carefully defined conditions (excess HF-pyridine complex, THF, 25 °C) to provide the primary alcohol **11** (70%) which was then oxidized to the carboxylic acid **12** by using Jones reagent (acetone, 0 °C, 95%). The use of the mildly acidic HF-pyridine complex[1b,16] reagent for the above desilylation provided a successful alternative to the basic, and in this case destructive, *n*-Bu_4NF reagent, and it should be useful in other cases as well. Acid treatment (10% aqueous HCl-THF, 1:1, 60 °C) of **12** or its methyl ester (CH_2N_2) gave the hydroxylactone **13** in 70% yield. The sterically demanding acetate **14** was smoothly formed by exposing **13** to excess Ac_2O (10 equiv), pyridine (10 equiv), and 4-(dimethylamino)-pyridine (1 equiv) in CH_2Cl_2 (25 °C, 85%). Treatment of **14** with $LiAl(O\text{-}t\text{-}Bu)_3H$ (2.1 equiv, THF, 25 °C) reduced both the ketone and the γ-lactone functions but not the macrolactone,[10b] giving rise to **15** (mixture of diastereoisomers, 40-50% yield based on ca. 50% conversion). DDQ (1.3 equiv, benzene, 25 °C) oxidation of **15** furnished selectively the dienone lactol **16** (86% yield). The lactone acetate **14** was more easily and directly prepared from the triol **8** by selective oxidation of the primary alcohol with Pt-O_2 in EtOAc (25 °C, 100%). Furthermore, this reaction provided considerable amounts of lactol **16** (30-40% yield based on ca. 50% conversion) by quenching prior to completion. The transformation of **16** to the final key intermediate **17** was smoothly achieved by ketalization ($HOCH_2CH_2OH$, camphorsulfonic acid, 25 °C).[17] Since **17** has already been converted to carbomycin B (**1**) and leucomycin A_3 (**2**),[4a,7d] the described sequence completes the synthesis of these macrolide antibiotics.

The total synthesis of the key intermediate **10** used in this synthesis is described in the accompanying paper.[9,18,19]

(16) For a related desilylation method using HF-H_2O-CH_3CN, see: Newton, R. F.; Reynolds, D. P.; Finch, M. A. W.; Kelly, D. R.; Roberts, S. M. *Tetrahedron Lett.* **1979**, 3981.

(17) Accompanying **17** in this ketalization procedure is the isomeric hydroxyethyl furanoside. The two products can be separated chromatographically.

(18) We are indebted to Professor S. Omura (Kitasato University, Japan) and Dr. H. Yamada (Yamanouchi Pharmaceutical Co., Japan) for generous gifts of leucomycin A_3.

(19) This work was financially supported by the National Institutes of Health (Grant GM26879), Merck Sharp and Dohme, and the A. P. Sloan Foundation.

Synthesis of 16-Membered-Ring Marcolide Antibiotics. 4.[1] Carbomycin B and Leucomycin A_3: Total Synthesis of Cyclic Key Intermediate

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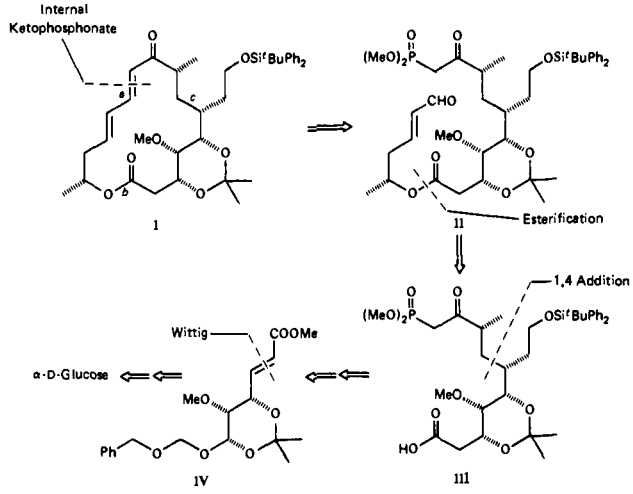
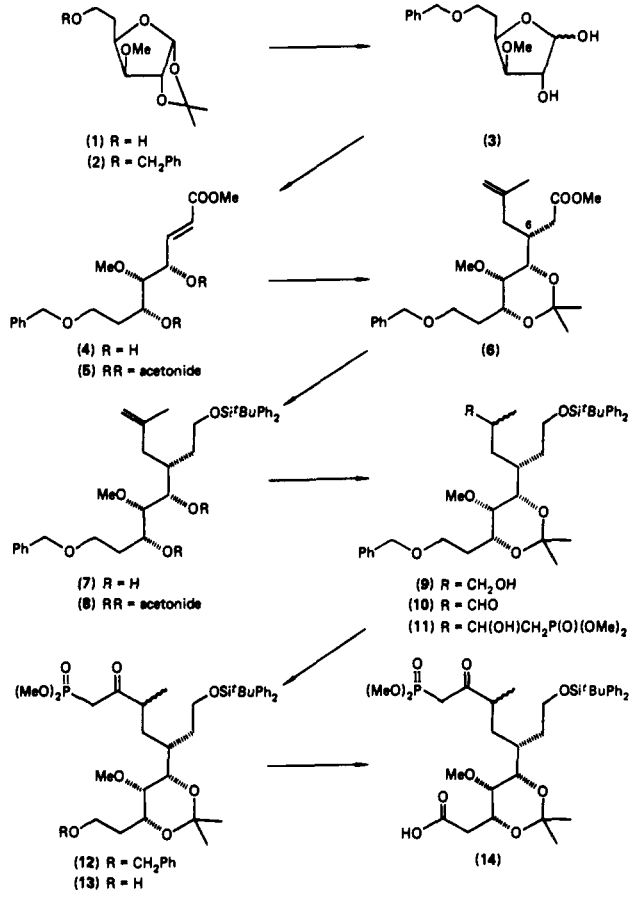
In the preceding paper[1] we described the partial synthesis of carbomycin B and leucomycin A_3 from the cyclic key intermediate I (Scheme I). In this paper we describe the total synthesis of this intermediate from α-D-glucose.

The synthesis of I was based on the retrosynthetic analysis depicted in Scheme I. Thus, careful inspection of structure I revealed three strategic bonds a, b, and c which upon sequential disconnection led to the progressively simpler intermediates II (internal ketophosphonate reaction), III (esterification), and IV (1,4 addition). Strategies for the synthesis of IV[3-5] from α-D-glucose and the stereoselective construction of bonds a[6] and c[3] were first reported by us[3,6] and subsequently by others.[4,5] Our convergent synthesis utilizes optically active starting materials and, therefore, produces I in its naturally occurring enantiomeric form.

Scheme I. Retrosynthetic Analysis of Cyclic Key Intermediate I



Scheme II



The synthesis of the C-1 to C-10 fragment (**14**, Scheme II) of these antibiotics started with α-D-glucose and proceeded via the readily available alcohol **1** (Scheme II) prepared as previously described.[3,5] Benzylation of **1** (1.3 equiv of $PhCH_2Br$, 1.3 equiv of NaH, DME, 60 °C) proceeded smoothly to afford **2**[7] (88%

† Fellow of the A. P. Sloan Foundation, 1979-1983; Recipient of a Camille and Henry Dreyfus Teacher-Scholar Award, 1980-1985.

(1) Part 3: Nicolaou, K. C.; Seitz, S. P.; Pavia, M. R. *J. Am. Chem. Soc.* **1981**, *103*, preceding paper in this issue.

(2) The total synthesis of this intermediate (I) was first reported at the 178th National Meeting of the American Chemical Society, Washington, DC, Sept 1979.

(3) Nicolaou, K. C.; Pavia, M. R.; Seitz, S. P. *Tetrahedron Lett.* **1979**, 2327.

(4) Ziegler, F. E.; Gilligan, P. J.; Chakraborty, U. R. *Tetrahedron Lett.* **1979**, 3371.

(5) Tatsuta, K.; Amemiya, Y.; Maniwa, S.; Kinoshita, M. *Tetrahedron Lett.* **1980**, 2837.

(6) Nicolaou, K. C.; Seitz, S. P.; Pavia, M. R.; Petasis, N. A. *J. Org. Chem.* **1979**, *43*, 4011.

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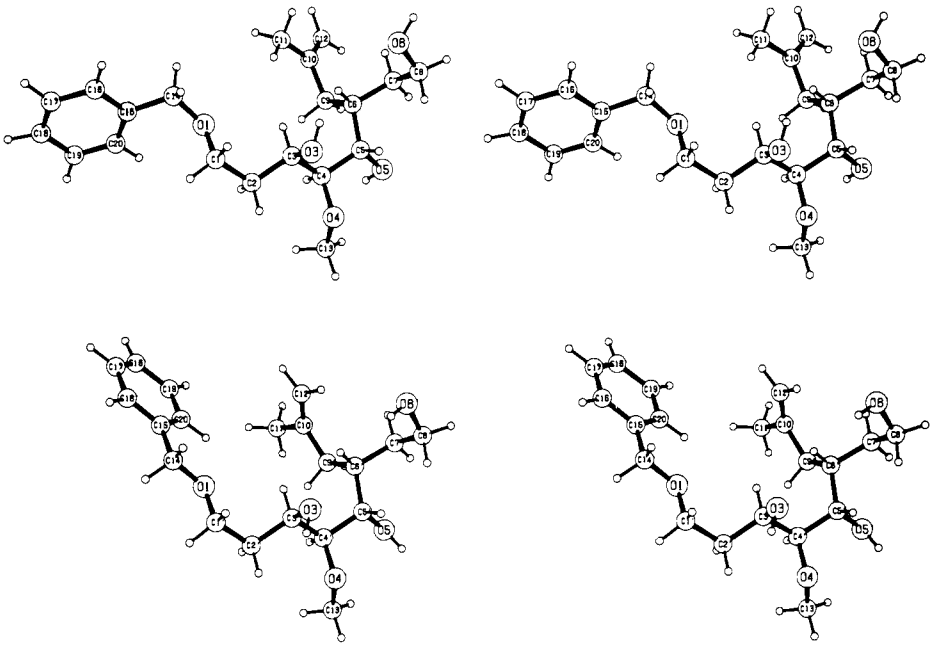
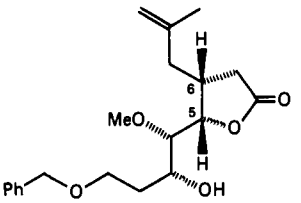


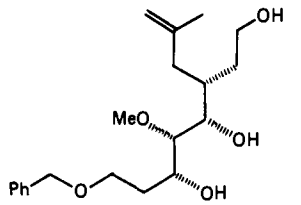
Figure 1. Stereorepresentation of triol **16** (courtesy of Dr. J. F. Blount and Mr. L. Todaro, ref 10).

yield) which was deprotected under acidic conditions (amberlite 1R-120, H_2O, 100 °C) leading to the lactol **3** (92%). Wittig reaction of **3** with (carbomethoxymethylene)triphenylphosphorane (1.3 equiv., toluene, 25 °C) furnished the *E* α,β-unsaturated methyl ester **4** (80%) which was immediately protected by exposure to 2,2-dimethoxypropane (8 equiv) and camphorsulfonic acid (0.1 equiv) in benzene at 25 °C, affording the acetonide **5** (87% yield) containing small amounts of its *Z* isomer (*E*:*Z* ca. 4:1). The unsaturated ester **5**, its *Z* isomer, or a mixture of the two proved to be exceptionally good Michael acceptors, undergoing efficient and stereoselective 1,4 additions and thus allowing for the extension of the chain at the 6-position. Thus, the cuprate reagent (4 equiv.) derived from methallyllithium[8] and cuprous iodide in THF at −40 °C reacted with **5** (−40 °C, 4 h) to afford, in 81% yield, a major product **6** and its C-6 diastereoisomer (ratio ca 93:7 by ^1H NMR spectroscopy).[9]

The stereochemical structure of **6** was proven by a combination of chemical and X-ray crystallographic[10] techniques. Thus, conversion of **6** to the triol **16** via lactone **15** [(1) catalytic 10%



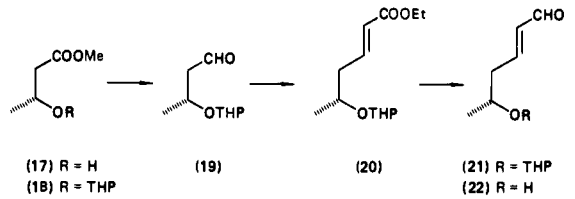
(15)



(16)

aqueous HCl–ethylene glycol, 25 °C, 90%; (2) LAH–ether, 0 °C, 98%] followed by chromatographic purification and crystallization from ether–hexane afforded colorless crystals, mp 50–50.5 °C. The X-ray-based[10] stereorepresentation of **16** is depicted in Figure 1. In connection with this stereochemical question, it was rather interesting to observe a larger coupling constant ($J_{5,6}$ = 6.6 Hz) for the *cis*-lactone **16** than its trans isomer[11] ($J_{5,6}$ = 4.4 Hz) despite

Scheme III



the usually noted reverse phenomenon.[12,13]

Having secured the correctness and homogeneity of the C-6 stereocenter, we returned to the main path of the synthesis by sequentially and selectively protecting the triol **16** [(a) 1.2 equiv of Ph_2-*t*-BuSiCl, 1.2 equiv of imidazole, DMF, 25 °C, 80%; (b) 8 equiv of 2,2-dimethyoxypropane, 0.1 equiv of camphorsulfonic acid, acetone, 98%) leading to the acetonide silyl ether **8**[14] via **7**. Hydroboration of **8** (1.0 equiv of borane, THF, 0 °C followed by NaOH–H_2O_2) gave the diastereomeric mixture of alcohols **9** in 92% yield. It was convenient to carry this mixture of epimers

(7) All new compounds gave satisfactory spectral, chromatographic, and analytical data. Yields refer to isolated, chromatographicaly homogeneous, and spectroscopically pure materials.

(8) Akiyama, S.; Hooz, J. *Tetrahedron Lett.* **1973**, 4115.

(9) Either geometrical isomer of **5** led to the same result and, therefore, the cuprate reaction was carried out routinely on the *E*/*Z* mixture.

(10) The X-ray analysis was carried out by Dr. J. F. Blount and Mr. L. Todaro of Hoffmann LaRoche, Nutley, NJ 07110. Full details will be published later.

(11) Obtained by (a) chromatographic separation of the organocuprate products (PLC, silica, 20% ether in petroleum ether, multiple developments; **6** R_f = 0.11; *epi*-**6**: R_f = 0.09) and (b) catalytic 10% aqueous HCl–ethylene glycol, 25 °C, 90%.

(12) Savostianoff, D.; Pfau, M. *Bull. Soc. Chim. Fr.* **1967**, *11*, 4162.

(13) Helpful discussions with Professors F. E. Ziegler and P. A. Bartlett on this subject are acknowledged.

(14) Important properties of key intermediates. **8**: R_f = 0.44 (silica, 40% ether in petroleum ether); $[\alpha]^{25}_D$ +17.16° (*c* 2.43, $CHCl_3$); IR ($CHCl_3$) ν_{max} 3070, 1646, and 1638 cm^{-1}; NMR (360 MHz, $CDCl_3$, Me_4Si), δ 7.63 (m, 4 H, aromatic), 7.33 (m, 11 H, aromatic), 4.67 and 4.60 (br s, 1 H each, olefin), 4.53 and 4.48 (d, *J* = 12 Hz, 1 H each, $PhCH_2O$), 3.90 (br d, *J* = 8.4 Hz, 1 H, H-3), 3.70 (t, *J* = 7.2 Hz, 2 H, H-6″), 3.57 (m, 3 H, H-1 + H-5), 3.45 (s, 3 H, OCH_3), 2.93 (s, 1 H, H-4), 2.5–1.5 (m, 7 H, H-2, H-6, H-6′, and H-7), 1.66 (s, 2 H, CH_2=CCH_3), 1.37 and 1.30 (s, 3 H each, acetonide), 1.04 (s, 9 H, *t*-Bu). 15: R_f = 0.19 (silica, 75% ether in petroleum ether); $[\alpha]^{25}_D$ + 22.28° (*c* 1.62, $CHCl_3$); IR ($CHCl_3$) ν_{max} 3490 (OH), 1772 (γ-lactone), and 1646 (olefin) cm^{-1}; NMR (360 MHz, $CDCl_3$, Me_4Si) δ 7.30 (m, 5 H, aromatic), 4.83 and 4.73 (s, 1 H each, olefin), 4.78 (dd, *J* = 6.6 and 3.8 Hz, 1 H, H-5), 4.53 (s, 2 H, $PhCH_2O$), 4.07 (m, 1 H, H-3), 3.76 (m, 1 H, H-1), 3.65 (td, *J* = 8.6 and 3.9 Hz, H-1′), 3.51 (s, 3 H, OCH_3), 3.35 (t, *J* = 2.7 Hz, 1 H, H-4), 3.12 (d, *J* = 4.5 Hz, 1 H, O*H*), 2.83 (m, 1 H, H-6), 2.45 (d, *J* = 8.4 Hz, 2 H, H-7), 2.20 + 2.10 (m, 1 H each, H-6′), 1.97 + 1.88 (m, 1 H each, H-2), 1.70 (s, 3 H, CH_2 = CCH_3). II: R_f = 0.28 (silica, 5% MeOH in ether); IR ($CHCl_3$) ν_{max} 2722 (C*H*O), 1731, 1708, and 1695 cm^{-1}; NMR (250 MHz, $CDCl_3$, Me_4Si) δ 9.55 (d, J = 7.6 Hz, 1H, C*H*O), 7.67 (m, 4H, aromatic), 7.41 (m, 6H, aromatic), 6.78 (dt, *J* = 15.9 and 7.0 Hz, H-13), 6.16 (dd, *J* = 15.7 and 8 Hz, 1 H, H-12), 5.15 (m, 1 H, H-15), 3.76 (m, 6 H, $P(OCH_3)_2$), 3.44 (s, 3 H, OCH_3), 1.36 and 1.30 (3 H each, acetonide), 1.03 (s, 9 H, t-Bu).

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.

Acknowledgment. We express our thanks to Dr. George T. Furst (Department of Chemistry, University of Pennsylvania) for his assistance in recording and interpreting NMR data, Dr. J. F. Blount and Mr. L. Todaro (Hoffmann-LaRoche) for the X-ray analysis, and Ms. Corinne E. Augelli for large scale preparations of early intermediates. This work was financially supported by the National Institutes of Health (Grant GM26879), Merck Sharp and Dohme, and the A. P. Sloan Foundation.

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(17) For some other recent ketophosphonate-based macrocyclizations, see: (a) Meyers, A. I.; Comins, D. L.; Roland, D. M.; Henning, R.; Shimizu, K. *J. Am. Chem. Soc.* **1979**, *101*, 7104. (b) Meyers, A. I.; Roland, D. M.; Comins, D. L.; Henning, R.; Fleming, M. P.; Shimizu, K. *Ibid.* **1979**, *101*, 4732. (c)Stork, G.; Nakamura, E. *J. Org. Chem.* **1979**, *44*, 4010. (d) Burri, K. F.; Cardone, R. A.; Chen, W. Y.; Rosen, P. *J. Am. Chem. Soc.* **1978**, *100*, 7069.
(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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