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Stereospecific Synthesis of Tetrasubstituted Z-Enol Silyl Ethers By A Three Component Coupling Process

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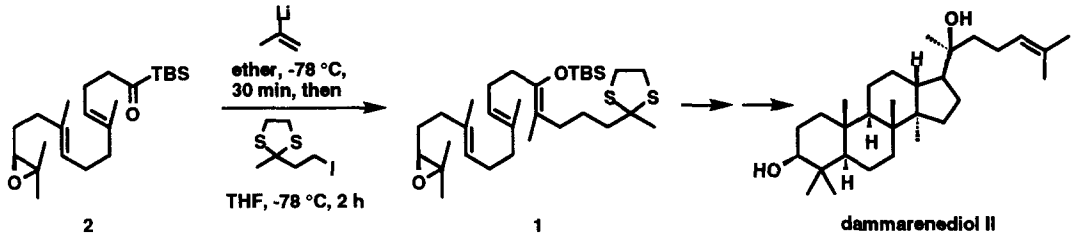
Abstract: *The coupling of an acylsilane, 2-propenyllithium and an alkyl halide produces tetrasubstituted Z-enol silyl ether in good yields, and provides the first route to these isomerically pure compounds.* © 1997 Elsevier Science Ltd.

Recently an unusually short enantioselective synthesis of dammarenediol II, a fundamental precursor of tetracylic plant triterpenoids, was accomplished by tetracyclization of the key intermediate **1**.[1] A critical part of the synthesis was the stereospecific construction of **1**, in particular the Z-tetrasubstituted enol silyl ether unit. This construction was carried out from the acylsilane **2** by sequential treatment with 2-propenyllithium and ethylene thioketal of 4-iodo-2-butanone, as shown below. In this paper we describe other examples of this three-component coupling reaction to document the efficiency and practicality of the synthetic method, which represents the first stereospecific route to tetrasubstituted enol silyl ethers.

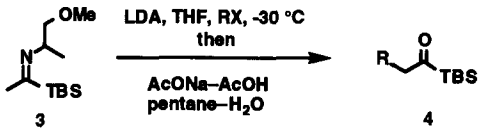


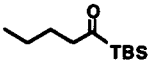
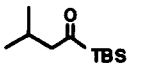
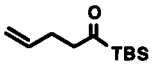
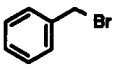
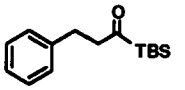
2 **1** **dammarenediol II**

The synthesis of the required acyl-*tert*-butyldimethylsilanes (**4**) was effected as outlined in Table 1 starting from the readily available Schiff base (**3**) of acetyl-*tert*-butyldimethylsilane[2,3] and 2-amino-1-methoxypropane (Aldrich Co.).[4] Deprotonation of **3** with 1.05 equiv of lithium diisopropylamide (LDA) in THF at -30 °C initially then at 0 °C for 30 min afforded a yellow solution of the azaenolate which was cooled to -30 °C and then treated with the R-Hal component listed in Table 1. The resulting alkylated imine was treated at 23 °C with a biphasic mixture of pentane and aqueous HOAc–NaOAc buffer with stirring to effect hydrolysis to the acyl-*tert*-butyldimethylsilanes (**4**) listed in Table 1 in good yield.

The acylsilanes **4** were transformed into tetrasubstituted Z-enol silyl ethers **5** as outlined in Table 2. Specifically, reaction of 2-propenyllithium and 3-phenylpropionyl-*tert*-butyldimethylsilane proceeded by a

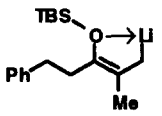
Table 1



Electrophile	Acylsilane	Yield
		94%
		81%
		81%
		85%

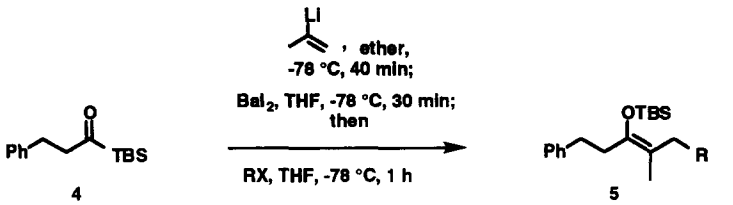
carbonyl addition-Brook rearrangement pathway to form the *Z*-allyllithium reagent (which can be formulated as **6**). Treatment of **6** with various alkylating agents produced in addition to the desired alkylation product a significant amount of homocoupling products, presumably by a process involving lithium-halogen exchange and subsequent coupling reactions. After a number of experiments it was discovered that the formation of homocoupling products could be suppressed by the addition of anhydrous barium iodide (made by the reaction of excess Ba pieces (*ca.* 5 x 5 x 0.5 mm) with I_2 in THF solution) prior to the alkylating agent. The high reactivity of the allylic organobarium reagent in coupling finds precedent in the work of H. Yamamoto.[5] As indicated in Table 2, the use of BaI_2 in the three component coupling resulted in good yields of a variety of alkylated *Z*-1-phenethyl-1-*tert*-butyldimethylsilyloxypropenes. ^1H NMR analysis of the crude products **5** revealed that only the *Z*-enol silyl ether was formed in each case.

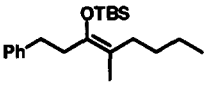
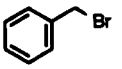
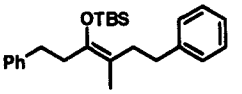
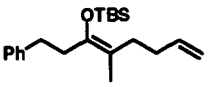
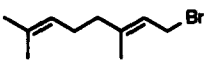
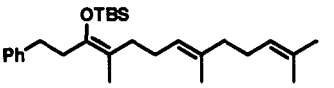
The following procedures provide illustrative experimental detail for the transformations summarized in Tables 1 and 2. The ready availability of a variety of *Z*-enol silyl ethers by the route described herein provides an



6

Table 2



Electrophile	Enolsilane	Yield
		82%
		72%
		75%
		76%

incentive for additional studies of their application, especially for cyclization and C–C bond-forming reactions.[6]

Imine 3. A solution of acetyl-*tert*-butyldimethylsilane (1.0 mL, 5.0 mmol; prepared by the procedure of Norwick and Danheiser)[2] and 2-amino-1-methoxypropane (Aldrich, 0.60 mL, 5.2 mmol) in 10 mL of benzene was heated at reflux in a Dean-Stark apparatus using 4 Å molecular sieves to remove water for 12 h. The solution was concentrated *in vacuo*, and the residue was distilled (60-65 °C at 1.5 torr) to give the imine **3** (0.98 g, 85%) as a colorless liquid. IR (film) 2929, 1247, 1114 cm^{-1}; ^1H NMR (500 MHz, C_6D_6) δ 3.95 (1 H, **ABX** q, J_{AX}= 7.1 Hz, J_{BX}= 5.9 Hz, J = 6.2 Hz), 3.38 (2 H, **ABX**, J_{AB}= 8.9 Hz, J_{AX}= 7.1 Hz, J_{BX}= 5.9 Hz), 3.15 (3 H, s), 1,70 (3 H, s), 1.11 (3 H, d, J = 6.2 Hz), 0.99 (9 H, s), 0.16 (6 H, s); HRMS (EI) calcd for $[C_{12}H_{27}NOSi]^+$: 229.18604, found: 229.1857.

Typical Procedure for the Synthesis of Acylsilanes 4. To a solution of LDA (1.8 mmol, prepared by reaction of 1.9 mmol of diisopropylamine and 1.8 mmol of BuLi in 8 mL of THF) at -30 °C was added imine **3** (0.5 mL, 1.7 mmol) via syringe, and the resulting yellow solution was allowed to warm up to 0 °C for 30 min. This solution was recooled to -30 °C, and the neat alkyl halide (2.0 mmol) was slowly added via

syringe. The reaction mixture was then allowed to slowly warmed up to -10 °C over 1 h, and quenched with saturated NH_4Cl (20 mL) at -30 °C. The volatile materials were removed *in vacuo*, and the imine product was extracted with 10:1 hexane-EtOAc (3x20 mL). The combined organic solution was washed with brine, dried (Na_2SO_4) and concentrated *in vacuo*. The yellow residue was dissolved in 9 mL of pentane, and was treated with 9 mL of AcOH-AcONa buffer (prepared by mixing 33 g of AcONa, 70 mL of AcOH and 300 mL of water). The mixture was stirred vigorously for 1.5 h to 10 h until TLC indicated complete consumption of the starting material. The organic layer was separated, and the aqueous layer was extracted with hexane (3x20 mL). The combined hexane solution was successively washed with saturated $NaHCO_3$ and brine, dried (Na_2SO_4) and concentrated *in vacuo*. The residue was purified by silica gel chromatography (50 : 1 hexane–EtOAc) to give the acylsilane **4**.

Typical Procedure for the Synthesis of *Z*-Enol Silyl Ether 5. To a solution of *t*-BuLi (1.6 M in pentane, 0.4 mL, 0.64 mmol) in 1 mL of anhydrous ether at -78 °C was added 2-bromopropene (60 μL, 0.64 mmol). After 30 min, a solution of acylsilane **4** (0.21 mmol) in 0.5 mL ether (plus a 0.5 mL rinse) was added slowly via cannula. After 40 min, a freshly made BaI_2 solution (0.19 M in THF, 2.0 mL, 0.37 mmol) was added slowly via syringe at -78 °C to give a yellow solution. After stirring for 30 min, the alkyl halide (0.66 mmol) was added slowly via syringe. After stirring at -78 °C for 1 h, the reaction was quenched with 1 mL of pH 7 phosphate buffer, and the volatile materials were removed *in vacuo*. The residue was partitioned between hexane and water, and the product was extracted with hexane (3x20 mL). The combined hexane solution was washed with brine, dried (Na_2SO_4) and concentrated *in vacuo*. The residue was purified by silica gel or neutral alumina chromatography (50 : 1 hexane–CH_2Cl_2) to give the *Z*-enol silyl ether **5**.

References and Notes:

1. Corey, E. J.; Lin, S. *J. Am. Chem. Soc.* **1996**, *118*, 8765.
2. For the method of preparation see: Nowick, J. S.; Danheiser, R. L. *Tetrahedron* **1988**, *44*, 4113.
3. For reviews on synthesis of acylsilanes, see: (a) Ricci, A.; Degl'Innocenti, A. *Synthesis* **1989**, 647. (b) Bulman Page, P. C.; Klair, S. S.; Rosenthal, S. *Chem. Soc. Rev.* **1990**, *19*, 147.
4. For prior work on silyl imines, see: Niznik, G. E.; Morrison, W. H. III; Walborsky, H. M. *J. Org. Chem.* **1974**, *39*, 600 .
5. Yanagisawa, A.; Yasue, K.; Yamamoto, H. *Synlett* **1993**, 686.

6. We are grateful to the National Institutes of Health for a Postdoctoral Fellowship to S. L. and a grant in support of this research.

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