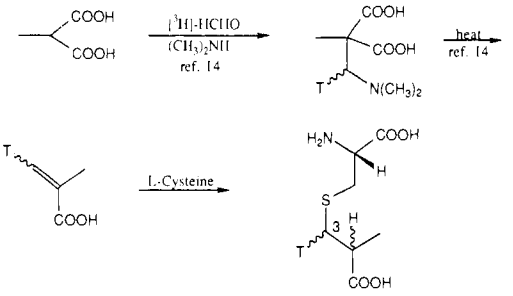
Scheme III



sulfide **4** with $K_3W_2Cl_9$. The reduced amino acid was purified by ion exchange (IR 120-plus) and by chromatography on cellulose, and it was then converted to the *N*-acetyl *p*-bromophenacyl ester. This derivative was recrystallized to constant radioactivity (0.25% incorporation) and constant isotopic ratio. The results, which are summarized in Table I (expt 1), demonstrate that C-1 to C-3 and the sulfur atom of CPC are incorporated specifically into **1**. Evidence for the intact incorporation of CPC into **1** was obtained by means of a double label experiment utilizing a mixture of 2(*RS*),6(*R*)-[5,6,7-^{14}C]CPC, prepared from methacrylic acid and [U-^{14}C]-L-cysteine, and the previously prepared [1-^{3}H]CPC. This doubly labeled precursor was converted into **1** without significant alteration of the isotopic ratio (Table I, expt 2).

The mechanism of the oxidative decarboxylation of CPC to *trans*-*S*-1-propenyl-L-cysteine sulfoxide was examined with the aid of two doubly labeled forms of CPC. The addition of L-cysteine to methacrylic acid in tritiated water yielded 2(*RS*),6-(*R*)-[2-^{3}H]CPC. The position of the isotopic label was confirmed by examination of the NMR spectrum of the corresponding deuterated amino acid prepared in D_2O. Administration of this form of specifically tritiated CPC to *A. cepa* in conjunction with 2(*RS*),6(*R*)-[^{35}S]CPC showed that there is no significant tritium loss from C-2 of CPC as the result of the oxidative decarboxylation (Table I, expt 3). This observation rules out the possibility that the reaction proceeds by dehydrogenation of CPC to (*Z*)-*S*-(2-carboxy-1-propenyl)-L-cysteine followed by decarboxylation of the α,β-unsaturated acid with retention of configuration.[9] The second experiment examined the fate of the hydrogen atoms present at C-3 of CPC. 2(*RS*),3(*RS*),6(*R*)-[3-^{3}H]CPC was synthesized by the route outlined in Scheme III. Administration of a mixture of this precursor and 2(*RS*),6(*R*)-[^{35}S]CPC to young onion plants yielded the amino acid **1** that exhibited ca. 53% loss of tritium (Table I, expt 4). This result suggests that the decarboxylation reaction proceeds with the stereospecific loss of one hydrogen atom from C-3 of CPC, and it rules out the intermediacy of a 3-keto CPC derivative.

The results of the preceding experiments suggest that the oxidative decarboxylation process associated with the biosynthesis of *trans*-(*S*)-1-propenyl-L-cysteine sulfoxide from CPC may be mechanistically related to the formation of the vinyl groups in heme and chlorophyll from propionic acid side chains.[10] The transformation also appears to resemble the formation of uneven numbered 1-alkenes from fatty acids in higher plants.[11] Additional studies of both a stereochemical and enzymatic nature will be required before a clear picture of the mechanism of formation of the amino acid **1** emerges.

Acknowledgment. We are pleased to acknowledge the support of this work by the National Science Foundation (CHE8604611) and the Robert A. Welch Foundation (C-729).

(9) See, for example: Parry, R. J. *Proc. Natl. Acad. Sci. U.S.A.* **1975**, *72*, 1681.

(10) Seehra, J. S.; Jordan, P. M.; Akhtar, M. *Biochem. J.* **1983**, *209*, 709. Battersby, A. R. *Experientia* **1978**, *34*, 1; Zaman, Z.; Akhtar, M. *Eur. J. Biochem.* **1976**, *61*, 215.

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Enantiomerically Pure Vinylketene Acetals as Dienes in the Diels-Alder Reaction†

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The asymmetric variant of the Diels-Alder reaction[1] has emerged in recent years as an important method for the construction of complex molecules in enantiomerically pure form. In most instances, diastereomeric transition states arise through the intervention of a chiral auxiliary attached to the *dienophile*. Conversely, there are few examples of the use of chiral *dienes* in the Diels-Alder reaction. While the first definitive experiments appeared in 1976,[2] it has only been in the last decade, through the work of Trost,[3] Kozikowski,[4] Frank,[5] McDougel,[6] and others,[7] that the synthetic versatility of this approach has become evident.

Our quest for an enantiomerically pure diene of general utility in cycloaddition reactions led us to consider vinylketene acetals such as **1**,[8,9] and in this communication we present the results of our preliminary experiments.

The rationale for the use of these reagents is presented in Scheme I, which depicts the normal endo transition state of the intermolecular Diels-Alder reaction. Due to the chirality of the system, approach of the dienophile from the top face of **1** (eq 1) is diastereomeric with approach from the bottom (eq 2). Within this context, steric hindrance between the electron-withdrawing group of the dienophile (Z) and the large -R group of **1** in the transition state of eq 2 will raise the energy of that reaction pathway relative to eq 1, where the complimentary interaction is between the relatively small hydrogen and the -Z group. This results in the net production of **2** at the expense of **3** and, consequently, net enantiomeric excess following ketal removal. Use of the opposite enantiomer of the chiral auxiliary results in production of the enantiomeric product.

The analysis above implies that the primary factor determining diastereomeric excess is steric,[10] which affords this approach simple predictive capabilities as to the major isomer produced. In addition, the product of the Diels-Alder reaction is a ketal,[11] fully

† Dedicated to Professor Carl Djerassi on the occasion of his 65th birthday.

‡ American Cancer Society Junior Faculty Research Awardee, 1987-1990.

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(7) (a) Dauben, W. G.; Bunce, R. A. *Tetrahedron Lett.* **1982**, *23*, 4875-8. (b) Reitz, A. B.; Jordan, A. D., Jr.; Maryanoff, B. E. *J. Org. Chem.* **1987**, *52*, 4800-2. (c) Posner, G. H.; Harrison, W. *J. Chem. Soc., Chem. Commun.* **1985**, 1786-7. (d) Lipshutz, B. H.; Nguyen, S. L.; Elworthy, T. R. *Tetrahedron* **1988**, *44*, 3355-64.

(8) For a recent report of the use of chiral *N,N*-ketene acetals, see: Gruseck, U.; Heuschmann, M. *Tetrahedron Lett.* **1987**, *28*, 2681-4 and 6027-30.

(9) Substituents with C-2 or local C-2 symmetry, as type **1** compounds possess, have found extensive employment in synthesis. See: Tomioka, K.; Nakajima, M.; Koga, K. *J. Am. Chem. Soc.* **1987**, *109*, 6213-5, and references therein.

(10) A similar steric arguement is made for the stereoselectivity of vinylallene cycloadditions. See: Reich, H. J.; Eisenhart, E. K.; Whipple, W. L.; Kelly, M. J. *J. Am. Chem. Soc.* **1988**, *110*, 6432-42.

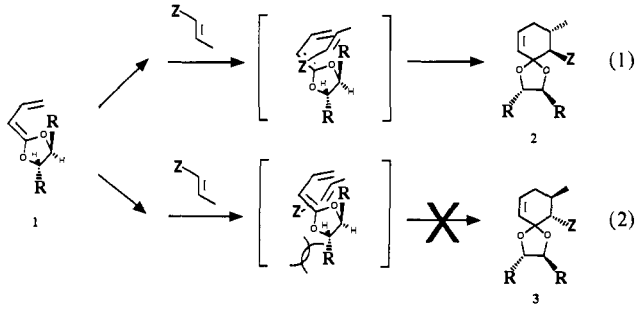
0002-7863/89/1511-4515$01.50/0

Table I

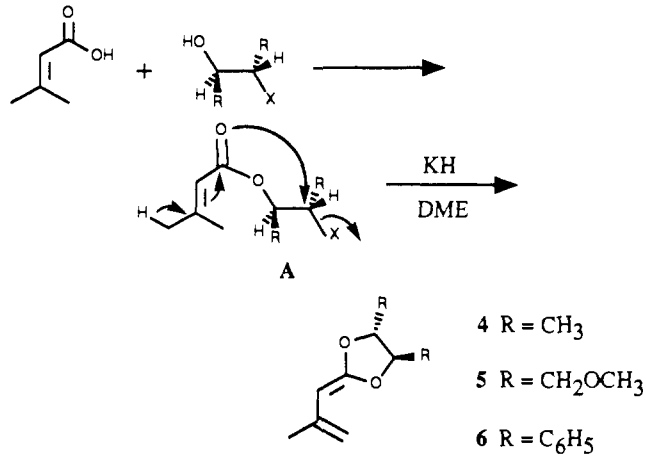
entry	diene	dienophile	solvent/temp	time[f,g]	diastereomer ratio[a]	% yield[b]
1	**4**, R = CH_3	methyl crotonate	toluene/reflux	80[f]	1.4:1	40
2	**5**, R = CH_2OCH_3	methyl crotonate	toluene/reflux	80[f]	1.3:1	55
3	**6**, R = C_6H_5	methyl crotonate	toluene/reflux	80[f]	3:1	75[c]
4	**6**, R = C_6H_5	ethyl fumarate	toluene/reflux	40[f]	2:1	70[d]
5	**6**, R = C_6H_5	*N*-methylmaleimide	$CHCl_3$/reflux	4[g]	95:5	67
6	**6**, R = C_6H_5	*N*-methylmaleimide	CH_2Cl_2/rt[e]	7[g]	98:2	95
7	**6**, R = C_6H_5	*N*-phenylmaleimide	CH_2Cl_2/rt[e]	7[g]	85:15	96
8	**6**, R = C_6H_5	maleic anhydride	C_6H_6/rt[e]	7[g]	59:41	56
9	**6**, R = C_6H_5	maleic anhydride	C_6H_6/reflux	4[g]	55:45	55

[a] Determined by 300 MHz ^{1}H NMR and/or GC analysis. [b] Isolated yield. [c] Absolute configuration determined, see text. [d] Combined yield for vinylketene acetal formation and Diels–Alder reaction. [e] rt stands for room temperature. [f] Time is in hours. [g] Time is in days.

Scheme I



Scheme II



functional as a protecting group for a number of subsequent synthetic manipulations and/or easily removed to afford a ketone functionality, one of the most useful in organic synthesis. Finally, the auxiliary is recyclable.

The synthesis of the desired vinylketene acetal arises from the corresponding β-halohydrin ester of the requisite α,β-unsaturated carboxylic acid (A, Scheme II). In these initial experiments 3,3-dimethylacrylic acid has been employed exclusively. We have recently reported the synthesis of a number of enantiomerically pure β-halohydrins, including both enantiomers of 2-chloro-1,2-diphenylethanol, from the corresponding enantiomerically pure diols.[12] Treatment of A with KH[13] in DME at room temperature, followed by Schlenk filtration and distillation, affords the desired dienes **4–6** as the only isolable product in yields of 60–90%.[14]

Table I outlines our preliminary investigations into the Diels–Alder reactions of vinylketene acetals with a variety of dienophiles. No reactions have been actively optimized, yet several conclusions can be drawn. First, the results employing **4** and **5** are poor (14–17% diastereomeric excess, entries 1 and 2), as would be expected. These results are a "worst case" situation in that both $-CH_3$ and $-CH_2OCH_3$ represent the smallest possible alkyl substituent.[15] In addition, these small alkyl groups would be expected to occupy a pseudoequatorial position on the dioxolane ring, thereby decreasing their steric effect at the reaction center. It is for this reason that we chose to synthesize **6** (R = C_6H_5). The crucial intramolecular nucleophilic attack by oxygen to afford ketene acetal **6** occurs at a benzylic position instead of a less reactive secondary aliphatic center.[14] Additionally, the phenyl group is quite large when compared to the methyl (or hydroxymethyl) group.[15] Thus, at a given dihedral angle,[16,17] the steric effect produced by a dienophile approaching **6** would be far greater than that produced upon approach to **4** and **5**.

The results given in Table I for ketene acetal **6** bear out this analysis.[18] While the reactions performed on **6** at high temperature show better diastereoselectivity than those employing **4** and **5** (entry 3), lowering the temperature of the reaction has a profound effect on both the yield and stereoselectivity of the process. Especially noteworthy are the reactions with *N*-methylmaleimide (entries 5 and 6). In the room temperature reaction (entry 6), the crystalline product is obtained in extremely high yield and diastereomeric purity. Entry 7, involving *N*-phenylmaleimide as dienophile, also shows high yield with decreased, but still valuable, diastereoselectivity. The origin of the poor performance of maleic anhydride is not understood at this time.

In order to ascertain the absolute stereochemistry of the newly formed chiral centers, (*R*)-3,5-dimethyl-2-cyclohexenone[19] is produced as the major isomer from the reaction of aqueous acid with the product mixture from entry 3. This major isomer is predicted based on the analysis given in Scheme I; namely, simple

(11) For the use of chiral ketals in synthesis, see: *J. Am. Chem. Soc.* **1987**, *109*, 2542–4, and references therein.

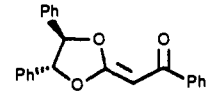
(12) Konopelski, J. P.; Boehler, M. A.; Tarasow, T. M., submitted for publication.

(13) For a general discussion on the uses of KH, see: Brown, C. A. *J. Org. Chem.* **1974**, *26*, 3913–8. For another use of the system KH/DME, see: Evans, D. A.; Baillargeon, D. J.; Nelson, J. V. *J. Am. Chem. Soc.* **1978**, *100*, 2242–4.

(14) The exception to this experimental procedure is the ester made from (3*S*,4*R*)-4-bromo-2,5-dimethyl-3-hexanol, which does not give any useful yield of ketene acetal upon treatment with KH/DME. Presumably this is due to steric constraints in the intramolecular S_N2 reaction.

(15) Hirsch, J. A. *Top. Stereochem.* **1967**, *1*, 199–222.

(16) Molecular mechanics calculations (Macromodel, Version 1.5) indicate that the dihedral angle between the –R groups of **4** and **6** are approximately equivalent (93°). Direct NMR analysis of 6 (benzene-d_6) indicates a coupling constant between the two benzylic hydrogens of 7.8 Hz, which corresponds to a dihedral angle of 114° between the phenyl groups. Likewise, acylketene acetal **i**, which is also under study in this laboratory,[17] exhibits a benzylic hydrogen coupling constant of 7.8 Hz.



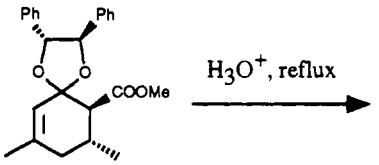
i

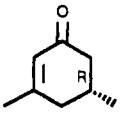
(17) Eid, C. N., Jr., unpublished results from this laboratory.

(18) Diastereomer ratios in Table I were determined by integration of the vinyl proton region of the 300 MHz ^{1}H spectrum. More accurate determinations for entries 5–7 were made by capillary column GC analysis.

(19) Allenger, N. L.; Riew, C. K. *J. Org. Chem.* **1975**, *40*, 1316–21.

steric considerations prevail. Enantiomerically pure hydrobenzoin is also isolated in good yield.





lit $[\alpha]_D = -138^\circ$

$[\alpha]_D = -61^\circ$

Current work in these laboratories include studies on solvent effects,[20] Lewis acid catalysis,[21] and pressure[22] on the course of these reactions. The use of this methodology in the total synthesis of more complex organic molecules is also in progress, and results from these efforts will be reported as they become available.[23]

Supplementary Material Available: Experimental details for the synthesis of **6** and the Diels-Alder reaction between **6** and *N*-methylmaleimide (4 pages). Ordering information is given on any current masthead page.

(20) For recent discussions on the effect of solvents on the Diels-Alder reaction, see: (a) Breslow, R.; Guo, T. *J. Am. Chem. Soc.* **1988**, *110*, 5613-7. (b) Dunams, T.; Hoekstra, W.; Pentaleri, M.; Liotta, D. *Tetrahedron Lett.* **1988**, *29*, 3745-8.

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(22) For a general discussion of the use of high pressure in the Diels-Alder reaction, see: Matsumoto, K.; Sera, A. *Synthesis* **1985**, 999-1027.

(23) Research support by the UC Santa Cruz Committee on Research and the American Cancer Society is gratefully acknowledged.

Substrate Selectivity in Epoxidation by Metalloporphyrin and Metallosalen Catalysts Carrying Binding Groups[1]

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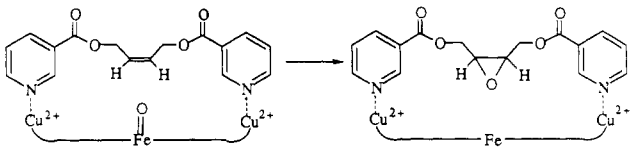
Despite extensive studies of hydroxylation and epoxidation reactions catalyzed by metalloporphyrins and other metal complexes, there are almost no examples of systems using auxiliary binding groups to select particular substrates. The most striking case is the recent example reported by Groves,[4] in which a steroid substrate is epoxidized or hydroxylated by a metalloporphyrin catalyst carrying substituents that create a shape-selective pocket in a micelle.

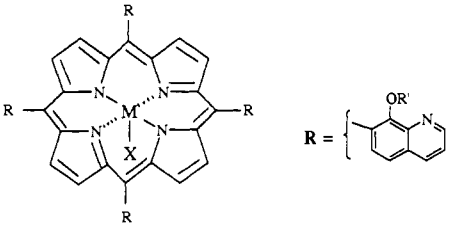
For some time we have been interested in constructing systems that can mimic the selectivities of enzymes in oxidations and other reactions[5] and have used metal binding as a force to hold substrates and catalysts together.[6] We have also described a system in which double binding (by ion pairing) of a substrate to a reagent was

Scheme I



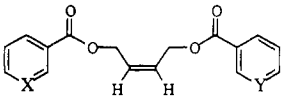
particularly effective in promoting selective functionalization of the substrate.[7] We now wish to report examples of the selective functionalization of substrates that can doubly bind to a metalloporphyrin at appended metal ligand groups (Scheme I) and also to a related non-porphyrin metal epoxidation catalyst.

Reaction of 8-methoxyquinoline-7-carboxaldehyde with pyrrole in propionic acid afforded the free base porphyrin **1a**.[8,9] This was metalated to form **1b**,[10] which with BBr_3 yielded **1c**.[11]

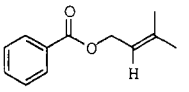


1a M = $2H^+$, X not present, R' = Me
1b M = Fe(III), X = Br, R' = Me
1c M = Fe(III), X = Br, R' = H

Addition of Cu^{2+} to **1c** produces a catalyst in which some of the atropisomers can bind appropriate substrates across the face of the metalloporphyrin, in a position to be epoxidized by the Fe=O intermediate.[12] As a double binding substrate we selected the bis-nicotinate **2a**.[13] We also examined the single binding substrate **2b** and with the salen catalyst the nonbinding analogue **2c**.



2a X = Y = N
2b X = N, Y = CH
2c X = Y = CH



3

All substrates were epoxidized with catalyst and PhI=O in direct competition with the nonbinding substrate prenyl benzoate (**3**), and 400 MHz proton NMR spectra were used (excess phenanthroline was added to complex the Cu^{2+}) to determine the extent of epoxidation of **2** and **3**; we define the ratio of **2**-epoxide/**3**-epoxide as the *selectivity*, *S*. Solutions containing 0.0125 mmol of both substrates in 14 mL of acetonitrile were allowed to react with 10% of porphyrin **1c** and 60% of PhI=O, with or without the addition of 4 equiv of $Cu(ClO_4)_2 \cdot 6EtOH$. Under these conditions the maximum conversion of **2a** to its epoxide was 18%, so the substrate ratios stayed fairly constant throughout the reaction. Control reactions with PhI=O and Cu^{2+} (in the presence or absence of bipyridyl) without **1c** led to <1% epoxidation of either substrate, so we are not dealing with copper-catalyzed oxidation chemistry.[14] Such copper catalysis would in any case

(1) Support of this work by the NSF and the NIH are gratefully acknowledged. Mass spectral determinations of salens were performed by the Midwest Center for Mass Spectrometry, a National Science Foundation Regional Instrumentation Facility (CHE 8620177).

(2) Recipient of an NIH postdoctoral fellowship.

(3) Recipient of an NSF predoctoral fellowship.

(4) Groves, J. T.; Neumann, R. *J. Am. Chem. Soc.* **1987**, *109*, 5045.

(5) Breslow, R. *Adv. Enzymol. Relat. Areas Mol. Biol.* **1986**, *58*, 1-60.

(6) Breslow, R.; Chipman, D. *J. Am. Chem. Soc.* **1965**, *87*, 4195.

(7) Breslow, R.; Rajagopalan, R.; Schwarz, J. *J. Am. Chem. Soc.* **1981**, *103*, 2904.

(8) For the preparation of other isomers, with the wrong geometry for our reactions, cf.: Sugata, S.; Matsushima, Y. *Chem. Pharm. Bull.* **1987**, *35*, 2623-2626.

(9) MS, FAB 939 (M + 1). ^1H NMR consistent with the structure.

(10) ^1H NMR (200 MHz, CD_2Cl_2) of $Fe^{II}(pyridine)_2$ complex consistent with the structure, including several peaks in the δ 3.81-2.76 region with a total area of 12 protons for the CH_3 groups of the various atropisomers.

(11) Crystallized from chloroform/hexane. Anal. Found (Calcd for $C_{56}H_{32}N_8O_4FeBr \cdot 7H_2O$): C, 59.08 (58.86); H, 3.41 (4.06); N, 9.74 (9.81); Fe 4.24 (4.89). The ^1H NMR spectrum of the reduced $Fe^{II}(pyridine)_2$ complex showed the expected peaks.

(12) Groves, J. T.; Haushalter, R. C.; Nakamura, M.; Nemo, T. E.; Evans, B. J. *J. Am. Chem. Soc.* **1981**, *103*, 2884.

(13) All substrates and the corresponding epoxide products were characterized by ^1H NMR and mass spectroscopy.

0002-7863/89/1511-4517$01.50/0