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Synthesis of a Cytotoxic Vernolepin Prototype. Ozonization of Silyloxyalkenes[1]

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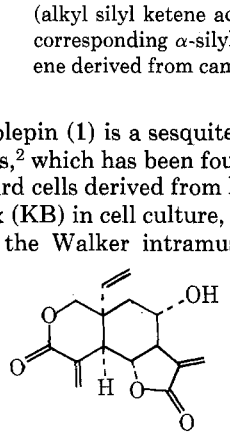
Received December 1, 1975

Regiospecific silyloxyalkene formation, followed by ozonization, has been used in two syntheses of α-methylene-δ-lactone **2**, a prototype of vernolepin, a sesquiterpene lactone possessing antitumor and cytotoxic properties. Compound **2** has been found to have moderate in vitro toxicity toward cells derived from human carcinoma of the nasopharynx (KB) in cell culture. Silyloxyalkenes react rapidly with ozone in methanol at −78 °C to give carboxylic acids. The silyloxyalkene double bond is sufficiently reactive that it may be selectively ozonized in the presence of certain normal double bonds. Since silyloxyalkenes may often be generated regiospecifically, the reaction constitutes an effective method for the regiospecific cleavage of ketones. Silyloxyalkenes derived from esters (alkyl silyl ketene acetals) give mixtures of the cleavage product (one-carbon degradation of the ester) and the corresponding α-silyloxy ester. This "abnormal" mode of oxidation is also observed for the hindered silyloxyalkene derived from camphor.

Vernolepin (**1**) is a sesquiterpene bislactone of the elemane class,[2] which has been found to show in vitro cytotoxicity toward cells derived from human carcinoma of the nasopharynx (KB) in cell culture, and in vivo antitumor activity against the Walker intramuscular carcinosarcoma 256.[3,4]



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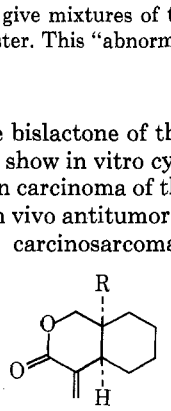
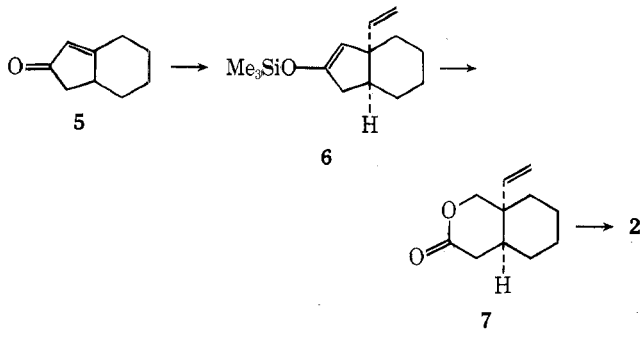


2, R = CH=CH$_2$
3, R = CH$_3$
4, R = CH$_2$CH$_3$

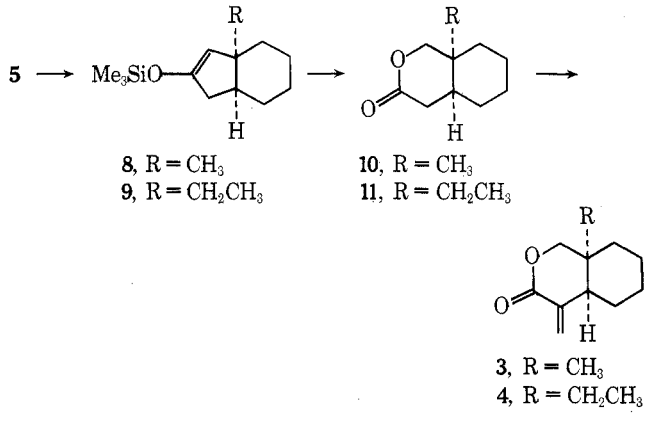
As a part of a general project aimed at the total synthesis of sesquiterpene antitumor lactones, we have developed two efficient synthetic routes to **2**, a prototype of vernolepin which contains only one of the two α-methylene lactone functions. One of the routes has also been utilized to synthesize vernolepin analogues **3** and **4**.

A key step in both synthetic routes involves ozonization of a silyloxyalkene. We have carried out a brief study of the scope of this new reaction. In this paper we report the results of these studies. Since we embarked upon this project, several other syntheses of lactone **2** have been reported.[5–8]

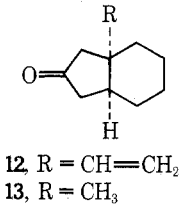
Lithium divinylcuprate is added to enone **5**[9] at −75 °C in dimethyl sulfide–THF, and the resulting reaction mixture is worked up by the addition of trimethylsilyl chloride, HMPT, and triethylamine.[10] Silyloxydiene **6** is obtained in 75% yield. Selective ozonization of the silyloxyalkene linkage in **6** proceeds at −75 °C without incident. After reduction of the intermediate methoxy hydroperoxide with sodium borohydride, the reaction mixture is acidified and worked up to obtain lactone **7** in 93% yield. Grieco's two-stage procedure was used to introduce the α-methylene group (**7** → **2**).[5,11] One advantage of this process for constructing the vernolepin A ring is that analogues may be prepared in which the angular vinyl group is replaced by other groups. Since Kupchan has shown that dihydrovernolepin retains the cytotoxic and antitumor properties of



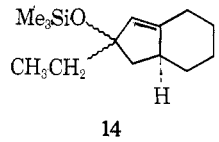
the parent,[4] such analogues may show physiological activity (vide infra). For example, we have prepared analogues **3** and **4** by similar procedures.



The procedure we have developed for the angular vinylation (**5** → **6**) is convenient and furnishes the 1,4 adduct in high yield, uncontaminated by the 1,2 adduct. We initially utilized Corey's procedure (vinyllithium and cuprous iodide in diisopropyl sulfide–THF).[12] However, the use of the volatile dimethyl sulfide as the solubilizing ligand for cuprous iodide in formation of the cuprate results in a much more convenient work-up procedure. House and coworkers have also discovered the efficacy of dimethyl sulfide in this context, and have introduced the use of the crystalline Me_2S–CuBr and Me_2S–CuI complexes as precursors for generation of cuprates.[13] A recent synthesis of the vinyl hydrindanone **12**, in which the vinyl group is introduced by a cuprate addition utilizing tributylphosphine as ligand, provided the material in poor yield.[14,15] A major disadvantage of the method is the current unavailability of good quality vinyllithium.[17]



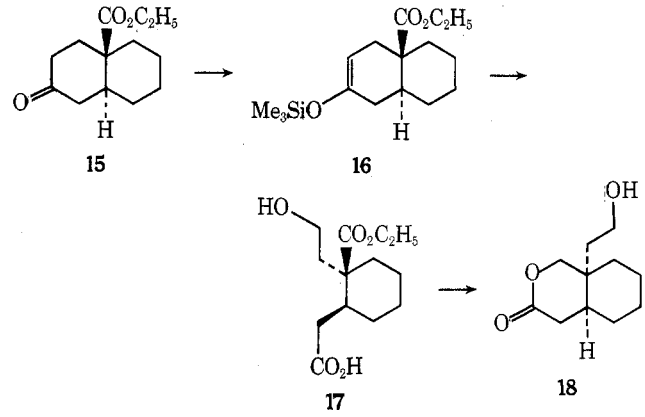
Compound **8** was prepared by the addition of lithium dimethylcuprate to enone **5** in ether at 0 °C; again, only the 1,4 adduct was produced. The ethyl derivative **9** was prepared by the copper-catalyzed addition of ethylmagnesium bromide in THF.[18] In this case, the desired 1,4 adduct was accompanied by about 30% of the 1,2 adduct **14**.



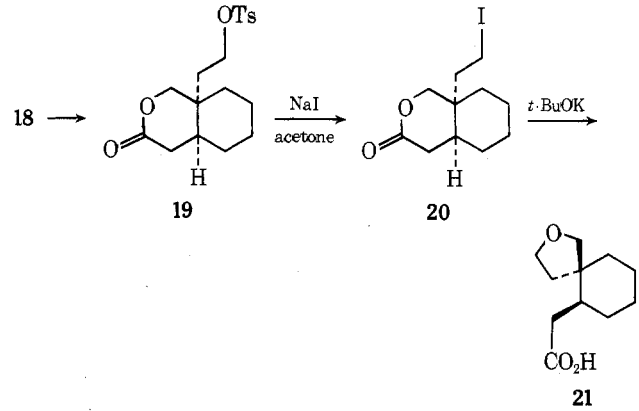
Compounds **6**, **8**, and **9** were produced in only one stereoisomeric form. On the basis of analogy,[12] the cis ring junction may be assumed. This assumption was confirmed in the case of compound **8** when it was hydrolyzed to the known[19] *cis*-8-methylhydrindanone (**13**).

Ozonization of silyloxydiene **6** is highly selective, as shown by the excellent yield of lactone **7** (93%). When the amount of ozone used is carefully monitored, we find no evidence of attack at the angular vinyl group. Since silyloxyalkenes may be regiospecifically generated in several ways,[10,20] this reaction constitutes a useful method for the regiospecific cleavage of a ketone.

We have employed the silyloxyalkene ozonization in an alternate synthesis of lactone **2**. Keto ester **15** reacts with trimethylsilyl chloride and triethylamine in DMF[20] to give silyloxyalkene **16** in 92% yield.[21] Ozonolysis of **16** at −70 °C in 1:1 methanol–methylene chloride, followed by sodium borohydride reduction, gives hydroxy acid **17**. Reduction of **17** with sodium in ethanol–ammonia, followed by acidic work-up, affords lactone **18** in 73% overall yield.

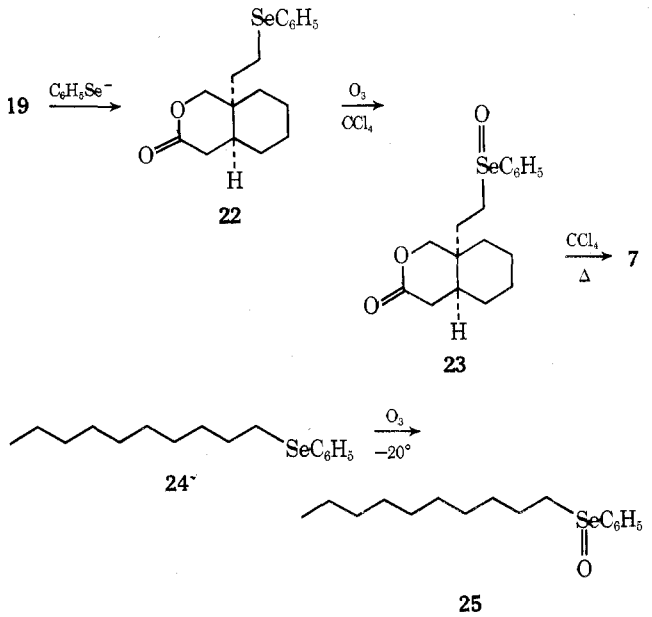


Conventional methods for conversion of the hydroxyethyl side chain to a vinyl group, such as elimination of iodide **20** with DBN or pyridine, gave no recognizable products. Attempted elimination with potassium *tert*-butoxide leads to acid **21**, presumably via a ketene intermediate.

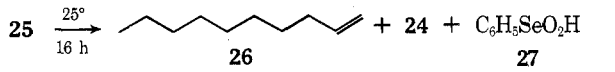


This problem was solved by conversion of tosylate **19** into phenyl selenide **22**, which is oxidized to selenoxide **23** by ozone in CCl_4 at −20 °C. When a cold solution of crude selenoxide **23** is added to refluxing CCl_4,[22] elimination is rapid, and vinyl lactone **7** is obtained in 60% overall yield from tosylate **19**.

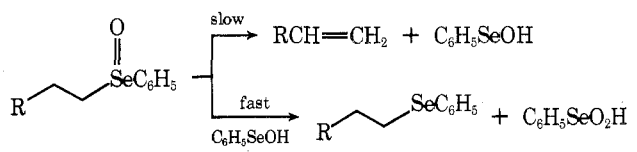
The mode in which selenoxide **23** is thermolyzed is important. If thermolysis is carried out by heating a CCl_4 solution of **23** from room temperature to reflux, a mixture of **7** and selenide **22** results. This phenomenon was explored briefly with phenyl 1-decylselenoxide (**25**), which was pre-



pared by the ozone oxidation of selenide **24** in CCl_4 or CH_2Cl_2 at −20 °C. When these oxidation mixtures are evaporated, selenoxide **25** is produced in quantitative yield. In contrast to secondary alkyl selenoxides, primary alkyl selenoxides such as **25** are relatively stable at room temperature. However, after sitting overnight at room temperature, a CCl_4 solution of **25** is converted into an equimolar mixture of 1-decene and selenide **24**; an equivalent amount of crystalline phenylselenic acid (**27**) separates from solution. Apparently, with primary alkyl selenoxides, thermoly-



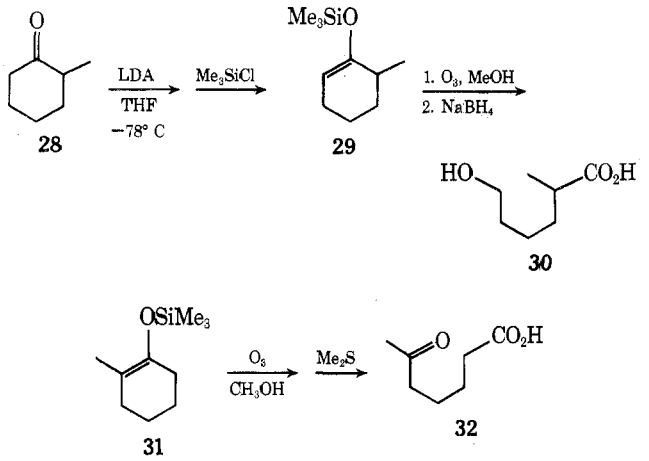
sis to alkene is slow, and the phenylseleninic acid produced rapidly reduces unreacted selenoxide back to selenide.



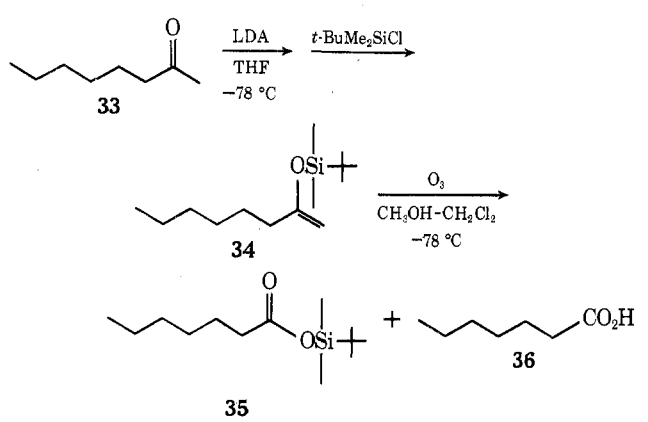
While we were investigating this phenomenon, we became aware of Reich's method for circumventing the problem,[22] which serves admirably. The disproportionation has also been observed by Sharpless[23] and by Grieco,[8,24] who introduced the idea of using nitrophenyl selenoxides, which decompose at much lower temperatures than do phenyl selenoxides.

Lactone **2** shows moderate in vitro toxicity in the KB cell culture screen (ED_{50} = 4.4–15 $\mu g\ ml^{-1}$),[25,26] For comparison, vernolepin (**1**) has ED_{50} = 1.8 $\mu g\ ml^{-1}$ in this screen.[4] In vivo results on lactone **2** have not yet been obtained. Lactone **3** is ineffective toward the L-1210 lymphoid leukemia (in vivo) at dose levels of 10 and 20 mg/kg. The compound is toxic (zero of six survivors) at doses of 400, 200, 100, and 40 mg/kg.

The silyloxyalkene ozonization reaction seemed sufficiently interesting to warrant a brief survey of its scope. Silyloxyalkene **29**, obtained by silylation of the kinetic enolate of 2-methylcyclohexanone (**28**),[10] was converted into hydroxy acid **30** in 94% yield. To further demonstrate the generality of the method, silyloxyalkene **31**[10] was cleaved. In this case, the initial oxidation product was reduced with dimethyl sulfide to produce keto acid **32** in 90% yield. To

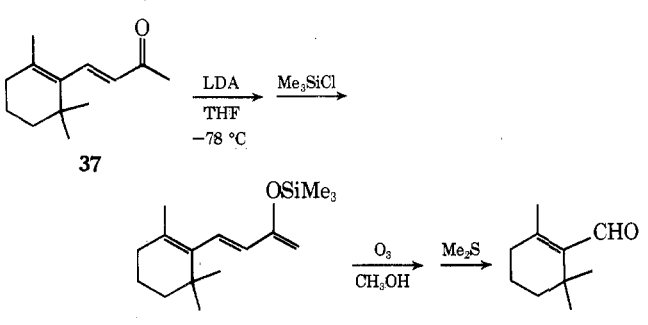


provide a further example of the regiospecific cleavage of an unsymmetrical ketone *away from the more highly alkylated side*, we oxidized 2-octanone (**33**) to heptanoic acid (**36**). In this case, we formed the silyloxyalkene from the ki-



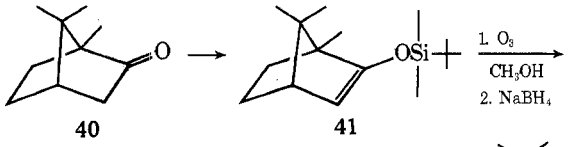
netic enolate[27] with *tert*-butyldimethylsilyl chloride.[29] Upon work-up, *tert*-butyldimethylsilyl ester **35** and heptanoic acid are obtained in a 4:1 ratio in a total yield of 90%. Since the *tert*-butyldimethylsilyloxy grouping is more stable to nucleophilic cleavage than the trimethylsilyloxy grouping,[29] it is necessary to hydrolyze the reaction product with mild acid to obtain acid **36**. Undoubtedly, use of trimethylsilyl chloride would provide heptanoic acid directly.

The trimethylsilyloxytriene **38** obtained in 82% yield from β-ionone (**37**) reacted anomalously. Even though only 1 equiv was used, oxidation occurred cleanly at the center double bond (which would appear to be the *least nucleophilic* of the three), giving β-cyclocitral (**39**) in good yield. From a preparative point of view, conversion of β-ionone to the silyl ether **38** is not necessary, since we found that selective ozonolysis of β-ionone itself gives **39** in good yield.

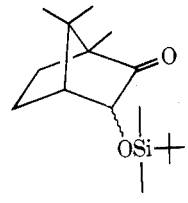


The silyloxyalkene **40** produced from camphor also gave an anomalous (and different) oxidation product; α-trial-

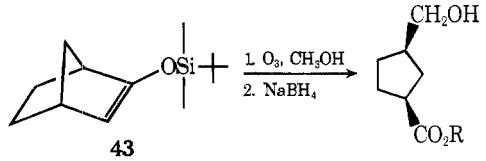
kylsilyloxy camphor **42** was produced in quantitative yield.[30] However, the analogous silyl ether prepared from norbornanone (**43**) reacted normally, giving hydroxy acid **44** as the only product.



40 **41**



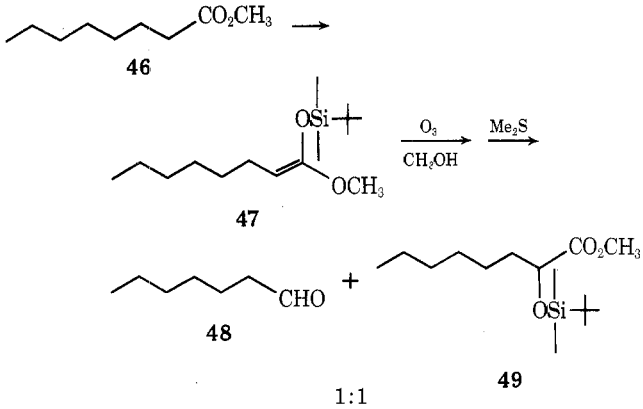
42



43

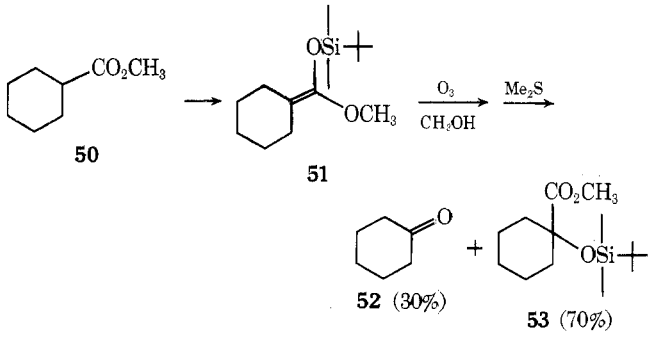
44, R = H
45, R = CH_3

Silyloxyalkenes derived from ester enolates[31] (trialkylsilyloxy alkyl ketene acetals) give mixture of the normal ozonization product (representing one-carbon degradation of the ester) and the α-trialkylsilyloxy ester. Thus, methyl octanoate is converted, via ketene acetal **47**, into an equimolar mixture of heptanal (**48**) and methyl α-(*tert*-butyldimethylsilyloxy)octanoate (**49**). Similar results are obtained with methyl cyclohexanecarboxylate.



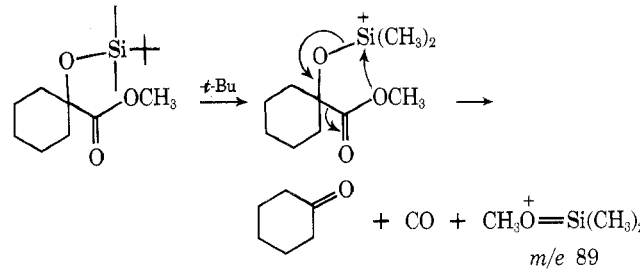
46 **47** **48** **49**

1:1

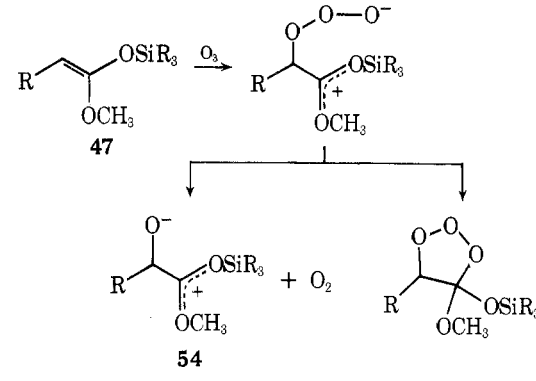


50 **51** **52** (30%) **53** (70%)

Both of the abnormal ozonization products **49** and **53** display a base peak in the mass spectrum at *m/e* 89 which corresponds to the fragment $[(CH_3)_2Si{=}OCH_3]^+$. This fragment probably arises from rearrangement of the initially formed ion as shown below.

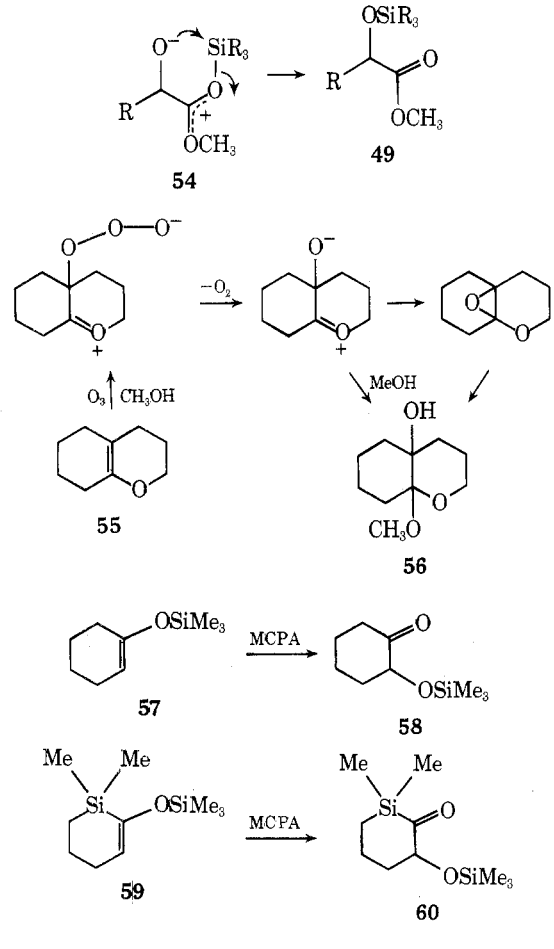


A reasonable mechanistic hypothesis which explains the anomalous oxidation of silyloxyalkenes **42**, **47**, and **51** involves formation of an intermediate zwitterion rather than a molozonide in the ozonization reaction. This might be expected to occur with an alkene which can give exceptional stabilization to the positive charge, such as **32** or **36**. Intramolecular silatropy in **54** would then yield the observed α-trialkylsilyloxy ester. Borowitz has found that ozonization



47 **54**

of certain enol ethers also gives products which might be produced via a similar zwitterion (**55** → **56**).[32] Subsequent



54 **49** **55** **56**

57 **58** **59** **60**

to our initial discovery of this unusual oxidation of silyloxyalkenes, similar reactions of silyloxyalkenes with peracids were observed by others (**57** → **58**,[33] **59** → **60**[34]).

Experimental Section

All melting and boiling points are uncorrected. Nuclear magnetic resonance (NMR) spectra were determined on a Varian T-60 spectrometer (in δ units with tetramethylsilane as internal reference). Infrared (ir) spectra were recorded on a Perkin-Elmer 137 infrared spectrophotometer. Mass spectra (MS) were obtained on a MS-12 mass spectrometer. Mass spectra are given as *m/e* with the relative intensity in parentheses. Preparative and analytical gas–liquid chromatography (GLC) was carried out on an Aerograph Model A90-P3 gas chromatograph, using the following stainless steel (10 ft × 0.25 in.) columns: column A, 5% SE-30; column B, 15% NPGS; column C, 15% SF-96. Microanalyses were performed by the University of California Microanalytical Laboratory, Berkeley, Calif.

3aβ-Ethenyl-2-trimethylsilyloxy-3a,4,5,6,7,7aβ-hexahydroindene (6). Vinyllithium (12.5 ml of a 2.4 M solution in THF, 30 mmol) was added to a suspension of purified copper(I) iodide[35] (3.30 g, 17.4 mmol) in ether (10 ml) and dimethyl sulfide (5 ml) at −75 °C. The black mixture was stirred for an additional 45 min at −75 °C, followed by the dropwise addition of enone **5** (1.36 g, 10 mmol) in ether (10 ml). The solution was stirred for 45 min at −75 °C and 15 min at −40 °C. The −40 °C solution was treated with HMPT (2 ml), triethylamine (3 ml), and trimethylchlorosilane (3 ml), then allowed to warm to room temperature over 1 h. After dilution with pentane (120 ml), the mixture was poured into cold 5% hydrochloric acid and the pentane layer was washed with 5% hydrochloric acid, water, and brine. The pentane was dried and evaporated and the residue distilled to give 1.75 g (74.2%) of silyl ether **6**: bp 70–75 °C (0.3 mm); ir (film) 6.12, 8.00, 11.56, 11.76 μ; NMR (CCl_4) δ 0.18 (s, 9 H), 1.2–1.6 (m, 9 H), 2.10 (m, 2 H), 4.40 (t, 1 H), 4.73–5.13 (BC portion of ABC, J_{AB} = 18, J_{AC} = 10, J_{BC} = 2 Hz, 2 H), 5.87 (A portion of ABC, 1 H); MS *m/e* 236 (40), 221 (14), 194 (23), 193 (100), 181 (18), 147 (18), 75 (21), 73 (66).

Anal. Calcd for $C_{14}H_{24}OSi$: C, 71.14; H, 10.02. Found: C, 70.96; H, 10.09.

8aβ-Ethenyl-4aβ-octahydro-3*H*-2-benzopyran-3-one (7). Ozone (2.42 mmol) from a Welsbach generator was passed into a −78 °C solution of silyl ether **6** (572 mg, 2.42 mmol) in methanol (10 ml) and methylene chloride (2 ml). The −78 °C solution was treated with sodium borohydride (320 mg, 8.46 mmol) over a 90-min period. After warming to room temperature, the mixture was evaporated and partitioned between 10% hydrochloric acid and ether. The ether was dried and evaporated to 402 mg (93%) of lactone **7** as a thick oil which slowly crystallized. An analytical sample was obtained by preparative GLC (column A, 200 °C): mp 44–46 °C (lit.[5,8] mp 44–45 °C; ir (film) 5.78, 6.10, 8.40, 9.43, 10.80 μ; NMR (CCl_4) δ 2.17, 2.62 (AB portion of ABX, J_{AB} = 18, J_{AX} = 7, J_{BX} = 5 Hz, 2 H), 4.13 (AB, Δν = 14.7 Hz, *J* = 11 Hz), 5.00–5.98 (eight-line ABC pattern, 3 H); MS *m/e* 180 (1), 150 (20), 108 (100), 93 (47), 79 (59), 78 (12), 77 (14).

Anal. Calcd for $C_{11}H_{16}O_2$: C, 73.33; H, 8.89. Found: C, 73.13; H, 8.87.

8aβ-Ethenyl-4-methylene-4aβ-octahydro-3*H*-2-benzopyran-3-one (2). This material was prepared in 40% yield from **7** according to the previously described procedure of Grieco,[11] and had spectral data in complete accord with that reported:[5,8] ir (film) 5.83, 6.10, 6.19, 8.00, 8.77, 9.61 μ; NMR (CCl_4) δ 2.53 (broad t, 1 H), 4.12 (AB, Δν = 24.6 Hz, *J* = 11 Hz, 2 H), 5.00–5.98 (eight-line ABC pattern, 3 H), 5.50 (t, *J* = 1 Hz, 1 H), 6.36 (t, *J* = 1 Hz, 1 H).

3aβ-Ethenyl-7aβ-hexahydroinden-2(1*H*)-one (12). Hydrolysis of silyl ether **6** with 5% hydrochloric acid gave the vinylated hydrindenone **12**, a colorless oil: ir (film) 3.14, 5.71, 6.10, 6.90, 7.14, 10.98 μ; NMR (CCl_4) δ 1.55 (broad s, 9 H), 2.15 (s, 4 H), 5.03 (dd, B portion of ABC, J_{AB} = 18, J_{BC} = 2 Hz, 1 H), 5.08 (dd, C portion of ABC, J_{BC} = 2, J_{AC} = 10 Hz, 1 H), 5.93 (six-line complex A portion of ABC, 1 H).

Anal. Calcd for $C_{11}H_{16}O$: C, 80.44; H, 9.82. Found: C, 80.35; H, 9.77.

3aβ-Methyl-2-trimethylsilyloxy-3a,4,5,6,7,7aβ-hexahydroindene (8). A solution of lithium dimethylcuprate was prepared from 3.02 g (16 mmol) of copper(I) iodide in ether (30 ml) and 18.2 ml of 1.6 M ethereal methyllithium at 0 °C. The colorless solution was cooled to −20 °C, and enone **5** (1.36 g, 10 mmol) in ether (25 ml) was added. The resulting bright yellow mixture was stirred for an additional 45 min at −20 °C, followed by the addition of HMPT (2.0 ml), triethylamine (3.5 ml), and trimethylchlorosilane (3.0 ml). After 3 h at room temperature the mixture was diluted with pentane and poured into cold 5% hydrochloric acid. The mixture was filtered through Celite and the pentane layer was washed with brine, dried, and evaporated to 2.24 g (96%) of silyl ether **8**, of suitable purity for the next conversion: ir (film) 6.10, 8.00 μ; NMR (CCl_4) δ 0.18 (s, 9 H), 0.94 (s, 3 H), 2.10 (m, 2 H), 4.40 (t, *J* = 1 Hz, 1 H).

8aβ-Methyl-4aβ-octahydro-3*H*-2-benzopyran-3-one (10). Ozonolysis of silyl ether **8** (2.0 g, 8.8 mmol) according to the procedure described for the preparation of **7** gave 1.05 g (70%) of lactone **10** after distillation: bp 105 °C (0.5 mm); ir (film) 5.78, 8.33, 9.43 μ; NMR (CCl_4) δ 1.07 (s, 3 H), 2.19 (dd, A portion of ABX, J_{AB} = 18, J_{AX} = 5 Hz, 1 H), 2.63 (dd, B portion of ABX, J_{BX} = 7 Hz, 1 H), 4.00 (AB, Δν = 27.5 Hz, *J* = 12 Hz, 2 H); MS *m/e* 150 (4), 96 (40), 81 (67), 79 (24), 68 (29), 67 (61), 41 (100).

Anal. Calcd for $C_{10}H_{16}O_2$: C, 71.39; H, 9.59. Found: C, 71.06; H, 9.50.

8aβ-Methyl-4-methylene-4aβ-octahydro-3*H*-2-benzopyran-3-one (3). Methylenation according to Grieco's procedure[11] gave **3** in 45% yield after distillation: bp 115 °C (0.3 mm); ir (film) 5.80, 7.19, 7.81, 8.70 μ; NMR (CCl_4) δ 1.05 (s, 3 H), 2.13 (m, 1 H), 4.03 (AB, Δν = 39.5 Hz, *J* = 11 Hz, 2 H), 5.43 (t, *J* = 1 Hz, 1 H), 6.33 (t, *J* = 1 Hz, 1 H); MS *m/e* 180 (4), 136 (24), 108 (41), 107 (100), 93 (80), 91 (40), 81 (65), 79 (91), 77 (41).

Anal. Calcd for $C_{11}H_{16}O_2$: C, 73.33; H, 8.89. Found: c, 73.03; H, 8.74.

3aβ-Methyl-7aβ-hexahydroinden-2(1*H*)-one (13). Hydrolysis of silyl ether **8** by stirring in 10% hydrochloric acid, followed by ether extraction, gave the crystalline ketone **13**: mp 38–39 °C (lit.[19b] mp 37–39 °C); ir (CCl_4) 5.73, 6.93, 7.13, 7.28, 7.98 μ; NMR (CCl_4) δ 1.13 (s, 3 H), 1.47 (broad s, 8 H), 2.00–2.40 (m, 5 H).

Anal. Calcd for $C_{10}H_{16}O$: C, 78.90; H, 10.59. Found: C, 78.78; H, 10.70.

8aβ-Ethyl-4-methylene-4aβ-octahydro-3*H*-2-benzopyran-3-one (4). A solution of ethylmagnesium bromide (100 mmol) in ether (100 ml) was cooled to 0 °C and copper(I) iodide (1.90 g, 10 mmol) was added. Enone **5** (6.80 g, 50 mmol) in ether (25 ml) was added dropwise to the black solution over a 25-min period. After an additional 30 min at 0 °C, the mixture was treated with HMPT (10 ml), triethylamine (10.1 g, 100 mmol), and trimethylchlorosilane (10.8 g, 100 mmol). The solution was stirred for 1 h, then diluted with pentane and washed with 5% hydrochloric acid and brine. The pentane was dried and evaporated to a colorless oil which was a 70:30 mixture of **9** and **14** by NMR analysis: ir (film) 6.10 μ; NMR (CCl_4) δ 4.40 (s, silyl ether vinyl, 1 H), 5.18 (s, 1,2 adduct vinyl, 1 H).

This material was ozonized in methanol–methylene chloride (1:1, 100 ml) at −70 °C and then treated with sodium borohydride (3.4 g). After solvent evaporation, the residue was taken into water and washed with methylene chloride. Acidification of the aqueous layer and methylene chloride extraction gave a colorless oil which was distilled to give 3.85 g (42.5% overall) of lactone **11**: bp 125 °C (1 mm); ir (film) 5.80 μ; NMR ($CDCl_3$) δ 0.87 (t, *J* = 7 Hz, 3 H), 2.46 (eight-line portion of ABX, 2 H), 4.10 (AB, Δν = 26.1 Hz, *J* = 12 Hz, 2 H).

Methylenation[11] of this material gave **4** in 38% yield after distillation (oven 100 °C, 5 μ): ir (film) 5.80, 7.18, 7.80, 8.70 μ; NMR ($CDCl_3$) δ 0.83 (t, *J* = 7 Hz, 3 H), 2.35 (m, 1 H), 4.25 (AB, Δν = 36.1 Hz, *J* = 12 Hz, 2 H), 5.56 (s, 1 H), 6.45 (s, 1 H); MS *m/e* 194 (3), 165 (14), 135 (50), 121 (62), 107 (66), 93 (60), 81 (68), 79 (83), 67 (69), 41 (100).

Anal. Calcd for $C_{12}H_{18}O_2$: C, 74.19; H, 9.34. Found: C, 74.16; H, 9.40.

4aβ-Ethoxycarbonyl-2-trimethylsilyloxy-1,4,4a,5,6,7,8,8aα-octahydronaphthalene (16). A solution of keto ester **15**[36] (55.0 g, 246 mmol) in DMF (100 ml) and triethylamine (82.6 ml) was treated with trimethylchlorosilane (38.1 ml), and the resulting slurry was refluxed for 20 h. The cooled mixture was diluted with pentane (300 ml) and washed with cold 5% sodium bicarbonate and water. The pentane was dried and evaporated and the residue was distilled to give 66.3 g (90.8%) of silyl ether **16**: bp 120 °C (2.0 mm); ir (film) 5.76, 6.01, 8.00, 8.40, 10.98 μ; NMR (CCl_4) δ 0.18 (s, 9 H), 1.26 (t, *J* = 7 Hz, 3 H), 4.10 (quartet, 2 H), 4.66 (m, 1 H); MS M^+ *m/e* 296 (9), 223 (56, M − CO_2Et), 222 (68), 75 (49).

8aβ-(2-Hydroxyethyl)-4aβ-octahydro-3*H*-2-benzopyran-3-one (18). A solution of silyl ether **16** (3.41 g, 11.5 mmol) in methanol (10 ml) and methylene chloride (10 ml) at −70 °C was treated with excess ozone. After purging with nitrogen, the cold solution was treated with sodium borohydride (0.5 g, 13 mmol) and allowed

to warm to room temperature. Extractive work-up gave 2.95 g (99.3%) of crude hydroxy acid **17**, ir (film) 2.8–4.3, 5.80 μ.

This material was dissolved in THF (10 ml) and added to a solution of ethanol (5 ml) and liquid ammonia (100 ml).[37] Small pieces of sodium were added until a blue color persisted, and the mixture was then quenched by addition of methanol. The ammonia was allowed to evaporate and the residue was taken into water and washed with ether. Acidification and extraction with methylene chloride gave 1.68 g (73.6% overall) of **18** as a colorless oil: ir (film) 2.90, 5.75, 6.90, 7.91, 9.51 μ; NMR ($CDCl_3$) δ 1.72 (t, J = 6 Hz, CH_2CH_2OH, 2 H), 2.26 (dd, A portion of ABX, J_{AB} = 18, J_{AX} = 4 Hz, 1 H), 2.80 (dd, B portion of ABX, J_{BX} = 7 Hz), 3.43 (s, hydroxyl H, 1 H), 3.73 (t, J = 6 Hz, 2 H), 4.23 (AB, $\Delta\nu$ = 20.7 Hz, J = 11 Hz, 2 H); MS *m/e* 198 (8), 180 (2), 144 (17), 108 (100), 95 (39), 74 (36), 58 (35).

Anal. Calcd for $C_{11}H_{18}O_3$: 198.1256. Found: 198.1293.

8aβ-(2-*p*-Toluenesulfonyloxyethyl)-4aβ-octahydro-3*H*-2-benzopyran-3-one (19). A mixture of alcohol **18** (460 mg, 2.32 mmol) and *p*-toluenesulfonyl chloride (572 mg, 3.00 mmol) in pyridine (5 ml) was maintained at 0 °C for 16 h. The solution was poured into water and extracted with ether to give 651 mg (80%) of tosylate **19** as a thick oil: ir (film) 5.75; 6.25; 7.41; 8.40, 9.51; 10.5 μ; NMR ($CDCl_3$) δ 1.82 (t, J = 6 Hz, 2 H), 2.23–2.76 (AB portion of ABX, J_{AB} = 18, J_{AX} = 4, J_{BX} = 7 Hz, 2 H), 2.46 (s, 3 H), 4.13 (t, J = 6 Hz, 2 H), 4.16 (AB, $\Delta\nu$ = 28.2 Hz, J = 11 Hz, 2 H).

2*c*-(2-Oxa-(5rC^1)-spiro[4.5]decanyl)acetic Acid[38] (21). The tosylate **19** (443 mg, 1.26 mmol) was refluxed overnight in acetone (20 ml) with sodium iodide (1.50 g) to give 389 mg (100%) of iodide **20** as a thick, colorless oil: NMR (CCl_4) δ 3.16 (t, J = 7 Hz, 2 H), 4.10 (AB, $\Delta\nu$ = 20.8 Hz, J = 12 Hz, 2 H).

A solution of iodide **20** (74 mg, 0.24 mmol) in *tert*-butyl alcohol (1 ml) was treated with 0.6 ml of 0.44 M potassium *tert*-butoxide in *tert*-butyl alcohol. A white solid separated immediately from the reaction mixture. After 1 h at room temperature, the solution was poured into 5% hydrochloric acid and extracted with ether to give 45.0 mg of acid **21**: ir (film) 2.80–4.00, 5.80, 8.56, 9.51 μ; NMR (CCl_4) δ 2.00–2.42 (m, 2 H), 3.46 (AB, $\Delta\nu$ = 16.7 Hz, J = 9 Hz, CH_2–OCH_2CH_2, 2 H), 3.73 (t, J = 6 Hz, OCH_2CH_2, 2 H).

Esterification of **21** with diazomethane gave a methyl ester: ir (film) 5.73, 8.00, 8.50, 9.52 μ; NMR (CCl_4) δ 2.00–2.40 (m, 2 H), 3.53 (AB, $\Delta\nu$ = 13.4 Hz, J = 9 Hz, 2 H), 3.67 (s, 3 H), 3.76 (t, J = 6 Hz, 2 H); MS *m/e* 181 (19, loss of OCH_3), 152 (38), 109 (43), 108 (70), 107 (30), 93 (70), 79 (81), 74 (44), 67 (69), 55 (61), 41 (100).

8aβ-Ethenyl-4aβ-octahydro-3*H*-2-benzopyran-3-one (7). Diphenyl diselenide (1.08 g, 3.47 mmol) in ethanol (25 ml) was treated with sodium borohydride (0.26 g, 6.94 mmol) in small portions until the solution was colorless. The solution was cooled in an ice bath, and tosylate **19** in THF (8 ml) was added. The mixture was stirred at room temperature for 4 h and then poured into 5% sodium carbonate and extracted with ether to give 2.08 g (98%) of crude selenide **22**: ir (film) 5.75, 6.31, 6.80, 8.55 μ; NMR ($CDCl_3$) δ 3.78 (t, J = 6 Hz, CH_2SePh, 2 H).

The crude selenide **22** (10.28 mmol) was ozonized at −20 °C in carbon tetrachloride (30 ml) with excess ozone until the solution was light blue. The cold solution, from which a white solid had precipitated, was then added over a 10-min period to 100 ml of refluxing carbon tetrachloride, using a small volume of methylene chloride to transfer the solid. Evaporation of solvents left a yellow oil which was chromatographed on 100 g of silica gel. Elution with pentane gave fractions containing diphenyl diselenide. Further elution with ether gave 1.12 g (60.5% from **19**) of crystalline lactone **7**, identical with that previously prepared in our laboratory.

Ozonization of Silyl Ether 29. A solution of silyloxyalkene **29**[10] (5.48 g, 29.8 mmol) in methylene chloride (5 ml) and methanol (20 ml) was treated with excess ozone at −70 °C. After nitrogen purge, the −70 °C solution was treated with sodium borohydride (1.13 g, 29.8 mmol). After stirring at −70 °C for 1 h, a second portion of sodium borohydride was added and the solution was allowed to warm to room temperature. The solvent was evaporated and the residue was partitioned between 5% hydrochloric acid and chloroform. The aqueous layer was extracted with chloroform, and the combined organic layers were dried and evaporated to 4.10 g (94.3%) of hydroxy acid **30**.

Esterification of this product (methanol–sulfuric acid) gave 3.50 g (73.5%) of methyl 6-hydroxy-2-methylhexanoate after distillation: bp 80 °C (1.0 mm); ir (film) 2.94, 5.75, 8.40, 8.62 μ; NMR (CCl_4) δ 1.13 (d, 3 H), 2.33 (m, 1 H), 2.98 (s, hydroxyl H, 1 H), 3.50 (t, 2 H), 3.64 (s, 3 H).

Anal. Calcd for $C_8H_{16}O_3$: C, 59.98; H, 10.07. Found: C, 60.01; H, 10.03.

Ozonization of Silyl Ether 31. Silyloxyalkene **31**[10] (1.0 g, 5.42 mmol) in methanol (10 ml) and methylene chloride (8 ml) was ozonized at −70 °C and then treated with dimethyl sulfide (1.0 ml) and allowed to warm to room temperature. Evaporation gave a mixture of dimethyl sulfoxide and keto acid **32** (>90% yield).

Esterification of this mixture with diazomethane and extractive work-up gave 602 mg (71.5%) of methyl 6-oxoheptanoate: ir (film) 5.75, 5.83, 7.40, 8.62 μ; NMR (CCl_4) δ 2.03 (s, 3 H), 2.10–2.50 (m, 4 H), 3.60 (s, 3 H).

Anal. Calcd for $C_8H_{14}O_3$: C, 60.74; H, 8.92. Found: C, 60.68; H, 9.14.

2-*tert*-Butyldimethylsilyloxy-1-octene (34). A solution of 2-octanone **33** (2.56 g, 20 mmol) in THF (7 ml) was added dropwise to a −70 °C solution of lithium diisopropylamide (24 mmol) in THF (20 ml). After stirring for 45 min at −70 °C, the solution was treated with HMPT (3 ml) and *tert*-butyldimethylsilyl chloride (3.30 g, 22 mmol) in pentane (5 ml). After warming to room temperature the mixture was diluted with pentane, washed with water, dried, and evaporated. Distillation gave **34** (2.60 g, 54%) as a colorless liquid which was pure by NMR and GLC (column B, 150 °C) analysis: bp 50 °C (0.3 mm); ir (film) 6.01, 6.12, 8.00, 9.09, 9.70, 11.97 μ; NMR (CCl_4) δ 0.17 (s, 6 H), 0.97 (s, 9 H), 2.00 (broad t, 2 H), 3.90 (sharp s, 2 H).

Anal. Calcd for $C_{14}H_{30}OSi$: C, 69.42; H, 12.44. Found: C, 69.36; H, 12.54.

Ozonization of Silyloxyalkene 34. A solution of **34** (2.37 g, 9.8 mmol) in 10 ml of methylene chloride and 20 ml of methanol was treated with excess ozone at −78°. Dimethyl sulfide (2 ml) was added and the solution was allowed to warm to room temperature. The solvent was evaporated and the residue was taken into ether and esterified with diazomethane to give 1.96 g of colorless oil. This was shown by NMR and GLC analysis (column B) to be an 80:20 mixture of silyloxy ester **35** and methyl heptanoate. Ester **35** was obtained by preparative GLC: ir (film) 5.80, 8.00, 8.47, 9.09, 11.23, 11.76 μ; NMR (CCl_4) δ 0.20 (s, 6 H), 0.90 (s, 9 H), 2.15 (t, J = 6 Hz, 2 H); MS *m/e* 229 (2), 187 (83), 131 (22), 87 (16), 75 (100), 73 (70), 60 (85). The methyl heptanoate was identical with an authentic sample by NMR and GLC comparison.

The following silyl enol ethers were prepared under conditions analogous to those described for the preparation of **34**.

Trimethylsilyl Ether from β-Ionone (38) (82.0% yield): ir (film) 6.12, 6.31, 7.66, 8.00, 9.80, 10.31 , 12.00 μ; NMR (CCl_4) δ 0.23 (s, 9 H), 1.07 (s, 6 H), 1.73 (s, 3 H), 2.00 (t, 2 H), 4.23 (s, 2 H), 5.77 (d, J = 11 Hz, 1 H), 6.33 (d, J = 11 Hz, 1 H).

***tert*-Butylmethylsilyl Ether from Camphor (41)** (90% yield): ir (film) 6.18, 6.85, 7.58, 8.20, 8.81, 9.98, 10.90 μ; NMR (CCl_4) δ 0.18 (s, 6 H), 0.73 (s, 3 H), 0.90 (s, 6 H), 0.98 (s, 9 H), 4.50 (d, J = 3 Hz, 1 H).

***tert*-Butyldimethylsilyl Ether from Norbornanone (43)** (95% yield): ir (film) 6.20, 6.85, 7.53, 8.15, 10.81 μ; NMR (CCl_4) δ 0.17 (s, 6 H), 0.98 (s, 9 H), 4.63 (d, J = 3 Hz, 1 H).

1-*tert*-Butyldimethylsilyloxy-1-methoxy-1-octene (47) (~95% yield): ir (film) 5.95, 6.83, 8.00, 8.60, 11.90 μ; NMR (CCl_4) δ 0.16 (s, 6 H), 0.98 (s, 9 H), 1.80 (broad t, 2 H), 3.46 (s, 3 H), 3.56 (m, 1 H).

Ketene Acetal 51 (>95% yield): ir (film) 5.90, 8.01, 8.60, 9.42, 10.58 μ; NMR (CCl_4) δ 0.12 (s, 6 H), 0.98 (s, 9 H), 3.43 (s, 3 H).

Ozonization of Silyl Ether 38. Silyl ether **38** (1.0 g, 3.8 mmol) was ozonized according to the procedure described for the ozonolysis of **34** (3.8 mmol of ozone). Evaporation of solvent and extractive work-up gave 503 mg (87%) of β-cyclocitral **39** which was pure by NMR and GLC analysis (column B): ir (film) 3.57, 5.97, 6.19, 7.30, 7.40 μ; NMR (CCl_4) δ 1.18 (s, 6 H), 2.08 (s, 3 H), 10.10 (s, 1 H).

Anal. Calcd for $C_{10}H_{16}O$: C, 78.90; H, 10.59. Found: C, 78.67; H, 10.77.

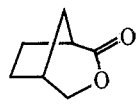
Ozonization of Silyl Ether 41. Silyl ether **41** was ozonized and worked up according to the procedure described for the ozonolysis of **6**. A colorless oil (2.44 g) was obtained which displayed two overlapping peaks on GLC at retention times 9.1 and 10.2 min (column B, 160 °C). The pure mixture of epimers **42** was obtained by preparative GLC: ir (film) 5.71, 8.00, 8.47, 10.52 μ; NMR (CCl_4) δ 0.13 (s, 6 H), 0.97 (s, 9 H), 0.90–1.0 (three overlapping singlets, 9 H), 1.3–1.9 (m, 5 H), 3.57–3.93 (m, $-CHOSiR_3$, two epimers, 1 H); MS *m/e* 267 (2), 225 (79), 171 (35), 169 (49), 115 (26), 75 (51), 73 (100).

Anal. Calcd for $C_{16}H_{30}O_2Si$: C, 68.08; H, 10.64. Found: C, 68.22; H, 10.57.

Ozonization of Silyl Ether 43. Ozonolysis of **43** (11.2 g, 50 mmol), followed by sodium borohydride reduction, gave 7.1 g of crude hydroxy acid **44**, which was esterified with diazomethane.

Distillation gave 3.95 g (50%) of hydroxy ester **45**: bp 100 °C (1.0 mm); ir (film) 2.90, 5.78, 8.35, 8.60 μ; NMR (CCl_4) δ 3.66 (d, J = 6 Hz, 2 H), 3.76 (s, 3 H).

Compound **45** lactonized on GLC (column C, 190 °C) to give **61**. An analytical sample of lactone **61** was obtained by preparative



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GLC (column C): ir (film) 5.74, 8.10, 9.30, 9.70 μ; NMR ($CDCl_3$) δ 4.16 (eight-line ABX, J_{AB} = 11, J_{AX} = 3, J_{BX} = 0.5 Hz, CH_2OCO, 2 H).

Anal. Calcd for $C_7H_{10}O_2$: 126.0701. Found: 126.0691.

Ozonization of 47. Ozonolysis of **47** (4.60 g, 15 mmol) with dimethyl sulfide reduction gave 3.21 g of colorless oil after extractive work-up to remove dimethyl sulfoxide. NMR and GLC analysis (column B, 170 °C) showed a 1:1 mixture of heptanal (by comparison with an authentic sample) and ester **49**. Compound **49** was obtained by preparative GLC: ir (film) 5.73, 8.01, 8.77, 11.00 μ; NMR (CCl_4) δ 0.12 (s, 6 H), 0.95 (s, 9 H), 3.67 (s, 3 H), 4.08 [broad t, $-CH(OSiR_3)CO_2Me$]; MS *m/e* 273 (3), 231 (83), 203 (23), 97 (32), 89 (100), 75 (34), 73 (73).

Ozonization of 51. Ozonolysis of compound **51** (1.28 g, 5 mmol) with dimethyl sulfide reduction gave a mixture of dimethyl sulfoxide, cyclohexanone **52**, and ester **53** after solvent evaporation. The ratio of **52** to **53** was 30:70 by NMR analysis. Compound **53** was obtained by preparative GLC (column B, 190 °C): ir (film) 5.73, 8.00. 8.70, 9.21 μ; NMR (CCl_4) δ 0.12 (s, 6 H), 0.95 (s, 9 H), 1.40–1.80 (m, 10 H), 3.70 (s, 3 H); MS *m/e* 257 (3), 215 (86), 213 (40), 187 (78), 89 (100), 75 (53), 73 (81).

Anal. Calcd for $C_{14}H_{28}O_3Si$: C, 61.76; H, 10.29. Found: C, 61.76; H, 10.18.

Acknowledgment. We thank the National Institutes of Health for financial support under grant CA-12617.

Registry No.—**2,** 42391-68-4; **3,** 53883-18-4; **4,** 58240-78-1; **5,** 39163-29-6; **6,** 53883-15-1; **7,** 42391-78-6; **8,** 53883-16-2; **9,** 58240-79-2; **10,** 53883-17-3; **11,** 58240-80-5; **12,** 58240-81-6; **13,** 13351-29-6; **14,** 58240-82-7; **15,** 1209-32-1; **16,** 58240-83-8; **17,** 58240-84-9; **18,** 58240-85-0; **19,** 58240-86-1; **20,** 58240-87-2; **21,** 58240-88-3; **22,** 58240-89-4; **29,** 19980-33-7; **31,** 19980-35-9; **33,** 111-13-7; **34,** 54251-60-4; **35,** 54251-63-7; **38,** 35156-36-6; **39,** 432-25-7; **41,** 54251-61-5; *exo*-**42,** 58240-90-7; *endo*-**42,** 58240-91-8; **43,** 58240-92-9; **45,** 58240-93-0; **47,** 54326-35-1; **49,** 54251-65-9; **51,** 54251-62-6; **53,** 54326-36-2; **61,** 766-71-2; trimethylchlorosilane, 75-77-4; *p*-toluenesulfonyl chloride, 98-59-9; 2*c*-(2-oxa-(5*rC*^{1})-spiro[4.5]decanyl)acetic acid methyl ester, 58240-94-1; diphenyl diselenide, 1666-13-3; methyl 6-hydroxy-2-methylhexanoate, 58240-95-2; methyl 6-oxoheptanoate, 2046-21-1; *tert*-butyldimethylsilyl chloride, 18162-48-6.

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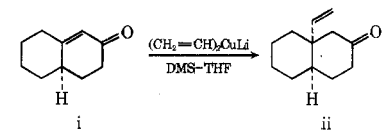
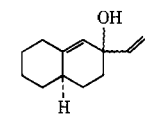
(14) A further demonstration of the utility of this procedure is provided by the conversion of octalone i to the *cis*-9-vinyl-2-decalone ii, uncontaminated by 1,2 adduct, in 90% yield.[16]



i ii

Copper-catalyzed addition of vinylmagnesium bromide to octalone i gives decalone ii and the 1,2 adduct iii in a ratio of 4:1.



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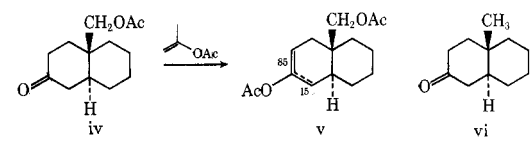
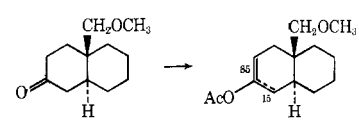
(21) Compound **15** gives only the $\Delta^{2,3}$ isomer upon enol acetylation or enol trimethylsilylation. We found that iv, on the other hand, gave ca. 15% of the $\Delta^{3,4}$ isomer. Compound vi also gives ca. 15% of the $\Delta^{3,4}$ enol acetate (D. Hart, private communication).



iv v vi

Grieco has obtained a similar mixture with compound vii.[8]



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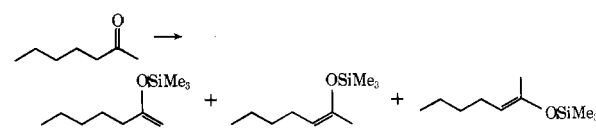
(26) Note that compound **2** is racemic. If the reasonable assumption is made that only one enantiomer is cytotoxic, then its ED_{50} would be 2.2–7.5 μg ml^{-1}. We are currently preparing resolved samples of lactone **2** in order to test this assumption.
(27) The *tert*-butyldimethylsilyloxyalkene **34** is the sole product of this reaction. Neither of the isomeric 2-alkenes can be detected by GLC or ^{1}H NMR. This result is in contrast to the results of House and co-workers,[28] who formed the kinetic enolate from 2-heptanone with lithium diisopropylamide in 1,2-dimethoxyethane. Upon quenching with trimethylsilyl chloride, silyloxyalkenes ix, x, and xi were produced in a ratio of 84:7:9.



ix x xi

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Carbon–Phosphorus Heterocycles. A One-Step Synthesis of Phosphindolines and Phosphinolines. Cyclization of Diphenylalkenylphosphine Oxides with Polyphosphoric Acid[1]

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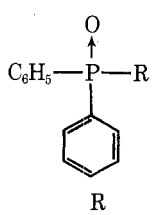
Received September 18, 1975

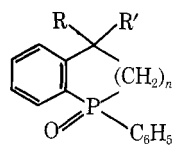
A convenient method of wide scope for the synthesis of phosphindoline and phosphinoline derivatives has been developed from the readily available starting materials. Cyclization of diphenylalkenylphosphine oxides occurred in the presence of 115% polyphosphoric acid (PPA) at 180 °C for 4 h to give C–P heterocyclic systems in modest to good yield (40–70%). Work-up of the reaction mixtures simply involved addition to ice–water. The resulting homogeneous solution was extracted with chloroform and dried; the solvent was evaporated under reduced pressure to yield the respective phosphindoline or phosphinoline. ^{1}H NMR, ^{31}P NMR, elemental, infrared, and mass spectral analyses supported the structure of these phosphorus analogues of the corresponding indole and tetrahydroquinoline heterocycles. This method of synthesis of phosphindoline and phosphinoline offers not only the merit of being simple and inexpensive but also a one-step and rapid process from appropriately substituted alkenyl (aryl) phosphine oxides.

In our studies directed toward the development of simple, new synthetic methods for the production of carbon–phosphorus heterocyclic compounds, we have investigated the possibility of cyclization of diphenylalkenylphosphine oxides in the presence of 115% polyphosphoric acid (PPA) as cyclizing agent. At present, reported pathways leading to the synthesis of phosphindoline or phosphinoline systems involve cyclization by intramolecular quaternization[3,4] and cyclization by cycloaddition of trivalent phosphorus compounds with a diene or diyne derivative.[5–7] Both methods usually employ very uncommon starting materials and long overall reaction times. The rare intermediates needed for the synthesis also limit their versatility. The ready availability of diphenylalkenylphosphine oxides **1a–g** encouraged us to investigate the possibility of their cyclization in the presence of PPA as the cyclizing agent. Certain oxides of **1** possess the correct functionality and geometry for cyclizations to give the corresponding phosphindoline and/or phosphinoline **2**. 3-Methyl-1-phenylphosphindoline 1-oxide (**2a**), which has been prepared from *o*-bromobenzoic acid through a long series of reactions (12 steps),[8] can be synthesized by the cyclization of diphenylallylphosphine oxide (**1a**) with PPA in one step.



R

	R
1a	$CH_2CH{=}CH_2$
b	$CH_2CH{=}CHCH_3$
c	$CH_2CH_2CH{=}CH_2$
d	$CH_2C(CH_3){=}CH_2$
e	$CH_2CH{=}C(CH_3)_2$
f	$CH(CH_3)CH{=}CH_2$
g	$CH(C_6H_5)CH{=}CH_2$



	R	R′	*n*
2a	H	CH_3	1
b	H	CH_3	2
c	CH_3	CH_3	1
d	CH_3	CH_3	2

Diphenylallylphosphine oxide can be obtained from chlorodiphenylphosphine and allyl alcohol in the presence of pyridine without the isolation of allyl diphenylphosphinite (**3**). The latter can be converted into oxide **1a** by heating

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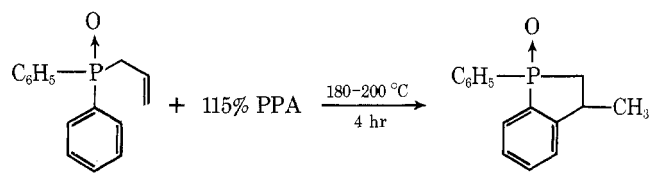
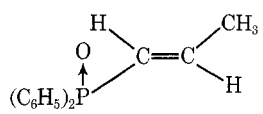
in situ at 140 °C.[9,10] In the presence of 115% PPA[11] at 180–200 °C for 4 h, the phosphine oxide **1a** underwent ring closure to 3-methyl-1-phenylphosphindoline 1-oxide (**2a**) in moderate yield (37%) along with a polymer. After 4 h,



1a **2a**

the reaction mixture was slowly poured into ice–water with stirring to give a homogeneous solution. Normal work-up gave a viscous yellow oil, which on distillation yielded pure **2a**. Oxide **2a** could be crystallized only with difficulty. In our attempts to optimize the reaction conditions, decreasing the reaction temperature to 120–150 °C gave the starting material *trans*-propenyldiphenylphosphine oxide[12] (**4**) and a polymeric product.



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Interestingly, the phosphine oxides **1b** and **1c** also underwent ring closure to produce 1,2,3,4-tetrahydro-4-methyl-1-phenylphosphinoline 1-oxide (**2b**). Tentatively, one could assume that protonation had occurred at the β carbon in **1b** and at the δ carbon in **1c** to create a secondary cation. The second step could reasonably involve an elec-