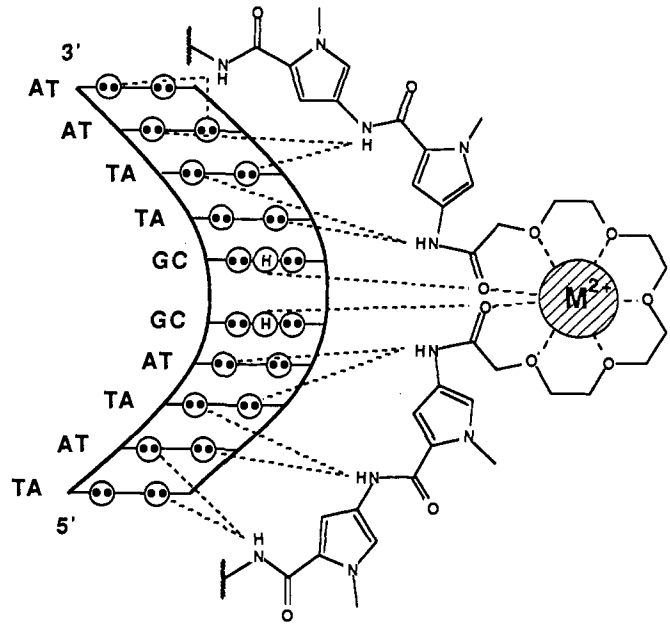


Figure 3. Hypothetical model for binding of **1** in the presence of a specific metal ion (M = Ba^{2+} or Sr^{2+}) to a ten base pair sequence 5'-TATAGGTTAA-3'.

tration indicates saturation binding. The decrease in cleavage efficiency above 10 mM Ba^{2+} may be due to displacement of **1**·Fe(II) from the DNA polyanion by the dication and/or competition for the EDTA moiety by Ba^{2+}.

For recognition of DNA by *N*-methylpyrrolecarboxamide we would expect that each dipeptide subunit of **1**, having three amide NHs, should bind to four contiguous A,T base pairs.[12,13] The observed binding site, 5'-AATA-3' reveals that monomeric binding can be facilitated by the presence of Ba^{2+} or Sr^{2+}. The fact that monomeric binding is metalloregulated indicates that the free ligand **1** may be in a conformational state that is less competent to bind unless a specific metal ion is present. Moreover, the observed ten base pair binding site, 5'-TATAGGTTAA-3', suggests that the dipeptides of **1**·Fe^{II} bind in a *dimeric mode* in the presence of Sr^{2+} or Ba^{2+} and produce an *additional* DNA-ion binding subunit specific for the central sequence, 5'-GG-3'. CPK models indicate that for a heptacoordinate pseudomacrocycle the lone pair electrons on the carboxamide oxygens anti to the metal coordination site may form hydrogen bonds with guanine N2 amino groups which protrude from the floor of the minor groove in right-handed double helical DNA[14] (Figure 3).

In conclusion, addition of Sr^{2+} or Ba^{2+} converts **1**·Fe(II) from a species which produces little DNA cleavage to a sequence specific DNA binding/cleaving molecule. We have thus demonstrated metalloregulation in the sequence specific binding of a small synthetic molecule to DNA. The effect is metal-ion specific, occurring with the heavier alkaline earth cations. We cannot yet dissect the relative contributions of cation size, coordination number and "hardness" to the metallospecificity.[15] Ba^{2+} and Sr^{2+} are known to bind more strongly to 18-crown-6 in water than either the alkali metals or the lighter alkaline earth metals.[8] Ba^{2+} is more effective than Sr^{2+} in producing sequence specific cleavage which is consistent with the greater affinity of Ba^{2+} for 18-crown-6 in water.[8] Why Ba^{2+} and Sr^{2+} are more effective than Cd^{2+} is not understood but may be due to the "harder" cations having higher affinity for the phosphate backbone of DNA.[16] Perhaps bound **1** in the minor groove of DNA creates a "cavity" for Sr^{2+} or Ba^{2+}, consisting of a neutral heptaoxamacrocycle capped on top and bottom by the phosphate oxygen anions on the neighboring DNA backbone. The observation of specific metal-ion dependent binding may be interpreted in terms of allosteric models in which complexation of Sr^{2+} or Ba^{2+} by **1** induces a change which allows monomeric binding and, at least at one DNA site, simultaneous binding of two subunits to form a crescent-shaped molecule complementary to the minor groove of DNA with dipeptides specific for $(A,T)_4$ flanking a podand/cation complex specific for $(G,C)_2$ (Figure 3).

Acknowledgment. We are grateful to the National Institutes of Health for research support (GM 27681) and to the National Science Foundation for a predoctoral fellowship to J.H.G.

(12) Youngquist, R. S.; Dervan, P. B. *Proc. Natl. Acad. Sci. U.S.A.* **1985**, *82*, 2565-2569.
(13) Kopka, M. L.; Yoon, C.; Goodsell, D.; Pjura, P.; Dickerson, R. E. *Proc. Natl. Acad. Sci. U.S.A.* **1985**, *82*, 137-138.
(14) For examples of synthetic molecules that bind DNA with mixed (G,C)(A,T) specificity, see: (a) Dervan, P. B.; Sluka, J. P. In *New Synthetic Methodology and Functionally Interesting Compounds*; Elsevier Scientific Publishing Co.: Amsterdam, 1986; pp 307-322. (b) Wade, W. S.; Dervan, P. B. *J. Am. Chem. Soc.* **1987**, *109*, 1574-1575.
(15) The effect is also strongly dependent on the structure of the podand. At 20 μM concentration, a molecule with one less ethyleneglycol unit than **1** binds weakly to DNA without added metal ions, and this binding is not altered by the addition of metal ions. Similarly, a molecule with one more ethyleneglycol unit than **1** exhibits no binding to DNA with or without added metal cations.
(16) Saenger, W. *Principles of Nucleic Acid Structure*; Cantor, C., Ed.; Springer Verlag: 1984; pp 201-219.

Metalation of Surfactant Porphyrins at Anionic Interfaces in Micelles and Reversed Micelles: Dramatic Effects of Chain Length and Atropisomer Structure on Reactivity

David C. Barber and David G. Whitten*

Department of Chemistry, University of Rochester
Rochester, New York 14627

Received May 28, 1987

Porphyrin metalation in solution has been well-studied; however, several mechanistic questions remain unresolved.[1-12] Metalation in microheterogeneous media has been less investigated,[13-20] although its biological occurrence,[21-23] the amphiphilic character of most natural porphyrins, and metal ion-porphyrin solubility

(1) Guilleaux, L.; Krausz, P.; Nadjo, L.; Uzan, R. *J. Chem. Soc., Perkin Trans. 2* **1985**, 951.
(2) Lavallee, D. K. *Coord. Chem. Rev.* **1985**, *61*, 55.
(3) Anzai, K.; Hatano, K. *Chem. Pharm. Bull.* **1984**, *32*, 2067.
(4) Pasternack, R. F.; Vogel, G. C.; Skowronek, C. A.; Harris, R. K.; Miller, J. G. *Inorg. Chem.* **1981**, *20*, 3763.
(5) Turay, J.; Hambright, P. *Inorg. Chem.* **1980**, *19*, 562.
(6) Longo, F. R.; Brown, E. M.; Rau, W. G.; Alder, A. D. In *The Porphyrins*; Dolphin, D., Ed.; Academic: New York, 1978; Vol. V, pp 459-481.
(7) Bain-Ackerman, M. J.; Lavallee, D. K. *Inorg. Chem.* **1979**, *18*, 3358.
(8) Fleischer, E. B.; Dixon, F. *Bioinorg. Chem.* **1977**, *7*, 129.
(9) Hambright, P. In *Porphyrins and Metalloporphyrins*; Smith, K. M., Ed.; Elsevier: New York, 1975; pp 233-278.
(10) Hambright, P.; Chock, P. B. *J. Am. Chem. Soc.* **1974**, *96*, 3123.
(11) Longo, F. R.; Brown, E. M.; Quimby, D. J.; Adler, A. D.; Meot-Ner, M. *Ann. N.Y. Acad. Sci.* **1973**, *206*, 420.
(12) Hambright, P. *Coord. Chem. Rev.* **1971**, *6*, 247.
(13) Rao, V. H.; Krishnan, V. *Inorg. Chem.* **1985**, *24*, 3538.
(14) Cole, G. M., Jr.; Doll, D. W.; Holt, S. L. *J. Am. Chem. Soc.* **1983**, *105*, 4477.
(15) Keiser, B.; Holt, S. L.; Barden, R. E. *J. Colloid Interface Sci.* **1980**, *73*, 290.
(16) Williams, G. N.; Williams, R. F. X.; Lewis, A.; Hambright, P. *J. Inorg. Nucl. Chem.* **1979**, *41*, 41.
(17) Schmehl, R. H.; Shaw, G. L.; Whitten, D. G. *Chem. Phys. Lett.* **1978**, *58*, 549.
(18) Letts, K.; Mackay, R. A. *Inorg. Chem.* **1975**, *14*, 2990.
(19) Letts, K.; Mackay, R. A. *Inorg. Chem.* **1975**, *14*, 2993.
(20) Lowe, M. B.; Phillips, J. N. *Nature (London)* **1961**, *190*, 262.
(21) Jones, M. S.; Jones, O. T. G. *Biochem. J.* **1970**, *119*, 453.
(22) Nishida, G.; Labbe, R. F. *Biochim. Biophys. Acta* **1959**, *31*, 519.
(23) Labbe, R. F. *Biochim. Biophys. Acta* **1959**, *31*, 589.

0002-7863/87/1509-6842$01.50/0

Table I. Observed and Microscopic Metalation Rate Constants for Picket Fence Porphyrins in Different Media[a,b]

		Cu^{2+} incorporation rate constants in					
		9:1 DMF–H_2O[c]		AOT–heptane–water reversed micelles[d]			aqueous SDS[e]
porphyrin		H_2TAc	H_2THex	H_2TAc	H_2THex	H_2THA	H_2TAc
[4,0]	k(obsd)	7.2×10^{-4}	3.5×10^{-4}	0.11	2.2	3.5	1.6×10^{-3}
	k(mic)[f]			0.0047	0.098	0.16	1.6×10^{-5}
[3,1]	k(obsd)	1.4×10^{-4}		1.5	1.5	1.1	7.6×10^{-2}
	k(mic)[f]			0.067	0.068	0.051	7.8×10^{-4}
cis[2,2]	k(obsd)	1.0×10^{-4}		12	0.57	0.25	1.5
	k(mic)[f]			0.54	0.026	0.011	1.5×10^{-2}
trans[2,2]	k(obsd)	7.5×10^{-5}		20	0.31	0.13	1.1
	k(mic)[f]			0.90	0.014	0.0060	1.1×10^{-2}

[a] T = 25 °C; units are M^{-1} s^{-1} assuming reactions are first order in $[Cu^{2+}]$. Preliminary investigations with [3,1] H_2TAc indicate that the calculated second-order rate constant decreases with increasing metal ion concentration in both microheterogeneous media studied. [b] H_2TPP metalated faster in homogeneous solution ($k(H_2TPP)/k$([4,0] H_2TAc) = 68.5) and slower in AOT reversed micelles ($k(H_2TPP) = 1.22 \times 10^{-4}$ M^{-1} s^{-1}) than the ortho-substituted derivatives, probably due to partitioning into the bulk heptane. [c] $[Cu(ClO_4)_2] = 0.15$ M; $[H_2P] = \sim 6 \times 10^{-5}$ M; DMF was distilled and stored over sieves. Second-order rate constants for metalation of H_2TPP in homogeneous solution with $Cu(ClO_4)_2$ and $CuSO_4$ decreased with increasing Cu^{2+} concentration; however, with $Cu(ClO_4)_2$ the reaction was nearly first order in metal ion. [d] [AOT] = 0.25 M; $[H_2O] = 2.5$ M; bulk phase is heptane; $[CuSO_4] = 0.0010$ M; $[H_2P] = \sim 2 \times 10^{-6}$ M. AOT (sodium bis(2-ethylhexyl)sulfosuccinate) was obtained from Aldrich and purified according to ref 35. [e] [SDS] = 60 mM; $[CuSO_4] = 7.5$ mM in Milli-Q deionized water; $[H_2P] = \sim 3 \times 10^{-6}$ M; SDS was obtained from Bio-Rad Laboratories and recrystallized twice from absolute ethanol. [f] k(mic) is the microscopic metalation rate constant, calculated by dividing k(obsd) by the volume fraction of water added to the reversed micelle or by using the micelle volume fraction calculated from a 16-Å-radius SDS micelle.

disparities make it an appealing subject. A particularly attractive series of porphyrins for mechanistic studies are the sets of atropisomers of "picket fence" porphyrins (Scheme I) in which the alkyl group of the tetracarboxamide is varied.[24] Herein we report studies of Cu^{2+} incorporation into different porphyrins in Aerosol OT (AOT) reversed micelles and sodium dodecyl sulfate (SDS) micelles and a comparison of reactivity at these anionic interfaces with homogeneous solution. Noteworthy results include marked enhancements for the surfactant solutions in both overall and "microscopic" rates and remarkable differences in reactivity compared to homogeneous solution for different compounds as well as for individual atropisomers.

The different "sets" of atropisomers studied most extensively are those of the acetamido (H_2TAc), hexanamido (H_2THex), and hexadecanamido (H_2THA) picket fence porphyrins in which the alkyl chains extend 1, 5, and 15 carbons beyond the carboxyl group. In addition, metalation of several intermediate-length amides has been studied for [4,0] atropisomers.[25] Metalation of these porphyrins in *N,N*-dimethylformamide (DMF) or 9:1 DMF–water proceeds with rates similar to those reported for related porphyrins under comparable conditions;[26] the relative order is [4,0] > [3,1] > cis[2,2] > trans[2,2]. Much more rapid metalation occurs when Cu^{2+} and porphyrin amides are cosolubilized in AOT–heptane–water reversed micelles (Table I).[27] Since these solutions consist of three discrete phases under the experimental conditions and the porphyrins and Cu^{2+} are essentially insoluble in the respective aqueous and heptane phases, it is reasonable to assume that metalation occurs at the surfactant–water interface according to eq 1 and 2. If equilibration

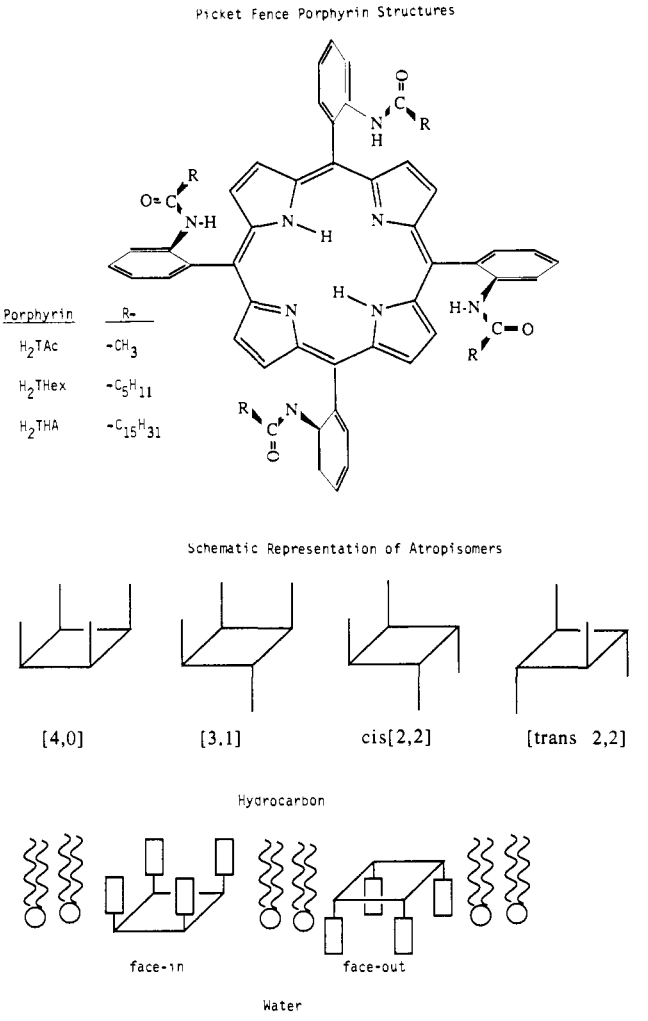
$$H_2P + I \overset{K}{\rightleftharpoons} H_2PI \quad (1)$$

$$H_2PI + Cu^{2+} \xrightarrow{k_2} CuPI + 2H^+ \quad (2)$$

between the continuous (heptane) phase and interface is rapid and all of the porphyrin is associated with the interface, a limiting rate = $k_2[H_2P]_0[Cu^{2+}]$, independent of the reversed micelle concentration, is predicted. Studies of [4,0] H_2TAc and trans[2,2] H_2TAc show that this limiting case has been attained under the conditions used, and thus for these atropisomers, for which a very large difference in reactivity is observed, the variation is solely due to differences in k_2. These rate constants show accelerations of 150- and (2.7×10^5)-fold compared to homogeneous (9:1 DMF–water) solution; correcting k_2 for the concentrating effect of the reversed micelle still leads to a 6.6-fold acceleration for [4,0] H_2TAc and a factor of 12000 for trans[2,2] H_2TAc.

Several significant trends in reactivity emerge for reversed micelle solutions of the porphyrins. For the [4,0] atropisomers

Scheme I



(24) Porphyrins used in this study were prepared according to: Freitag, R. A.; Whitten, D. G. *J. Phys. Chem.* **1983**, *87*, 3918.

(25) Metalation reactions were monitored by UV–vis spectroscopy and were found to be first order in H_2P over more than 3 half-lives.

(26) Turay, J.; Hambright, P. *Inorg. Chim. Acta* **1981**, *53*, L147.

(27) No atropisomerization of [4,0], [3,1], and trans[2,2] H_2TAc as checked by HPLC was observed upon Cu^{2+} incorporation in the reversed micelles studied.

there is a small and smooth decrease (total ca. 40%) in rate as the chain length is reduced from 15 to 5 carbons; as the alkyl chain length further decreases there is a much sharper decrease, which is most pronounced in the series R = 3, 2, 1 (k_{obsd} = 0.68, 0.33, and 0.11 M^{-1} s^{-1}, respectively). In contrast, reactivity of trans[2,2] and cis[2,2] atropisomers increases sharply with decrease in chain length while reactivity of the [3,1] atropisomers remains nearly constant. Thus, overall reactivity of a series follows the "normal" solution order for H_2THA and H_2THex atropisomers but the reactivity sequence is exactly reversed for H_2TAc in reversed micelles. A limited study of metalation of H_2TAc atropisomers in SDS micelles shows trends similar to those for reversed micelles;[28] rates slightly slower than those in the reversed micelle are measured and the order is cis[2,2] ~ trans[2,2] > [3,1] > [4,0].[29] Thus, overall reactivity of all atropisomers is enhanced (Table I) relative to homogeneous solution, even after correcting for the concentrating effect of the microheterogeneous medium.

The striking changes in reactivity for metalation of different porphyrins in anionic surfactant media must be associated with the presence and reactivity of the reagents at an anionic interface. Enhanced reactivity of the porphyrin in general can be attributed to an effective augmentation of its basicity; similar increases have been observed for neutral bases in other studies.[31,32] Preliminary studies using the H_2TAc isomers in SDS indicate good correlation of porphyrin basicity with reactivity toward Cu^{2+}. To explain the striking differences between reactivity of atropisomers as the length of the alkyl chain is varied, we propose that a major factor for [4,0] atropisomers can be attributed to a change in preferred orientation. For these isomers two limiting orientations with respect to the aqueous phase at the interface, "face-in" and "face-out", may be defined as shown in Scheme I. When the "pickets" are long alkyl chains we expect the more hindered face to be strongly hydrophobic such that a "face-in" orientation should be favored; here it is reasonable that metalation should be quite rapid. When the pickets are shorter chain carboxamide groups, their hydrophilicity should increase, favoring the "face-out" orientation. This should lead not only to a decrease in reactivity as the chain length is decreased for the [4,0] isomers but to a reversal in the normal order among atropisomers. For trans[2,2] and cis[2,2] atropisomers the above-described orientations are degenerate and other configurations may be of lower energy; increases in reactivity as the chain length decreases could be most simply ascribed to an internal reduction in steric hindrance. For the [3,1] atropisomers it is reasonable that changes in "face-in"-"face-out" equilibria similar to that proposed for the [4,0] and a variation in the steric effect play nearly offsetting roles in maintaining an overall constant reactivity through the series.

In summary, the present results demonstrate striking net effects which can be obtained by the interplay of hydrophobic and steric interactions for reactions at interfaces in microheterogeneous media. The control of reactivity by a charged interface observed in these studies shows a clear relationship to the topological control of thermal and photochemical reactivity observed for quite different processes.[33,34] Further studies of other metalation reactions are under way.

Acknowledgment. We are grateful to the U.S. Army Research Office (Grant DAAG29-84-K-0011) and the National Science Foundation (Grant CHE-8616361) for support of this research.

(28) For cis[2,2] and trans[2,2] H_2TAc in SDS, addition of Cu^{2+} produces an intermediate species, whose spectrum resembles the porphyrin diacid,[8] which converts to metalloporphyrin.

(29) Interestingly, Hambright et al.[30] have found a parallel order for a water-soluble porphyrin with isonicotinamide "pickets" for Zn^{2+} incorporation but the "normal" order for Cd^{2+}.

(30) Valiotti, A.; Adeyemo, A.; Williams, R. F. X.; Ricks, L.; North, J.; Hambright, P. *J. Inorg. Nucl. Chem.* **1981**, *43*, 2653.
(31) Hartley, G. S. *Trans. Faraday Soc.* **1934**, *30*, 444.
(32) Fernandez, M. S.; Fromherz, P. *J. Phys. Chem.* **1977**, *81*, 1755.
(33) Takagi, K.; Suddaby, B. R.; Vadas, S. L.; Backer, C. A.; Whitten, D. G. *J. Am. Chem. Soc.* **1986**, *108*, 7865.
(34) Nikles, J. A.; Sukenik, C. *Tetrahedron Lett.* **1982**, *23*, 4211.
(35) Backer, C. A.; Whitten, D. G. *J. Phys. Chem.* **1987**, *91*, 865.

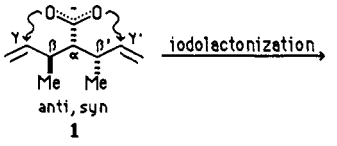
Double Diastereoselection in the Iodolactonization of 1,6-Heptadien-4-carboxylic Acids[1]

Mark J. Kurth* and Edward G. Brown

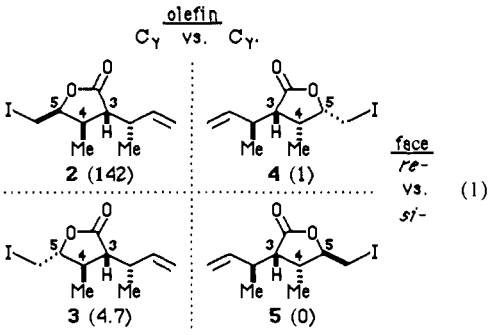
Department of Chemistry, University of California Davis, California 95616

Received May 26, 1987

Synthetic strategies employing reactions which selectively engage one of two diastereotopic functional groups provide a unique exploitation of molecular symmetry. Notable examples of this concept include Hoye's kinetic hydroxyazelaic acid lactonization[2] and Schreiber's thermodynamic trihydroxynonanone spiroketalization.[3] We describe here the efficient stereoselective functionalization of heptadienoate **1** via its iodolactonization, *a transformation which proceeds with concomitant group and face selectivity*. Consider the four isomeric iodolactones possible from iodolactonization of **1**: **2** and **3** versus **4** and **5** reflects diastereotopic olefin selectivity (i.e., *group selectivity*) and **2** and **4** versus **3** and **5** reflects diastereotopic re versus si selectivity (i.e., *face selectivity*). A preponderance of one product would thus evidence concomitant group and face selectivity.



1



(1)

It is noteworthy that Barlett's pioneering iodolactonization studies[4] suggested significant potential for the thermodynamic cyclization of **1** (e.g., 10:1 thermodynamic selectivity with 3-methylpent-4-enoic acid)[4a] but offered little encouragement with regard to the kinetic cyclization of **1** (e.g, 3:1 kinetic selectivity with 3-methylpent-4-enoic acid).[4a] Moreover, at the outset the question of olefin selectivity was a matter of conjecture as there were no previous reports of diastereotopic olefin selectivity in this type of transformation.

Preliminary attempts to iodolactonize **1**[5] under thermodynamic

(1) E. G. Brown presented this work in part at the 193rd National Meeting of the American Chemical Society, Denver, CO, April 1987; paper ORGN 88.

(2) (a) Hoye, T. R.; Peck, D. R.; Trumper, P. K. *J. Am. Chem. Soc.* **1981**, *103*, 5618. (b) Hoye, T. R.; Peck, D. R.; Swanson, T. A. *J. Am. Chem. Soc.* **1984**, *106*, 2738.

(3) Schreiber, S. L.; Wang, Z. *J. Am. Chem. Soc.* **1985**, *107*, 5303.

(4) (a) Bartlett, P. A.; Myerson, J. *J. Am. Chem. Soc.* **1978**, *100*, 3950. (b) Bartlett, P. A.; Myerson, J. *J. Org. Chem.* **1979**, *44*, 1625. (c) Bartlett, P. A.; Richardson, D. P.; Myerson, J. *Tetrahedron* **1984**, *40*, 2317. (d) Gonzâlez, F. B.; Bartlett, P. A. *Org. Synth.* **1985**, *64*, 175.

(5) (a) The heptadienoic acids corresponding to carboxylates **1**, **6**, and **9** were prepared from (*E*)-crotyl 3-methylpent-4-enoate by an Ireland "kinetic enolate" Claisen rearrangement.[5c] As anticipated, this process delivered a 4:1:4.1 **1**:**6**:**9** mixture paralleling the well-precedented 7 to 11:1 (i.e., **1** + **9**:**6**, 8.1:1) erythro selectivity[5b] anticipated for this transformation. *meso*-**9** was easily differentiated from *dl*-**1**, thus corroborating these stereochemical assignments, by ^{13}C-NMR: *meso*-**9** [($CDCl_3$) δ 16.3, 37.6, 55.7, 114.6, 141.4, and 180.1] and *meso*-**6** [($CDCl_3$) δ 18.1, 37.7, 56.3, 115.0, 140.4, and 180.2] each give only six carbon resonances while *d,l*-**1** [($CDCl_3$) δ 17.8, 19.0, 37.7, 37.8, 56.0, 115.7, 115.23, 139.7, 141.3, and 180.1] gives 10 carbon resonances. (b) See: Table III, p 2871 in ref 5c. (c) Ireland, R. E.; Mueller, R. H.; Willard, A. K. *J. Am. Chem. Soc.* **1976**, *98*, 2868.

0002-7863/87/1509-6844$01.50/0