

(Ph)N(CH₃)C(Ph)N(CH₃)⁺ occurs from the Cp side.²⁶ The initial attack of C₁ at C₃ is strongly supported by earlier work on reactions of electrophilic carbene complexes.^{9,10,27}

In the model presented, the assumption is made that the major reaction pathway proceeds via the anticlinal isomers of 1SS and 1RS. For the alkylidene complexes, Cp(NO)(PPh₃)Re=CHR⁺ (R = CH₃, CH₂CH₃), the anticlinal isomer is favored with respect to the synclinal isomer by ca. 9:1.^{24b,f} Taking into account the low rotational barrier around the iron-carbon bond,^{10,28} there must be rapid equilibration between anticlinal and synclinal isomers of 1SS and 1RS, as shown above. Although the anticlinal isomer is likely favored, it is possible that transfer occurs via a minor, but more reactive, synclinal isomer. For example, a mechanism consistent with our results is styrene attack over CO on the synclinal isomers of 1SS and 1RS followed by *backside* displacement of Cp(CO)(PPh₂R*)Fe⁺ by the developing electrophilic center at C₂.^{10b,c} A second, perhaps more likely consequence of the presence of minor amounts of synclinal 1SS and 1RS is that the minor enantiomers arise via these isomers.

Compared to the high ee's in ethylidene transfer from 1SS and 1RS to styrene, methylene transfer from Cp(CO)(PPh₃)FeCH₂X derivatives to *trans*-β-methylstyrene occurs with substantially less stereoselectivity, only 10–35%.^{5,6} The difference is likely due to the fact that in 1SS and 1RS the carbene carbon, C₁, is prochiral whereas in Cp(CO)(PPh₃)FeCH₂X it is not. In analogy with nucleophilic attack on Cp(NO)(PPh₃)Re=CHC₆H₅⁺,²⁴ high asymmetric induction in the present systems results from selective attack of styrene on one face of the prochiral ethylidene ligand in 1SS and 1RS, controlled by a preferred orientation of the carbene ligand and large steric differences in the ancillary ligands.²⁹

In enantioselective catalysis, optically active metal ligands, usually phosphines, carry the chiral information.³⁰ During catalysis the metal atom itself can become a chiral center, and the role of the metal chirality in enantioselective transformations has been discussed.^{30–33} The present cyclopropanation of styrene is of interest in this respect. 1SS and 1RS contain the same optically active phosphine ligand yet have opposite metal configurations. The fact that 1SS and 1RS give cyclopropanes of *opposite* configurations in almost identical optical purities indicates that the chirality at the *iron* is primarily responsible for asymmetric induction and that the phosphine chirality plays little or no role, demonstrating the potential for control by the metal configuration in enantioselective catalysis.

The present results show that chiral carbene complexes of the type Cp(CO)(PR₃)Fe=CHR⁺ will be generally useful for asymmetric syntheses of cyclopropanes. The features critical to high enantioselectivity and further applications of these reactions are being investigated.

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Supplementary Material Available: CD spectra of (S_{Fe})- and (R_{Fe})-Cp(CO)(PPh₂R*)FeCOCH₃, R* = (S)-2-methylbutyl, and spectral data (¹H NMR, IR, optical rotations) for 2SS, 2RS, 3SS, and 3RS (3 pages). Ordering information is given on any current masthead page.

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Application of the Furan-Carbonyl Photocycloaddition Reaction to the Synthesis of the Bis(tetrahydrofuran) Moiety of Asteltoxin

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Asteltoxin **1**, isolated from toxic maize cultures of *Aspergillus stellatus* by Vleggaar and co-workers,² is a potent inhibitor of *E. coli* BF₁-ATPase activity and serves as a valuable fluorescent probe of mitochondrial F₁- and bacterial BF₁-ATPase.³ Evidence suggests that the bis(tetrahydrofuran) moiety is responsible for the inhibition and binding properties of asteltoxin.³ Analysis of this hindered ring system (Scheme I) revealed that the open (hydrolyzed) form of asteltoxin, **3**, would be obtained from a threo-aldol condensation of **4** and **5** or their equivalents in the indicated manner. We have recently reported a method for stereoselective threo-aldol formation, which employs the Paterno-Büchi photocycloaddition of a furan and an aldehyde.^{4,5} The application of this methodology to the synthesis of **2** is reported herein.

The functionalized photoaldol **9** was conveniently prepared in multigram quantities by a two-step sequence (Scheme II).⁶ Irradiation of 3,4-dimethylfuran⁷ (12 g) and β-(benzyloxy)propanal (8.9 g) in benzene (200 mL, 0.27 M) for 6 h with a 450 W Hanovia lamp equipped with a Vycor filter afforded a single exo-photoadduct **8** that was most efficiently treated directly with MCPBA to provide **9** (10.7 g, 45% from **7**). Hydrolysis afforded the aldehyde **10**, which exists as the monocyclic hemiacetal. *It should be noted that this three-step reaction sequence provides the threo-aldol **10** with complete control of stereochemistry at the quaternary carbon.*

Protection of the more reactive⁸ aldehyde with dimethylhydrazine produced the hydrazone **11**. Introduction of the β-ethyl side chain could be achieved with complete stereochemical control by chelation-controlled^{12c} addition of excess EtMgBr to the latent α-hydroxy aldehyde **11**.⁹ Internal protection of the hydrolysis product as the acetonide afforded **12**. Deprotection of the benzyl ether, selenenylation,¹⁰ and selenoxide elimination gave **15** in high yield.

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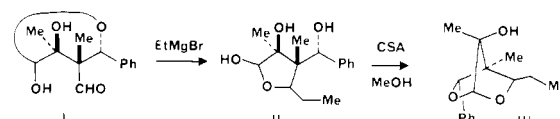
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(5) For related studies, see: Zamojski, A.; Kozluk, T. *Tetrahedron* **1983**, *39*, 805.

(6) All compounds reported gave ¹³C NMR (22.5 MHz), ¹H NMR (500 MHz), FT-IR, and mass spectra (low resolution) in accord with the structure given. Exact mass measurements (CI) were obtained for compounds **2**, **9**, **11**, **12**, **15**, and **23**. Spectral data are available in the supplementary material.

(7) Prepared by thermolysis of 2-butyne and 4-phenyloxazole, cf.: Hutton, J.; Potts, B.; Southern, P. F. *Synth. Commun.* **1979**, *9*, 789. Graf, F.; König, H. *Ger. Offen* 1 935 009. Liotta, D.; Saindane, M.; Ott, W. *Tetrahedron Lett.* **1983**, *24*, 2473.

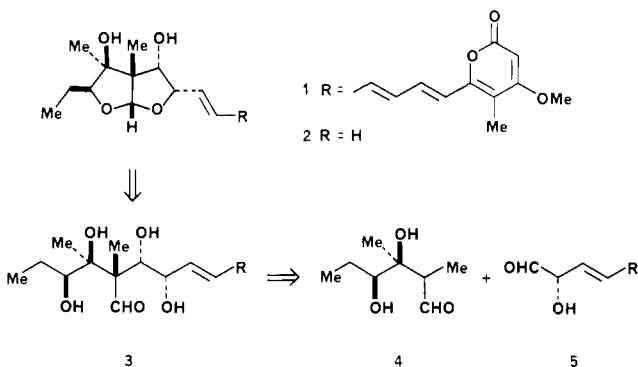
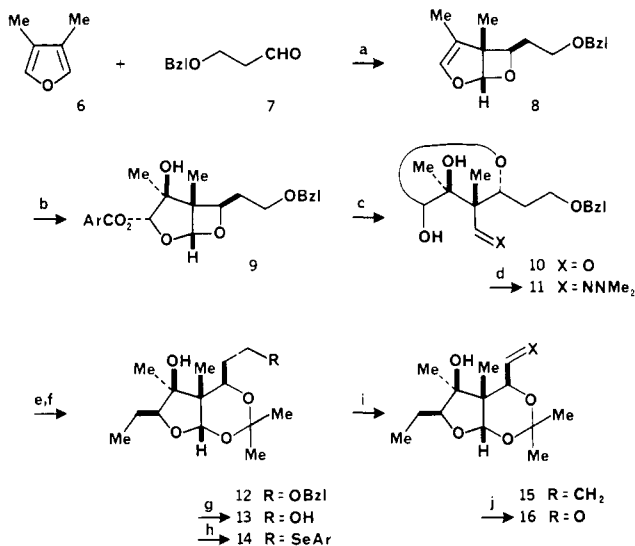
(8) Treatment of the related compound **i** with 3 equiv of EtMgBr provided a single product **ii** resulting from addition to the exposed aldehyde, which afforded the bridged acetal **iii** after acid-catalyzed cyclization in methanol.



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Scheme I

Scheme II^a

^a (a) Benzene, Et₂O, *hν* (Vycor), 6 h, 63%; (b) MCPBA, NaHCO₃, CH₂Cl₂, 80%; (c) THF, 3 N HCl (3:1); (d) Me₂NNH₂, CH₂Cl₂, MgSO₄, 72% from 9; (e) EtMgBr, THF, room temperature, 48 h; (f) acetone, CuSO₄, CSA, 55% from 11; (g) Li, NH₃, Et₂O, 98%; (h) *o*-NO₂C₆H₄SeCN, Bu₃P, THF; (i) H₂O₂, THF, 81% from 13; (j) O₃, CH₂Cl₂, MeOH, Me₂S, 92%.

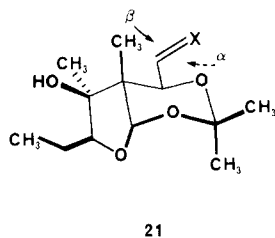
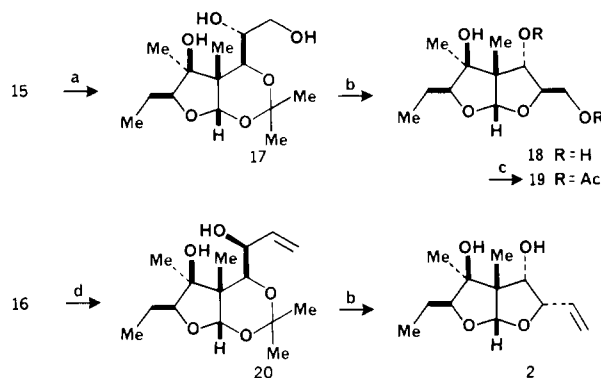


Figure 1.

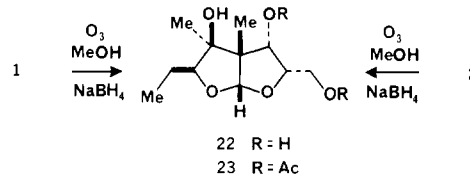
Osmylation of 15 proceeded with high diastereofacial selectivity to provide 17 as the only detectable product (Scheme III). The stereochemistry was demonstrated by its conversion to 18,¹¹ which was shown to be epimeric at the hydroxymethyl side chain to the oxidative degradation product 22 derived from asteltoxin (vide infra). Similarly, bis(acetate) 19 was not identical with 23.

Ozonolysis of 15 provided 16, which exhibited the same degree and sense of diastereofacial selectivity upon treatment with vinyl magnesium bromide. Chelation-controlled addition¹² (21, X =

Scheme III^a

^a (a) OsO₄, THF, H₂S, 85%; (b) HCl, MeOH, 90%; (c) Ac₂O, Et₃N, DMAP, 90%; (d) CH₂=CHMgBr, THF, 94%.

Scheme IV



O) from the α face was expected under these conditions and, in the event, provided 20 as a single addition product (Figure 1). Osmylation of the same rotamer (21, X = CH₂) from the α face would provide an explanation for the stereoselectivity observed in this reaction.^{13,14}

Acid-catalyzed cyclization of 20 in methanol afforded 2. The NMR spectrum of 2 exhibited close similarities in chemical shifts and coupling constants to an authentic sample of asteltoxin provided by Dr. Vleggaar. Rigorous structure proof was ascertained by the degradation of asteltoxin 1 and synthetic 2 to their corresponding triols 22 (and bis(acetates) 23), which exhibited identical TLC properties and 500-MHz ¹H NMR and mass spectral data (Scheme IV).

In summary, the synthesis of (\pm)-bis(tetrahydrofuran) 2 requires 12 steps and proceeds in 12% overall yield. Further synthetic and mechanistic studies of the furan-carbonyl photocycloaddition reaction, including excited-state asymmetric induction and application to asteltoxin synthesis, are in progress.

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Supplementary Material Available: Spectral data for compounds 2, 8–13, 15, 18–20, 22, and 23 (33 pages). Ordering information is given on any current masthead page.

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(13) Molecular mechanics calculations (MM2) indicate that two slightly lower energy conformers exist which place the allylic C–O bond nearly parallel to the π system (ca. +90° and –90° rotations of the vinyl group in Figure 1). However, we favor reaction from rotamer 21 since the $\pi \rightarrow \sigma^*$ delocalization which can exist in the lower energy rotamers should raise the energy of their corresponding transition states in an electrophilic osmylation reaction.

(14) Professor Kishi has recently reported his extensive studies on the stereochemistry of osmium tetroxide oxidation of allylic alcohol systems (personal communication), see: Kishi, Y.; Cha, J. K.; Christ, W. J. *Tetrahedron Lett.*, in press. The stereochemical outcome of the reaction 15 \rightarrow 17 is in accord with his proposed model.

(11) That cyclization provides the dioxabicyclo[3.3.0]octane ring system (and not the isomeric dioxabicyclo[4.3.0]nonane) was confirmed by an unambiguous synthesis. Monopivaloylation of the primary hydroxyl of 17 and acid-catalyzed cyclization provided the corresponding bis(tetrahydrofuran), which gave rise to 18 upon removal of the pivalate (LiAlH₄).