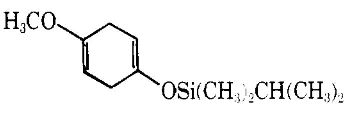
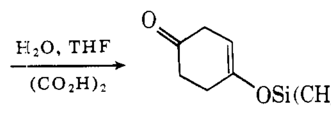


13a



27 (54%)

Acknowledgment. This investigation was supported by Grant Number CA-19689-01, awarded by The National Cancer Institute, DHEW.

References and Notes

(1) This ratio was obtained by NMR analysis of the mixture of oxygen and carbon acetylated products which result from quenching the **2a/4** reaction with acetic anhydride.

(2) (a) S. Murai, Y. Kuroki, K. Hasegawa, and S. Tsutsumi, *J. Chem. Soc., Chem. Commun.*, 946 (1972); (b) K. Narasaka, K. Soai, and T. Mukaiyama, *Chem. Lett.*, 1223 (1974); (c) T. Mukaiyama, K. Banno, and K. Narasaka, *J. Am. Chem. Soc.*, **96,** 7503 (1974); (d) T. Mukaiyama, H. Ishihara, and K. Inomata, *Chem. Lett.*, 527 (1975); (e) *ibid.*, 531 (1975); (f) K. Narasaka, K. Soai, Y. Aikawa, and T. Mukaiyama, *Bull. Chem. Soc. Jpn.*, **49,** 779 (1976); (g) M. Miyashita, T. Yanami, and A. Yoshikoshi, *J. Am. Chem. Soc.*, **98,** 4679 (1976); (h) S. Danishefsky, T. Kitahara, R. McKee, and P. F. Schuda, *ibid.*, **98,** 6715 (1976).

(3) (a) G. Stork and P. F. Hudrlik, *J. Am. Chem. Soc.*, **90,** 4462 (1968); (b) *ibid.*, 4464 (1968); (c) H. O. House, L. J. Czuba, M. Gall, and H. D. Olmstead, *J. Org. Chem.*, **34,** 2324 (1969); (d) G. Stork and J. d'Angelo, *J. Am. Chem. Soc.*, **96,** 7114 (1974); (e) M. E. Jung and C. A. McCombs, *Tetrahedron Lett.*, 2935 (1976), and references contained therein.

(4) I. Kuwajima and E. Nakamura, *J. Am. Chem. Soc.*, **97,** 3257 (1975).

(5) The phenyl silyl ethers were easily prepared (average 94% yield,[7–9] 20 cases) by reaction of the appropriate phenol with either *tert*-butyldimethylchlorosilane[5a] or isopropyldimethylchlorosilane[5b] in DMF with imidazole as catalyst.[5a] (a) E. J. Corey and A. Venkateswarlu, *J. Am. Chem. Soc.*, **94,** 6190 (1972). (b) E. J. Corey and R. K. Varma, *ibid.*, **93,** 7319 (1971).

(6) The following experiment is typical of the procedure employed for the reduction of dimethyl-*tert*-butyl and dimethylisopropylsilyl aryl ethers. A 500-mL three-necked flask is fitted with a mechanical stirrer, dry ice condenser, a Claisen adaptor to allow for the use of a septum for introducing reagents, and a stopcock for introducing ammonia gas. The system is flame dried, flushed with N_2 gas, and, after cooling, 100 mL of THF [distilled from $Na/(C_6H_5)_2CO$] and 15.0 mL of *tert*-butyl alcohol (160 mmol, distilled from sodium) are introduced via a syringe. Ammonia (250 mL, distilled from lithium) is condensed into the flask and 25 cm of lithium–1% sodium wire (0.0423 g/cm, 150 mmol) is added with cooling. After the lithium has dissolved (~10 min) the silyl aryl ether is added (25.0 mmol) and the mixture is maintained at reflux (−33 °C). After 15 min, 7.5 additional mL of *tert*-butyl alcohol (80 mmol) is added to the reaction mixture. After an additional 30 min, the excess lithium is quenched with solid anhydrous NH_4Cl. (Caution! Cooling is necessary at this point to avoid bumping.) When the blue color has been discharged, the reaction mixture is poured carefully into a vigorously stirred mixture of 750 mL of hexane/750 mL of saturated aqueous NH_4Cl. The layers are separated and the aqueous layer is extracted with 300 mL of hexane. The hexane fractions are combined, dried ($MgSO_4$), and evaporated in vacuo. The product is then vacuum distilled. Kugelrohr distillation is usually sufficient. Similarly to the corresponding reductions of alkyl phenyl ethers [W. S. Johnson, B. Bannister, and R. Pappo, *J. Am. Chem. Soc.*, **78,** 6331 (1956); A. L. Wilds and N. A. Nelson, *ibid.*, **75,** 5360 (1953)], the reduction of 1,2,3-trisubstituted isomers **14a,b** requires more forcing conditions. This reduction can be realized by treating the substrate (25 mmol) with 50 cm of lithium–1% sodium wire (250 mmol) in 60 mL of THF/120 mL of NH_3/28 mL of *t*-BuOH (300 mmol) for 2 h at reflux (−33 °C) followed by the usual workup procedure. The dihydroaryl silyl ethers are modestly sensitive to oxidative rearomatization, especially in basic media, and are best kept cold under nitrogen for extended storage.

(7) Yields refer to isolated material of >95% purity.

(8) These compounds have spectral properties (IR, NMR, mass spectra) in accord with their assigned structures.

(9) These compounds exhibit analytical properties (exact mass and/or elemental analysis) in accord with their assigned structures.

(10) A lower boiling co-product (~10%) formed in the reductions of **13a,b** is the silyl enol ether of cyclohexanone. This product is formally derived via reductive cleavage[10a,b] of the conjugated isomer of dienes **13a,b** followed by further reduction. Control experiments suggest that **13b** is not the precursor of the observed reduction product—even with extended reaction times. (a) B. Weinstein and A. H. Fenselau, *J. Org. Chem.*, **29,** 2102 (1964). (b) J. A. Marshall and N. H. Anderson, *ibid.*, **30,** 1292 (1965).

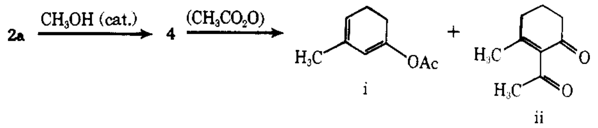
(11) Substantial (35–40%) amounts of an over-reduction product,[10] the silyl enol ether of 2,6-dimethylcyclohexanone, is also produced in this reaction, which is run under more vigorous conditions.[6]

(12) A lower boiling by-product (2–6%), 1,4,5,6,7,8-hexahydronaphthalene, is also produced in this reaction (cf. footnote 10).

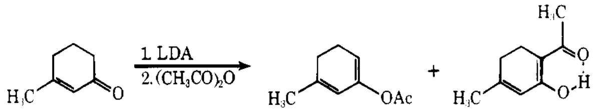
(13) Cleavage of the *tert*-butyldimethylsilyl substrate **7a** with methyllithium was far more sluggish (cf. ref 3a,b).

(14) The endocyclic structure of this enol is assigned on the basis of spectral similarity with previously studied acylcyclohexanones.[14a–c] (a) E. W. Garbisch, Jr., *J. Am. Chem. Soc.*, **87,** 505 (1965). (b) S. Hunig and H. Hoch, *Justus Liebigs Ann. Chem.*, **716,** 68 (1968). (c) H. Sterk, *Monatsh. Chem.*, **100,** 1246 (1969).

(15) Samples of oxygen and carbon acetylated compounds i[8,9] and ii[8,9] were independently prepared via acylation of enolate **4** (obtained by methanol catalized equilibration of enolate **2a**) and were shown to be absent (<1%) from the crude **2a** acetylation reaction as judged by NMR, TLC, and VPC analyses.



(16) Samples of oxygen and carbon acetylated compounds iii[8,9] and iv[8,9,14] were independently prepared from 3-methyl-2-cyclohexen-1-one and were shown to be absent (<1%) from the crude **2a** acetylation reaction as judged by NMR, TLC, and VPC analysis.



(17) Alternate approaches for the direct alkylation of dihydroaryl silyl ethers are currently being evaluated.

(18) Since this reaction is run under relatively neutral conditions, it provides a useful compliment to the standard *acidic* hydrolysis of dihydroaryl alkyl ethers [cf. W. S. Jdhnson, J. A. Marshall, J. F. W. Keana, R. W. Franck, D. G. Martin, and V. J. Bauer, *Tetrahedron Suppl., No. 8,* Part 2, 541 (1966)].

(19) The corresponding hydrolysis of the *tert*-butyldimethyl silyl ethers **7a, 8a,** and **13a** is less satisfactory. The longer required reaction times allow several reactions to become competitive (particularly product isomerization).

(20) Treatment of silyl enol ethers **7b, 8b,** and **13b** (2.0 mmol) with 4.0 mmol of $(n\text{-}C_4H_9)_4N^+F^-$ and 2.0 mmol of H_3BO_3 in 5.0 mL of H_2O/32 mL of THF (homogeneous solution) at 10 °C for 10 min (**7b** requires longer reaction time, 20 min) gives the corresponding ketone. The reaction mixture is then added to a vigorously stirred mixture of 200 mL of H_2O/100 mL of $CHCl_3$ at 5 °C (emulsion removed by filtration). The aqueous layer is extracted with 50 mL of $CHCl_3$. The $CHCl_3$ fractions are combined, washed with 2 × 100 mL of H_2O, dried ($MgSO_4$), and evaporated at 15 mm. The product is vacuum distilled (Kugelrohr, 0.5 mm, 40 °C). In the purification of ketone **23,** temperatures must be kept below 40 °C during evaporation and distillation to prevent double-bond isomerization.

(21) The corresponding isopropyldimethyl silyl ethers **8b,** and **13b** give lower yields owing to competitive hydrolysis of both vinyl ether moieties.

(22) **8a** (5.0 mmol) is treated with a homogeneous solution of $(HO_2C)_2 \cdot 2H_2O$ (65 mmol, 8.2 g) in 20 mL of THF at 30 °C for exactly 10 min (cleavage of **13a** requires 7 min). The reaction mixture is quickly added to 200 mL of hexane/200 mL of 5% Na_2CO_3. (Caution! Foaming may occur.) The aqueous layer is extracted with 100 mL of hexane. The hexane fractions are combined, dried ($MgSO_4$), and evaporated in vacuo. The product is kept under vacuum (0.5 mm) for 4 h to remove *tert*-butyldimethylsilanol and is then distilled.

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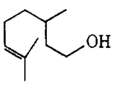
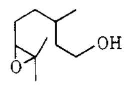
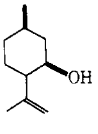
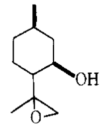
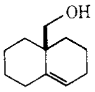
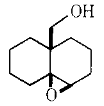
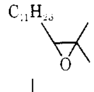
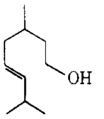
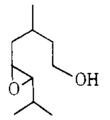
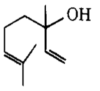
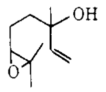
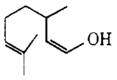
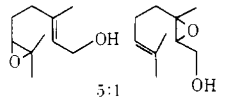
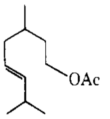
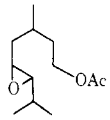
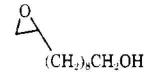
Organoselenium Chemistry. Epoxidation of Olefins with Benzeneseleninic Acid and Hydrogen Peroxide ("Benzeneperoxyseleninic Acid")

Summary: Benzeneseleninic acid and hydrogen peroxide generate in situ "benzeneperoxyseleninic acid" which functions as an epoxidizing agent.

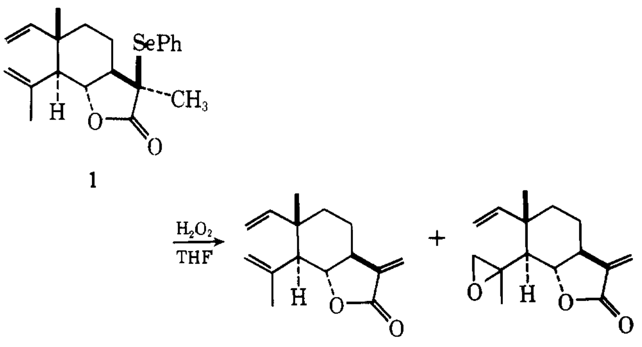
Sir: We have observed the formation of epoxides during the oxidation (50% aqueous hydrogen peroxide) and subsequent elimination of phenylseleno groups adjacent to carbonyls.[1]

Table I. Epoxidation of Olefins with Benzeneperoxyseleninic Acid[a]

Starting olefin	Product	Solvent	PhSeOOH, equiv	Hydrogen peroxide, equiv	Reaction[b] time, min	% yield[c] of epoxide, % recovered starting material
		MeOH THF	1.2 1.2	1.2 1.2	20 20	75 85
		MeOH THF	1.2 1.0	1.2 1.0	20 20	71 81
		MeOH	1.2	1.8	20	75
$CH_3(CH_2)_{10}CH{=}C(CH_3)_2$		THF/MeOH/EtOH	1.2	1.4	45	85
		MeOH	1.2	1.4	20	47 (42)
		MeOH	1.2	1.4	30	63 (8)
		MeOH	1.2	1.4	30	65
		MeOH	1.2	1.4	30	58 (26)
$CH_2{=}CH(CH_2)_8CH_2OH$		MeOH	1.2	1.4	20	35 (48)

[a] All reactions were carried out at pH 7 in phosphate buffered solution. [b] After the indicated time the reaction mixture was treated with silica gel for ~60 min. [c] All compounds were fully characterized by spectral methods. Yields reported are for isolated, chromatographically pure substances.

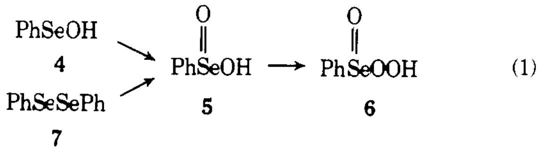
During the elimination of benzeneselenenic acid from the selenoxide derived from treatment of selenide 1 with 8.0 equiv of 50% hydrogen peroxide there was obtained in addition to dehydrosaussurea lactone 2 (18%) a 30% yield of epoxide 3.[2]



1 2 3

On the basis of previous work[3] we had anticipated the smooth conversion of selenide 1 to dehydrosaussurea lactone (2) in high yield. When exactly 2.0 equiv of hydrogen peroxide was employed, no epoxide formation could be detected and a 93% yield of dehydrosaussurea lactone was realized.

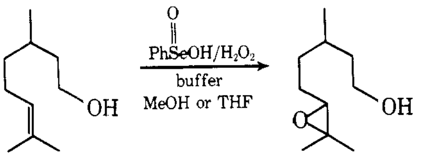
It has previously been established that benzeneselenenic acid (4) produced during the elimination of a selenoxide reacts further with hydrogen peroxide to generate benzeneseleninic acid (5) (eq 1).[4] We now suggest on the basis of the preliminary



$$\begin{array}{l}\underset{4}{PhSeOH} \searrow \\ \underset{7}{PhSeSePh} \nearrow\end{array} \underset{5}{PhSe(=O)OH} \longrightarrow \underset{6}{PhSe(=O)OOH} \qquad (1)$$

results above that benzeneseleninic acid in the presence of hydrogen peroxide generates in situ benzeneperoxyseleninic acid (6) which functions as an epoxidizing agent (vide infra).[5] To our knowledge no prior report on the generation and epoxidizing ability of benzeneperoxyseleninic acid has appeared in the literature.[6,7] Benzeneseleninic acid is commonly prepared by the treatment of diphenyl diselenide (7) with hydrogen peroxide.[8]

We now report that olefins undergo smooth epoxidation in either methanol or tetrahydrofuran using benzeneperoxyseleninic acid readily generated in situ from benzeneseleninic acid and 50% hydrogen peroxide (Table I).[9] The reactions are best carried out in buffered (pH 7, phosphate) solution to avoid diol formation.[10] We have also observed that the rate of the reaction and yield are highly dependent upon the nature of the workup. For example, treatment of citronellol (8) with 1.0 equiv of benzeneseleninic acid and 2.0 equiv of 50% hydrogen peroxide in tetrahydrofuran buffered at pH 7 revealed on TLC analysis after $\sim$20 min the complete conversion of starting olefin to the desired epoxide **9**. NMR analysis of the crude product after workup revealed that $>$90% of the starting olefin remained. If, however, after initial mixing of reagents ($\sim$20 min) one pours the reaction contents onto a silica gel plate (for convenience) and elutes after $\sim$60 min, an 85% yield of pure epoxide **9** can be realized. In buffered methanol solution using 1.2 equiv of benzeneseleninic acid and 1.2 equiv of 50% hydrogen peroxide citronellol gave, using the same silica gel treatment, a 75% isolated yield of pure epoxide.



8 **9**

The stereoselectivity observed in the epoxidation of olefinic alcohols with benzeneperoxyseleninic acid complements that observed in the transition metal catalyzed epoxidations of olefinic alcohols by *tert*-butyl hydroperoxide.[11] Geraniol and linalool are selectively oxidized in the presence of vanadium or molybdenum catalysts by alkyl hydroperoxides to 2,3-epoxygeraniol and 1,2-epoxylinalool, respectively. In contrast, linalool and geraniol were epoxidized with benzeneperoxyseleninic acid predominantly at the olefin furthest removed from the hydroxyl group (see Table I).[12]

The following experimental procedure indicates the simplicity of the method. A solution of benzeneseleninic acid (454 mg, 2.4 mmol) in 4 mL of methanol was treated with 160 μL (2.4 mmol) of 50% hydrogen peroxide. After $\sim$5 min, 1.5 mL of phosphate buffer (pH 7) was added followed by the addition of citronellol (312 mg, 2.0 mmol) in 2 mL of methanol. The reaction was quenched after 20 min with 20 g of silica gel. After 60 min the silica gel was washed with a 1:1 mixture of ether and hexane leaving 302 mg of crude product. Purification on 15 g of silica gel gave 264 mg (75%) of pure epoxide (**9**) as a colorless liquid.

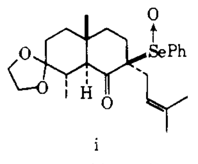
In summary, benzeneperoxyseleninic acid represents a new reagent for the facile, rapid, high yield conversion of substituted olefins into epoxides. The syn-directive effect observed in both the peracid and the transition metal/hydroperoxide epoxidation of allylic alcohols does not appear to play a major role in epoxidation with benzeneperoxyseleninic acid.

Acknowledgment. We thank the National Institutes of Health (CA 13689-05), Glidden Organics, and Shell Development Co. for support of this research. We thank Mr. George Majetich for providing us with a sample of 10-hydroxymethyl-$\Delta^{1,9}$-octalin.

References and Notes

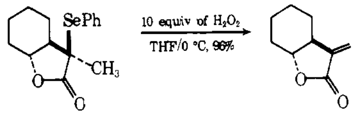
(1) For the use of α-phenylseleno carbonyl compounds as precursors to α,β-unsaturated ketones and esters, see H. J. Reich, I. L. Reich, and J. M. Renga, *J. Am. Chem. Soc.*, **95**, 5813 (1973); K. B. Sharpless, R. F. Lauer, and A. Y. Teranishi, *ibid.*, **95**, 6137 (1973).

(2) During the elimination of benzeneselenenic acid from selenoxide i in the presence of excess hydrogen peroxide we have observed epoxidation of the prenyl double bond.



i

(3) We have previously demonstrated [P. A. Grieco and M. Miyashita, *J. Org. Chem.*, **39**, 120 (1974)] that α-methyl-α-phenylselenolactones undergo oxidation with excess hydrogen peroxide providing after elimination of benzeneselenenic acid near-quantitative yields of α-methylene lactones (cf. ii → iii).



ii iii

(4) K. B. Sharpless and R. F. Lauer, *J. Am. Chem. Soc.*, **95**, 2697 (1973).

(5) $PhSeO_3H$ has been proposed as the active reagent in hydrogen peroxide oxidations of divalent selenium compounds.[6b]

(6) (a) K. B. Sharpless and K. M. Gordon, R. F. Lauer, D. W. Patrick, S. P. Singer, and M. W. Young, *Chem. Scr.*, **8A**, 9 (1975); (b) H. J. Reich, J. M. Renga, and I. L. Reich, *J. Am. Chem. Soc.*, **97**, 5434 (1975); (c) D. L. Klayman and W. H. H. Gunther, "Organic Selenium Compounds: Their Chemistry and Biology", Wiley-Interscience, New York, N.Y., 1973.

(7) Hydrogen peroxide in the presence of selenium dioxide has been reported to hydroxylate olefins [N. Sonoda and S. Tsutsumi, *Bull. Soc. Chem. Jpn.*, **38**, 958 (1965)].

(8) J. D. McCullough and E. S. Gould, *J. Am. Chem. Soc.*, **71**, 674 (1949).

(9) Use of diphenyl diselenide in place of benzeneseleninic acid during epoxidation of citronellol in tetrahydrofuran with excess hydrogen peroxide gave a 69% yield of epoxide **9**.

(10) The epoxidation reaction appears to be catalytic with respect to benzeneseleninic acid; however, the reaction requires very long reaction times during which diol formation predominates.

(11) K. B. Sharpless and R. C. Michaelson, *J. Am. Chem. Soc.*, **95**, 6136 (1973).

(12) Epoxidation of geraniol and linalool with standard peracids (e.g., *m*-chloroperbenzoic acid) results in poor selectivity.

(13) Fellow of the Alfred P. Sloan Foundation.

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Sydney Gilman, Mugio Nishizawa
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Received February 8, 1977

Stereocontrolled Synthesis of the Ecdysone Side Chain via Organopalladium Chemistry

Summary: Two stereocontrolled syntheses of (22*R*)-25-dihydroxycholesterol and one of the 22*S* isomer from 6β-methoxy-3,5-cycloandrostan-17-one are reported.

Sir: The ability to introduce a cholesterol-type side chain with stereochemical control continues as a major challenge that has been heightened by the importance of natural products containing modified side chains.[1–5] Most noteworthy are the hydroxylated side chains that appear in the ecdysones[2,3] and the metabolites of vitamin D.[4,5] We wish to report the stereocontrolled synthesis of (22*R*)-25- and (22*S*)-25-dihydroxycholesterol which, by known procedures,[3] could be converted into the insect molting hormones. This approach demonstrates the use of the palladium-based alkylations for control of acyclic stereochemistry,[6] the versatility of the α-sulfonyl esters, and the introduction of a vinyl group at an allylic carbon with control of stereochemistry at that carbon.

The key intermediate is the sulfone ester 4 available from 6β-methoxy-3,5-cycloandrostan-17-one (1),[7,8] mp 65–66 °C, as outlined in Scheme I. Condensations with ethylidenetriphenylphosphorane followed by epoxidation gave **2**,[8] mp 97–98 °C. Treatment with 10 equiv of lithium diisopropylamide in 4:1 hexane–DME initially at −78 °C and subsequently warming to room temperature gave in 77% isolated yield the desired allylic alcohol **3a**, oil, $[\alpha]^{25}_{D}$ +38.4° ($CHCl_3$, *c* 0.742).[9] Addition of a solution of methyl phenylsulfonylisodioacetate in THF to a solution of **3b**[8] and 9 mol % tetrakis(triphenylphosphine)palladium in THF at room temperature and subsequent reflux led to an 85% yield of **4**,[8] mp 166–167