Synthetic Studies on Cembranolides. Stereoselective Synthesis of a Crassin Acetate Synthon

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A stereoselective synthesis of the lactone tetrol derivative **21**, a possible synthetic precursor of the cembranolide crassin acetate (**1**), is described. The cycloheptenone **5** provides the requisite seven-carbon chain of tetrol **21**. The acetic acid moiety was introduced via alkylation with ethyl iodoacetate followed by saponification. Selenolactonization of the resulting keto acid afforded lactone **8**, which was reduced to hydroxy lactone **9**. Protection as the silyl ether **10** and oxidation with *m*-chloroperoxybenzoic acid and then treatment with acetic anhydride yielded the rearranged acetate **13**. Selenoxide elimination gave enol acetate **14**, which was brominated and dehydrobrominated to the enone **18**. Addition of lithium tetramethylalanate gave the alcohol **19** as the sole stereoisomer. Protection as the (methoxyethoxy)methyl ether **20** followed by ozonolysis and borohydride reduction afforded the desired diol **21** as a crystalline substance. The structure of this intermediate was confirmed by single-crystal X-ray analysis.

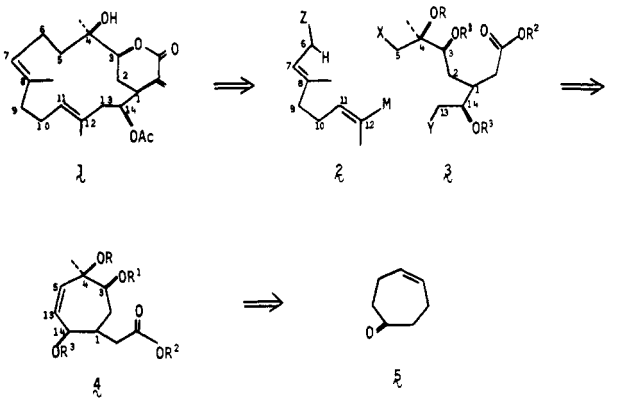
Crassin acetate (**1**), a major constituent of the Caribbean gorgonian *Pseudoplexaura porosa*, was the first cembranolide to be isolated from marine sources.[1] In the ensuing 12 or so years, a host of others have been identified in various gorgonians and soft corals.[2] The structural diversity and possible biological activity of this growing class of diterpenes stimulated our interest in further developing their chemistry[3] and exploring possible total synthesis schemes. We now describe some initial studies on the stereoselective synthesis of an intermediate with potential for elaboration to cembranolide systems such as crassin acetate (**1**).

Our synthetic plan calls for the construction of two major pieces (Scheme I), the diene **2** and an α,ω-difunctional triol acid **3** or a derived lactone. Sequential coupling of these pieces via extrusion first of MY[4] and then XZ[5] followed by deblocking and, if needed, lactone transposition[3] completes the synthesis. The lactone derivative **21** (Chart I) of triol acid **3** is the subject of this report.

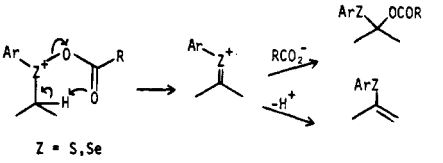
The known cycloheptenone **5** was selected as the source of the seven contiguous carbon atoms of lactone **21**.[6] We foresaw several advantages in this strategy. Foremost, the inherent rigidity of bridged ring systems (e.g., **8**, Chart I) could be used to introduce chiral centers in a predictable and controlled manner. The cycloalkene approach (Scheme I) also permits storage of the two functionalized chain termini in **3** as a double bond, thereby minimizing functionality in synthetic precursors. Finally, the scheme starts with a symmetrical ketone and proceeds via internally directed functionality elaboration, thereby avoiding regiochemical problems.

Alkylation of cycloheptenone **5**[6] with ethyl iodoacetate followed by saponification afforded keto acid **7** in 72% yield. Selenolactonization[7a] was best effected with benzeneselenenyl bromide in methylene chloride at low temperature, whereupon seleno lactone **8** was produced in up to 75% yield along with recovered acid **7**. This temperature-dependent cyclization appears to be reversible with closure favored at lower temperature.

Scheme I



Scheme II



The selective reduction of keto lactone **8** could be effected with sodium borohydride but lithium tri-*tert*-butoxyaluminum hydride gave better results. In both cases a single lactone product was produced with the spectral properties of γ-lactone **9** rather than the expected δ-lactone. Fortunately, we have shown that interconversion of γ- and δ-lactone moieties can be achieved on the intact cembranolide structure[3] so the γ-lactone **9** is still a useful intermediate.

The stereochemistry of lactone **9** is set by the direction of hydride attack on keto lactone **8**. The bridged nature of this intermediate clearly directs addition to the convex face of the ring system, thereby producing a transient cis hydroxy lactone. The aforementioned predilection of this

(1) Weinheimer, A. J.; Matson, J. A. *Lloydia* **1975**, *38*, 378. Hossain, M. B.; van der Helm, D. *Recl. Trav. Chim. Pays-Bas* **1969**, *88*, 1413.
(2) Weinheimer, A. J.; Chang, C. W. J.; Matson, J. A., *Fortschr. Chem. Org. Naturst.* **1979**, *36*, 286.
(3) Marshall, J. A.; Karas, L. J.; Coghlan, M. J., *J. Org. Chem.*, following article in this issue.
(4) For example, vinyl cuprate alkylation. Cf. Corey, E. J.; Nicolaou, K. C.; Beames, D. J. *Tetrahedron Lett.* **1974**, 2439. Normant, J. F.; Cahiez, G.; Chuit, C.; Alexakis, A.; Villieras, J. *J. Organomet. Chem.* **1972**, *40*, C49.
(5) For example, allyl phenyl sulfide anion cycloalkylation. Cf. Kodama, M.; Matsuki, T.; Ito, S. *Tetrahedron Lett.* **1975**, 3065; **1977**, 2763.
(6) Bahurel, Y.; Collouges, F.; Menet, A.; Pautet, F.; Poneet, A.; Descoste, G., *Bull. Soc. Chim. Fr.* **1971**, 2203; Wilson, S. R.; Wiesler, D. P. *Synth. Commun.* **1980**, *10*, 339. We are indebted to Professor Wilson for helpful advice on the preparation of enone **5**.
(7) (a) Cf. Clive, D. L.; Russell, C. G.; Chittattu, G.; Singh, A. *Tetrahedron* **1980**, *36*, 1399. Nicolaou, K. C.; Seitz, S. P.; Sipio, W. J.; Blount, J. F. *J. Am. Chem. Soc.* **1979**, *101*, 3884. (b) Clive, D. L. J.; Kâtê,, V. N. *J. Org. Chem.* **1981**, *46*, 231.

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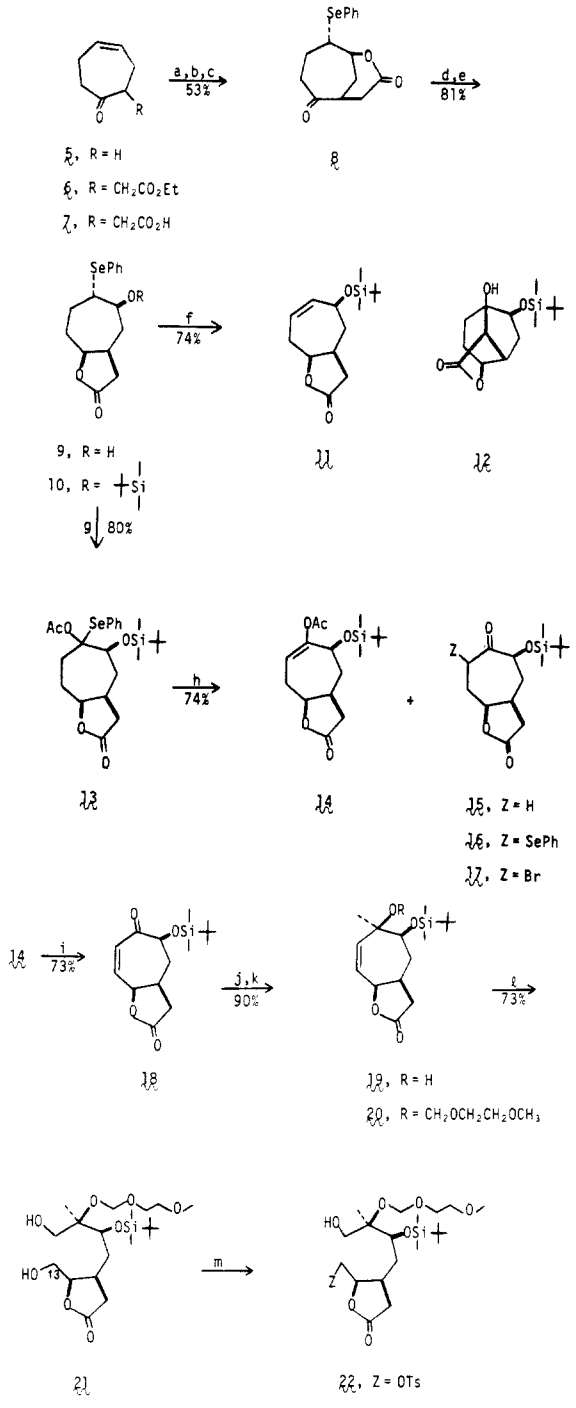
Chart I



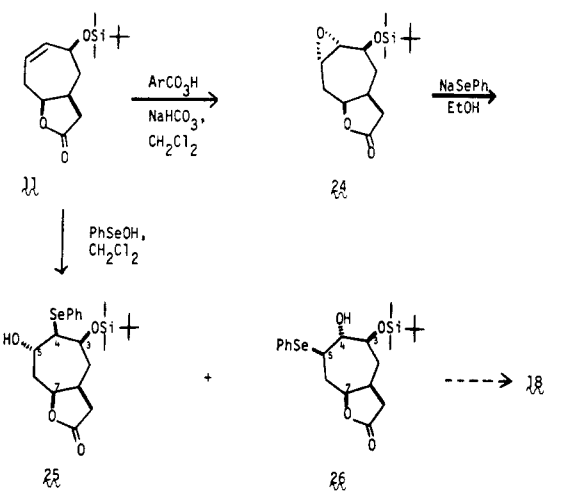
a) $(iPr)_2NLi$, THF, -78°C; ICH_2CO_2Et b) KOH, EtOH, 25°C; HCl c) PhSeBr, Et_3N, CH_2Cl_2, -20°C d) $LiAl(O\underline{t}\text{-}Bu)_3H$, THF, -10°C e) $\underline{t}$-$BuMe_2SiCl$, imidazole, 25°C f) H_2O_2, CH_2Cl_2 g) $\underline{m}$-$ClC_6H_4CO_3H$, THF, -78°C; Ac_2O, THF, 65°C h) H_2O_2, pyridine, CH_2Cl_2 i) Br_2, CH_2Cl_2, 0°C; $CH_3CON(CH_3)_2$, $CaCO_3$, 170°C j) $LiAlMe_4$, $PhCH_3$, 25°C k) $ClCH_2OCH_2CH_2OCH_3$, i-Pr_2NEt, THF, 70°C l) O_3, CH_2Cl_2, MeOH, -78°C; $NaBH_4$, -78°C - 0°C m) $\underline{p}$-TsCl, C_5H_5N, 25°C

intermediate for translactonization supports the stereochemical assignment.

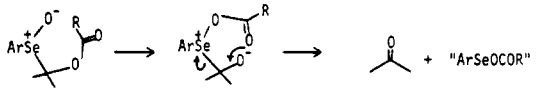
The *tert*-butyldimethylsilyl-protected hydroxy lactone **10** was transformed via selenoxide elimination to olefin **11**. A number of seemingly plausible schemes (Chart II) were examined for converting this olefin to enone **18**.[8] The first

(8) Royce, R. D., Jr., unpublished results.

Chart II



Scheme III



involved the epoxy lactone **24** obtained by treatment of **11** with *m*-chloroperoxybenzoic acid. The stereochemistry of this epoxide is based on the assumption of attack by the peroxy acid on the less hindered convex face of the double bond. Unfortunately, the addition of sodium phenyl selenide[9a] gave rise to a nearly 1:1 mixture of regioisomers **25** and **26** in low yield. Consequently, the approach was abandoned. Phenylselenenic acid added cleanly to the double bond of lactone **11**, but the sole product was the phenylselenohydrin **25** of undesired regiochemistry. Since olefin **11** could not be readily transformed to enone **18**, we turned to a more direct approach using the selenophenyl grouping of **10** as a carbonyl precursor. The equivalent transformation is well documented for sulfides as the Pummerer reaction.[10] It entails the treatment of a sulfoxide with an acylating agent to afford a geminal acyloxy sulfide, the formal result of elimination and readdition of a carboxylic grouping (Scheme II).

Surprisingly, there are but a few examples of the corresponding reaction of selenoxides.[11] Our initial efforts with selenide **10** were encouraging and eventually, through careful monitoring of experimental conditions, we were able to realize an 80% yield of acetoxy selenide **13** along with 10–15% of a vinylic selenide. The former product appeared homogeneous by chromatographic and spectral criteria, but no effort was made to ascertain its stereochemistry. Vinyl selenides were major products from attempted Pummerer-type rearrangements of several model seleno lactones examined in ancillary studies. In these cases, though, we did not try to optimize the experimental conditions.

Oxidation of acetoxy selenide **13** with aqueous hydrogen peroxide and in situ elimination of the selenoxide yielded a 3:1 mixture of enol acetate **14** and ketone **15**. The two products are produced simultaneously and thus the latter does not arise through fortuitous hydrolysis of the former. Its genesis most likely entails acyl transfer and subsequent

(9) (a) Cf. Sharpless, K. B.; Lauer, R. F. *J. Am. Chem. Soc.* **1973**, *85*, 2697. (b) Cf. Hori, T.; Sharpless, K. B. *J. Org. Chem.* **1978**, *43*, 1689.

(10) Pummerer, R. *Chem. Ber.* **1909**, *42*, 2282. Cf. Becker, H. D.; Mikol, G. J.; Russel, G. A. *J. Am. Chem. Soc.* **1963**, *85*, 3410.

(11) Cf. Reich, H. J.; Renga, J. M.; Reich, I. L. *J. Am. Chem. Soc.* **1975**, *97*, 5434; *J. Org. Chem.* **1974**, *39*, 2133. Reich, H. J.; Shah, S. K. *J. Org. Chem.* **1977**, *42*, 1773.

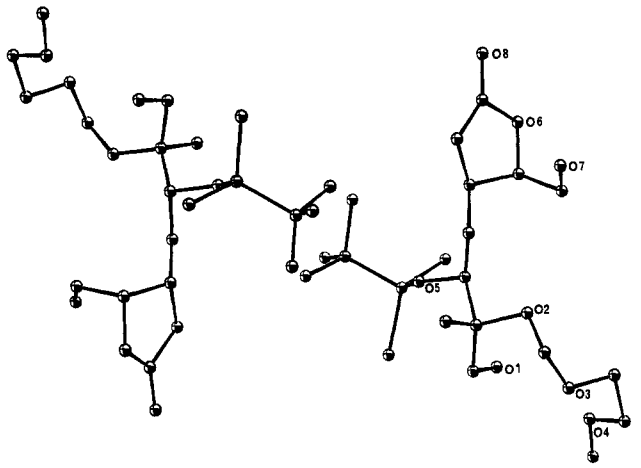


Figure 1. ORTEP drawing of diol **21**, a *d,l* pair. The origin and crystallographic center of symmetry relating the two enantiomers are in the center of the drawing. The oxygen atoms are designated by numbers.

elimination of phenylseleninic acetic anhydride (Scheme III).

Attempts to convert ketone **15** to the α-phenylselenide **16** and thence enone **18**[11] were thwarted by intramolecular Claisen condensation leading to tricyclic alcohol **12** under basic conditions. However, the conversion could be effected with benzeneselenenyl chloride in acid.[12] Treatment of the resulting selenide with hydrogen peroxide afforded enone **18** but only in 40% overall yield. Enone **18** could be obtained more efficiently via bromination of enol acetate **14** and subsequent dehydrobromination of the resulting α-bromo ketone **17** with calcium carbonate in hot *N,N*-dimethylacetamide.[13]

We were unable to effect addition of methyllithium or methylmagnesium iodide to keto lactone **18**. Our efforts led to hydroxy lactone product mixtures devoid of *C*-methyl resonance in the NMR spectra. Evidently, a Claisen cyclization analogous to that leading to lactone **12** was taking place. We therefore examined less basic nucleophilic methylating agents. Our first trials with trimethylaluminum gave promising results. Two isomeric methyl adducts were produced in ratios that varied between 1:1 and 3.5:1, depending upon reaction temperature.[14a] These adducts are most likely stereoisomers of general structure **19**. With lithium tetramethylalanate[14b] only one of these isomers was produced. We expected nucleophilic attack on ketone **18** to preferably take place trans to the silyl ether substituent, producing alcohol **19** as the major methyl adduct. This alcohol contains the essential features and stereochemistry of the seven contiguous centers, C-13 to C-5, of the crassin acetate system (Scheme I). Accordingly, the cycloheptene ring has fulfilled its function as a stereochemical control element and the stage is set for ring cleavage. Toward that end, alcohol **19** was protected as the (methoxyethoxy)methyl ether **20**.[15] Low-temperature ozonolysis followed by reduction of the intermediate ozonide in situ with sodium borohydride led to diol **21**. This diol could be crystallized in a form suitable for X-ray analysis which confirmed the assigned structure (Figure 1).[16]

For our projected synthesis of cembranolides (Scheme I), it was necessary to convert diol **21** to a suitable derivative for coupling with the diene **2**. We felt that steric factors would permit selective esterification of the C-13 (crassin acetate numbering) hydroxyl group of **21**. In fact, this selective transformation was readily effected with *p*-toluenesulfonyl chloride in pyridine. The structure of tosylate **22** thus obtained was confirmed by the NMR spectrum. Work is now in progress on coupling reactions with tosylate **22** along the lines depected in Scheme I.

Experimental Section[17]

4-Cycloheptenone (5). The procedures of Bahurel and Wilson were modified.[6] A 2-L three-necked flask equipped with a reflux condenser, two glass stoppers, and a magnetic stirring bar was charged with 1.1 L of absolute ethanol. Sodium metal (58.4 g, 2.54 mol) was carefully added in small pieces with vigorous stirring over 0.5 h. After all of the metal had dissolved, 150 g (1.15 mol) of ethyl acetoacetate was added and the resultant green solution was stirred at 25 °C for 0.5 h. A 3-L three-necked flask equipped with a reflux condenser, a 250-mL addition funnel, a glass stopper, and a magnetic stirring bar was charged with 300 mL of absolute ethanol and 158 g (1.27 mol) of *cis*-1,4-dichloro-2-butene. This solution was brought to reflux. The light-green enolate solution was added via cannula (with the aid of positive nitrogen pressure) to the addition funnel attached to the 3-L flask. The enolate solution was then carefully added to the hot dichloride over 1 h; the addition funnel was refilled as necessary via the cannula. After the addition was complete, the reaction mixture was stirred at reflux an additional 1 h, cooled, and diluted with 500 mL of water. Most of the ethanol was removed by rotary evaporator and the product was then diluted with 1.2 L of ether. The ether was washed with three 300-mL portions of water and dried over magnesium sulfate. The solvent was removed under reduced pressure and the product was purified by distillation [bp 51–61 °C (0.3 torr)], affording 127 g (74%) of ethyl 1-acetyl-2-vinylcyclopropanecarboxylate as a 2:1 mixture of the cis and trans isomers: IR (film) λ_{max} 3.25, 3.36, 5.76, 5.85, 6.07, 6.90, 8.85, 10.81 μm; NMR ($CDCl_3$, Me_4Si) δ 5.0–4.8 (vinyl, m, 3 H), 4.18 (CH_2CH_3, q, J = 7.5 Hz), 2.30 (CH_3CO, s, trans), 2.21 (CH_3CO, s, cis), 2.15 (cyclopropane, m, 1 H), 1.90–1.15 (cyclopropane, m, 2 H), 1.29 (CH_3CH_2, t, J = 7.5 Hz).

A solution of 127 g (0.847 mol) of the above keto ester, 258 g (4.6 mol) of potassium hydroxide, and 2.3 L of water was stirred at 25 °C for 16 h. Extraction of the solution with three 800-mL portions of ether served to remove undesired byproducts. The aqueous phase was then heated to reflux for 30 h and cooled, and the product was isolated with ether. The ether was removed by distillation and the product was distilled [60 °C (12 torr)] affording 20 g (30%) of ketone **5** as a colorless oil: IR (film) λ_{max} 3.30, 3.38, 3.51, 5.85, 6.92, 7.41, 8.30, 11.49 μm; NMR ($CDCl_3$, Me_4Si) δ 5.73 (vinyl, t, J = 4 Hz, 2 H), 2.67 (m, 4 H), 2.34 (m, 4 H).

Ethyl 2-(2-Oxo-5-cycloheptenyl)acetate (6). A solution of 22.2 g (0.219 mol) of diisopropylamine and 600 mL of tetrahydrofuran was cooled to −78 °C and 95 mL of 2.3 M *n*-butyllithium (0.219 mol) in hexane was added dropwise. A solution of 22.0 g (0.199 mol) of ketone **5** in 50 mL of tetrahydrofuran was then added over 0.5 h and the resultant solution was stirred an additional 1.5 h. Ethyl iodoacetate (42.7 g, 0.219 mol) was then introduced rapidly via syringe and the reaction mixture was stirred for 1.5 h at −78 °C. The mixture was slowly allowed to come to −20 °C and was quenched by adding 400 mL of 5% hydrochloric acid. Isolation with ether afforded the crude product. Purification by short-path distillation (oven temperature 80 °C, 0.05 torr) gave 29.5 g (76%) of keto ester **6** as a colorless oil: IR (film) λ_{max} 3.27, 3.36, 3.40, 5.76, 5.87, 7.25, 8.30, 9.62 μm; NMR ($CDCl_3$, Me_4Si) δ 5.72 (vinyl, m, 2 H), 4.11 (CH_2CH_3, q, J = 7.5 Hz), 3.6–3.15 (H-1,

(12) Sharpless, K. B.; Lauer, R. F.; Teranishi, A. Y. *J. Am. Chem. Soc.* **1973**, *95*, 6137.
(13) Marshall, J. A.; Andersen, N. H. *J. Org. Chem.* **1966**, *31*, 667.
(14) (a) Cf. Yankee, E. W.; Axen, V.; Bundy, G. L. *J. Am. Chem. Soc.* **1974**, *96*, 5865. (b) Cf. Zweifel, G.; Steele, R. B. *J. Am. Chem. Soc.* **1967**, *89*, 2754.
(15) Corey, E. J.; Gras, J.; Ulrich, P. *Tetrahedron Lett.* **1976**, 809.
(16) The crystal structure determination was carried out by Professor E. L. Amma and Dr. E. A. H. Griffith at the University of South Carolina.

(17) The prefixes "α" and "β" are used to denote relative stereochemistry in racemic compounds. Microanalyses were performed by Micro-Tech Laboratories, Inc., Skokie, IL. Melting points were determined on a calibrated Thomas capillary melting point apparatus. Melting points are not corrected. High-pressure liquid chromatography (HPLC) was performed on Waters Associates ALC-201 Model 6000 and Model LC500 instruments using Porasil, μ-Porasil, and Corasil II columns.

m), 2.8–2.0 (m, 8 H), 1.23 (CH_2CH_3, t, J = 7.5 Hz). Anal. Calcd for $C_{11}H_{16}O_3$: C, 67.37; H, 8.21. Found: C, 66.98; H, 8.46.

2-(2-Oxo-5-cycloheptenyl)acetic Acid (7). A solution of 16.7 g (0.085 mol) of keto ester **6**, 26 g (0.464 mol) of potassium hydroxide, and 500 mL of absolute ethanol was stirred at 25 °C for 1 h. The mixture was diluted with 200 mL of water and the ethanol was removed by rotary evaporator. The alkaline residue was diluted with 750 mL of water and extracted with two 200-mL portions of ether. The aqueous phase was acidified with 60 mL of concentrated hydrochloric acid. Isolation with ethyl acetate afforded 13.3 g (93%) of the crude keto acid **7**, which was not purified: IR (film) λ_{max} 5.78, 5.85, 7.04, 8.20 μm; NMR ($CDCl_3$, Me_4Si) δ 10.52 (COOH, s), 5.58 (vinyl, m, 2 H), 3.4–3.0 (H-1, m), 2.7–2.1 (m, 8 H).

2-[6β-Hydroxy-2-oxo-5α-(phenylseleno)cyclohept-1β-yl]acetic Acid Lactone (8). The procedure of Nicolaou[18] was employed. A flame-dried 1-L three-necked flask equipped with a 250-mL addition funnel, two glass stoppers, and a magnetic stirring bar was charged with a solution of 13.3 g (79.1 mmol) of keto acid **3**, 8.8 g (87 mmol) of triethylamine, and 300 mL of dichloromethane. Another small magnetic stirring bar was placed in the addition funnel which was charged with a solution of 13.6 g (43.5 mmol) of diphenyl diselenide in 125 mL of dichloromethane. Both solutions were stirred magnetically as 43.5 mL (43.5 mmol) of a 1 M solution of bromine in dichloromethane was added by syringe over 15 min to the diphenyl diselenide solution. The keto acid was then cooled to −78 °C and the resultant black-red solution of benzeneselenenyl bromide was added from the addition funnel over 0.5 h. The reaction mixture was slowly warmed to −20 °C and further stirred at −20 °C for 60 h. The reaction mixture was poured into 300 mL of saturated sodium bicarbonate solution and diluted with 600 mL of ethyl acetate. The aqueous layer was removed and the solution was washed with two 300-mL portions of sodium bicarbonate solution and once with 200 mL of brine. The product was dried over magnesium sulfate, and the solvents were removed under reduced pressure. The excess benzeneselenenyl bromide was removed by filtration with hexane through 400 g of silica gel. The column was then washed with 50% ethyl acetate–hexane, affording 19.3 g (75%) of keto lactone **8** as a light yellow solid.

An analytical sample, mp 121–123 °C, was prepared by recrystallization from 50% ethyl acetate–hexane: IR (KBr) λ_{max} 3.27, 3.40, 5.75, 5.87, 6.33, 7.49, 8.20, 9.48, 12.58 μm; NMR ($CDCl_3$, Me_4Si) δ 7.49 (aromatic, m, 2 H), 7.21 (aromatic, m, 3 H), 4.90 (H-3, dd, J = 6.5, 4.0 Hz), 3.89 (H-4, dt, J = 6.5, 1.5 Hz), 3.2–1.8 (m, 7 H). Anal. Calcd for $C_{15}H_{16}O_3Se$: C, 55.75; H, 4.99. Found: C, 55.82; H, 4.95.

2-[2β,6β-Dihydroxy-5α-(phenylseleno)cyclohept-1β-yl]acetic Acid γ-Lactone (9). A slurry of 2.90 g (76.3 mmol) of lithium aluminum hydride and 400 mL of tetrahydrofuran was cooled to 10 °C and 16.9 g (0.229 mol) of *tert*-butyl alcohol was added dropwise over 0.5 h. The resultant solution was stirred for 0.5 h at 25 °C and then cooled to −10 °C at which time a solution of 18.4 g (56.9 mmol) of seleno lactone **8** in 50 mL of tetrahydrofuran was added. After being stirred for 1 h at −10 °C, the reaction mixture was carefully quenched with 10% hydrochloric acid and the product was isolated with ethyl acetate. Recrystallization from 30% ethyl acetate–hexane afforded 15.3 g (83%) of hydroxy lactone **9** as beige needles: mp 118–120 °C; IR (KBr) λ_{max} 2.92, 3.26, 3.41, *5.63*, *5.75*, 6.31, 8.44, 10.15 μm; IR ($CHCl_3$) λ_{max} 2.92, 3.25, 3.40, *5.63*, 6.31, 8.40, 10.10 μm; NMR ($CDCl_3$, Me_4Si) δ 7.40 (aromatic, m, 2 H), 7.18 (aromatic, m, 3 H), 4.5–4.1 (H-7, ddd, J = 15, 8, 2 Hz) 3.4–1.4 (m, 12 H). Anal. Calcd for $C_{15}H_{18}O_3Se$: C, 55.40; H, 5.58. Found: C, 55.28; H, 5.47.

2-[6β-(*tert*-Butyldimethylsiloxy)-2β-hydroxy-5α-(phenylseleno)cyclohept-1β-yl]acetic Acid Lactone (10). The method of Corey[19] was employed. A solution of 10.3 g (31.6 mmol) of hydroxy lactone **9**, 6.02 g (40.0 mmol) of *tert*-butyldimethylsilyl chloride, 5.44 g (80.0 mmol) of imidazole, and 50 mL of dimethylformamide was stirred at 25 °C for 12 h. The reaction was diluted with 500 mL of ether and washed 5 times with 75-mL portions of 5% hydrochloric acid and once with 75 mL of brine. The ether was dried over magnesium sulfate, and the solvents and the *tert*-butyldimethylsilyl chloride were removed under reduced pressure, affording 13.7 g (98%) of silyl ether **10** as a white solid.

An analytical sample, mp 81–84 °C, was prepared by recrystallization from hexane: IR (film) λ_{max} 3.25, 3.38, 3.40, 3.44, 3.49, 5.60, 6.31, 6.78, 7.97, 11.90 μm; NMR ($CDCl_3$, Me_4Si) δ 7.48 (aromatic, m, 2 H), 7.24 (aromatic, m, 3 H), 4.50 (H-7, m), 3.72 (H-3, m), 3.33 (H-4, m), 2.97–1.40 (m, 9 H), 0.88 (*tert*-butyl, s), 0.12, 0.08 ($SiCH_3$). Anal. Calcd for $C_{21}H_{32}O_3SeSi$: C, 57.40; H, 7.34. Found: C, 57.49; H, 7.29.

2-[6β-(*tert*-Butyldimethylsiloxy)-2β-hydroxy-4-cyclohepten-1β-yl]acetic Acid Lactone (11). A two-phase system containing 2.10 g (4.78 mmol) of selenide **10**, 25 mL of dichloromethane, and 25 mL of 5% aqueous hydrogen peroxide was stirred vigorously for 2 h at 25 °C. The reaction was diluted with 100 mL of saturated sodium carbonate solution and the product was isolated with dichloromethane. Purification was accomplished by recrystallization from hexane, affording 997 mg (74%) of lactone **11** as white needles: mp 56–57 °C; IR (KBr) λ_{max} 3.30, 3.38, 3.50, 5.60, 6.83, 7.94, 8.40, 9.35, 12.82 μm; NMR ($CDCl_3$, Me_4Si) δ 5.42 (vinyl, m, 2 H), 4.75–3.90 (H-3 and H-7, m), 3.1–1.8 (m, 7 H), 0.89 (*tert*-butyl, s), 0.11 (dimethyls, s). Anal. Calcd for $C_{15}H_{26}O_3Se$: C, 63.79; H, 9.28. Found: C, 63.55; H, 9.27.

Epoxy Lactone 24. A solution of 0.890 g (3.15 mmol) of unsaturated lactone **11**, 1.84 g (10.7 mmol) of 95% *m*-chloroperoxybenzoic acid, 0.750 g (9.04 mmol) of sodium bicarbonate, and 20 mL of dichloromethane was stirred for 10 h at 25 °C. The mixture was diluted with 50 mL of ethyl acetate and washed with four 10-mL portions of 10% sodium hydroxide and once with 10 mL of brine. The solution was dried over magnesium sulfate, and the solvents were removed by rotary evaporator. Purification by distillation (oven temperature 190 °C, 0.05 torr) afforded 0.817 g (87%) of epoxide **24**, which was homogeneous by HPLC and TLC: IR (film) λ_{max} 3.38, 3.40, 3.44, 3.49, 5.59, 6.80, 7.91, 9.66, 11.83, 12.82 μm; NMR ($CDCl_3$, Me_4Si) δ 4.55 (H-7, m), 3.90 (H-3, m), 3.01 (H-1 and H-4, m), 2.85–1.55 (m, 7 H), 0.85 (*tert*-butyl, s), 0.10 (dimethyls, s).

Reaction of Epoxy Lactone 24 with Sodium Phenyl Selenide. The procedure of Sharpless was employed.[20] To a solution of 124 mg (0.40 mmol) of diphenyl diselenide in 50 mL of absolute ethanol was added 30 mg (0.79 mmol) of sodium borohydride. A solution of 200 mg (0.69 mmol) of epoxide **24** in 10 mL of absolute ethanol was added to the colorless reaction mixture. The reaction was heated to reflux for 12 h, cooled, and diluted with 50 mL of saturated sodium bicarbonate solution. The products were isolated with ethyl acetate. Purification by HPLC afforded 37 mg (12%) of hydroxy selenide **25**, 42 mg (14%) of hydroxy selenide **26**, and 21 mg of an unidentified carboxylic acid. Structures were assigned from the NMR spectra. Further purification was not attempted.

25: IR (film) λ_{max} 2.90, 3.25, 3.37, 3.39, 5.63, 6.33, 6.86, 9.26 μm; NMR ($CDCl_3$, Me_4Si) δ 7.57 (aromatic, m, 2 H), 7.33 (aromatic, m, 3 H), 4.91–3.40 (H-3, H-4, H-5, and H-7, m), 3.4–1.7 (m, 10 H), 0.90 (*tert*-butyl, s), 0.11 (dimethyl, s).

26: IR (film) λ_{max} 2.87, 3.26, 3.37, 3.39, 5.65, 6.31, 7.94, 11.90 μm; NMR ($CDCl_3$, Me_4Si) δ 7.58 (aromatic, m, 2 H), 7.28 (aromatic, m, 3 H), 4.95 (H-7, m), 4.14 (H-3 and H-5, m), 3.45 (H-4, dd, $J_{4,5}$ = 5.4 Hz, $J_{4,3}$ = 2.9 Hz), 2.8–1.8 (m, 10 H), 0.90 (*tert*-butyl, s), 0.08 (dimethyls, s).

Reaction of Unsaturated Lactone 11 with Benzeneselenenic Acid. The procedure of Sharpless was employed.[20] A solution of 845 mg (2.71 mmol) of diphenyl diselenide and 15 mL of dichloromethane was cooled to 0 °C and 0.25 mL (2.71 mmol) of 30% aqueous hydrogen peroxide solution was added dropwise with stirring. After 0.5 h, 436 mg (3.62 mmol) of magnesium sulfate was added and stirring was continued for 0.5 h. The solution was allowed to warm to 25 °C and 510 mg (1.81 mmol) of the unsaturated lactone **11** was added in 5 mL of dichloromethane. After 18 h at 25 °C the reaction was diluted with ethyl acetate. Isolation of the product with ethyl acetate gave 621 mg (78%) of an orange oil identical with hydroxy selenide **25** obtained from the sodium phenyl selenide opening of epoxy lactone **24**.

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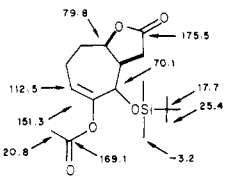
Acetoxy Selenide 13. A 1-L three-necked flask equipped with a reflux condenser, two glass stoppers, and a magnetic stirring bar was charged with 150 mL of tetrahydrofuran and 4.12 g (22.8 mmol) of 95% *m*-chloroperoxybenzoic acid. After the acid had dissolved, the solution was cooled to −78 °C and a solution of 10.0 g (22.8 mmol) of silyl ether **10** in 25 mL of tetrahydrofuran was added dropwise via syringe with stirring. After 20 min, 10 mL (0.105 mol) of acetic anhydride and 5.0 g (0.060 mol) of anhydrous sodium acetate were added, and the solution was allowed to warm slowly to 20 °C. The reaction mixture was heated to reflux for 3 h. The mixture was cooled to 30 °C, 50 mL of methanol was added, and stirring was continued for 0.5 h. The solution was diluted with 300 mL of ethyl acetate and washed with four 75-mL portions of 10% sodium hydroxide and once with 100 mL of brine. The solution was dried over magnesium sulfate, and the solvents were removed by rotary evaporator, affording 10.3 g (96%) of crude product. Purification by medium-pressure liquid chromatography afforded 8.40 g (80%) of acetoxy selenide **13** as a yellow oil: IR (film) λ_{max} 3.26, 3.38, 3.40, 3.50, 5.60, 5.78, 6.33, 7.30, 7.94, 9.76, 11.83 μm; NMR ($CDCl_3$, Me_4Si) δ 7.52 (aromatic, m, 2 H), 7.20 (aromatic, m, 3 H), 4.51 (H-7 and H-3, m), 3.1–1.7 (m, 9 H), 2.04 (CH_3CO, s), 0.92 (*tert*-butyl, s), 0.09 (dimethyls, s). This material was used without further purification.

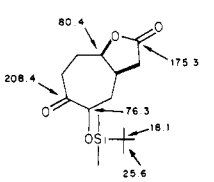
Oxidative Elimination of Acetoxy Selenide 13. A 1-L three-necked flask equipped with an argon inlet, two glass stoppers, and a magnetic stirring bar was charged with 10.0 g (20.1 mmol) of acetoxy selenide **13**, 2 mL (24.8 mmol) of pyridine, 20 mL (0.214 mol) of 30% aqueous hydrogen peroxide, 100 mL of dichloromethane, and 80 mL of water. This two-phase system was stirred vigorously for 3.5 h. The reaction was neutralized by carefully adding 5 g of sodium carbonate. The solution was poured into 300 mL of ethyl acetate and the aqueous phase was removed. The solution was washed with two 100-mL portions of saturated sodium bicarbonate solution and once with 75 mL of brine. The product was dried over magnesium sulfate, and the solvents were removed by rotary evaporator. Purification by column chromatography (silica gel, 30% ethyl acetate–hexane) gave 3.89 g (57%) of enol acetate **14**, mp 87–88 °C, and 1.11 g (17%) of ketone **15**, mp 86–88 °C.

14: IR (film) λ_{max} 3.38, 3.50, 5.60, 5.71, 5.95, 6.80, 7.30, 9.71, 11.50, 11.90 μm; NMR ($CDCl_3$, Me_4Si) δ 5.41 (H-5, dd, J = 9.0, 5.5 Hz), 4.70 (H-7, ddd, J = 14, 7, 1 Hz), 4.31 (H-3, ddd, J = 12, 7, 0.5 Hz), 3.0–1.7 (m, 7 H), 2.12 (OCH_3, s), 0.90 (*tert*-butyl, s), 0.10 (dimethyls, s); ^{13}C NMR ($CDCl_3$, Me_4Si).



Remaining resonances δ 35.5, 35.0, 32.3, 25.2. Anal. Calcd for $C_{17}H_{28}O_5Si$: C, 59.97; H, 8.29. Found: C, 60.00; H, 8.33.

15: IR (film) λ_{max} 3.37, 3.39, 5.57, 5.75, 6.80, 7.94, 11.76, 12.66 μm; NMR ($CDCl_3$, Me_4Si) δ 4.67 (H-7, m), 4.19 (H-3, t, J = 6.0 Hz), 3.0–1.7 (m, 9 H), 0.87 (*tert*-butyl, s), 0.10, 0.05 (dimethyls, s); ^{13}C NMR ($CDCl_3$, Me_4Si).



Remaining resonances δ 36.6, 35.6, 35.2, 34.1, 24.5, −2.6, −3.3. Anal. Calcd for $C_{15}H_{26}O_4Si$: C, 60.37; H, 8.78. Found: C, 60.10; H, 8.79.

Bromo Ketone 17. A solution of 105 mg (0.31 mmol) of enol acetate **14**, 200 mg (1.89 mmol) of sodium carbonate, and 7 mL of carbon tetrachloride was cooled to 0 °C and treated dropwise with 0.32 mL (0.032 mol) of a 1 M solution of bromine in dichloromethane. The mixture was stirred 15 min at 0 °C and then diluted with water. Isolation of the product with ether afforded 112 mg (100%) of the unstable α-bromo ketone **17** as a light green oil. The material was used without purification. **17**: IR (film) λ_{max} 3.38, 3.50, 5.60, 5.80, 6.85, 7.94, 9.71, 11.90, 12.20 μm; NMR ($CDCl_3$, Me_4Si) δ 5.2–4.7 (H-3, H-5, and H-7, m), 3.0–1.7 (m, 7 H), 0.90 (*tert*-butyl, s), 0.10, 0.07 (dimethyl, s).

2-[6β-(*tert*-Butyldimethylsiloxy)-2β-hydroxy-5-oxo-3-cyclohepten-1β-yl]acetic Acid Lactone (18). The procedure of Andersen was modified.[13] A 100-mL three-necked flask equipped with a reflux condenser, two glass stoppers, and a magnetic stirring bar was charged with 35 mL of dimethylacetamide and 1.8 g (18 mmol) of calcium carbonate. This slurry was heated in an oil bath to 170 °C and 1.80 g (4.77 mmol) of α-bromo ketone **17** in 5 mL of dimethylacetamide was added. After 15 min at 170 °C the mixture was rapidly cooled in an ice bath. The solution was carefully decanted from the calcium carbonate and the residue was washed with four 70-mL portions of ether which were combined with the dimethylacetamide. The solution was washed with four 50-mL portions of water and once with 50 mL of brine and dried over magnesium sulfate. The solvent was removed by rotary evaporator, affording a light yellow oil, which was purified by column chromatography (silica gel, 30% ethyl acetate–hexane), affording 1.03 g (73%) of a colorless oil. Satisfactory values for C and H combustion analysis could not be obtained owing to trace contamination by starting bromo ketone **17**. Efforts to remove this impurity were unsuccessful. **18**: IR (film) λ_{max} 3.40, 3.50, 5.61, 5.97, 8.00, 8.85, 9.80, 11.90, 12.99 μm; NMR ($CDCl_3$, Me_4Si) δ 6.50 (H-6, dd, $J_{6,5}$ = 12.7 Hz, $J_{6,7}$ = 2.7 Hz), 6.14 (H-5, dd, $J_{5,6}$ = 12.7 Hz, $J_{5,7}$ = 2.7 Hz), 5.31 (H-7, dt, $J_{7,1}$ = 9.0 Hz, $J_{7,6} = J_{7,5}$ = 2.7 Hz), 4.11 (H-3, dd, $J_{3,2a}$ = 10.7 Hz, $J_{3,2b}$ = 1.5 Hz), 3.15 (H-1, m), 0.91 (*tert*-butyl, s), 0.17, 0.06 (dimethyls).

2-[6β-(*tert*-Butyldimethylsiloxy)-2β,5β-dihydroxy-5α-methyl-3-cyclohepten-1β-yl]acetic Acid γ-Lactone (19). A solution of lithium tetramethylalanate was prepared as follows.[14b] To a solution of 1.01 mL of 2.0 M trimethylaluminum in toluene and 10 mL of benzene was added 1.44 mL of 1.4 M methyllithium in ether. This cloudy, white solution was further stirred for 10 min at 25 °C and then added rapidly by syringe to a solution of 499 mg (1.69 mmol) of enone **18** in 25 mL of benzene. After being stirred an additional 10 min, the reaction mixture was cooled to 0 °C and 10 mL of saturated ammonium chloride solution was added dropwise. The gelatinous mixture was diluted with ethyl acetate and filtered through 10 g of Celite. Isolation of the products with ethyl acetate gave 478 mg (91%) of alcohol **19** as a light yellow oil, which was not purified. No evidence was found for the other alcohol stereoisomer by NMR or HPLC. **19**: IR (film), λ_{max} 2.82, 3.38, 5.61, 6.83, 7.91, 9.71, 12.53 μm; NMR ($CDCl_3$, Me_4Si) δ 5.62 (H-6, dd, $J_{6,5}$ = 12.7 Hz, $J_{6,7}$ = 2.4 Hz), 5.44 (H-5, dd, $J_{5,6}$ = 12.7 Hz, $J_{5,4}$ = 2.4 Hz), 5.13 (H-7, dt, $J_{7,1}$ = 8.8 Hz, $J_{7,6} = J_{7,5}$ = 2.4 Hz), 3.64 (H-3, dd, $J_{3,2a}$ = 9.8 Hz), 2.92 (H-1, m), 2.88 (OH, s), 1.25 (CH_3, s), 0.92 (*tert*-butyl, s), 0.12, 0.10 (dimethyls). Anal. Calcd for $C_{16}H_{28}O_4Si$: C, 60.93; H, 8.39. Found: C, 60.59; H, 8.86.

(Methoxyethoxy)methyl Ether 20. The procedure of Corey[15] was modified. A solution of 510 mg (1.63 mmol) of alcohol **19**, 3.64 g (28.2 mmol) of diisopropylethylamine, 2.18 g (1.75 mmol) of (β-methoxyethoxy)methyl chloride, and 4 mL of tetrahydrofuran was heated to 70 °C for 2 h. The reaction mixture was cooled, diluted with 50 mL of 50% ethyl acetate-hexane, and filtered through 15 g of silica gel. The product was washed twice with 10% hydrochloric acid, twice with 5% sodium hydroxide, and dried over magnesium sulfate. The solvents were removed under reduced pressure, affording 645 mg (99%) of pure (methoxyethoxy)methyl ether **20** as a colorless oil: IR (film) λ_{max} 3.38, 5.62, 6.85, 7.75, 9.80, 11.90, 12.82 μm; NMR ($CDCl_3$, Me_4Si) δ 5.50 (vinyl, m, 2 H), 5.04 (H-7, m), 4.90 (OCH_2O, m), 3.60 (OCH_2CH_2O, and H-3, m), 3.35 (OCH_3, s), 1.40 (CH_3, s), 0.90 (*tert*-butyl, s), 0.10 (dimethyls, s). Anal. Calcd for $C_{20}H_{36}O_6Si$: C, 59.97; H, 9.06. Found: C, 59.89; H, 8.87.

Diol 21. The procedure of Grieco[21] was modified. A 100-mL three-necked flask equipped with a gas dispersion tube and two glass stoppers was charged with 500 mg (1.25 mmol) of (methoxyethoxy)methyl ether **20**, 35 mL of methanol, and 35 mL of dichloromethane. The solution was cooled to −78 °C and ozone was slowly admitted through the dispersion tube until a very light blue color persisted. The gas dispersion tube was removed and a magnetic stirring bar was placed in the flask. Sodium boro-

hydride (200 mg, 5.28 mmol), was added to the mixture in four 50-mg (1.32 mmol) portions, once every 15 min. The solution was allowed to warm to 25 °C over 1.5 h. The solvent volume was reduced to about 10 mL by rotary evaporator and the cloudy residue was diluted with 150 mL of ethyl acetate. The solution was washed with four 40-mL portions of 1.5% aqueous sodium hydroxide and once with 40 mL of brine. The solution was dried over magnesium sulfate and the solvent was removed under reduced pressure. The crude product was purified by column chromatography (silica gel, ethyl acetate), affording 398 mg (73%) of diol **21** as a white solid.

An analytical sample was prepared by recrystallization from cyclohexane–ethyl acetate, affording colorless prisms: mp 95–97 °C; IR (film) λ_{max} 2.87, 3.39, 5.62, 6.85, 7.25, 7.94, 9.57, 9.62, 11.90, 13.16 μm; NMR ($CDCl_3$, Me_4Si) δ 4.94 (one H of OCH_2O, half of ABq, J = 7 Hz), 4.51 (one H of OCH_2O, half of ABq, J = 7 Hz), 4.49 (H-6, m), 4.0–3.8 (m, 3 H), 3.6–3.5 (m, 3 H), 3.40 (OCH_3, s), 2.98 (H-1, m), 1.02 (CH_3, s), 0.87 (*tert*-butyl, s), 0.15, 0.11 (dimethyls). Anal. Calcd for $C_{20}H_{40}O_8Si$: C, 55.02; H, 9.23. Found: C, 55.06; H, 9.22.

Monotosylate 22. A small test tube (13 mm × 100 mm) equipped with a rubber septum and a small stirring bar was flame-dried and flushed with nitrogen and charged with 85 mg (0.195 mmol) of diol **21**, 10 mg (0.052 mmol) of *p*-toluenesulfonyl chloride, and 0.3 mL of pyridine. The solution was stirred at 25 °C for 4 h at which time an additional 10 mg (0.052 mmol) of *p*-toluenesulfonyl chloride was added. Stirring was continued 4 h longer and 17 mg (0.089 mmol) of *p*-toluenesulfonyl chloride was added. The solution was stirred for 48 h and then diluted with 20 mL of ethyl acetate and washed with three 5-mL portions of 5% sulfuric acid and once with 5 mL of brine. The solution was dried over magnesium sulfate and the solvent was removed under reduced pressure. The crude product was purified by chromatography (silica gel, 50% ethyl acetate–hexane), affording 91 mg (79%) of monotosylate **22** as a white solid, mp 104–108 °C, and 13 mg (15%) of unreacted diol **21**. **22**: IR (film) λ_{max} 2.87, 3.40, 3.43, 3.51, 5.62, 6.29, 6.87, 7.35, 0.55, 12.20, 13.70 μm; NMR ($CDCl_3$, Me_4Si) δ 7.75 (aromatic, half of ABq, J = 8 Hz, 2 H), 7.35 (aromatic, half of ABq, 2 H), 4.95 (one H of OCH_2O, half of ABq, J = 7 Hz), 4.68 (one H of OCH_2O, half of ABq, J = 7 Hz), 4.59 (H-6, dt, J = 7, 2 Hz), 4.53 (one H of CH_2OTs, half of *ABX*, J_{AB} = 6.5 Hz, J_{AX} = 2.0 Hz), 4.19 (one H of CH_2OTs, half of *ABX*, J_{BA} = 6.5 Hz, J_{BX} = 1.9 Hz), 3.98 (m, 1 H), 3.78 (m, 1 H), 3.65–3.41 (m, 5 H), 3.39 (OCH_3, s), 2.99 (H-1, m), 2.45 ($OC_6H_4CH_3$, s), 1.00 (CH_3, s), 0.87 (*tert*-butyl, s), 0.13, 0.07 (dimethyls). Anal. Calcd for $C_{27}H_{46}O_{10}SSi$: C, 54.89; H, 7.85. Found: C, 54.94; H, 7.47.

X-ray Crystal Structure Analysis of Diol 21. The crystals of diol **21** were triclinic $P\bar{1}$ with a = 11.065 (4) Å, b = 12.665 (6) Å, c = 10.381 (4) Å, α = 109.91 (4)°, β = 96.53 (3)°, γ = 112.03 (4)°, and d_{calcd} = 1.19 g cm^{-3} for Z = 2 ($C_{20}H_{40}O_8Si$, mol wt 436.62). The intensity data were measured on a Enraf-Nonius CAD-4 diffractometer[22] (interfaced to a PDP-11/40) with monochromatic Mo Kα radiation λ = 0.710 73 Å by θ–2θ scans to a $2\theta_{max}$ of 60°. The crystal used for the data collection was 0.30 × 0.14 × 0.40 mm with faces (0$\bar{1}$0) (110)($\bar{1}$00)(001)(00$\bar{1}$) and ($\bar{1}$10). Mini and maximum and transmission factors were calculated with a μ value of 1.40 cm^{-1} to be 0.955 and 0.982, respectively. A total of 7097 reflections were measured of which 2794 were observed and used in the solution and refinement of the structure [$I > 4.0\sigma(I)$, > F_{min} = 4.0]. The structure was solved by a combination of direct and Patterson methods.[23] Final full-matrix least-squares refinement,[24] including anisotropic temperature factors, was terminated at R = 0.69 with the final shift/error of 0.025. Some of the hydrogen atoms were readily observable in difference maps and others were not found. Hence, none of the hydrogen atoms were included in the final refinement. An ORTEP[25] drawing with atom notation along with the atomic coordinates and thermal parameters, bond distances and angles, and F_o, F_c tables may be obtained as supplementary materal.

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Registry No. **5**, 19686-79-4; **6**, 80263-50-9; **7**, 80263-51-0; **8**, 80263-52-1; **9**, 80263-53-2; **10**, 80263-54-3; **11**, 80263-55-4; **13**, 80263-56-5; **14**, 80263-57-6; **15**, 80263-58-7; **17**, 80263-59-8; **18**, 80263-60-1; **19**, 80263-61-2; **20**, 80263-62-3; **21**, 80263-63-4; **22**, 80263-64-5; **24**, 80263-65-6; **25**, 80263-66-7; **26**, 80263-67-8; ethyl acetoacetate, 141-97-9; *cis*-1,4-dichloro-2-butene, 1476-11-5; *cis* ethyl 1-acetyl-2-vinylcyclopropanecarborylate, 80288-44-4; *trans* ethyl 1-acetyl-2-vinylcyclopropanecarboxylate, 80288-45-5; ethyl iodoacetate, 623-48-3; benzeneselenyl bromide, 34837-55-3; β-methoxyethoxymethyl chloride, 3970-21-6.

Supplementary Material Available: Figure showing atom notation and tables containing atomic coordinates and thermal parameters and bond distances and angles (4 pages). Ordering information is given on current masthead page.

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