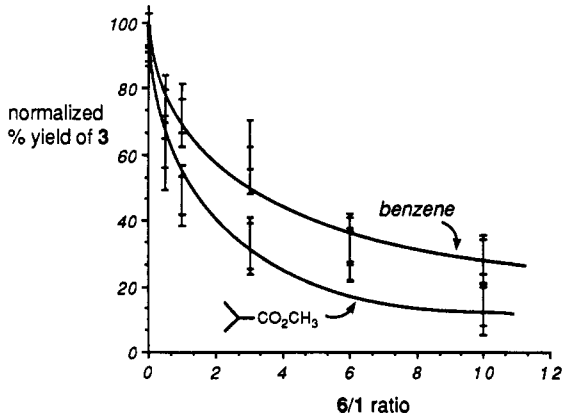


Figure 1. Yield of macrocycle **3** as a function of added methyl ester terminator **6**.

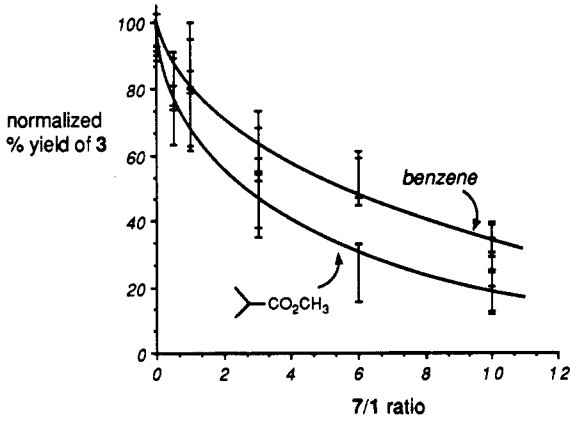
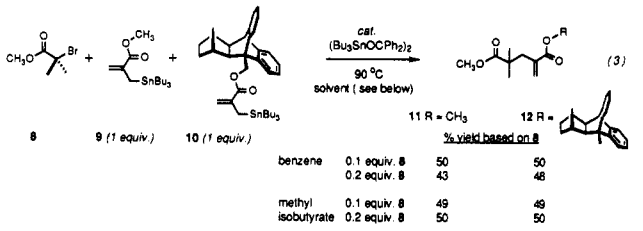


Figure 2. Yield of macrocycle **3** as a function of added model template ester terminator **7**.

The interpretation of these data is not entirely straightforward. The control experiment shown in eq 3, which uses a simple MMA radical derived from **8** as a model for template bound radical **2** (n = 0 or 1), narrows the range of possible explanations. Thus, the formation of adducts **11** and **12** in essentially equal yields provides unequivocal evidence that the two terminators (modeled



(3)

by **9** and **10**) exhibit identical *reactivity* with the simple MMA radical derived from **8** in either solvent. Our current working hypothesis to rationalize these observations focuses on the possibility that a "solvophobic effect"[4] conspires to force the growing oligomeric chain against the template to a greater extent in benzene than in the structurally similar (to the growing oligomeric chain) solvent methyl isobutyrate. Once packed against the template, interception of an intermediate radical by external terminator (i.e., bimolecular termination) may then be suppressed for steric reasons with the bulkier **7** more so than the smaller **6**, and hence, the opportunities for (desirable) intramolecular termination will be enhanced. Thus, a *solvent induced* steric effect may underlie the differential reactivity of the growing chain radical with the two terminators in the two solvents. Experiments designed to exploit these unusual solvent effects as a means for maximizing production of macrocycle **3** are planned.

Acknowledgment. We thank the NSF and the donors of The Petroleum Research Fund (23040-AC), administered by the American Chemical Society, for support of this research and Dr. R. Funk for helpful discussions.

Supplementary Material Available: Experimental procedures and compound characterization data (8 pages). This material is contained in many libraries on microfiche, immediately follows this article in the microfilm version of the journal, and can be ordered from the ACS; see any current masthead page for ordering information.

(4) (a) Abraham, M. H. *J. Am. Chem. Soc.* **1982**, *104*, 2085. (b) Dunams, T.; Hoekstra, W.; Pentaleri, M.; Liotta, D. *Tetrahedron Lett.* **1988**, *29*, 3745. (c) Breslow, R.; Guo, T. *J. Am. Chem. Soc.* **1988**, *110*, 5613. (d) Ito, M. M.; Kato, J.; Takagi, S.; Wakashiro, E.; Sato, T.; Yamada, Y.; Saito, H., Namiki, T.; Takamura, I.; Watasuki, K.; Suzuki, T.; Endo, T. *J. Am. Chem. Soc.* **1988**, *110*, 5147.

Vinylcyclopropane Oxygenation. Anti Diastereoselectivity through an Unexpected Transition-State Geometry

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Summary: Ester-substituted vinylcyclopropanes react with molecular oxygen via a radical-mediated [3-atom + 2-atom] addition to form 1,2-dioxolanes with predominantly anti stereochemistry. The degree of anti stereoselectivity can be controlled by the electronic nature of the radical stabilizing substituent R.

Molecular oxygen can be combined with substituted vinylcyclopropanes to furnish 1,2-dioxolanes via a radical-mediated [3-atom + 2-atom] addition.[1] The reaction is believed to occur by the mechanism shown in Scheme I in which dioxolane stereochemistry is set during ring closure of substituted 5-hexenylperoxy radical **5**. With **1**, R = Ph or CH=$CHCO_2Me$, high levels of syn dioxolane product are observed (Table I, entries **a** and **b**). In this paper we report recent advances in this chemistry which (1) give further insight into the transition-state structures and attendant steric interactions which accompany cy-

(1) Feldman, K. S.; Simpson, R. E. *J. Am. Chem. Soc.* **1989**, *111*, 4878.

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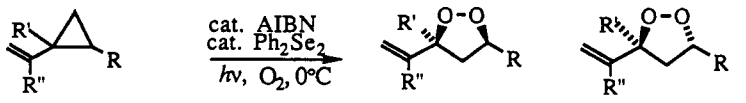
Table I.

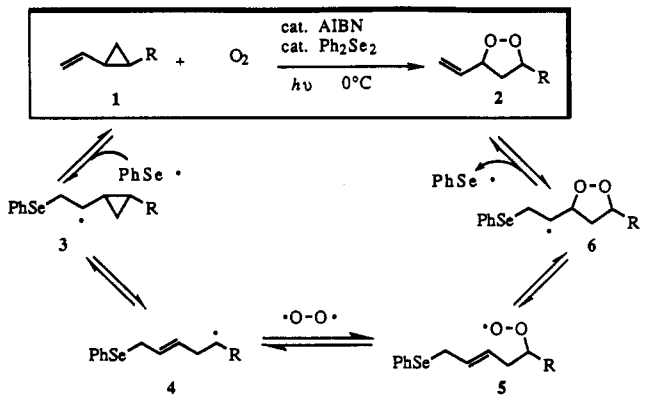


1 7 8

entry	R′	R″	R	syn	anti[a]	yields (%)	ref
a	H	H	C_6H_5	>10	>1.0	63[b]	*d*
b	H	H	$CH{=}CHCO_2Me$	6.5	1.0	44[b]	*d*
c	H	H	CO_2-*t*-Bu	1.0	1.8	66[c]	*d*
d	H	CH_3	CO_2-*t*-Bu	1.0	1.7	70[c]	*d*
e	H	$C(CH_3)_3$	CO_2-*t*-Bu	1.0	1.0	84[c]	*d*
f	CH_3	H	CO_2-*t*-Bu	1.6	1.0	83[c]	*e*
g	H	H	$CO_2CH(CF_3)_2$	1.0	6.0	70[c]	*e*
h	H	H	$CO_2CH(CF_3)_2$ (−50 °C)	<1.0	>10.0	65[c]	*e*
i	H	H	$CO_2C_6H_5$	1.0	3.0	63[c]	*e*
j	H	H	$CO_2C_6H_4$(*p*-OCH_3)	1.0	2.9	43[c]	*e*
k	H	H	$CO_2C_6F_5$	1.0	5.4	60[c]	*e*
l	H	H	COS-*t*-Bu	1.0	2.8	52[c]	*e*
m	H	H	$COSC_6H_5$	1.0	3.4	46[c]	*e*
n	H	H	$CONHC(CH_3)_2CH_2C(CH_3)_3$	1.0	1.4	40[c]	*e*
o	H	H	$CH{=}CHCO_2CH(CF_3)_2$	2.2	1.0	58[c]	*e*

[a] All ratios were determined by integration of characteristic protons in the ^1H NMR spectrum. [b] Isolated yields. [c] Due to the instability of these dioxolanes to SiO_2 chromatography, the yields were determined by comparison with an added internal standard (methyl singlet of anisole) in the ^1H NMR spectrum of the crude reaction mixture. [d] Reference 1. [e] This work.

Scheme I



clization of **5** and (2) allow, for the first time, preparation of the anti dioxolane product with high levels of diastereoselectivity.

Previously, we had shown that in contrast to the phenyl and vinyl ester-containing substrates **1a** and **1b**, oxygenation of vinylcyclopropyl ester **1c** led to a 1.8:1 anti–syn ratio of dioxolanes **8** and **7**, respectively. This surprising reversal in stereoselectivity compared to entries **a** and **b** led us to probe the origin of anti selectivity through oxygenation of substrates **1d–f**.[2] Thus, it appears that while variation in the size of R″ does not influence product stereochemistry in a significant manner (Table I, entries **c–e**), enlarging R′ from H to CH_3 (entry **f**) reverses the anti stereochemical preference and syn dioxolane **7f** is formed as the major product. We interpret these results in terms of transition states resembling the four possible low-energy geometries of peroxy radical **5** shown below (Scheme II), e.g., two boatlike (**10** and **12**) and two chairlike (**9** and **11**) cyclohexane conformations. Chairlike conformer **9** with a pseudoequatorial substituent R is expected to be the low-energy geometry and thus the syn product **7** is anticipated, in accord with much prior work in this area.[3-5] *However, the question then arises, which transition state precedes anti product, 11 or 12*? By evaluating the effects of the size of R′ and R″ (cf. **1c–f**) on product stereochemistry this question can be resolved. Since variation in the size of R″ has little effect on product stereochemistry, it is unlikely that transition-state model **12**, which should experience an increasingly destabilizing flagpole interaction as R″ increases in size, is operational. In contrast, increasing R′ in size correlates with an increased production of syn isomer, an observation consistent with formation of anti product **8** through the alternative axial R transition state model **11**.

These results highlight a counterintuitive aspect of this chemistry: peroxy radical **5** (R = ester) apparently prefers to cyclize through chairlike geometry **11** with a *pseudoaxial* ester, rather than the alternative conformer **12** with a presumably less sterically demanding *psuedoequatorial* ester. In an attempt to detect an (unanticipated) electronic effect in this cyclization which may contribute to this stereochemical outcome, the electronic nature of the substituent R was varied (Table I, entries **g–o**). It was found that the strongly polarized **1g** and **1k** underwent oxygenation with a strong preference for the anti diastereomer without compromising yield. In fact, the anti diastereomer **8i** can be obtained essentially free of the syn contaminant

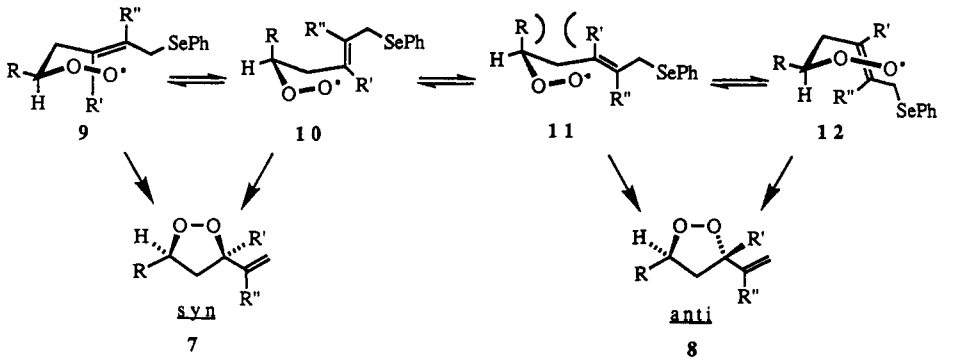
(2) General procedure for oxygenation of vinyl cyclopropanes: A 25 mM solution of vinylcyclopropane **1** in acetonitrile (reagent grade) was placed under an O_2 atmosphere and cooled to 0 °C. A 20 mM solution of diphenyl diselenide (0.2 equiv) and AIBN (0.1 equiv) in CH_3CN was added dropwise over 6 h by motor-driven syringe pump with concomitant sunlamp irradiation. When TLC indicated complete consumption of vinylcyclopropane **1**, the solvent was removed in vacuo. While accurate syn–anti ratios and product yields were determined by ^1H NMR analysis, small amounts of pure dioxolanes could be isolated following SiO_2 (flash) chromatography in a column jacketed with a dry ice/acetone bath.

(3) Beckwith, A. L. J.; Wagner, R. D. *J. Am. Chem. Soc.* **1979**, *101*, 7099; Beckwith, A. L. J.; Lawrence, T.; Serelis, A. K. *J. Chem. Soc., Chem. Commun.* **1980**, 484. Beckwith, A. L. J.; Wagner, R. D. *J. Org. Chem.* **1981**, *46*, 3638. Barker, P. J.; Beckwith, A. L. J.; Fung, Y. *Tetrahedron Lett.* **1983**, *24*, 97.

(4) Roe, A. N.; McPhail, A. T.; Porter, N. A. *J. Am. Chem. Soc.* **1983**, *105*, 1199. Kahn, J. A.; Porter, N. A. *Angew. Chem., Int. Ed. Engl.* **1982**, *21*, 217.

(5) O'Connor, D. E.; Mihelich, E. D.; Coleman, M. C. *J. Am. Chem. Soc.* **1984**, *106*, 3577.

Scheme II



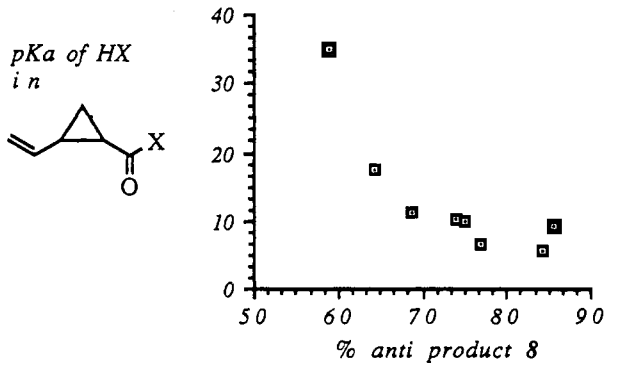


Figure 1.

at −50 °C, while a similar drop in reaction temperature upon oxygenation of the simple ester **1c** only marginally affected the diastereoselectivity (−45 °C, 2.4:1 anti–syn, 29% yield). Further evidence for this significant effect of fluoro substituents on the transition state of cyclization is seen with **1o**. Thus, when R = $CH{=}CHCO_2CH(CF_3)_2$, there is a marked decrease in syn diastereoselectivity relative to the analogous methyl ester case (Table I, compare entries **b** and **o**).

The source of this preference for a pseudoaxial orientation of the ester appendage in the transition state for 5-hexenylperoxy radical cyclization remains a matter of some speculation. Clearly, the electronegativity of the carbonyl moiety is important, as a graph of pK_a (as a measure of electron demand at the carbonyl) of the carbonyl substituent vs % anti dioxolane product formed reveals a striking correlation (Figure 1). Other parameters, such as carbonyl dipole moment[6] or ^{13}C resonance of the carbonyl carbon (see supplementary material), do not show a discernible relationship with anti dioxolane production. At present, we are utilizing computational techniques to probe the manner by which this attribute of the carbonyl functionality is translated into a (electronic?) preference for the axial ester moiety upon cyclization.

In summary, these probes into the mechanistic details of oxygenation lead us to suggest that the transition state preceding anti dioxolane product when R = ester is best represented as a chairlike construct with a *pseudoaxial* ester. Utilizing electron-withdrawing esters affords the otherwise difficultly obtainable anti dioxolane product with excellent stereoselectivity (e.g., Table I, entry **h**), although a precise mechanistic rationale presently eludes us.

Acknowledgment. We thank NIH (GM37681) and NSF (CHE 86-57016) for financial support.

Supplementary Material Available: Characterization data and NMR spectra of **7f–o** and **8f–o** (30 pages). This material is contained in many libraries on microfiche, immediately follows this article in the microfilm version of the journal, and can be ordered from the ACS; see any current masthead page for ordering information.

(6) Dipole moments of model compounds. CH_3CO_2-t-Bu 1.93 (22 °C, PhH); Donle, H. L. *Z. Physik Chem.* **1931**, *B14*, 362. CH_3CO_2NHt-Bu 3.90 (30 °C, dioxane): Kumler, W. D.; Porter, C. W. *J. Am. Chem. Soc.* **1934**, *56*, 2549. n-$C_{17}H_{35}COSCH_3$ 1.37 (30 °C, PhH): Hirabayashi, Y. *Bull. Chem. Soc. Jpn.* **1965**, *38*, 175. n-Bu(Et)$CHCO_2CH_2(CF_2)_8H$ 2.8 (20 °C, PhH): Romans, J. B.; Callinan, T. D. *J. Electrochem. Soc.* **1957**, *104*, 357.

(7) pK_a's, except for the amine from **1n**, are found in: Sergeant, E. P.; Dempsey B. *Ionisation Constants of Organic Acids in Aqueous Solution*; Pergamon Press: Oxford, 1979. The pK_a of Et_2NH is used as a model for the amine in **1n** and can be found in: Carey, F. A.; Sundberg, R. J. *Advanced Organic Chemistry, Part B: Reactions and Synthesis*, 2nd ed.; Plenum Press: New York, 1977p p 3.

Face Selectivity of the Protonation of Glycals

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Summary: The proton-catalyzed addition of alcohols to glycals is shown not to be a trans diaxial addition.

We wish to describe our preliminary studies on the stereochemistry of protonation of glycals, the only important reaction of glycals which has not hitherto undergone detailed stereochemical scrutiny.[1] Very recently, Bollitt, Mioskowski, Lee, and Falck (BMLF) disclosed that triphenylphosphine hydrobromide (TPP–HBr) was the

(1) (a) Ferrier, R. J. *The Carbohydrates*, 2nd ed.; Pigman, W., Horton, D., Wander, J., Eds.; Academic Press: New York, 1980; Vol. 1B, pp 843–875. (b) Grewal, G. Ph.D. dissertation, CUNY 1991, Chapter 2, to be published.

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