appropriate mechanism, the inefficiency of this low-temperature quenching process points to the negligible contribution of tunneling to electron transfer in Zn-cyto $c/a_5Ru^{II,III}$. Other possible mechanisms are magnetic dipole induced relaxation by the magnetic moment of Ru^{III} and energy transfer. The energy transfer process would require the existence of a suitable acceptor energy level of a_5Ru^{III}his below that of $^3ZnP^*$ (39 kcal/mol). Since $10Dq$ for $Ru^{III}(NH_3)_6$ has been estimated to be ca. 91 kcal/mol,[35] $t_2 \rightarrow e$ excitations would not be effective. On the other hand, the degeneracy of the t_2^5 configuration is reduced by the combination of an axial ligand field distortion and spin-orbit coupling to produce some low-lying electronic states[35] that could conceivably quench $^3ZnP^*$ by an energy transfer mechanism.

Transitions to these states should be highly forbidden by electric dipole selection rules, and thus coupling to the $^3ZnP^*$ might be expected to occur preferentially either by an electronic exchange mechanism[36] or by a magnetic dipolar mechanism. The latter mechanism should be sensitive to the spin orientation of the donor sublevel of $^3ZnP^*$, but we do not know enough about the electronic energy level structure of a_5Ru^{III}his to speculate further.

Thermally Activated Electron Transfer. With regard to the thermally activated electron transfer occurring above 100 K, the appearance of two distinct Arrhenius-type regions with differing activation energies is of interest. This particular temperature dependence may be an oversimplification because of the limited temperature range investigated. However, simple Arrhenius behavior definitely is not the case. The observed temperature dependence could be the result of conformationally gated electron transfer proposed recently by Hoffman and Ratner,[6] which has received experimental support from McLendon, et al.[7] Conformational gating is based on a theory of Agmon and Hopfield,[37] in which reaction rates in proteins are modulated by diffusional motions of the medium perpendicular to the reaction coordinate. The protein medium assumes the role of the outer solvent sphere in the Marcus-Hush theory,[20] while the inner solvent sphere coordinates (local bond lengths and angles) undergo Hamiltonian or "ballistic" motion.[37] Hoffman and Ratner show that in a protein such as cytochrome c, which undergoes a structural change upon reduction,[38] electron transfer can be conformationally gated if two or more stable protein conformations exhibit differing rate constants for electron transfer. It is expected that there will be a change in the activation energy for electron transfer as the protein motions slow down and the medium becomes frozen into a single stable conformation, i.e., that which is energetically most favorable to the precursor state. Other, less specific models for protein dynamics could also lead to non-Arrhenius behavior, however.

(35) Sham, T. K. *J. Am. Chem. Soc.* **1983**, *105*, 2269.
(36) Dexter, D. L. *J. Chem. Phys.* **1953**, *21*, 836.
(37) Agmon, N.; Hopfield, J. J. *J. Chem. Phys.* **1983**, *78*, 6947; *Ibid.* **1983**, *79*, 2042.

Conclusions

Measurements of the rate constant for the decay of ^3ZnP in Zn-cyto c/a_5Ru^{III} over a wide range of temperature reveal a temperature-independent region below 100 K for quenching of ^3ZnP by Ru^{III}, with a rate constant of $k_q = 3.6 \pm 0.22\ s^{-1}$. In this range, electron transfer, which is coupled to nuclear tunneling, may be responsible for the quenching. Other possible mechanisms that are discussed are energy transfer and magnetic-dipole-induced quenching. Above 100 K, two regions of Arrhenius-type activated electron transfer are found with $E_a = 1.6$ kcal/mol below 150 K and $E_a = 5.6$ kcal/mol above this transition temperature. It is suggested that this behavior may be a manifestation of conformational gating utilizing two or more stable protein conformations. Transient ODMR measurements made at 1.2 K, where spin-lattice relaxation is quenched suggest that the T_z sublevel of ^3ZnP has a quenching rate constant ($k_{z,q} = 5.2 \pm 1.4\ s^{-1}$) that exceeds the average of the three sublevels, and thus that the process, which governs the temperature-independent quenching of ^3ZnP by Ru^{III}, varies with the orientation of spin angular momentum in the precursor state. The larger ODMR line widths exhibited by Zn-cyto c/a_5Ru^{III} relative to Zn-cyto c and Zn-cyto c/a_5Ru^{II} result from greater local heterogeneity of the porphyrin environment in the former protein. The increased local heterogeneity may result from disorder induced by tunneling processes, or the disordering may be static.

Acknowledgment. We are grateful to J. R. Winkler for a gift of the proteins used in these measurements and for several informative discussions. This research was partially supported by a research grant (CHE 85-08752) from the National Science Foundation and a Graduate Student Research Award to L.-H.Z. from the University of California, Davis.

(38) Takano, T.; Richardson, R. E. *J. Mol. Biol.* **1981**, *153*, 79, 95.

Synthesis of Cytochalasins: The Route to Sulfur-Bridged [11]Cytochalasans

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Abstract: The sulfur-mediated syntheses of the sulfur-bridged [11]cytochalasans **23** and **30** are described in full. Key steps include the highly selective Diels-Alder addition of **5a** and **6** to give **7a**, the generation and hetero-Diels-Alder trapping of the transient thioaldehyde **13**, and the conversion of **19** into the sulfur-bridged 11-membered carbocycles **23** + **24** via a 2,3-sigmatropic rearrangement of an intermediate sulfonium ylide **22**. Treatment of **23** with LDA followed by methyl iodide gave **30** via a bridgehead enolate **29**. Structure **30** contains all of the ring carbon atoms and all but two of the asymmetric centers found in the most complex of the naturally occurring cytochalasins and zygosporins.

The cytochalasins have been known since the isolation and structure determination of cytochalasin B (phomin, **1**) by Rothweiler and Tamm (1966) and independently by Turner et al. (1967).[1,2] Several related 11-membered carbocycles ("[11]-cytochalasans") were soon discovered including zygosporins A (later renamed cytochalasin D, **2**) and E (**3**).[3,4] The lactam ring common to these substances is derived from phenylalanine, but closely related structures that incorporate tryptophan (chaeto-

(1) Rothweiler, W.; Tamm, C. *Experientia* **1966**, *22*, 750.
(2) Aldridge, D. C.; Armstrong, J. J.; Speake, R. N.; Turner, W. B. *Chem. Commun.* **1967**, 26.
(3) Hayakawa, S.; Matsushima, T.; Kimura, T.; Minato, H.; Katagiri, K. *J. Antibiot. (Tokyo)* **1968**, *21*, 523.
(4) Aldridge, D. C.; Turner, W. B. *J. Chem. Soc. C* **1969**, 923. Minato, H.; Katayama, T. *J. Chem. Soc. C* **1970**, 45. Aldridge, D. C.; Burrows, B. F.; Turner, W. B. *Chem. Commun.* **1972**, 148.

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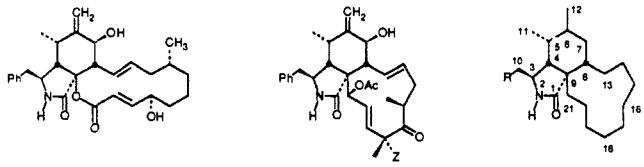
Chart I



1 Cytochalasin B (Phomin)

2 Z = OH (Cytochalasin D)
3 Z = H (Zygosporin E)

4 [11]cytochalasan

globosins)[5] or leucine (aspochalasins) in the corresponding position are also known.[6] More than 40 cytochalasins have been isolated to date from a variety of microorganisms.

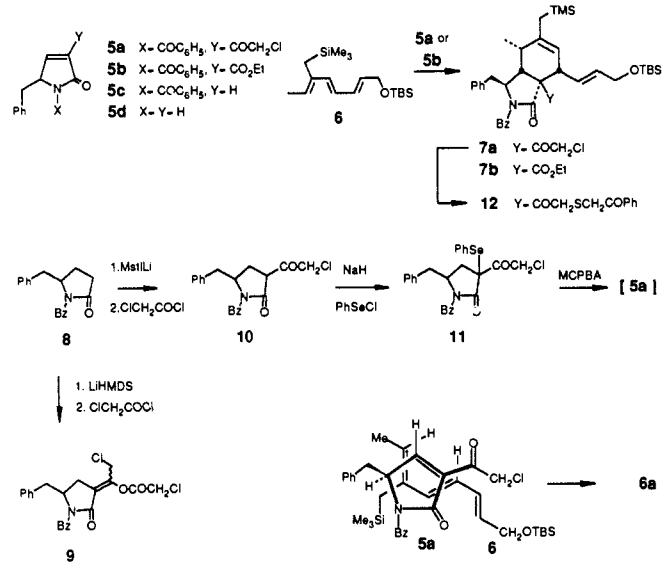
The natural cytochalasins attracted attention because they strongly influence mammalian cell morphology and interfere with normal cell division.[6] Cytochalasin interaction with actin, a key cell membrane protein involved in microfilament function, is associated with many of these effects, and cytochalasin D (**2**) in particular has been used as a probe to study the role of actin in biological processes.[7] Certain cytochalasins (including **1**) also have the ability to inhibit hexose transport across the cell membrane, but this effect involves a different receptor site.[8] As part of a program designed to define the structural requirements for specific cytochalasin effects, we have been interested in synthesis of cytochalasin D (**2**), zygosporin E (**3**), and analogues based on the [11]cytochalasan nucleus **4** (Chart I). We now describe details of our sulfur-mediated route up to the stage of sulfur-bridged [11]cytochalasans. The following paper elaborates on the topics of sulfur removal and introduction of substituents into the 11-membered ring, culminating in the total synthesis of zygosporin E and 18-desmethylcytochalasin D.

The Isoindolone Subunit: Diels–Alder Addition of Doubly Activated *N*-Benzoyl-3-pyrrolinones

Background. Initial studies in our laboratory developed the direct Diels–Alder strategy to the bicyclic isoindolone ring system based on the 2 + 4 cycloaddition of *N*-acyl-3-pyrrolin-2-one dienophiles.[9] The unsubstituted parent molecule **5d** is not reactive in the Diels–Alder sense, and the substance is difficult to handle due to its tendency to equilibrate with a hydroxypyrrole tautomer. However, we found that the *N*-benzoyl derivative **5c** is quite stable and that it has useful dienophilic reactivity comparable to that of acyclic *N*-acyl acrylamides. Additional optimization was required to maximize regio- and stereocontrol in connection with the cytochalasin synthesis. In 1982, a report from our laboratory described the highly selective Diels–Alder reactions of the doubly activated dienophile **5b**.[10] Coupled with the observation of Stork et al. that unsymmetrical 1,3,5-trienes react preferentially at the most substituted 1,3-diene unit,[11] this approach provides access to bicyclic structures **7b** with excellent regiocontrol. The best preparative version of the Diels–Alder method uses the doubly activated chloroacetyl analogue **5a** as described in the next section.

A key feature of the plan is the use of a silicon-substituted triene **6** in the Diels–Alder step.[10] The resulting allylic silane subunit in **7** or in subsequent intermediates was intended to serve as a latent source of the sensitive allylic alcohol segment of target structures such as **2** or **3**. We had assumed that the desired transformation could be effected easily by simple epoxidation from

Scheme I



the convex β-face of the cis-fused bicyclic system. Surprisingly, the MCPBA epoxidation occurred instead from the α-face,[10] and a different solution to the problem of conversion of the allylic silane into an allylic alcohol had to be devised. An efficient alternative technique using electrophilic selenium reagents has been developed[13] as described in the accompanying paper.[13]

Early in the development of practical 3-pyrrolin-2-one derivatives, several other Diels–Alder diene–dienophile combinations had been investigated independently.[14-16] The most promising alternative approaches for effective stereocontrol employ a maleiimide dienophile,[14] or an acyclic malonylidene dienophile,[16] and one total synthesis using the latter approach has been reported.[16b] The other demonstrated routes to naturally occurring cytochalasans described to date all rely on some version of the *N*-acyl-3-pyrrolin-2-one methodology, including singly or doubly activated derivatives analogous to **5c** or **5a**, respectively.[11,13c,17]

Results. In 1984, a preliminary account from our laboratory described the doubly activated dienophile **5a**.[12] Our original route involved treatment of *N*-benzoyl-5-benzyl-2-pyrrolidinone (**8**) with lithium hexamethyldisilazide followed by chloroacetyl chloride to provide an enol chloroacetate **9**, which was then hydrolyzed to the desired C-acylated product **10**. However, low yields were obtained as the scale of the hydrolysis reaction was increased (77% on 2.0-g scale; 37% on 18-g scale). Fortunately, a simple alternative was available in the excellent enolate C-acylation methodology of Seebach et al.[18] The amine-free lithium enolate was generated from *N*-benzoyl lactam **8**[10] by using mesityllithium, and the enolate was added to chloroacetyl chloride at −78 °C with careful temperature control. This procedure afforded a nearly

(5) (a) Natori, S. *Bioact. Mol.* **1986**, *1*, 185. (b) Natori, S. *Chem. Pharm. Bull.* **1987**, *35*, 902.
(6) Keller-Schierlein, W.; Kupfer, E. *Helv. Chim. Acta* **1979**, *62*, 1501.
(7) (a) Tanenbaum, S. W. ed., *Cytochalasins: Biochemical and Cell Biological Aspects*; North-Holland Publishing Company: Amsterdam, 1978. (b) for a review on the effect of cytochalasins on actin, see: Cooper, J. A. *J. Chem. Biol.* **1987**, *105*, 1474.
(8) Lin, S.; Lin, D. C.; Flanagan, M. D. *Proc. Nat. Acad. Sci. U.S.A.* **1978**, *75*, 329.
(9) Vedejs, E.; Gadwood, R. C. *J. Org. Chem.* **1978**, *43*, 376.
(10) Vedejs, E.; Campbell, J.; Gadwood, R. C.; Spear, K. L.; Rodgers, J. D.; Watanabe, Y. *J. Org. Chem.* **1982**, *47*, 1534.
(11) Stork, G.; Nakahara, Y.; Nakahara, Y.; Greenlee, W. J. *J. Am. Chem. Soc.* **1978**, *100*, 7775. Stork, G.; Nakamura, E. *J. Am. Chem. Soc.* **1983**, *105*, 5510.
(12) Vedejs, E.; Reid, J. G. *J. Am. Chem. Soc.* **1984**, *106*, 4617.
(13) (a) Vedejs, E.; Rodgers, J. D.; Wittenberger, S. J. *Tetrahedron Lett.* **1988**, *29*, 2287. (b) Vedejs, E.; Ahmad, S. *Tetrahedron Lett.* **1988**, *29*, 2291. (c) Vedejs, E.; Rodgers, J. D.; Wittenberger, S. J. *J. Am. Chem. Soc.* **1988**, *110*, 4822.
(14) Kim, M. Y.; Starrett, J. E., Jr.; Weinreb, S. M. *J. Org. Chem.* **1981**, *46*, 5383 and references therein.
(15) Pyne, S. G.; Hensel, M. J.; Fuchs, P. L. *J. Am. Chem. Soc.* **1982**, *104*, 5719. Pyne, S. G.; Spellmeyer, D. C.; Chen, S.; Fuchs, P. L. *J. Am. Chem. Soc.* **1982**, *104*, 5728.
(16) (a) Schmidlin, T.; Gamboni, R.; Strazewski, P.; Tamm, C. *Helv. Chim. Acta* **1983**, *66*, 1796. (b) Trost, B. M.; Ohmori, M.; Boyd, S. A.; Okawara, H.; Brickner, S. J. *J. Am. Chem. Soc.* **1989**, *111*, 8281.
(17) Tapolczay, D. J.; Thomas, E. J.; Whitehead, J. W. F. *J. Chem. Soc., Chem. Commun.* **1985**, 143. Thomas, E. J.; Whitehead, J. W. F. *Ibid.* **1986**, 724, 727. Sauter, R.; Thomas, E. J.; Watts, J. P. *Ibid.* **1986**, 1449. Dyke, H.; Sauter, R.; Steel, P.; Thomas, E. J. *Ibid.* **1986**, 1447. Hawkins, S. A.; Jones, R. H.; Tapolczay, D. J.; Thomas, E. J. *J. Chem. Soc., Perkin Trans. 1* **1989**, 489. Thomas, E. J.; Whitehead, J. W. F. *Ibid.* **1989**, 499, 507. Sauter, P.; Thomas, E. J.; Whitehead, J. W. F. *Ibid.* **1989**, 507. Sauter, P.; Thomas, E. J.; Watts, J. P. *Ibid.* **1989**, *519*. Dyke, H.; Steel, P. G.; Thomas, E. J. *Ibid.* **1989**, 525.
(18) Beck, A. K.; Hoekstra, M. S.; Seebach, D. *Tetrahedron Lett.* **1977**, *18*, 1187.

quantitative yield of the C-acylated imide **10** with no detectable enol chloroacetate side product, regardless of scale (Scheme I).

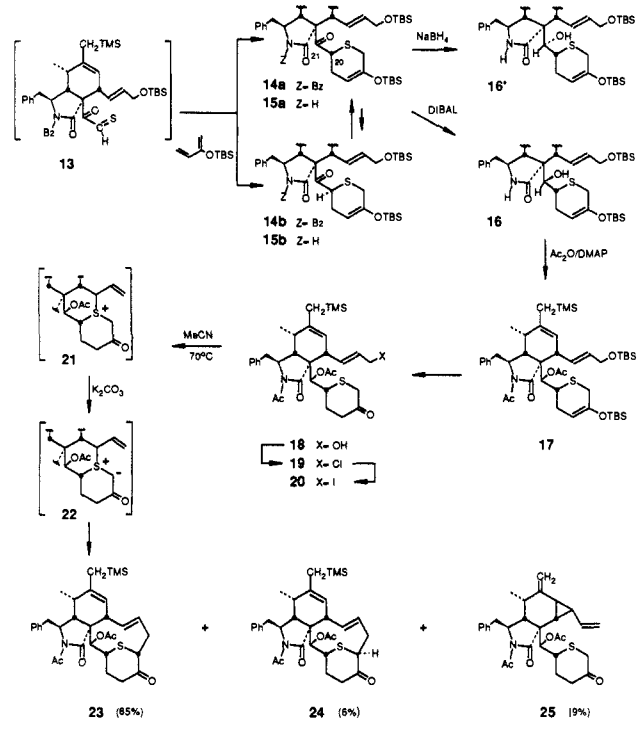
Selenenylation of **10** to give **11** was accomplished by standard means, and oxidation of **11** with MCPBA generated the desired dienophile **5a** *in solution*. Attempts to purify **5a** failed, but efficient Diels–Alder reaction occurred at room temperature upon addition of the triene **6**[10] to give **7a** (93% isolated from **11**). No regioisomeric adducts were detected, and the only byproduct isolated (3–4%) had the NMR signals expected for the exo transition state derived diastereomer of **7a**. High (ca. 30:1) endo selectivity is therefore maintained even though two different activating carbonyl groups are present. Since the stereochemistry of **7a** is proved by the eventual conversion to *dl*-zygosporin E,[19a] the constrained cyclic imide carbonyl group must dominate over the free rotor chloroacetyl substituent with regard to secondary orbital interactions in the Diels–Alder transition state. Bonding between the triene and the dienophile occurs on the least hindered face of **5a** as shown in the perspective drawing of Scheme I, and there is no detectable formation of regioisomers.

During the optimization experiments in our laboratory, we examined several combinations of *N*-benzoyl-3-pyrrolin-2-one dienophiles with various dienes and trienes.[10,19b] Qualitatively similar results were obtained with the use of the simple acetyl analogue of **5a** (replace Cl by H). Silyl-substituted dienes analogous to the triene **6** also reacted with useful selectivity in the range of 15:1 in favor of the desired stereoisomers. However, we found that products such as **7** are sensitive to equilibration via the retro-Diels–Alder reaction at temperatures near 100 °C. Furthermore, the triene corresponding to **6** having the trimethylsilyl group replaced by hydrogen afforded an inseparable 2:1 mixture of isomers (76%) believed to be the endo and exo adducts.[19b] The silicon substituent is *essential* for the highly selective Diels–Alder reaction, and temperature control is also important. These factors may be partly responsible for the relatively low endo selectivity observed by Thomas et al. in the intramolecular adaptation of the Diels–Alder strategy using essentially the same doubly activated *N*-benzoyl-3-pyrrolin-2-ones.[17] In their case, the 4-π component is a methyl-substituted triene tethered at the 4-position. The intramolecular approach simultaneously produces a medium-sized ring fused to the isoindolone, but typically affords ca. 1:1 mixtures of endo/exo adducts.

The [11]Cytochalasan Ring System: Sulfur-Mediated Synthesis of 11-Membered Carbocycles

Methods for the attachment of the 11-membered carbocyclic ring present in **2** or **3** have been studied extensively in model systems.[20a] The sequence is based on a sulfur ylide mediated rearrangement as summarized in eqs 2–4. Internal S-alkylation in the simple substrate of eq 3 is believed to generate a chair-like environment for the bicyclic sulfonium salt, and 2,3-sigmatropic rearrangement of the derived ylide affords a sulfur-bridged 11-membered carbocycle (eq 4). Synthesis of the required 6-membered sulfide substrates was initially achieved via the hetero-Diels–Alder reaction of dithioesters with 2-(trialkylsiloxy)-1,3-butadienes,[20b] but by far the best approach proved to be the more direct thioaldehyde procedure (eq 2). Thioaldehydes had seldom been used as synthetic intermediates in the previous literature, but early results in our laboratory were so promising[21a] that the thioaldehyde technology was incorporated into plans for the cytochalasin sequence. The method of choice for thioaldehyde generation in a complex substrate is the photochemical procedure using the fragmentation of a phenacyl sulfide (eq 1).[21a,c] The phenacyl unit is relatively sensitive to acid, base, or oxidants and is best introduced just prior to thioaldehyde generation. The chloroacetyl group in **5a** and **7a** serves as a convenient phenacyl sulfide precursor that easily survives the earlier synthetic transformations.

Scheme II



Nucleophilic chlorine displacement in **7a** by phenacyl mercaptan[22] gave phenacyl sulfide **12**, the precursor of the complex thioaldehyde **13**. When sunlamp photolysis of **12** was performed in the presence of 2-(*tert*-butyldimethylsiloxy)-1,3-butadiene, a thioaldehyde Diels–Alder adduct **14** could be isolated in 66% yield as a ca. 2:1 mixture of diastereomers at the carbon α to sulfur (C_{20}). The product ratio was of concern because we had planned to use the stereochemistry α to sulfur to control other asymmetric centers. Fortunately, treatment of the kinetic mixture with base resulted in equilibration that favored **14a** over **14b** by a ratio of 10:1 (57% of **14a** isolated). The reasons for the thermodynamic result are not known, but efficient conversion of the thioaldehyde adduct mixture into one dominant isomer **14a** is the key to introduction of the correct relative stereochemistry at C_{21}.

Reduction of the adduct **14a** with borohydride reagents occurred according to the Felkin–Nguyen (Anh) facial preference to give the unnatural C_{21} diastereomer **16'**,[23,24] while DIBAL reduction

(19) (a) Stereochemistry was also confirmed by X-ray structure determination of a related intermediate corresponding to **19** + two equatorial methyl groups in the α, α' positions of the 6-membered ketone: Rodgers, J. D. Ph.D. Dissertation, University of Wisconsin, 1985. (b) Reid, J. G. Ph.D. Dissertation, University of Wisconsin, 1984.

(20) (a) Vedejs, E.; Arnost, M. J.; Eustache, J. M.; Krafft, G. A. *J. Org. Chem.* **1982**, *47*, 4384. Vedejs, E.; Fedde, C. L.; Schwartz, C. E. *J. Org. Chem.* **1987**, *52*, 4269. (b) Vedejs, E.; Arnost, M. J.; Dolphin, J. M. Eustache, J. J. *Org. Chem.* **1980**, *45*, 2601.

(21) Vedejs, E.; Eberlein, T. H.; Varie, D. L. *J. Am. Chem. Soc.* **1982**, *104*, 1445. Vedejs, E.; Perry, D. A. *J. Am. Chem. Soc.* **1983**, *105*, 1683. Vedejs, E.; Perry, D. A.; Wilde, R. G. *J. Am. Chem. Soc.* **1986**, *108*, 2985. Vedejs, E.; Eberlein, T. H.; Mazur, D. J.; McClure, C. K.; Perry, D. A.; Ruggeri, R.; Schwartz, E.; Stults, J. S.; Varie, D. L.; Wilde, R. G.; Wittenberger, S. *J. Org. Chem.* **1986**, *51*, 1556.

(22) For the preparation of phenacyl mercaptan, see: Vedejs, E.; Perry, D. A. *J. Org. Chem.* **1984**, *49*, 573.

(23) Vedejs, E.; Stults, J. S.; Wilde, R. G. *J. Am. Chem. Soc.* **1988**, *110*, 5452.

gave the desired isomer **16** (Scheme II). Chelation control is conceivable in the DIBAL experiment, but previous studies in our laboratory suggest that an α-sulfenyl substituent by itself is not sufficient to provide effective chelation.[23] Interpretation of the stereochemical result is complicated by the observation that DIBAL attacks the imide *N*-benzoyl group of **14a** faster than it reduces the C_{21} ketone. Subsequent ketone reduction may involve an organoaluminum derivative of the lactam **15** or of a hemiaminal obtained from **14a** by hydride attack at the benzoyl carbonyl group. Since the exact nature of the intermediate that undergoes reduction at C_{21} is not known, we cannot comment on the origins of selectivity for **16** under the DIBAL conditions.

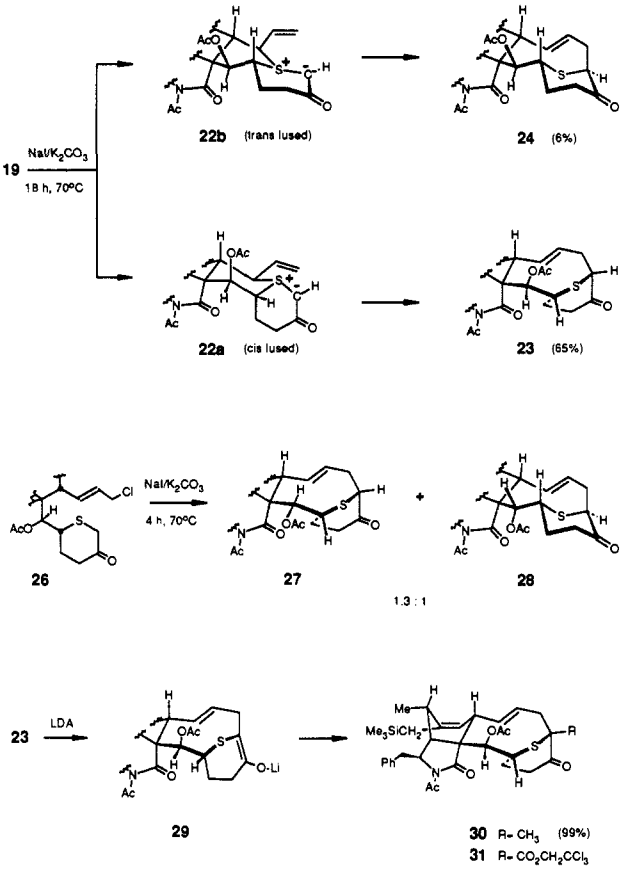
A synthetically useful 12:1 ratio in favor of **16** over **16'** was eventually achieved, but both the reduction and the workup procedure were difficult to control and efficient conversion was problematic. Reproducible results were finally obtained by first cleaving the *N*-benzoyl group of **14a** with $LiEt_3BH$, followed by the sequential addition of DIBAL and methanol in several portions. This procedure gave **16** (60%), the diastereomeric alcohol **16'** (5%), and recovered **15a** (15%) on preparative scale.

Treatment of the alcohol **16** under the Steglich acylation conditions (Ac_2O/DMAP/Et_3N/THF, room temperature, 2 weeks) resulted in acylation of the lactam nitrogen as well as the alcohol oxygen to afford **17**. The competing N-acylation was not anticipated, but the *N*-acyl group posed no immediate complications and could be removed later as desired. After removal of the *O*-silyl ether groups of **17** (Et_3NHF/MeOH–THF), the allylic alcohol **18** was converted cleanly into the allylic chloride **19** with the tri-*n*-butylphosphine/carbon tetrachloride reagent[25] in 40% overall yield from **16**. These transformations followed the precedents developed in eqs 1–4 and provided the functionality required for 11-membered ring synthesis.

The critical generation of sulfur ylide intermediates was carried out with conditions that had been optimized in the model series,[20a,26] but the reaction of the allylic iodide **20** proved unusually slow. Thus, prolonged heating of **19** with NaI/K_2CO_3 in acetonitrile (70 °C, 16–18 h) was required for complete conversion. Two isomeric sulfur-bridged carbocycles were obtained in a 10:1 ratio (71%). Since both of the carbocyclic products contain characteristic *E*-alkene as well as isoindolone NMR signals, they can only differ in the stereochemistry of the newly formed asymmetric center at the bridgehead carbon of **23** and **24**. The stereochemical assignment was not known initially, but could be deduced from enolization phenomena to be described later. In addition to the desired carbocycles **23** and **24**, a minor product that had lost the trimethylsilyl group was also formed from **19** in the above experiment. The vinylcyclopropane structure **25** (9%) follows from the presence of $C{=}CH_2$ and $CH{=}CH_2$ protons in the NMR spectrum, from the characteristic molecular ion, and from NMR comparisons with a related vinylcyclopropane.[13a]

The sequence of steps leading to the sulfur-bridged carbocycles **23** and **24** begins with conversion of **19** into the iodide **20**, providing sufficient activation for internal S-alkylation at sulfur. The resulting sulfonium salt **21** is deprotonated in situ by potassium carbonate to afford an ylide **22** and [2,3]-sigmatropic shift then connects the [11]cytochalasan carbon periphery, producing **23** and **24**. The stereochemical result differs from earlier experience with the unnatural C_{21} epimeric **26**, obtained from the alcohol **16'**. In this series, the internal S-alkylation and ylide rearrangement sequence was complete in only 4 h and the diastereomeric sulfur bridged carbocycles **27** and **28** were produced in a 1.3:1.0 ratio.[12] The corresponding divinylcyclopropane product was not observed starting from **26**. Since the internal S-alkylation of **20** is relatively slow, it is not surprising that allylsilane participation with the allylic halide sidechain competes more effectively, resulting in a significant yield of **25**. However, the stereochemical issues are not so simple, as discussed below.

Scheme III



Cyclization of the allylic chloride **19** (via **20**) can lead to four diastereomeric sulfonium salts (cis- or trans-fused bicyclic sulfonium skeleton; α or β vinyl stereochemistry) (Scheme III). The S-alkylation step from **20** is probably reversible at least in part, as in a related case where sulfonium ylides are generated by internal S-alkylation/deprotonation.[27] Therefore, four ylide diastereomers have to be considered, not to mention chair or boat conformers and cisoid vs transoid vinyl rotamers. In simpler systems, rearrangement products can often be associated with that ylide stereoisomer that is capable of efficient orbital overlap and a strain-free 5-center transition state.[26] However, this analysis is not helpful with **22** because all of the ylide isomers suffer severe bond angle and transannular strain due to the steric constraints imposed by the rigid isoindolone subunit.

We suggest that the diastereomers **22a** and **22b** are the most likely precursors to **23** and **24**, respectively. The principal basis for selecting these diastereomers is that they are capable of conformations that resemble the geometries of the eventual products **23** and **24**. The idealized drawings imply relatively easy approach of ylide and vinyl carbons as required for overlap and 2,3-sigmatropic shift, but molecular models are not nearly so promising; overlap requires considerable distortion of natural bond angles and distances with both of these ylide diastereomers. Several other diastereomers or conformers appear at least marginally capable of rearrangement to the syn-fused bicycle **23**, but none of the isomers, including **22b**, has intuitively reasonable overlap geometry for a concerted rearrangement to **24** via an early transition state. On the other hand, a transition state geometry with substantially advanced bond formation that increasingly resembles **24** is almost free of bond angle strain according to models. Alternative stepwise mechanisms (homolytic C–S bond cleavage) cannot be ruled out, but they are unlikely because typical

(24) (a) Shimagaki, M.; Maeda, T.; Matsuzaki, Y.; Hori, T.; Nakata, T.; Oishi, T. *Tetrahedron Lett.* **1984**, *25*, 4775. (b) Nakata, T.; Tanaka, T.; Oishi, T. *Tetrahedron Lett.* **1983**, *24*, 2653. (c) Vedejs, E.; Buchanan, R. A.; Conrad, P.; Meier, G. P.; Mullins, M. J.; Watanabe, Y. *J. Am. Chem. Soc.* **1987**, *109*, 5878. (d) Carreno, M. C.; Dominguez, E.; Garcia-Ruano, J. L.; Rubio, A. *J. Org. Chem.* **1987**, *52*, 3619.

(25) Hooz, J.; Gilani, S. S. H. *Can. J. Chem.* **1968**, *46*, 86.

(26) Vedejs, E. *Acc. Chem. Res.* **1984**, *17*, 358.

(27) Vedejs, E.; Mullins, M. J.; Meier, G. P.; Schaffhausen, J.; Schwartz, C. E. *J. Am. Chem. Soc.* **1989**, *111*, 8421.

Stevens rearrangement products were not detected. The late-transition-state argument is consistent with the forcing conditions required for rearrangement and suggests a concerted rearrangement with substantial rehybridization. If this is correct, then **22b** is the only plausible precursor stereochemistry for the anti bicycle **24**. Increased formation of the corresponding anti-fused **28** from **26** can then be attributed to the somewhat smaller transannular interactions of the pseudoequatorial acetoxy group in a productlike transition state.

Attempts to equilibrate the anti-fused **24** or **28** to the syn isomers failed. Treatment of **24** or **28** with DBU did not affect the substrates, while stronger bases such as LDA or lithium hexamethyldisilazide resulted in degradation. Enolization at the bridgehead carbon is not a formal Bredt's rule violation due to the size of the bridging ring, but the bridgehead C–H bond in **24** is orthogonal to the carbonyl π-system in the chairlike conformer **24** shown, and deprotonation by base is too slow for practical purposes. Orbital overlap possibilities for bridgehead deprotonation of the syn isomer **23** are somewhat improved according to molecular models, but the α-CH_2 group at C_{18} is an obvious alternative site for kinetic attack by base. Nevertheless, **23** was found to enolize with surprising ease at the bridgehead position with a variety of bases including LDA or mesityllithium. Even the standard procedure of heating **23** with triethylamine/trimethylsilyl chloride in acetonitrile was sufficient to induce partial conversion to the corresponding bridgehead enol silane. In all of these experiments, aqueous workup gave no evidence for the formation of **24** by enolate reprotonation (<5%). Only the syn isomer **23** was recovered. Furthermore, enolate trapping at C_{16} with methyl iodide or trichloroethyl chloroformate resulted in the formation of a single diastereomeric product **30** or **31**, respectively. Treatment of **31** with zinc/acetic acid resulted in smooth deprotection and decarboxylation of the β-keto acid, again resulting in conversion into the starting ketone **23**.

The selective enolization behavior of **23** and **24** can be understood by examining molecular models of the enolate. Only the *E* enolate isomer **29** is possible due to the constraints imposed by the 6-membered ring, and removal of the bridgehead proton results in a substantially altered geometry compared to **23**. The effect is to flatten the 6-membered ring, and this change reduces transannular interactions in **29** vs **23**. Once formed, **29** is strongly biased for bond formation from the "outside" (β) face of the enolate because of severe transannular hindrance by the bridging carbocyclic chain. Bonding from the α-face is precluded, and products of enolate protonation or alkylation must have the syn-fused bicyclic structure. Since kinetic protonation of **29** regenerates **23** and not **24**, the starting ketone must have the syn stereochemistry as assumed earlier. At first glance, the geometry of anti-fused **24** is not so different from the enolate geometry, and enolization appears conceivable. However, **24** differs from **29** in that sulfur is on the "inside" of the medium-sized ring. A conformational inversion of sulfur through the plane of the 11-membered carbocycle would be necessary for enolization to occur, and conversion to **29** cannot compete with decomposition pathways under the enolization conditions.

With the carbocyclic periphery of [11]cytochalasans in place, the next problem was to develop methods for the introduction of the medium ring substituents of cytochalasins and zygosporins. The sequence of steps is determined by issues of stereocontrol and of eventual sulfur removal and is discussed in the following paper.

Experimental Section

General. Analytical thin-layer chromatography (TLC and ATLC) was performed on precoated glass-backed silica gel plates (Merck 60F-254). Coarse silica gel corresponds to Davisil 62 60–200-mesh silica gel. Flash silica gel chromatography was done with use of Merck 60 230–400-mesh silica gel. High-pressure liquid chromatography (HPLC) separations were done with use of a Whatman Partisil Magnum 9 preparative column. Melting points are uncorrected (Meltemp apparatus).

1-Benzoyl-5-benzyl-3-(chloroacetyl)-2-pyrrolidinone (10). Mesityllithium[18] was prepared by the method of Seebach. To a solution of mesityl bromide (Aldrich; 1.75 mL, 11.4 mmol) in THF (40 mL) at 0 °C was added *t*-BuLi (Aldrich; 1.7 M in pentane, 13.4 mL, 22.8 mmol). The resulting yellow solution was stirred at 0 °C for approximately 5 min and then cooled to −78 °C. *N*-Benzoyl-5-benzyl-2-pyrrolidinone (**8**,[10] 3.18 g, 11.4 mmol) in THF (20 mL) was added via cannula over 25 min. The resulting solution was stirred for 10 min at −78 °C and was added via a dry ice cooled cannula to a mechanically stirred solution of chloroacetyl chloride (Aldrich; 1.4 mL, 17.6 mmol) in THF (30 mL) at −78 °C over 45 min. Following the addition, the reaction mixture was stirred at −78 °C for approximately 5 min and then was poured into a mixture of saturated $NaHCO_3$ (75 mL) and ether (75 mL). The organic extract was washed with saturated $NaHCO_3$ (2 × 75 mL) and brine (1 × 75 mL). The combined aqueous layers were back-extracted with ether (2 × 75 mL), and the combined organics were dried ($MgSO_4$) and evaporated (aspirator). The residual oil was chromatographed on silica gel (3 in. × 9 in.) eluting with 10% ether/hexane to remove mesitylene followed by ether to yield **10** (4.11 g, 100%) as a mixture of diastereomers which was sufficiently pure for use in the next step.

1-Benzoyl-5-benzyl-3-(chloroacetyl)-3-(phenylseleno)-2-pyrrolidinone (11). Sodium hydride (Alfa; 22 mg of a 50% dispersion in oil, 0.45 mmol) was washed twice with THF and was suspended in THF (10 mL). After the suspension was cooled to 0 °C, a solution of **10** (137 mg, 0.385 mmol) in THF (5 mL) was added dropwise. After stirring for 20 min, the solution was cooled to −78 °C and a solution of benzeneselenenyl chloride (Aldrich; 110 mg, 0.57 mmol) in THF (3 mL) was added dropwise. After stirring for 5 min, the resulting yellow solution was added to saturated NH_4Cl (25 mL) and the organic layer was extracted with ether (40 mL). The ether fractions were combined and dried over anhydrous $MgSO_4$, and the solvent was removed (aspirator). Column chromatography of the crude product (silica gel; hexane, followed by 30% ethyl acetate/hexane) afforded **11** as a pale yellow oil (5:2 mixture of diastereomers, 195 mg, 0.381 mmol), sufficiently pure for the next step. Crystallization of **11** from ether (1 mL) yielded the major diastereomer: mp 109–110 °C; MS calcd for $C_{26}H_{22}ClNO_3Se$, 511.0455, found 511.0454 (0.2 ppm error); analytical TLC R_f = 0.35 (20% ethyl acetate/hexane); IR ($CHCl_3$, cm^{-1}) 1725, 1715, 1685; 270-MHz ^1H NMR (major diastereomer, $CDCl_3$) δ 7.6–7.2 (15 H, m), 4.90 (1 H, d, J = 16 Hz), 4.68 (1 H, qd, J = 3.1, 7.6 Hz), 4.54 (1 H, d, J = 16 Hz), 3.26 (1 H, dd, J = 3.1, 13.3 Hz), 2.84 (1 H, dd, J = 8.6, 13.3 Hz), 2.41 (1 H, dd, J = 7.7, 14.7 Hz), 1.99 (1 H, dd, J = 6.6, 14.7 Hz).

Synthesis of Diels–Alder Adduct 7a. A solution of 85% MCPBA (Aldrich; 646 mg, 3.18 mmol) in CH_2Cl_2 (30 mL) was added dropwise to a cooled (−78 °C) CH_2Cl_2 solution (20 mL) of selenide **11** (811 mg, 1.59 mmol). After 30 min the dry ice bath was replaced with an ice bath. Three minutes later, dimethyl sulfide (0.25 mL, 3.4 mmol) was added, and the reaction mixture was poured into saturated Na_2CO_3 (30 mL). The layers were separated, and the organic layer was reextracted with saturated Na_2CO_3, dried quickly over anhydrous $MgSO_4$ (10 s), and filtered into a flask containing neat triene **6**[10] (1.55 g, 4.77 mmol). The reaction mixture was concentrated at room temperature (aspirator). Ten minutes after the addition to the triene, the reaction mixture was purified by column chromatography (1 1/4 × 12 in., silica gel, 5% ether/hexane, then 10% ether/hexane) to give a forerun of excess triene **6** followed by product **7a** which was a white foam (1.065 g, 99%): TLC R_f = 0.54, 7:2:1 hexane/methylene chloride/ether; IR ($CHCl_3$, cm^{-1}) 1730, 1720, 1680; 270-MHz ^1H NMR ($CDCl_3$) δ 7.5–7.1 (10 H, m), 5.91 (1 H, dd, J = 15.4, 9.6 Hz), 5.47 (1 H, dt, J = 15.4, 5.1 Hz), 5.28 (1 H, br s), 4.29 (1 H, m), 4.23 (1 H, d, J = 17.5 Hz), 4.02 (2 H, br d, J = 5.1 Hz), 3.30 (1 H, dd, J = 13.6, 6.2 Hz), 3.03 (1 H, dd, J = 9.6, 3.7 Hz), 2.94 (1 H, d, J = 17.5 Hz), 2.85 (2 H, m), 2.53 (1 H, m), 1.62 (2 H, br s), 1.14 (3 H, d, J = 7 Hz), 0.85 (9 H, s), 0.00 (9 H, s), −0.01 (3 H, s), −0.02 (3 H, s).

Phenacyl Sulfide 12. Anhydrous K_2CO_3 (1.3 g, 9.35 mmol) was suspended in THF (25 mL). A solution of **7a** (1.27 g, 1.87 mmol) in THF (25 mL) was added followed by dropwise addition of neat phenacyl mercaptan[22] (850 mg, 5.60 mmol). The solution was stirred for 17 h and was added to ether (50 mL) and saturated Na_2CO_3 (100 mL) followed by saturated NaCl (100 mL). The ether was dried ($MgSO_4$) and evaporated (aspirator) to give a pale yellow oil. Purification via HPLC (Waters Prep 500, Bondapak, 15% ether/hexane) gave 1.30 g (88%) of a pale yellow oil pure by ^1H NMR analysis: R_f = 0.42, 7:2:1 hexane/methylene chloride/ether; IR ($CHCl_3$, cm^{-1}) 1735, 1725, 1685, 1685; 270-MHz ^1H NMR ($CDCl_3$) δ 8.0–7.1 (15 H, m), 6.08 (1 H, dd, J = 9.7, 15.5 Hz), 5.51 (1 H, dt, J = 5.6, 15.5 Hz), 5.26 (1 H, br s), 4.30 (1 H, m), 4.06 (2 H, br d, J = 5.6 Hz), 3.87 (2 H, AB quartet, J = 14.6 Hz), 3.41 (2 H, AB quartet, J = 15.2 Hz), 3.14 (1 H, dd, J = 2.4, 13.0 Hz), 3.02–2.87 (3 H, m), 2.40 (1 H, m), 1.57 (2 H, br s), 0.85 (9 H, s), 0.81 (3 H, d, J = 7 Hz), 0.01 (3 H, s), 0.00 (3 H, s), −0.03 (9 H, s).

Thioaldehyde Diels–Alder Adduct 14. Phenacyl sulfide **12** (4.40 g, 5.54 mmol) and 2-(*tert*-butyldimethylsiloxy)-1,3-butadiene[21] (12.3 g, 66.5 mmol) were dissolved in benzene (220 mL), and the resulting solution was divided into 23 equal portions. Four portions at a time were placed

in a Pyrex crystallizing dish designed to act as a constant temperature bath (25–30 °C) and then photolyzed through the bottom of the cooling bath with a 275-W sunlamp for 3 h. At this point, ^{1}H NMR analysis of the crude mixture indicated a 3:2 ratio of **14a/14b**, but this ratio changed during chromatography. The portions were then recombined and chromatographed (silica gel, 3 in. × 16 in., hexane) to give pure unreacted diene followed by a mixture enriched in two cycloadducts (5% ether/hexane) **14a,b** (together with a trace of acetophenone). This mixture was purified further via HPLC (Waters Prep 500, Bondapak, 3% ether/hexane) to yield 1.55 g (32%) of pure **14a** as the major, less polar fraction, followed by 1.60 g (34%) of a 1:2 mixture of **14a/14b** that was equilibrated as described below to give additional **14a**. Major cycloadduct **14a**: R_f = 0.6 (7:2:1 hexane/CH_2Cl_2/ether): IR ($CHCl_3$, cm^{-1}) 1720, 1690, 1670; 270-MHz ^{1}H NMR ($CDCl_3$) δ 7.7–7.1 (10 H, m), 6.17 (1 H, dd, J = 15.4, 9.9 Hz), 5.52 (1 H, dt, J = 15.4, 5.9 Hz), 5.20 (1 H, br s), 4.99 (1 H, br s), 4.32 (2 H, m), 4.05 (2 H, d, J = 5.9 Hz), 3.27 (1 H, dd, J = 13.0, 2.7 Hz), 2.94 (1 H, dd, J = 5.7, 2.4 Hz), 2.86 (1 H, dd, J = 9.6, 3.7 Hz), 2.78 (2 H, br s), 2.65 (1 H, dd, J = 12.9, 9.9 Hz), 2.41 (2 H, br s), 2.33 (1 H, m), 1.51 (2 H, br s), 0.95 (9 H, s), 0.85 (9 H, s), 0.54 (3 H, d, J = 7.2 Hz), 0.22 (3 H, s), 0.20 (3 H, s), 0.01 (6 H, s), –0.07 (9 H, s).

Careful shaving of the more polar fraction allowed isolation of a small sample of **14b**: IR ($CHCl_3$, cm^{-1}) 1720, 1690, 1670; 270-MHz ^{1}H NMR ($CDCl_3$) δ 7.6–7.2 (10 H, m) 6.20 (1 H, dd, J = 15.5, 9.6 Hz), 5.62 (1 H, dt, J = 15.4, 5.8 Hz), 5.25 (1 H, br s), 4.91 (1 H, q, J = 4.4 Hz) 4.27 (1 H, m), 4.09 (2 H, d, J = 5.5 Hz), 4.02 (1 H. t. J = 5.7 Hz), 3.52 (1 H, dd, J = 9.3, 4 Hz), 3.18 (1 H, dd, J = 13, 2.4 Hz), 3.10 (2 H, br s), 3.04 (1 H, m), 2.65 (1 H, dd, J = 13, 9.5 Hz). 2.50–2.30 (3 H, m), 1.51 (2 H, br s). 0.92 (9 H, s). 0.85 (9 H, s), 0.65 (3 H, d, J = 6.4 Hz), 0.18 (3 H, s), 0.16 (3 H, s), 0.01 (6 H, s), –0.05 (9 H, s).

Epimerization of the Minor Cycloadduct 14b to the Major Adduct 14a. The 1:2 mixture of **14a** and **14b** from above (1.60 g, 1.86 mmol) was dissolved in THF (50 mL) and cooled to 0 °C. A catalytic amount of DBU (Aldrich; 0.05 mL) was added and the reaction mixture was stirred for 6 h. The reaction mixture was diluted with ether (50 mL) and saturated NH_4Cl (50 mL). The layers were separated, the organic layer was washed with saturated NH_4Cl (50 mL), back-extracted with ether (50 mL), and dried ($MgSO_4$), and the solvent was removed (aspiroator). The residue was filtered through coarse silica gel as above and purified via HPLC by the same method to give an additional 0.96 g of **14a** and 0.46 g of a mixture of isomers. After repurification of the mixture, a total of 1.14 g of **14a** was obtained in addition to the 1.55 g isolated earlier (total yield, 57%). ^{1}H NMR analysis of the equilibrium mixture indicated a ratio of **14a/14b** = ca. 10:1.

Debenzoylation of Imide 14a. Lactam 15a. To a solution of imide **14a** (2.37 g, 2.76 mmol) in THF (55 mL) at –78 °C was added Superhydride (Aldrich; $LiHBEt_3$ 1.0 M in THF, 6.9 mL, 6.9 mmol) dropwise via syringe. The reaction was stirred at –78 °C for 8 min following the addition and was then warmed to –35 to –30 °C over 7 min and then to 0 °C for 5 min. The reaction was quenched by addition of saturated NH_4Cl (2 mL), diluted with ether (50 mL), and washed sequentially with saturated NH_4Cl, saturated $NaHCO_3$, and brine (50 mL each). The combined aqueous portions were extracted with ether (50 mL). The combined organics were dried ($MgSO_4$) and filtered and the solvents were evaporated to give a residue that was purified by flash silica gel chromatography (column 5 cm × 40 cm, 2:1:7 ether/CH_2Cl_2/hexane) to give the lactam **15a**, 2.03 g (98%), sufficiently pure for the next step.

DIBAL Reduction to Alcohol 16. The debenzoylated lactam **15a** prepared as above (0.38 g, 503 μmol) was dissolved in toluene (10 mL) and cooled to 0 °C. To the solution was added diisobutylaluminum hydride (DIBAL; Aldrich; 1.0 M in hexanes, 1.0 mL, 1.0 mmol) followed in 5 min by methanol (40 μL, 1.0 mmol). After 5 min the DIBAL and methanol additions were repeated. Three minutes after the second methanol addition, excess methanol addition, excess methanol (0.2 mL) was added, and the reaction was stirred 5 min at 0 °C. NaOH (5%; 10 mL) and CH_2Cl_2 (30 mL) were then added, and the mixture was stirred for 15 min. The reaction mixture was then poured into a separatory funnel, the layers were separated, and the organics were washed with 5% NaOH (10 mL). The combined aqueous layers were extracted with CH_2Cl_2 (3 × 10 mL), and then the combined organic portions were dried ($MgSO_4$) and filtered through a 2 in. pad of Celite. The solvents were removed, and flash silica gel chromatography of the residue (3 cm × 35 cm, 1:1:2 ether/CH_2Cl_2/hexane) gave 81 mg of a 3:1 mixture of starting ketone **15a** (16%) and undesired alcohol diastereomer **16'** (5%) followed by 240 mg of desired alcohol **16** (63%). **16'**: oil. analytical TLC (silica gel F254), 2:1:7 ether/methylene chloride/hexane, R_f = 0.27; IR (neat, cm^{-1}) O—H 3410, N—H 3260, C=O 1685; 270-MHz ^{1}H NMR ($CDCl_3$) δ 7.35–7.08 (5 H, m), 6.04 (1 H, ddt. J = 9.5, 15.2, 1.2 Hz), 5.64 (1 H, dt, J = 15.2, 5.6 Hz), 5.34 (1 H, s), 5.26 (1 H, s), 4.96 (1 H. t, J = 4.2 Hz), 4.21 (2 H, dt, J = 1.4, 5.0 Hz), 3.98 (1 H, dd, J = 1.23, 3.9 Hz), 3.27–3.13 (3 H, m), 3.07–2.91 (3 H. m), 2.87 (1 H, t, J = 4.2 Hz), 2.69–2.56 (2 H, m), 2.54–2.42 (3 H, m), 1.65 (2 H, s), 1.23 (3 H, d, J = 7.5 Hz), 0.94 (9 H, s), 0.88 (9 H, s), 0.15 (6 H, s), 0.08 (9 H, s), 0.01 (6 H, s). Desired alcohol **16**: oil. analytical TLC (silica gel F254), 3:3:4 ether/methylene chloride/hexane, R_f = 0.39; MS no peak match, parent; a fragment corresponding the retro-Diels–Alder fragmentation M – 324.2295 was obserbed: 431.1996, calcd = 431.1950, error = 10.5 ppm; IR (neat, cm^{-1}) O—H 3375, N—H 3230, C=O 1680; 270 MHz ^{1}H NMR ($CDCl_3$) δ 7.35–7.11 (5 H, m), 5.86 (1 H, dd, J = 8.3, 15.2 Hz), 5.62 (1 H, dt, J = 15.2, 5.4 Hz), 5.43 (1 H, s), 5.30–5.25 (1 H, m), 5.05–4.99 (1 H, m), 4.21–3.87 (4 H, m), 3.47–3.36 (2 H, m), 3.28–3.20 (1 H, m), 3.13–3.01 (2 H, m), 2.87 (1 H, d, J = 16.7 Hz), 2.75–2.22 (5 H, m), 1.58 (2 H, d, J = 4.8 Hz), 1.20 (3 H, d, J = 7.2 Hz), 0.93 (9 H, s), 0.86 (9 H, s), 0.17 (6 H, s), 0.03 (9 H, s), 0.02 (6 H. s).

Acylation of Alcohol 16 to Acetate 17. To alcohol **16** (0.83 g, 1.10 mmol) dissolved in THF (47 mL) was added acetic anhydride (Mallinckrodt, distilled from P_2O_5; 5.2 mL, 55.2 mmol), triethylamine (Aldrich, distilled from CaH_2; 4.6 mL, 19.9 mmol) and 4-(dimethylamino)-pyridine (DMAP; Aldrich; 0.27 g, 2.21 mmol). The reaction flask was sealed with a ground-glass stopper and parafilm and stirred for 13 days when TLC indicated that the reaction was complete. The dark reaction mixture was poured into a 500-mL Erlenmeyer flask containing saturated $NaHCO_3$ (100 mL) and ether (150 mL) and was stirred for ca. 10 min. The layers were separated, and the organics were washed with brine (75 mL), 5% H_2SO_4 (100 mL), and brine (75 mL). The combined aqueous layers (still acidic) were extracted with ether (50 mL) and discarded. The combined organic portions were dried ($MgSO_4$) and filtered, and the solvents were removed in vacuo. The residue was filtered over silica gel (2 in. × 8 in.) and eluted with ether. The solvents were removed, and the residual oil was subjected to flash silica gel chromatography (3 cm × 30 cm. 25% ether/hexane) to give the acetate, 0.81 g (87%) as an oil: analytical TLC (silica gel F254), 2:1:7 ether/methylene chloride/hexane, R_f = 0.35; MS exact mass calcd for $C_{45}H_{73}O_6NSSi_3$ = 839.4466, found = 839.4446, error = 2.3 ppm; IR (neat, cm^{-1}) C=O 1760, C=O 1735, C=O 1700, 270-MHz ^{1}H NMR ($CDCl_3$) δ 7.40–7.28 (5 H, m), 6.12 (1 H, dd, J = 8.6. 15.4 Hz), 5.74 (1 H, dt, J = 15.4, 5.0 Hz), 5.64 (1 H, d, J = 4.5 Hz), 5.13 (1 H, s), 5.00–4.93 (1 H, m), 4.27 (2 H, dt, J = 1.5, 5.1 Hz). 3.89 (1 H, dt, J = 2.7, 5.6 Hz), 3.41–3.23 (3 H, m), 3.13–3.05 (1 H, m), 2.86 (1 H, d. J = 17.0 Hz). 2.59–2.47 (3 H, m), 2.41 (3 H, s), 2.35–2.14 (2 H, m), 2.09 (3 H, s), 1.40 (2 H, s), 0.92 (18 H, s), 0.31 (3 H, d, J = 6.8 Hz), 0.17 (6 H, s), 0.12 (9 H, s), 0.07 (6 H, s).

Desilylation of Acetate 17 to Allylic Alcohol 18. To a solution of acetate **17** (0.81 g, 0.96 mmol) in a mixture of THF (4 mL) and MeOH (20 mL) was added $HNEt_3F$ (0.50 mL, 4.2 mmol). After 4 h at room temperature a second portion of $HNEt_3F$ (0.20 mL, 1.7 mmol) was added and stirring was continued 8 h longer. The reaction was diluted with EtOAc (200 mL) and washed with brine (2 × 100 mL). The combined aqueous layers were extracted with EtOAc (3 × 50 mL), the combined organics were dried ($MgSO_4$) and filtered, and the solvents were evaporated to give an oil that was purified by flash silica gel chromatography (3:2 EtOAc/hexane) to afford allylic alcohol **18**: 0.50 g (85%): oil; analytical TLC (silica gel F254), 1:1 EtOAc/hexane, R_f = 0.15; IR (neat, cm^{-1}) O—H 3490, C=O 1750, C=O 1745, C=O 1725, C=O 1700; 270-MHz ^{1}H NMR ($CDCl_3$) δ 7.40–7.22 (5 H, m), 6.21 (1 H, dd, J = 8.9, 15.2 Hz), 5.86 (1 H, dt, J = 15.2. 5.6 Hz), 5.65 (1 H, d, J = 5.7 Hz), 5.14 (1 H, s), 4.22 (2 H, d, J = 5.0 Hz), 3.95 (1 H, dt, J = 10.1, 2.7 Hz). 3.53 (1 H, p,J = 4.8 Hz), 3.34–3.13 (4 H, m), 2.64–2.05 (8 H, m), 2.42 (3 H, s), 2.11 (3 H, s), 1.43 (2 H, s), 0.39 (3 H, d, J = 7.4 Hz), –0.06 (9 H, s).

Conversion of Allylic Alchol 18 to Allylic Chloride 19. To carbon tetrachloride (Mallinckrodt, freshly distilled from P_2O_5, 10 mL) was added tri-*n*-butylphosphine[25] (Aldrich; 1.00 mL. 4.08 mmol), and the resulting cloudy solution was stirred for 30 s, and the allylic alcohol (0.50 g, 0.82 mmol) in CCl_4 (15 mL) was added quickly (over approximately 2 min) via cannula. The reaction was stirred for 5 min, and was added to a brine (50 mL) and $CHCl_3$ (50 mL). The layers were separated, and the organics were washed with brine (50 mL). The combined aqueous layers were extracted with $CHCl_3$ (2 × 25 mL), the combined organics were dried ($MgSO_4$) and filtered, and the solvents were removed (aspirator). After filtration over silica gel (2 × 4 cm, ether) the residue was placed on a flash silica gel column (1 in. × 8 in.) and eluted (2:2:6 ether/CH_2Cl_2/hexane) to give allylic chloride **19**, 0.48 g (92%): oil; analytical TLC (silica gel F254), 1:1 EtOAc/hexane, R_f = 0.60: MS no peak match, parent, M – 36 (HCl), 593.2624, calcd = 593.2631, error = –1.2 ppm; formula = $C_{33}H_{44}O_5ClNSSi$; IR (neat, cm^{-1}) C=O 1750, C=O 1720, C=O 1700; 270-MHz ^{1}H NMR ($CDCl_3$) δ 7.39–7.23 (5 H, m). 6.40 (1 H, dd, J = 8.9. 15.5 Hz), 5.81 (1 H, dt, J = 15.5, 7.2 Hz). 5.64 (1 H, d. J = 6.2 Hz), 5.10 (1 H, s), 4.15 (2 H, d, J = 7.2 Hz), 3.96 (1 H, dt, J = 10.1. 2.4 Hz). 3.59–3.51 (1 H. m), 3.35–3.17 (2 H, m),

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.

0002-7863/90/1512-4357$02.50/0