

Communications to the Editor

A Sulfur-Mediated Total Synthesis of Zygospurin E[†]

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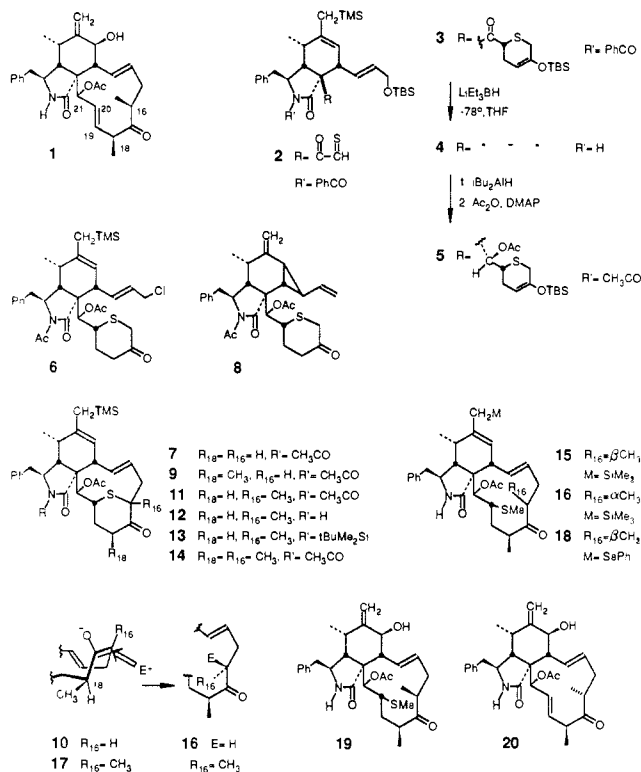
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In an earlier report, we had described access to the [11]cytochalasan carbon nucleus that is found in biologically potent cytochalasins and zygosporins.¹ These substances are known for their profound effects on mammalian cell morphology and for their ability to influence transport phenomena at the cell membrane.^{2a} Now, we outline the sulfur-mediated introduction of medium ring stereochemistry in *d,l*-zygospurin 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*-butyldimethylsilyloxy-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 C₂₀ 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 C₂₁ and C₁₈.

Reduction at C₂₁ using NaBH₄ or LiBH₄ 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 (Ac₂O/DMAP/Et₃N-THF; 2 weeks, 20 °C) and gave **5** (52% overall, \geq 12:1 isomer ratio). Precedented steps¹ then converted **5** into the allylic chloride **6** (78% from **5**). Sulfur ylide ring expansion¹ occurred upon heating **6** with NaI/K₂CO₃/CH₃CN 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 C₁₈ enolate methylation from the less hindered β face. Reductive C₁₆-S bond cleavage might then produce enolates that are predicted to undergo C₁₆ methylation from the peripheral (desired) direction subject



to local conformer control by pseudoequatorial C₁₈ 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 C₁₈ proved difficult even after the kinetically more acidic bridgehead proton at C₁₆ had been replaced by methyl and was best achieved after conversion of **11** into **13** via selective deacylation to **12** (K₂CO₃/CH₃OH, -15 °C), followed by N-silylation (*t*-C₄H₉Me₂SiCl/DMAP/DBU/CH₃CN). With this modification, enolization at C₁₈ took place without further complications (LiN[SiMe₃]₂, THF, -78 to -40 °C), and highly selective methylation (CH₃I) occurred to give a single major product **14** after desilylation (HNET₃F/THF-MeOH) and reacylation at nitrogen (Ac₂O/DMAP/Et₃N-THF, 60% from **11**).

As might be expected from the local conformer argument outlined earlier, reductive desulfenylation of **14** via treatment with Me₃O⁺BF₄⁻ followed by Rieke zinc⁸ (DME/THF/HOAc, room temperature) and N-deacylation (K₂CO₃/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 (K₂CO₃/CH₃OH) and electrophilic selenylation of **15** using the PhSeSe⁺(CH₃)PhBF₄⁻ reagent⁹ 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, CaCO₃ buffer) gave *d,l*-zygospirin 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*-zygospirin E, **20**, 70% yield for sulfoxide pyrolysis and 44% overall from **16**.¹¹

The synthesis of zygospirin 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⁺(CH₃)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 zygospirin 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.

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Highly Efficient Synthesis of Carbacyclin Analogue. Stereospecific Synthesis of Aryl-Substituted Exocyclic Olefin¹

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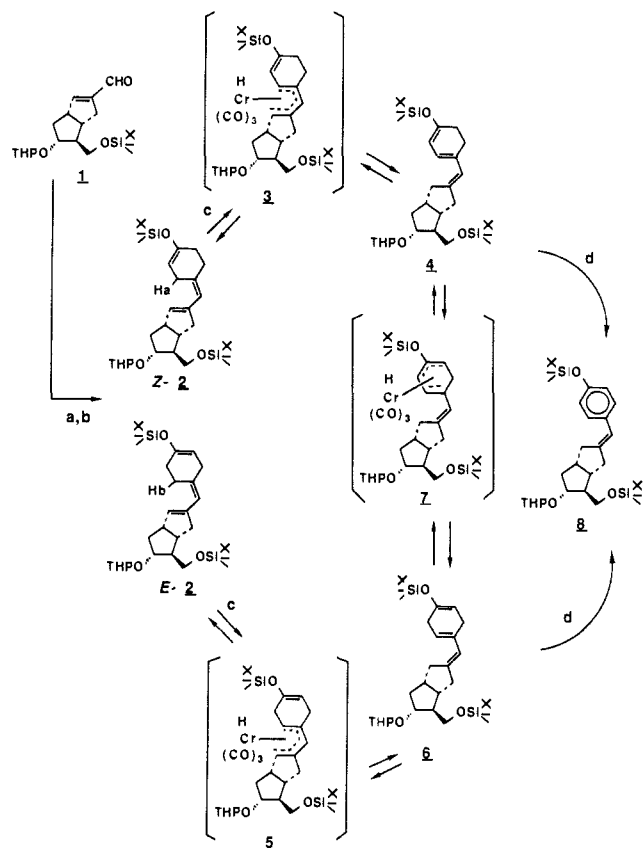
Although exocyclic olefins are now readily available in a stereocontrolled manner,² the stereospecific synthesis of aryl-substituted exocyclic olefins³ still remains a challenging problem in organic synthesis.⁴ A few years ago, on the basis of molecular design, we took an interest in the synthesis of 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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(3) For interesting compounds having an aryl-substituted exocyclic olefin, see: (a) Mason, C. P.; Edwards, K. R.; Carlson, R. E.; Pignatello, J.; Gleason, F. K.; Wood, J. M. *Science (Washington, D. C.)* **1982**, *215*, 400. (b) Flohé, L.; Böhlke, H.; Frankus, E.; Kim, S.-M. A.; Lintz, W.; Loschen, G.; Michel, G.; Müller, B.; Schneider, J.; Seipp, U.; Vollenberg, W.; Wilsmann, K. *Arzneim.-Forsch./Drug Res.* **33** **1983**, (II) Nr. 9. (c) Noyori, R.; Ohta, M.; Hsiao, Yi; Kitamura, M.; Ohta, T.; Takaya, H. *J. Am. Chem. Soc.* **1986**, *108*, 7117.

(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 1^a



^a (a) TBDMsO-C₆H₄-SO₂tol, *n*-BuLi, THF, -52 °C, then Ac₂O; (b) Na-Hg (5%), NaH₂PO₄, MeOH; (c) (naphthalene)Cr(CO)₃, acetone, 19 °C; (d) MnO₂, 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 **8**, 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.

(7) Sodeoka, M.; Shibasaki, M. *Chem. Lett.* **1984**, 579 (now commercially available from Nissan Chemical Industries, Ltd, Japan).