3.31 (1 H, d, J = 13.8 Hz), 3.21 (1 H, d, J = 13.8 Hz), 2.64-2.41 (5 H, m), 2.43 (3 H, s), 2.31-2.14 (2 H, m), 2.13 (3 H, s), 1.42 (2 H, s), 0.38 (3 H, d, J = 7.2 Hz), -0.06 (9 H, s).

Ring Expansion of Allylic Chloride 19 to Sulfur-Bridged Carbocycle 23. To a solution of allylic chloride **19** (335 mg, 531 μmol) in CH_3CN (52 mL) was added anhydrous K_2CO_3 (flame-dried under vacuum immediately prior to use, 0.42 g, 3.0 mmol) and a solution of NaI in CH_3CN (prepared by dissolving vacuum dried NaI in CH_3CN, 0.47 M, 1.13 mL, 531 μmol). The resulting heterogeneous mixture was heated at 68-70 °C for 17 h, cooled to room temperature and then partitioned between ether (150 mL) and brine (75 mL). The layers were separated, and the organics were washed with brine (75 mL). After the combined aqueous layers were extracted with ether (2 × 75 mL), the combined organics were dried ($MgSO_4$) and filtered, and the solvents were evaporated. Flash silica gel chromatography (column 1 in. × 8 in., 2:2:6 ether/CH_2Cl_2/hexane) provided first the sulfur-bridged carbocycles **23** + **24**, 225 mg (71%), followed by a mixture of allylic halides (X = Cl,I), ca. 20 mg, and finally the divinylcyclopropane **25**, 26 mg (9%). Sulfur-bridged carbocycle **23** (major diastereomer): White crystals from ether/hexane; mp 159-161 °C dec; analytical TLC (silica gel F254), 1:1:2 ether/CH_2Cl_2/hexane, R_f = 0.37; MS exact mass calcd for $C_{33}H_{43}O_5NSSi$ = 593.2631, found = 593.2604, error = 4.6 ppm; IR (neat, cm^{-1}) C=O 1735, C=O 1730, C=O 1700; 270-MHz ^1H NMR ($CDCl_3$) δ 7.38-7.11 (5 H, m); 6.15 (1 H, dd, J = 10.4, 15.8 Hz), 6.01-5.84 (1 H, m), 5.30 (1 H, s), 5.28 (1 H, d, J = 6.5 Hz), 4.25-4.13 (1 H, m), 3.99 (1 H, dt, J = 10.7, 2.1 Hz), 3.62 (1 H, dd, J = 3.6, 11.9 Hz), 3.34 (2 H, dd, J = 2.8, 12.5 Hz), 2.95-2.78 (1 H, m), 2.65-1.97 (8 H, m), 2.44 (3 H, s), 2.25 (3 H, s), 1.38 (2 H, s), 0.34 (3 H, d, J = 7.1 Hz), -0.07 (9 H, s). Sulfur-bridged carbocycle **24** (minor diastereomer): oil, analytical TLC (silica gel F254), 1:1:2 ether/CH_2Cl_2/hexane, R_f = 0.38; 270-MHz ^1H NMR ($CDCl_3$) δ 7.38-7.09 (5 H, m), 6.19 (1 H, dd, J = 10.6, 16.0 Hz), 5.27 (1 H, ddd, J = 4.7, 11.0, 16.0 Hz), 5.26 (1 H, d, J = 10.7 Hz), 5.16 (1 H, s), 3.76 (1 H, dt, J = 3.0, 9.5 Hz), 3.71 (1 H, dd, J = 1.8, 5.6 Hz), 3.34 (1 H, ddd, J = 1.8, 4.2, 12.2 Hz), 3.24 (1 H, dd, J = 2.6, 12.8 Hz), 3.18 (1 H, dd, J = 2.6, 12.8 Hz), 3.09 (1 H, d, J = 10.7 Hz), 2.81 (1 H, ddd, J = 4.5, 10.7, 13.0 Hz), 2.51-2.22 (3 H, m), 2.46 (3 H, s), 2.16-2.02 (4 H, m), 2.13 (3 H, s), 1.44 (2 H, s), 0.37 (3 H, d, J = 7.1 Hz), 0.06 (9 H, s). Vinylcyclopropane **25**: white crystals from ether/hexane; mp 166-167 °C; analytical TLC (silica gel F254), 1:1:2 ether/CH_2Cl_2/hexane, R_f = 0.19; MS exact mass calcd for $C_{30}H_{35}O_5NS$ = 521.2236, found = 521.2235, error = 0.1 ppm; IR (neat, cm^{-1}) C=O 1755, C=O 1740, C=O 1720, C=O 1700; 270-MHz ^1H NMR ($CDCl_3$) δ 7.35-7.18 (3 H, m), 7.12-7.04 (2 H, m), 5.42 (1 H, d, J = 7.7 Hz), 5.35 (1 H, dd, J = 10.1, 17.0 Hz), 5.29 (1 H, s), 5.11 (1 H, s), 4.94 (1 H, d, J = 17.0 Hz), 4.88 (1 H, d, J = 10.1 Hz), 3.93-3.84 (1 H, m), 3.47 (1 H, dd, J = 5.6, 14.0 Hz), 3.28-3.17 (1 H, m), 3.20 (2 H, s), 2.80 (1 H, dd, J = 2.7, 14.0 Hz), 2.59-2.49 (2 H, m), 2.50 (3 H, s); 2.44-2.01 (5 H, m), 1.61 (3 H, s), 1.25 (1 H, dd, J = 5.1, 3.3 Hz), 1.15 (3 H, d, J = 6.3 Hz), 0.91-0.87 (1 H, m).

Bridgehead Methylation of 23. Preparation of 30. Lithium diisopropylamide (LDA) was prepared at 0 °C by addition of n-BuLi (2.00 M in hexanes, 0.20 mL, 400 μmol) to a solution of diisopropylamine (Aldrich, distilled from CaH_2; 59 μL, 420 μmol) in THF (3.0 mL). The LDA solution was cooled to -78 °C, and a THF solution of the ketone **23** (217 mg, 366 μm, in 7 mL) was added dropwise via cannula over 25 min. The ketone-containing flask was rinsed with additional THF (2.0 mL) which was added to the reaction. The solution was stirred at -78 °C for 1 h before iodomethane (Aldrich, freshly distilled from P_2O_5; 0.23 mL, 3.7 mmol) was added all at once via syringe. The reaction was stirred at -78 °C for 50 min and was then warmed to 0 °C with an ice bath for 45 min. The reaction was quenched by addition of saturated NH_4Cl (1 mL) and then partitioned between saturated NH_4Cl (20 mL) and ether (60 mL), and the layers were separated. The organics were washed with saturated NH_4Cl (20 mL), saturated $NaHCO_3$ (20 mL), and brine (20 mL). The combined aqueous layers were extracted with ether (2 × 25 mL), dried ($MgSO_4$), and filtered, and the solvents were removed in vacuo. The residue was chromatographed on silica gel (1 in. × 8 in.) and eluted (1:1:2 ether/CH_2Cl_2/hexane) to give bridgehead methylated ketone **30**, 220 mg (99%): white crystals from ether/hexane; mp 195-196 °C; analytical TLC (silica gel F254), 1:1:2 ether/CH_2Cl_2/hexane, R_f = 0.47; MS exact mass calcd for $C_{34}H_{45}O_5NSSi$ = 607.2788, found = 607.2792, error = 0.7 ppm; IR ($CHCl_3$, cm^{-1}) C=O 1730, C=O 1705, OAc 1300; 270-MHz ^1H NMR ($CDCl_3$) δ 7.35-7.15 (5 H, m), 6.16 (1 H, dd, J = 10.1, 15.8 Hz), 6.06-5.92 (1 H, m), 5.28 (1 H, s), 5.23 (1 H, d, J = 7.4 Hz), 4.29-4.19 (1 H, m), 3.98 (1 H, d, J = 9.8 Hz), 3.42-3.29 (2 H, m), 2.72-2.35 (6 H, m), 2.44 (3 H, s), 2.26 (3 H, s), 2.25-1.99 (3 H, m), 1.42 (3 H, s), 1.38 (2 H, s), 0.35 (3 H, d, J = 7.1 Hz), -0.07 (9 H, s).

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Supplementary Material Available: Table of mass spectral fragmentation patterns (1 page). Ordering information is given on any current masthead page.

The Total Syntheses of *dl*-Zygosporin E and *dl*-C_{18}-Desmethylcytochalasin D

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Abstract: The title syntheses are completed starting from the sulfur-bridged 11-membered carbocycles **1** and **2**. Key steps include the reductive cleavage of the C-S bond from **11** to **14** and from **2** to **22** and the conversion of allylic silanes **15** and **22** into allylic alcohols **17** and **24**, respectively. In the zygosporin synthesis, final sulfur removal is achieved by sulfoxide elimination from **18a** to **19a**, while in the desmethylcytochalasin D (**32**) synthesis, sulfur elimination occurs during conversion of allylic sulfoxide **29** to **31**. Both synthetic routes depend on control of relative stereochemistry based on local conformational preferences and on the predictable consequences of reactions that introduce stereochemistry in the vicinity of C-S bonds.

The preceding paper describes the synthesis of sulfur-bridged [11]cytochalasans **1** and **2**.[1] Five of the six asymmetric centers of the isoindolone subunit have been controlled by the Diels-Alder synthesis, and the acetoxy stereochemistry at cytochalasan C_{21} has been introduced by using methods that rely upon sulfur-mediated control of relative stereochemistry. Procedures for the attachment of a hydroxyl group at C_7 with the necessary β orientation have also been established. Further conversion into cytochalasins,[2] zygosporins,[2] or their analogues now requires control of C_{16} and C_{18} stereochemistry, as well as eventual removal of sulfur. The C_{16}—sulfur bond must be replaced by hydrogen,

(1) Vedejs, E.; Reid, J. G.; Rodgers, J. D.; Wittenberger, S. J. *J. Am. Chem. Soc.*, preceding paper in this issue. For a preliminary account of the zygosporin E synthesis, see: Vedejs, E.; Rodgers, J. D.; Wittenberger, S. J. *J. Am. Chem. Soc.* **1988**, *110*, 4822.

(2) Tanenbaum, S. W. Ed. *Cytochalasins: Biochemical and Cell Biological Aspects*; North-Holland Publishing Company: Amsterdam, 1978.

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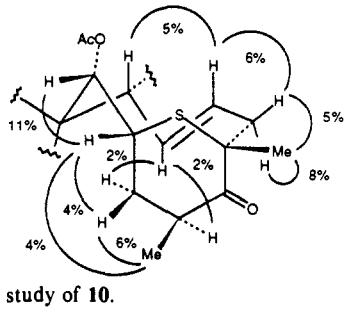
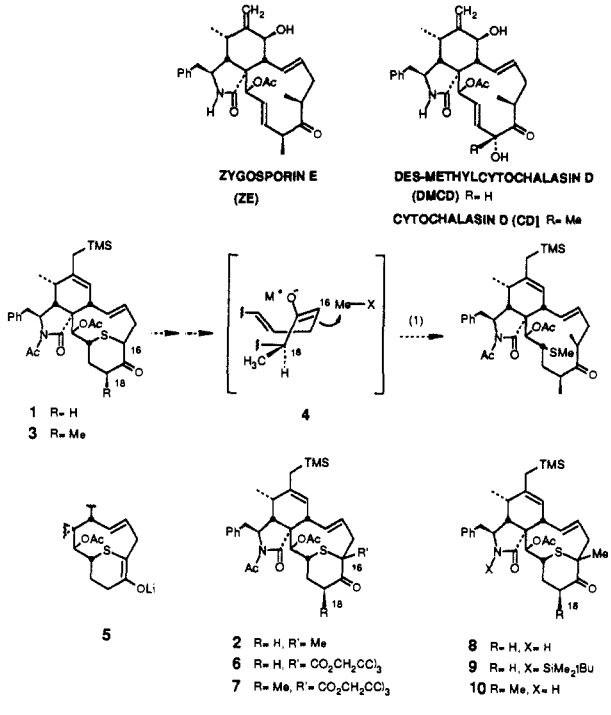


Figure 1. NOE study of **10**.

Scheme I

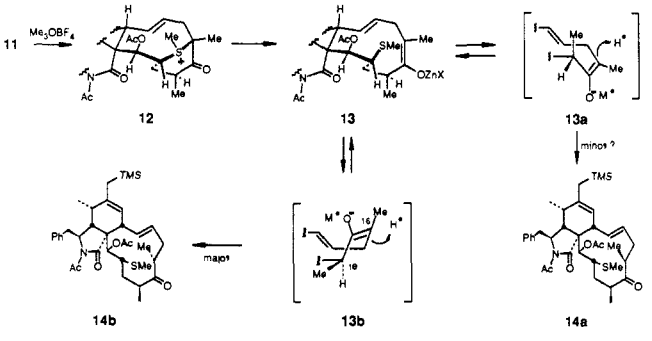


while the C_{20} C—S linkage ideally would serve as the precursor of the C_{19}=C_{20} olefinic linkage.

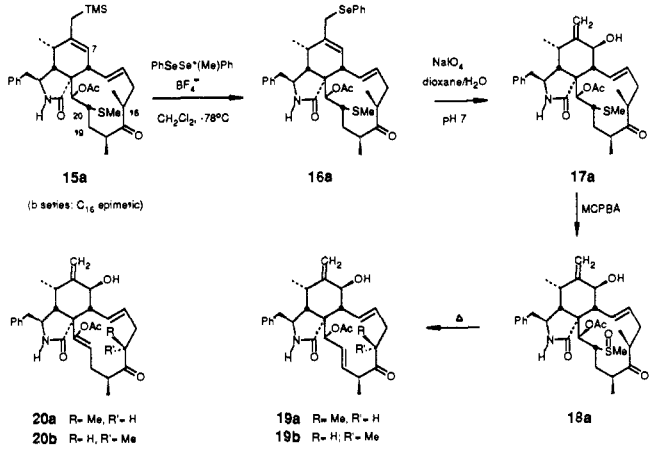
The original plan called for enolate generation from **1** at C_{18} and methylation from the less hindered β-face to give **3**. Subsequent reductive C_{16}–S bond cleavage to enolate **4** was expected to allow C_{16} methylation from the peripheral (desired) direction as shown in eq 1 (Scheme I). This stereochemical prediction assumes that the favored alkylation transition state will be determined by the preference for a pseudoequatorial C_{18} methyl group (local conformer control).[3] However, deprotonation of **1** at C_{18} could not be achieved directly due to the surprisingly high kinetic acidity of the bridgehead proton (C_{16}-H). All attempts to induce kinetically or thermodynamically controlled enolization afforded the enolate **5**. It was possible to block the C_{16} position, as in the β-keto ester **6**, but a practical overall yield for the alkylation at C_{18} with subsequent deblocking of **7** to **3** could not be achieved. The simplest alternative was to proceed with **2** and to control C_{16} stereochemistry by other means. This approach was eventually successful, but a series of problems had to overcome.

Direct methylation of **2** at C_{18} was precluded by competing enolization at the *N*-acetyl group. The problem was solved by deacylation to **8** (K_2CO_3/MeOH) and temporary protection as the *N*-*tert*-butyldimethylsilyl amide **9** (TBSCl/DMAP, TBS = Me_2tBuSi, DMAP = (dimethylamino)pyridine). Enolization with lithium hexamethydisilazide (LiHMDS) then occurred without further difficulties, and C_{18} methylation gave a single product **10** (60% from **2**) after cleavage of the *N*-silyl protecting group with

Scheme II



Scheme III



Et_3NHF. The desired C_{18} stereochemistry of **10** corresponds to alkylation from the less congested β-face of the enolate, subject to control by the C_{20} stereochemistry.[1] This assignment was supported by an NOE study, summarized in Figure 1, and by the eventual conversion into zygosporin E.

Reductive cleavage of the C_{16} C–S bond was the next obstacle. The sulfide was relatively unreactive toward zinc reduction, probably because the C–S bond is nearly orthogonal to the activating carbonyl π-orbitals. This problem had been overcome in model systems by sulfide activation via S-methylation and reductive cleavage of the sulfonium salt.[4] The best results were achieved by reacylating **10** at nitrogen to prevent competing lactam O-methylation (Ac_2O/DMAP, 88%), followed by S-methylation with trimethyloxonium tetrafluorobrate in the presence of allyltrimethylsilane as an acid scavenger. The resulting sulfonium salt **12** (Scheme II) was then reductively cleaved by Rieke zinc[5] with acetic acid as the proton donor. This procedure afforded a mixture of two methyl sulfides **14a** and **14b** in a ratio of 1:2.6 (87% yield). Replacement of acetic acid by methanol as the proton donor in the reductive cleavage step gave ratios of **14a**:**14b** as high as 1:4.3.

The stereochemistry of the two diastereomers **14a** and **14b** was not initially known with certainty, but the assignment follows from a consideration of enolate geometry. Due to the constraints imposed by the bicyclic framework, only the enolate isomer **13** can be formed from **12**. The enolate double bond (formally, the *E* isomer) has the "*Z*" configuration with respect to medium ring substituents. It will therefore prefer a local geometry **13b** that is controlled by the tendency of the C_{18} methyl group to occupy a pseudoequatorial orientation.[3] An alternative local conformation **13a** encounters reduced eclipsing interactions between C_{18}-CH_3 and C_{17} oxygen, but this conformation suffers from increased transannular interactions with the pseudoaxial C_{18}-CH_3 group. Assuming that the transition state for zinc enolate protonation resembles the enolates, protonation should occur preferentially

(3) Vedejs, E.; Dent, W. H., III; Gapinski, D. M.; McClure, C. K. *J. Am. Chem. Soc.* **1987**, *109*, 5437.

(4) Vedejs, E.; Reid, J. G. *J. Am. Chem. Soc.* **1984**, *106*, 4617. Vedejs, E.; Fedde, C. L.; Schwartz, C. E. *J. Org. Chem.* **1987**, *52*, 4269.

(5) Arnold, R. T.; Kulenovic, S. T. *Synth. Commun.* **1977**, *7*, 223.

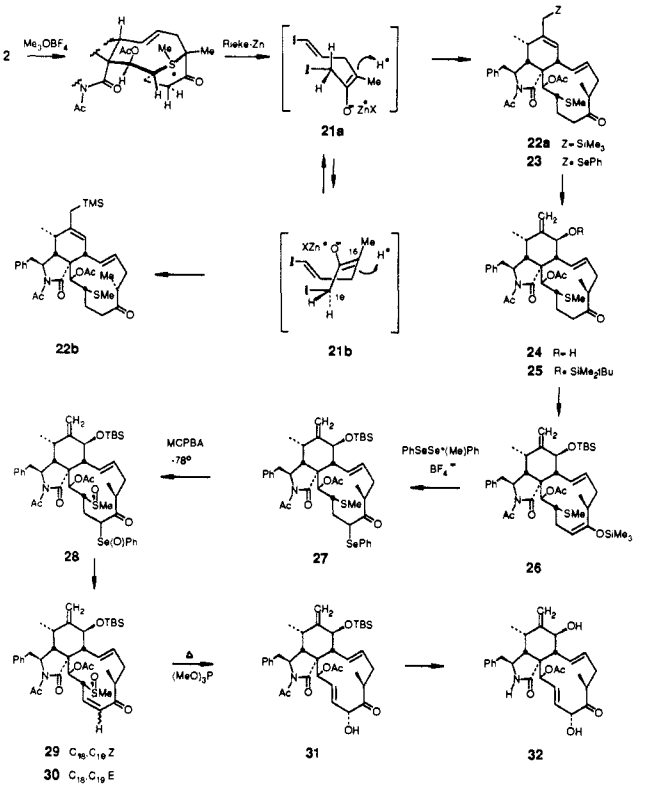
via **13b**, resulting in **14b** as the major product. Since the order of attachment of methyl and hydrogen substituents at C_{16} in the above scheme was inverted relative to the initial plan, the stereochemical outcome to favor the unnatural C_{16} epimer was no surprise. The assignment was eventually confirmed by the conversion of **14a** into zygosporin E, as described shortly.

Even though good selectivity for **14a** could not be achieved, the sequence allowed completion of a synthesis of *dl*-zygosporin E (**19a**, Scheme III). Both the natural (*a*) and C_{16}-epi (*b*) series were taken through subsequent steps without major problems. First, cleavage of the *N*-acetyl group with methanolic potassium carbonate produced **15** without complications from C_{21} acetate cleavage (**a** series, 70% **b** series, 82%). Conversion of the allyl silane into the allylic alcohol at C_7 was then performed with the reagent prepared from diphenyl diselenide + trimethyloxonium tetrafluorobrate.[6] This source of electrophilic selenium generated the thermodynamically more stable allyl selenide **16** in excellent yield. An isomeric C_7 selenide is probably the kinetic product and is rapidly isomerized to **16** under the reaction conditions. Subsequent treatment of the selenides **16** with sodium periodate resulted in selective oxidation and spontaneous selenoxide rearrangement to the allylic alcohols **17** (**a** series, 85%; **b** series, 99% from **15**) with C–O bonding from the less hindered β-alkene face.

With **17a** and **17b** in hand, all that remained was to introduce the C_{19},C_{20} double bond by the thermal elimination of the sulfoxides **18**, available by low-temperature oxidation of **17** with MCPBA (75–78%). Thermolysis of the C_{16}-epi isomer **18b** proceeded smoothly at 135 °C in xylene in the presence of calcium carbonate buffer and gave the alkene **19b** in 70% yield. A minor byproduct could not be characterized due to the small amount isolated, but the enol acetate structure **20b** is a possibility by analogy to the behavior of **18a**. In the natural series starting from **18a**, similar thermolysis resulted in elimination of the sulfoxide to *dl*-zygosporin E (**19a**, 52%) together with the isomeric **20a** (45%). Increased competition from the unusual elimination toward oxygen may be related to the formation of a ca. 1:1 mixture of diastereomers at sulfoxide sulfur in **18a**, but the isomers could not be separated to test whether each sulfoxide was the unique precursor of one of the elimination products. Extensive analysis of NMR spectra and chromatographic properties established the identity of the sythetic zygosporin E by comparison with natural material (see Experimental Section).[7]

The successful completion of the zygosporin E synthesis confirmed the stereochemical assignment at C_{16} that had been made earlier at the stage of the reductive C–S cleavage step. As already mentioned, the major product from **12** was the epimer **14b**, presumably due to local conformer control in the enolate protonation step by the C_{18} methyl group. However, an alternative approach to control of the C_{16} stereocenter was possible where the reductive cleavage step was performed earlier, prior to functionalization at C_{18}. Thus, treatment of **2** with trimethyloxonium tetrafluoroborate (Scheme IV) followed by Rieke zinc as before gave a mixture of **22a** and **22b** (75% combined). NMR comparisons indicated the expected similarities with the related compounds **14a** and **14b**. In particular, the chemical shifts of the C_{16} methyl groups (δ 1.21 in **14a** and 1.30 in **22a**; 1.03 or 1.06 in **14b** and 1.07 in **22b**) supported the stereochemical assignment, as did similar comparisons in derived compounds. As in the zygosporin E series, the ratio of reductive cleavage products depended somewhat on the proton donor, and the optimum ratio of 3.7:1 was obtained by using Rieke zinc in THF containing a small amount of isopropanol. Apparently, the C_{18}-unsubstituted enolate **21** prefers a transition state similar to the conformation **21a** and undergoes protonation from the β-face. Evaluation of alternative conformations of the relatively rigid ring indicates few viable options and suggests that **21b** is a reasonable geometry for the transition state leading to the minor product. Since there are no allylic substituents to control local conformational preferences, this is a case where long-range effects have to be taken into

Scheme IV



account. Due to the complex environment, only a qualitative evaluation is possible. However, the stability of enolate **21a** relative to **21b** should be improved compared to the methylated analogue **13a** vs **13b** because the unfavorable transannular interaction of C_{18}-CH_3 is no longer an issue. This factor may be responsible for the inversion in enolate face protonation selectivity to favor the natural epimer **22a**.

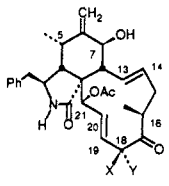
The above approach solves the problem of C_{16} stereochemistry and, in principle, allows entry into the most complex cytochalasin or zygosporin systems.[2] Among the most challenging target structures are the α-hydroxy ketone members of these families. We have therefore explored the conversion of **22a** into **32**, the C_{18} desmethyl analogoue of cytochalasin D.[2]

Activation at C_{18} could be achieved upon treatment of the major C_{16} methyl diastereomer **22a** with LiHMDS + TMSCl in situ (THF, 78°) resulting in a C_{17},C_{18} enol silane. The NMR spectrum suggested that a single geometrical isomer of the C_{17},C_{18} enol ether was formed (geometry unknown), but the spectrum also indicated the presence of byproducts due to enolization of the C_{21} acetate. Reaction of **22a** with DBU/TMSCl/CH_3CN likewise produced a single enol ether isomer but in this case the C_6,C_7 olefin proton signal was too small, indicating byproducts derived from isoindolone double bond migration to the tetrasubstituted position. In order to circumvent this problem, the allylic silane was elaborated into the allylic alchol **24** as in the zygosporin series by using the $PhSeSe^+(Me)Ph{\cdot}BF_4^-$ reagent.[6] After oxidation with $NaIO_4$ in dioxane/H_2O and selenoxide rearrangement, the alcohol was protected as the *tert*-butyldimethylsilyl ether **25** (TBSCl/DMAP) in ca. 80% overall yield from **22a**. Trimethylsilyl enol ether formation under the DBU/TMSCl/CH_3CN conditions now proved to be uneventful, and **25** provided one major C_{17},C_{18} enol silane **26**. No evidence for the more substituted enol silane resulting from enolization at C_{16} was observed. The reasons for this selectivity are not known, but the result provides an opportunity to combine the ultimate sulfur removal step with the introduction of oxygen functionality at C_{18} via allylic sulfoxide rearrangement.

To set the stage for sulfur removal, **26** was reacted with the selenenylating reagent $PhSeSe^+(Me)Ph{\cdot}BF_4^-$ (used earlier for a different purpose) to yield a single major C_{18} selenide **27** (93%). The keto selenide **27** was then treated with MCPBA at −78 °C to induce oxidation at both selenium and sulfur, resulting in the

(6) Vedejs, E.; Rodgers, J. D.; Wittenberger, S. J. *Tetrahedron Lett.* **1988**, *29*, 2287.

Table I. ^{1}H NMR Comparisons



proton(s)	chemical shifts ($CDCl_3$, ppm) DMCD (32) (X = H, Y = OH)	CD (X = Me, Y = OH)	ZE (19a) (X = Me, Y = H)
H_{21}	5.55	5.62	5.52
H_{20}	6.50	6.10	6.01
H_{19}	5.10	5.12	4.77
C_{18}-Me		1.49 (s)	1.26 (d)
C_{16}-Me	1.11*	0.91	1.00
H_{16}	2.86	ca. 2.8	2.85
H_{14}	5.37	5.32	5.28
H_{13}	5.77	5.69	5.73
H_7	3.82	3.79	3.80
C_5-Me	1.15*	1.18	1.15

* Indicates that assignments may be reversed.

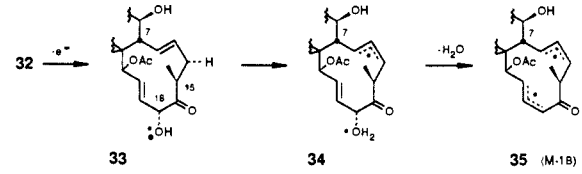
selenoxide sulfoxide **28**. Selenoxide elimination required some warming, but conversion occurred to afford a mixture of enones **29** (66%) and **30** (ca. 20%), each as a single sulfoxide diastereomer. The enones were reluctant to undergo the allylic sulfoxide–sulfenate rearrangement. Usually, the [2,3]-sigmatropic rearrangement occurs at ambient temperature and can be driven toward the allylic alcohol in the presence of thiophiles. In the specific case of cis-enone **29** the conditions required to cause the rearrangement were especially harsh, but heating in trimethylphosphite/*n*-propanol at 105–110 °C for 23 h provided the rearranged allylic alcohol **31** (53% yield) as the only isolable product. The α-stereochemistry of the C_{18} hydroxyl was assigned with confidence since the sulfur stereochemistry at C_{20} was known. The hydroxyl configuration in **31** follows from the well known cyclic transition state governing the [2,3]-sigmatropic rearrangement of the allylic sulfoxide.

The isomeric *E*-enone **30** decomposed under the same forcing conditions without furnishing any isolable allylic alcohol products. Inspection of molecular models indicates that the presence of two *E* double bonds in addition to the trans ring fusion in **30** allows few conformational options, and the transition state for [2,3]-shift is highly destabilized by transannular interactions. The situation is not much better in the cis isomer **29**, but the greater flexibility of the molecule is a helpful factor.

Selective N-deacylation of **31** could be effected (K_2CO_3/MeOH–THF, −20 °C) followed by silyl ether cleavage with aqueous HF, 0 °C (70% yield) to provide *dl*-C_{18}-desmethylcytochalasin D **32**. Support for the structure **32** is provided by the spectral evidence. Key signals from the ^{1}H NMR spectra of relevant [11]cytochalasans are compared in Table I. Although the signals of the different compounds show some chemical shift variations depending on the presence or absence of the C_{18}-OH group, signal appearance due to closely analogous coupling constants is qualitatively very similar.

The structure and 11-membered ring stereochemistry of **32** is also supported by characteristic fragmentation patterns in the mass spectrum. Comparison of desmethylcytochalasin D (**32**), cytochalasin D (CD), and zygosporin E (ZE) revealed interesting trends. As expected, the three compounds (**32**, CD, and ZE) have in common the loss of several neutral fragments: CO (cyclic ketone), OAc and HOAc (acetate), C_7H_7 (benzyl), and combinations thereof (see supplemental material for a table of mass spectral data for **32**, CD, and ZE). There are several homologous fragments that differ by the absence of a CH_2 unit in **32** compared to CD (240 and 254, 268 and 282, 314 and 328, 324 and 338), and there also are several identical fragments (172, 212, 240, 268) in both **32** and CD which underscore the similarity in structure. Most informative is the strong M − 18 fragment corresponding to facile dehydration of diols **32** and CD. This fragment was not unexpected, but the mass spectrum of ZE did not show any significant M − 18 peak. Since all three compounds have an identical C_7-OH group, this implies that the C_{18} hydroxyls of **32** and CD are responsible for the M − 18 fragment. A possible pathway is depicted in Scheme V. Initial ionization of the C_{18} oxygen (**33**) triggers an intramolecular hydrogen transfer from C_{15} to the C_{18} oxygen via a six-membered transition state to give allylic radical **34** which loses water to give the observed ion **35**. This is a common mechanism for decomposition of alcohol molecular ions.[8] Since the process involves an internal H-transfer, there should be a conformational and stereochemical dependence. The similarity in this key fragmentation pathway between **32** and cytochalasin D therefore provides strong support for the C_{18} stereochemical assignment for **32**.

Scheme V



With the completion of the zygosporin E and C_{18}-desmethylcytochalasin D syntheses, techniques are established for the control of stereochemistry at all of the asymmetric centers of the [11]-cytochalasans. The remaining challenge in this series is cytochalasin D, the most complex of the natural [11]cytochalasans. Further progress on this problem will be reported in due course.

Experimental Section

See Supplementary Material for details of the route to C_{16}-*epi*-zygosporin E.

Deacylation of 2 to Amide 8. To a solution of imide **2** (18 mg, 29.6 μmol) in THF (0.50 mL) and MeOH (2.0 mL) at 0 °C was added anhydrous K_2CO_3 (flame-dried in vacuo, 30 mg, 220 μmol). The heterogeneous reaction mixture was stirred for 35 min before it was diluted with ether (20 mL) and washed with brine (2 × 10 mL). The combined aqueous layers were extracted with ether (2 × 5 mL) and the combined organics were dried ($MgSO_4$) and filtered, and the solvents were removed in vacuo. Flash silica gel chromatography (0.5 cm × 15 cm, 40% EtOAc/hexane) yielded amide **8**, 16.5 mg (98%), sufficiently pure for the next step. White crystals from ether/hexane, mp 198–203 °C dec, analytical TLC (silica gel F254), 1:1:2 ether/CH_2Cl_2/hexane, R_f = 0.16; IR (neat, cm^{-1}) N—H 3300, C=O 1730, C=O 1700, C=O 1675; 270-MHz NMR ($CDCl_3$) δ 7.36–7.09 (5 H, m), 6.33 (1 H, dd, J = 10.3, 15.7 Hz); 5.94 (1 H, ddd, J = 5.3, 10.7, 15.7 Hz), 5.42 (1 H, s), 5.34 (1 H, s), 5.18 (1 H, d, J = 7.1 Hz), 4.12 (1 H, ddd, J = 6.5, 7.1, 11.8 Hz), 3.38 (1 H, d, J = 10.3 Hz), 3.21–3.12 (1 H, m), 2.82–2.73 (1 H, m), 2.81 (1 H, dd, J = 4.2, 13.0 Hz), 2.69–2.34 (6 H, m), 2.24 (3 H, s), 2.16–2.01 (2 H, m), 1.52 (2 H, s), 1.41 (3 H, s), 1.04 (3 H, d, J = 6.8 Hz), −0.04 (9 H, s).

Silylation of Amide 8 to *N*-Silyl Amide 9. To a solution of amide **8** (146 mg, 258 μmol) in CH_3CN (3.5 mL) were added *tert*-butyldimethylsilyl chloride (Petrarch; 130 mg, 862 μmol), (dimethylamino)-pyridine (DMAP, Aldrich; 25 mg, 208 μmol), and diazabicycloundecene (DBU; Aldrich; distilled from CaH_2, 0.15 mL, 1.0 mmol) in that order. The solution was stirred at room temperature for 4 h after which time it was diluted with hexane (20 mL) and washed with saturated $NaHCO_3$ (2 × 10 mL). The combined aqueous layers were extracted with hexane (2 × 10 mL). The combined organics were dried ($MgSO_4$) and filtered and the solvents were removed in vacuo. The residual oil was flash chromatographed on silica gel (1 in. × 3 in., washed with 5% Et_3N/hexane followed by hexane), and eluted with hexane to remove silicon-containing impurities, followed by 10% EtOAc/hexane to give the *N*-silyl amide **9** (133.5 mg, 76%), and then 50% EtOAc/hexane to recover starting material **8** (29.3 mg, 20%): oil; analytical TLC (silica gel F254), 1:4 ether/hexane, R_f = 0.22; MS exact mass calcd for $C_{38}H_{57}NO_4SSi_2$ = 679.3547, found = 679.3522, error = 3.7 ppm; IR (neat cm^{-1}) C=O 1730, C=O 1705, C=O 1665; 270-MHz NMR ($CDCl_3$) δ 7.34–7.06 (5 H, m), 6.35 (1 H, dd, J = 10.4, 15.5 Hz), 5.93 (1 H, ddd, J = 4.5, 10.7, 15.5 Hz), 5.36 (1 H, d, J = 7.5 Hz), 5.23 (1 H, s), 4.28 (1 H, dt, J = 12.8, 6.6 Hz), 3.25 (2 H, d, J = 9.8 Hz), 3.07 (1 H, dd, J = 2.9, 12.8 Hz), 2.94–2.55 (3 H, m), 2.57 (1 H, d, J = 10.8 Hz), 2.46 (1 H, d, J = 12.2 Hz), 2.41–2.29 (1 H, m), 2.24 (3 H, s), 2.18–1.99 (3 H, m), 1.41 (2 H, s), 1.40 (3 H, s), 0.99 (9 H, s), 0.36 (3 H, s), 0.25 (3 H, s), 0.21 (3 H, d, J = 6.8 Hz), −0.07 (9 H, s).

Alkylation of *N*-Silyl Amide 9 and Desilylation to 10. To a solution of lithium hexamethyldisilazide (64 μmol, prepared from $HN(SiMe_3)_2$

(14 μL, 67 μmol) and *n*-BuLi (2.07 M, 31 μL, 64 μmol) in THF (0.56 mL) at 0 °C) at −78 °C was added *N*-silyl keto amide **9** (40 mg, 58 μmol) in THF (0.60 mL). The reaction was stirred at −78 °C for 5 min, warmed to −40 °C for 5 min, and then cooled back to −78 °C for 5 min before iodomethane (75 μL, 1.2 mmol) was added. The cold bath was removed and the reaction flask was allowed to warm to room temperature over 10 min and quenched by addition of saturated NH_4Cl (0.5 mL) and ether (2 mL). The layers were separated, and the organics were washed with saturated NH_4Cl (3 mL), saturated $NaHCO_3$ (3 mL), and then brine (3 mL). The combined aqueous layers were extracted with ether (2 × 3 mL) and the combined organic layers were dried ($MgSO_4$) and filtered, and the solvents were evaporated (aspirator). The residual oil was applied to a flash silica gel plug (0.5 in. × 3 in.) and eluted with 1:1 EtOAc/hexane to give 38.5 mg of crude product which was dissolved in THF (3 mL) and MeOH (7 mL). To this solution was added Et_3NHF (0.1 mL, 844 μmol) and the reaction was stirred for 1.5 h at room temperature. The reaction was then diluted with ether (70 mL) and washed with brine (2 × 30 mL). The combined aqueous layers were extracted with ether (2 × 20 mL). The combined organics were dried ($MgSO_4$) and filtered, and the solvents were removed in vacuo. The residual oil was applied to a flash silica gel column ($^1/_2$ in. × 5 in.) and eluted with 20% ether/hexane to remove silicon containing impurities and then with 50% EtOAc/hexane to give the methylated amide **10**, 26.5 mg (79%): oil; analytical TLC (silica gel F254), 1:1 EtOAc/hexane, R_f = 0.47; MS exact mass calcd for $C_{33}H_{45}NO_4SSi$ = 579.2839, found = 579.2823, error = 2.7 ppm; IR (neat, cm^{-1}) N—H 3270, C=O 1735, aC=O 1705, C=O 1670; 270-MHz NMR ($CDCl_3$) δ 7.37–7.09 (5 H, m), 6.37 (1 H, dd, *J* = 10.4, 15.5 Hz), 6.08 (1 H, ddd, *J* = 6.6, 8.6, 15.5 Hz); 5.38 (1 H, s), 5.37 (1 H, s), 5.17 (1 H, d, *J* = 7.1 Hz), 3.98 (1 H, ddd, *J* = 6.9, 7.1, 9.2 Hz), 3.41 (1 H, d, *J* = 10.4 Hz), 3.21–3.12 (1 H, m), 2.99 (1 H, ddq, *J* = 3.9, 6.5, 7.1 Hz), 2.83 (1 H, dd, *J* = 4.5, 13.7 Hz), 2.71 (1 H, ddd, *J* = 6.5, 8.9, 14.9 Hz), 2.58 (1 H, dd, *J* = 9.5, 13.4 Hz), 2.53–2.38 (1 H, m), 2.33–2.29 (2 H, m), 2.24 (3 H, s), 2.11–1.96 (2 H, m), 1.52 (2 H, s), 1.38 (3 H, s), 1.21 (3 H, d, *J* = 7.1 Hz), 1.05 (3 H, d, *J* = 7.4 Hz), 0.01 (9 H, s).

Acylation of Amide 10 to Imide 11. To a solution of the amide **10** (26 mg, 44 μmol) in THF (1.90 mL) were added Et_3N (0.11 mL, 0.80 mmol), Ac_2O (0.21 mL, 2.24 mmol) and DMAP (12.6 mg, 0.10 mmol). The reaction was sealed and stirred at room temperature for 6 days. The reaction was quenched by addition of saturated $NaHCO_3$ (2 mL) and stirred 10 min before it was diluted with ether (10 mL) and the layers were separated. The organic portion was washed with saturated $NaHCO_3$ (7 mL), saturated NH_4Cl (7 mL), and brine (7 mL). After the combined aqueous layers were extracted with ether (2 × 10 mL), the combined organic portions were dried ($MgSO_4$) and filtered, and the solvents were removed under reduced pressure. The residual oil was placed on a flash silica gel column (1 cm × 15 cm) and eluted with 2:1:7 ether/CH_2Cl_2/hexane to give imide **11**, 24.1 mg (88%): oil; analytical TLC (silica gel F254), 2:2:6 ether/CH_2Cl_2/hexane, R_f = 0.43; MS exact mass calcd for $C_{35}H_{47}NO_5SSi$ = 621.2944, found = 621.2955, error = 1.7 ppm; IR (neat, cm^{-1}) C=O 1730, C=O 1700; 270-MHz NMR ($CDCl_3$) δ 7.34–7.20 (5 H, m), 6.27–6.19 (2 H, m), 5.33 (1 H, s), 5.25 (1 H, d, *J* = 7.4 Hz), 4.09–4.01 (2 H, m), 3.48–3.39 (2 H, m), 3.25–3.12 (1 H, m), 2.58–2.46 (2 H, m), 2.50 (3 H, s), 2.42–2.33 (2 H, m), 2.30 (3 H, s), 2.29–2.20 (1 H, m), 2.18–2.03 (2 H, m), 1.42 (2 H, s), 1.42 (3 H, s), 1.23 (3 H, d, *J* = 6.8 Hz), 0.37 (3 H, d, *J* = 7.1 Hz), −0.03 (9 H, s).

Preparation of Rieke Zinc.[5] To a solution of naphthalene (106 mg, 828 μmol) in THF (1.50 mL) was added several small pieces of freshly cut Na (18.4 mg, 800 μmol). The reaction rapidly turned very dark green and was stirred for ca. 3 h to ensure complete reaction of the Na metal. The green solution was then added via cannula to a solution of anhydrous $ZnCl_2$ (fused in vacuo prior to use; 87 mg, 0.64 μmol) in THF (2.0 mL) providing the zinc metal as a very finely divided black suspension (ca. 0.11 M) in THF.

Reductive C–S Cleavage: 14a and 14b. To a solution of keto sulfide **11** (30 mg, 48 μmol) and allyltrimethylsilane (Aldrich; 140 μL, 969 μmol) in DME (1.5 mL) was added $Me_3O^+ \cdot BF_4^-$ (Alfa; 50 mg, 340 μmol) all at once. The heterogeneous reaction mixture was warmed to ca. 35 °C and stirred for 3.25 h at which time TLC analysis indicated complete reaction of starting material. The reaction was cooled to room temperature over 10 min and glacial acetic acid (17.5 M, 50 μL, 880 μmol) was added followed quickly by freshly prepared Rieke zinc (ca. 0.11 M in THF, 2.0 mL, 0.22 mmol). The black suspension was stirred 20 min at room temperature before it was partitioned between ether (10 mL) and saturated $NaHCO_3$ (10 mL). The layers were separated, and the organics were washed with brine (10 mL). The combined aqueous layers were extracted with ether (2 × 10 mL). The combined organic portions were dried ($MgSO_4$) and filtered, and the solvents were removed. The oily crystalline residue was placed on a flash silica gel column ($^1/_2$ in. × 5 in.) and eluted first with hexane to remove naphthalene and then with ether. The ethereal fraction was divided into two portions and purified by ATLC (plate 20 cm × 10 cm, 1:1:4 ether/CH_2Cl_2/hexane, two elutions) to give as the faster moving component **14b** (epi series; 19.3 mg, 63%) and as the lower R_f component **14a** (natural series, 7.2 mg, 24%). **14b**: oil; analytical TLC (silica gel F254), 1:1:2 ether/CH_2Cl_2/hexane, R_f = 0.55; MS exact mass calcd for $C_{36}H_{51}NO_5SSi$ = 637.3257, found = 637.3207, error = 7.9 ppm; IR (neat, cm^{-1}) C=O 1730, C=O 1700; 270-MHz NMR ($CDCl_3$) δ 7.36–7.19 (5 H, m), 6.19 (1 H, dd, *J* = 10.1, 15.8 Hz), 5.63 (1 H, ddd, *J* = 5.6, 8.6, 15.8 Hz), 5.25 (1 H, d, *J* = 7.7 Hz), 5.08 (1 H, s), 4.09–4.01 (2 H, m), 3.32 (1 H, dd, *J* = 3.0, 12.8 Hz), 3.12–2.87 (3 H, m), 2.55 (1 H, dd, *J* = 10.1, 12.8 Hz), 2.49 (3 H, s), 2.46–2.22 (2 H, m), 2.18 (3 H, s), 2.15–1.98 (3 H, m), 1.97 (3 H, s), 1.79 (1 H, ddd, *J* = 2.4, 9.5, 15.2 Hz), 1.38 (2 H, s), 1.06 (3 H, d, *J* = 6.8 Hz), 1.03 (3 H, d, *J* = 6.9 Hz), 0.38 (3 H, d, *J* = 6.9 Hz), −0.08 (9 H, s). Natural series, **14a**: oil; analytical TLC (silica gel F254), 1:1:2 ether/CH_2Cl_2/hexane, R_f = 0.53; MS exact mass calcd for $C_{36}H_{51}NO_5SSi$ = 637.3257, found = 637.3240, error = 2.8 ppm; IR (neat, cm^{-1}) C=O 1750, C=O 1740, C=O 1735, C=O 1700; 270-MHz NMR ($CDCl_3$) δ 7.39–7.16 (5 H, m), 6.11 (1 H, dd, *J* = 10.1, 15.7 Hz), 5.49 (1 H, ddd, *J* = 3.8, 10.6, 15.7 Hz), 5.37 (1 H, d, *J* = 7.4 Hz), 5.12 (1 H, s), 4.08 (1 H, d, *J* = 10.0 Hz), 3.47–3.32 (3 H, m), 3.09–2.96 (2 H, m), 2.91–2.78 (1 H, m), 2.59–2.49 (1 H, m), 2.47 (3 H, s), 2.23 (3 H, s), 2.09 (3 H, s), 2.06–1.92 (5 H, m), 1.34 (2 H, s), 1.21 (3 H, d, *J* = 6.5 Hz), 1.05 (3 H, d, *J* = 6.2 Hz), 0.32 (3 H, d, *J* = 6.8 Hz), −0.10 (9 H, s).

Deacetylation of 14a (Natural Series) to Amide 15a. To a solution of imide **14a** (6.0 mg, 9.4 μmol) in THF (0.45 mL) and MeOH (0.75 mL) at −15 °C was added anhydrous K_2CO_3 (flame-dried in vacuo; 21 mg, 150 μmol). The reaction was stirred for 2 h and then was partitioned between EtOAc (10 mL) and brine (10 mL). The layers were separated, and the organic layer was washed with brine (10 mL), extracted with EtOAc (2 × 10 mL), dried ($MgSO_4$) and filtered, and the solvents were removed in vacuo. Flash silica gel chromatography (0.5 cm × 6 cm, 30% EtOAc/hexane) of the residual oil gave amide **15a**, 3.9 mg (70%): oil; analytical TLC (silica gel F254), 1:2 EtOAc/hexane, R_f = 0.30; MS exact mass calcd for $C_{34}H_{49}NO_4SSi$ = 595.3152, found = 595.3137, error = 2.5 ppm; IR (neat, cm^{-1}) N—H 3420, C=O 1740, C=O 1690; 270-MHz NMR ($CDCl_3$) δ 7.35–7.11 (5 H, m), 6.21 (1 H, ddd, *J* = 1.2, 10.4, 15.4 Hz), 5.49 (1 H, s), 5.44 (1 H, ddd, *J* = 4.2, 10.9, 15.4 Hz), 5.29 (1 H, d, *J* = 5.3 Hz), 5.16 (1 H, s), 3.53 (1 H, ddd, *J* = 1.5, 5.3, 12.7 Hz), 3.25–3.16 (1 H, m), 3.07–2.77 (3 H, m), 2.66 (1 H, dd, *J* = 9.2, 13.0 Hz), 2.56–2.43 (1 H, m), 2.37–2.17 (2 H, m), 2.21 (3 H, s), 2.16 (3 H, s), 2.12–1.91 (4 H, m), 1.47 (2 H, s), 1.18 (3 H, d, *J* = 6.8 Hz), 1.06 (3 H, d, *J* = 6.8 Hz), 0.98 (3 H, d, *J* = 7.1 Hz), −0.03 (9 H, s).

Preparation of Selenylating Reagent PhSeSe$^+$(Me)Ph·BF$_3^-$.[6] To a suspension of $Me_3O^+ \cdot BF_4^-$ (Alfa; 152 mg, 1.03 mmol) in CH_2Cl_2 (1.40 mL) was added PhSeSePh (Aldrich; 343 mg, 1.10 mmol) in CH_2Cl_2 (3.0 mL) via cannula. The diselenide containing flask was rinsed with additional solvent (1.0 mL, total solvent = 5.40 mL, 0.19 M). The yellow heterogeneous mixture was sealed and stirred at room temperature overnight (12–15 h) in the dark (the reagent darkens upon prolonged exposure to light) by which time all the solids had dissolved and the solution was orange-red in color. The reagent was used as a 0.19 M solution and was stored in a covered desiccator at ca. −30 °C in the freezer.

Selenylation of Allylic Silane 15a to Allylic Selenide 16a. To a solution of PhSeSe$^+$(Me)Ph·BF$_4^-$ (0.19 M in CH_2Cl_2, 40 μL, 7.5 μmol) at −78 °C was added, via cannula, allylic silane **15a** (3.9 mg, 6.5 μmol) in CH_2Cl_2 (0.3 mL) and the allylic silane containing flask was rinsed with additional CH_2Cl_2 (0.2 mL). The reaction was stirred for ca. 7 min and then the cold reaction was poured into saturated $NaHCO_3$ (5 mL) with CH_2Cl_2 (10 mL). The layers were separated, and the organic layer was washed with brine (5 mL). Following extraction of the aqueous layers (CH_2Cl_2, 3 × 3 mL), the combined organic portions were dried ($MgSO_4$) and filtered, and the solvents were evaporated. The residue was placed on a flash silica gel column (0.5 cm × 5 cm) and eluted with 5% ether/hexane to remove PhSeMe and then with 50% EtOAc/hexane to give allylic selenide **16a**, 4.3 mg (97%): oil; analytical TLC (silica gel F254), 1:2 EtOAc/hexane, R_f = 0.23; MS no peak match, parent, M − 59 (OAc) = 620.2102, calcd = 620.2101, error = 0.2 ppm; formula = $C_{37}H_{45}NO_4SSe$; IR (neat, cm^{-1}) N—H 3440, C=O 1740, C=O 1710, C=O 1690; 270-MHz NMR ($CDCl_3$) δ 7.37–7.11 (10 H, m), 6.15 (1 H, dd, *J* = 10.7, 15.4 Hz), 5.40 (1 H, ddd, *J* = 3.8, 10.7, 15.4 Hz), 5.35 (1 H, s), 5.29 (1 H, d, *J* = 5.6 Hz), 5.21 (1 H, s), 4.19–4.09 (1 H, m), 3.54 (1 H, d, *J* = 11.8 Hz), 3.52–3.38 (1 H, m), 3.46 (1 H, d, *J* = 11.8 Hz), 3.06–2.81 (2 H, m), 2.82 (1 H, dd, *J* = 5.6, 13.6 Hz), 2.67 (1 H, dd, *J* = 9.5, 13.0 Hz), 2.55–2.41 (1 H, m), 2.37–2.21 (2 H, m), 2.19 (3 H, s), 2.14 (3 H, s), 2.11–1.89 (2 H, m), 1.25 (2 H, s), 1.17 (3 H, d, *J*

= 6.8 Hz), 1.05 (3 H, d, J = 6.8 Hz), 0.86 (3 H, d, J = 6.8 Hz).

Oxidation of Selenide 16a to Allylic Alcohol 17a. To a solution of allylic selenide **16a** (4.3 mg, 6.3 μmol) in dioxane (0.50 mL) and pH 7 buffer solution (1 part Aldrich pH 7 buffer concentrate to 24 parts water, 0.21 mL) at 0 °C was added $NaIO_4$ (0.168 M in water, 42 μL, 7.0 μmol). The cold bath was immediately removed and the reaction stirred for 2.6 h. The reaction was then partitioned between EtOAc (10 mL) and brine (5 mL). The layers were separated, and the organics were washed with brine (5 mL). The combined aqueous layers were extracted with CH_2Cl_2 (2 × 5 mL), dried ($MgSO_4$) and filtered, and the solvents were removed in vacuo. The residual oil was placed on a flash silica gel column (0.5 cm × 5 cm) and eluted with 10% ether/hexane (PhSeSePh) then EtOAc to give allylic alcohol **17a**, 3.0 mg (88%): oil; analytical TLC (silica gel F254), EtOAc, R_f = 0.49; MS exact mass calcd for $C_{31}H_{41}NO_5S$ = 539.2706, found = 539.2719, error = 2.5 ppm; IR (neat, cm^{-1}) N—H 3440, O—H 3260, C=O 1650; 270-MHz NMR ($CDCl_3$) δ 7.37–7.11 (5 H, m), 6.08 (1 H, dd, J = 10.1, 15.4 Hz), 5.63 (1 H, dddd, J = 0.6, 4.2, 10.9, 15.4 Hz), 5.50 (1 H, s), 5.36 (1 H, br s), 5.24 (1 H, s), 5.23 (1 H, d, J = 5.6 Hz), 5.04 (1 H, s), 3.95 (1 H, d, J = 10.4 Hz), 3.42 (1 H, ddd, J = 1.5, 5.6, 12.7 Hz), 3.26–3.19 (1 H, m), 3.09–2.97 (1 H, m), 2.87 (1 H, ddd, J = 2.4, 7.4, 12.2 Hz), 2.81–2.71 (3 H, m), 2.64–2.51 (2 H, m), 2.34 (1 H, t, J = 7.1 Hz), 2.21 (3 H, s), 2.16 (3 H, s), 2.07–1.92 (3 H, m), 1.19 (3 H, d, J = 6.8 Hz), 1.07 (3 H, d, J = 6.8 Hz), 0.88 (3 H, d, J = 6.8 Hz).

Oxidation of Methyl Sulfide 17a to Sulfoxide 18a. To a solution of sulfide **17a** (3.0 mg, 5.6 μmol) in CH_2Cl_2 (1.0 mL) with suspended $NaHCO_3$ (flame-dried in vacuo, ca. 10 mg, 120 μmol) at −78 °C was added MCPBA (Aldrich; 0.16 M in CH_2Cl_2, 40 μL, 6.6 μmol). The reaction was stirred for 30 min before methyl sulfide (Aldrich; 0.16 M in CH_2Cl_2, 40 μL, 6.6 μmol). The reaction was stirred for 30 min before methyl sulfide (Aldrich, 10 μL, 136 μmol) was added to quench excess peroxy acid. After stirring at −78 °C for 10 min the cold bath was removed and the reaction was allowed to warm to room temperature over 5 min and was added to saturated Na_2CO_3 (5 mL) with CH_2Cl_2 (10 mL). The layers were separated, and the organics were washed with saturated Na_2CO_3 (5 mL) and brine (5 mL). The combined aqueous layers were extracted with CH_2Cl_2 (2 × 5 mL), dried ($MgSO_4$), and evaporated. The residual oil was placed on a flash silica gel column (0.5 cm × 5 cm) and eluted with 3:1 EtOAc/hexane to remove nonpolar impurities and then 5% MeOH/EtOAc to give sulfoxide **18a**, 2.4 mg (77%) as a ca. 1:1 mixture of diastereomers: oil; analytical TLC (silica gel F254), 1:19 MeOH/EtOAc, R_f = 0.51; IR (neat, cm^{-1}) N—H 3420, O—H 3250, C=O 1700, S=O 1040; 270-MHz NMR ($CDCl_3$, partial) δ 7.41–7.08 (5 H, m), 6.10 (0.5 H, dd, J = 8.8, 14.8 Hz), 5.97 (0.5 H, dd, J = 10.0, 15.7 Hz), 5.72–5.56 (1 H, m), 5.67 (0.5 H, s), 5.66 (0.5 H, s), 5.46 (0.5 H, d, J = 6.8 Hz), 5.43 (0.5 H, s), 5.41 (0.5 H, d, J = 5.6 Hz), 5.31 (0.5 H, s), 5.08 (1 H, s), 2.87 (1.5 H, s), 2.77 (1.5 H, s), 2.24 (1.5 H, s), 2.19 (1.5 H, s), 1.22 (1.5 H, d, J = 6.5 Hz), 1.21 (1.5 H, d, J = 6.8 Hz), 1.09 (1.5 H, d, J = 6.5 Hz), 1.07 (1.5 H, d, J = 6.8 Hz), 0.93 (1.5 H, d, J = 6.8 Hz).

Sulfoxide 18a Elimination to *dl*-Zygosporin E (19a). To a solution of sulfoxide **18a** (2.4 mg, 4.3 μmol) in xylenes (0.4 mL) was added $CaCO_3$ (flame-dried in vacuo; ca. 20 mg, 200 μmol). The reaction was placed in an oil bath at 135 °C for 55 min, cooled to room temperature, and then filtered through a pad of Celite ($CHCl_3$). The solvents were removed in vacuo, and the residue was purified via ATLC (plate 5 cm × 10 cm, 100% EtOAc) to give two products; the higher R_f component was identified as *dl*-zygosporin E (**19a**), 1.1 mg (52%), and the lower R_f component was tentatively assigned as enol acetate **20a**, 1.0 mg (47%). *dl*-Zygosporin E (**19a**) (synthetic): white needles from acetone/hexane; mp 209–210 °C; analytical TLC (silica gel F254), EtOAc, R_f = 0.45; MS exact mass calcd for $C_{30}H_{37}NO_5$ = 491.2672, found = 491.2695, error = 4.7 ppm; IR (neat, cm^{-1}) N—H 3413, O—H 3266, C=O 1733, C=O 1701, C=O 1689; 270-MHz NMR ($CDCl_3$) δ 7.39–7.09 (5 H, m), 6.01 (1 H, ddd, J = 1.2, 2.4, 15.7 Hz), 5.73 (1 H, dd, J = 9.5, 16.0 Hz), 5.52 (1 H, s), 5.45 (1 H, s), 5.34 (1 H, d, J = 1.2 Hz), 5.28 (1 H, ddd, J = 5.3, 10.7, 16.0 Hz), 5.11 (1 H, s), 4.77 (1 H, ddd, J = 2.1, 7.4, 15.7 Hz), 3.81 (1 H, d, J = 11.8 Hz), 3.28–3.21 (2 H, m), 2.89–2.73 (2 H, m), 2.86 (1 H, d, J = 13.3 Hz), 2.67–2.55 (2 H, m), 2.47–2.31 (1 H, m), 2.26 (3 H, s), 2.10 (1 H, t, J = 4.2 Hz), 2.06–1.90 (2 H, m), 1.26 (3 H, d, J = 6.8 Hz), 1.15 (3 H, d, J = 6.8 Hz), 1.00 (3 H, d, J = 6.8 Hz). Natural zygosporin E:[7] colorless needles from acetone/hexane; mp 218–223.5 °C; analytical TLC (silica gel F254), EtOAc, R_f = 0.45; IR (neat cm^{-1}) N—H 3414, O—H 3260, C=O 1740, C=O 1706, C=O 1685; 270-MHz NMR ($CDCl_3$) δ 7.38–7.09 (5 H, m), 6.01 (1 H, ddd, J = 1.2, 10.8, 15.8 Hz), 5.73 (1 H, dd, J = 9.8, 15.5 Hz), 5.52 (1 H, dd, J = 2.4, 3.6 Hz), 5.44 (1 H, s), 5.34 (1 H, s), 5.28 (1 H, s), 5.28 (1 H, ddd, J = 4.8, 11.0, 15.5 Hz), 5.11 (1 H, s), 4.77 (1 H, ddd, J = 2.4, 7.5, 15.8 Hz), 3.80 (1 H, d, J = 11.0 Hz), 3.29–3.20 (2 H, m), 2.89–2.81 (1 H, m), 2.85 (1 H, d, J = 13.4 Hz), 2.79–2.58 (2 H, m), 2.64 (1 H, d, J = 13.4 Hz), 2.47–2.35 (1 H, m), 2.26 (3 H, s), 2.10 (1 H, t, J = 4.5 Hz), 2.03–1.94 (1 H, m), 1.98 (1 H, d, J = 1.5 Hz), 1.26 (3 H, d, J = 6.8 Hz), 1.15 (3 H, d, J = 6.9 Hz), 1.00 (3 H, d, J = 6.8 Hz). Enol acetate **20a**: very fine white needles from ether/hexane; mp 204–205 °C; analytical TLC (silica gel F254), EtOAc, R_f = 0.42; MS exact mass calcd for $C_{30}H_{37}NO_5$ = 491.2672, found = 491.2637, error = 7.1 ppm; IR (neat, cm^{-1}) N—H 3360, O—H 3254, C=O 1756, C=O 1704, C=O 1694; 270-MHz NMR ($CDCl_3$) δ 7.38–7.09 (5 H, m), 5.88 (1 H, dd, J = 9.2, 14.2 Hz), 5.49–5.29 (2 H, m), 5.39 (1 H, s), 5.21 (1 H, s), 5.02 (1 H, s), 4.57–4.09 (2 H, m), 3.76–3.60 (2 H, m), 3.25–3.19 (1 H, m), 2.74–2.36 (6 H, m), 2.33 (3 H, s), 2.28–2.20 (2 H, m), 2.07–1.88 (1 H, m), 1.17 (3 H, d, J = 7.1 Hz), 1.14 (3 H, d, J = 7.4 Hz), 0.84 (3 H, d, J = 6.8 Hz).

Sulfur Alkylation/Reduction of 2. Preparation of 22a and 22b. To a solution of **2** (11 mg, 18.1 μmol) and allyltrimethylsilane (Aldrich, distilled; 50 μL, 315 μmol) in DME (0.6 mL) was added $Me_3O^+ \cdot BF_4^-$ (Alfa; 26.9 mg, 181 μmol) all at once. The heterogeneous reaction mixture was stirred at ambient temperature for 2.3 h by which time all of the sulfide had gone to a baseline spot by TLC. Methyl sulfide (Aldrich; 20 μL, 272 μmol) was added to quench the excess oxonium salt. The reaction was stirred for 2 min before isopropyl alcohol (EM Science, reagent grade; 50 μL) was added followed by freshly prepared Rieke zinc[5] (ca. 0.2 M in THF, 1.0 mL, 0.2 mol). The black reaction mixture was stirred for ca. 35 min before it was partitioned between ether (10 mL) and saturated NH_4Cl (5 mL). The layers were separated and the organics were washed with saturated $NaHCO_3$ and then brine (5 mL each). The combined aqueous layers were extracted with ether (2 × 5 mL), and the combined organics were dried ($MgSO_4$) and filtered, and the solvents were evaporated. The oily crystalline residue was placed on a flash silica gel column (0.5 cm × 5 cm) and eluted with hexane (naphthalene) followed by 1:3 EtOAc/hexane to give 12.8 mg of crude product. The compound was purified by HPLC (15% EtOAc/hexane) to give the C_{16} methyl diastereomers **22a** (6.7 mg, 59% yield) and **22b** (1.8 mg, 16% yield) in a 3.7:1 ratio. **22a**: oil; analytical TLC (silica gel F254), 1:1:2 ether/CH_2Cl_2/hexane, R_f = 0.54; MS exact mass calcd for $C_{35}H_{49}NO_5SSi$ = 623.3101, found = 623.3120, error = 3.1 ppm; IR (neat, cm^{-1}) C=O 1745, C=O 1725, C=O 1700; 270-MHz NMR ($CDCl_3$) δ 7.38–7.19 (5 H, m), 6.41 (1 H, ddd, J = 1.2, 10.1, 15.2 Hz), 5.76 (1 H, ddd, J = 3.9, 10.7, 15.2 Hz), 5.38 (1 H, d, J = 9.5 Hz), 5.09 (1 H, s), 4.09 (1 H, d, J = 10.1 Hz), 3.45–3.31 (2 H, m), 3.16–2.98 (2 H, m), 2.73–1.94 (9 H, m), 2.45 (3 H, s), 2.26 (3 H, s), 2.14 (3 H, s), 1.34 (2 H, s), 1.30 (3 H, d, J = 6.9 Hz), 0.29 (3 H, d, J = 7.1 Hz), −0.09 (9 H, s). **22b**: white crystals from ether/hexane; mp 170–172 °C, analytical TLC (silica gel F254), 1:1:2 ether/CH_2Cl_2/hexane, R_f = 0.58; MS exact mass calcd for $C_{35}H_{49}NO_5SSi$ = 623.3101, found = 623.3101, error = 0.1 ppm; IR (neat, cm^{-1}) C=O 1740, C=O 1715, C=O 1700, C=O 1685; 270-MHz NMR ($CDCl_3$) δ 7.38–7.19 (5 H, m), 6.32 (1 H, dd, J = 9.6, 15.0 Hz), 5.59 (1 H, ddd, J = 6.9, 8.1, 15.0 Hz), 5.38 (1 H, d, J = 9.5 Hz), 5.09 (1 H, t, J = 2.4 Hz), 4.08 (1 H, d, J = 10.1 Hz), 3.47–3.27 (2 H, m), 3.07–2.92 (2 H, m), 2.87–2.77 (1 H, m), 2.54 (1 H, t, J = 11.3 Hz), 2.45 (3 H, s), 2.41–2.35 (1 H, m), 2.33–2.26 (2 H, m), 2.24 (3 H, s), 2.15 (3 H, s), 2.12–1.95 (3 H, m), 1.69–1.57 (1 H, m), 1.33 (2 H, s), 1.07 (3 H, d, J = 6.5 Hz), 0.28 (3 H, d, J = 6.9 Hz), −0.09 (9 H, s).

Conversion of Allylic Silane 22a to Silyl Ether 25. To a solution of $PhSeSe^+(Me)Ph \cdot BF_4^-$ (prepared as described earlier, 125 mM, 285 μL, 36 μmol) at −78 °C was added a solution of allylic silane **22a** (18.5 mg, 29 μmol) in CH_2Cl_2 (1.0 mL) via cannula. The silane-containing flask was rinsed with additional solvent (0.4 mL) that was added to the reaction. After ca. 5 min the reaction was poured into a separatory funnel containing saturated $NaHCO_3$ (5 mL) with CH_2Cl_2 (10 mL). The layers were separated, the organics were washed with brine (5 mL), and the combined aqueous layers were extracted with CH_2Cl_2 (2 × 5 mL). The combined organic portions were dried ($MgSO_4$) and filtered, and the solvents were removed in vacuo. The residue was placed on a flash silica gel plug (1 cm × 2 cm) and eluted with 5% ether/hexane (PhSeMe) followed by ether to give the allylic selenide **23**, 21.5 mg (theoretical yield = 20.5 mg), which was carried on without further purification: oil; analytical TLC (silica gel F254), 1:1:2 ether/CH_2Cl_2/hexane, R_f = 0.49; MS exact mass calcd for $C_{38}H_{45}NO_5SSe$ = 707.2183, found = 707.2178, error = 0.8 ppm; 270-MHz NMR ($CDCl_3$) δ 7.42–7.17 (10 H, m), 6.39 (1 H, dd, J = 10.7, 15.1 Hz), 5.72 (1 H, ddd, J = 3.3, 10.7, 15.1 Hz), 5.41 (1 H, d, J = 9.0 Hz), 5.39 (1 H, s), 4.27 (1 H, dd, J = 2.7, 11.6 Hz), 3.53–3.42 (2 H, m), 3.37–3.28 (2 H, m), 3.10–2.96 (2 H, m), 2.70–2.51 (3 H, m), 2.36 (3 H, s), 2.30–2.05 (5 H, m), 2.26 (3 H, s),

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(8) McLafferty, F. W. Interpretation *of Mass Spectra*; University Science Books: Mill Valley, CA, 1980.

2.13 (3 H, s), 1.60–1.51 (1 H, m), 1.29 (3 H, d, J = 7.1 Hz), 0.44 (3 H, d, J = 6.8 Hz).

The allylic selenide **23** from above (21.5 mg, 29 μmol) was dissolved in *p*-dioxane (1.50 mL) to which was added pH 7 buffer solution (Aldrich; 1 part concentrate to 24 parts water, 0.30 mL) and $NaIO_4$ (0.19 M in H_2O, 0.46 mL, 89 μmol). The reaction was stirred at ambient temperature during which time it gradually yellowed and deposited a white precipitate. After 70 min the excess periodate was quenched by the addition of Na_2SO_3 (aqueous) and the mixture was partitioned between EtOAc (10 mL) and brine (5 mL). The layers were separated, the organics were washed with brine (5 mL), the aqueous layers were extracted with EtOAc (2 × 5 mL), the combined organics were dried ($MgSO_4$) and filtered, and the solvents were removed. The residue was placed on a flash silica gel plug (1 cm × 2 cm) and eluted with 15% EtOAc/hexane to give a yellow forerun (PhSeSePh) followed by 3:1 EtOAc/hexane to give ca. 15 mg of crude product. This was then purified by flash silica gel chromatography (column 0.5 cm × 15 cm, 1:1 EtOAc/hexane) to give the rearranged allylic alcohol **24**, 13.6 mg (81% from the allylic silane): oil; analytical TLC (silica gel F254), 1:1 EtOAc/hexane, R_f = 0.28; MS exact mass calcd for $C_{32}H_{41}NO_6S$ = 567.2654, found = 567.2621, error = 5.9 ppm; IR (neat, cm^{-1}) O—H 3450, C=O 1744, C=O 1723, C=O 1700; 270-MHz NMR ($CDCl_3$) δ 7.39–7.18 (5 H, m), 6.27 (1 H, dd, J = 9.2, 15.1 Hz), 5.89 (1 H, ddd, J = 3.5, 10.9, 15.1 Hz), 5.36 (1 H, d, J = 9.5 Hz), 5.04 (1 H, s), 4.89 (1 H, s), 4.00 (1 H, dd, J = 1.2, 10.7 Hz), 3.87 (1 H, d, J = 9.5 Hz), 3.42 (1 H, dd, J = 2.6, 12.4 Hz), 3.26 (1 H, ddd, J = 2.1, 9.5, 11.6 Hz), 3.08 (1 H, ddd, J = 1.5, 12.7, 14.5 Hz), 2.76 (1 H, dd, J = 9.2, 9.8 Hz), 2.75–2.57 (3 H, m), 2.43 (3 H, s), 2.41–2.29 (3 H, m), 2.28 (3 H, s), 2.26–2.20 (1 H, m), 2.14 (3 H, s), 2.10 (1 H, d, J = 6.2 Hz), 1.70 (1 H, s), 1.65–1.55 (1 H, m), 1.31 (3 H, d, J = 7.1 Hz), 0.24 (3 H, d, J = 6.8 Hz).

To a solution of the allylic alcohol **24** (13.6 mg, 24 μmol) in DMF (1.1 mL) were added imidazole (Aldrich; 33 mg, 486 μmol), DMAP (Aldrich; 6 mg, 49 μmol) and TBSCl (Petrarch; 28.4 mg, 188 μmol). The resulting solution was stirred at ambient temperature for 16 h and then was diluted with hexane (ca. 15 mL), and washed successively with saturated $NaHCO_3$ (5 mL), saturated NH_4Cl (2 × 5 mL), and brine (5 mL). The combined aqueous layers were extracted with hexane (2 × 5 mL), dried ($MgSO_4$), and filtered, and the solvents were evaporated. The residue was placed on a flash silica gel column (1 cm × 5 cm) and eluted with hexane to remove silicon impurities followed by 25% EtOAc/hexane to give the crude silyl ether **25** (17.3 mg, theoretical yield = 16.3 mg), sufficiently pure for the next step: oil; analytical TLC (silica gel F254), 15% EtOAc/hexane, R_f = 0.19; MS no peak match, parent, loss of Me_3C, M − 57, 624.2887, calcd = 624.2815, error = 4.4 ppm, formula = $C_{38}H_{55}NO_6SSi$; IR (neat, cm^{-1}) C=O 1745, C=O 1723, C=O 1702; 270-MHz NMR ($CDCl_3$) δ 7.41–7.18 (5 H, m), 6.14 (1 H, ddd, J = 0.9, 9.5, 15.4 Hz), 5.67 (1 H, ddd, J = 3.5, 10.3, 15.4 Hz), 5.35 (1 H, d, J = 9.8 Hz), 4.80 (1 H, s), 4.76 (1 H,s), 4.01 (1 H, ddd, J = 0.9, 2.1, 11.2 Hz), 3.86 (1 H, d, J = 8.3 Hz), 3.42 (1 H, dd, J = 3.3, 13.0 Hz), 3.23 (1 H, ddd, J = 1.5, 9.5, 11.0 Hz), 3.10 (1 H, ddd, J = 1.5, 12.7, 17.4 Hz), 2.71–2.56 (5 H, m), 2.42 (3 H, s), 2.39–2.36 (2 H, m), 2.30 (3 H, s), 2.22–2.18 (1 H, m), 2.14 (3 H, s), 2.04 (1 H, dd, J = 0.9, 6.5 Hz), 1.64–1.50 (1 H, m), 1.30 (3 H, d, J = 6.8 Hz), 0.76 (9 H, s), 0.22 (3 H, d, J = 7.1 Hz), −0.08 (6 H, s).

Selenenylation of 25 to Selenide 27 (Major C_{16} Methyl Series). A solution of the ketone **25** (17 mg, 24 μmol), TMSCl (freshly distilled from CaH_2; 60 μL, 470 μmol) and DBU (75 μL, 500 μmol) in CH_3CN (2.0 mL) was heated at 70–75 °C for ca. 12 h. The very dark reaction was diluted with hexane (25 mL) and washed with saturated $NaHCO_3$ (2 × 10 mL) and then 0.1 N citric acid (10 mL). The combined aqueous layers were extracted with hexane (2 × 10 mL), dried ($MgSO_4$), and filtered, and the solvents were removed in vacuo. The residue was placed on a short flash silica gel plug (0.5 cm × 5 cm) and eluted with 15% EtOAc/hexane to give the crude silyl enol ether **26**, 21 mg (theoretical yield = 18.1 mg), that was used directly in the next step: oil; analytical TLC (silica gel F254), 15% EtOAc/hexane, R_f = 0.43; 270-MHz NMR ($CDCl_3$, partial) δ 6.00 (1 H, dd, J = 9.8, 14.5 Hz), 5.43 (1 H, d, J = 9.5 Hz), 5.35 (1 H, ddd, J = 3.5, 10.9, 14.5 Hz), 4.78 (1 H, s), 4.75 (1 H, s), 4.48 (1 H, t, J = 7.7 Hz), 4.03 (1 H, ddd, J = 1.2, 2.7, 10.9 Hz).

To a solution of $PhSeSe^+(Me)Ph\cdot BF_4^-$ prepared as described earlier (125 mM, 0.23 mL, 29 μmol) at −78 °C was added the silyl enol ether **26** (21.3 mg, 24 μmol) in CH_2Cl_2 (0.7 mL) via cannula. The silyl enol ether containing flask was rinsed with additional solvent (0.3 mL) that was added to the reaction. After ca. 10 min the reaction was poured into a separatory funnel containg saturated $NaHCO_3$ (5 mL) with CH_2Cl_2 (10 mL). The layers were separated, the organics were washed with brine (5 mL), aqueous layers were extracted with CH_2Cl_2 (2 × 5 mL), organics were dried ($MgSO_4$) and filtered, and solvents were removed. The residue was placed on a flash silica gel column (1 cm × 6 cm) and eluted with 5% ether/hexane (PhSeMe) followed by ether to give C_{16}-selenide **27**, 18.6 mg (93% two steps): oil; analytical TLC (silica gel F254), 15% EtOAc/hexane, R_f = 0.23; IR (neat, cm^{-1}) C=O 1747, C=O 1723, C=O 1700, C=O 1690; 270-MHz NMR ($CDCl_3$) δ 7.62–7.18 (10 H, m), 6.15 (1 H, ddd, J = 1.6, 10.4, 15.4 Hz), 5.66 (1 H, ddd, J = 3.9, 10.7, 15.4 Hz), 5.29 (1 H, d, J = 10.1 Hz), 4.78 (1 H, s), 4.75 (1 H, s), 4.03 (1 H, dd, J = 2.7, 11.6 Hz), 3.98 (1 H, ddd, J = 1.5, 2.7, 11.0 Hz), 3.85 (1 H, d, J = 8.3 Hz), 3.38 (1 H, dd, J = 2.4, 12.4 Hz), 3.09 (1 H, ddd, J = 1.8, 8.3, 10.1 Hz), 2.92–2.78 (1 H, m), 2.71–2.56 (3 H, m), 2.49–2.24 (3 H, m), 2.37 (3 H, s), 2.06–1.93 (2 H, m), 2.00 (3 H, s), 1.96 (3 H, s), 1.63 (3 H, d, J = 7.1 Hz), 0.75 (9 H, s), 0.19 (3 H, d, J = 6.8 Hz), −0.08 (6 H, s).

Selenoxide Elimination of 27 to Enones 29 and 30. To a stirred suspension of $NaHCO_3$ (flame-dried in vacuo; 3 mg, 35 μmol) and C_{18}-selenide **27** (5.1 mg, 6.1 μmol) in CH_2Cl_2 (0.25 mL) at −78 °C was added MCPBA (Aldrich; 0.14 M in CH_2Cl_2, 94 μL, 13.4 μmol) via syringe. The reaction was stirred at −78 °C for 35 min before it was allowed to warm slowly to −20 °C over 35 min. At this point methyl sulfide (Aldrich; 5 μL, 68 μmol) and triethylamine (Aldrich, distilled from CaH_2; ca. 15 μL, ca. 100 μmol) were added and the cold bath was removed. After warming to room temperature, chloroform (0.5 mL) was added and the reaction was warmed to ca. 50 °C for 70 min. After returning to room temperature, the reaction mixture was washed with saturated Na_2CO_3 (2 × 5 mL), saturated NH_4Cl (5 mL), and brine (5 mL). The combined aqueous layers were extracted with $CHCl_3$ (2 × 5 mL), the organics were dried ($MgSO_4$) and filtered, and the solvents were removed. A flash silica gel plug (0.5 cm × 5 cm) eluted with 10% EtOAc/hexane (PhSeSePh) followed by EtOAc afforded 4.4 mg of crude product. Purification by ATLC (plate 5 cm × 10 cm, 2:1 EtOAc/hexane) gave as the major product cis-enone **29** (2.8 mg, 66%) and a minor product trans-enone **30** (ca. 0.8 mg, ca. 20%). **29**: oil; analytical TLC (silica gel F254), 2:1 EtOAc/hexane, R_f = 0.26; IR (neat, cm^{-1}) C=O 1750, C=O 1715, C=O 1705, C=O 1683, S=O 1062; 270-MHz NMR ($CDCl_3$) δ 7.43–7.17 (5 H, m), 6.74 (1 H, d, J = 12.1 Hz), 6.05 (1 H, d, J = 9.2 Hz), 5.85 (1 H, dd, J = 9.5, 14.2 Hz), 5.66 (1 H, ddd, J = 3.9, 9.8, 14.2 Hz), 5.62 (1 H, dd, J = 11.8, 12.1 Hz), 4.82 (1 H, s), 4.79 (1 H, s), 4.56 (1 H, dd, J = 9.2, 11.8 Hz), 4.07 (1 H, ddd, J = 2.1, 3.0, 11.0 Hz), 3.87 (1 H, d, J = 8.9 Hz), 3.46 (1 H, dd, J = 3.2, 13.3 Hz), 2.85–2.63 (4 H, m), 2.68 (3 H, s), 2.49–2.38 (1 H, m), 2.40 (3 H, s), 2.27–2.23 (1 H, m), 2.25 (3 H), 2.21–2.09 (1 H, m), 1.40 (3 H, d, J = 7.4 Hz), 0.74 (9 H, s), 0.25 (3 H, d, J = 7.1 Hz), −0.07 (6 H, s). **30**: oil; analytical TLC (silica gel F254), 2:1 EtOAc/hexane, R_f = 0.23; 270-MHz NMR ($CDCl_3$) δ 7.50–7.21 (5 H, m), 6.69 (1 H, m, dd, J = 7.4, 17.5 Hz), 6.30 (1 H, s), 6.15 (1 H, d, J = 17.5 Hz), 5.83 (1 H, dd, J = 9.8, 16.0 Hz), 5.42 (1 H, ddd, J = 7.4, 9.5, 16.0 Hz), 4.81 (1 H, s), 4.79 (1 H, s), 4.124 (1 H, d, J = 7.4 Hz), 0.09 (1 H, dd, J = 9.2, 14.5 Hz), 3.82 (1 H, d, J = 8.3 Hz), 3.54 (1 H, d, J = 8.0 Hz), 3.43 (1 H, dd, J = 2.7, 13.6 Hz), 3.33–3.26 (1 H, m), 2.79–2.33 (4 H, m), 2.61 (3 H, s), 2.46 (3 H, s), 2.24 (3 H, s), 2.16–2.01 (1 H, m), 1.22 (3 H, d, J = 6.8 Hz), 0.74 (9 H, s), 0.30 (3 H, d, J = 6.5 Hz), −0.07 (6 H, s).

Allylic Sulfoxide 29 Rearrangement to Allylic Alcohol 31. A solution of **29** (1.8 mg, 2.6 μmol) and trimethylphosphite (Aldrich, freshly distilled from CaH_2; 0.15 mL) and 1-propanol (EM Science, reagent grade; 0.05 mL) was heated at 100–105 °C. After ca. 5 h, additional trimethyl phosphite (0.15 mL) was added and heating continued 18 h longer. After the reaction was allowed to cool to room temperature, the volatiles were removed in vacuo. The residue was taken up in EtOAc (10 mL) and was washed with brine (2 × 5 mL). The combined aqueous layers were extracted with EtOAc (2 × 5 mL). The combined organic portions were dried ($MgSO_4$) and filtered, and the solvents were removed in vacuo. The residue was passed through a flash silica gel plug (0.5 cm × 2 cm, 1:2 EtOAc/hexane) and further purified by ATLC (plate 5 cm × 10 cm, 1:2 EtOAc/hexane) to give rearranged allylic alcohol **31**, 0.9 mg (53% yield): oil; analytical TLC (silica gel F254), 1:2 EtOAc/hexane, R_f = 0.36; MS no peak match, parent, M − 57 (*tert*-butyl) = 592.2753, calcd = 592.2730, error = 3.4 ppm, formula = $C_{37}H_{51}NO_7Si$; IR (neat, cm^{-1}) O—O 3415, C=O 1745, C=O 1723, C=O 1705; 270-MHz NMR ($CDCl_3$) δ 7.35–7.18 (5 H, m), 6.08 (1 H, dd, J = 0.9, 16.3 Hz), 5.71 (1 H, dd, J 11.6, 14.8 Hz), 5.70 (1 H, dd, J = 0.9, 2.4 Hz), 5.29 (1 H, ddd, J = 6.8, 8.3, 14.8 Hz), 5.09 (1 H, ddd, J = 2.4, 5.0, 14.8 Hz), 4.87 (1 H, s), 4.84 (1 H, dd, J = 3.3, 5.0 Hz), 4.81 (1 H, s), 3.97 (1 H, ddd, J = 1.5, 4.1, 10.3 Hz), 3.76 (1 H, d, J = 8.9 Hz), 3.27 (1 H, dd, J = 2.4, 12.1 Hz), 3.17 (1 H, ddq, J = 3.3, 8.9, 7.1 Hz), 2.88–2.82 (1 H, m), 2.79 (1 H, dd, J = 8.6, 9.5 Hz), 2.59 (1 H, dd, J = 10.7, 12.2 Hz), 2.54–2.06 (4 H, m), 2.49 (3 H, s), 2.29 (3 H, s), 1.19 (3 H, d, J = 7.1 Hz), 0.76 (9 H, s), 0.31 (3 H, d, J = 6.8 Hz), −0.07 (6 H,s).

Deprotection of 31 to *dl*-C_{18}-Desmethylcytochalasin D (32). To a solution of **31** (0.9 mg, 1.4 μmol) in THF (0.1 mL) and MeOH (0.2 mL) at ca. −20 °C (CCl_4/CO_2 bath) was added K_2CO_3 (flame-dried in vacuo, 6.8 mg, 49 μmol). The suspension was stirred at ca. −20 °C for 70 min

before it was partitioned between EtOAc (10 mL) and brine (5 mL). The layers were separated, and the organics were washed with brine (5 mL), and the combined aqueous layers were extracted with EtOAc (2 × 5 mL). The organics were dried ($MgSO_4$) and filtered, and the solvents were removed to give 0.7 mg of the deacylated amide as a slightly yellow oil that was used in the next step without further purification: oil; analytical TLC (silica gel F254), 1:1 EtOAc/hexane, R_f = 0.30; 270-MHz NMR ($CDCl_3$) δ 7.39-7.12 (5 H, m), 6.41 (1 H, ddd, J = 1.8, 3.9, 16.0 Hz), 5.63 (1 H, dd, J = 5.6, 15.4 Hz), 5.59 (1 H, d, J = 2.3 Hz), 5.46 (1 H, s), 5.34 (1 H, d, J = 5.3 Hz), 5.17 (1 H, ddd, J = 7.1, 7.7, 15.4 Hz), 5.15 (1 H, s), 5.05 (1 H, ddd, J = 4.4, 6.8, 16.0 Hz), 4.99 (1 H, s), 4.77-4.74 (1 H, m), 3.90 (1 H, d, J = 3.29 Hz), 3.29-3.19 (1 H, m), 2.92-2.73 (3 H, m), 2.61 (1 H, dd, J = 9.8, 13.3 Hz), 2.46-2.43 (1 H, m), 2.35-2.,26 (1 H, m), 2.23 (3 H, s), 2.13-1.96 (2 H, m), 1.15 (3 H, d, J = 7.1 Hz), 1.02 (3 H, d, J = 7.1 Hz), 0.81 (9 H, s), -0.03 (6 H, s).

The amide (0.7 mg) was dissolved in CH_3CN (0.1 mL) and cooled to 0 °C then 48% (aqueous) HF was added (1 μL, 24 μmol) and the reaction was stirred for 100 min at 0 °C and then partitioned between EtOAc (5 mL) and brine (5 mL). The organics were washed with brine (5 mL), the combined aqueous layers were bakc-extracted with EtOAc (2 × 5 mL), and then the organic portion was dried ($MgSO_4$) and filtered, and the solvents were evaporated. The residue was purified by ATLC (5 cm × 10 cm, 3:1 EtOAc/hexane) to give *dl*-C_{18}-desmethylcytochalasin D (**32**), 0.5 mg (ca. 70% for two steps): white crystals from acetone/hexane; mp 232-236 °C dec; analytical TLC (silica gel F254), 3:1 EtOAc/hexane, R_f = 0.41; MS exact mass calcd for $C_{29}H_{35}NO_6$ 493.2464, found 493.2472, error = 1.6 ppm; IR (neat, cm^{-1}) N H and OH 3340, C=O 1740, C=O 1690, C=O 1685; 270-MHz NMR ($CDCl_3$) δ 7.35-7.11 (5 H, m), 6.50 (1 H, dd, J = 1.8, 16.0 Hz), 5.77 (1 H, dd, J = 9.2, 15.4 Hz), 5.55 (1 H, dd, J = 2.4, 2.7 Hz), 5.51 (1 H, d, J = 0.9 Hz), 5.44 (1 H, s), 5.37 (1 H, ddd, J = 6.8, 7.4, 15.4 Hz), 5.10 (1 H, ddd, J = 2.7, 5.0, 16.0 Hz), 4.78-4.75 (1 H, m), 3.82 (1 H, dd, J = 1.5, 10.9 Hz), 3.35-3.25 (2 H, m), 2.94 (1 H, dd, J = 3.88, 13.3 Hz), 2.80 (1 H, dd, J = 10.0, 11.0 Hz), 2.80-2.73 (1 H, m), 2.56 (1 H, dd, J = 9.8, 13.3 Hz), 2.38-2.28 (2 H, m), 2.21 (3 H, s), 2.19-2.05 (3 H, m), 1.97 (1 H, s), 1.15 (3 H, d, J = 7.1 Hz), 1.11 (3 H, d, J = 6.8 Hz).

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Supplementary Material Available: Table of mass spectral fragmentation patterns for **32**, CD, and ZE and details of the route to C_{16}-*epi*-zygosporin E (5 pages). Ordering information is available on any current masthead page.

Synthesis of Cyclobutanones by the Photolytic Reaction of Chromium Carbene Complexes with Olefins: Inter- and Intramolecular Reactions

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Abstract: Cyclobutanones were synthesized in good yield and with a high degree of stereo- and regioselectivity by the photolytic reaction between a variety of chromium alkoxycarbene complexes and olefins. Bicyclic cyclobutanones were synthesized in good yield and with a high degree of stereo- and regioselectivity by the photolysis of chromium alkoxycarbenes having remote double bonds in the alkoxy group.

Photolysis reactions of heteroatom-stabilized (Fischer) chromium carbene complexes are becoming increasingly useful for the synthesis of novel organic compounds under exceptionally mild conditions. Thus photolysis, using visible light and a Pyrex reaction vessel, in solvents ranging from hexane through acetonitrile, of methoxycarbenes[1] and aminocarbenes[2] with imines produced β-lactams in excellent chemical yield. Use of optically active aminocarbene complexes[3] resulted in the production of optically active β-lactams in good yield and with high stereoselectivity.[4] Photolysis of aminocarbene complexes in the presence of alcohols produced α-amino acid esters.[5] During the development of these reactions it became clear that photolysis of chromium carbene complexes produced species that reacted as if they were ketenes, although no evidence for the generation of free ketenes was observed.[6] This suggested that other classes of reactions in which ketenes engaged should be examined.

Stereospecific [2 + 2] cycloaddition[7] reactions of ketenes and olefins to produce cyclobutanones[8] have been extensively developed, although the use of electron-rich O- or N-containing ketenes is uncommon.[9] In contrast, *intra*molecular versions of this process

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