$(Ph)N(CH_3)C(Ph)N(CH_3)^+$ occurs from the Cp side.[26] The initial attack of C_1 at C_3 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 1*SS* and 1*RS*. For the alkylidene complexes, $Cp(NO)(PPh_3)Re{=}CHR^+$ (R = CH_3, CH_2CH_3), 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 1*SS* and 1*RS*, 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 1*SS* and 1*RS* followed by *backside* displacement of $Cp(CO)(PPh_2R^*)Fe^+$ by the developing electrophilic center at C_2.[10b,c] A second, perhaps more likely consequence of the presence of minor amounts of synclinal 1*SS* and 1*RS* is that the minor enantiomers arise via these isomers.

Compared to the high ee's in ethylidene transfer from 1*SS* and 1*RS* to styrene, methylene transfer from $Cp(CO)(PPh_3)FeCH_2X$ derivatives to *trans*-β-methylstyrene occurs with substantially less stereoselectively, only 10–35%.[5,6] The difference is likely due to the fact that in 1*SS* and 1*RS* the carbene carbon, C_1, is prochiral whereas in $Cp(CO)(PPh_3)FeCH_2X$ it is not. In analogy with nucleophilic attack on $Cp(NO)(PPh_3)Re{=}CHC_6H_5^+$,[24] high asymmetric induction in the present systems results from selective attack of styrene on one face of the prochiral ethylidene ligand in 1*SS* and 1*RS*, 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. 1*SS* and 1*RS* contain the same optically active phosphine ligand yet have opposite metal configurations. The fact that 1*SS* and 1*RS* 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 $Cp(CO)(PR_3)Fe{=}CHR^+$ will be generally useful for asymmetric syntheses of cyclopropanes. The features critical to high enantioselectivity and further applications of these reactions are being investigated.

Acknowledgment is made to the U.S. Army Research Office and the donors of the Petroleum Research Fund, administered by the American Chemical Society, for support of this research.

Supplementary Material Available: CD spectra of $(S_{Fe}S_C)$- and $(R_{Fe}S_C)$-$Cp(CO)(PPh_2R^*)FeCOCH_3$, R* = (*S*)-2-methylbutyl, and spectral data (^1H NMR, IR, optical rotations) for 2*SS*, 2*RS*, 3*SS*, and 3*RS* (3 pages). Ordering information is given on any current masthead page.

(26) Brunner, H.; Wachter, J.; Bernal, I.; Reisner, G. M.; Benn, R. *J. Organomet. Chem.* **1983**, *243*, 179.
(27) Casey, C. P.; Polichnowski, S. W.; Shusterman, A. J. *J. Am. Chem. Soc.* **1979**, *101*, 7282.
(28) Brookhart, M.; Tucker, J. R.; Flood, T. C.; Jensen, J. *J. Am. Chem. Soc.* **1980**, *102*, 1203.
(29) This statement assumes that initial attack of the carbene takes place solely at C_β of styrene, and therefore, attack of the two enantiotopic faces of styrene leads to cis and trans isomers not to different enantiomers.
(30) Kagan, H. B. In "Comprehensive Organometallic Chemistry"; Wilkinson, G., Stone, F. G. A.; Abel, E. W., Eds.; Pergamon Press: Oxford, 1982; p 436.
(31) Brunner, H. *Acc. Chem. Res.* **1979**, *12*, 255.
(32) Brunner, H.; Agrifoglio, G. *Monatsh. Chem.* **1980**, *111*, 275.
(33) Pino, P., Consiglio, G. "Fundamental Research in Homogeneous Catalysis"; Plenum Press: New York and London, 1977; p 156.

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

Stuart L. Schreiber*[1] and Kunio Satake

Department of Chemistry, Yale University
New Haven, Connecticut 06511

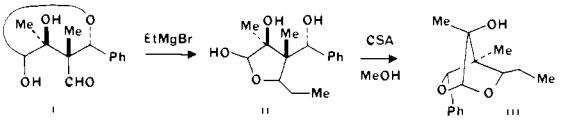
Received July 20, 1983

Asteltoxin **1**, isolated from toxic maize cultures of *Aspergillus stellatus* by Vleggaar and co-workers,[2] is a potent inhibitor of *E. coli* BF_1-ATPase activity and serves as a valuable fluorescent probe of mitochondrial F_1- and bacterial BF_1-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[4] **9** was conveniently prepared in multigram quantities by a two-step sequence (Scheme II).[6] Irradiation of 3,4-dimethylfuran[7] (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 reactive[8] 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.

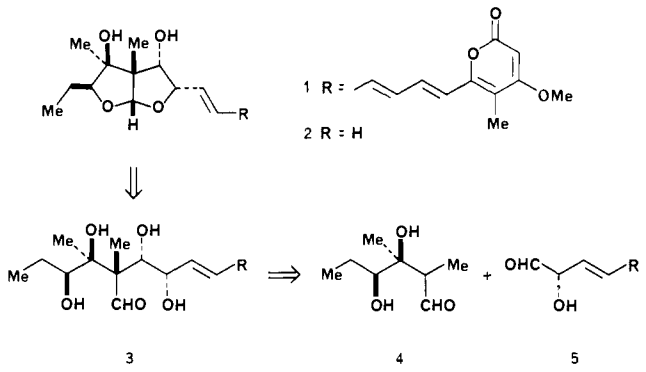
(1) Searle Scholar 1982–1985.
(2) Kruger, G. J.; Steyn, P. S.; Vleggaar, R. *J. Chem. Soc., Chem. Commun.* **1979**, 441.
(3) Satre, M. *Biochem. Biophys. Res. Commun.* **1981**, *100*, 267.
(4) Schreiber, S. L.; Hoveyda, A. H.; Wu, H.-J. *J. Am. Chem. Soc.* **1983**, *105*, 660.
(5) For related studies, see: Zamojski, A.; Kozluk, T. *Tetrahedron* **1983**, *39*, 805.
(6) All compounds reported gave ^{13}C 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.; Konig, 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.



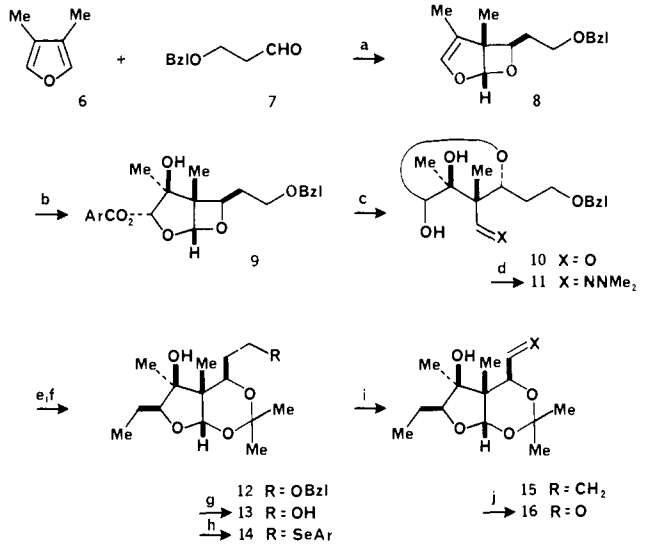
(9) Stocker, J. H. *J. Org. Chem.* **1964**, *29*, 3593.
(10) Grieco, P. A.; Gilman, S.; Nishizawa, M. *J. Org. Chem.* **1976**, *41*, 1485.

0002-7863/83/1505-6723$01.50/0

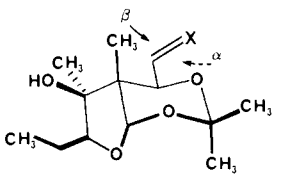
Scheme I



Scheme II[a]



[a] (a) Benzene, Et_2O, $h\nu$ (Vycor), 6 h, 63%; (b) MCPBA, $NaHCO_3$, CH_2Cl_2, 80%; (c) THF, 3 N HCl (3:1); (d) Me_2NNH_2, CH_2Cl_2, $MgSO_4$, 72% from **9**; (e) EtMgBr, THF, room temperature, 48 h; (f) acetone, $CuSO_4$, CSA, 55% from **11**; (g) Li, NH_3, Et_2O, 98%; (h) *o*-$NO_2C_6H_4SeCN$, Bu_3P, THF; (i) H_2O_2, THF, 81% from 13; (j) O_3, CH_2Cl_2, MeOH, Me_2S, 92%.



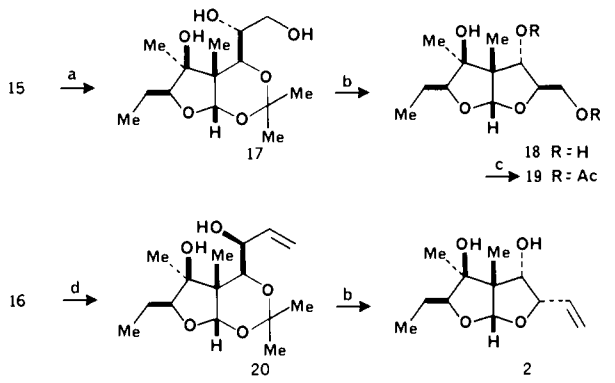
21

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**.

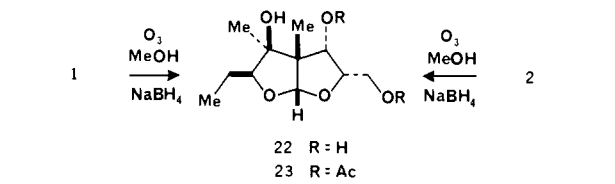
Ozonolysis of **15** provided **16**, which exhibited the same degree and sense of diastereofacial selectivity upon treatment with vinyl magnesium bromide. Chelation-controlled addition[12] (**21**, X = O) from the α face was expected under these conditions and, in the event, provided **20** as a single addition product (Figure 1). Osmylation of the same rotamer (**21**, X = CH_2) from the α face would provide an explanation for the stereoselectivity observed in this reaction.[13,14]

Scheme III[a]



[a] (a) OsO_4, THF, H_2S, 85%; (b) HCl, MeOH, 90%; (c) Ac_2O, Et_3N, DMAP, 90%; (d) CH_2=CHMgBr, THF, 94%.

Scheme IV



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 (±)-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.

Acknowledgment. This investigation was supported by the Institute for General Medical Sciencies of the National Institutes of Health (GM-32527) to whom we are grateful. NMR spectra were obtained through the auspices of the Northeast Regional N.S.F./N.M.R. Facility at Yale University, which was supported by the N.S.F. Chemistry Division Grant C.H.E. 7916210. Molecular mechanics calculations were carried out by Jeff Reagan of these laboratories.

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.

(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 pivaloate ($LiAlH_4$).

(12) (a) Wolfson, M. L.; Hanessian, S. *J. Org. Chem.* **1962**, *27*, 1800. (b) Nakata, T.; Kishi, Y. *Tetrahedron Lett.* **1978**, 2745. (c) Still, W. C.; Schneider, J. A. *Ibid.* **1980**, 1035.

(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** → **17** is in accord with his proposed model.