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A CHEMOSELECTIVE DESULFURIZATION METHOD VIA HOMOGENEOUS NICKEL CATALYSIS

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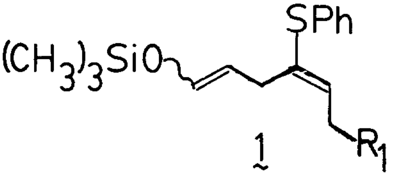
Summary: Isopropylmagnesium bromide in the presence of bis-(triphenylphosphino) nickel(II) chloride reduces vinyl sulfides stereospecifically to the corresponding olefins without overreduction - a process which serves as a key step in the synthesis of the sex pheromone of the Douglas fir tussock moth.

The vinyl sulfide moiety has been shown to be a useful intermediate in organic synthesis, not only as a carbonyl protecting group[1] but in a variety of other synthetic transformations as well.[2] One interesting aspect of vinyl sulfide chemistry is their potential to serve as olefin synthons via hydrogenolysis. However, the common desulfurization method employing Raney nickel is often plagued by overreduction of the olefin formed to saturated by-products.[3] In our investigations of selective functional group transformations of the 1,4-dienes 1 derived from the bifunctional cyclopropyl reagent 2,[5] we have developed a clean stereospecific reduction of vinyl sulfides to olefins with Grignard reagents and nickel(II) salts.



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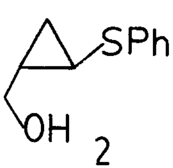
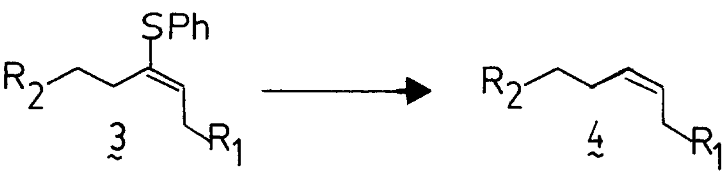


2

Treatment of a THF solution of an *E*-vinyl sulfide 3[4,5,6] with ethereal 2-propylmagnesium bromide in the presence of 3-8 mol% $(Ph_3P)_2NiCl_2$ at reflux for 36-48 hours produces, after chromatography and distillation, good yields of the corresponding *Z*-olefins 4 (equation 1; Table 1). The stereohomogeneity of



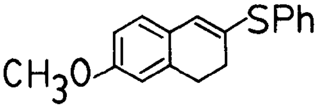
(1)

each olefin formed has been verified by ^1H and ^{13}C NMR. The combination of

2-propylmagnesium bromide and the nickel salt serve as an *in situ* source of "NiH."

This reduction methods appears to be a novel, general method for conversion of vinyl sulfides to olefins. To the degree that a vinyl sulfide can be stereo- and regiospecifically generated in cyclic and acyclic systems from carbonyl compounds, this method then serves as a stereo- and regiospecific ketone and aldehyde to olefin transformation.

TABLE 1. Vinyl Sulfide Reductions[a]

3	R_1	R_2	Yield % 4[b]
a	C_6H_5	$(CH_3O)_2CH$	76
b	nC_3H_7	$(C_2H_5O)_2CH$	66
c	CH_3	$(C_2H_5O)_2CH$	65
d	CH_3	$(CH_3O)_2CH$	50
e	nC_4H_9	$THPOCH_2$	75
			70

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[a] All reactions run 1:1 THF/Et$_2$O with 3 eq. 2-propylmagnesium bromide and 5 mole% $(Ph_3P)_3NiCl_2$ at reflux (bath temp. 60-65°C) for 36-48 hr.

[b] Isolated yield after chromatography and distillation

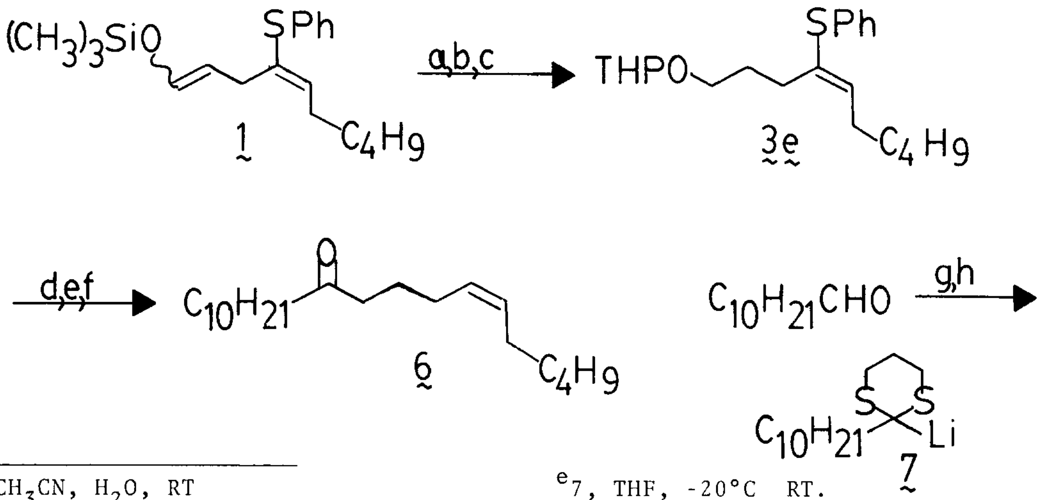
Some advantages of this reduction should be noted. Clean reduction of the vinyl sulfide to olefin is seen, with no overreduction being detected. Within the limits of our analytical methods (270.071 MHz ^1H and 15.04 MHz ^{13}C NMR), no crossover to the *E*-olefins has been observed for the reduction of *E*-vinyl sulfides 3. Acetals, ethers, aromatic systems and isolated olefins appear to be compatible with these reaction conditions. The byproducts of the reaction are minimal (gaseous H_2S, trace of phosphines and nickel salts) and are easily removed from the products.

A typical procedure is as follows: To a solution of 3a (330 mg, 1.01 mmoles) in 2 ml dry THF is added $(Ph_3P)_2NiCl_2$ (33 mg, 0.05 mmoles). After stirring under N_2 for 5 minutes at room temperature, 2-propylmagnesium bromide (1.6 ml of a 1.87 M solution in ether) is added via syringe. After an initial exothermic reaction, the resultant black mixture is heated to reflux (bath temperature 65°C) for 36 h. The mixture is then cooled to RT and quenched by dropwise addition of 5% aq. Na_2HPO_4 (∿0.75 ml). The mixture is added to ether (∿50 ml) and 10% $NaHSO_4$ (∿ 5 ml) and filtered through a glass wool plug into a separatory funnel. The aqueous layer is separated, the organic layer washed with 1N KOH (20 ml), brine (20 ml), dried over $MgSO_4$, filtered and concentrated *in vacuo*. Chromatography on SiO_2 (preparative TLC, 25% Et$_2$O/hexane) and Kugelrohr distillation (pot temp 80-90° at 0.005 torr) affords 185 mg (76%) of

4a as a clear, colorless, pungent liquid.[7]

To demonstrate the utility of this chemoselective and stereospecific reduction method, we have prepared the sex pheromone of the Douglas fir tussock moth **6**[8] (Scheme 1) with the vinyl sulfide moiety serving as the penultimate olefin precursor. Selective enol silyl ether hydrolysis of the diene **1** (R_1 = n-C_4H_9 , obtained in 57% yield from **2**[5]) with 50% aq. KF in CH_3CN, followed by reduction and protection afforded the vinyl sulfide **3e** in 68% yield from **1**. Desulfurization of **3e** gave a 75% yield of only Z-olefin **4e**.[6] Transformation of the THP ether directly to the corresponding bromide **9** followed by alkylation with lithio dithiane **7** and hydrolysis gave the desired pheromone **6** in 42% yield from **4e** and 16% overall yield from **2**.

SCHEME 1. Preparation of Douglas Fir Tussock Moth Pheromone **6**



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[a] KF, CH_3CN, H_2O, RT

[b] $NaBH_4$, C_2H_5OH, 0°C.

[c] DHP, p-TSA, CH_2Cl_2, $-40° \rightarrow 0°C$.

[d] $Ph_3P \cdot Br_2$, CH_2Cl_2, $0°C \rightarrow RT$.

[e] **7**, THF, -20°C RT.

[f] $HgCl_2$, H_2O, CH_3CN, THF, reflux.

[g] $HS(CH_2)_3SH$, $(C_2H_5)_2O \cdot BF_3$, $CHCl_3$, 0°C

[h] n-BuLi, THF, -20°C.

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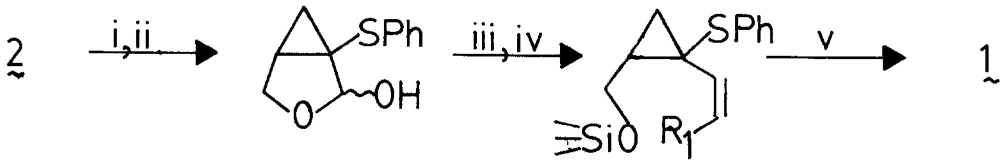
   The dienes **1** are prepared via the following scheme from **2**:



^{i}3.4 eq. *n*-BuLi, hexane, RT. ^{ii}THF, DMF, 0°C. $^{iii}Ph_3\overset{+}{P}CH_2R_1\overset{-}{Br}$, THF, KO*t*-$C_4H_9$, 0° → -78°C → RT. $^{iv}(CH_3)_3SiCl$, $(C_2H_5)_2O$, C_5H_5N, RT. ^{v}Flash vacuum pyrolysis, 454-650°C, 0.05-0.30 torr.

The vinyl sulfide is generated 100% *E* in the rearrangement. The enolsilyl ether is an *E*/*Z* mixture. The acetals **3a-d** are formed in one step and 71-84% yield from the dienes **1** by treatment with either CH_3OH, $(CH_3O)_3CH$, HCl or C_2H_5OH, $(C_2H_5O)_3CH$, HCl. The cyclopropane reagent **2** is prepared in 5 steps and 45% overall yield from thiophenol and γ-butyrolactone.

6. All new compounds were characterized by NMR, IR, Mass spectrum and either exact mass or combustion analysis.
7. **4a** IR ($CDCl_3$) cm^{-1}: 3020, 2920, 1595, 1490, 1445. ^1H NMR($CDCl_3$): δ7.19 (m, 5H), 5.57(dt, J=11, 6.8 Hz, 1H), 5.51 (dt, J=11, 6.8 Hz, 1H), 4.39 (t, J=5.5 Hz, 1H), 3.40 (d, J=6.8 Hz, 2H), 3.31 (s, 3H), 2.22 (m, 2H), 1.70 (m, 2H). ^{13}C NMR ($CDCl_3$): δ140.8, 129.7, 128.8, 128.4, 125.8, 104.0, 52.7, 33.5, 32.5, 22.5. Ms m/e (rel%): 220(0.0). Calculated for $C_{14}H_{20}O_2$: 76.33% C, 9.15% H. Found: 76.42% C, 9.11% H.
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