s, 3H), 1.12 (s, 3H), 1.07 (d, 3H, J = 6.6 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 213.0, 159.5, 153.4, 151.2, 130.9, 123.6, 52.7, 41.6, 34.2, 29.8, 26.7, 25.0, 24.8, 24.0, 23.5, 14.7; HRMS calcd for $C_{24}H_{38}N_2O_3$ 434.2603, found 434.2598.

General Protocol for the Preparation of Alcohols 17–20. The requisite trisyl hydrazone (1 equiv) was dissolved in dry THF (0.05 M) and cooled at –78 °C under an inert atmosphere. To this was added excess tBuLi (1.7 M in pentane, 4 equiv) and the resulting yellow solution was stirred for 15 min before warming to 0 °C. The reaction was stirred at 0 °C until the evolution of nitrogen ceased (1–5 min). The solution was then cooled to –78 °C for 5 min and the resulting vinyllithium reagent was quenched with the appropriate aldehyde (neat, 1.2 equiv). After 10 min the reaction was quenched with water and the product was extracted into ether. The ether layer was dried over $MgSO_4$, filtered, and concentrated. Alcohols **17** and **18** were purified by flash chromatography through silica gel. Alcohols **19** and **20** were purified by flash chromatography through Florisil.

Alcohol 17: IR (neat, cm^{-1}) 3329(br), 2955, 2905, 2840, 1462, 1252, 1052, 836, 773; ^1H NMR (400 MHz, $CDCl_3$) δ 7.2–7.5 (m, 5H), 5.69 (t, 1H, J = 3.5 Hz), 5.42 (d, 1H, J = 4.7 Hz), 4.21 (s, 2H), 2.65 (d, 2H, J = 3.5 Hz), 1.73 (s, 3H), 1.34 (s, 3H), 1.12 (s, 3H), 0.91 (s, 9H), 0.09 (s, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 147.6, 144.3, 135.3, 128.9, 127.6, 127.0, 126.6, 122.6, 72.1, 58.8, 38.3, 33.4, 27.1, 27.0, 25.9, 19.0, 18.4, –5.4; HRMS calcd for $C_{23}H_{36}O_2Si$ 372.2485, found 372.2485.

Alcohol 18: IR (neat, cm^{-1}) 3448(br), 2926, 2853, 1449, 1360, 1252, 1054, 836, 773; ^1H NMR (400 MHz, $CDCl_3$) δ 5.80 (t, 1H, J = 3.5 Hz), 4.20 (s, 2H), 3.75 (dd, 1H, J = 8.5, 5.2 Hz), 2.72 (dd, 1H, J = 23, 3.5 Hz), 2.65 (dd, 1H, J = 23, 3.5 Hz), 2.13 (d, 1H, J = 12.9 Hz), 1.74 (s, 3H), 1.5–1.8 (m, 5H), 1.21 (s, 3H), 1.05 (s, 3H), 1.1–1.3 (m, 4H), 0.9 (s, 9H), 0.8–1.0 (m, 2H), 0.1 (s, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 146.6, 135.3, 128.7, 119.2, 74.2, 58.8, 43.2, 38.0, 33.2, 30.3, 29.5, 26.7, 26.5, 26.4, 26.1, 26.0, 25.9, 19.0, 18.4, –5.4; HRMS calcd for $C_{23}H_{42}O_2Si$ 378.2954, found 378.2938.

Alcohol 19 (3:2 mixture of diastereomers): IR (neat, cm^{-1}) 3436 (br), 2972, 2931, 1709, 1452, 1380, 1015, 701; ^1H NMR (400 MHz, $CDCl_3$) (major diastereomer) δ 7.2–7.5 (m, 5H), 5.83 (dd, 1H, J = 6.0, 2.2 Hz), 5.36 (d, 1H, J = 4.5 Hz), 2.85 (m, 1H), 2.55 (m, 1H), 2.20 (m, 1H), 1.85 (d, 1H, J = 4.5 Hz), 1.41 (s, 3H), 1.12 (s, 3H), 1.09 (d, 3H, J = 6.5 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) (major diastereomer) δ 215.7, 147.4, 143.2, 128.4, 127.6, 126.7, 124.6, 72.7, 47.9, 38.5, 33.4, 27.6, 22.8, 14.3; HRMS calcd for $C_{16}H_{20}O_2$ 244.1463, found 244.1466.

Alcohol 20 (single diastereomer): IR (neat, cm^{-1}) 3446 (br), 2925, 2851, 1706, 1449, 1362, 993; ^1H NMR (400 MHz, $CDCl_3$) δ 5.93 (dd, 1H, J = 6.2, 2.2 Hz), 3.71 (dd, 1H, J = 8.2, 5.8 Hz), 2.82 (m, 1H), 2.52 (m, 1H), 2.10 (m, 2H), 1.50–1.90 (m, 4H), 1.30 (s, 3H), 1.12 (s, 3H), 1.09 (d, 3H, J = 6.5 Hz), 0.8–1.4 (m, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 216.0, 147.6, 121.6, 74.3, 47.9, 42.9, 38.7, 33.3, 30.3, 29.0, 27.2, 26.4, 26.3, 26.0, 22.2, 14.2; HRMS calcd for $C_{16}H_{26}O_2$ 250.1933, found 250.1926.

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Supplementary Material Available: Copies of the spectra for compounds **4**, **5**, **6a**, **6b**, **11a–f**, **13**, **15**, **17–20** (32 pages). This material is contained in libraries on microfiche, immediately follows this article in the microfilm version of the journal, and can be ordered from the ACS; see any current masthead page for ordering information.