through the following sequence without separation until a later stage. Oxidation of **9** to the aldehyde required carefully defined conditions (10 equiv of PCC in 0.02 M CH_2Cl_2 solution at 0 °C) but proceeded well (95% yield). The final carbon of the C-1 to C-10 segment was attached by reaction of the aldehyde **10** with the anion derived from dimethyl methylphosphonate (1.5 equiv) and *n*-BuLi (1.5 equiv) in THF at −78 °C, leading to the hydroxyphosphonate **11** which, without isolation, was oxidized (1.5 equiv, PCC, CH_2Cl_2, 25 °C) to the ketophosphonate **12** (91% overall from **10**). The C-1 hydroxyl group was then liberated selectively (10% Pd–C, H_2, EtOAc, 25 °C, 100%) and oxidized by Jones reagent (acetone, 0 °C) to the carboxylic acid **14** (72% yield), thus completing the synthesis of the C-1 to C-10 fragment of carbomycin B and leucomycin A_3.

The C-11 to C-15 fragment (**22**) (Scheme III) of these 16-membered ring antibiotics was synthesized in its optically active form from (*R*)-β-hydroxybutyric acid[15] as outlined in Scheme III. This hydroxy acid was sequentially converted to the methyl ester **17** (CH_2N_2, ether, 100%) and the methyl ester tetrahydropyranyl ether **18** (1.5 equiv of dihydropyran, 0.1 equiv of *p*-TsOH, ether, 0–25 °C, 65%). Transformation of **18** to the aldehyde was most efficiently carried out (75% yield overall) by reduction to the corresponding alcohol (3.0 equiv of DIBAL, CH_2Cl_2, −78 °C) followed by oxidation (1.5 equiv of PCC, CH_2Cl_2, 25 °C). Reaction of **19** with (carbethoxymethylene)triphenylphosphorane (1.5 equiv) in toluene at 70 °C led smoothly to the *E* α,β-unsaturated ester **20** in 84% yield. Completion of the construction of **22** required (i) reduction of **20** (3.0 equiv of DIBAL, CH_2Cl_2, −78 °C, 99%) to the corresponding allylic alcohol, (ii) oxidation (1.5 equiv of PCC, CH_2Cl_2, 25 °C, 87%) to the α,β-unsaturated aldehyde **21**, and finally (iii) deprotection (3:2:2 AcOH–THF–H_2O, 55 °C, 65%).

The two fragments **14** (1 equiv) and **22** (1.5 equiv) were then coupled under mild esterification conditions (1.5 equiv of DCC, 0.1 equiv of 4-(dimethylamino)pyridine, ether, 25 °C)[16] to afford the ketophosphonate aldehyde II (Scheme I) together with its C-8 epimer (70% yield). This mixture of epimers was subjected to our previously reported[6] ketophosphonate-based cyclization reaction[17] (1.5 equiv of Na, toluene, 40 °C, high dilution conditions) to produce the desired key intermediate I (Scheme I) (20% yield)[18,19] identical in all respects to the degradatively obtained material.[1] In view of the conversion of I to carbomycin B[1] and leucomycin A_3,[1] this work completes the synthesis of these 16-membered ring macrolide antibiotics.

The general strategy for the synthesis of the carbomycin B aglycone described here allows extension to the construction of other members of this important class of macrolide antibiotics including tylosin and amphotericin. Work in this area is continuing in our laboratories.

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(18) Separation of the two C-8 epimers of the acyclic series can be best carried out chromatographically (PLC, silica, 5% MeOH in ether) at the stage of compound **13** (R_f = 0.15) and its epimer (R_f = 0.13). The pure isomers can then be carried through to the ketophosphonate precursors II and its C-8 epimer which upon cyclization give different results. Thus II affords, in addition to I (R_f = 0.17, silica, 30% ether in petroleum ether), a more polar compound (Rf = 0.11) presumed to be the C-8 epimer of *I*, whereas only the C-8 epimer of I is obtained from the epimer of II. It is possible that under the reaction conditions the epimerization of I to its C-8 epimer is a favorable process whereas the reverse is not.
(19) This material is accompanied by a more polar compound presumed to be the C-8 epimer of I.[18]

Photoatropisomerization of "Picket-Fence" Porphyrins and Their Metal Complexes

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The occurrence of room temperature stable atropisomers (geometric isomers stable by virtue of restricted rotation about a formal single bond) has been demonstrated for a number of organic structures, most notably substituted biphenyls and more recently various ortho-substituted tetraphenylporphyrins.[1-4] For the biphenyl compounds it has been found that interconversion (in this case racemization) of the atropisomers can be accomplished by heating or photolysis.[5-7] The origin of the latter process has been ascribed to an increase in the central bond order occurring upon excitation which favors attainment of a symmetrical state.[6,7] The ortho-substituted tetraphenylporphyrins have been the subject of considerable recent investigation, particularly the *o*-amido-substituted picket-fence porphyrins[3,8] in which long chain or bulky ortho substituents prevent rotation about the porphyrin–phenyl bond at room temperature. Thus, four diastereomeric atropisomers, corresponding to the four ways of distributing the substituents between the two sides of the porphyrin plane (Figure 1), can be isolated. In the present paper we report results of an investigation of the photoinduced and thermal atropisomerization of two picket-fence porphyrins and their metal complexes. Atropisomerization phenomena are particularly interesting for these compounds in that the presence of four sites for isomerization suggests a variety of possible interconversion pathways. Our preliminary results suggest that a simple one-bond isomerization process occurs for both free-base and metal complexes in the thermal process but the photoatropisomerization of the free-base picket-fence porphyrins likely involves a different path.

The various atropisomers of *meso*-tetra(*o*-hexadecylamidophenyl)porphyrin (H_2PF,THA) were prepared by condensation of the desired atropisomer of *meso*-tetra(*o*-aminophenyl)porphyrin (H_2PF,Tam) with palmitoyl chloride.[9] Separated isomers of H_2PF,Tam were first obtained from a statistical mixture by preparative thin-layer chromatography (silica gel).[10] Samples of the (4,0) and (3,1) atropisomers of H_2PF,THA prepared in this way gave satisfactory elemental analyses (C, H, N).[11]

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(9) In analagous fashion to Collman's synthesis of *meso*-tetra(*o*-pivalamidophenyl)porphyrin.
(10) The general techniques employed by Collman et al. for the equilibration and separation of the four atropisomers of H_2PF,Tam have been used in this work. We found it necessary to use thin-layer rather than column chromatography for the isolation of all four isomers.

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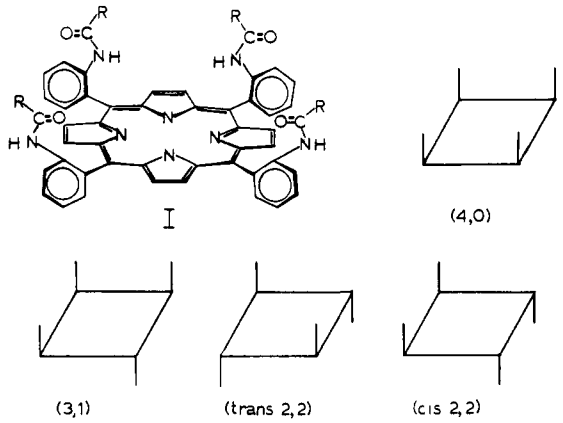

Figure 1. The structure of a picket-fence porphyrin (I = H_2PF,THA for R = $(CH_2)_{15}CH_3$; I = H_2PF,TPiv for R = $C(CH_3)_3$). The four atropisomers are depicted schematically.

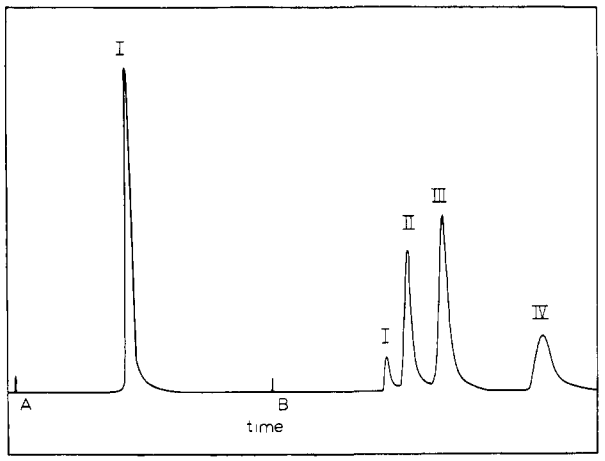

Figure 2. (A) Chromatogram of benzene solution of (4,0) H_2PF,THA detected at 423 nm (λ_{max} Soret band), (B) chromatogram of same colution following irradiation at $\lambda > 350$ nm, showing presence of all four atropisomers [I = (4,0); II = (trans 2,2); III = (3,1); IV = (cis 2,2)].

Electronic absorption spectra of these two isomers were found to be identical; extinction coefficients measured for the five visible bands were found to agree within experimental error (in benzene ϵ_{423} 290000, ϵ_{515} 1730, ϵ_{515} 1730, ϵ_{549} 4440, ϵ590 5130, ϵ_{646} 1400). Since absorption spectra remained constant during thermal and photochemical isomerizations (vide infra), comparable spectroscopic properties can be assumed for the (cis 2,2) and (trans 2,2) isomers. *meso*-Tetra(*o*-pivalamidophenyl)porphyrin (H_2PF,TPiv)[8] and the Zn(II),[12] Cu(II),[12] and Pd(II)[13] picket-fence porphyrin complexes were prepared by techniques previously reported. The purity of the metal complexes, in particular the absence of unmetallated porphyrin, was confirmed by high-performance liquid chromatography (HPLC) and fluorescence.

HPLC was found to be useful for separation of atropisomers and analysis of their relative concentrations in a mixture. For H_2PF,THA and ZnPF,THA, the isomers were well separated by using a Whatman Partisil 5/25 HPLC column with chloroform–hexane as the eluting solvent (Figure 2). Atropisomers of H_2PF,THA were detected by optical absorbance at 423 nm. Elution order of the four H_2PF,THA isomers was determined by synthesis of each isomer from the separated isomers of H_2PF,Tam. The identities of the H_2PF,Tam isomers were determined on the basis of their ratios in a thermally produced mixture (a statistical mixture is obtained upon heating in which the ratio of (4,0):(3,1):(cis 2,2):(trans 2,2) isomers is 1:4:2:1[8]). Since absorbance at 423 nm is the same for the four atropisomers of H_2PF,THA, it was possible to follow thermal and photolytic isomerization reactions quantitatively by HPLC. The total peak area of the four isomers was found to remain unchanged throughout an isomerization reaction when the total concentration of porphyrin was kept constant.

Table I. Rate Constants and Activation Parameters for the Thermal Atropisomerism of Picket-Fence Porphyrins and Metalloporphyrins

compd	T, °C	k, s^{-1}	$\Delta G^{\ddagger}$, kcal/mol	$\Delta H^{\ddagger}$, kcal/mol	ΔS, eu
H_2PF, THA	81	1.7×10^{-4}	27.0	13.0	−40
	108	4.5×10^{-4}	28.3		
	136	2.2×10^{-3}	29.2		
ZnPF, THA	111	1.8×10^{-5}	31.0	26.4	−12
	137	1.7×10^{-4}	31.3		
CuPF, THA	108	1.1×10^{-4}	29.4	24.1	−14
	138	1.2×10^{-3}	29.8		
H_2PF, TPiv	108	2.5×10^{-5}	30.5	32.2	+3
	138	5.6×10^{-4}	30.4		

Thermal interconversion of the picket-fence porphyrin free-base and metal complexes is unimportant at room temperature and below; however, heating of solutions results in interconversion of the atropisomers. This evidently involves a one-bond isomerization process in each case, since heating of pure (4,0) isomer gives initially only the (3,1) isomer. Isomerization rates and activation parameters obtained by studying the reaction in boiling toluene and boiling xylenes are given in Table I for H_2PF,THA and its copper and zinc complexes as well as for the more bulky H_2PF,TPiv. These values are comparable to those obtained for other systems of atropisomers,[14] such as *meso*-tetra(*o*-hydroxyphenyl)porphyrin ($\Delta G^{\ddagger}$ = 24 kcal/mol)[1] and *meso*-tetra(*o*-tolyl)porphinatonickel(II) ($\Delta G^{\ddagger} > 26$ kcal/mol).[2] For none of the bulky picket-fence porphyrins used in this study was a statistical mixture obtained. For H_2PF,THA the equilibrium mixture produced contained 4% (4,0), 47% (3,1), 29% (cis 2,2), and 20% (trans 2,2) isomers.

Irradiation with visible or ultraviolet light results in interconversion of the atropisomers of H_2PF,THA, H_2PF,TPiv, and their zinc and palladium complexes. No photoatropisomerization was observed for CuPF,THA, evidently due to the short excited-state lifetimes exhibited by copper porphyrins. To date, our most extensive investigations have focused on H_2PF,THA and its zinc complex. Irradiation of a degassed benzene solution of the (4,0) atropisomer of H_2PF,THA at 436 nm at room temperature leads to an initial quantum yield for disappearance of 0.005. The reaction evidently originates from the triplet state, since admission of oxygen completely quenches the photoatropisomerization even under conditions where there is negligible fluorescence quenching. For H_2PF,THA and its palladium and zinc complexes, photoatropisomerization was the only process observed after 1–2 h of irradiation at $\lambda > 350$ nm (100-W tungsten source; 10% T at 350 nm, 30% T at 380 nm) in benzene; however, for the irradiation of PdPF,THA in pentane other products were found to appear upon prolonged irradiation (10–20 h). These appear to be related to photoreduction and photoaddition reactions previously observed with other porphyrins and their metal complexes.[15] Irradiation for several hours of the various isomers or mixtures thereof leads to the same photostationary state in each case (for H_2PF,THA, the distribution is 5% (4,0), 48% (3,1), 27% (cis 2,2), and 20% (trans 2,2)).[16] This differs appreciably from a statistical mixture of isomers [12.5% (4,0), 50% (3,1), 25% (cis 2,2), and 12.5% (trans

(11) HPLC revealed that samples prepared in this way retained isomeric purity.
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(14) For rotational barriers of substituted biphenyl systems, see: Testa, B. "Principles of Organic Stereochemistry"; Marcel Dekker: New York, 1979 and references therein. Depending on number and bulk of ortho substituents, rotational energy barriers range from 14–30 kcal/mol.
(15) Mercer-Smith, J. A., unpublished results.
(16) For ZnPF,THA the photostationary state obtained is 7% (4,0), 49% (3,1), 26% (cis 2,2), and 18% (trans 2,2).

2,2)], only for the (4,0) and (trans 2,2) isomers. These deviations are not surprising, since the (4,0) isomer is the most sterically hindered of the four, while the (trans 2,2) is the least hindered isomer.

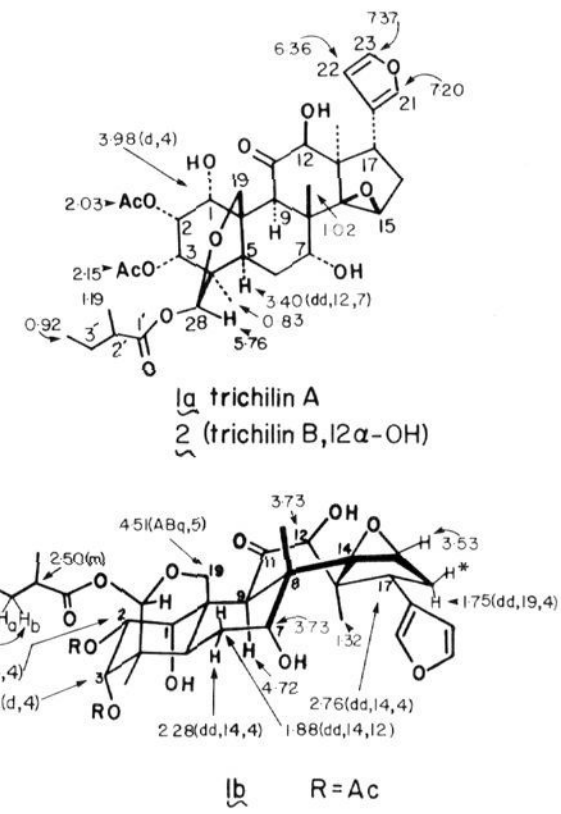
Time-dependent irradiations of each of the atropisomers of H_2PF,THA were carried out and monitored by HPLC. Since there are four potential sites for isomerization, there are several feasible mechanisms ranging from one-bond-only isomerization to simultaneous four-bond isomerization. It appears that for H_2PF,THA, photointerconversion of the atropisomers occurs neither by a step-by-step one bond process in which only one bond rotates (or is labilized) upon excitation nor by a random process in which all phenyl rings can rotate simultaneously in the excited state. Irradiation of (4,0) H_2PF,THA yields (3,1) H_2PF,THA and (trans 2,2) H_2PF,THA as initial photoproducts. Appearance of the (cis 2,2) isomer occurs only after a substantial buildup of the (3,1) isomer is achieved. Thus, it is evident that, due to either the geometry or the electron distribution of the porphyrin excited state, two trans porphine–phenyl bonds have lowered barriers to rotation. Studies of the initial photoproducts from the other isomers give results consistent with this picture. Although additional study is necessary to provide additional support, these results could be consistent with a picture of the free-base porphyrin triplet as a nonplanar structure warped or ruffled in such a way as to permit enhanced rotation of opposite bridge substituted groups.

Interestingly, in contrast to our findings with the free base, irradiation of (4,0) ZnPF,THA initially yields only (3,1) ZnPF,THA. Thus the presence of the metal apparently affects the excited state structure such that only a step-by-step one-bond isomerization process applies.[16,17] Studies with other picket-fence-type porphyrins and a variety of metal complexes are in progress to determine the effect of group size, excited state lifetime, and metal–ligand coordination on the rate and mechanism of the photoatropisomerization process.

Acknowledgment. We thank the U.S Army Research Office (Grant DAA629-77-6-0063) and National Institutes of Health (Grant GM 15,238) for support of this work.

(17) Initial product studies of PdPF,THA, as well as of H_2 PF,TPiv and its metal complexes have so far been hindered by incomplete resolution of isomers by HPLC.

Scheme I



[a] ^{1}H NMR data ($CDCl_3$), 300 MHz, in ppm (multiplicity and J values); the data are shown in both **1a** and **1b**. The 16β-H (*) is obscured by the acetate peaks.

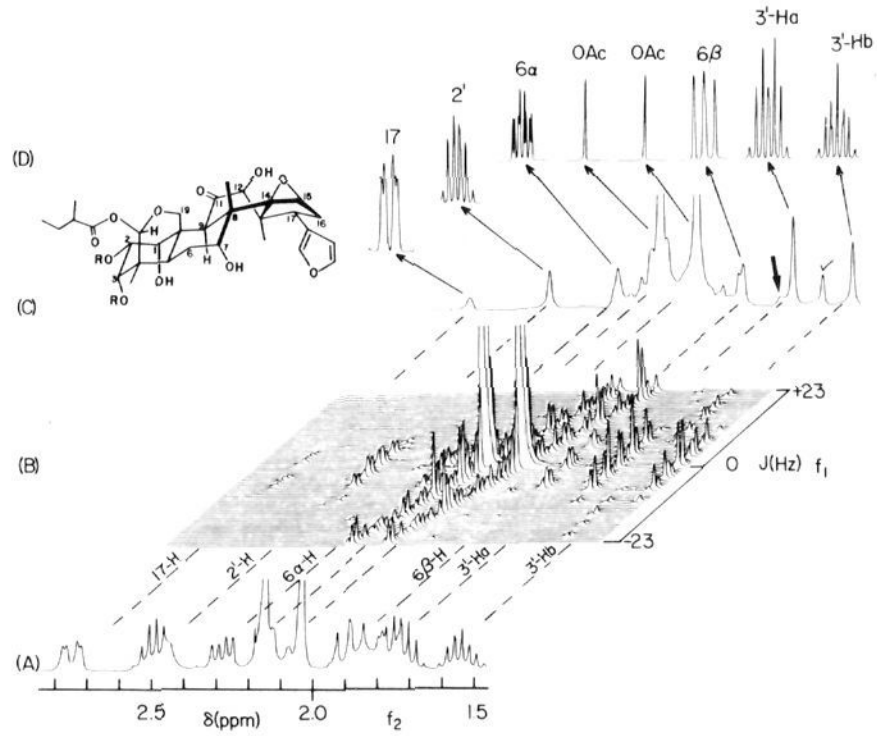


Figure 1. Partial spectra of **1** measured in $CDCl_3$ at 300 MHz. (A) Conventional NMR spectrum, (B) two-dimensional J spectrum (absolute value stacked plot, 64 traces are shown), (C) "proton-decoupled-proton" spectrum from a projection of (B) onto the horizontal (f_2) axis, and (D) J spectra (cross sections of the stacked plot). The short thick arrow in trace C is the 16α-H signal (see test).

Isolation and Structures of Trichilins, Antifeedants against the Southern Army Worm

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The root bark of the East African plant *Trichilia roka* (Meliaceae) has yielded a series of new limonoids, "trichilins", which are antifeedants[1] against the North American pest insects, the Southern army worm (*Spodoptera eridania*), and the Mexican bean beetle (*Epilachna varivestis*). They are one of the few antifeedants active against the voracious *S. eridania* caterpillar.[2] The isolation of the various congeners A–F, which was monitored by army worm assay, was a tedious process requiring very careful use of high-performance LC. The root bark (365 g)[3] was defatted with petroleum ether and extracted with ether to yield 2.9 g of an extract. The extract was flash chromatographed[4] with Et_2O/hexane, and the active fraction was rechromoatographed on a flash column with 1.5% MeOH/CH_2Cl_2. Repeated passage through a high-performance LC, Whatman Partisil M9 semiprep column, by using 0.4–1% MeOH in CH_2Cl_2 as the solvent finally gave the following trichilins: (A) 100 mg; mp 191–192 °C (dec); UV(MeOH) 213 nm (ϵ 4050); CD (MeOH) $\Delta\epsilon_{213}$ +2.6, $\Delta\epsilon_{304}$ −3.7. (B) 40 mg; UV 209 (ϵ 4600); CD $\Delta\epsilon_{217}$ +1.2, $\Delta\epsilon_{306}$ −1.9. (C) 2.8 mg; UV 214(ϵ 4400); CD $\Delta\epsilon_{212}$ +3.2, $\Delta\epsilon_{291}$ −1.0. (D) 7 mg; UV 212(ϵ 2800); CD $\Delta\epsilon_{288}$ +0.4, $\Delta\epsilon_{205}$ −1.1, $\Delta\epsilon_{298}$ − 3.1. (E) 2 mg.

(1) (a) Nakanishi, K. *Pontif. Accad. Sci. Scr. Varia* **1977**, *41*, 185. (b) Kubo, I.; Nakanishi, K. *ACS Symp. Ser.* **1977**, *62*, 165.

(2) Of the antifeedants that we have isolated so far, the trichilins are the only compounds besides azadirachtin (see ref 16) which are active against *S. eridania*. Electrophysiological studies are in progress to clarify the mode of action of antifeedants: Zack, C., unpublished data.

(3) Collected by the authors in June 1979 at Simba Hill near Mombasa, Kenya.

(4) Still, W. C.; Kahn, M.; Mitra, A. *J. Org. Chem.* **1978**, *43*, 2923. This rapid chromatography method is well suited for compounds which decompose from being in contact with SiO_2 over an extended period. The trichilins could not be isolated when treated with $CHCl_3$ and conventional SiO_2 columns.

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