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A Mild Procedure for Synthesis of the Cytochalasin Isoindolone; Allyl Selenides from Allyl Silanes and $PhSeSe^{+}(CH_3)Ph\ BF_4^{-}$

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Summary. The title reagent converts allyl silanes into the most stable allyl selenides.

This report describes a new electrophilic selenenylating agent which has been developed as part of our program in cytochalasin synthesis.[1,2] We had encountered difficulty in the sulfur ylide mediated transformation of **1** into **3**.[2,3] Under conditions of internal sulfur alkylation ($AgBF_4/CH_3NO_2$;0°) and ylide formation, the allylic chloride **1** gave 52% of the 11-membered carbocycle **3** and 25% of the undesired vinyl cyclopropane **5** resulting from internal allyl silane participation. The sidereaction proved more serious in the case of diastereomer **2**, and reasonable yields of 11-membered carbocycle were not realized until the allylic acetate **7** was used as the substrate. Internal S-alkylation ($AgBF_4$ in toluene) and ylide generation (iPr_2NEt) produced the Z-olefin **8** in 38% yield and not the E-isomer **9** expected by analogy to the reaction of **1**.[3]

The above result is interesting in the context of sulfonium ylide geometry, but it precludes use of the substrate **7** for cytochalasin synthesis because the E-double bond is necessary. On the other hand, the method for electrophilic selenenylation of the allylic silane **1** to give **5** has proved very useful because **5** affords an allylic alcohol **6** via selenoxide rearrangement upon treatment with MCPBA. The stereochemistry corresponds to that observed in the natural cytochalasins according to the characteristic vicinal diaxial coupling constant for the (HO)CH-CH subunit (9.9 Hz)[4] and results from selenoxide 2,3-sigmatropic shift with bonding to the less hindered alkene face.[5]

Selenenylation of **2** to **5** was accomplished in 93% yield using a reagent prepared by reacting PhSeSePh with one equivalent of $Me_3O^{+}BF_4^{-}$ in CH_2Cl_2. The resulting orange solution is assumed to contain $PhSeSe^{+}(CH_3)Ph\ BF_4^{-}$, **10**, and behaves as a source of highly electrophilic

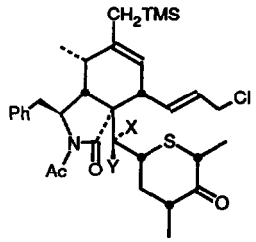
selenium.[6] We do not know whether fluoride availability from the BF_4^- ion is a factor, but the reagent allows facile conversion of allyl silanes into allylic selenides at low temperatures. By comparison, PhSeCl was less reactive and gave product mixtures containing chlorides as well as selenides.[3]

To study the question of reaction intermediates, trimethyl([4-tert-butyl-1-cyclohexenyl]methyl)silane **11**[7] was treated with the reagent **10** at -78 °C. After quenching ($NaHCO_3/H_2O$) and warming to room temperature, the allylic selenide **12** was obtained together with methyl phenyl selenide. The isomeric **13** was not detected in the product mixture. However, this isomer probably could not have survived the reaction and workup conditions. Wittig olefination of 4-tert-butyl-2-phenylselenocyclohexanone afforded a product which had partially equilibrated to a 1:11 mixture of **12** and **13**. Exposure to silica gel, or to a catalytic amount of the reagent **10** resulted in a ≥30:1 ratio of **12**:**13**. Thus, the most highly substituted double bond isomer is strongly favored, and the rearrangement is facile.

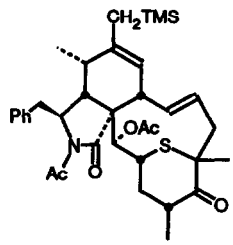
A second example provided further evidence for gamma-selenenylation followed by equilibration to the more stable allylic selenide. Thus, E,E-diene ester **14**[1b] was treated with **10** at -78 °C. After quenching (-78 °C; $H_2O/NaHCO_3$) and warming to room temperature, a mixture of E,Z isomers **15** and **16** was obtained (88% yield). Since the products are stable to the reaction conditions, the formation of E,Z-isomers can be understood if an intermediate **17** is formed which rearranges prior to isolation. So far, the thermodynamically less stable allyl selenide has not been observed directly in any of the examples studied (Table 1), but its intermediacy is likely in all cases based on the above evidence. The issue of fluoride participation in the desilylation step remains open. However, the kinetic preference for the allyl silane over the other double bonds in the above examples is understandable on simple electronic grounds. The double bond of allylic chlorides, ethers or conjugated esters is deactivated relative to the trisubstituted cyclohexene. On the other hand, structures similar to **3** are not suitable substrates. Here, electrophilic selenium attacks the medium ring double bond with internal sulfur participation.

As indicated in Table 1, the new selenenylating agent **10** is effective with a variety of cytochalasin-related allyl silanes. Other examples will be described in papers dealing with total synthesis of cytochalasins, zygosporins, and their analogues.

Acknowledgement. This work was supported by the National Institutes of Health (CA 17918)



1 X= OAc, Y= H
2 X= H, Y= OAc



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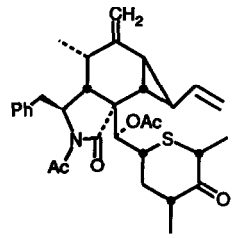

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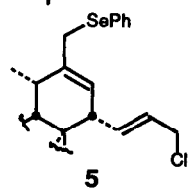
PhSeSe⁺(Me)Ph BF_4^- **10**



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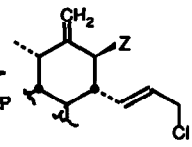
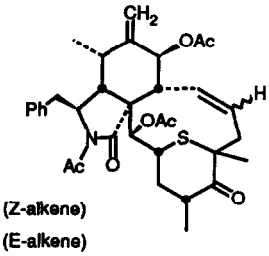
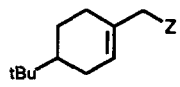
1) MCPBA
2) Ac_2O/DMAP



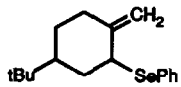
6 Z= OH
7 Z= OAc



8 (Z-alkene)
9 (E-alkene)



11 Z= $SiMe_3$
12 Z= SePh



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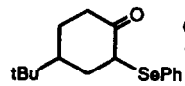
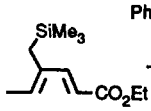


CH_2=PPh_3 **12 + 13**

PhSeSe⁺(Me)Ph BF_4^-



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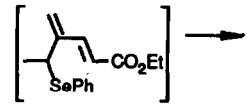

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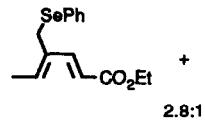

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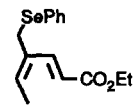

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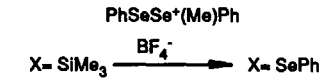
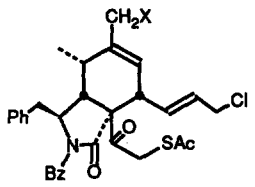
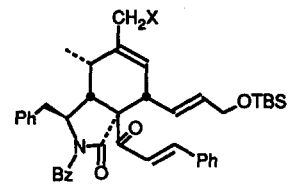
Table 1. Conversion of Allyl Silanes into Selenides.





72 %



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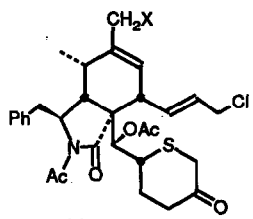
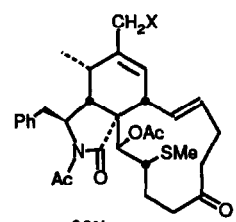


94 %



96%

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1. a) Vedejs, E.; Gadwood, R.C. *J. Org. Chem.* **1978**, *43*, 376; b) Vedejs, E.; Campbell, J.; Gadwood, R.G.; Spear, K.L.; Rodgers, J.D.; Watanabe, Y. *J. Org. Chem.* **1982**, *47*, 1534; c) Vedejs, E.; Arnost, M. J.; Eustache, J. M. *J. Org. Chem.* **1982**, *47*, 4384.

2. Vedejs, E.; Reid, J. G. *J. Am. Chem. Soc.* **1984**, *106*, 4617.

3. Rodgers, J.D., Ph.D. Dissertation, University of Wisconsin, **1985**.

4. J=10 Hz is typical: Binder, M.; Tamm, C. *Helv. Chim. Acta* **1973**, *56*, 966; see also ref. 1b.

5. For the same stereochemical result in a related sulfoxide case, see ref. 1b.

6. For a related electrophilic sulfenylating reagent, see Trost, B. M.; Shibata, T.; Martin, S. J. *J. Am. Chem. Soc.* **1982**, *104*, 3228; Caserio, M.C.; Kim, J. K. *J. Am. Chem. Soc.* **1982**, *104*, 3231.

7. Prepared by coupling the enol phosphonate of 4-tert-butylcyclohexanone with Me_3SiCH_2MgCl in the presence of $Ni(acac)_2$ (ref.8).

8. Hayashi, T.; Katsuro, Y.; Kumada, M. *Tetrahedron Lett.* **1980**, *21*, 3915.

9. Selenide NMR: (Se-C-C=C<u>H</u> & PhSe-C<u>H</u>) **12**, δ 5.41 (1H, m) & 3.49 (2H, br s + d, $J_{Se\text{-}C\text{-}H}$ = 12.7 Hz); **13** cis, δ 5.07 (1H, d, J=1.2 Hz), 4.88 (1H, d, J=1.5 Hz), & 3.87 (1H, m, J_{ax}=13.1 Hz); trans, δ 4.55 (1H, "t", J=2.1 Hz), 4.45 (1H, "t", J=1.8 Hz), & 3.87 (1 H, m); **15**, 6.02 (1H, q, 7.4 Hz) & 3.71 (2 H, br s); **16**, 5.68 (1H, q, J=7.4 Hz), & 3.66 (2H, br s).

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