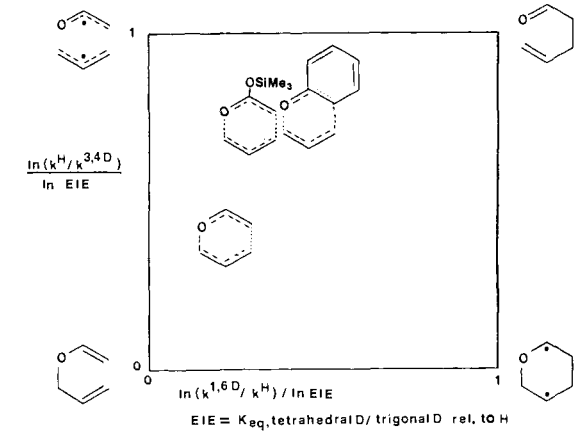
Table I. Deuterium Effects and *d* Values for Bond Making and Breaking

compound	*t*, °C	C-6 k^H/k^{D_2}	C-6 EIE[c]	C-6 *d* BM[d]	C-4 k^H/k^{D_2}	C-4 EIE[e]	C-4 *d* BB[d]
3-oxa-1,5-hexadiene	160.3[a]	1/1.025	1/1.16	0.17 (0.04)	1.09	1.23	0.42 (0.02)
2-(trimethylsiloxy)-1,5-hexadiene	25.0[b]	1/1.09 (0.03)	1/1.35	0.29 (0.10)	1.48 (0.06)	1.59	0.85 (0.07)

[a] Gas phase. [b] In CCl_4. [c] Reference 4: $\log K^{H/D_2} = (291.6/(2.3RT)) - 0.0818$. [d] Std dev in parentheses, from std dev in KIE. [e] From correlation of EIEs of all Claisen rearrangements studied by IEs and Shiner's unpublished FFs: $\log K^{H/D_2} = (500.1/(2.3RT)) - 0.1621$.

fecting the ground-state–transition-state isotopic fractionation are the same as those affecting the EIE, which appears to be the case in the Cope rearrangement.[4] A More O'Ferrall–Jencks diagram



provides a useful pictorial description of the transition state in each of the Claisen rearrangements examined to date.

It is clear that 2-Me_3SiO substitution results in a transition state with much more bond breaking than that in the parent rearrangement. The remarkable facility of the Ireland–Claisen reaction therefore is not due to "greater concert" but *to the enhanced stability of the 2-(trimethylsiloxy)-1-oxaallyl moiety resulting in alteration in transition-state structure and energy to resemble this species.*

The experimental fact can be rationalized by thermochemical kinetic considerations[11] and the activation free energy response surface equations developed to correlate the rates of [3,3]-sigmatropic shifts[12] provided that the siloxy group can be treated like a methoxy group. The heats of formation (in kcal/mol) of the allyl radical and the $\cdot CH_2COOMe$ radical are known to be 40.6 and −51 (4),[13] respectively, and that of allyl methyl ketene acetal can be estimated to be −48.3 from Benson group contributions, assuming that the two oxygens of the ketene acetal are each treated like a vinyl ether oxygen. The difference in heats of formation is only 38 kcal/mol, which is 15 kcal/mol *less* than the corresponding difference in the cleavage of allyl vinyl ether itself. This difference is probably the difference in the ester resonance energy in the 2-methoxy-1-oxaallyl radical and the additional resonance energy of the ketene acetal. The implication here is that the additional oxygen is not stabilizing the free electron but the π bond associated with this highly unsymmetrical oxaallyl species. There is the further implication that any substituent that conjugates strongly with a carbonyl group will strongly stabilize the bond-breaking alternative when substituted on C-2 of an allyl vinyl ether, a fact borne out by the rearrangements of lithioallyl acetate,[5] 2-fluoroallylvinyl ethers,[14] and perhaps even O-allyl amide acetals[15] and *S*-allyl thioamide acetals.[16]

With reasonable estimates of the relative free energies of the two allyl species, of 1-(trimethylsiloxy)-2-oxacyclohexane-1,4-diyl, and of the product silyl ester, 35, 60, and −28 kcal/mol, respectively, the 3,3-shift correlation equation of ref 12 predicts an activation free energy of 26 (2) kcal/mol at 25 °C for the allyl methyl ketene acetal rearrangement, a value within experimental error of that observed for the Ireland–Claisen rearrangement.

A further demonstration of the transition-state structure in this reaction is provided by the rates of rearrangement of α-, β-, and γ-phenylallyl trimethylsiloxy ketene acetal relative to the parent: >77, 4.3, and 1, respectively. The α-phenyl derivative has a half-life of less than 5 min at room temperature indicating substantial radical character at C-α. The small effect of β-phenyl indicates little radical, cationic, or anionic character at this site. The lack of effect at C-γ appears to be consistent with radical stabilizing groups being counterbalanced by the same effects prevalent in Diels–Alder and polymerization reactions. These rates above are also correlated by the equations of ref 12. Given the success of the correlation equations in Claisen rearrangements, it should be noted that unless electron-withdrawing groups stabilize radicals or destabilize π bonds, our model predicts that these groups should have no effect on Claisen rearrangements despite the predictions of the Carpenter model. Thus the success of the Carpenter model with cyano groups may be attributable to the radical stabilization associated with cyano not necessarily its negative inductive effect. Indeed, examination of Claisen rearrangements substituted with trifluoromethyl groups might assess the strengths of the two models unless Carpenter's model does not apply to σ-inductive substituents as suggested by a referee.

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(11) Benson, S. W. "Thermochemical Kinetics", 2nd ed., Wiley-Interscience: New York, 1976.
(12) Gajewski, J. J. *J. Am. Chem. Soc.* **1979**, *101*, 4393. Gajewski, J. J.; Gilbert, K. E. *J. Org. Chem.* **1984**, *49*, 11.
(13) Bartmess, J. E.; McIver, R. T., Jr. In "Gas Phase Ion Chemistry"; Bowers, M. R., Ed.; Academic Press: 1979; Vol. 2, p 111.
(14) Normant, J. F.; Reboul, D.; Sauvetre, R.; Deshayes, H.; Masure, D.; Villieras, J. *Bull. Soc. Chim. Fr.* **1974**, 2072.
(15) Felix, D.; Gschwend-Steen, K.; Wick, A. E.; Eschenmoser, A. *Helv. Chim. Acta* **1969**, *52*, 1030.
(16) Tamaru, Y.; Furukawa, Y.; Mizutani, M. M.; Kitao, O.; Yoshida, Z. *J. Org. Chem.* **1983**, *48*, 3631.
(17) McMichael, K. D.; Korver, G. L. *J. Am. Chem. Soc.* **1979**, *101*, 2746.

Total Synthesis of 5(*S*),15(*S*)-Dihydroxy-6,13-*trans*-8,11-*cis*-eicosatetraenoic Acid (5,15-DiHETE) and 8(*S*),15(*S*)-Dihydroxy-5,11-*cis*-9,13-*trans*-eicosatetraenoic Acid (8,15-DiHETE): Two Novel Metabolites of Arachidonic Acid

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5(*S*),15(*S*)-Dihydroxy-6,13-*trans*-8,11-*cis*-eicosatetraenoic acid (5,15-DiHETE, **1**)[1,2] and 8(*S*),15(*S*)-dihydroxy-5,11-*cis*-9,13-

[†] Fellow of the A. P. Sloan Foundation, 1979–1983; recipient of a Camille and Henry Dreyfus Teacher-Scholar Award, 1980–1984; J. S. Guggenheim Fellow, 1984.
(1) Van Os, C. P. A.; Rijke-Schilder, G. P. M.; Van Halbeck, H.; Verhagen, J.; Vliegenthart, J. F. G. *Biochem. Biophys. Acta* **1981**, *663*, 177.

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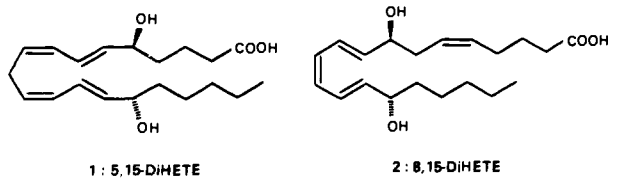
trans-eicosatetraenoic acid (8,15-DiHETE, **2**)[1,3] are two of the



1: 5,15-DiHETE **2**: 8,15-DiHETE

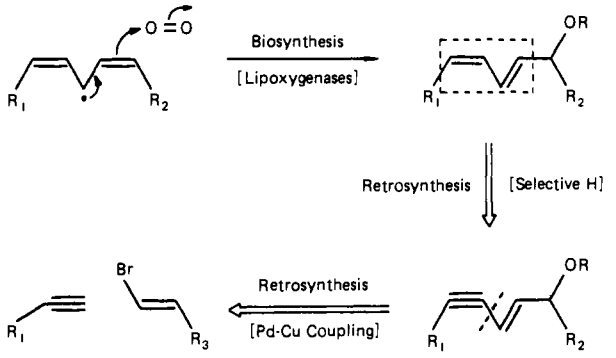
most recent and important metabolites of arachidonic acid (AA). 5,15-DiHETE (**1**) is formed by soybean lipoxygenase[1] or elicited rat peritonial mononuclear cells from AA via either lipoxygenase-catalyzed 5(*S*)-oxygenation of 15(*S*)-HETE or 15(*S*)-oxygenation of 5(*S*)-HETE.[2] Human leukocytes also produce 5,15-DiHETE (**1**) presumably via a similar pathway.[2] 8,15-DiHETE (**2**) is also formed from AA by the action of soybean lipoxygenase.[1,3] This novel eicosanoid possesses chemotactic activity for human polymorphonuclear leukocytes comparable to that of leukotriene B_4 (LTB_4)[4,5] but in contrast to LTB_4 is relatively inactive as an inducer of either degranulation or generation of superoxide anion radicals by cytochalasan B treated leukocytes.[3] As in the case of LTB_4, 8,15-DiHETE has been suggested as a possible and important mediator of inflammation.[3] In view of the intense current interest in this area[6] and the potential biological and medicinal significance of these and other similar substances available only in minute quantities from natural sources, their total syntheses were undertaken. In this communication we report the first total syntheses of these new bioregulators in their natural enantiomeric forms by a general and efficient technology based on palladium–copper coupling reactions.

The accepted biosynthetic pathway[6] to these DiHETE's and other linear oxygenated eicosanoids such as leukotrienes,[6] HETE's[6] and lipoxins[7] leads, almost invariably, to a conjugated *cis,trans*-diene system (Scheme I). It occurred to us that focusing on a stereocontrolled and efficient construction of this *cis,trans*-diene system may provide a general entry into this family of compounds. Scheme I outlines two simple retrosynthetic operations suggesting a terminal acetylene and a vinyl bromide as potential precursors to these polyunsaturated molecules. The synthetic planning for 5,15- and 8,15-DiHETE's can then be based on simple strategic bond disconnections of *cis,trans*-diene systems present in structures *1* and *2*

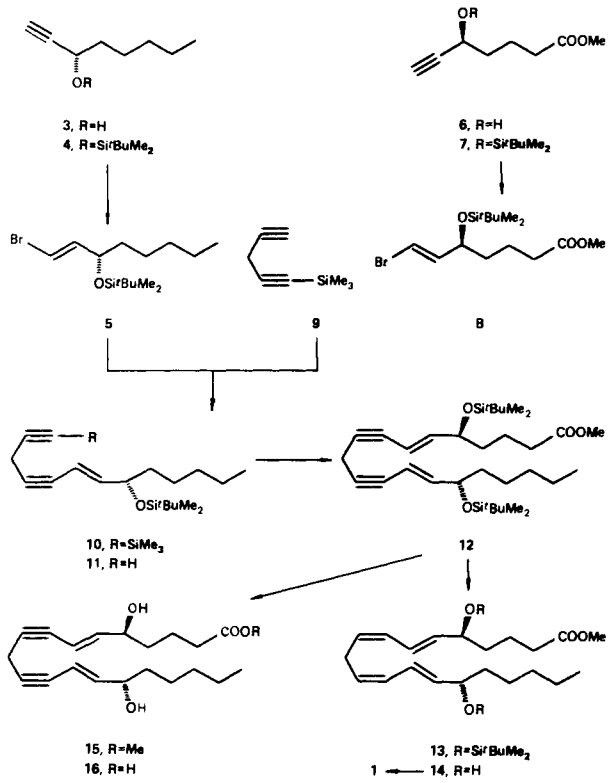
The synthetically most challenging problems of 5,15- and 8,15-DiHETE's can be easily recognized as (i) securing the stereochemistry of the remotely situated hydroxy-bearing chiral centers in their natural enantiomeric form and (ii) controlling the geometry of the double bonds. With the recent advances in asymmetric synthesis and by choosing convergent routes, the chirality aspect of the problem was well attended to, whereas for the geometrical requirements we had to rely on the premise that (a) selective hydrogenation of an acetylene function at the final stages would result in the generation of the desired cis stereochemistry with high selectivity and yield and (b) palladium/copper-catalyzed coupling[8] of terminal acetylenes with *trans*-vinyl bromides would result in the exclusive formation of *trans*-enynes with retention of stereochemistry. These goals were fully realized as the following execution of the synthetic plans toward **1** and **2** demonstrates.

For the total synthesis of 5,15-DiHETE (**1**) (Scheme II), enantiomerically enriched alcohol **3** (*S*:*R* ca. 95:5)[9] was transformed

Scheme I. Biosynthesis and Retrosynthesis of Linear Eicosanoids



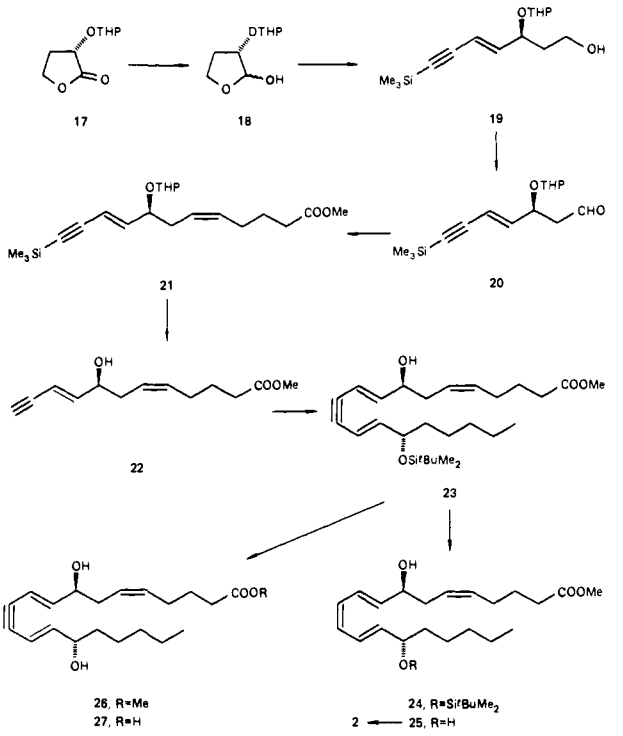
Scheme II. Total Synthesis of 5,15-DiHETE (1)



to its silyl ether **4** (1.5 equiv of t-$BuMe_2SiOSO_2CF_3$, 2.2 equiv of 2,6-lutidine, CH_2Cl_2, 0 °C, 95%)[10] and thence to the vinyl bromide **5** by n-Bu_3SnH addition (1.5 equiv of n-Bu_3SnH, AIBN catalyst, 130 °C, 2 h) followed by brominolysis (1.1 equiv of Br_2, CCl_4, −20 °C) in 93% overall yield (≥98% *E*).[11,12] In a similar fashion the hydroxymethyl ester **6** (*S*:*R* ca. 96:4)[5] was converted to **7** (90%) and then to **8** (87% overall, ≥98% *E*). Coupling of **5** with an excess (2 equiv) of the readily available **9**[13] under strictly defined conditions [0.04 equiv of $(Ph_3P)_4Pd$, 1.2 equiv of $PrNH_2$, 0.16 equiv of CuI, benzene, 25 °C][8] resulted in the exclusive formation of compound **10** (82% yield) with the expected retention of geometry. Liberation of the terminal acetylene (2.0 equiv of $AgNO_3$, 2 equiv of KCN, EtOH–H_2O, 25 °C) followed by a second coupling employing **11** and the vinyl bromide **8** and according to the above procedure led to the desired skeleton **12** in

(2) Maas, R. L.; Turk, J.; Oates, J. A.; Brash, A. R. *J. Biol. Chem.* **1982**, *257*, 7056.
(3) Shak, S.; Perez, H. D.; Goldstein, I. M. *J. Biol. Chem.* **1983**, *258*, 14948.
(4) Isolation: Borgeat, P.; Samuelsson, B. *J. Biol. Chem.* **1979**, *254*, 2643.
(5) Synthesis: Nicolaou, K. C.; Zipkin, R. E.; Dolle, R. E.; Harris, B. D. *J. Am. Chem. Soc.* **1984**, *106*, 3548 and references cited therein.
(6) For some recent reviews in this area, see: (a) Samuelsson, B. *Angew. Chem., Int. Ed. Engl.* **1983**, *22*, 805. (b) Corey, E. J. *Experientia* **1982**, *38*, 1259. (c) Hammarstrom, S. *Annu. Rev. Biochem.* **1983**, *52*, 355.
(7) Samuelsson, B.; Hammarstrom, S. International Conference on Prostaglandins and Leukotrienes, Washington, DC, May 1984.
(8) (a) Sonogashira, K.; Tohda, Y.; Hagihara, N. *Tetrahedron Lett.* **1975**, 4467. (b) Ratovelomana, V.; Linstrumelle, G. *Synth. Commun.* **1981**, *11*, 917.
(9) Midland, M. M.; McDowell, D. C.; Hatch, R. L.; Tramontano, A. *J. Am. Chem. Soc.* **1980**, *102*, 867.
(10) Corey, E. J.; Cho, H.; Rücker, C.; Hua, D. H. *Tetrahedron Lett.* **1981**, *22*, 3455.
(11) For the preparation of the corresponding racemic triethylsiloxy derivative, see: Chen, S.-M.; Schaub, R. E.; Grudzinskas, C. V. *J. Org. Chem.* **1978**, *43*, 3450.
(12) The 250-MHz ^1H NMR spectrum of the corresponding desilylated product (HF·pyr–THF) did not reveal any detectable amounts of the *Z* isomer.
(13) Verkruijsse, H. D.; Hasselaar, M. *Synthesis*, *1979*, 292.

Scheme III. Total Synthesis of 8,15-DiHETE (2)



76% overall yield and with exclusive *E* geometry at the newly generated double bond.

Selective hydrogenation (Lindlar catalyst, H_2, hexane, 25 °C)[14] of the acetylene groupings of **12** proceeded smoothly, furnishing the 5,15-DiHETE derivative **13** in 80% yield. Desilylation of this intermediate with excess HF·pyr (THF, 25 °C)[15] led to the methyl ester of 5,15-DiHETE (**14**) in 80% yield. Finally, alkaline hydrolysis (3.0 equiv of LiOH, THF–H_2O, 1:1, 25 °C) of **14** furnished 5,15-DiHETE (**1**) in essentially quantitative yield. Both synthetic **1** and its methyl ester **14** were spectroscopically (IR, MS, ^1H NMR, UV) and chromatographically (TLC, HPLC) identical with naturally derived samples.[16] This synthetic route also provided the novel diacetylenic analogues **15** and **16** by desilylation and saponification of **12** as described above.

The construction of 8,15-DiHETE (**2**) proceeded along Scheme III. Lactone **17**, readily available from (*S*)-malic acid according to Still[17] and Ohfune,[18] was reduced with DIBAL (1.1 equiv of, CH_2Cl_2, −78 °C) to afford lactol **18** (95% yield). Upon reaction (THF, −78 → 25 °C) with excess ylide derived from $Me_3SiC{\equiv}CCH_2P^+Ph_3Br^-$ and *n*-BuLi (3.0 equiv of each, THF, −78 °C),[19] lactol **18** furnished hydroxy enyne **19** in 60% yield (R_f 0.29, silica, 70% ether in petroleum ether) together with its cis isomer (25%, R_f 0.50 silica, 70% ether in petroleum ether). Oxidation of **19** with PCC (1.5 equiv of CH_2Cl_2, 25 °C) led to aldehyde **20** (82% yield), which reacted (DME, −10 → 25 °C) with the ylide derived from (4-carboxybutyl)triphenylphonium bromide (3.0 equiv) and $NaN(SiMe_3)_2$ (6.0 equiv (DME, −10 °C) furnishing, after diazomethane treatment and chromatography, methyl ester **21** (80% yield) in essentially pure geometrical form.[20] Removal of the tetrahydropyranyl ether protecting group (0.1 equiv of PPTS, MeOH, 50 °C) followed by desilylation (1.1 equiv of *n*-Bu_4NF, THF, 0 °C) led to the key intermediate terminal acetylene **22** in 95% overall yield. Coupling of **22** with vinyl bromide **8** (Scheme II) (1.0 equiv) under carefully controlled conditions [0.04 equiv of $(Ph_3P)_4Pd$, 1.2 equiv of $PrNH_2$, 0.05 equiv of CuI, benzene, 25 °C][8] proceeded smoothly to furnish product **23** in 80% yield and with complete preservation of geometry. Selective hydrogenation of **23** (Lindlar catalyst, H_2, hexane)[14] afforded smoothly compound **24** (87% yield based on ca. 50% conversion). Finally, desilylation of **24** (excess HF·pyr, THF, 25 °C)[15] furnished, in essentially quantitative yield, the methyl ester **25**, which exhibited the expected properties [^1H NMR, MS, IR, UV, $[\alpha]_D$] for natural 8,15-DiHETE methyl ester.[1,3] Free 8,15-DiHETE (**2**) was prepared by alkaline hydrolysis (1.5 equiv of LiOH, THF–H_2O, 3:1, 25 °C, 95% yield) of its methyl ester (**25**). Furthermore, desilylation and saponification of the acetylenic derivative **23** afforded the novel analogues **26** and **27**.

With 5,15- and 8,15-DiHETE's and analogues synthetically available, extensive biological investigations in this area are now possible. Furthermore, these short and stereocontrolled total syntheses demonstrate the generality and efficiency of the developed Pd/Cu-based technology for the construction of linear eicosanoids as well as other, tailored-made biological tools of similar structures. Other applications are currently in progress.[21,22]

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Supplementary Material Available: Listing of ^1H NMR and IR spectral data for compounds **12–15** and **22–25** (4 pages). Ordering information is given on any current masthead page.

(14) We thank Dr. John Partridge of Hoffmann-La Roche Co., Nutley, NJ, for a generous gift of a superior Lindlar catalyst.

(15) Nicolaou, K. C.; Seitz, S. P.; Pavia, M. R.; Petasis, N. A. *J. Org. Chem.* **1979**, *44*, 4011.

(16) We thank Professor Alan Brash of the Department of Pharmacology and Medicine, Vanderbilt University School of Medicine, Nashville, TN, for an authentic sample of 5,15-DiHETE (**1**).

(17) Still, W. C.; McDonald, J. H., III; Collum, D. B. *J. Am. Chem. Soc.* **1980**, *102*, 2117.

(18) Ohfune, Y.; Masako, T.; Kyosuke, N. *J. Am. Chem. Soc.* **1981**, *103*, 2409.

(19) Jones, E. R. H.; Ahmed, M.; Barley, G.; Hearn, M. T. W.; Thaller, V.; Yates, J. *J. Chem. Soc., Perkin Trans. 1* **1974**, 1981.

(20) In some runs, considerable desilylation was observed in which case the material was taken through the next two steps as a mixture.

(21) All new compounds were characterized by full spectroscopic and analytical and/or exact mass data. Yields refer to spectroscopically and chromatographically homogeneous materials.

(22) For an application of the present strategy to the synthesis of LTB_4, see ref 5.

Cytochrome Oxidase Heme–Protein Dynamics: A Transient Raman Study of Carbon Monoxide Photolysis from Cytochrome a_3

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The characterization of the local structures about the redox centers of mammalian cytochrome oxidase has recently been the focus of extensive investigations.[1,2] A variety of physical techniques such as electron paramagnetic resonance (EPR), resonance Raman, and x-ray absorption fine structure (XAFS) have been employed in these studies, and significant structural insights concerning the protein configurations about the active sites in the equilibrium forms of the protein have been obtained.[3-14]

(1) For a good general review, see: Wikström, M.; Krab, K.; Saraste, M. "Cytochrome Oxidase: A Synthesis"; Academic Press: New York, 1981.

(2) Wilson, D. F.; Erecinska, M. In "The Porphyrins"; Dolphin, D., Ed.; Academic Press: New York, 1979; Vol. 3, pp 1–70.

(3) Brudvig, G. W.; Stevens, T. H.; Morse, R. H.; Chan, S. I. *Biochemistry* **1981**, *20*, 3912–3921.

(4) Dunham, W. R.; Sands, R. H.; Shaw, R. W.; Beinert, H. *Biochim. Biophys. Acta* **1983**, *748*, 73–85.

(5) Hartzell, C. R.; Hansen, R. E.; Beinert, H. *Proc. Natl. Acad. Sci. U.S.A.* **1973**, *70*, 2477–2481.

0002-7863/84/1506-5736$01.50/0