β-HYDROXYSILANES IN THE SYNTHESIS AND LABELLING OF UNSATURATED PHEROMONES.

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Abstract: The use of β-hydroxysilanes to protect olefins during catalytic hydrogenation and deuteration is described. Either (Z)- or (E)- olefins can be stereoselectively regenerated from the key intermediates.

Key Words: olefin protection; deuteration; TBDMS-acetate conversion; hydroxysilane
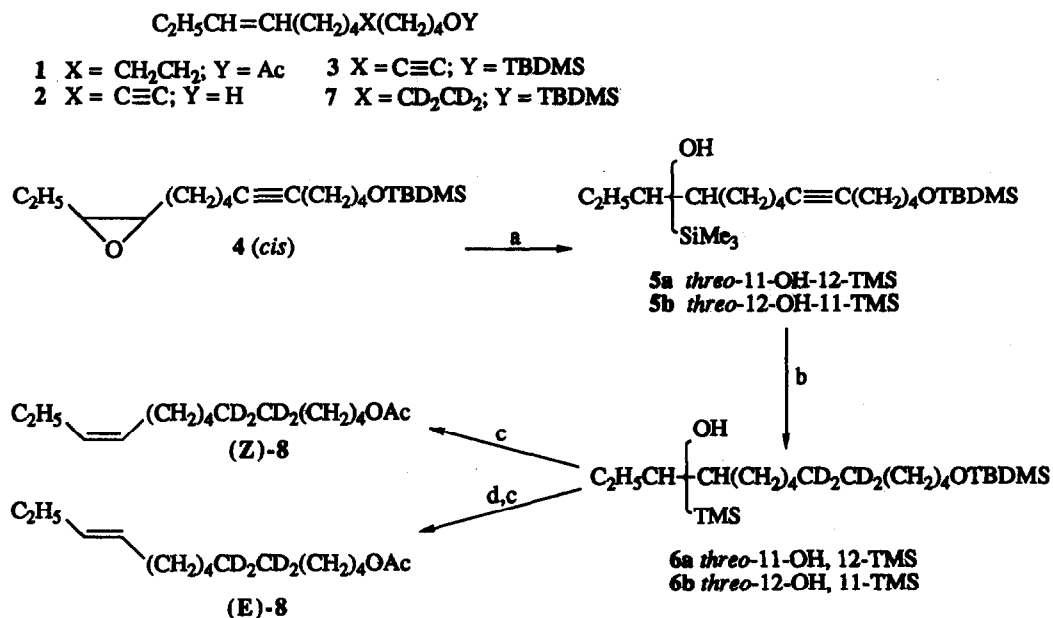
Recently, Klun and coworkers have begun to address the post recognition fate of the European corn borer (*Ostrinia nubilalis*) pheromone, and have postulated that the unsaturated acetates (Z)-1 and (E)-1 are cleared from antennal receptor sites by processes involving hydrolysis, oxidation to the carboxylic acid, and rapid B-oxidation.[1] Further experiments have been designed that require additional radiolabelled (E)-1 and (Z)-1 of high specific activity; additional requirements are well-defined label location remote from either the oxygen or double bond functionalities, and the availability of each of the geometric isomers.

The presence of a double bond in the pheromone complicates the introduction of several atoms of tritium per molecule. Furthermore, economics and radioactive waste management dictate against introducing the label early in a synthesis, particularly prior to construction of the carbon skeleton. Accordingly, we sought a means of selectively protecting a double bond in the presence of an acetylenic linkage, using a functionality that would be stable to catalytic reduction but that could then be stereoselectively reconverted to an olefin of desired geometry. We here report the selection of β-hydroxysilanes to fulfill these requirements; additionally, our need for both geometric isomers of 1 make this methodology doubly attractive, since either geometric isomer can be regenerated from a single precursor. In spite of the ubiquity and importance of unsaturated natural products, olefin protecting groups are quite uncommon, and we anticipate that β-hydroxysilanes should prove useful in the labelling and syntheses of a variety of unsaturated compounds.

β-Hydroxysilanes are perhaps best known as intermediates in the Peterson olefination reaction[2] or from the Peterson-Hudrlik procedure,[3] but they can also be stereospecifically formed from epoxides and silyl anions.[4,5] Stereoselective *syn*-elimination is known to occur upon treatment of β-hydroxysilanes with bases such as potassium hydride[5,6] or potassium t-butoxide,[7] whereas stereoselective *anti*-

elimination occurs with acidic reagents such as boron trifluoride etherate[6] or Nafion-H.[8] Since epoxides are normally formed by *cis*-epoxidation, *syn*-elimination generates an olefin of inverted geometry[5] whereas the *anti*-process regenerates the original olefin. Thus either a (Z)- or (E)- starting olefin ought to equally well produce whichever geometry is required in the final product.

(Z)-11-Tetradecen-5-yn-1-ol[9] **2** was converted to its TBDMS ether **3** and epoxidized. Reaction of epoxide **4**[10] with trimethylsilyllithium[11] gave a pair of regioisomers **5a,5b**[12] which, although not separated, were found to be stable to flash chromatography and to storage (at least several months at 5°C). Catalytic hydrogenation (H$_2$, Pt, 1 atm) reduced the triple bond whereupon treatment with Nafion-H[7] (overnight, room temperature) achieved the desired *anti*-elimination to regenerate the (Z)-olefin. When acetic anydride was included, conversion of the TBDMS ether to the corresponding acetate occurred simultaneously[13], and (Z)-1 was isolated in excellent yield.

$$C_2H_5CH=CH(CH_2)_4X(CH_2)_4OY$$

1 X = CH$_2$CH$_2$; Y = Ac   **3** X = C≡C; Y = TBDMS
2 X = C≡C; Y = H   **7** X = CD$_2$CD$_2$; Y = TBDMS

5a *threo*-11-OH-12-TMS
5b *threo*-12-OH-11-TMS

6a *threo*-11-OH, 12-TMS
6b *threo*-12-OH, 11-TMS

(Z)-8

(E)-8

Scheme 1   a. Me$_3$SiLi, THF / HMPA   b. ^{2}H$_2$, (ϕ_3P)$_3$RhBr, C$_6$H$_6$ c. Nafion, Ac$_2$O
        d. KO-t-Bu, THF

This process would not be suitable for regiospecific deuteration because of extensive hydrogen-deuterium scrambling associated with heterogeneous catalysis.[14] Hydrogenation and deuteration of **5a,5b** with tris(triphenylphosphine)-rhodium chloride, and with the somewhat more active tris(triphenylphosphine)-rhodium bromide[15,16], were slower and occasionally less reproducible than those achieved with the platinum catalyst, but the use of relatively large amounts of homogeneous catalyst in carefully degassed benzene permitted conversion of **5a,5b** to **6a,6b**-$^2H_4$ with no detectable deuterium scrambling.

Treatment of tetradeuterated **6a,6b** with Nafion-H and acetic acid/acetic anhydride gave labeled (Z)-pheromone (**Z**)-**8**. To produce the geometric isomer (**E**)-**8**, the **6a,6b** mixture was treated with potassium t-butoxide in THF (overnight, room temperature) to provide (**E**)-**7**. Conversion of TBDMS to acetate with Nafion/acetic anhydride gave (**E**)-**8**. Chemical ionization mass spectrometry demonstrated complete and precise tetradeuteration in each case (no $^2H_3$ or $^2H_5$ components were detected in either (**Z**)-**8** or (**E**)-**8**).[17] Chemical yields were about 80%, and regeneration of the olefins were within experimental error of 100% stereoselectivity.[18]

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10. Mass spectrum of **4** (ei) m/z (%): 147 (15), 141 (6), 133 (12), 131(6), 121 (15), 119 (14), 109 (8), 107 (11), 105 (20), 101 (7), 95 (17), 93 (19), 91 (23), 81 (24), 79 (25), 77 (10), 75 (100), 73 (24), 67 (26),59(15),55(15). ^{1}H-NMR (CDCl$_3$), ∂ 0.05 (6H, s, MeSi); 0.89 (9H. s, t-Bu);1.04, (3H, t, J=5.5, H-14); 1.55,(ca. 12 H, methylene); 2.22 (4H, m, H-4 + H-7); 2.99 (2H, m, H-11 + H-12), 3.62 (2H, t, J=6.25, H-1).

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12. Because of their chromatographic similarity, **5a** and **5b** were not individually characterized beyond their mass spectra. In spite of being positional isomers, **5a** and **5b** produce essentially superimposable mass spectra (presumably elimination of the elements of trimethylsilanol preceeds other fragmentation processes): m/z (%): 189 (20), 147 (51), 135 (10), 133 (16), 107 (12), 95 (29), 93 (16), 91 (12), 81 (23), 79 (15), 75 (100), 73 (80), 69 (12), 67 (24).

13. At least two other procedures have been reported to directly convert TBDMS ethers to acetates: $FeCl_3/Ac_2O$: Ganem, B. and Small, V.R., Jr. *J. Org. Chem.* **1974**, *39*, 3728; $ZnCl_2/AcCl$: Kim, S. and Lee,W.J. *Synth. Commun.* **1986**, *16*, 659. The procedure described here (from several to twenty-four hours at room temperature) appears to be the simplest offered to date. Under the same conditions, a methoxyethoxymethyl (MEM) ether was converted to a mixture of acetate and acetoxymethyl ether, with the latter predominating.

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17. The mass spectra of (*Z*)-**8** and (*E*)-**8** (both electron ionization and chemical ionization) were virtually identical, so only the data for (*E*)-**8** are presented: (ei) m/z (%): 198 (10), 197 (14), 113 (11), 112 (12), 100 (18), 99 (26), 98 (31), 97 (28), 96 (21), 95 (15), 86 (17), 85 (31), 84 (42), 83 (46), 82 (74), 81 (23), 72 (11), 71 (22), 70 (34), 69 (53), 68 (100), 67 (50), 61 (19), 58 (17), 57 (28), 56 (33), 55 (53). Chemical ionization (ammonia): m/z (%): 276 (100), 277 (14), 278 (5), M+ NH_4^+: 293 (70), 294 (13), 295 (10),M+ $N_2H_7^+$.

18. Procedure: Tris(triphenylphosphine)rhodium bromide[15] (31 mg) was suspended in a perforated polypropylene capsule above 2 mL of degassed (argon atmosphere) benzene, and the system was repeatedly evacuated and refilled with deuterium. The flask was suspended in the bath of a sonic cleaner and sonicated five min., after which the catalyst was added. After five additional minutes of sonication, a solution of **5a** and **5b** (22 mg) in benzene (20 μL) was injected, and sonication was continued 1 hr. The solvent was evaporated, and 20% ether in hexane (3.5 mL in several portions) was employed to extract the residue and filter the product through a disposable silica gel extraction cartridge (Baker # 7086). The eluate (**6a** + **6b**)was divided into two roughly equal portions, and each was concentrated with a stream of argon. To one portion was added acetic anhydride (100 μL), acetic acid (50 μL), and six Nafion-H beads (*ca.* 30 mg). After about sixteen hr. at room temperature, solvent was evaporated with a stream of argon and the residue was transferred to a silica gel extraction cartridge with hexane. The cartridge was eluted successively with hexane (2.5 mL), 20% ether in hexane (3 mL), and 50% ether in hexane (3 mL). The 20 % ether eluate contained (*Z*)-**8** (5.6 mg). The remaining 1/2 of the **6a/6b** mixture was allowed to stand overnight in tetrahydrofuran (500 μL) to which potassium t-butoxide (21 mg) had been added. Acetic acid (50 μL) was added, the solvent was concentrated, and pentane (3 x 1 mL) was used to filter off the potassium acetate. The pentane was evporated and the residue was treated with Nafion/acetic anhydride/acetic acid as described above; the 20% ether fraction yielding 5.4 mg of (*E*)-**8**. The combined recoveries of (*Z*)-**8** and (*E*)-**8** represent 80% yield from **5a+5b**; the composition of (*Z*)-**8** was judged by capillary GC to be 98% (*Z*) & 2% (*E*); that of (*E*)-**8** was 99% (*E*) & 1% (*Z*)--these values can be compared to the composition of the starting alcohol 2 which had been assayed at 97% (*Z*) & 3% (*E*).