Stereochemical Studies on the Intramolecular Imino Diels–Alder Reaction[1,2]

Bassam Nader, Thomas R. Bailey, Richard W. Franck, and Steven M. Weinreb*[3]

Contribution from the Departments of Chemistry, Fordham University, Bronx, New York 10458, and The Pennsylvania State University, University Park, Pennsylvania 16802.
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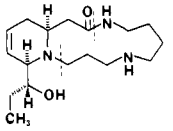
Abstract: The intramolecular Diels–Alder cycloaddition of some *N*-acylimines has been shown to be a totally stereoselective process producing tetrahydropyridine systems having a trans relationship of hydrogens α to nitrogen. Thus, thermolysis of **13** or **14** led to a 55:45 mixture of trans-6,5-fused cycloadducts **16** and **17**, respectively. The stereostructures of these compounds were established by direct correlation with authentic methyl dihydropalustramate diastereomers **3**, **4**, and **6**. Similarly, precursor **29** cyclized to give exclusively trans-6,5-cyclo adduct **30**, whose structure was established by X-ray crystallography on the derived dihydro acid **32**. The homologous Diels–Alder precursor **36** also cyclized stereoselectively to give the trans-6,6-fused system **37**, which was characterized by X-ray crystallography on acid **38**. These stereochemical results have been rationalized on the basis of an azafumarate-type of acylimine intermediate **40** which cyclizes via transition state C, having the N-acyl group endo and the carbomethoxyl group exo.

In recent years synthetic chemists have become increasingly aware of the power of intramolecular cycloadditions for construction of complex polycyclic molecules. In particular, the intramolecular Diels–Alder reaction has been the subject of intensive study.[4] Despite the fact that Diels–Alder cycloadditions using various imines as dienophiles have been known for almost 40 years,[5] the first intramolecular variations of this reaction have only recently been described.[6,7] We have been involved in a program of alkaloid synthesis which uses the intramolecular imino Diels–Alder reaction as the primary strategy,[7] and within the context of this work, it was important that we know about the stereochemistry of the process. The stereochemistry of some intermolecular Diels–Alder cycloadditions of acyclic *N*-acylimines and *N*-sulfonylimines has been elegantly elucidated by Krow,[8] but nothing at all was known when we began concerning the stereochemical course of the analogous intramolecular versions.

It seemed to us that an intramolecular imino Diels–Alder approach might nicely serve for construction of the tetrahydropyridine portions of spermidine derived alkaloids such as plaustrine (**1**)[9] and/or anhydrocanabisativine (**2**).[10] We were particularly



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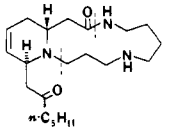

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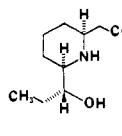
attracted by the possibility of using this type of cyclization to establish the relative stereochemistry of the centers α to nitrogen in the tetrahydropyridine ring of such a system. Since we were not sure initially as to what the stereochemical outcome of these proposed cyclizations would be (nor did we even know whether they would be stereoselective), we chose initially to explore synthesis of piperidines **3–6**. Methyl dihydropalustramate (**3**) is a degradation product of palustrine (**1**), and it, along with the remaining three diastereomers **4–6**, has been synthesized by



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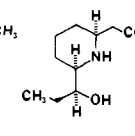

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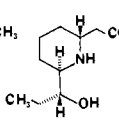

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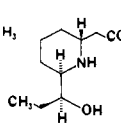

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* Dedicated to Professor George Büchi on the occasion of his 60th birthday.

Eugster and co-workers.[9] We felt that the availability of these isomers would greatly simplify the nontrivial task of identifying and correlating stereochemistry in our imino Diels–Alder adducts, and such proved to be the case.

Results

The starting material for the initial study was dienone **7**, which could be prepared via two different routes. Condensation of ylide **8** with acrolein gave **7**, but in only 24% yield. Alternatively, dienone **7** could be efficiently synthesized in 42% yield by reaction of butadiene with propionyl chloride catalyzed by $TiCl_4$, followed by treatment of the crude product with calcium carbonate.[11] Reduction of **7** with lithium aluminum hydride in ether gave

7

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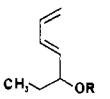

9 R = H

10 R = $CONH_2$

alcohol **9**. The infrared spectrum of **9** showed a strong band at

(1) Portions of this work have appeared in preliminary form: Nader, B.; Franck, R. W.; Weinreb, S. M. *J. Am. Chem. Soc.* **1980**, *102*, 1153.

(2) Taken, in part, from the Ph.D. thesis of Bassam Nader, Fordham University, 1980.

(3) Fellow of the A. P. Sloan Foundation, 1975–1979; recepient of a Research Cancer Development Award from the National Institutes of Health (HL-00541), 1975–80; to whom correspondence should be addressed at The Pennsylvania State University.

(4) For recent reviews, see: (a) Oppolzer, W. *Angew. Chem., Int. Ed. Engl.* **1977**, *16*, 10. (b) Oppolzer, W. *Synthesis* **1978**, 793. (c) Brieger, G.; Bennett, J. N. *Chem. Rev.* **1980**, *80*, 63.

(5) (a) Lora-Tamayo, M. In "1,4-Cycloaddition Reaction", Hamer, J., Ed.; Academic Press: New York, 1967; pp 127–42. (b) Weinreb, S. M.; Levin, J. I. *Heterocycles* **1979**, *12*, 949.

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(7) (a) Weinreb, S. M.; Khatri, N. A.; Shringarpure, J. *J. Am. Chem. Soc.* **1979**, *101*, 5073. (b) Schmitthenner, H. F.; Weinreb, S. M. *J. Org. Chem.* **1980**, *45*, 3372. (c) Khatri, N. A.; Schmitthenner, H. F.; Shringarpure, J.; Weinreb, S. M. *J. Am. Chem. Soc.* **1981**, *103*, 6387.

(8) (a) Krow, G. R.; Johnson, C.; Boyle, M. *Tetrahedron Lett.* **1978**, 1971. (b) Krow, G.; Rodebaugh, R.; Carmosin, R.; Figures, W.; Pannella, H.; DeVicaris, G.; Grippi, M. *J. Am. Chem. Soc.* **1973**, *95*, 5273.

(9) (a) Walchli, P. C.; Eugster, C. H. *Helv. Chim. Acta* **1978**, *61*, 885. (b) Rüedi, P.; Eugster, C. H. *Ibid.* **1978**, *61*, 899. (c) Mayer, C.; Green, C. L.; Trueb, W.; Wälchli, P. C.; Eugster, C. H. *Ibid.* **1978**, *61*, 905. (d) Wälchli, P. C.; Mukherjee-Müller, G.; Eugster, C. H. *Ibid.* **1978**, *61*, 921. (e) Wälchli-Schaer, E.; Eugster, C. H. *Ibid.* **1978**, *61*, 928.

(10) Elsohly, M.; Turner, C. E.; Phoebe, C. H.; Knapp, J. E.; Schiff, P. L.; Slatkin, D. J. *J. Pharm. Sci.* **1978**, *67*, 124.

(11) (a) Adams, D. R.; Bhatnagar, S. P.; Cookson, R. C.; Tuddenham, R. M. *Tetrahedron Lett.* **1974**, 3197. (b) Cookson, R. C.; Tuddenham, R. M. *J. Chem. Soc., Chem. Commun.* **1973**, 742.

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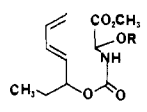
Table I. Total Yield of Intramolecular Diels-Alder Adducts 16 and 17 from Various Acylimine Precursors

precursor	solvent	temp, °C	reaction time, h	cyclization procedure	isolated % yield of 16 and 17
12	o-$Cl_2C_6H_4$	178	10	A[a]	0
12	o-$Cl_2C_6H_4$	550		B	trace
12	xylene	500		B	trace
13	C_6H_5Br	156	12	A	trace
13	C_6H_5Br	500		B	21
13	C_6H_5Br	260		B	40
13	C_6H_5Br	230-240	2.5	C	46
13	C_6H_5Br	room temp		D	0
14	$C_6H_5CH_3$	210	2	C	59
15	$C_6H_5CH_3$	210	22.5	C	18

[a] A = solvent at reflux; B = hot tube, short contact; C = sealed at temperature shown; D = $BF_3 \cdot Et_2O$ catalysis (see Experimental Section for details).

928 cm^{-1} (and no absorption at 860–620 cm^{-1}), indicating the presence of a trans-disubstituted double bond. The alcohol was then transformed to carbamate **10** with sodium cyanate/TFA in ether.[12]

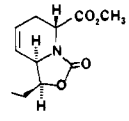
This carbamate combined cleanly with methyl glyoxylate[13] to afford the methylol derivative **11**,[14] which was intended to be our acylimine precursor for the proposed Diels–Alder cyclization. Compound **11** itself did not, in fact, prove useful, and a number



11 R = H
12 R = CH_3
13 R = $COCH_3$
14 R = CONHPh
15 R = $CONHCH_3$

of derivatives of it were prepared. Treatment of **11** with methanol/TFA gave ether **12**. Acetylation of **11** with acetic anhydride/pyridine afforded acetate **13**. The mixed carbamates **14** and **15** were formed in good yield by treating **11** with phenyl isocyanate and methyl isocyanate, respectively.

Cyclization experiments were conducted with compounds **12–15**, affording in all successful cases what proved to be an inseparable 55:45 mixture of stereoisomers **16** and **17**, respectively (vide infra).



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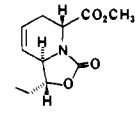

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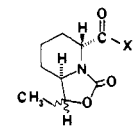
None of the isomers having the cis relationship of the two hydrogens α to nitrogen were found. Table I shows some of the reaction conditions which were examined, and the total yields of the mixture of cyclization products **16** and **17** which were actually isolated from various precursors. Optimum yields were obtained by heating acetate **13** in bromobenzene at 230–240 °C (46%) or similarly by heating mixed carbamate **14** at a slightly lower temperature (59%). Lewis acid catalysis did not prove at all effective, probably due to a tendency of the diene moieties of the acyclic precursors to polymerize. At present, it is not clear whether the high temperatures necessary for cyclization of these precursors reflect difficulty in the initial elimination step to form the intermediate acylimine (see Discussion) or a sluggishness in the [4 + 2] cycloaddition process.

Considerable effort went into establishing the ratio of **16** and **17** in a mixture of adducts, and into assigning stereostructures to each of these compounds. Catalytic hydrogenation of the mixture gave the inseparable piperidines **18**, which on basic hydrolysis afforded epimeric carboxylic acids **19**. The acid mixture was converted to the corresponding acid chlorides **20** with PCl_5



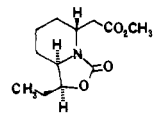
18 X = OCH_3
19 X = OH
20 X = Cl

21 X = $OCH_2C_6H_4$-p-NO_2

and treatment with p-nitrobenzyl alcohol gave the esters **21**. We were able to separate these epimeric p-nitrobenzyl esters (but with difficulty) by HPLC on an analytical reverse phase column, thus establishing the 55:45 ratio of stereoisomers mentioned above. However, the two compounds could not be separated on a preparative scale.

In order to determine the stereochemistry of the Diels–Alder cycloadducts **16** and **17**, it was necessary to directly correlate our compounds with the dihydropalustramate isomers **3–6**. Thus, the mixture of acid chlorides **20** was treated successively with: (1) diazomethane and (2) Ag_2O/CH_3OH (Arndt–Eistert sequence), affording the homologated esters **22** and **23**, once again as an inseparable epimeric mixture. Samples of authentic compounds **3**, **4**, and **6**, very kindly provided by Professor C. H. Eugster,[9] were transformed to oxazolones **24**, **25**, and **22**, respectively, upon reaction with carbonyl diimidazole.[15] TLC comparison of pure **24**, **25**, and **22** with our inseparable synthetic mixture of **22** and **23** indicated that none of the former two compounds were present, and that the latter compound had R_f identical with that of our material.

Comparison of the 200 MHz ^1H NMR spectra of **22**, **24**, and **25** derived from Eugster's samples with our mixture of **22** and **23** further established the identity of these compounds. Specifically, ester **22** shows the hydrogens α to the carbomethoxyl group as an eight-line pattern (AB of ABX, J = 14,49, 7.70, 8.34 Hz) centered at δ 2.61.[28] Our synthetic mixture of **22** and **23** shows



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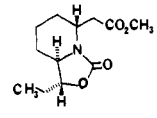

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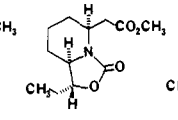

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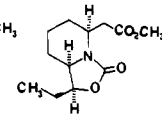

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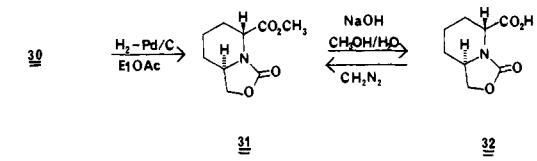
two overlapping eight-line patterns at the same chemical shift value, one of which superimposes perfectly with that of authentic **22**. Both cis isomers **24** and **25** on the other hand have the protons α to their methyl ester group as two quartets at about δ 2.7 and 3.5, thus quite different from those of the trans isomers. The octet due to isomer **22** was slightly larger than that of **23**, indicating that adduct **16** was probably the epimer formed in greatest amount in the Diels–Alder step.

Since a number of chemical transformations were required in proving the structures of adducts **16** and **17**, and since it was never possible to separate compounds epimeric at the ethyl-bearing carbon, we decided to confirm the above stereochemical results in a somewhat simpler system. Thus, Diels–Alder precursor **29** was prepared as outlined in Scheme I starting from diene alcohol **26**,[16] using the same methodology as described above.

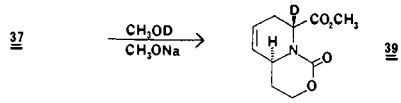
Pyrolysis of **29** in toluene at 215 °C produced a *single* cycloadduct **30** in 30% yield. The poor yield in this step is undoubtedly due to the tendency of diene **29** to readily polymerize. Adduct **30** was then hydrogenated to afford **31**, which upon basic hydrolysis produced the crystalline acid **32**. In order to be certain that ester group epimerization did not occur during the hydrolysis step, acid **32** was reesterified with diazomethane, producing **31**. The structure and configuration of acid **31** were unambiguously established as shown by single-crystal X-ray analysis.[17] Figure 1 shows an ORTEP plot of **31**.

(12) Loev, B.; Kormendy, M. F. *J. Org. Chem.* **1963**, *28*, 3421.
(13) Kelly, T. R.; Schmidt, T. E.; Haggerty, J. G. *Synthesis* **1972**, 544.
(14) Zoller, U.; Ben Ishai, D. *Tetrahedron* **1975**, *31*, 863.
(15) Cf. Kutney, J. P.; Ratcliffe, A. H. *Synth. Commun.* **1975**, *5*, 47.
(16) Oida, S.; Ohki, E. *Chem. Pharm. Bull.* **1969**, *17*, 1990.
(17) We are grateful to Marguerite Bernheim for carrying out X-ray structure determinations.



We next decided to investigate whether the stereochemical results in the two cyclizations described above were dependent upon the length of the chain connecting diene and dienophile. Therefore we prepared the homologated Diels–Alder precursor **36** as shown in Scheme II. Diene ester **33**, readily available to deconjugation of methyl sorbate,[18] was reduced with $LiAlH_4$ to diene alcohol **34**, which was transformed to acetate **36** again using the methodology employed in the above cases. On heating at 210 °C in toluene for 2 h, **36** cleanly cyclized (80% yield) to give bicyclic adduct **37**. As in the previous cases, none of the cis stereoisomer was detected. The structure of **37** was unambiguously established by a single-crystal X-ray analysis[17] on the derived acid **38**, formed by basic hydrolysis of the ester. An ORTEP drawing of **38** is shown in Figure 2.

It is evident from the crystal-structure data that the carbomethoxyl group of **38** is in a pseudo-axial orientation. Treatment of ester **37** with sodium methoxide in CH_3OD gave only the trans-deuterated product **39**. This experiment indicates that the thermodynamic product in this system is the one with the trans relationship of hydrogens α to nitrogen. One might explain this phenomenon by arguing that the cis isomer would be destabilized by an unfavorable $A^{1,3}$-strain interaction[19] between its pseudo-equatorial carbomethoxyl group and the carbamate carbonyl oxygen. A similar deuterium exchange was attempted on ester **30**, but led only to decomposition products.



Discussion

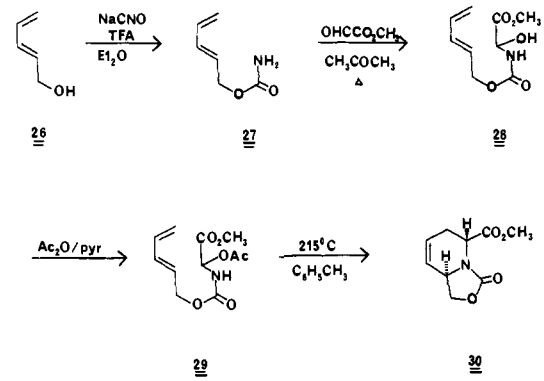
There are a number of problems in interpreting the stereochemical results of Diels–Alder reactions which utilize acyclic imino dienophiles.[8] One major difficulty is that the types of electron-deficient imines which are normally the most effective dienophiles are unstable and cannot be isolated.[5] Therefore, one cannot easily determine imine configuration. Another problem is that it is not possible to use product relative stereochemistry as a probe of reactant imine geometry since nitrogen lone-pair inversion results in loss of this information. For these reasons, an analysis of our results must necessarily be rather speculative.

We believe that Diels–Alder precursors such as **29** and **36** probably lose acetic acid thermally to give either an intermediate *Z*-imine **39** (an azamaleate) or an *E*-imine **40** (an azafumarate) (Scheme III). Although one would expect that azafumarate **40** would be more stable, it is not unreasonable that the thermal interconversion of **39** and **40** could be rapid relative to the rate of cycloaddition.[20] Thus, in principle, either **39** or **40** could be the actual reacting imine.

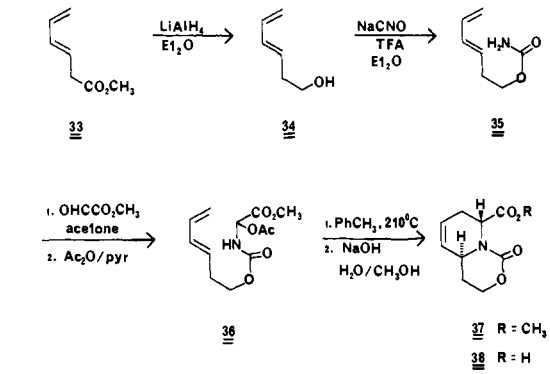
Azamaleate **39** can cyclize via transition states A or B (Scheme III). A has both carbomethoxyl and *N*-acylimine carbonyls endo and would lead to the cis cycloadduct **41**. Transition state B, which has both carbonyl groups exo, would afford the observed trans product **42**. Azofumarate **40** can also cyclize via two possible transition states. The trans cycloadduct **42** would result from transition state C, having the N-acyl group endo and the carbomethoxyl group exo. Alternatively, transition state D, which has the N-acyl group exo and the ester carbonyl endo, would give the cis isomer **41**. Based upon the observed products, our cycloadditions must go through either transition state B or C.

It seems likely that B, having both carbonyls exo, would be energetically unfavorable relative to A (and probably to C and D as well) since carbonyldiene secondary orbital effects would necessarily be precluded. A few examples are known of intramolecular "all-carbon" Diels–Alder cycloadditions forming 6/5 fused ring systems which apparently proceed via such exocarbonyl transition states.[21,22] Roush has offered an explanation for these

Scheme I



Scheme II



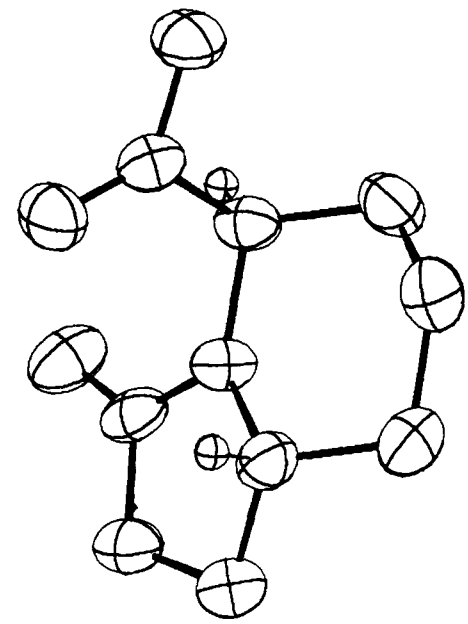
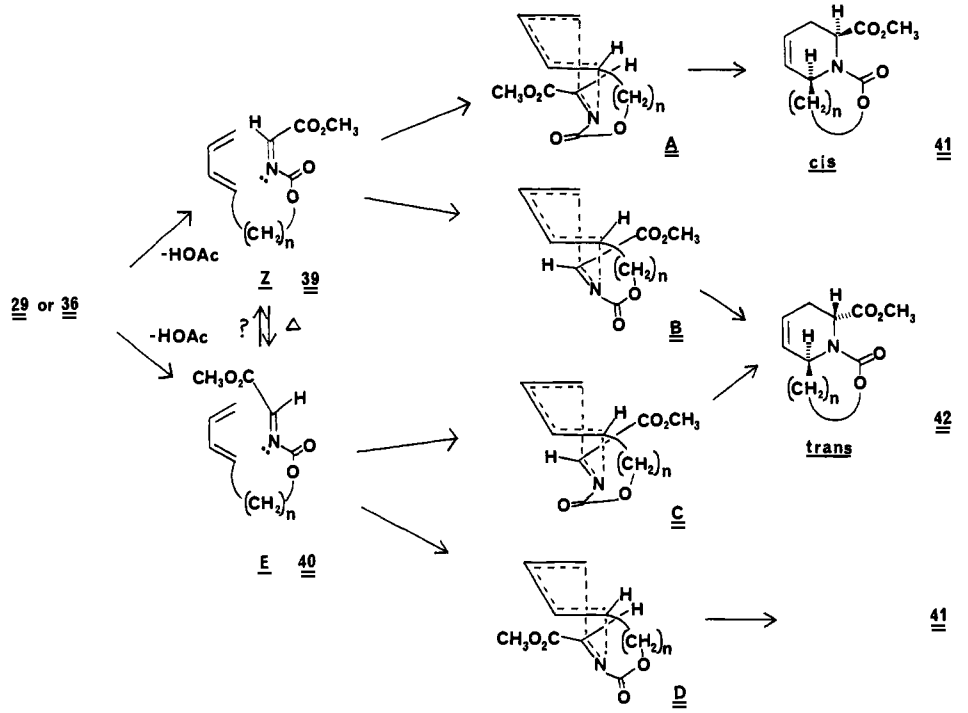


Figure 1. ORTEP plot of acid **32**. Hydrogens α to nitrogen are shown; all other hydrogens are omitted for clarity.

(18) Stevens, R. V.; Cherpeck, R. E.; Harrison, B. L.; Lai, J.; Lapalme, R. *J. Am. Chem. Soc.* **1976**, *98*, 6317.
(19) Johnson, F. *Chem. Rev.* **1968**, *68*, 375.
(20) Kalinowski, H. O.; Kessler, H. In "Topics in Stereochemistry", Allinger, N. L., Eliel, E. L., Eds.; Wiley-Interscience: New York, 1973; Vol. 7, p 295.
(21) Roush, W. R. *J. Org. Chem.* **1979**, *44*, 4008. We thank Dr. Roush for a preprint and helpful discussions.
(22) White, J. D.; Sheldon, B. G.; Solheim, B. A.; Clardy, J. *Tetrahedron Lett.* **1978**, 5189.

Scheme III



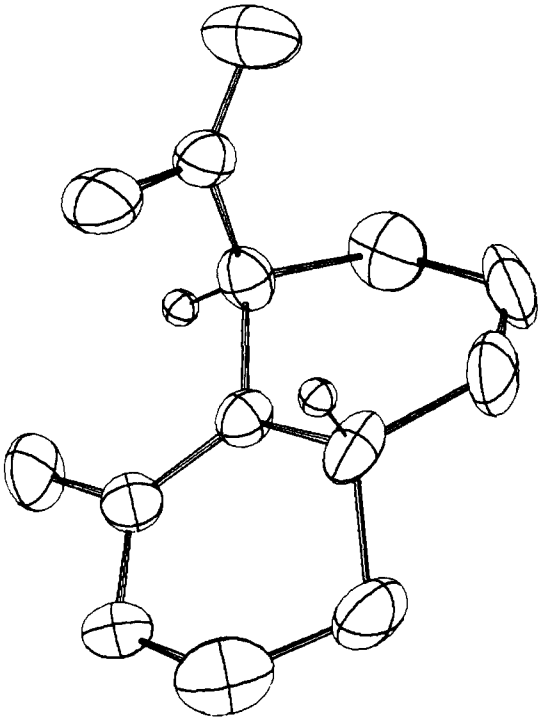
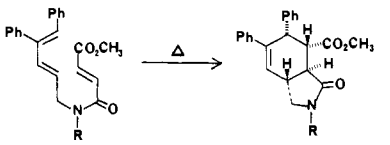


Figure 2. ORTEP plot of acid, **38**. Hydrogens α to nitrogen are shown; all other hydrogens are omitted for clarity.

exceptional cases[21] based upon subtle steric and conformational effects induced by the number of bridging atoms between diene and dienophile. We believe that an exo-azamaleate transition state as shown in B cannot reasonably be invoked in our cases, since we have shown that bridging chain length has no effect on product stereochemistry (vide supra). Since transition state A would lead to the incorrect product, we generally discount an azamaleate as being the reacting acylimine in our cycloadditions, and propose that these reactions proceed via an azafumarate **40** cyclizing through transition state C.

It is more difficult to explain why transition state C, leading to the observed trans product, is preferable to D, which would provide the unobserved cis cycloadduct. Krow has found in intermolecular cases that an N-acyl group on an imino dienophile generally has a very strong endo directing ability relative to a competing C-acyl function.[8] Intuitively, one might attribute this directing effect to better secondary orbital overlap of diene with the more electron deficient N-acyl group. However, there is as yet no theoretical basis for this supposition.

Interestingly, in similar "all carbon" intramolecular Diels–Alder reactions of fumarate dienophiles the terminal carbonyl is always the endo director.[4a] Thus, in the conversion of **43** to **44**, a transition state such as D (N: = CH) must be in operation.[23,24] In our imino cases, the product stereochemistry is reversed, since the "internal" carbonyl is apparently the endo director.[25]



Summary

We have demonstrated in the cases examined to date that intramolecular imino Diels–Alder cycloadditions are totally stereoselective. Similar intermolecular imino Diels–Alder reactions are less stereoselective, normally giving product mixtures.[8a] The method seems ideal for synthesis of tetrahydropyridines having the trans relationship of hydrogens α to nitrogen. We are thus attempting to use this methodology in a total synthesis of anhydrocannisbisativene (**2**). This work will be reported shortly.

Experimental Section

Melting points were determined on a Fisher-Johns apparatus and are uncorrected. Infrared spectra were recorded on a Perkin-Elmer Model 710B, Model 137, or Model 197 spectrophotometer. ^{1}H nuclear magnetic resonance spectra (60 MHz) were recorded on either a Perkin-Elmer R12B, Varian A-60A, or Varian EM-360 NMR spectrometer. ^{1}H NMR

(23) Gschwend, H. W. *Helv. Chim. Acta* **1973**, *56*, 1763.
(24) Cox, M. T. *J. Chem. Soc., Chem. Commun.* **1975**, 903.
(25) A less likely explanation, which we cannot rule out at present, is that these imino Diels–Alder reactions are reversible, and thus give the thermodynamic products. Although we have shown that **37**, in fact, has the thermodynamic stereochemistry, we feel it is probably also the kinetic Diels–Alder product.

spectra at 100 MHz were obtained on either a Varian XL-100 or a JEOL PFT-100 Fourier transform NMR spectrometer, and at 200 MHz on a Brüker WP 200 spectrometer. Chemical shifts are reported in delta (δ) units, using tetramethylsilane as an internal standard. The multiplicity of signals is reported as follows: singlet, s; doublet, d; triplet, t; quartet, q; multiplet, m. All spectra were taken in deuteriochloroform. Carbon-13 magnetic resonance (^{13}C NMR) spectra were obtained on a Varian CFT-20 NMR spectrometer. Elemental analyses were performed by Spang Microanalytical Laboratory, Eagle Harbor, MI, and by MicroTech Laboratories, Inc., Skokie, IL. Low-resolution mass spectra (MS) were obtained at 70 eV by electron impact (EI) on a CEC 21-104 mass spectrometer, or an Associated Electrical Industries, Ltd. MS-902 double-focusing mass spectrometer. Analytical and preparative thin-layer chromatography was performed using E. M. Merck Silica Gel 60 PF-254, and column chromatography was done using 70-230 mesh Silica Gel 60 (E. M. Merck) as the stationary phase. HPLC analyses were done on a Waters Model 440 Liquid Chromatograph equipped with a UV detector using either a μBondapack C_{18} or a μAlkyl Phenyl prepacked reverse phase column.

Propionylmethylenetriphenylphosphorane (8). A stirred suspension of methyltriphenylphosphonium bromide (17.85 g, 50 mmol) in anhydrous ether (200 mL) under nitrogen was treated with a 1.6 M solution of *n*-butyllithium in hexane (33 mL, 52.8 mmol) over 3 min. After being stirred at room temperature for 0.5 h, the resulting orange-red solution was added during 5 min to a stirred ice-cold solution of propionyl chloride (5.55 g, 60 mmol) in anhydrous ether (100 mL). A solid immediately precipitated. The supernatant liquid was decanted, and the solid was dissolved in water (200 mL) and treated with 15% NaOH (100 mL) giving a solid precipitate. The mixture was extracted with two 250-mL portions of CH_2Cl_2. The organic phase was dried over anhydrous $MgSO_4$, concentrated in vacuo to a pasty solid mass, and dried in a vacuum oven at 70 °C for 32 h to afford 7.28 g (44%) of the crude ylide **8**. An analytical sample was prepared by recrystallization of **8** from absolute ethanol: mp 206–207 °C; IR ($CHCl_3$) 1538, 1398, 1110, 870 cm^{-1}; ^1H NMR δ 1.17 (3 H, t, J = 7.5 Hz), 2.31 (2 H, q, J = 7.5 Hz), 3.45–3.90 (1 H, m), 7.30–7.72 (15 H, complex m); mass spectrum, m/e (relative intensity) 332 [M^+] (16), 303 (100), 275 (73.5).

Anal. Calcd for $C_{22}H_{21}OP$: C, 79.50, H, 6.37. Found: C, 79.28; H, 6.39.

(*E*)-4,6-Heptadien-3-one (7). Procedure A. A stirred ice-cold solution of phosphorus ylide **8** (5.9 g, 17.77 mmol) in anhydrous CH_2Cl_2 (40 mL) under nitrogen was treated with a solution of freshly distilled acrolein (1.5 g, 26.79 mmol) in anhydrous CH_2Cl_2 (10 mL) over 5 min, and the resulting solution was stirred at room temperature for 17 h. The solvent was removed in vacuo, and the residue was thoroughly triturated with anhydrous ether. The ethereal solution was filtered and concentrated in vacuo to an oily residue, which on bulb-to-bulb distillation (Kugelrohr apparatus) under reduced pressure (15–20 torr, oven temperature 75–82 °C) afforded 0.501 g (24%) of ketone **7**: IR (film) 1692, 1670, 1622, 1598, 928 cm^{-1}; ^1H NMR δ 1.12 (3 H, t, J = 7 Hz), 2.59 (2 H, q, J = 7 Hz), 5.48 (2 H, m), 6.05–6.60 (2 H, m), 6.95–7.23 (1 H, dd, J = 11, 17 Hz).

Procedure B. To a stirred solution of anhydrous stannic chloride (92 mL, 0.8 mol) in CH_2Cl_2 (500 mL) under nitrogen was added a solution of propionyl chloride (75 mL, 0.865 mol) in CH_2Cl_2 (400 mL). The solution was cooled in a dry ice–acetonitrile bath at −42 °C, and a dry ice–acetonitrile condenser was attached to the flask. Simultaneously, butadiene (130 mL) was condensed under nitrogen into a flask equipped with a dry ice–acetonitrile condenser and cooled in a dry ice–acetonitrile bath. The cooling bath and condenser were removed, and the latter flask was connected by means of a Tygon tube to the reaction flask so that the butadiene evaporated and recondensed into the reaction mixture during about 1.5 h. The resulting yellow solution was allowed to warm to −10 °C over about 1 h, and was carefully poured into a mixture of dilute HCl and ice (700 mL). The organic phase was separated and washed successively with 500-mL portions of water and brine. Drying the solution over anhydrous $MgSO_4$ and removal of the solvent in vacuo resulted in about 200 mL of a yellow liquid from which HCl gas soon started evolving as it darkened gradually. An excess of $CaCO_3$ was carefully added to the product, the flask was equipped with a reflux condenser, and the mixture was rapidly stirred and heated in an oil bath at 80–85 °C for 30 h. The dark liquid was decanted and distilled under reduced pressure through a 15-cm Vigreaux column. Collection of the fraction distilling between 98 and 103 °C (15–20 torr) afforded 39.96 g (42%) of the crude ketodiene **7** which without further purification was immediately reduced to the corresponding alcohol purification. The product gave IR and ^1H NMR spectra identical with those reported for the material obtained by procedure A.

(*E*)-4,6-Heptadien-3-ol (9). A stirred suspension of $LiAlH_4$ (4.94 g, 0.141 mol) in anhydrous ether (150 mL) under nitrogen was cooled in an ice-water bath and treated with a solution of ketone **8** (15.5 g, 0.141 mol) in anhydrous ether (100 mL) over 0.5 h, and the resulting mixture was stirred at room temperature for 3 h. The flask was cooled in an ice-water bath and the mixture was treated successively while stirring with water (10 mL), 15% NaOH (20 mL), and water (50 mL). The supernatant ethereal solution was decanted, and the solid residue was washed with ether. The combined ether phase was dried over anhydrous $MgSO_4$ and concentrated in vacuo to a yellowish oil. Fractional distillation of the crude product through a 10 cm Vigreaux column afforded 14.51 g (92%) of the alcohol: bp 26–30 °C (0.08 torr); IR (film) 3360, 1602, 902 cm^{-1}; ^1H NMR δ 0.93 (3 H, t, J = 7 Hz), 1.55 (2 H, m), 2.49 (1 H, s), 3.92–4.11 (1 H, m), 4.97–5.30 (2 H, m), 5.49–5.78 (1 H, m), 6.00–6.48 (2 H, m).

Anal. Calcd for $C_7H_{12}O$: C, 74.95; H, 10.78. Found: C, 75.06; H, 10.84.

(*E*)-1-Ethyl-2,4-pentadienyl Carbamate (10). A stirred solution of alcohol 9 (0.56 g, 5 mmol) in ether (3 mL) was treated with sodium cyanate (0.65 g, 10 mmol).[12] Trifluoroacetic acid (0.77 mL, 10 mmol) was added, and the mixture was stirred very slowly for 16 h. Water (2 mL) was added, and the mixture was stirred rapidly for 30 s. The organic phase was separated, diluted with ether (5 mL), washed successively with 5-mL portions of water and brine, dried over anhydrous $MgSO_4$, and concentrated in vacuo to give a colorless oil which solidified to a white mass. Purification of this material by chromatography on silica gel (25 g), eluting with hexane–ethyl acetate (4:1), afforded 0.424 g (55%) of carbamate **10** (mp 58–61 °C). A small amount of product was further purified by sublimation in vacuo (mp 60–61.5 °C): IR ($CHCl_3$) 1720, 1605, 908 cm^{-1}; ^1H NMR δ 0.92 (3 H, t, J = 7 Hz), 1.61 (2 H, m), 4.74 (2 H, br s), 5.08 (2 H, d, J = 7 Hz), 5.20–5.71 (2 H, m), 6.07–6.40 (2 H, m); mass spectrum, m/e (relative intensity) 155 [M^+] (9.9), 154 (100), 95 (2.2). The carbamate was stored under nitrogen in a freezer, but after 1 month was found to have polymerized to a dark gummy insoluble material.

Methyl [[[(1-Ethyl-2,4-pentadienyl)oxy]carbonyl]amino]hydroxyacetate (11). A stirred solution of carbamate **10** (1.65 g, 10.68 mmol) and methyl glyoxylate[13] (1.90 g, 21.59 mmol) in acetone (55 mL) was heated at reflux for 18 h, and the solvent was removed in vacuo. The residue was taken up in ether (40 mL), washed with four 25-mL portions of H_2O, dried over anhydrous $MgSO_4$, and concentrated in vacuo to give an oily residue that solidified to a pale white mass. Purification of this material by chromatography on silica gel (50 g), eluting with hexane–ethyl acetate (4:1), gave **11** as a white solid (2.15 g, 83%; mp 65–67 °C): IR ($CHCl_3$) 3430, 3340, 1750, 1705, 1605, 908 cm^{-1}; ^1H NMR δ 0.90 (3 H, t, J = 7 Hz), 1.65 (2 H, m), 3.83 (3 H, s), 4.40 (1 H, br s), 5.02–5.70 (5 H, m), 5.96–6.40 (3 H, m).

Anal. Calcd for $C_{11}H_{17}NO_5$: C, 54.31; H, 7.04; N, 5.76. Found: C, 54.39; H, 7.01; N, 5.82.

Methyl [[[(1-Ethyl-2,4-pentadienyl)oxy]carbonyl]amino]methoxyacetate (12). A stirred solution of alcohol **11** (171.4 mg, 0.705 mmol) in anhydrous methanol (5 mL) was treated dropwise with trifluoroacetic acid (0.5 mL, 6.5 mmol) and the solution was heated at reflux in an oil bath for 20 h. The resulting mixture was cooled and concentrated in vacuo. The residue was taken up in ether (5 mL), washed with two 5-mL portions of water, dried over anhydrous $MgSO_4$, and concentrated in vacuo to a viscous oily residue. Purification of this oil by preparative TLC on silica gel, eluting with benzene–ethyl acetate (4:1), afforded 110 mg (61%) of the methyl ether **12**: IR (film) 3350, 1745 cm^{-1} (broad); ^1H NMR δ 0.90 (3 H, t, J = 7 Hz), 1.62 (2 H, m), 3.45 (3 H, s), 3.82 (3 H, s), 5.02–6.38 (8 H, m); mass spectrum, m/e (relative intensity) 226 (10), 198 (58).

Methyl (Acetyloxy)[[[(1-ethyl-2,4-pentadienyl)oxy]carbonyl]amino]-acetate (13). A stirred solution of the alcohol **11** (0.69 g, 2.85 mmol) and anhydrous pyridine (6.9 mL) in CH_2Cl_2 (40 mL) under nitrogen was treated with acetic anhydride (4 mL, 42.4 mmol) over 2 min. The solution was heated at reflux for 16 h. The mixture was cooled and poured into ice–water (30 mL). The organic phase was separated and washed successively with 30-mL portions of dilute HCl, water, saturated $NaHCO_3$, water, and brine. The extract was dried over anhydrous $MgSO_4$ and concentrated in vacuo to give 0.724 g (89%) of crude acetate **13** as a slightly yellowish oil that was used immediately without further purification: IR (film) 3350, 1740 (broad), 1605 cm^{-1}; ^1H NMR δ 0.90 (3 H, t, J = 7 Hz), 1.65 (2 H, m), 2.10 (3 H, s), 3.81 (3 H, s), 5.02–5.72 (5 H, m), 6.04–6.38 (3 H, m).

Methyl [[[(1-Ethyl-2,4-pentadienyl)oxy]carbonyl]amino][[(phenylamino)carbonyl]oxy]acetate (14). A stirred solution of alcohol **11** (102 mg, 0.4197 mmol) in CH_2Cl_2 (1.5 mL) under nitrogen was treated with phenyl isocyanate (0.18 mL, 1.658 mmol). The solution was heated at reflux for 18 h, cooled, and treated with water (4 mL); the mixture was stirred rapidly for a few minutes to hydrolyze any remaining isocyanate. The mixture was diluted with CH_2Cl_2 (5 mL), and the organic phase was

separated and washed successively with 5-mL portions of water and brine. The solution was dried over anhydrous $MgSO_4$ and concentrated in vacuo to give 204 mg (99%) of **14** as a colorless oil that was used immediately without further purification: IR (film) 3350 (broad), 1745 cm^{-1} (broad); ^1H NMR δ 0.90 (3 H, t, J = 7 Hz), 1.64 (2 H, m), 3.80 (3 H, s), 4.98–5.26 (3 H, m), 5.42–5.68 (2 H, m), 6.03–6.48 (4 H, m), 6.90–7.47 (5 H, m).

Methyl [[[(1-Ethyl-2,4-pentadienyl)oxy]carbonyl]amino][[(methylamino)carbonyl]oxy]acetate (15). A stirred solution of alcohol **11** (539 mg, 2.218 mmol) in anhydrous CH_2Cl_2 (6 mL) under nitrogen was treated with methyl isocyanate (0.65 mL, 11.03 mmol) and heated at reflux in an oil bath for 24 h. The solution was cooled and treated with water (7.5 mL) with rapid stirring to hydrolyze any remaining isocyanate. The organic phase was separated, washed successively with 4-mL portions of dilute HCl, saturated $NaHCO_3$, water, and brine, dried over anhydrous $MgSO_4$, and concentrated in vacuo to an oil that changed into a white foam under high vacuum. The crude product was found to be of acceptable purity by TLC and NMR, and was used immediately without further purification: 592 mg (89%); IR ($CHCl_3$) 3370 (broad), 1738 cm^{-1} (broad); ^1H NMR δ 0.90 (3 H, t, J = 7 Hz), 1.64 (2 H, m), 2.77 (3 H, d, J = 5 Hz), 2.98 (2 H, m), 3.80 (3 H, s), 5.05–5.75 (5 H, m), 6.00–6.58 (2 H, m).

Diels–Alder Reactions. General Procedure A: Solvent at Reflux. A solution of the acylimine precursor in a large volume of solvent [molar ratio (solvent/solute) > 250:1] was heated at reflux for the desired period of time. The solution was cooled, and the solvent was removed. The residue was chromatographed on preparative silica gel plates, eluting with hexane–ethyl acetate (1:1). The results are listed in Table I.

General Procedure B: Hot Tube. A vertical Pyrex tube packed with glass beads or glass helices or alternating layers of both, and jacketed with electric heating coil, was equipped with a Hershberg addition funnel, a nitrogen inlet tube, and a receiving flask with a side arm connected to a bubbler. The temperature at the tube walls was measured by a thermocouple. The column was slowly flushed with nitrogen and heated at the desired temperature while passing pure solvent dropwise through it. Once thermal equilibrium at the desired temperature was achieved, a dilute solution of the acylimine precursor in the same solvent was slowly dripped onto the column, and the receiving flask at the bottom was cooled in ice to condense the vapors. The resulting solution was concentrated and the product was isolated by preparative TLC in the same manner as in Procedure A above. The results are listed in Table I.

General Procedure C: Sealed Tube. A solution of the imine precursor in a large volume of solvent was placed in a thick-walled Pyrex tube. The tube was flushed with nitrogen, cooled in a dry ice–chloroform bath, and sealed. The tube was heated in an oil bath at the temperature of choice for the desired period of time. Purification of the product was performed in the same manner as in Procedure A above. The results are listed in Table I.

Methyl (1α,5β,8aβ)-1-Ethyl-1,5,6,8a-tetrahydro-3-oxo-3*H*-oxazolo[3,4-*a*]pyridine-5-carboxylate (16) and Methyl (1α,5α,8aα)-1-Ethyl-1,5,6,8a-tetrahydro-3-oxo-3*H*-oxazolo[3,4-*a*]pyridine-5-carboxylate (17). The adduct mixture was obtained as an oil after preparative TLC on silica gel of the crude product obtained by any of the procedures A, B, or C: R_f 0.38, hexane–ethyl acetate (1:1); IR (film) 1755–1740, 701 cm^{-1}; ^{H} NMR δ 1.05 (3 H, dt, $J_1 = J_2$ = 7 Hz), 1.42–1.98 (2 H, dm, $J_1 = J_2$ = 7 Hz), 2.59 (2 H, m), 3.76 (3 H, s), 3.96–4.82 (3 H, m), 5.54–5.98 (2 H, m); ^{13}C NMR δ 8.51, 9.35, 23.60 (2 lines), 25.35, 25.87, 26.79, 29.33, 49.60, 50.25, 52.10, 53.11, 54.91, 79.13, 80.41, 82.06, 122.32, 124.36, 124.58, 125.67, carbonyl region not scanned; mass spectrum, m/e 225 [M^+], 181.

Anal. Calcd for $C_{11}H_{15}NO_4$: C, 58.66; H, 6.71; N, 6.22. Found: C, 58.63; H, 6.69; N, 6.11.

Preparation of Epimeric Dihydroadducts 18. The mixture of esters **16/17** (176 mg, 0.783 mmol) in ethyl acetate (15 mL) and 5% Pd/C (167 mg) was stirred under hydrogen (1 atm) at room temperature for 3 h. Filtration of the reaction mixture through Celite and concentration of the filtrate in vacuo afforded 176 mg (99%) of **18** as a colorless oil: IR (film) 1770–1730 cm^{-1} (broad); ^1H NMR δ 1.04 (3 H, t, J = 7 Hz), 1.20–2.30 (8 H, m), 3.75 (3 H, s), 3.85–4.64 (3 H, m).

Hydrolysis of Esters 18. A stirred solution of the mixture of saturated esters **18** (51 mg, 0.225 mmol) in methanol (5 mL) was treated with 5% aqueous NaOH (0.9 mL). After being stirred at room temperature for 2.5 h, the solution was cooled in an ice bath and acidified carefully with dilute HCl. The mixture was extracted with five 10-mL portions of ethyl acetate, and the combined organic extract was dried over anhydrous $MgSO_4$ and concentrated in vacuo to leave an oily residue that changed to a white solid on standing (46 mg, 95%). A small amount was recrystallized from water to give tiny needles: mp 125.5–127.5 °C; IR ($CHCl_3$) 1730–1690 cm^{-1} (broad); ^1H NMR δ 1.05 (3 H, t, J = 7 Hz), 1.20–2.32 (8 H, m), 3.86–4.68 (3 H, m), 8.51 (1 H, s); mass spectrum, m/e (relative intensity) 213 [M^+] (1.5), 169 (100).

Anal. Calcd for $C_{10}H_{15}NO_4$: C, 56.33; H, 7.09; N, 6.57. Found: C, 56.16; H, 6.90; N, 6.41.

Preparation of Acid Chlorides 20. A stirred suspension of the mixture of epimeric acids **19** (50 mg, 0.235 mmol) in anhydrous ether (2 mL) was treated with phosphorus pentachloride (100 mg, 0.48 mmol) and the mixture was warmed in a water bath at 40–45 °C in a tightly stoppered flask for 0.5 h. The solvent was removed in vacuo, and the residue was stirred rapidly with anhydrous hexane (3 mL) for 5 min to precipitate the excess PCl_5. The mixture was filtered and concentrated in vacuo to afford 49 mg (91%) of the acid chloride as a colorless oil that solidified to colorless prisms on standing: IR (film) 1802, 1740 cm^{-1}; ^1H NMR δ 1.05 (3 H, t, J = 7 Hz), 1.20–2.04 (6 H, m), 2.28–2.59 (2 H, m), 3.84–4.90 (3 H, m).

Preparation of *p*-Nitrobenzyl Esters 21. A stirred solution of the mixture of acid chlorides **20** (47 mg, 0.202 mmol) in anhydrous THF (2 mL) under nitrogen was treated with triethylamine (0.07 mL, 0.502 mmol), and the resulting white suspension was treated with 4-nitrobenzyl alcohol (40 mg, 0.261 mmol). After being stirred at room temperature for 0.5 h, the mixture was heated in a water bath kept at 50–55 °C for 5 h and then was stirred at room temperature for 13 h. The mixture was diluted with ether (10 mL) and washed successively with 10-mL portions of water, dilute HCl, saturated $NaHCO_3$, water, and saturated brine. The organic phase was dried over anhydrous $MgSO_4$, filtered, and concentrated in vacuo to a yellow oily residue. Purification of the crude product by preparation TLC on silica gel eluting with benzene–acetone (9:1) afforded 40 mg (57%) of the *p*-nitrobenzyl esters **21** as a slightly yellowish oil: IR (film) 1745–1710 cm^{-1} (broad); ^1H NMR δ 1.04 (3 H, m), 1.20–2.35 (8 H, m), 4.03 (1 H, m), 4.42 (1 H, m), 4.65 (1 H, m), 5.29 (2 H, s), 7.49 (2 H, d, J = 8 Hz), 8.19 (2 H, d, J = 8 Hz).

The mixture of isomers could be separated by HPLC on an analytical scale on either a μBondapack C_{18} or a μAlkyl Phenyl prepacked reverse phase column, with water–acetonitrile (70:30) as the elution solvent. Base-line separation could be achieved only by recycling five times. The isomer ratio in the mixture was determined from several runs as 55:45. All attempts to perform a preparative scale separation under similar conditions were unsuccessful.

Methyl (1α,5β,8aβ)-1-Ethylhexahydro-3-oxo-3*H*-oxazolo[3,4-*a*]-pyridine-5-acetate (22) and Methyl (1α,5α,8aα)-1-Ethylhexahydro-3-oxo-3*H*-oxazolo[3,4-*a*]-pyridine-5-acetate (23). A solution of acid chlorides **20** (49 mg, 0.213 mmol) in anhydrous ether (1 mL) was added to an ice-cold freshly prepared solution of diazomethane (ca. 10 equiv) in ether (4 mL), and the mixture was stirred at room temperature for 8 h. Concentration of the mixture in vacuo afforded 40 mg (80%) of the crude diazoketone as a colorless viscous oil that was used immediately in the next step: IR (film) 2100, 1760, 1740 cm^{-1}.

A stirred solution of the freshly prepared diazoketone (40 mg, 0.171 mmol) in absolute CH_3OH (3 mL) was treated with freshly prepared silver(I) oxide (2 mg). After 15 min another portion of Ag_2O (1 mg) was added, and the mixture was stirred at room temperature for 30 h. Filtration of the mixture through Celite and concentration of the filtrate in vacuo left a dark oily residue. Chromatography of the crude product on silica gel (1 g), eluting with hexane–ethyl acetate (1:1), afforded 22 mg (55%) of the mixture of methyl esters **22** and **23** as a colorless oil: IR (film) 1745, 1730 cm^{-1}; ^1H NMR δ 1.05 (3 H, dt, $J_1 = J_2$ = 7 Hz), 1.22–1.94 (8 H, unresolved m), 2.50–2.70 (2 H, m), 3.75 (3 H, s), 3.79–4.60 (3 H, m).

Reaction of Authentic Esters 3, 4, and 5 with *N,N'*-Carbonyldiimidazole. General Procedure. A stirred solution of the amino ester in anhydrous THF under nitrogen was heated at reflux and treated with a solution of carbonyldiimidazole (5 equiv) in anhydrous THF during a period of 30 h. Refluxing was continued for an additional 15 h, and the mixture was cooled and concentrated in vacuo. The residue was taken up in ethyl acetate and washed with dilute HCl. The organic phase was dried over anhydrous $MgSO_4$ and concentrated in vacuo. The desired products were isolated by preparative TLC of the crude oily products on silica gel eluting with hexane–ethyl acetate (1:1).

22: IR (film) 2950, 2860, 1740, 1410, 1260, 1030, 965, 800, 765, 655 cm^{-1}; NMR[28] δ 1.04 (3 H, t, J = 7.35 Hz), 1.25–1.87 (8 H, m), 2.56 (B of ABX, 1 H, q, J_{AB} = 14.49 Hz, J_{BX} = 7.70 Hz), 2.67 (A of ABX, 1 H, q, J_{AX} = 8.34 Hz), 3.69 (3 H, s), 3.70–3.78 (1 H, m), 4.30–4.48 (1 H, m), 4.49–4.54 (1 H, m); mass spectrum, m/e (relative intensity) 242 (0.7) [M^+ + 1], 241 (0.3) [M^+], 197 (19.8), 182 (100), 168 (41.4), 124 (95.5), 108 (16.8), 96 (24.3), 82 (68.7), 70 (16.1), 55 (68.4); R_f 0.22, hexane–ethyl acetate (1:1).

24: NMR δ 1.01 (3 H, t, J = 7.35 Hz), 1.25–2.00 (8 H, m), 2.54 (1 H, dd, J = 5.15, 16.0 Hz), 3.22–3.48 (1 H, m), 3.56–3.69 (1 H, m), 3.71 (3 H, s), 3.74–3.94 (1 H, m); R_f 0.30, hexane–ethyl acetate (1:1).

25: IR (film) 2950, 2865, 1750, 1435, 1380, 1355, 1225, 1200, 1165, 980, 780 cm^{-1}; NMR δ 1.02 (3 H, t, J = 7.35 Hz), 1.25–1.76 (8 H, m),

1.95–2.00 (1 H, m), 2.69 (1 H, dd, J = 6.71, 16.78 Hz), 3.47 (1 H, dd, J = 7.02, 16.78 Hz), 3.56–3.65 (1 H, m), 3.70 (3 H, s), 4.29–4.35 (1 H, m); mass spectrum, m/e (relative intensity) 241 (2.7) [M^+], 210 (8.9), 197 (13.1), 182 (26.4), 181 (26.3), 168 (16.9), 155 (21.3), 154 (19.2), 124 (33.9), 122 (17.5), 109 (21.8), 96 (21.8), 86 (63.2), 84 (100), 82 (48), 81 (25.2), 67 (21); R_f 0.30, hexane–ethyl acetate (1:1).

Preparation of Carbamate 27. A stirred solution of pentadienol **26**[16] (4.2 g, 0.05 mol) in ether (100 mL) was treated with sodium cyanate (6.5 g, 0.1 mol). Trifluoroacetic acid (7.7 mL, 0.1 mol) was added over 1 min, and the heterogeneous mixture was stirred very slowly for 20 h.[12] Water (20 mL) was added, and the mixture was stirred rapidly for 5 min. The organic phase was separated, washed with water (10 mL) followed by brine (10 mL), dried over anhydrous $MgSO_4$, and concentrated in vacuo to a colorless oil. This material solidified to a white mass on standing that was found to be of acceptable purity by TLC and NMR for further reactions (4.45 g, 70%). An analytical sample was prepared by sublimation of **27** in vacuo (mp 62.5–64 °C). The carbamate **27** decomposed to a brownish insoluble gum after about 2 weeks on storage in the freeze under nitrogen: IR ($CHCl_3$) 3430, 1720, 1660, 1615, 908 cm^{-1}; ^1H NMR δ 4.45–6.45 (complex m).

Anal. Calcd for $C_6H_9NO_2$: C, 56.68; H, 7.13. Found: C, 56.24; H, 6.74.

Methyl [[[(*E*)-(2,4-Pentadienyl)oxy]carbonyl]amino]hydroxyacetate (28). A stirred solution of carbamate **27** (1.39 g, 10.95 mmol) and methyl glyoxylate[13] (2 g, 22.73 mmol) in acetone (55 mL) was heated at reflux in an oil bath for 18 h. The solvent was removed in vacuo, and the residue was taken up in ether (40 mL) and washed with four 25-mL portions of water. The organic phase was dried over anhydrous $MgSO_4$ and concentrated in vacuo to an oily residue that solidified on standing to a slightly yellowish solid. Purification of the crude product by chromatography on silica gel (50 g), eluting with hexane–ethyl acetate (4:1), afforded 1.178 g (50%) of the alcohol **28** as a white fluffy solid (mp 58–60 °C). All attempts to recrystallize the product were unsuccessful: IR ($CHCl_3$) 3500–3300, 1720, 1660, 1600, 907 cm^{-1}; ^1H NMR δ 3.90 (3 H, s), 4.65 (2 H, d, J = 7 Hz), 5.10–6.40 (7 H, m).

Anal. Calcd for $C_9H_{13}NO_5$: C, 50.23; H, 6.09; N, 6.51. Found: C, 50.29; H, 6.28; N, 6.40.

Methyl (Acetyloxy)[[[(*E*)-(2,4-pentadienyl)oxy]carbonyl]amino]acetate (29). A stirred solution of the alcohol **28** (0.935 g, 4.35 mmol) and anhydrous pyridine (10.5 mL) in CH_2Cl_2 (55 mL) under nitrogen was treated dropwise with acetic anhydride (6.2 mL, 65.77 mmol) over 15 min. The solution was heated at reflux for 16 h. The mixture was cooled and poured into ice–water (35 mL), and the organic phase was separated and washed successively with 35-mL portions of dilute HCl, water, saturated $NaHCO_3$, water, and brine. The solution was dried over anhydrous $MgSO_4$ and concentrated in vacuo to give the desired product as a pale yellow oil (0.936 g, 84%): IR (film) 1753–1720 cm^{-1} (broad); ^1H NMR δ 2.10 (3 H, s), 3.79 (3 H, s), 4.62 (2 H, d, J = 6.5 Hz), 5.02–6.40 (6 H, m).

Methyl *cis*-1,5,6,8a-Tetrahydro-3-oxo-3*H*-oxazolo[3,4-*a*]pyridine-5-carboxylate (30). The adduct was obtained as an oil (30%) after preparative TLC on silica gel of the crude product obtained by pyrolysis of **29** by procedure C described above ($C_6H_5CH_3$, 215 °C, 2 h): IR (film) 1770–1720 cm^{-1} (broad); ^1H NMR δ 2.58 (2 H, m), 3.77 (3 H, s), 3.85–4.01 (1 H, t, J = 6 Hz), 4.42–4.80 (3 H, m), 5.55–5.93 (2 H, m); ^{13}C NMR δ 25.86, 29.70, 50.08, 50.24, 52.60, 68.43, 124.97, 157.19, 170.77.

Anal. Calcd for $C_9H_{11}NO_4$: C, 54.81; H, 5.62; N, 7.10. Found: C, 54.51; H, 5.77; N, 7.02.

***cis*-Hexahydro-3-oxo-3*H*-oxazolo[3,4-*a*]pyridine-5-carboxylic Acid (32).** A mixture of the ester **30** (86 mg, 0.437 mmol) in ethyl acetate (5 mL) and 5% Pd/C (93 mg) was stirred under an atmosphere of hydrogen (1 atm) at room temperature for 2.5 h. Filtration of the reaction mixture through Celite, and concentration of the filtrate in vacuo, afforded 85 mg (98%) of the product as a colorless oil: IR (film) 2955, 1770–1720 (broad), 1420, 1045, 765 cm^{-1}; ^1H NMR δ 1.15–1.98 (6 H, m), 3.78 (3 H, s), 3.87–4.16 (2 H, m), 4.39–4.64 (2 H, m).

A stirred solution of ester **31** (51 mg, 0.256 mmol) in methanol (5 mL) was treated with 5% aqueous NaOH (1 mL). After being stirred for 2.5 h at room temperature, the solution was cooled in an ice bath, acidified carefully with dilute HCl, and extracted with five 10-mL portions of ethyl acetate. The combined organic extract was dried over anhydrous $MgSO_4$, filtered, and concentrated in vacuo to a colorless oil that solidified on standing. Recrystallization of this product from benzene–ethyl acetate (9:1) afforded 45 mg (95%) of acid **32**. A second recrystallization from benzene–ethyl acetate (5:1) afforded colorless prisms (mp 122.5–124 °C) which were used for the X-ray structure analysis: IR ($CHCl_3$) 3500–3200 (broad), 1765–1720 cm^{-1} (broad); ^1H NMR δ 1.16–1.97 (6 H, m), 3.88–4.20 (2 H, m), 4.40–4.68 (2 H, m), 11.75 (1 H, br s).

X-ray Crystal Structure Determination of Carboxylic Acid (32).[26] A crystal was mounted in a random orientation on a CAD-4 four-circle counter diffractometer (Enraf-Nonius). Unit cell dimensions were determined from 25 reflections at moderate 2θ angles indicated on an orthorhombic cell of dimensions: a = 10.421 (2) Å, b = 13.220 (4) Å, c = 6.270 (5) Å, and γ = 863.81 (1) Å^3. The observed volume is consistent with that expected for Z = 4, with p_0 = 1.4 g/cm^3. Application of the zero-moment test of Howells, Phillips, and Rogers[27] indicated an acentric cell and the systematic absences of $h0l$ for $h = 2n + 1$ and $0kl$ for $k + l = 2n + 1$ uniquely determined the space group as $Pna2_1$.

A graphite crystal incident beam monochromator was used with Mo $K\alpha_1$ radiation [λ(Mo $K\alpha_1$) 0.70930 Å] and the data collection at a take-off angle of 2.80°. A total of 2175 independent reflections were collected out to 2θ = 70°, and of these 571 had intensities with $I > 3\sigma(I)$ and were considered observed. These data were corrected for Lorentz and polarization factors and used in the refinement of the structure.

The starting positions for atoms of both rings were obtained from a Multan E-map synthesis where E_{min} = 1.60. Isotropic refinement of these positions, using full-matrix least-squares, yielded R_1 = 0.321 and R_2 = 0.381. Subsequent different Fouriers located the remaining non-hydrogen atoms. Isotropic least-square values at this stage were R_1 = 0.099 and R_2 = 0.097.

Hydrogens were located at reasonable distances about their respective atoms from a difference Fourier map. Hydrogen positional parameters (isotropic B values fixed at one more than the average value of the carbon atoms) and anisotropic non-hydrogen atom refinement converged at R_1 = 0.0387, R_2 = 0.0335 and with an ESD of an observation of unit weight of 1.504. Convergence was considered complete when all the shifts were less than one-tenth their standard deviation.

Table II contains final positional and thermal parameters. Table III shows observed and calculated structure factors, Table IV lists bond angles and Table V bond lengths. (See Supplementary Material.) The final difference map was smooth with maxima and minima in the range ±0.17 e/Å^3.

(*E*)-3,5-Hexadien-1-ol (34). To 100 mL of absolute ether was added 1.64 g (0.0432 mol) of $LiAlH_4$, followed by the slow addition of a solution of methyl *trans*-3,5-hexadienoate (**33**, 5.45 g, 0.0432 mol) in 25 mL of absolute ether under N_2 at 0 °C. The resulting mixture was stirred at room temperature for 2 h, cooled in an icewater bath and treated while being stirred with 20 mL of water followed by 20 mL of 5% NaOH and water (50 mL). The solvent was decanted and the solid was washed with ether. The combined ether phase was dried over anhydrous Na_2SO_4 and concentrated in vacuo, giving a clear oil. The crude product was distilled (0.05 torr/28 °C) affording 3.62 g (73%) of pure alcohol **34**: IR (film) 3325, 1645, 1005, 955, 900 cm^{-1}; ^1H NMR δ 2.3 (2 H, q, J = 6 Hz), 2.98 (1 H, t, J = 4 Hz), 3.33–3.8 (2 H, m), 4.7–6.75 (5 H, m).

(*E*)-3,5-Hexadienyl Carbamate (35). A stirred solution of dienol **34** (2.3 g, 0.0239 mol) in 4 mL of absolute ether was treated with 3.15 g (0.0485 mol) of sodium cyanate. Trifluoroacetic acid (3.6 mL, 0.0485 mol) was slowly added over a period of 24 h to the *very* slowly stirred mixture. The reaction mixture was stirred vigorously while 10 mL of water was added and was extracted with ether. The organic layer was washed with water, dried over $MgSO_4$, and concentrated in vacuo resulting in **35** as an oily, white solid of acceptable purity (as indicated by IR, NMR, and TLC) which was used directly in the next step (2.65 g, 80%): IR (film) 3400, 1680, 1605, 1410, 1340, 1050, 1000, 895 cm^{-1}; ^1H NMR δ 2.4 (2 H, q, J = 6 Hz), 4.1 (2 H, t, J = 6 Hz), 4.8–6.7 (7 H, m).

Preparation of Acetate 36. To a solution of freshly distilled methyl glyoxylate (1.1 g, 13 mmol) in 25 mL of reagent grade acetone was added 0.49 g (3.5 mmol) of carbamate **35**, and the mixture was refluxed under N_2 for 38 h. After cooling, the solvent was removed in vacuo, and the residue was extracted with ether. The organic phase was washed with water, dried over anhydrous $MgSO_4$, and concentrated in vacuo, yielding the methylol as an oily, white solid (0.46 g, 58%): IR (film) 3325, 2960, 1755, 1700, 1545, 1225, 1005, 900 cm^{-1}; ^1H NMR δ 2.2–2.6 (2 H, m), 3.78 (3 H, s), 4.1 (2 H, t, J = 6 Hz), 4.4 (1 H, s), 4.8–6.5 (7 H, m).

A stirred solution of this methylol in 6 mL of acetic anhydride was treated with 2 drops of pyridine, and the mixture was stirred at room

(26) All the programs used for this study were part of the Enraf-Nonius Structure Determination Package (SDP), Enraf-Nonius, Delft, Holland, 1975; revised 1977 and implimented on a PDP 11/34 computer.

(27) Howells, E. R.; Phillips, D. C.; Rogers, D. *Acta Crystallogr.* **1950**, *3*, 210.

(28) **Note Added in Proof**: Coupling constants for compound **22** were calculated from the observed spectrum using iterative analysis via program PANIC on a Bruker Aspect 2000 computer. We thank Professor L. M. Jackman for these calculations.

temperature for 2 h. The mixture was extracted with methylene chloride. The organic extract was washed with water, dried over anhydrous $MgSO_4$, and concentrated in vacuo. The resulting yellow oil was chromatographed on 10 g of silica gel with 1:1 hexane/ethyl acetate as the eluant giving acetate **36** (0.44 g, 81%): IR (film) 3350, 2960, 1750, 1530, 1220, 1010, 910 cm^{-1}; ^1H NMR δ 2.14 (3 H, s), 2.2–2.6 (2 H, m), 3.8 (3 H, s), 4.0–4.4 (2 H, m), 4.95–6.5 (7 H, m).

Methyl (3α,4aβ,8β)-4,4a,7,8-Tetrahydro-1-oxo-1*H*,3*H*-pyrido[1,2-c][1,3]oxazine-8-carboxylate (37). A solution of acetate **36** (0.387 g, 1.4 mmol) in 8 mL of reagent grade toluene was sealed in a 8 in. × 1 in. thick walled glass tube and was heated at 210 °C in an oil bath for 2 h. After cooling, the solution was concentrated in vacuo, and the resultant oil passed through a short column of silica gel (ethyl acetate), giving **37** as an oil which crystallized as white plates (0.239 g, 80%): mp 80–81 °C; IR (KBr) 2960, 2850, 1740, 1690, 1430, 1210, 775 cm^{-1}; ^1H NMR δ 1.8–2.2 (2 H, m), 2.5–2.7 (2 H, m), 3.74 (3 H, s), 4.3–4.4 (3 H, m), 5.3–5.9 (3 H, m); ^{13}C NMR δ 26.22, 28.89, 50.32, 51.47, 52.50, 65.58, 123.96, 126.55, 153.19, 171.32; mass spectrum, *m/e* (relative intensity) 211 (11.8) [M^+], 179 (11.0), 152 (74.8), 108 (100), 93 (36.8), 80 (50.2), 67 (38.6), 53 (20.4).

Anal. Calcd for $C_{10}H_{13}NO_4$: C, 56.87; H, 6.20. Found: C, 56.92; H, 6.17.

3α,4aβ,8β-4,4a,7,8-Tetrahydro-1-oxo-1*H*,3*H*-pyrido[1,2-c][1,3]oxazine-8-carboxylic Acid (38). A solution of the Diels–Alder adduct **37** (0.27 g, 1.3 mmol) in 25 mL of methanol was treated with 1 mL of 5% aqueous NaOH. The reaction mixture was stirred at room temperature for 2 h. The mixture was neutralized with 5% aqueous HCl, and the solvent was removed in vacuo. The residue was extracted with ethyl acetate, washed with water, dried over anhydrous $MgSO_4$, and evaporated. The crude product was crystallized from methanol by slow evaporation, giving acid **38** as leafy, white crystals (0.223 g, 89%): mp 168–170 °C; IR (film) 3400, 1660, 1420, 1023, 1000 cm^{-1}; ^1H NMR δ 1.6–2.3 (2 H, m), 2.4–2.7 (2 H, m), 4.3–4.4 (3 H, m), 5.4–6.0 (3 H, m); mass spectrum, *m/e* (relative intensity) 197 [M^+] (16.4), 152 (45.8), 124 (20.5), 108 (100), 80 (91.8).

Anal. Calcd for $C_9H_{11}NO_4$: C, 54.82; H, 5.62. Found: C, 54.49; H, 5.61.

X-ray Crystal Structure Determination of Carboxylic Acid 38.[26] Unit cell dimensions determined from 25 reflections at moderate 2θ angles indicated an orthorhombic cell of dimensions: a = 10.596 (4) Å; b = 6.693 (5) Å; c = 12.895 (2) Å, and v = 912.2 (1.9) Å^3. The observed volume is consistent with that expected for Z = 4, using a calculated density of 1.43 gm cm^{-3}. Observed systematic absences of $h\phi l$ for l = $2n + 1$ and $hk\phi$ for $h = 2n + 1$ gave possible space group choices as either *Pmca* or $P2_1ca$. Application of the zero-moment test of Howells, Phillips, and Rogers[27] indicated an acentric cell, thereby uniquely determining the space group as $P2_1ca$.

Data were collected using molybdenum Kα radiation [λ(Mo Kα) 0.70930 Å]. A total of 2310 reflections were collected out to a 2θ of 70°; of these 654 had intensities with $I \geq 3\sigma(I)$ (23.1%) and were considered observed. These data were corrected for Lorentz and polarization factors and used in the refinement of the structure.

Starting positions for the nitrogen, four oxygens, and eight of the carbon atoms were obtained from a MULTAN E-map synthesis where E_{min} = 1.35 and only data out to θ = 25°. Three cycles of isotropic least-squares refinement of these atoms yielded R_1 = 0.181 and R_2 = 0.214. The difference Fourier constructed at this stage revealed the remaining carbon atom and isotropic refinement of all non-hydrogen atoms resulted in R_1 = 0.106 and R_2 = 0.141.

Conversion to anisotropic thermal parameters and inclusion of the remaining data (θ = 25–35°) lowered R_1 = 0.098 and R_2 = 0.115 after 3 cycles of least-squares refinement. Subsequent difference Fourier/least-squares refinement located all the hydrogen atoms of the molecule. Inclusion of the hydrogens (B = 4.0) and refinement of their positional parameters along with full-matrix anisotropic refinement of the non-hydrogen atoms converged R_1 = 0.068 and R_2 = 0.087 with esd = 2.179. Convergence was considered complete when all shifts were less than one-tenth their standard deviations.

Final positional and thermal parameters are presented in Table V. Table VII shows observed and calculated structure factors, Table VIII lists bond angles, and Table IX gives bond lengths. (See Supplementary Material.) The final difference Fourier map was smooth with maxima and minima in the range of ±0.22 e/Å^3.

Basic Equilibration of Ester 37. To 2 mL of absolute CH_3OD was added 5 mg of sodium metal, and upon cessation of gas evolution, the ester **38** (0.052 g, 0.24 mmol) was added. The mixture was refluxed under N_2 for 24 h, and the solution was neutralized with acidic methanol. The solvent was removed in vacuo, and the crude product extracted with methylene chloride. The organic phase was washed with water, dried over anhydrous $MgSO_4$, and concentrated in vacuo affording the monodeuterated ester **39** as a light yellow oil (0.0448 g, 87%): IR (film) 2930, 2850, 1740, 1690, 1430, 1200, 760 cm^{-1}; ^1H NMR δ 1.8–2.2 (2 H, m), 2.5–2.7 (2 H, m), 3.74 (3 H, s), 4.3–4.4 (3 H, m), 5.4–5.9 (2 H, m); mass spectrum, *m/e* (relative intensity) 212 [M^+] (13.2), 153 (45.5), 109 (75), 94 (23.9), 81 (100), 68 (33.7), 53 (28.9), 41 (47.6).

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Supplementary Material Available: Tables II–IX contain X-ray data on compounds **32** and **38** (16 pages). Ordering information is given on any current masthead page.

Activation of Molecular Oxygen. Mechanistic Studies of the Oxidation of Hindered Phenols with Cobalt–Dioxygen Complexes

Alan Zombeck, Russell S. Drago,* Barry B. Corden, and John H. Gaul

Contribution from the School of Chemical Sciences, University of Illinois, Urbana, Illinois 61801. *Received December 22, 1980*

Abstract: Mechanistic studies of the oxidation of various substituted phenols by cobalt(II) bis(3-(salicylideneamino)-propyl)methylamine, CoSMDPT, are reported. The reaction is first order in [O_2], [substrate], and [Co]. A series of experiments are reported to provide strong support for a mechanistic scheme that involves reaction of coordinated dioxygen. Coordination of O_2 to this cobalt(II) complex enhances the ability of the dioxygen to abstract hydrogen atoms and to react with phenoxy radicals. The mechanism provides a rationale for the influence of several variables on the reaction and suggests steps that were taken to retard catalyst deactivation.

Determining the ways dioxygen can be activated by a metal center is important for understanding both biological and commercial systems.[1,2] Though homogeneous catalytic oxidations have been classified in many different fashions,[3,4] they can be separated into four broad categories: (1) free radical autoxidations

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