Communications to the Editor

A Sulfur-Mediated Total Synthesis of Zygosporin E†

E. Vedejs,* J. D. Rodgers, and S. J. Wittenberger

S. M. McElvain Laboratory of Organic Chemistry
Department of Chemistry, University of Wisconsin
Madison, Wisconsin 53706

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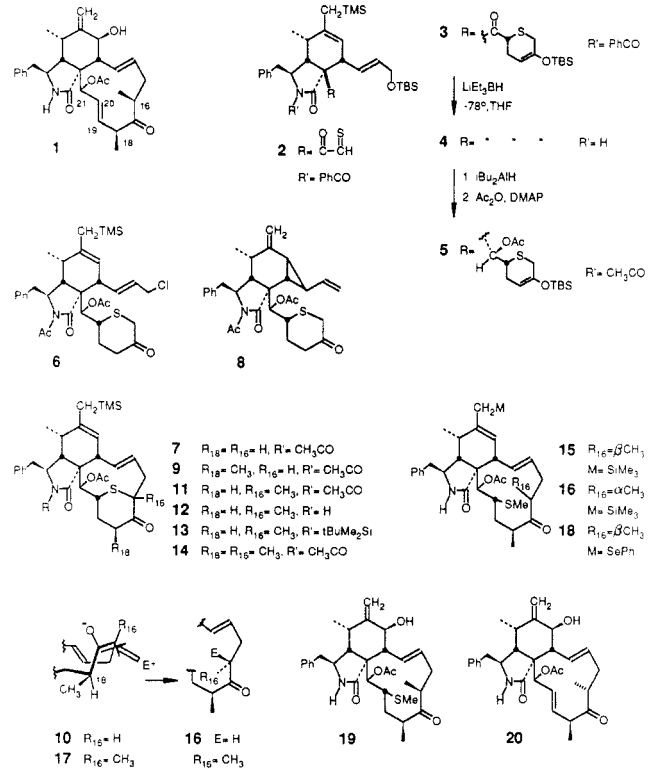
In an earlier report, we had described access to the [11]cytochalasan carbon nucleus that is found in biologically potent cytochalasins and zygosporins.[1] These substances are known for their profound effects on mammalian cell morphology and for their ability to influence transport phenomena at the cell membrane.[2a] Now, we outline the sulfur-mediated introduction of medium ring stereochemistry in *d,l*-zygosporin E (**1**),[2b] the most complex carbocyclic cytochalasin obtained to date by total synthesis.[2,3]

As previously reported, photochemical generation of thioaldehyde **2** in the presence of 2-[*tert*-butyldimethylsiloxy]-1,3-butadiene affords **3** [43% over six steps from 4-benzyl-1-benzoylpyrrolidin-2-one].[1] The assignment is secure from the X-ray crystal structure of a related adduct,[4] and the indicated diastereomer **3** is favored kinetically (1.5:1) and considerably more after equilibration (10:1, DBU, THF, 0 °C). Although the C_{20} stereocenter will be removed at a later stage, stereochemistry α to sulfur is critical to our approach because this center will be used to govern the introduction of new asymmetric centers at C_{21} and C_{18}.

Reduction at C_{21} using $NaBH_4$ or $LiBH_4$ gave the unnatural α alcohol isomer in accordance with the Felkin–Anh facial preference expected of an α-sulfenyl ketone.[5] However, the desired selectivity was achieved by treatment of the debenzoylated lactam **4** with diisobutylaluminum hydride (toluene, 0 °C) followed by Steglich acylation (Ac_2O/DMAP/Et_3N–THF; 2 weeks, 20 °C) and gave **5** (52% overall, ≥12:1 isomer ratio). Precedented steps[1] then converted **5** into the allylic chloride **6** (78% from **5**). Sulfur ylide ring expansion[1] occurred upon heating **6** with NaI/K_2CO_3/CH_3CN and gave the desired **7** (71%) via sulfur participation, together with the vinyl cyclopropane **8** (9%) resulting from participation by the allylsilane.

The original plan was to convert **7** into **9** by C_{18} enolate methylation from the less hindered β face. Reductive C_{16}–S bond cleavage might then produce enolates that are predicted to undergo C_{16} methylation from the peripheral (desired) direction subject



to local conformer control by pseudoequatorial C_{18} methyl, as illustrated for the most likely (less strained) (*E*)-enolate **10** (cisoid double bond with respect to the medium ring).[6,7] Although the general principle was supported by subsequent findings, this specific plan was partly derailed when all attempts to deprotonate **7** gave only the bridgehead enolate, and methylation afforded **11** (100%). Enolization at C_{18} proved difficult even after the kinetically more acidic bridgehead proton at C_{16} had been replaced by methyl and was best achieved after conversion of **11** into **13** via selective deacylation to **12** (K_2CO_3/CH_3OH, −15 °C), followed by N-silylation (t-$C_4H_9Me_2SiCl$/DMAP/DBU/CH_3CN). With this modification, enolization at C_{18} took place without further complications ($LiN[SiMe_3]_2$, THF, −78 to −40 °C), and highly selective methylation (CH_3I) occurred to give a single major product **14** after desilylation ($HNEt_3F$/THF–MeOH) and reacylation at nitrogen (Ac_2O/DMAP/Et_3N–THF, 60% from **11**).

As might be expected from the local conformer argument outlined earlier, reductive desulfenylation of **14** via treatment with $Me_3O^+BF_4^-$ followed by Rieke zinc[8] (DME/THF/HOAc, room temperature) and N-deacylation (K_2CO_3/MeOH) gave a 1:2.6 ratio of **15**:**16** (87% yield) due to enolate protonation via the preferred transition state geometry **17**. No equilibration of the diastereomers was observed under conditions of reduction, N-deacylation, or other variations that did not cause degradation. Subsequent transformations were performed on either the natural (**15**) or unnatural epi (**16**) series. First, N-deacylation (K_2CO_3/CH_3OH) and electrophilic selenylation of **15** using the $PhSeSe^+(CH_3)PhBF_4^-$ reagent[9] gave the thermodynamically most stable allylic selenide **18** (68%). Upon periodate oxidation, **18**

† Dedicated to Professor E. J. Corey on the occasion of his 60th birthday.

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was selectively converted into the allylic alcohol **19** (88%) via the 2,3-sigmatropic shift of a selenoxide with bonding to the more accessible alkene β-face. Finally, MCPBA oxidation (77%) and thermal sulfoxide elimination (135 °C, xylene, $CaCO_3$ buffer) gave *d,l*-zygosporin E (52% isolated), identical with natural material according to spectroscopic and chromatographic data.[10,11] None of the isomeric (*Z*)-olefin was detected.[12] The same sequence of steps from **16** produced *d,l*-16-*epi*-zygosporin E, **20**, 70% yield for sulfoxide pyrolysis and 44% overall from **16**.[11]

The synthesis of zygosporin E illustrates the use of sulfide bridge stereochemistry as a relay for stereochemical information in medium-sized rings. High selectivity at eight of the nine asymmetric centers in **1** has been achieved. More important, the synthesis demonstrates that remote stereocontrol in a complex macrocycle is not restricted to the coupling of optically pure subunits.[5c,13]

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Registry No. **1**, 114651-74-0; **4**, 90741-78-9; **5**, 114634-51-4; **6**, 114634-52-5; **7**, 114634-53-6; **8**, 114634-54-7; **11**, 114634-55-8; **12**, 114634-56-9; **13**, 114634-57-0; **14**, 114634-58-1; **15**, 114651-83-1; **16**, 114651-84-2; **18**, 114634-61-6; **19**, 114634-62-7; **20**, 114634-63-8; $PhSeSe^+(CH_3)PhBFu^-$, 114634-60-5.

Supplementary Material Available: Analytical and spectral data for compounds **5–8**, **11–16**, **18–20**, and **1** (6 pages). Ordering information is given on any current masthead page.

(10) We are grateful to Dr. H. Minato for a comparison sample of natural zygosporin E.
(11) Characterization data for key intermediates, see: Supplementary Material.
(12) A byproduct tentatively identified as the enol acetate resulting from the other regiochemistry of sulfoxide elimination was also formed.
(13) Recent examples: Still, W. C.; Novack, V. J. *J. Am. Chem. Soc.* **1984**, *106*, 1148. Still, W. C.; Romero, A. G. *J. Am. Chem. Soc.* **1986**, *108*, 2105. Schreiber, S. L.; Sammakia, T.; Hulin, B.; Schulte, G. *J. Am. Chem. Soc.* **1986**, *108*, 2106. Vedejs, E.; Buchanan, R. A.; Conrad, P.; Meier, G. P.; Mullins, M. J.; Watanabe, Y. *J. Am. Chem. Soc.* **1987**, *109*, 5878.

Highly Efficient Synthesis of Carbacyclin Analogue. Stereospecific Synthesis of Aryl-Substituted Exocyclic Olefin[1]

Mikiko Sodeoka, Shoji Satoh, and Masakatsu Shibasaki*

Faculty of Pharmaceutical Sciences
Hokkaido University, Sapporo 060, Japan
Received February 16, 1988

Although exocyclic olefins are now readily available in a stereocontrolled manner,[2] the stereospecific synthesis of aryl-substituted exocyclic olefins[3] still remains a challenging problem in organic synthesis.[4] A few years ago, on the basis of molecular design, we took an interest in the synthesis of the carbacyclin analogue with an aryl-substituted exocyclic olefin **13**. In this

(1) Dedicated to Professor E. J. Corey on the occasion of his 60th birthday.
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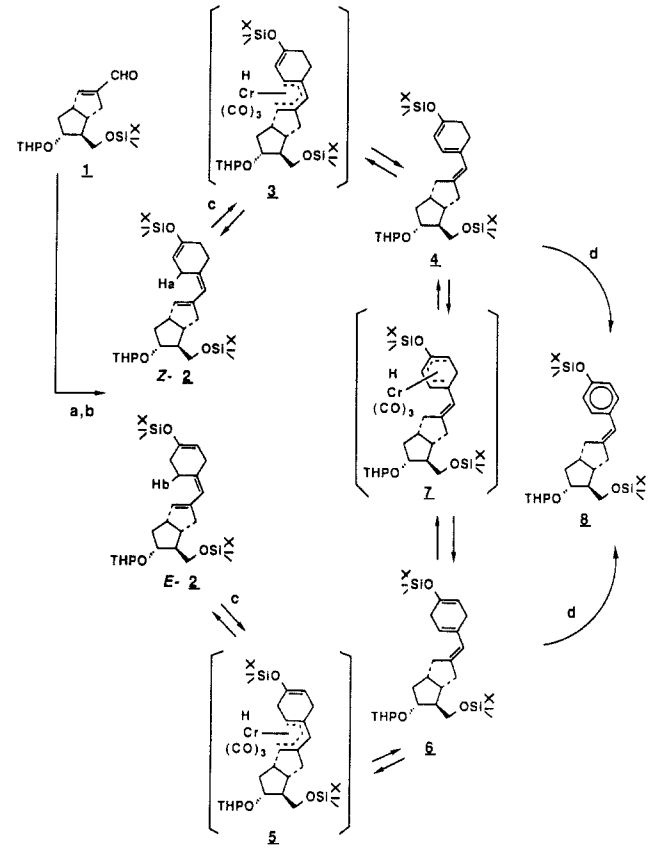
(4) Pd-catalyzed vinyl/aryl coupling might be one of the most promising methods for the stereospecific synthesis of aryl-substituted exocyclic olefins. However, unfortunately, no method for the stereospecific synthesis of exocyclic vinyl halides is available now.

Scheme I[a]



[a] (a) TBDMSO—⟨⟩—SO_2tol, *n*-BuLi, THF, −52 °C, then Ac_2O; (b) Na–Hg (5%), NaH_2PO_4, MeOH; (c) (naphthalene)$Cr(CO)_3$, acetone, 19 °C; (d) MnO_2, molecular sieves 4Å, benzene, reflux.

communications we wish to report a stereospecific synthesis of the various simple molecules **18**, **19**, **20**, **21**, **24**, and **25** as well as a highly stereoselective synthesis of **13**.

In the synthesis of carbacyclin by (methyl benzoate)$Cr(CO)_3$ catalyzed 1,4-hydrogenation reaction, we had already detected the stereo- and regiocontrolled 1,5-hydrogen shift of the conjugated diene, which proceeds at 130 °C via the U-shaped η^5-pentadienyl hydride intermediate with 18-electron configuration.[5,6] Furthermore, very recently, we found that this isomerization reaction proceeds smoothly even at 20 °C by the use of (naphthalene)-$Cr(CO)_3$ as a catalyst. On the basis of the argument described above, it was envisioned that both of (*Z*)-**2** and (*E*)-**2** would be converted to **8** stereospecifically by (naphthalene)$Cr(CO)_3$ catalyzed isomerization followed by aromatization. Thus a mixture of (*Z*)-**2** and (*E*)-**2** was first synthesized from the enal **1**, obtainable from the Corey lactone in a stereo- and regiocontrolled manner (ca. 70% overall yield),[7] via a three-step sequence of reactions (73%, (*Z*)-**2**:(*E*)-**2** = ca. 1:1). It was expected that (*Z*)-**2** would be isomerized to the most stable **4** in a stereo- and regiocontrolled manner through the U-shaped η^5-intermediate **3** generated by abstraction of the hydrogen Ha. Likewise, (*E*)-**2** was anticipated to be first isomerized to **6** through **5** formed by abstraction of the hydrogen Hb. We further expected that **6** would be isomerized to **4**, because it is known that cyclic 1,4-dienes are converted to 1,3-dienes by (arene)$Cr(CO)_3$ complexes.[8] Namely, regardless

(5) (a) See: ref 2a. (b) Tucker, J. R.; Riley, D. P. *J. Organomet. Chem.* **1985**, *275*, 49.
(6) The 1,5-hydrogen shift of conjugated dienes catalyzed by (arene)$Cr(CO)_3$ complexes was already known. However, the stereochemistry of the reaction had been clarified by us,[2a] indicating that perfect formation of U-shaped η^5-pentadienyl hydride intermediates makes the complete stereochemical control of isomerized products possible.
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