Stereochemical Control in Cyclofunctionalization of Olefinic Alcohols and Olefinic Phenols with Benzeneselenenyl Chloride

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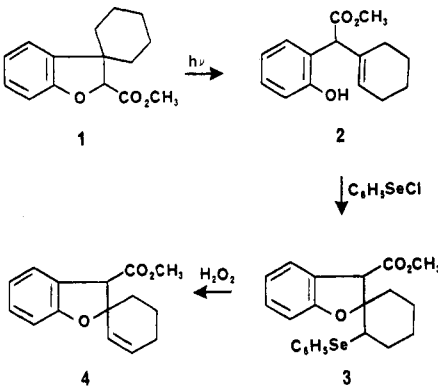
Olefinic alcohols **8a–c** are prepared from condensations of the lithium enolate derived from γ-butyrolactone (**5**) with cyclohexanone, 4-methylcyclohexanone, and 4,4-dimethylcyclohexanone to give lactonic alcohols **6a–c**, followed by dehydration with phosphorous pentoxide and Celite to give cyclohexenes **7a–c** and lactone saponification and esterification with diazomethane; dehydration of **6b** gives **7b** as an equimolar mixture of two diastereoisomers, which requires that olefinic alcohol **8b** also is a mixture of two diastereoisomers. Cyclofunctionalization of **8a** with benzeneselenenyl chloride gives a single spirocyclic selenide **9** by a transition state, **17**, in which the phenylselenenyl group is oriented anti to the carbomethoxy group rather than a transition state, **16**, involving participation by the neighboring carbomethoxy group. The structure of **9** is determined by both chemical interconversions and NMR spectroscopy. One diastereoisomer of olefinic alcohol **8b** gives the spirocyclic selenide **20** in analogy with the conversion **8a** → **9**. The other diastereoisomer fails to give selenide **21** because of severe 1,3-diaxial interactions in the transition state for cyclofunctionalization and does not give selenide **22** because of steric interactions between the phenylselenenyl group and the syn-oriented carbomethoxy group. Instead, cyclization occurs to give the fused ring selenide **23**, again from a transition state in which the phenylselenenyl group is oriented anti to the carbomethoxy group. Olefinic alcohol **8c** gives selenides **28** (51%) and **29** (4%). In the absence of 1,3-diaxial interactions in the transition state for cyclofunctionalization, olefinic phenols of type **3** lead to spirocyclic benzodihydrofurans with the phenylselenenyl group disposed anti to the carbomethoxy group. In the presence of 1,3-diaxial interactions, spirocyclization can occur to give a syn-oriented carbomethoxy selenide; e.g., **32** → **33**.

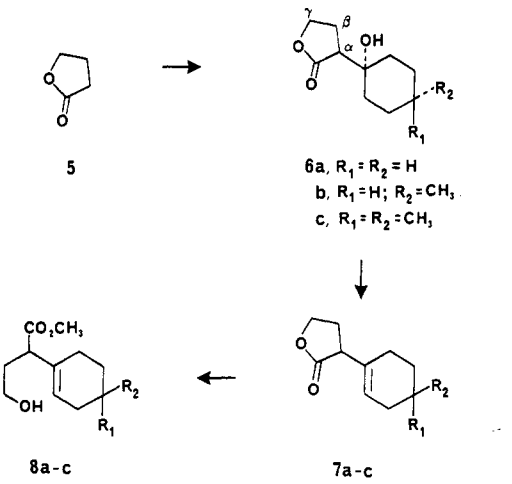
In a recent analysis of the stereochemistry of photorearrangement of benzodihydrofuran **1** to olefinic phenol **2**, we converted **2** to selenide **3** for purposes of structural characterization.[1] A modification of the *o*-alkenylphenol



cyclofunctionalization procedure described by Clive and co-workers was used.[2] Thus, reaction of **2** with benzeneselenenyl chloride in methylene chloride at −78 °C produced a single diastereoisomer of selenide **3**. The high degree of diastereoselectivity in the conversion of **2** into **3** was confirmed by the oxidative elimination of **3** to a single olefin **4** in 94% isolated yield.

At the time, it was not necessary to establish the relative configuration of **3**; however, we were intrigued by the high degree of stereoselectivity apparently resulting from the influence of the carbomethoxy group. Inasmuch as there does not appear to be a recorded analysis of the effect of neighboring carbalkoxy groups on the stereoselectivity of cyclofunctionalizations and because further application (e.g., **30** → **31** and **32** → **33**)[3] of this process required an understanding of the stereochemical control, we initiated a study of the stereoselectivity of cyclizations of related olefinic alcohols; e.g., **8a–c**. Herein, we report the details of this study.

Scheme I



Results and Discussion

Olefinic alcohols **8a–c** are prepared as outlined in Scheme I. Condensations of the lithium enolate derived from γ-butyrolactone (**5**)[4] with cyclohexanone, 4-methylcyclohexanone, and 4,4-dimethylcyclohexanone give lactonic alcohols **6a–c** in 93–98% isolated yields. The stereoselectivity of addition of the enolate of **5** to 4-methyl-

(1) Schultz, A. G.; Napier, J. J.; Lee, R. *J. Org. Chem.* **1979**, *44*, 663. For additional details, see: Napier, J. J. Ph.D. Thesis, Cornell University, 1981.

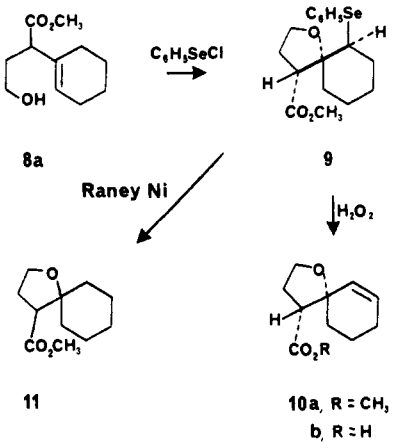
(2) Clive, D. L. J.; Chittattu, G.; Curtis, N. J.; Kiel, W. A.; Wong, C. K. *J. Chem. Soc., Chem. Commun.* **1977**, 725. For related work, see: Nicolaou, K. C.; Lysenko, Z. *Tetrahedron Lett.* **1977**, 1257. Clive, D. L. J.; Chittattu, G. *J. Chem. Soc., Chem. Commun.* **1977**, 484. Nicolaou, K. C.; Sertz, S. P.; Sipio, W. J.; Blount, J. F. *J. Am. Chem. Soc.* **1979**, *101*, 3884. Ley, S. V.; Lygo, B. *Tetrahedron Lett.* **1982**, *23*, 4625. For an excellent review of modern organoselenium chemistry, see: Clive, D. L. J. *Tetrahedron* **1978**, *34*, 1049.

(3) Schultz, A. G.; Napier, J. J.; Sundararaman, P., *J. Am. Chem. Soc.*, in press.

(4) (a) Kuwajima, I.; Minami, N.; Sato, T. *Tetrahedron Lett.* **1976**, 2253. (b) For earlier studies of the reactivity of the enolate of γ-butyrolactone, see: Herrmann, J. L.; Schlessinger, R. H. *J. Chem. Soc., Chem. Commun.* **1973**, 711. Grieco, P. A.; Pogonowski, C. S.; Burke, S. *J. Org. Chem.* **1975**, *40*, 542.

0022-3263/84/1949-2455$01.50/0

Scheme II



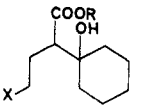
cyclohexanone is remarkable in that only one diastereoisomer (mp 102 °C) is obtained. Stereochemistry in **6b** is assigned on the basis of the well-established preference for equatorial attack by carbanions on 4-substituted cyclohexanones.[5] Exceptional stereochemical control may be a result of reversible addition[6] to give the more stable product with the methyl and butyrolactone substituents in equatorial positions.[7] The discovery of high stereochemical control in the addition of an enolate of **5** to 4-substituted cyclohexanones has been used to advantage in an important stereochemical correlation; e.g., **27c** → **26** and **20** → **26**.

Dehydrations of **6a–c** by reaction with phosphorus pentoxide and Celite[8] in benzene give cyclohexenes **7a–c** in excellent yield. Conversions of **7a–c** to **8a–c** are accomplished by lactone saponification and esterification with diazomethane. With use of this procedure, β,γ-unsaturated esters **8a–c** are obtained uncontaminated with the corresponding α,β-isomers.

We assume that **6b** undergoes dehydration to give **7b** as an equimolar mixture of two diastereoisomers. This means that **8b** also is a mixture of two diastereoisomers. We have not been able to resolve these isomers by chromatographic separation or by spectral analysis. This is not surprising, because the chiral centers in **7b** and **8b** are separated by three carbon atoms, which are contained in a relatively symmetrical ring. The chemical reactivity of **8b** (vide infra) clearly requires that two diastereoisomers are present in equimolar amounts.

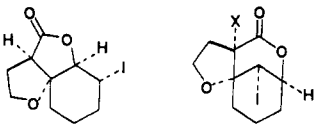
Initial Experiments. A standard procedure was developed for the reaction of **8a–c** with benzeneselenenyl chloride (Scheme II). Thus, a solution of **8a** in methylene chloride at −78 °C is treated with a solution of benzeneselenenyl chloride (1.3 equiv) in methylene chloride also cooled to −78 °C. After 1 h at −78 °C, 1 N $NaHCO_3$ is added, and the reaction mixture is allowed to warm to room temperature before separation of organic and aqueous phases. The spirocyclic selenide **9** is isolated in 99% yield by preparative high pressure liquid chromatography (HPLC) as a crystalline solid (mp 45 °C), from which an analytically pure sample is prepared by crystallization from ethanol (mp 50.5 °C). This material appears to be homogeneous by chromatographic analysis, ^1H and ^{13}C NMR spectral analysis, and chemical reactivity. Oxidation of **9** with hydrogen peroxide gives olefin **10a** in 93% isolated yield, while treatment with Raney nickel produces spirocyclic ether **11** in 98% yield.

For purposes of structural confirmation, spirocyclic ether **11** was prepared by an alternative regiochemically defined process. Thus, saponification of lactonic alcohol **6a** gives carboxylic acid **12a**. Esterification of **12a** with diazomethane gives **12b**, which is converted to mesylate **12c**. Cyclization of **12c** occurs on standing at room temperature to give a substance, **11**, identical with that prepared by reaction of **9** with Raney nickel.

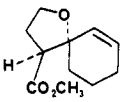


12a, R = H; X = OH
b, R = CH_3; X = OH
c R = CH_3; X = OMs

In an effort to gain additional information about the relative stereochemistry of **9**, we prepared carboxylic acid **10b** and investigated the reactivity of **10b** under iodolactonization conditions. We assumed that iodolactonization would not occur if the carboxylic acid group is anti to the olefinic bond as shown in **10b**. This supposition is based on the expectation of excessive ring strain in any lactones derived directly from **10b**. On the other hand, if a syn relationship is present, then iodo lactones of type **13** and/or **14** should be produced. In fact, iodolactonization produces three lactonic products and returns unreacted (and unepimerized) **10b** with excellent mass balance. The recovered carboxylic acid is shown to be identical with **10b** by IR and ^1H NMR spectral comparisons and by reconversion to **10a** on esterification with diazomethane. The three lactonic products are separated by preparative HPLC to give crystalline solids, the structures of which are assigned as **13** (mp 147 °C), **14a**



13 **14a**, X = H
b, X = I



15a, X = H
b, X = CH_3

(mp 93 °C), and **14b** (mp 126 °C, dec) by elemental analysis for C, H, and I, together with IR and ^1H NMR spectral analysis (see Experimental Section). Furthermore, **13**, **14a**, and **14b** are all converted to a new olefinic carboxylic acid **15a** on reductive elimination with zinc dust in ethanol. This new carboxylic acid is not present, within the limits of detection (~5%), in recovered carboxylic acid from the iodolactonization experiment with **10b**.

Carboxylic acid **15a** was shown to be epimeric with **10b** by esterification with diazomethane to give a new olefinic ester **15b**. Treatment of **10a** with potassium carbonate in

(5) Mulzer, J.; unpublished results for the addition of enolates to 4-substituted cyclohexanones. For additional examples of preferential equatorial attack in additions of carbanions to 4-substituted cyclohexanones, see: Abenhaim, D.; Henry-Basch, E.; Freon, P. *Bull. Soc. Chim. Fr.* **1969**, 4038. Jones, P. R.; Goller, E. J., Kauffman, W. J. *J. Org. Chem.* **1969**, *34*, 3566. Houlihan, W. J. *Ibid.* **1962**, *27*, 3860. House, H. O.; Prespess, W. L. *Ibid.* **1965**, *30*, 301 and references cited within these papers.

(6) Schultz, A. G.; Yee, Y. K. *J. Org. Chem.* **1976**, *41*, 4044.

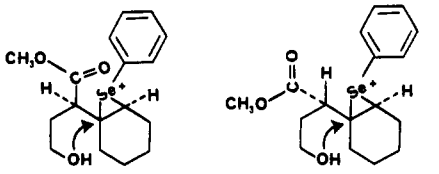
(7) For a classical example of C(4)-substituted cyclohexanone-derived equilibration studies, see: Eliel, E. L.; Rerick, M. N. *J. Am. Chem. Soc.* **1960**, *82*, 1367.

(8) Phalnikar, N. L.; Nargund, K. S. *Indian J. Chem.* **1963**, *14*, 736.

refluxing methanol results in partial epimerization to give a mixture of **10a** and **15b** in a ratio of 1:3. We presume that this product ratio represents an equilibrium mixture.

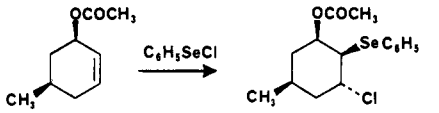
It is clear that olefinic carboxylic acid **10b** does not undergo iodolactonization. Under alkaline reaction conditions, **10b** is epimerized to **15a**, from which rapid iodolactonization occurs to give **13**, **14a**, and **14b**. All these chemical data are consistent with the assignment of structure for selenide **9a**. NMR data confirm this assignment (see Experimental Section).

Mechanistic Analysis. A priori, there are two important transition states to consider for spirocyclization of **8a**; these are represented in formulations **16** and **17**. An



16 **17**

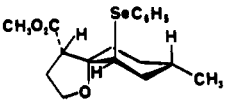
assumption implicit in both representations is that spirocyclization occurs from an intermediate seleniranium ion[9] by a process of trans diaxial olefin addition.[2] In **16**, neighboring-group participation between the selenium atom and the carbomethoxy group might be possible. While sterically more congested than the alternative transition state, **17**, **16** seemed viable, particularly in light of the extensive studies of Liotta, Zima, and Saindane,[10] who have reported the addition of benzeneselenenyl chloride to cyclohexenyl esters. Liotta and co-workers propose that an allylic acetate group is capable of directing syn phenylselenenylation from an equatorial position. For example, **18** was reported to give **19** as the only observable product.



18 **19**

It is clear that in the conversion of **8a** into **9**, the phenylselenenyl group enters anti to the carbomethoxy group. In this reaction, **17** is the more appropriate representation of the transition state leading to **9**. Thus, stereocontrol in the phenylselenenylation of **8a** is directed by steric considerations rather than neighboring-group participation as depicted in **16**.

Additional Studies. Olefinic alcohol **8b** was prepared in order to examine the effect of 1,3-diaxial interactions on the stereochemistry and regiochemistry of the cyclofunctionalization process. As already noted, **8b** must exist as a mixture of two diastereoisomers. We expected that one diastereoisomer would lead to spirocyclic selenide **20** with a reaction rate comparable to that for the conversion **8a** → **9**, while cyclization of the other diastereoisomer to **21** would be relatively more difficult. These suppositions are based on a mechanism for cyclofunctionalization that occurs by trans diaxial addition to the olefinic bond.[2] Formation of **21** would be disfavored because of the 1,3-diaxial interaction between the phenylselenenyl group and ring methyl substituent. Such a 1,3-diaxial interaction would not be present in the alternative product **22**, in which the phenylselenenyl group has entered syn to the



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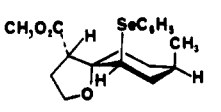

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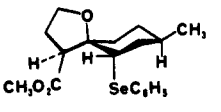

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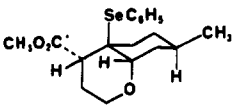
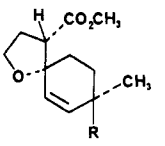


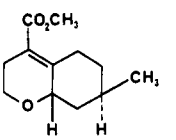
23

carbomethoxy group. If a syn disposition of groups is destabilizing rather than stabilizing, then the alternative regioisomer **23**, which lacks any of these steric problems, might be formed.

Reaction of **8b** with benzeneselenenyl chloride by the previously discussed method gives an equimolar mixture of two cyclization products isolated as a mixture by preparative HPLC in 87% yield. Further chromatographic fractionation of this mixture by preparative utilization of analytical HPLC affords pure spirocyclic selenides **20** (oil) and crystalline **23**. Oxidation of the mixture of **20** and **23** with hydrogen peroxide gives olefins **24a** and **25**, which were separated by preparative HPLC.



24a, R = H
b, R = CH_3



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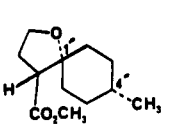
Chemical confirmation of structure **20** was obtained by treatment of **20** with Raney nickel to give **26** in 96% isolated yield. This material was found to be identical with **26** prepared from lactone alcohol **6b**, via carboxylic acid **27a**, methyl ester **27b**, and mesylate **27c**. Thus, assign-



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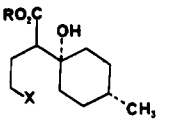


27a, R = H; X = OH
b, R = CH_3; X = OH
c, R = CH_3; X = OMs

ment of relative stereochemistry at C(1′) and C(4′) in **26** and therefore **20** is secure. Regiochemical assignment for **23** is supported by the conversion of **23** to **25**, while stereochemistry, in turn, must be assigned because of the stereochemical relationship between **23** and **20**; e.g., both compounds are produced from *diastereoisomers* of structure **8b**.

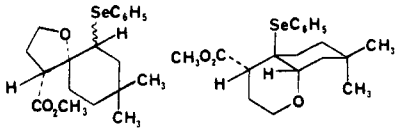
These experiments demonstrate that a neighboring-group participation of the type noted in transition-state representation **16** cannot operate in these cyclofunctionalization reactions. Instead, the phenylselenenyl and carbomethoxy groups appear to be mutually repulsive. This is demonstrated by the conversion of **8b** to **23** rather than to **22**.

As another test of the effect of 1,3-diaxial interactions in the control of regio- and stereochemistry, we investigated the reactivity of 4,4-dimethylcyclohexanone derivative **8c**. Reaction of **8c** with benzeneselenenyl chloride

(9) Schmid, G. H.; Garratt, D. G. *Tetrahedron Lett.* **1975**, 3991.
(10) Liotta, D.; Zima, G.; Saindane, M. *J. Org. Chem.* **1982**, *47*, 1258.

gives considerable recovered starting material along with selenides **28** (51%) and **29** (4%). Structural assignment for **28** is based primarily on ^{1}H NMR data and the conversion of **28** to **24b** on treatment with hydrogen peroxide. Unfortunately, the relative configuration of the phenylselenyl-bearing carbon atom cannot be assigned by available spectroscopic data. Stereochemical control is not readily apparent on mechanistic grounds, because formation of **28** by a trans diaxial opening of a seleniranium ion would result in severe 1,3-diaxial interactions with one of the cyclohexane ring methyl substituents. While less precedented, a syn addition to the cyclohexene ring would offer a sterically less congested reaction pathway.

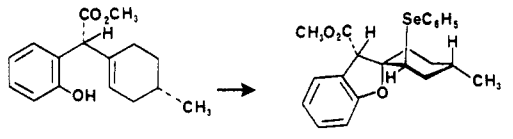
Pyran **29** is formed in low yield, presumably because of the 1,3-diaxial interaction between the ring oxygen atom and a cyclohexane ring methyl substituent. Relative



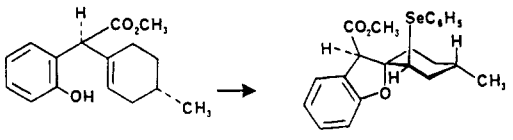
28 **29**

stereochemistry in **29** is assigned on the basis of ^{1}H NMR data, from which key resonances were found to be essentially identical with those obtained from **23**. It is noteworthy that stereochemistry in **29** (and, of course, in **23**) also demands that cyclization occurs from an intermediate seleniranium ion in which the phenylselenenyl group is anti to the carbomethoxy group.

Stereochemistry of Phenolic Olefin Cyclization. In connection with the photochemical study noted at the beginning of this paper, we prepared the two phenolic olefin isomers **30** and **32**. A configurational assignment



30 **31**

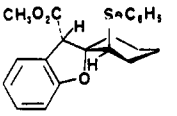


32 **33**

for these two materials was needed, and we elected to use the benzeneselenenyl chloride cyclofunctionalization as an analytical tool. Treatment of **30** by the method already described gives spirocyclic selenide **31** as a crystalline material (mp 69 °C) in 94% isolated yield. Similarly, **32** gives **33** (mp 84 °C) in >80% yield.[11]

The spirocyclization of **30** to give **31** parallels the stereo- and regiocontrol displayed by **8b**. It is noteworthy that diastereoisomer **32** does not give the equivalent of the ring fused pyran **23** but rather undergoes spirocyclization to **33**. With ^{1}H NMR spectral data for **31**, **33**, and **3** available, the relative configuration in **3** could be assigned with confidence as shown in stereorepresentation **34**. These results demonstrate that a syn disposition of phenylselenenyl and carbomethoxy groups can occur during cyclofunctionalization of olefinic phenols when there would be serious 1,3-diaxial interactions in the alternative transition state for spirocyclization. In the absence of such

(11) The details of this study are presented in ref 3.



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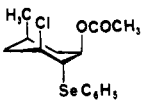

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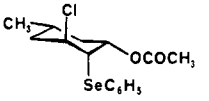
overriding steric constraints, olefinic phenols of type **3** (e.g., **3** and **30**) provide spirocyclic benzodihydrofurans with the phenylselenenyl group disposed anti to the carbomethoxy group.

Conclusion

We have demonstrated that cyclofunctionalizations of olefinic alcohols **8a–c** and olefinic phenols **2**, **30**, and **32** with benzeneselenenyl chloride occur with remarkably high regio- and stereoselectivity. The carbomethoxy group exerts a dramatic effect (presumably steric) in directing the introduction of the phenylselenenyl group anti to itself. These observations stand in contrast to the mechanistic rational offered by Liotta and co-workers in their report concerning reactions of type **18** → **19**.[10] We, therefore, feel obliged to comment on the literature work but do not wish to directly compare our studies with those of Liotta. Clearly, transition states for the two reactions are very different.

In the addition of phenylselenenyl chloride to olefin **18**, it should be appreciated that formation of the alternative stereoisomer (i.e., that leading to anti disposition of phenylselenenyl and acetate groups) by a process of trans diaxial olefin addition would have resulted in severe 1,3-diaxial interactions as noted in stereorepresentation **35**. The same process leading to the observed product, **19**, occurs without serious 1,3-diaxial interactions as is obvious in stereorepresentation **36**. Thus, **18** and the two other systems studied[10] do not appear to provide a useful stereochemical probe of the issue of neighboring-group participation in the cyclohexane ring system.



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The stereocontrol discovered for cyclofunctionalization of olefinic phenols provides the foundation for an analytical procedure that can be used to examine subtle features of the stereochemistry associated with the photoreaction **1** → **2**. The results of this study appear in a subsequent paper.[3]

Experimental Section

Instrumentation, Solvents, and General Procedures. ^{1}H NMR spectra were obtained on Varian T-60 (60 MHz), Varian XL-200 (200 MHz), and Hitachi-Perkin-Elmer R-600 (60 MHz) NMR spectrometers using tetramethylsilane as an internal standard. ^{13}C NMR spectra were recorded on the Varian XL-200 spectrometer. Infrared spectra were recorded on either a Perkin-Elmer 137B or 298 spectrometer. Ultraviolet spectra were obtained on a Perkin-Elmer 552 spectrophotometer. Melting points were measured on a calibrated Thomas-Hoover capillary melting point apparatus and were reported uncorrected. Mass spectra were obtained on a Finnigan OWA-1020, 3300 gas chromatograph–mass spectrometer. Mass spectrum refers to electron-impact mass spectrum. Preparative high-pressure liquid chromatography (HPLC) was performed on a Waters Associates preparative LC 500 Unit. Analytical vapor-phase chromatography (VPC), using a 6 ft × $^1/_8$ in. column packed with 10% SE-30 on Chromasorb W, was performed on a Hewlett-Packard HP 5710A gas chromatograph equipped with a flame ionization detector (300

°C) and nitrogen carrier gas. Microanalyses were carried out by Spang Microanalytical Laboratory, Eagle Harbor, MI, and Galbraith Laboratories, Knoxville, TN.

The light source for all photochemistry was a Hanovia 450-W medium-pressure mercury arc lamp. The lamp was placed in a water-cooled Pyrex immersion well. Reaction vessels containing solutions to be irradiated were attached to the immersion well and were saturated with argon prior to irradiation.

Tetrahydrofuran (THF) was dried by distillation in the presence of potassium or sodium metal under a nitrogen atmosphere by using benzophenone ketyl as indicator. Diisopropylamine was distilled from calcium hydride and stored over 4-Å molecular sieves. Methylene chloride was distilled from phosphorus pentoxide and stored over 4-Å molecular sieves. Mallinckrodt or J. T. Baker anhydrous ethyl ether was used without further purification. Solvents were removed at reduced pressure with a Buchi Rotovapor-R rotary evaporator. The last traces of solvent were removed by evacuation at room temperature by using a Welch Duo-Seal floor pump (0.05 mm).

α-(1-Hydroxycyclohexyl)-γ-butyrolactone (6a). General Procedure for Addition of γ-Butyrolactone Enolate to Cyclohexanones. A solution of lithium diisopropylamide (21 mmol) was prepared at 0 °C from diisopropylamine (2.13 g, 21 mmol) and *n*-butyllithium (1.55 M, 13.55 mL, 21 mmol) in THF (25 mL). After being cooled at −78 °C, a solution of γ-butylrolactone (1.81 g, 21 mmol) in THF (10 mL) was added and the reaction mixture was stirred for 20 min. After addition of cyclohexanone (2.06 g, 21 mmol), stirring was continued for 1 h at −40 °C (acetonitrile–dry ice bath). Cooling was discontinued and the reaction was quenched with saturated ammonium chloride solution (10 mL). Extraction with ether (3 × 20 mL), washing with brine (20 mL), drying over anhydrous $MgSO_4$, solvent removal, and Kugelrohr distillation (152 °C/0.7 mmHg) afforded α-(1-hydroxycyclohexyl)-γ-butyrolactone (**6a**) (3.58 g, 92.5% (lit.[4a] yield 91%)) as a colorless oil: IR (neat) 3450, 1740 cm^{-1}; ^1H NMR δ 1.4–1.9 (br s, 8 H), 2.0–3.0 (m, 5 H), 3.05 (br s, 1 H, exchangeable with D_2O), 3.9–4.6 (m, 2 H).

Anal. Calcd for $C_{10}H_{16}O_3$: C, 65.19; H, 8.76. Found: C, 64.97; H, 8.91.

α-(1-Hydroxy-4-methylcyclohexyl)-γ-butyrolactone (6b), prepared from γ-butyrolactone (724 mg, 8.4 mmol) and 4-methylcyclohexanone (942 mg, 8.4 mmol) and crystallized from ethanol–water (1.63 g, 98%, mp 102 °C): IR ($CHCl_3$) 3500, 1740 cm^{-1}; ^1H NMR δ 0.88 (br s, 3 H), 1.11–1.76 (m, 6 H), 1.76–2.85 (m, 5 H), 3.0 (br s, exchangeable with D_2O, 1 H), 3.36–4.58 (m, 2 H).

Anal. Calcd for $C_{11}H_{18}O_3$: C, 66.64; H, 9.15. Found: C, 66.70; H, 9.60.

4,4-Dimethylcyclohexanone.[12] 4,4-Dimethyl-2-cyclohexen-1-one (5.0 g, 40 mmol) in ethanol (80 mL) was hydrogenated over 5% Pd/C (300 mg) until ~1 L of H_2 was absorbed. Filtration, concentration of filtrate, and distillation (73 °C/14 mmHg) gave 4,4-dimethylcyclohexanone (5.0 g, 99%, mp 38–40 °C).

α-(1-Hydroxy-4,4-dimethylcyclohexyl)-γ-butyrolactone (6c), prepared from γ-butyrolactone (724 mg, 8.4 mmol) and 4,4-dimethylcyclohexanone (1.058 g, 8.4 mmol) and crystallized from ether–hexanes (1.71 g, 96%, mp 83 °C): IR ($CHCl_3$) 3500, 1750 cm^{-1}; ^1H NMR δ 0.88 (s, 3 H), 0.95 (s, 3 H), 1.0–1.8 (m, 8 H), 2.31 (m, 2 H, C_β protons), 2.71 (dd, J = 8 Hz, 6 Hz, 1 H, C_α proton), 2.86 (br s, 1 H, exchangeable with D_2O), 4.17, 4.36 (two m, 1 H each, C_γ protons).

Anal. Calcd for $C_{12}H_{20}O_3$: C, 67.89; H, 9.50. Found: C, 67.95; H, 9.50.

α-(Cyclohex-1-enyl)-γ-butyrolactone (7a). General Procedure for Preparation of 7a–c. Celite (25 g) and P_2O_5 (13.5 g) were added to a solution of **6a** (3.00 g, 16.3 mmol) in benzene (380 mL), and the mixture was stirred under N_2 for 12 h, after which TLC analysis (hexane–ethyl acetate, 7:3) showed complete disappearance of starting material. Anhydrous ether (500 mL) was added and a precipitate was removed by filtration. The filtrate was washed successively with saturated $NaHCO_3$, water, and brine and dried over $MgSO_4$. Removal of solvents and Kugelrohr distillation (123 °C/0.7 mmHg) of the residue gave α-(cyclohex-1-enyl)-γ-butyrolactone (**7a**) (2.64 g, 97.4%) as a colorless oil: IR (neat) 2950, 1760 cm^{-1}; ^1H NMR δ 1.5–2.2 (m, 10 H), 3.16 (t, J = 8 Hz, 1 H), 4.29 (m, 2 H), 5.67 (br s, 1 H); mass spectrum, m/e (relative intensity) 166 (M^+, 79.5), 138 (100).

α-(4-Methylcyclohex-1-enyl)-γ-butyrolactone (7b), prepared from **6b** (1.63 g, 8.15 mmol) by the procedure described for **7a** (1.25 g, 90%, bp 140 °C/0.8 mmHg): IR (neat) 2900, 1760 cm^{-1}; ^1H NMR δ 0.90 (d, J = 7.2 Hz, 3 H, C_4-methyl group), 1.08–2.66 (m, 9 H), 3.05 (dd, J = 18 Hz, 8 Hz, 1 H, C_α proton), 4.25 (m, 2 H, C_γ protons), 5.61 (br s, 1 H, vinyl proton); mass spectrum, m/e (relative intensity) 180 (M^+, 62), 152 (52), 121 (63), 107 (39), 100 (100), 93 (52), 91 (29).

α-(4,4-Dimethylcyclohex-1-enyl)-γ-butyrolactone (7c), prepared from **6c** (1.06 g, 5 mmol) by the procedure described for **7a** (870 mg, 89.7%, bp 130 °C/0.8 mmHg): IR (neat) 2900, 1760 cm^{-1}; ^1H NMR δ 0.91 (s, 3 H), 0.92 (s, 3 H), 1.42 (m, 2 H), 1.85 (m, 2 H), 2.05 (m, 2 H), 2.30 (m, 2 H), 3.18 (t, J = 6 Hz, 1 H, C_α proton), 4.27 (m, 2 H, C_γ protons), 5.59 (br s, 1 H, vinyl proton).

Anal. Calcd for $C_{12}H_{18}O_2$: C, 74.19, H, 9.34. Found: C, 74.20; H, 9.29.

2-(Cyclohex-1-enyl)-4-hydroxybutanoic Acid, Methyl Ester (8a). General Procedure for Preparation of 8a–c. 7a (2.25 g, 13.55 mmol) in 2 N NaOH (10 mL) was heated at reflux temperature for 45 min. After being cooled to room temperature and addition of saturated ammonium chloride solution (20 mL), the reaction mixture was cooled to 5 °C, acidified to pH 4.0 with 10% H_2SO_4, and extracted with ether (3 × 25 mL). The combined extracts were washed with brine, dried over $MgSO_4$, and evaporated to give 2-(cyclohex-1-enyl)-4-hydroxybutanoic acid (2.50 g, 100%) as a thick gum: IR (neat) 3400, 1700 cm^{-1}; ^1H NMR δ 1.45–2.20 (m, 10 H), 3.20 (t, J = 8 Hz, 1 H), 5.1–5.8 (br m, 3 H, collapsed into a br s at 5.76 of 1 H intensity on D_2O exchange).

The crude acid (2.50 g, 13.5 mmol) was esterified with diazomethane in ether (10 mL). Excess diazomethane was destroyed with glacial acetic acid (1 mL), and the etheral solution was washed with saturated $NaHCO_3$ and dried over $MgSO_4$. Removal of ether followed by flash chromatography (ethyl acetate–hexanes, 2:3) of the residue afforded 2-(cyclohex-1-enyl)-4-hydroxybutanoic acid, methyl ester (**8a**) (2.23 g, 82.9%) as a colorless oil: IR (neat) 3440, 1730 cm^{-1}; ^1H NMR δ 1.4–2.4 (m, 6 H), 3.7 (t, J = 7 Hz, 1 H), 3.45–3.8 (m, with sharp peak at 3.70, 5 H), 4.3 (br s, exchangeable with D_2O, 1 H), 5.75 (br s, 1 H); mass spectrum, m/e (relative intensity) 198 (M^+, 42.9), 180 (29.8), 166 (100).

Anal. Calcd for $C_{11}H_{18}O_3$: C, 66.64; H, 9.15. Found: C, 66.40; H, 9.30.

2-(4-Methylcyclohex-1-enyl)-4-hydroxybutanoic acid, methyl ester (8b), prepared from the lactone **7b** (360 mg, 2 mmol) by the procedure described for **8a**; carboxylic acid (390 mg, 100%): IR (neat) 3330, 1720 cm^{-1}; ^1H NMR δ 0.90 (d, J = 4.8 Hz, 3 H), 1.00–2.68 (m, 9 H), 3.20 (t, J = 8 Hz, 1 H), 3.60 (m, 2 H), 5.63 (br s, 1 H), 5.97 (br s, exchangeable with D_2O, 2 H); mass spectrum, m/e (relative intensity) 180 (M^+, 62), 152 (52), 121 (63), 107 (39), 100 (100), 93 (52), 91 (29). Methyl ester **8b** (420 mg, 98%) was purified by flash chromatography (ethyl acetate–hexanes, 1:4): IR (neat) 3430, 1740 cm^{-1}; ^1H NMR δ 0.94 (d, J = 6 Hz, 3 H), 1.2–2.2 (m, 10 H), 3.16 (t, J = 8 Hz, 1 H), 3.62 (m, 2 H), 3.68 (s, 3 H), 5.60 (br s, 1 H); mass spectrum, m/e (relative intensity) 212 (M^+, 18), 194 (12), 180 (49), 168 (56), 152 (56), 135 (100).

2-(4,4-Dimethylcyclohex-1-enyl)-4-hydroxybutanoic acid, methyl ester (8c), prepared from lactone **7c** (700 mg, 3.61 mmol) by the procedure described for **8a**; carboxylic acid (720 mg, 94.1%): IR (neat) 3400, 1710 cm^{-1}; ^1H NMR δ 0.90 (br s, 6 H), 1.3–3.0 (m, 8 H), 3.17 (t, J = 6 Hz, 1 H), 3.68 (m, 2 H), 5.59 (br s, 1 H). Methyl ester **8c** (700 mg, 93.8%) was purified by flash chromatography (ethyl acetate–hexane, 1:4): IR (neat) 3400, 1730 cm^{-1}; ^1H NMR δ 0.88 (s, 3 H), 0.89 (s, 3 H), 1.37 (t, J = 6.4 Hz, 1 H), 1.60–2.40 (m, 6 H), 3.18 (t, J = 6 Hz, 1 H), 3.64 (m, 2 H), 3.68 (s, 3 H), 5.56 (br s, 1 H).

Anal. Calcd for $C_{13}H_{22}O_3$: C, 69.00, H, 9.80. Found: C, 69.14; H, 9.94.

Spiro[tetrahydrofuran-2(3*H*),1′-2′-(phenylseleno)cyclohexane]-3-carboxylic Acid, Methyl Ester (9a). Standard Procedure for Reaction of Benzeneselenenyl Chloride with 2-(Cyclohex-1-enyl)-4-hydroxybutanoic Acid, Methyl Esters 8a–c. A solution of 2-(cyclohex-1-enyl)-4-hydroxybutanoic acid,

(12) von Auwers, K.; Lange, E. *Liebigs Ann. Chem.* **1913**, *401*, 315.

methyl ester (**8a**) (1.00 g, 5 mmol) in methylene chloride (40 mL) was cooled to −78 °C under N_2, and a solution of benzeneselenenyl chloride (1.26 g, 6.5 mmol) in methylene chloride (10 mL) was added over 5 min. The reaction mixture was stirred for 1 h; 1 N $NaHCO_3$ was added at −78 °C and the mixture was allowed to warm to room temperature. The organic layer was separated and washed with brine, dried over $MgSO_4$, and concentrated to give a yellow oil (2 g). TLC analysis (methylene chloride) of this material showed complete disappearance of starting material and appearance of a single spot (R_f 0.72) along with some diphenyl diselenide. Preparative HPLC (ethyl acetate–hexanes, 1:14) afforded the spirocyclic selenide **9** as a crystalline solid (1.75 g, 99%, mp 45 °C). Recrystallization from 95% ethanol gave analytically pure **9**: mp 50.5 °C; IR ($CHCl_3$) 2910, 1730, 1580, 1470, 1430, 1355, 1165, 1060, 740 cm^{-1}; ^1H NMR δ 1.44–2.40 (m, 10 H), 3.37 (br t, J = 4 Hz, 1 H, $C_{2'}$ proton), 3.47 (dd, J = 8.2 Hz, 5 Hz, 1 H, C_3 proton), 3.71 (s, 3 H, ester methyl group), 3.87, 4.06 (two m, 1 H each, C_2 protons), 7.32 (m, 3 H, aromatic protons) 7.62 (m, 2 H, aromatic protons); ^{13}C NMR δ 22.14, 22.15 (two overlapping t), 29.61 (t), 30.29 (t), 31.25 (t), 51.29 (d, $C_{2'}$), 51.63 (q), 53.52 (d, C_3), 66.4 (t, C_5), 87.01 (s, C_2), 127.41 (d), 129 (d), 130.76 (s), 134.09 (d), 174.05 (s, C=O).

Anal. Calcd for $C_{17}H_{22}O_3Se$: C, 57.79; H, 6.28; Se, 22.35. Found: C, 58.00; H, 6.42; Se, 22.35.

Spiro[tetrahydrofuran-2(3*H*),1′-cyclohex-2′-ene]-3-carboxylic Acid, Methyl Ester (10a). General Procedure for H_2O_2 Oxidation of Spirocyclic Selenides. A solution of 30% hydrogen peroxide (0.7 mL, 7.5 mmol, 1.5 equiv) was added to a solution of the spirocyclic selenide **9** (1.75 g, 5 mmol) in THF (5 mL) at 0 °C with stirring under N_2. After 1 h the mixture was allowed to warm to room temperature and stirring was continued for 24 h. TLC (ethyl acetate–hexanes, 1:9) and VPC (T_1 = 150 °C, T_2 = 250 °C, 16 °C/min) analysis showed complete disappearance of starting material. The reaction mixture was poured into a separatory funnel containing ether (50 mL) and 1 N $NaHCO_3$ (20 mL). The organic layer was separated, washed with brine, dried over $MgSO_4$, concentrated, and chromatographed (preparative HPLC, ethyl acetate–hexanes, 1:9) to give **10a** (910 mg, 93%) as a colorless oil: IR (neat) 2940, 1740, 1630, 1430, 1560, 1165, 1030, 942, 900 cm^{-1}; ^1H NMR δ 1.4–1.9 (m, 4 H), 2.02 (m, 2 H, $C_{4'}$ protons), 2.22, 2.42 (two m, 1 H each, C_4 protons), 2.89 (t, J = 8 Hz, 1 H, C_3 proton), 3.70 (s, 3 H), 4.02 (m, 2 H, C_5 protons), 5.62 (d, J = 10 Hz, 1 H, $C_{2'}$ proton), 5.95 (m, 1 H, $C_{3'}$ proton); irradiation of resonance centered at δ 2.02 resulted in the collapse of the vinylic proton signals to a clean quartet centered at δ 5.8, J = 10 Hz; irradiation of resonances centered at δ 2.22 and 2.42, individually, resulted in the collapse of the multiplet at δ 2.89 into a doublet in each instance as well as simplification of the multiplicity of signals centered at δ 4.02; ^{13}C NMR δ 19.19 (t), 24.89 (t), 28.98 (t), 30.07 (t), 51.70 (q), 53.44 (d, C_3), 65.68 (t, C_5), 80.82 (s, C_2), 130.35 (d), 131.56 (d), 172.75 (s, C=O).

Anal. Calcd for $C_{11}H_{16}O_3$: C, 67.32; H, 8.22. Found: C, 67.14; H, 8.31.

Spiro[tetrahydrofuran-2(3*H*),1′-cyclohexane]-3-carboxylic Acid, Methyl Ester (11). General Procedure. A solution of the spirocyclic selenide **9** (65 mg, 0.184 mmol) in THF (2 mL) was added to a suspension of Raney Ni (~300 mg) in THF (5 mL) and the mixture was stirred at room temperature for 1 h. The solids were removed by filtration through a Celite filter bed and were washed several times with ethanol. Concentration of combined filtrate and washings and flash chromatography (ethyl acetate–hexanes, 3:7) gave the spirocyclic ether **11** (36 mg, 98%) as a colorless oil: IR (neat) 2900, 1740 cm^{-1}; ^1H NMR δ 1.11–1.14 (m, 2 H), 1.15–1.70 (m, 8 H), 2.13 (m, 1 H), 2.34 (m, 1 H), 2.73 (dd, J = 8.6 Hz, 7.8 Hz, 1 H, C_3 proton), 3.71 (s, 3 H), 3.83, 3.96 (two m, 1 H each, C_5 protons); ^{13}C NMR δ 22.24 (t), 25.54 (t), 28.67 (t), 31.90 (t), 36.85 (t), 51.61 (q, ester methyl group), 53.53 (d, C_3), 65.32 (t, C_5), 83.36 (s, C_2), 173.22 (s, C=O); mass spectrum, m/e (relative intensity) 198 (M^+, 1.0), 169 (2.2), 155 (26), 100 (35), 68 (60), 59 (33), 54 (75), 40 (100).

2-(1-Hydroxycyclohexyl)-4-hydroxybutanoic Acid (12a) and Its Methyl Ester (12b). The lactonic alcohol **6a** (184 mg, 1 mmol) was saponified by the general procedure described for **7a**. Recrystallization from ether gave **12a** (196 mg, 97%, mp 120 °C): IR ($CHCl_3$) 3400, 2920, 1720 cm^{-1}. Methyl ester **12b** was prepared by esterification of **12a** (101 mg, 0.5 mmol) with diazomethane in ethyl acetate (5 mL); **12b** (96 mg, 90%) was isolated as a colorless oil: IR (neat) 3400, 1730 cm^{-1}; ^1H NMR δ 1.2–2.1 (m, 12 H), 2.62 (dd, J = 8 Hz, 4 Hz, 1 H), 3.68 (m, 2 H), 3.73 (s, 3 H).

Mesylation of 12b. A solution of the dihydroxy ester **12b** (96 mg, 0.46 mmol) and triethylamine (50 mg, 0.5 mmol) in methylene chloride (3 mL) was cooled to −20 °C (ice–salt bath) and methanesulfonyl chloride (57 mg, 0.5 mmol) was added under N_2. After 20 min, the reaction mixture was allowed to warm to 0 °C and cold 1 N HCl (10 mL) was added. The mixture was quickly extracted with methylene chloride (2 × 10 mL), washed with cold water and brine, and dried over $MgSO_4$. Removal of solvent under vacuum gave **12c** (140 mg, ~100%): IR ($CHCl_3$) 3500, 1730, 1435, 1360, 1170, 970, 920 cm^{-1}; ^1H NMR δ 1.40–1.82 (m, 10 H), 2.15 (m, 2 H), 2.56 (br s, exchangeable with D_2O, 1 H), 2.62 (dd, J = 10 Hz, 6 Hz, 1 H), 3.01 (s, 3 H), 3.71 (s, 3 H), 4.2 (m, 2 H). **12c** was slowly converted on standing at room temperature to spiro[tetrahydrofuran-2(3*H*),1′-cyclohexane]-3-carboxylic acid, methyl ester, whose IR and ^1H NMR spectra were superimposable on those of **11** obtained from reaction of the spirocyclic selenide **9** with Raney Ni.

Spiro[tetrahydrofuran-2(3*H*),1′-cyclohex-2′-ene]-3-carboxylic Acid (10b). To a solution of **10a** (480 mg, 2.45 mmol) in methanol (5 mL) was added 1 N KOH (5 mL), and the mixture was stirred at room temperature under N_2 for 12 h. Saturated NH_4Cl (10 mL) was added, and, after being cooled to 5 °C, the mixture was acidified to pH 2–3 with 1 N H_2SO_4. The cold reaction mixture was extracted with ether (3 × 20 mL). The combined organic extract was washed with brine, dried over $MgSO_4$, and concentrated in vacuo to give the carboxylic acid **10b** (405 mg, 90.8%) as a thick gum: IR (neat) 3400, 1720 cm^{-1}; ^1H NMR δ 1.40–1.90 (m, 4 H), 2.02 (m, 2 H, $C_{4'}$ protons), 2.30 (m, 2 H, C_4 protons), 2.93 (t, J = 8 Hz, 1 H), 4.0 (m, 2H, C_5 protons), 5.65 (d, J = 10 Hz, 1 H, C_2H), 5.93 (m, 1 H, C_3H). A small portion of **10b** (10 mg, 0.049 mmol) was reacted with diazomethane to give an ester (~10 mg), whose IR and ^1H NMR spectra were superimposable on those of **10a**.

Iodolactonization of Spiro[tetrahydrofuran-2(3*H*),1′-cyclohex-2′-ene]-3-carboxylic Acid (10b). The spirocarboxylic acid **10b** (200 mg, 1.1 mmol) was dissolved in 0.5 N $NaHCO_3$ (6.3 mL) containing 1 N KOH (0.3 mL; pH 8.0). After 15 min, a solution of potassium iodide (1.86 g, 11 mmol) and iodine (630 mg, 2.5 mmol) in water (5 mL) was added and the mixture was stirred under N_2 in the dark at room temperature for 72 h. The reaction mixture was transferred to a separatory funnel and extracted with chloroform (4 × 15 mL). The combined chloroform extracts were poured into a second separatory funnel containing 10% $Na_2S_2O_3$. The organic layer was separated, washed twice with saturated $NaHCO_3$, dried over $MgSO_4$, and concentrated in vacuo to give a brown oil (182 mg). TLC analysis (ethyl acetate–hexanes, 3:7) of this material showed three spots at R_f 0.44, 0.2, and 0.16. Clean separation of three components was accomplished by HPLC (ethyl acetate–hexanes, 1:4) to afford the following.

(A) Diiodo lactone 14b (40 mg, R_f 0.44); needles (ether), mp 126 °C dec; IR ($CHCl_3$) 1730 cm^{-1}; ^1H NMR δ 1.72 (m, 2 H), 1.98 (m, 2 H), 2.45 (m, 2 H), 2.88 (m, 2 H), 4.1 (m, 1 H), 4.27 (m, 1 H), 4.62 (br s, 1 H), 4.85 (br s, 1 H).

Anal. Calcd for $C_{10}H_{12}O_3I_2$: C, 27.67; H, 2.79; I, 58.48. Found: C, 27.78; H, 2.80; I, 58.35.

(B) Iodo lactone 14a (30 mg, R_f 0.2); needles (ether–hexanes), mp 93 °C; IR ($CHCl_3$) 1730 cm^{-1}; ^1H NMR δ 1.6 (m, 2 H), 1.97 (m, 2 H), 2.3 (m, 3 H), 2.6 (m, 1 H), 3.2 (dd, J = 11.0, 9.4, 1 H), 3.98 (12-line m, 2 H), 4.42 (br s, 1 H), 4.84 (br s, 1 H); mass spectrum, m/e (relative intensity) 309 (M^+, 0.2), 308 (2.60), 181 (40.15), 163 (3.18), 153 (4.60), 137 (81.90), 127 (9.01), 109 (19.56), 84 (89.49), 69 (88.91), 55 (81.75), 41 (100).

Anal. Calcd for $C_{10}H_{13}O_3I$: C, 38.98; H, 4.25; I, 41.19. Found: C, 39.07; H, 4.26; I, 41.05.

(C) Iodo lactone 13 (62 mg, R_f 0.16): needles (ether–hexanes), mp 147 °C; IR ($CHCl_3$) 1785 cm^{-1}; ^1H δ 1.30 (m, 1 H), 1.64 (m, 2 H), 1.98 (m, 2 H), 2.40 (m, 3 H), 3.03 (d, J = 8 Hz, 1 H, C_3 proton), 3.63 (eight-line m, 1 H, $C_{3'}$ proton), 3.79 (m, 1 H, C_5 protons), 4.00 (m, 1 H, C_5 proton), 4.70 (d, J = 10 Hz, 1 H, $C_{2'}$ proton); mass spectrum, m/e (relative intensity) 309 (M^+, 0.05), 308 (0.9), 183 (1.18), 182 (6.15), 181 (77.78), 163 (7.80), 153 (12.14),

137 (14.71), 127 (18.84), 128 (8.63), 123 (8.33), 119 (10.05), 109 (7.65), 107 (48.67), 91 (26.7), 79 (48.48), 69 (97.98), 55 (80.93), 41 (100).

Anal. Calcd for $C_{10}H_{13}O_3I$: C, 38.98; H, 4.25. Found: C, 38.94; H, 4.43.

The basic aqueous layers were combined, decolorised with solid $Na_2S_2O_3$, acidified with 10% HCl, and extracted with chloroform (4 × 15 mL). The combined chloroform extracts were washed with brine, dried over $MgSO_4$, and concentrated in vacuo to give spiro[tetrahydrofuran-2(3*H*),1′-cyclohex-2′-ene]-3-carboxylic acid (115 mg), whose IR and ^1H NMR spectra were superimposable on those of the starting spirocarboxylic acid **10b**. Reaction with diazomethane afforded an ester whose spectra (IR, ^1H NMR) were identical with those of **10a**.

Reductive Elimination of Iodo Lactones 13 and 14a,b. Zinc dust (10 equiv) was added to a solution of each iodo lactone (1 equiv, 1 mL) in ethanol, and the mixture was heated at reflux temperature under N_2. The reaction mixture was cooled and filtered, and the combined filtrate and washings were concentrated in vacuo. The residue was partitioned between ether and 1 N HCl. The ether layer was washed with brine, dried over $MgSO_4$, and evaporated to give the same olefinic carboxylic acid **15a** (90–95%) from each iodo lactone **13**, **14a**, and **14b**: IR (neat) 3400–3100 (br), 1730 cm^{-1}; ^1H NMR δ 1.6–2.1 (m, 6 H), 2.1–2.3 (m, 1 H), 2.37–2.56 (m, 1 H), 2.87 (t, J = 8 Hz, 1 H, C_3 proton), 3.57 (q, J = 7.2 Hz, 1 H, C_5 proton), 4.07 (six-line m, 1 H, C_5 proton), 5.62 (d, J = 10 Hz, 1 H, $C_{2'}$ proton), 5.9 (six-line m, 1 H, $C_{3'}$ proton). Carboxylic acid **15a** (10 mg, 0.049 mmol) was reacted with diazomethane to give olefinic ester **15b** (10 mg, ~100%): IR ($CHCl_3$) 1735 cm^{-1}; ^1H NMR δ 1.7–2.0 (m, 6 H), 2.20 (m, 1 H), 2.5 (m, 1 H), 2.86 (t, J = 8.2 Hz, 1 H, C_3 proton), 3.66 (s, 3 H), 3.86 (q, J = 7.2 Hz, 1 H, C_5 proton), 4.05 (six-line m, 1 H, C_5 proton), 5.5 (br d, J = 10 Hz, 1 H, $C_{2'}$ proton), 5.9 (six-line m, 1 H, $C_{3'}$ proton).

Epimerization of 10a. Carboxylic acid **10a** (10 mg, 0.049 mmol) in methanol (2 mL) was heated to reflux temperature with K_2CO_3 (20 mg) under N_2 for 12 h. The solids were removed by filtration and the filtrate was concentrated in vacuo. The residue was partitioned between ether and 1 N HCl. The organic layer was separated, washed with brine, dried over $MgSO_4$, and concentrated to give a mixture of isomeric acids **10b** and **15a** (8 mg, ~100%). This mixture was esterified with diazomethane to afford a mixture of isomeric esters **10a** and **15b** in a ratio 1:3 as determined by ^1H NMR analysis.

Reaction of 8b with Benzeneselenenyl Chloride. 8b (530 mg, 2.5 mmol) was treated with benzeneselenenyl chloride (504 mg, 2.63 mmol) by the procedure described for conversion of **8a** to **9**. Purification by preparative HPLC (ethyl acetate–hexanes, 1:9) afforded 798 mg (87%) of a colorless oil, which appeared to be homogeneous by TLC (R_f 7.0, methylene chloride) and VPC analysis (t_R 1.8 min; 250 °C): IR (neat) 1735, 1725 cm^{-1}; ^1H NMR δ 0.92, 0.95 (two overlapping d, J = 10 Hz in the ratio 1:1, 3 H), 1.10–2.50 (m, 9 H), 2.90 (m, 0.5 H), 3.20 (m, 1 H), 3.34 (m, 0.5 H), 3.50 (m, 0.5 H), 3.72, 3.74 (two sharp s in the ratio 1:1, 3 H), 3.75–4.75 (m, 1.5 H). Further chromatographic fractionation of this mixture (120 mg) by preparative utilization of analytical HPLC (ethyl acetate–isooctane, 1:39, flow rate 2 mL/min), afforded the following.

(A) Spiro[tetrahydrofuran-2(3*H*),1′-[4′-methyl-2′-(phenylseleno)cyclohexane]]-3-carboxylic acid, methyl ester (20) (56 mg, t_R 7.2 min, oil): IR (neat) 2920, 1730, 1580, 1430, 1350, 1170, 1050, 1030, 740, 690 cm^{-1}; ^1H NMR δ 0.91 (d, J = 6 Hz, 3 H, $C_{4'}$-methyl group), 1.2–1.68 (m, 4 H), 2.25 (m, 1 H), 3.34 (br t, 1 H, $C_{2'}$ proton), 3.50 (dd, J = 8 Hz, 4 Hz, 1 H, C_3 proton), 3.71 (s, 3 H, ester methyl group), 3.84 (six-line m, 1 H, C_5 proton), 4.05 (four-line m, 1 H, C_5 proton), 7.29 (m, 3 H, aromatic protons), 7.65 (m, 2 H, aromatic protons); ^{13}C NMR δ 21.81 (q), 27.30 (d), 29.66 (t), 30.13 (t), 30.50 (t), 51.60 (overlapping d and q, $C_{2'}$ and ester methyl group), 52.70 (d, C_3), 66.22 (t, C_5), 86.67 (s, C_2), 127.45 (d), 129.20 (d), 131.15 (s), 133.93 (d), 174.01 (s, C=O).

Anal. Calcd for $C_{18}H_{24}O_3Se$: C, 58.85; H, 6.59. Found: C, 58.70; H, 6.59.

(B) Perhydrochromene derivative 23 [52 mg, t_R 8 min, mp 70–71 °C (ethanol)]: IR ($CHCl_3$) 2940, 1730, 1585, 1430, 1365, 1250, 1190, 960, 690 cm^{-1}; ^1H NMR δ 0.95 (d, J = 6 Hz, 3 H), 1.4–1.7 (m, 4 H), 1.71–2.15 (m, 2 H), 2.16–2.43 (m, 3 H), 2.89 (dd, J = 12.8 Hz, 4 Hz, 1 H), 3.95–3.30 (m, 2 H), 3.74 (s, 3 H), 3.91 (dd, J = 11 Hz, 5 Hz, 1 H), 7.30–7.50 (m, 3 H), 7.7–7.83 (m, 2 H); ^{13}C NMR δ 22.16 (q), 26.17 (d), 26.54 (t), 27.33 (t), 36.20 (t), 50.88 (s), 50.73 (q), 51.37 (d), 67.19 (t), 78.43 (d), 125.58 (s), 128.83 (d), 129.05 (d), 138.68 (d), 172.87 (s).

Anal. Calcd for $C_{18}H_{24}O_3Se$: C, 58.85; H, 6.59; Se, 21.50. Found: 58.78; H, 6.55; Se, 21.41.

Oxidation of a 1:1 Mixture of 20 and 23. The mixture of **20** and **23** (368 mg, 1 mmol) was reacted with 30% hydrogen peroxide (0.15 mL, 1.5 mmol) in THF (5 mL) for 30 h. VPC analysis (T_1 = 150 °C, T_2 = 250 °C, 16 °C/min) showed complete disappearance of starting selenides and appearance of two compounds eluating at t_R 1.7 min (**24a**) and t_R 2.3 min (**25**). HPLC (ethyl acetate–hexanes, 1:9) of the residue (210 mg, 100%) afforded the following.

(A) Spiro[tetrahydrofuran-2(3*H*),1′-4′-methylcyclohex-2′-ene]-3-carboxylic acid, methyl ester (24a) (100 mg, ~50%): IR (neat) 1730 cm^{-1}; ^1H NMR δ 0.96 (d, J = 6 Hz, 3 H), 1.20–1.42 (m, 2 H), 1.47–1.82 (m, 2 H), 1.95–2.52 (m, 3 H), 2.89 (t, J = 8 Hz, C_3 proton), 3.66 (s, 3 H, ester methyl group), 3.96 (m, 2 H, C_5 protons), 5.58 (m, 1 H, $C_{2'}$ proton), 5.78 (m, 1 H, $C_{3'}$ proton); ^{13}C NMR δ 20.4 (q), 25.2 (t), 28.90 (t), 29.64 (t), 30.82 (d), 51.73 (q), 53.56 (d, C_3), 65.79 (t, C_5), 80.45 (s, C_2), 129.27 (d), 138.03 (d), 172.71 (s, C=O).

Anal. Calcd for $C_{12}H_{18}O_3$: C, 68.54; H, 8.63. Found: C, 68.38; H, 8.39.

(B) Bicyclic ether 25 (98 mg, ~50%): IR (neat) 1710 cm^{-1}; ^1H NMR δ 1.01 (d, J = 8 Hz, 3 H), 1.5–1.7 (m, 3 H), 1.8–2.6 (m, 5 H), 3.35–3.65 (m, 2 H), 3.74 (s, 3 H), 3.98 (m, 1 H), 4.25 (m, 1 H); ^{13}C NMR δ 18.26 (q), 24.06 (t), 27.60 (t), 26.69 (t), 27.42 (d), 32.1 (t), 39.87 (t), 51.38 (q), 62.9 (t), 71.74 (d), 119.93 (s), 151.98 (s), 168.06 (s).

Anal. Calcd for $C_{12}H_{18}O_3$: C, 68.54; H, 8.63. Found: C, 68.39; H, 8.55.

Spiro[tetrahydrofuran-2(3*H*),1′-4′-methylcyclohexane]-3-carboxylic acid, methyl ester (26), obtained from selenide **20** (9.18 mg, 0.025 mmol) by reaction with Raney Ni; 5.1 mg (96%): IR (neat) 1735 cm^{-1}; ^1H NMR δ 0.89 (d, J = 6 Hz, 3 H), 1.0–1.7 (m, 9 H), 2.12 (m, 1 H), 2.35 (m, 1 H), 2.72 (t, J = 8 Hz, 1 H), 3.70 (s, 3 H), 3.72–4.08 (m, 2 H); ^{13}C NMR δ 22.23 (q), 28.52 (t), 30.54 (t), 31.37 (t), 31.42 (t), 31.84 (d), 51.66 (q), 53.75(d), 65.35 (t), 82.72 (s), 173.09 (s).

Anal. Calcd for $C_{12}H_{20}O_3$: C, 67.89; H, 9.50. Found: C, 67.95; H, 9.49.

2-(1-Hydroxy-4-methylcyclohexyl)-4-hydroxybutanoic acid (27a), prepared from **6b** (400 mg, 2 mmol) by the general procedure; 438 mg; mp 132 °C (ether–hexanes); 96.9%; IR ($CHCl_3$) 3400–3000 (br), 2920, 1720 cm^{-1}. Esterification of **27a** (226 mg, 1 mmol) with diazomethane in ethyl acetate gave **27b** (240 mg, 100%) as a colorless oil, which slowly solidified (mp 100 °C): IR ($CHCl_3$) 3400, 1730 cm^{-1}; ^1H NMR δ 0.91 (d, J = 4 Hz, 3 H), 1.2–2.2 (m, 12 H, with one D_2O exchangeable proton), 2.57 (dd, J = 8 Hz, 4 Hz, 1 H), 2.8 (br s, 1 H, exchangeable with D_2O), 3.65 (m, 2 H), 3.72 (s, 3 H).

Mesylation of 27b. The dihydroxy ester **27b** (120 mg, 0.5 mmol) was reacted with methanesulfonyl chloride in methylene chloride (3 mL) in the presence of triethylamine (52 mg, 0.5 mmol) at −20 °C. Crystallization from ether gave **27c** (226 mg, 71%, mp 55–56 °C): IR ($CHCl_3$) 3500, 2920, 1730, 1435, 1365, 1170, 970 cm^{-1}; ^1H NMR δ 0.90 (d, J = 4 Hz, 3 H), 1.1–1.6 (m, 7 H), 1.86 (m, 1 H), 2.89 (br s, 1 H, exchangeable with D_2O), 2.2 (m, 3 H), 2.51 (dd, J = 6.6 Hz, 6.0 Hz, 1 H), 3.00 (s, 3 H), 3.75 (s, 3 H), 4.25 (m, 2 H). The crystalline mesylate **27c** at room temperature slowly converted into a spiro[tetrahydrofuran-2(3*H*),1′-4′-methylcyclohexane]-3-carboxylic acid, methyl ester, whose IR and ^1H NMR spectra were superimposable on those of **26** obtained by reaction of **20** with Raney Ni.

Reaction of 8c with Benzeneselenenyl Chloride. 8c (416 mg, 1.84 mmol) was treated with benzeneselenenyl chloride (384 mg, 2 mmol) as described for the conversion of **8a** into **9**. The usual workup gave a crude oily gum (632 mg). TLC analysis (methylene chloride) showed three spots, R_f 0.80 (**28**), 0.68 (**29**), and 0.55 (**8c**). VPC analysis (T_1 = 150 °C, T_2 = 250 °C, 16 °C/min) showed three peaks t_R 1.4 min (**8c**), 5.3 min (**29**), and 5.8 min (**28**). Flash chromatography on silica gel (methylene chloride–hexanes, 7:3) afforded the following.

(A) Perhydrochromene derivative 29 (30 mg, 4.3%, mp 104 °C, from 95% EtOH): IR ($CHCl_3$) 2940, 1730, 1430, 1165, 1105, 965, 690 cm^{-1}; ^1H NMR δ 0.98 (s, 3 H), 1.08 (s, 3 H), 1.2–1.6 (m, 3 H), 1.7–2.0 (m, 2 H), 2.10–2.60 (m, 2 H), 2.80–3.20 (m, 2 H), 3.30 (br s, 1 H), 3.74 (s, 3 H), 3.89 (dd, J = 8 Hz, 4.4 Hz, 1 H), 7.40 (m, 3 H), 7.75 (m, 2 H); ^{13}C NMR δ 23.02 (q), 23.42 (t), 27.43 (t), 29.52 (t), 33.90 (q), 35.68 (s), 39.67 (t), 50.58 (d), 51.28 (s), 51.38 (q), 67.00 (t), 78.95 (d), 125.82 (s), 128.81 (d), 129.06 (d), 138.74 (d), 172.92 (s).

Anal. Calcd for $C_{19}H_{26}O_3Se$: C, 59.84; H, 6.87; Se, 20.70. Found: C, 59.82; H, 6.90; Se, 20.59.

(B) Spiro[tetrahydrofuran-2(3*H*),1′-[4′,4′-dimethyl-2′-(phenylseleno)cyclohexane]]-3-carboxylic acid, methyl ester (28) (340 mg, 48.3%, liquid): IR ($CHCl_3$) 2940, 1730, 1575, 1475, 1430, 1360, 1160, 1070, 990, 740, 690 cm^{-1}; ^1H NMR δ 0.88 (s, 3 H), 0.94 (s, 3 H), 1.0 (six-line m, 1 H), 1.31 (six-line m, 1 H), 1.62 (six-line m, 1 H), 1.79 (d, J = 8 Hz, 2 H, $C_{3'}$ protons), 2.04 (six-line m, 1 H), 2.30 (m, 2 H, C_4 protons), 3.30 (dd, J = 7 Hz, 6 Hz, 1 H, C_3 proton), 3.70 (t, J = 8 Hz, 1 H, $C_{2'}$ proton), 3.71 (s, 3 H, ester methyl group), 3.94 (m, 2 H, C_5 protons), 7.3 (m, 3 H), 7.65 (m, 2 H); ^{13}C NMR δ 25.17 (q), 31.33 (t), 31.66 (s, C_4), 32.15 (q), 32.55 (t), 35.79 (t), 45.14 (t), 48.31 (d, $C_{2'}$), 51.60 (q), 52.16 (d, C_3), 66.95 (t, C_5), 87.76 (s, C_2), 127 (d), 128.9 (d), 130.53 (s), 133.57 (d), 174.36 (s, C=O).

Anal. Calcd for $C_{19}H_{26}O_3Se$: C, 59.84; H, 6.87; Se, 20.70. Found: C, 59.94; H, 6.97; Se, 20.52.

8c (200 mg, 48.1%) also was isolated.

Spiro[tetrahydrofuran-2(3*H*),1′-4′,4′-dimethylcyclohex-2′-ene]-3-carboxylic acid, methyl ester (24b), prepared by reaction of **28** (192 mg, 0.5 mmol) with H_2O_2 (30%, 0.07 mL, 0.75 mmol) by the procedure described for conversion of **9** into **10a**. Preparative HPLC (ethyl acetate–hexanes, 1:9) afforded **24b** (95 mg, 84%) as a colorless oil: IR (neat) 2940, 1730, 1355, 1160, 1040, 890, 750 cm^{-1}; ^1H NMR δ 0.94 (s, 3 H), 1.02 (s, 3 H), 1.34 (m, 1 H), 1.66 (m, 3 H), 2.21, 2.41 (two m, 1 H each, C_4 protons), 2.88 (t, J = 8 Hz, C_3 proton), 3.70 (s, 3 H), 3.95 (m, 2 H, C_5 protons), 5.60 (q, J = 10 Hz, 2 H, vinyl protons); ^{13}C NMR δ 2.70 (t), 27.68 (q), 28.84 (s, $C_{4'}$), 29.59 (q), 31.68 (t), 33.62 (t), 51.63 (q), 53.33 (d), 65.68 (t), 80.81 (s, C_2), 127.75 (d), 141.62 (d), 172.70 (s).

Anal. Calcd for $C_{13}H_{20}O_3$: C, 69.61; H, 9.01. Found: C, 69.65; H, 9.01.

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Reaction Manifolds of Alkenes with [Hydroxy(tosyloxy)iodo]benzene: Stereospecific *syn*-1,2-Ditosyloxylation of the Carbon–Carbon Double Bond and Other Processes

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The treatment of various alkenes with [hydroxy(tosyloxy)iodo]benzene (**1**) in CH_2Cl_2 gives moderate yields of the corresponding *vic*-bis(tosyloxy)alkanes (**2**). When *cis*- and *trans*-2-butenes, *cis*- and *trans*-2-pentenes, *cis*-3-hexene, *cis*-4-octene, and cyclohexene are reactants, the tosyloxy ligands are introduced with syn stereospecificity. With *cis*- and *trans*-stilbenes, however, a mixture of *meso*- and *dl*-1,2-diphenyl-1,2-bis(tosyloxy)ethanes results from either alkene. Some alkenes react with **1** in a different way. Thus, *trans*-3-hexene and *trans*-4-octene with **1** give low yields of 2,5-bis(tosyloxy)-3-hexene and 3,6-bis(tosyloxy)-4-octene, respectively. Evidence is presented that the formation of the bis(tosyloxy)alk*enes* proceeds via initial oxidation of the trans alkenes by **1** to conjugated dienes and subsequent conjugate ditosyloxylation of the dienes. In a few cases, molecular rearrangements occur. Thus, norbornene with **1** gives 2,7-bis(tosyloxy)norbornane, among other products, while 1,1-diphenylethylene gives deoxybenzoin (major product) and (β,β-diphenylethenyl)phenyliodonium tosylate. The reaction of styrene with **1** depends on the medium; when CH_2Cl_2 is present, the product is 1-phenyl-1,2-bis(tosyloxy)ethane, but in the absence of solvent, the product is 1,1-bis(tosyloxy)-2-phenylethane. Most alkenes react with **1** to give *p*-toluenesulfonic acid as a byproduct, and, in rare instances, (iodoxy)benzene is obtained. A mechanism for the *vic*-ditosyloxylation of alkenes by **1**, consistent with the observed syn stereospecificity, is proposed.

We recently described the reactions of several alkenes and alkynes with [hydroxy(tosyloxy)iodo]benzene (**1**),[1] a readily available, crystalline organoiodine(III) compound.[2-4] Particularly relevant is the observation that cyclohexene, 2,3-dimethyl-2-butene, styrene, and *cis*- and *trans*-stilbenes were converted directly by **1** to the corresponding *vic*-bis(tosyloxy)alkanes (**2**) (eq 1); in the case of cyclohexene, only the *cis*-1,2-bis(tosyloxy)cyclohexane was isolated.

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