Design and Synthesis of a Trifunctional Chiral Porphyrin with C_2 Symmetry as a Chiral Recognition Host for Amino Acid Esters

Tadashi Mizutani,* Tadashi Ema, Takashi Tomita, Yasuhisa Kuroda, and Hisanobu Ogoshi*

Contribution from the Department of Synthetic Chemistry and Biological Chemistry, Faculty of Engineering, Kyoto University, Sakyo-ku, Kyoto, 606 Japan

*Received May 24, 1993. Revised Manuscript Received March 1, 1994**

Abstract: An intrinsic chiral recognition host, (*R*,*R*)- or (*S*,*S*)-[*trans*-5,15-bis(2-hydroxyphenyl)-10-{2,6-bis((methoxycarbonyl)methyl)phenyl}-2,3,17,18-tetraethylporphyrinato]zinc(II) (**1**), was synthesized by the coupling between (3,3′,4,4′-tetraethyl-5,5′-bis(α-hydroxy-2-methoxybenzyl)-2,2′-dipyrryl)methane (**8**) and dimethyl 2-(bis(2-pyrryl)-methyl)-1,3-benzenediacetate (**16**). This pyrrylmethanol method made it possible to perform the regiospecific coupling between differently functionalized dipyrromethane units. Host **1** was designed to have three recognition elements: metal coordination, hydrogen bond donor, and hydrogen bond acceptor (and/or steric repulsion) groups. These groups are arranged in a convergent fashion, forming a chiral recognition pocket. Host **1** was resolved into two enantiomers, (+)-**1** and (−)-**1**. The binding constants in $CHCl_3$ were determined by UV–vis titration. Host (+)-**1** was found to show an enantioselectivity of 2.0–2.8 in respect to L- and D-enantiomers of Ile–OMe, Leu–OMe, Leu–OBzl, Val–OMe, Pro–OMe, and Phe–OMe. Host (+)-**1** showed an enantioselectivity of 0.47 in respect to L- and D-enantiomers of serine benzyl ester, indicating that the enantioselectivity was reversed. Reference porphyrins **2**–**4**, which lack some of recognition groups, were also synthesized by the pyrrylmethanol method to clarify the roles of the recognition groups of (+)-**1** in thermodynamics of the binding processes. Total free energy change upon binding of L- and D-Ile–OMe to host (+)-**1** ($\Delta G°_{total}$ for L, −5.05, and D, −4.46 kcal/mol) was separated into three terms: metal coordination energy ($\Delta G°_{Zn}$), −4.15 kcal/mol; hydrogen bond energy ($\Delta\Delta G°_{OH}$), −1.30 kcal/mol; and steric repulsion energy ($\Delta\Delta G°^{L}_{COOMe}$ or $\Delta\Delta G°^{D}_{COOMe}$), +0.40 kcal/mol for L- and +0.99 kcal/mol for D-Ile–OMe. The third recognition group (CH_2CO_2Me) of (+)-**1** was found to destabilize the complexes due to steric repulsions. In contrast, the CH_2CO_2Me group was found to stabilize the complex between D-Ser–OBzl and (+)-**1**, suggesting that hydrogen bonding between the OH group of serine and the C=O group of (+)-**1** takes place. On the basis of these thermodynamic studies, chiral recognition was found to be achieved by cooperative functions of these three recognition groups.

Introduction

Chiral recognition and substrate recognition of a molecule is a fundamental process for a range of chemical and biological phenomena. Detailed understanding of the interactions operating in the recognition will be helpful in developing a new method of, for example, asymmetric synthesis and chromatographic enantiomer separation.[1] The molecular recognition of amino acids has been the important subject of investigations, since the strict amino acid recognition by aminoacyl tRNA synthetase[2] is not fully understood from a chemical point of view. How to recognize a flexible molecule like an amino acid by a synthetic host is thus an interesting problem. The minimum number of recognition groups necessary for chiral recognition depends on the shape of the host: three recognition groups should be fixed to a flat host, two recognition groups be fixed to a cylindrical host, and one recognition group be fixed to a helical host. In all cases, the recognition groups should be fixed in a convergent fashion to constitute a chiral recognition pocket. Therefore, to develop a chiral recognition (or substrate recognition) system, complementary disposition of recognition groups to make a chiral recognition pocket and exploitation of the synthetic route to the required structure should be simultaneously pursued. Several approaches to the design and preparation of a chiral or substrate recognition host have been reported.[3–7] Macrocyclic compounds such as cyclodextrins, cyclophanes, and crown ethers have been functionalized to chiral recognition hosts, and helical dimeric compounds have been used as chiral recognition hosts. It is

* Abstract published in *Advance ACS Abstracts*, April 15, 1994.

(1) (a) Pirkle, W. H.; Pochapsky, T. C. *J. Am. Chem. Soc.* **1987**, *109*, 5975. (b) Topiol, S.; Sabio, M.; Moroz, J.; Caldwell, W. B. *J. Am. Chem. Soc.* **1988**, *110*, 8367.

(2) (a) Alberts, B.; Bray, D.; Lewis, J.; Raff, M.; Roberts, K.; Watson, J. D. In *Molecular Biology of the Cell*; Garland Publishing, Inc.: New York, 1989; Chapter 5. (b) Attias, J.; Schlesinger, M. J.; Schlesinger, S. *J. Biol. Chem.* **1969**, *244*, 3810. (c) Brick, P.; Bhat, T. N.; Blow, D. M. *J. Mol. Biol.* **1989**, *208*, 83. (d) Kohno, T.; Kohda, D.; Haruki, M.; Yokoyama, S.; Miyazawa, T. *J. Biol. Chem.* **1990**, *265*, 6931.

(3) For chiral binaphthyl hosts, see: (a) Lehn, J. M.; Simon, J.; Moradpour, A. *Helv. Chim. Acta* **1978**, *61*, 2407. (b) Peacock, S. C.; Domeier, L. A.; Gaeta, F. C. A.; Helgeson, R. C.; Timko, J. M.; Cram, D. J. *J. Am. Chem. Soc.* **1978**, *100*, 8190. (c) Newcomb, M.; Toner, J. L.; Helgeson, R. C.; Cram, D. J. *J. Am. Chem. Soc.* **1979**, *101*, 4941. (d) Castro, P. P.; Georgiadis, T. M.; Diederich, F. *J. Org. Chem.* **1989**, *54*, 5835. (e) Castro, P. P.; Diederich, F. *Tetrahedron Lett.* **1991**, *32*, 6277. (f) Garcia-Tellado, F.; Albert, J.; Hamilton, A. D. *J. Chem. Soc., Chem. Commun.* **1991**, 1761.

(4) For chiral cyclophane hosts, see: (a) Petti, M. A.; Shepodd, T. J.; Barrans, R. E., Jr.; Dougherty, D. A. *J. Am. Chem. Soc.* **1988**, *110*, 6825. (b) Sanderson, P. E. J.; Kilburn, J. D.; Still, W. C. *J. Am. Chem. Soc.* **1989**, *111*, 8314. (c) Webb, T. H.; Suh, H.; Wilcox, C. S. *J. Am. Chem. Soc.* **1991**, *113*, 8554. (d) Hong, J.-I.; Namgoong, S. K.; Bernardi, A.; Still, W. C. *J. Am. Chem. Soc.* **1991**, *113*, 5111. (e) Bhattarai, K. M.; Bonar-Law, R. P.; Davis, A. P.; Murray, B. A. *J. Chem. Soc., Chem. Commun.* **1992**, 752. (f) Yoon, S. S.; Still, W. C. *J. Am. Chem. Soc.* **1993**, *115*, 823.

(5) For chiral molecular clefts, see: (a) Rebek, J., Jr.; Askew, B.; Ballester, P.; Doa, M. *J. Am. Chem. Soc.* **1987**, *109*, 4119. (b) Jeong, K.-S.; Muehldorf, A. V.; Rebek, J., Jr. *J. Am. Chem. Soc.* **1990**, *112*, 6144. (c) Famulok, M.; Jeong, K.-S.; Deslongchamps, G.; Rebek, J., Jr. *Angew. Chem., Int. Ed. Engl.* **1991**, *30*, 858.

(6) For cyclodextrin hosts, see: (a) Tabushi, I.; Kuroda, Y.; Mizutani, T. *J. Am. Chem. Soc.* **1986**, *108*, 4514. (b) Impellizzeri, G.; Maccarrone, G.; Rizzarelli, E.; Vecchio, G.; Corradini, R.; Marchelli, R. *Angew. Chem., Int. Ed. Engl.* **1991**, *30*, 1348. (c) Lipkowitz, K. B.; Raghothama, S.; Yang, J. *J. Am. Chem. Soc.* **1992**, *114*, 1554.

(7) For other chiral hosts, see: (a) Echavarren, A.; Galán, A.; Lehn, J.-M.; de Mendoza, J. *J. Am. Chem. Soc.* **1989**, *111*, 4994. (b) Dobashi, Y.; Dobashi, A.; Ochiai, H.; Hara, S. *J. Am. Chem. Soc.* **1990**, *112*, 6121. (c) Galan, A.; Andreu, D.; Echavarren, A. M.; Prados, P.; de Mendoza, J. *J. Am. Chem. Soc.* **1992**, *114*, 1511. (d) Wang, X.; Erickson, S. D.; Iimori, T.; Still, W. C. *J. Am. Chem. Soc.* **1992**, *114*, 4128.

0002-7863/94/1516-4240$04.50/0

important to design a host–guest system so that the nature of the elementary interactions can be clarified unambiguously.

Thermodynamic analysis of the recognition process gives a valuable outline. In molecular recognition processes, a negative enthalpy change (attractive forces between recognition groups) is utilized to produce a negative entropy change (an ordered state of guest or host). The question to be clarified is "which kind of negative entropy (translational, rotational, internal rotational, vibrational, or electronic entropy) should be produced to generate a function, and how much enthalpy is necessary to achieve it?" A usual molecular recognition process involves the restriction of translational motion of the guest. To achieve chiral recognition, the rotational motion of the guest relative to the host (three degrees of rotational motion) should be restricted in addition to the restriction of translational motion. For chiral recognition of molecules having internal degrees of motional freedom like amino acid derivatives, further restriction of internal rotation is necessary. Thus, the negative enthalpy change should effectively induce the negative entropy change associated with internal rotational motion of the guest molecule.

The assignment of the free energy changes of complexation to the interaction between each recognition group will be helpful in clarifying the mechanism of multiple molecular recognition. By considering $n - 1$ hypothetical intermediate states between the initial (an uncomplexed state) and the final states (a complexed state), the total free energy change can be separated into n terms.

$$\Delta G^\circ_{\text{total}} = \Delta G^\circ_1 + \Delta G^\circ_2 + \cdots + \Delta G^\circ_n \qquad (1)$$

where ΔG°_1 is the free energy difference between the initial state (an ideal solution containing a standard concentration (1 M) of host and a standard concentration of guest with no association complex formation) and the one-point adduct state (an ideal solution containing a standard concentration of a host–guest complex, in which only recognition group 1 of the host and recognition group 1 of the guest interact with each other and other recognition groups have no specific interactions). ΔG°_2 is similarly defined as the free energy change between the one-point adduct state and the two-point adduct state. Similarly, the total enthalpy change and the total entropy change can be separated into contributions from each recognition pair:

$$\Delta H^\circ_{\text{total}} = \Delta H^\circ_1 + \Delta H^\circ_2 + \cdots + \Delta H^\circ_n \qquad (2)$$

$$\Delta S^\circ_{\text{total}} = \Delta S^\circ_1 + \Delta S^\circ_2 + \cdots + \Delta S^\circ_n \qquad (3)$$

where ΔH°_i and ΔS°_i are defined in a manner similar to that for ΔG°_i. The one-point adduct state and two-point adduct state can be realized by using reference hosts and/or reference guests which lack some of the recognition groups.[8]

The entropy change can also be separated according to the motional changes.

$$\begin{aligned}\Delta S_{\text{total}} = {} & \sum_{\text{complex}} S_{\text{trans}} + S_{\text{rot}} + S_{\text{int.rot}} + S_{\text{vib}} + S_{\text{electronic}} + \\ & S_{\text{solvation}} - \sum_{\text{host}} S_{\text{trans}} + S_{\text{rot}} + S_{\text{int.rot}} + S_{\text{vib}} + S_{\text{electronic}} + \\ & S_{\text{solvation}} - \sum_{\text{guest}} S_{\text{trans}} + S_{\text{rot}} + S_{\text{int.rot}} + S_{\text{vib}} + S_{\text{electronic}} + \\ & S_{\text{solvation}} = \Delta S_{\text{trans}} + \Delta S_{\text{rot}} + \Delta S_{\text{int.rot}} + \Delta S_{\text{vib}} + \Delta S_{\text{electronic}} + \\ & \Delta S_{\text{solvation}} \qquad (4)\end{aligned}$$

where ΔS_{trans} is the translational entropy change of the host and guest, ΔS_{rot} is the rotational entropy change of the host and guest, $\Delta S_{\text{int.rot}}$ is the internal rotational entropy change of the host and guest, ΔS_{vib} is the vibrational entropy change of the host and guest, $\Delta S_{\text{electronic}}$ is the electronic entropy change of the host and guest, and $\Delta S_{\text{solvation}}$ is the entropy change due to changes in solvation. By considering the motional changes caused by the interaction between recognition groups, we can assign each term in eq 4 to the term in eq 3. For example, the ΔS°_1 term corresponds to the difference between the initial state and the one-point adduct state, which involves the translational entropy change and most of the rotational entropy change: $\Delta S^\circ_1 \sim -T(\Delta S_{\text{trans}} + \Delta S_{\text{rot}})$. The translational and rotational entropy change is the largest term in eq 4. The term $(-T(\Delta S_{\text{trans}} + \Delta S_{\text{rot}}))$ amounts to approximately 10–15 kcal/mol for porphyrin–amino acid complexation at 300 K. Therefore the recognition enthalpy $-\Delta H^\circ_1$ should be large enough to overcome $-T(\Delta S_{\text{trans}} + \Delta S_{\text{rot}})$, so that we can determine experimentally the free energy change associated with the first recognition pair: $\Delta G^\circ_1 = \Delta H^\circ_1 - T\Delta S^\circ_1 \sim \Delta H^\circ_1 - T(\Delta S_{\text{trans}} + \Delta S_{\text{rot}})$. Other entropy terms ($\Delta S_{\text{int.rot}}$, ΔS_{vib}, and $\Delta S_{\text{electronic}}$), which are much smaller in magnitude, can be ascribed to ΔS°_2, ΔS°_3, and so on. If the condition above does not hold, the enthalpy change $-\Delta H^\circ_1$ would be largely compensated for by a large negative entropy change ($\Delta S_{\text{trans}} + \Delta S_{\text{rot}}$). That results in a very small free energy change of ΔG°_1, and experimental determination of ΔG°_1 would be difficult.

To design a host which satisfies the requirement above, we utilized porphyrin's rigid framework and a metal coordination site. The coordination site serves as the first recognition element which is the strongest binding site for the amino group of the guest among recognition sites of the host.[9] Recognition groups were introduced to the phenyl groups in meso (5, 10, or 15) positions. With this strategy, it is easy to synthesize the analogous hosts with varying recognition groups (reference hosts), which turned out to be very effective in clarifying the roles of each recognition interaction in the molecular recognition processes. The conformational flexibility of functional groups introduced into the porphyrin framework was reduced due to the rigid structure of the aromatic macrocycle. Substituents on the β-position of the pyrrole were also used to further reduce the flexibility of recognition sites attached to the meso positions (rotation of the substituent at the meso position, atropisomerism). In addition to the rigidity and the metal coordination site of porphyrins, a large π-electron system of porphyrin can be a good probe when host–guest interactions are investigated. Even a small difference in complexation energy can be precisely determined by use of sensitive UV–vis spectroscopy or of large chemical shift anisotropy in NMR spectra.

Another advantage of using porphyrins as a host is that these host–guest systems could be a model for the substrate–heme protein interactions. For example, cytochrome P-450 binds camphor by hydrophobic interaction and hydrogen bonding to the Tyr side chain.[10] Fixation of a guest molecule in the proximity of a porphyrin plane is believed to be necessary to achieve the high selectivity of the enzyme reaction.

In the present paper we report the synthesis of a new chiral porphyrin and its reference porphyrins together with the features for binding of chiral α-amino acid esters to these hosts. A new method to introduce functional groups to the porphyrin periphery recently developed[11] was used to introduce recognition sites to the porphyrin regiospecifically. We introduced three recognition groups (zinc ion, *o*-hydroxyphenyl, and 2,6-bis((methoxycarbonyl)methyl)phenyl) into the porphyrin framework. Roles of

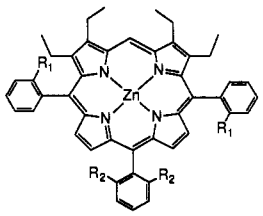
(8) The enzyme–substrate binding energy was analyzed in a similar manner, see: (a) Wells, T. N. C.; Fersht, A. R. *Biochemistry* **1986**, *25*, 1881. (b) Ho, C. K.; Fersht, A. R. *Biochemistry* **1986**, *25*, 1891.

(9) The condition $\Delta H^\circ_1 > -T(\Delta S_{\text{trans}} + \Delta S_{\text{rot}})$ and $\Delta G^\circ_1 >> \Delta G^\circ_2, \Delta G^\circ_3$ is one of the reasons that the chiral recognition free energy ($|\Delta G^{\circ}_{\text{L}}| - |\Delta G^{\circ}_{\text{D}}|$) is not large for the present system. In developing a host with high chiral selectivity, $\Delta G^\circ_1 \sim \Delta G^\circ_2 \sim \Delta G^\circ_3$. In that case, however, separation of $\Delta G^\circ_{\text{total}}$ is difficult.

(10) Poulos, T. L. In *Cytochrome P-450*; Ortiz de Montellano, P. R., Ed.; Plenum Press: New York, 1986; pp 505.

(11) (a) Wallace, D. M.; Smith, K. M. *Tetrahedron Lett.* **1990**, *31*, 7265. (b) Ema, T.; Kuroda, Y.; Ogoshi, H. *Tetrahedron Lett.* **1991**, *32*, 4529. (c) Mizutani, T.; Ema, T.; Tomita, T.; Kuroda, Y.; Ogoshi, H. *J. Chem. Soc., Chem. Commun.* **1993**, 520.

Chart 1



	R_1	R_2
1	OH	CH_2COOCH_3
2	OH	H
3	H	CH_2COOCH_3
4	H	H

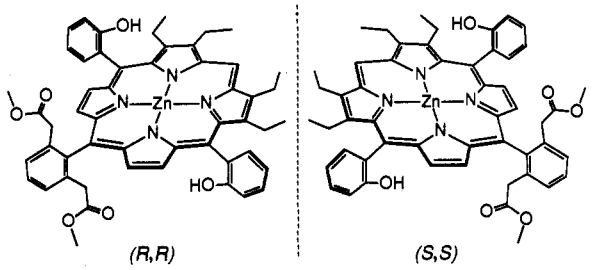
the three recognition sites, the zinc ion, the OH group, and the CH_2CO_2Me group, in thermodynamics of the binding processes of amino acid esters are discussed on the basis of the binding experiments.

Results and Discussion

Design and Synthesis of a Chiral Porphyrin by the Pyrrylmethanol Method. Host **1** and reference hosts **2–4**, which lack some of the recognition elements, were prepared to investigate the roles of the recognition groups in thermodynamics of the binding process. Hosts **1** and **2**, the trans isomers, have C_2 symmetry and thus two enantiomers exist (Figure 1). The reference hosts **3** and **4** are all optically inactive. In these hosts, the environments on both sides of the porphyrin plane are identical.

Host **1** has a metal coordination site (the zinc ion), a hydrogen bonding site (the phenolic hydroxyl group), and a steric repulsion and/or hydrogen bonding acceptor site (the methoxycarbonyl group). All these groups with varying recognition abilities form a chiral recognition pocket. Both the OH and CH_2CO_2Me groups are introduced into the ortho positions of the *meso*-phenyl moieties to maximize intermolecular contact with guest molecules. Zinc ion was used because the zinc complex of porphyrin is known to form only a 1:1 complex with amines.[12] In the design of host **1**, four ethyl groups on the β-positions of the pyrrole rings were introduced (1) to prevent the free rotation of the *o*-hydroxyphenyl groups (atropisomerism[13]), (2) to improve solubility of hosts in organic solvents, and (3) to facilitate synthesis of dipyrromethane (*vide infra*). It is quite important to give rigidity to the host structure and to fix the distance between recognition groups because flexibility of the recognition site will reduce the selectivity of molecular recognition considerably. In the reference host molecules, **2–4**, one of the two recognition groups (OH or CH_2CO_2Me groups) or both of them were replaced with hydrogen and were used as hosts to evaluate the free energy changes involving one-point adduct and two-point adduct states.

The porphyrin host **1** was prepared by the pyrrylmethanol method,[14] which has been reported earlier.[11] To synthesize the porphyrin with C_2 symmetry, we undertook a stepwise approach: an *o*-methoxyphenyl group was attached to a pyrrylmethanol unit, and a 2,6-bis((methoxycarbonyl)methyl)phenyl moiety was attached to a dipyrrylmethane unit (Scheme 1). These two units were prepared separately and coupled to give an unsymmetrically functionalized porphyrin in a regiospecific manner. Porphyrins unsymmetrically substituted at meso positions can be prepared suitably in this method, and this approach is especially effective if we design a host according to the concept of molecular preorganization.[15] Conventional cyclization of pyrroles and aldehydes (the mixed-aldehyde method[16] or the mixed-dipyrromethane method[17]) would give a mixture of many regioisomers when applied to the preparation of unsymmetrically substituted porphyrins, where separation is usually difficult and laborious. Hosts **1–4** were prepared by the condensation of appropriate pyrrylmethanols (**8** and **23**) with dipyrromethanes (**16** and **20**) (Scheme 2). The pyrrylmethanols (**8** and **23**) and dipyrromethanes (**16** and **20**) were prepared according to Scheme 1.



1

Figure 1. Two enantiomers of host **1**.

Compound **8** was prepared from diethylpyrrole **5** by acylation with anisoyl chloride followed by condensation with dimethoxymethane and reduction with $NaBH_4$. This compound (**8**) was acid sensitive and gradually decomposed in air, on silica gel TLC, and on alumina TLC, so it was used for the condensation reaction without purification. Attempts to prepare a pyrrylmethanol having no diethyl groups on the β-position via a similar route were unsuccessful because the condensation of 2-benzoylpyrrole with dimethoxymethane (Scheme 1, step c) did not proceed when 2-benzoylpyrrole was used instead of **6** or **21**. Therefore β-ethyl groups on the pyrrole were found to be necessary for the condensation reaction with dimethoxymethane to proceed. In view of the host design, the rotational freedom of *o*-hydroxyphenyl groups should be restricted. The rotation of the *o*-hydroxyphenyl groups causes fluctuation in the distance between recognition sites (OH···Zn distance), which in turn may reduce the selectivity of the binding. The β-ethyl groups provide the rigidity to the host structure and also improve the solubility of the host in organic solvents. To prevent fluctuation of the OH recognition groups, we also tried to prepare hosts with similar structures in which the *o*-hydroxyphenyl group was replaced by either the 2-hydroxy-6-methylphenyl or the 2-hydroxy-1-naphthyl group. However, attempts to reduce the carbonyl group to a hydroxymethine group (Scheme 1, step d) were unsuccessful when the *o*-methoxyphenyl group in **7** was replaced with either the 2-methoxy-6-methylphenyl or the 2-methoxy-1-naphthyl group. Steric hindrance by the naphthyl or methyl group may make the reducing agents ($NaBH_4$ and $LiAlH_4$) inaccessible to the carbonyl group.[18] We also observed that **7** was less reactive toward $NaBH_4$ than **22**, which has no methoxy groups on the phenyl rings. The reduction of **22** was completed in 6 h, while stirring for 48 h was necessary for the reduction of **7**. These results indicate that the reduction of the carbonyl groups is affected by the ortho-substituents on the benzene rings.

Another coupling unit **16** was prepared via eight steps from 1,3-dicyanobenzene (**9**). Methylation of **9** with LDA/MeI[19] followed by saponification[20] afforded dicarboxylic acid **11**. Insertion of methylene groups between the carboxylic groups and the benzene ring was accomplished by the Arndt–Eistert reaction, giving dimethyl ester **13**. The oxidation of the methyl group of **13** in two steps (photobromination and Me_2SO oxidation[21])

(12) (a) Miller, J. R.; Dorough, G. D. *J. Am. Chem. Soc.* **1952**, *74*, 3977. (b) Kirksey, C. H.; Hambright, P.; Storm, C. B. *Inorg. Chem.* **1969**, *8*, 2141.

(13) (a) Gottwald, L. K.; Ullman, E. F. *Tetrahedron Lett.* **1969**, 3071. (b) Eaton, S. S.; Eaton, G. R. *J. Am. Chem. Soc.* **1975**, *97*, 3660. (c) Freitag, R. A.; Mercer-Smith, J. A.; Whitten, D. G. *J. Am. Chem. Soc.* **1981**, *103*, 1226. (d) Young, R.; Chang, C. K. *J. Am. Chem. Soc.* **1985**, *107*, 898.

(14) (a) Little, R. G. *J. Heterocycl. Chem.* **1981**, *18*, 833. (b) Wallace, D. M.; Smith, K. M. *Tetrahedron Lett.* **1990**, *31*, 7265.

(15) Cram, D. J. *Angew. Chem., Int. Ed. Engl.* **1988**, *27*, 1009.

(16) (a) Little, R. G.; Anton, J. A.; Loach, P. A.; Ibers, J. A. *J. Heterocycl. Chem.* **1975**, *12*, 343. (b) Walker, F. A.; Balke, V. L.; McDermott, G. A. *Inorg. Chem.* **1982**, *21*, 3342. (c) Milgrom, L. R. *J. Chem. Soc., Perkin Trans. 1* **1984**, 1483.

(17) Aoyama, Y.; Uzawa, T.; Saita, K.; Tanaka, Y.; Toi, H.; Ogoshi, H. *Tetrahedron Lett.* **1988**, *29*, 5271.

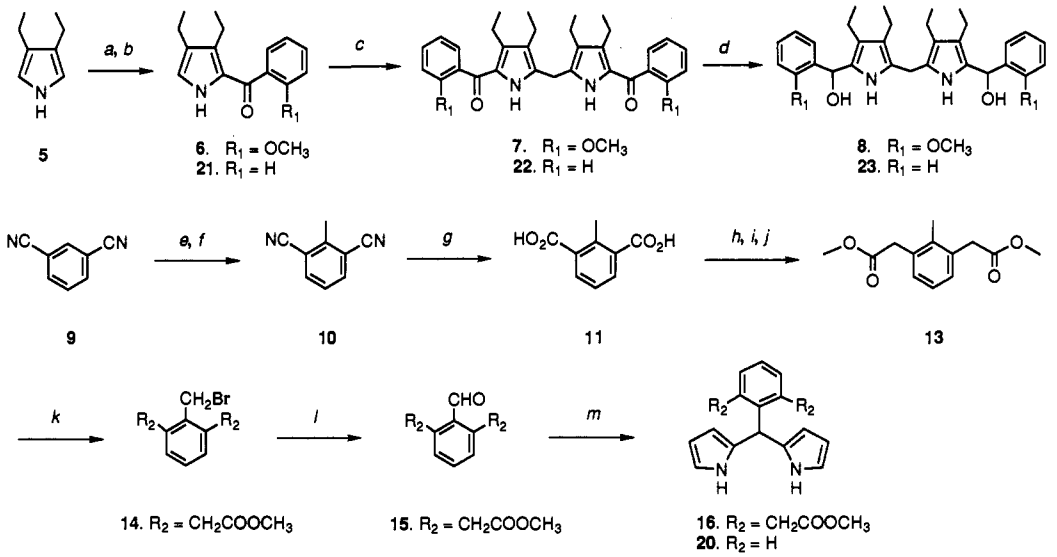
(18) No reaction occurred in the case of $NaBH_4$, and decomposition of the substrate was observed in the case of $LiAlH_4$.

(19) Krizan, T. D.; Martin, J. C. *J. Org. Chem.* **1982**, *47*, 2681.

(20) Lindsay, W. S.; Stokes, P.; Humber, L. G.; Boekelheide, V. *J. Am. Chem. Soc.* **1961**, *83*, 943.

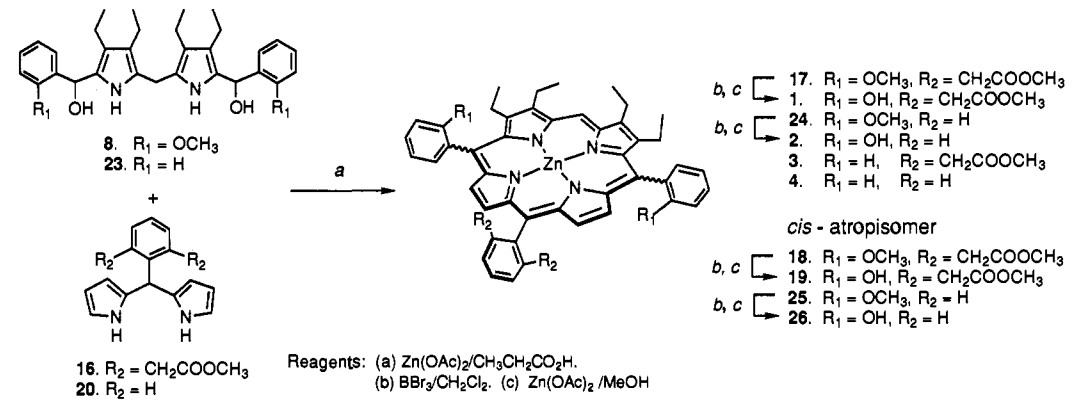
(21) Kornblum, N.; Jones, W. J.; Anderson, G. J. *J. Am. Chem. Soc.* **1957**, *79*, 4113.

Scheme 1[a]

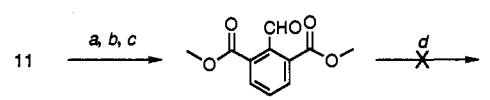


[a] Reagents: (a) EtMgBr/Et_2O. (b) *o*-$R_1C_6H_4COCl$/toluene. (c) $CH_2(OCH_3)_2$/conc. HCl/EtOH. (d) $NaBH_4$/EtOH. (e) LDA/THF. (f) CH_3I. (g) KOH/H_2O. (h) $SOCl_2$. (i) CH_2N_2/Et_2O. (j) Ag_2O/MeOH. (k) $Br_2/CCl_4/h\nu$. (l) $Me_2SO/NaHCO_3$. (m) pyrrole(excess)/*p*-$CH_3C_6H_4SO_3H$/MeOH.

Scheme 2[a]



Scheme 3[a]



[a] Reagents: (a) H_2SO_4/MeOH. (b) $Br_2/CCl_4/h\nu$. (c) $Me_2SO/NaHCO_3$. (d) pyrrole(excess)/*p*-$CH_3C_6H_4SO_3H$/benzene.

afforded aldehyde **15**. The bromination reaction was carried out by carefully controlling the amount of added bromine, the rate of the bromine addition, and the reaction temperature because the methylene groups of **13** were also brominated under uncontrolled conditions. The condensation with excess pyrrole afforded the desired dipyrromethane unit **16**.

We first attempted to carry out the condensation of dimethyl 2-formyl-1,3-benzenedicarboxylate (**27**) with pyrrole (Scheme 3). Compound **27** was similarly prepared from 2-methyl-1,3-benzenedicarboxylic acid (**11**). However, the condensation reaction did not proceed at room temperature. By refluxing the reaction mixture in benzene, **27** disappeared, giving a mixture of many unidentified products. This unusual reactivity of **27** toward pyrrole can be ascribed to the presence of two electron-withdrawing groups at the positions ortho to the formyl group. We also found that 2,6-dinitrobenzaldehyde did not react with pyrrole under similar conditions.[22] This difficulty was avoided by using compound **15**, where methylene groups were inserted between the methoxycarbonyl groups and the benzene ring.

Cyclization to the porphyrin ring was performed by a modified Adler–Longo procedure.[23] Pyrrylmethanol **8** and dipyrromethane **16** (both ca. 0.02 M) were condensed in propionic acid in the presence of $Zn(OAc)_2$ at 95 °C, giving a mixture of trans (**17**) and cis (**18**) isomers without forming any other regioisomers (Scheme 2). The yield was in the range of 9–17%. The cyclization completed within 10 min at 90–100 °C. Reaction temperatures higher than 105 °C gave many byproducts which exhibit close R_f values on TLC, and consequently, chromatographic separation was difficult.[24] The addition of $Zn(OAc)_2$ was needed to obtain reproducible results. Other cyclization conditions (trifluoroacetic acid/CH_2Cl_2,[22,26] or *p*-toluenesulfonic acid/MeOH,[14d] followed by oxidation with 2,3,5,6-tetrachlorobenzoquinone) were also employed but gave unsatisfactory results (no product obtained and only 2% yield, respectively).

The separation of the trans (**17**) from cis isomers (**18**) can be performed at this stage (or after cleaving the methyl ether) by

(22) (a) Lecas-Nawrocka, A.; Levisalles, J.; Mariacher, C.; Renko, Z.; Rose, E. *Can. J. Chem.* **1984**, *62*, 2054, 2059. (b) Lindsey, J. S.; Wagner, R. W. *J. Org. Chem.* **1989**, *54*, 828.

(23) Adler, A. D.; Longo, F. R.; Finarelli, J. D.; Goldmacher, J.; Assour, J.; Korsakoff, L. *J. Org. Chem.* **1967**, *32*, 476.

(24) ^1H NMR and UV-vis spectra of the byproduct indicated that the phenyl groups at the meso positions disappeared. See also ref 25.

(25) Ogoshi, H.; Sugimoto, H.; Nishiguchi, T.; Watanabe, T.; Matsuda, Y.; Yoshida, Z. *Chem. Lett.* **1978**, 29.

(26) Lindsey, J. S.; Schreiman, I. C.; Hsu, H. C.; Kearney, P. C.; Marguerettaz, A. M. *J. Org. Chem.* **1987**, *52*, 827.

column chromatography on silica gel. Cleavage of the methyl ether by use of BBr_3[27] was carried out without affecting the ester groups, giving the free base of trans (**1**) or cis (**19**) host molecules. In the ether cleavage reaction, longer reaction time lowered the yield considerably. Because BBr_3 induced demetalation of the porphyrin complex, zinc was inserted again. The ^1H NMR spectrum of the less polar fraction (**1**) is characterized by a single signal assignable to the ester methyl protons appearing at 2.89 ppm, while that of the more polar fraction (**19**), by two signals assignable to the ester methyl protons at 2.87 and 2.88 ppm. In the cis isomer, the hydroxyl groups on the phenyl rings bring about different magnetic environments for the ester methyl protons above and below the porphyrin ring. Therefore the more polar fraction (**19**) was identified as the cis and less polar fraction (**1**) as the trans isomer. Other evidence for the above assignment is that the less polar fraction isomer can be separated into two peaks by HPLC with a chiral column, while the more polar fraction isomer cannot. This observation is consistent with the fact that the trans isomer is optically active and the cis isomer is not. The assignment above agreed with a trend observed for the similar systems[29] that the cis isomer is more polar than the trans isomer. Trans to cis (and cis to trans) isomerization (atropisomerization[13]) occurred in $CHCl_3$ solution for 1–2 days at 65 °C and for 1 month at room temperature. The first-order rate constant[28] for the atropisomerization in $CHCl_3$ at 25 °C was 1.56×10^{-6} s^{-1} for the free base of **1** and 1.49×10^{-7} s^{-1} for zinc complex **1**. Attempts to prepare similar hosts which have more bulky substituents at the meso positions and thus are less likely to undergo atropisomerization were unsuccessful (*vide supra*). The separated sample can be stored at −20 °C as a dry powder for at least several months.

The proton NMR spectra of the C_2 symmetric porphyrin **1** are characterized by two sets of signals corresponding to the ethyl protons at pyrrole β-positions. One set of the ethyl protons appears as a triplet and a quartet at almost the same chemical shifts as those observed for octaethylporphyrin. The other set of the ethyl protons appears at a higher magnetic field, as would be expected for ethyl protons in the shielding region of a nearby phenyl group. The chemical shifts of the hydroxyl protons and the ester protons of host **1** are almost the same as those of the corresponding hydroxyl protons of host **2** and the ester protons of host **3**, respectively. These observations together with the following binding experiments indicate that intramolecular hydrogen bonding between the CH_2CO_2Me and the OH group does not occur in host **1**. On the basis of these observations, it is expected that the two groups (OH and CH_2CO_2Me) act as independent recognition sites for the guest binding.

The enantiomer separation of the free base of **1** was performed by HPLC with a chiral column.[30] Host (+)-**1** was used for the binding experiments. Both enantiomers exhibited very weak circular dichroism (CD) in the Soret region. Therefore, CD spectra were recorded after converting **1** to the benzyl ether, [*trans*-5,15-bis(2-(benzyloxy)phenyl)-10-{2,6-bis(methoxycarbonyl)methyl)phenyl}-2,3,17,18-tetraethylporphyrinato]zinc(II). The enantiomer separation of the benzyl ether was also carried out by HPLC.[31] It was confirmed that the benzyl ether of (+)-**1** was also the first eluted fraction on this column. The benzyl ether of (+)-**1** exhibited positive and negative peaks in the Soret region ($[\theta] = -1.6 \times 10^4$ at 420 nm, $[\theta] = +1.0 \times 10^4$ at 431 nm), as did that of (−)-**1** ($[\theta] = +1.6 \times 10^4$ at 420 nm, $[\theta] = -1.0 \times 10^4$ at 431 nm).

Reference hosts **2**–**4** were also prepared in a similar manner (Schemes 1 and 2).

Table 1. Binding Constants (K) of Amino Acid Esters and Zinc Porphyrins[a]

	K (M^{-1})			
	(+)-**1**	**2**[b]	**3**	**4**
L-Ile–OMe	6 780	13 700	780	1 420
D-Ile–OMe	2 420			
L-Leu–OMe[c]	6 160	13 300	680	1 130
D-Leu–OMe[c]	2 460			
L-Val–OMe	6 130	12 600	650	1 240
D-Val–OMe	2 440			
L-Pro–OMe	48 100	113 000	6 700	13 200
D-Pro–OMe	21 100			
L-Phe–OMe	4 130	9 650	1 000	1 770
D-Phe–OMe	2 060			
L-Ala–OMe	1 590	3 460	720	740
D-Ala–OMe	1 420			
L-Leu–OBzl	3 450	10 100	560	1 060
D-Leu–OBzl	1 540			
L-Ser–OBzl	1 340	2 400	920	480
D-Ser–OBzl	2 840			
(*R*)-1-PhEtNH_2	700	1 460	1 250	1 570
(*S*)-1-PhEtNH_2	680			
aminoethanol	5 040	4 500	5 250	2 410

[a] At 15 °C in $CHCl_3$. Standard deviations were within 4%. [b] A racemic mixture of (±)-**2** was used throughout the present study. [c] The binding constants for the enantiomer host (−)-**1** were K((−)-**1**, L-Leu–OMe) = 2660 M^{-1} and K((−)-**1**, D-Leu–OMe) = 5490 M^{-1}.

Enantioselective Binding of Amino Acid Esters by the Chiral Porphyrin Host. A. Binding Constant Determinations by Visible Spectroscopic Titration Experiments. Association constants between hosts **1**–**4** and a series of amino acid esters (methyl esters of alanine, valine, leucine, isoleucine, phenylalanine, and proline and benzyl esters of serine and leucine), 1-phenylethylamine (1-PhetNH_2), and aminoethanol were determined by UV–vis spectrophotometric titration. The methyl ester of serine showed poor solubility in $CHCl_3$, so the benzyl ester was used instead. Results are summarized in Table 1. For optically active host **1**, the first eluted enantiomer (+)-**1** was used. The ratios of the binding constants of (+)-**1** and the L-amino acid ester to those of (+)-**1** and the D-isomer were in the range 2.0–2.8 for Ile–OMe, Leu–OMe, Leu–OBzl, Val–OMe, Pro–OMe, and Phe–OMe, and 0.5 for Ser–OBzl. It was confirmed that the enantiomer host (−)-**1** showed the reversed enantioselectivity for Leu–OMe. Host (+)-**1** showed enantioselectivities except for Ala–OMe and 1-PhetNH_2. It is interesting to note that the enantioselectivity was reversed for Ser–OBzl. Before discussing the mechanism of the chiral recognition, we first discuss the roles of the three recognition groups, zinc ion (a metal coordination site), the *o*-hydroxyphenyl groups (a hydrogen bond donor site), and the 2,6-bis((methoxycarbonyl)methyl)phenyl group (a hydrogen bond acceptor and/or steric repulsion site) of host (+)-**1**, by comparing the association constants between hosts (+)-**1** and **2**–**4** and a series of amino acid esters.

The total free energy change ΔG°_{total} for the complexation of **1** and the guest is the free energy difference between the initial uncomplexed state (an ideal solution containing a standard concentration of **1** and the guest) and the final complexed state. We assume two intermediate states between the initial state and the final state: (1) a one-point adduct state in which the coordination interaction between the Zn ion and the NH_2 group is operating and other specific interactions (the hydrogen bonding, for example) are absent, and (2) a two-point adduct state in which both the coordination interaction between the Zn ion and the NH_2 group and the hydrogen bonding interaction between

(27) McOmie, J. F. W.; Watts, M. L.; West, D. E. *Tetrahedron* **1968**, *24*, 2289.

(28) The rate of trans to cis isomerization was measured. The molar ratio of trans to cis at equilibrium was 1:1 for both **1** and the free base of **1**.

(29) (a) Ogoshi, H.; Saita, K.; Sakurai, K.; Watanabe, T.; Toi, H.; Aoyama, Y. *Tetrahedron Lett.* **1986**, *27*, 6365. (b) Aoyama, Y.; Saita, K.; Toi, H.; Ogoshi, H.; Okamoto, Y. *Tetrahedron Lett.* **1987**, *28*, 4853.

(30) HPLC was performed by use of YMC A-K03 (Yamamura Chemical Labs. Co., Ltd.) using hexane:$CHCl_3$:ethanol = 19:80:1 as the eluent. Because the peak separation was not complete, column chromatographic separation was repeated until the optically pure free base of (+)-**1** was obtained. Attempts to resolve the zinc complex **1** were unsuccessful.

(31) A chiral column, Daicel Chiralcel OD, was used with hexane:isopropyl alcohol = 4:1 as the eluent.

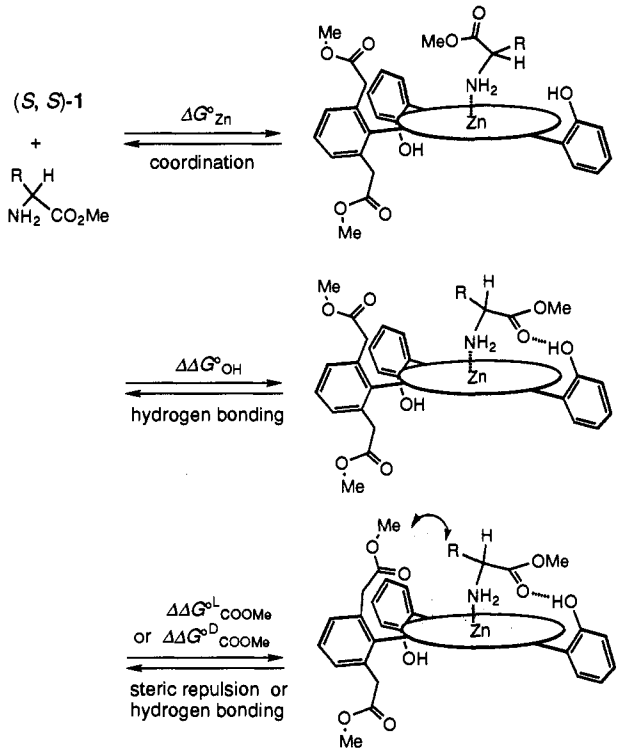


Figure 2. Schematic representation of the roles of the recognition groups. The binding to (*S*,*S*)-host **1** of amino acid esters is assumed to occur in three steps.

Table 2. Contribution from Various Recognition Interactions to Total Free Energy Changes upon Complexation (kcal/mol)[a,b]

	$\Delta G°_{Zn}$	$\Delta\Delta G°_{OH}$	$\Delta\Delta G°^{L}_{COOMe}$	$\Delta\Delta G°^{D}_{COOMe}$	$\Delta\Delta G°_{COOMe}$
Ile–OMe	–4.15	–1.30	+0.40	+1.00	+0.35
Leu–OMe	–4.02	–1.41	+0.44	+0.97	+0.29
Val–OMe	–4.08	–1.33	+0.41	+0.94	+0.37
Pro–OMe	–5.43	–1.23	+0.49	+0.96	+0.39
Phe–OMe	–4.28	–0.97	+0.49	+0.89	+0.33
Ala–OMe	–3.78	–0.89	+0.45	+0.51	+0.02
Leu–OBzl	–3.99	–1.29	+0.61	+1.08	+0.37
Ser–OBzl	–3.53	–0.92	+0.33	–0.10	–0.37
1-PhEtNH$_2$	–4.24	+0.04	+0.44	+0.42	+0.13
aminoethanol	–4.46	–0.36	*c*	*c*	–0.45

[a] At 15 °C in $CHCl_3$. [b] $\Delta G°_{Zn} = -RT \ln K(4)$, $\Delta\Delta G°_{OH} = -RT \ln (K((\pm)\text{-}2)/K(4))$, $\Delta\Delta G°^{L}_{COOMe} = -RT \ln (K((+)\text{-}1,L)/K((\pm)\text{-}2))$, $\Delta\Delta G°^{D}_{COOMe} = -RT \ln (K((+)\text{-}1, D)/K((\pm)\text{-}2))$, $\Delta\Delta G°_{COOMe} = -RT \ln (K(3)/K(4))$. [c] $-RT \ln (K((+)\text{-}1)/K((\pm)\text{-}2)) = -0.06$ kcal/mol.

the OH group of the host and the C=O group of the guest are operating while there is no specific interaction between the CH_2CO_2Me group of host **1** and the guest (Figure 2). These two intermediate states are hypothetical, and the thermodynamic properties between these states cannot be determined directly. We assume that the complex between **4** and the guest approximates the one-point adduct state and the complex between **2** and the guest approximates the two-point adduct state. Thus we can determine the free energy changes between these states and consequently can assign these free energy changes to each recognition element.

Free energy changes associated with the metal coordination interaction between the zinc ion and the amino group of the guest were estimated from the association constants for host **4**. The metal coordination energies ($\Delta G°_{Zn}$) were calculated by $\Delta G°_{Zn} = -RT \ln K(4)$ and were almost the same for Ile–OMe, Leu–OMe, and Val–OMe (Table 2). Much stronger binding was observed for Pro–OMe, which can be ascribed to a strong basicity of the secondary amino group of proline. Slightly stronger binding for Phe–OMe may be ascribed to the additional attractive energy owing to the aryl–aryl interaction.

The *o*-hydroxyphenyl groups of hosts (+)-**1** and **2** were also found to stabilize the host–guest complexes as evident from comparisons of $K(2)$ and $K(4)$ (or of $K((+)\text{-}1)$ and $K(3)$). The stabilization energies owing to the OH group were evaluated from $\Delta\Delta G°_{OH} = -RT \ln (K(2)/K(4))$ and are listed in Table 2. The stabilization energies amount to –1.2 to –1.4 kcal/mol for Ile–OMe, Leu–OMe, Leu–OBzl, Val–OMe, and Pro–OMe, whereas the stabilization energies for Phe–OMe, Ala-OMe, and Ser–OBzl were smaller. These energies and trends are similar to the binding of amino acid esters to [*trans*-5,15-bis(2-hydroxynaphthyl)-2,3,7,8,12,13,17,18-octaethylporphyrinato]-zinc(II),[32] indicating that the stabilization can be ascribed to hydrogen bonding between the OH group of the host and the C=O group of the guest. The hydrogen bonding interaction has been well characterized by thermodynamic analysis, ^1H NMR, and circular dichroism spectra.[32] A comparison of $K((+)\text{-}1)$ and $K(3)$ indicates that the OH groups in (+)-**1** can also stabilize the complex even in the presence of the 2,6-bis((methoxycarbonyl)-methyl)phenyl group. These observations indicate that hydrogen bonding between the OH groups of host (+)-**1** and the C=O groups of the guest takes place. The differential stabilization energies calculated from $-RT \ln (K((+)\text{-}1)/K(3))$ range from –1.1 to –1.3 kcal/mol for L-Ile–OMe, L-Leu–OMe, L-Val–OMe, and L-Pro–OMe and –0.6 to –0.8 kcal/mol for the D-enantiomers. These values of free energy differences are comparable to the hydrogen bonding energies observed for similar systems,[32] supporting that no intramolecular hydrogen bonding between the OH groups and the CH_2CO_2Me groups takes place within host (+)-**1**.

The third recognition group, the CH_2CO_2Me group, was found to serve three different functions depending on the chirality and the side chain group of the guest. It acted as (1) a minor repulsive site for L-amino acid esters, (2) a major repulsive site for D-amino acid esters except Ser–OBzl, and (3) an attractive interaction site for D-Ser–OBzl. The repulsive function of the CH_2CO_2Me group can be clearly indicated by comparing $K((+)\text{-}1)$ and $K(2)$ or $K(3)$ and $K(4)$. Table 1 shows that the ratios of $K((+)\text{-}1)$ to $K(2)$ ranged between 0.42 and 0.56 for all the L-isomers. This result implies that the CH_2CO_2Me groups of host (+)-**1** restrict the size of the recognition pocket, resulting in a weak inhibitory effect on the binding. These effects were not sensitive to the variations of the side chain groups of the guests. In the case of D-isomers, the ratios of $K((+)\text{-}1)$ to $K(2)$ ranged between 0.18 and 0.21 except for Ser–OBzl, Ala–OMe, and 1-PhEtNH$_2$, indicating the larger inhibitory effects of the CH_2CO_2Me groups in the D-enantiomers. The repulsive energies between the CH_2CO_2Me groups of host (+)-**1** and the guests were calculated by $\Delta\Delta G°^{L}_{COOMe} = -RT \ln (K((+)\text{-}1, L)/K(2))$, $\Delta\Delta G°^{D}_{COOMe} = -RT \ln (K((+)\text{-}1, D)/K(2))$, and $\Delta\Delta G°_{COOMe} = -RT \ln (K(3)/K(4))$ and are listed in Table 2. For most of the complexes, $\Delta\Delta G°^{L}_{COOMe}$ is nearly equal to $\Delta\Delta G°_{COOMe}$ while $\Delta\Delta G°^{D}_{COOMe}$ is larger than $\Delta\Delta G°_{COOMe}$. These trends indicate that steric repulsion between the CH_2CO_2Me group of the host and the side chain of the guest is almost the same between the two-point adduct and one-point adduct in the case of L-amino acid esters, whereas the steric repulsion is larger in the two-point adduct than the one-point adduct in the case of D-amino acid esters. Therefore the second recognition (the hydrogen bonding interaction) and the third recognition (steric repulsion) operate cooperatively in the present host–guest system. It is noteworthy that, in the case of the D-isomer, the interaction energies were sensitive to the variations (sizes and functionalities) of the side chain groups of the amino acid esters. Small enantioselectivity observed for Ala–OMe and 1-PhEtNH$_2$ indicates that both bulkiness of the guest molecule and a hydrogen bonding acceptor site are important in the present chiral recognition.

(32) Mizutani, T.; Ema, T.; Yoshida, T.; Kuroda, Y.; Ogoshi, H. *Inorg. Chem.* **1993**, *32*, 2072.

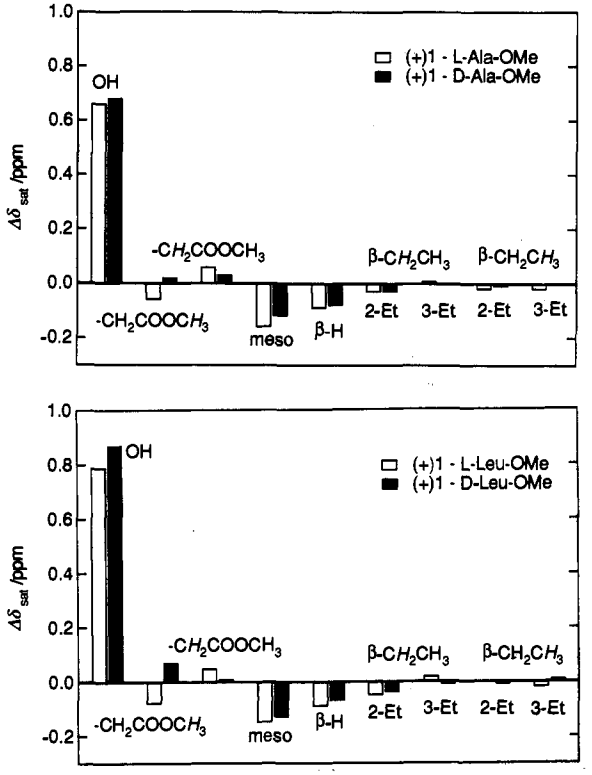


Figure 3. ^{1}H NMR complexation-induced shifts ($\Delta\delta_{sat}$) of host (+)-**1** upon binding of Ala–OMe or Leu–OMe in $CDCl_3$ at 25 °C determined by ^{1}H NMR (500 MHz) titration experiments: (top) Ala–OMe and (bottom) Leu–OMe.

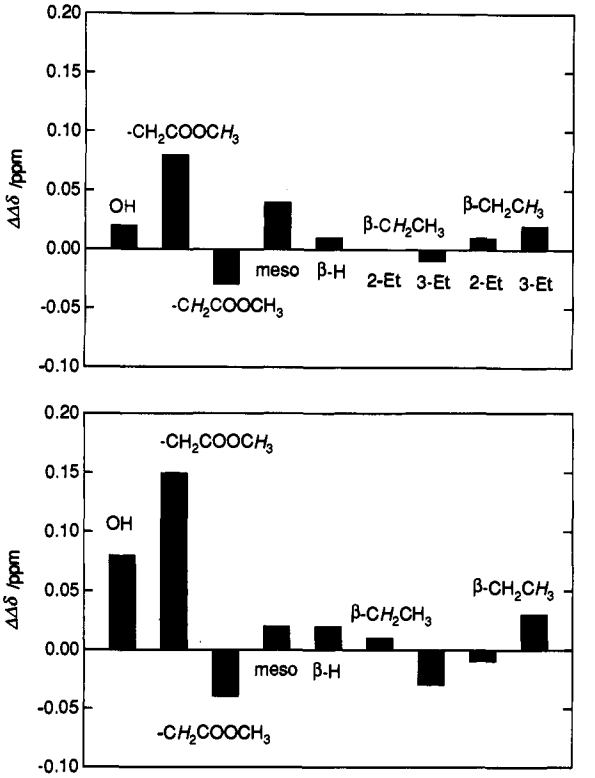


Figure 4. Difference in ^{1}H NMR complexation-induced shifts ($\Delta\delta_{sat}$) of host (+)-**1** upon binding of Ala–OMe or Leu–OMe between the D-guest and the L-guest ($\Delta\Delta\delta$): (top) Ala–OMe and (bottom) Leu–OMe.

In the case of D-Ser–OBzl (and aminoethanol), comparisons of K((+)-**1**) with K(**2**) indicate that the CH_2CO_2Me groups stabilized the binding to host (+)-**1**. Consequently, the enantioselectivity of host (+)-**1** was reversed for Ser–OBzl. Because host (+)-**1** binds L-Leu–OBzl more strongly than the D-isomer, the reversal of enantioselectivity cannot be ascribed to the benzyl ester but can be ascribed to the serine side chain. The differential stabilization energy ($\Delta\Delta G°_{L\,COOMe}$) was –0.10 kcal/mol for the D-Ser–OBzl–(+)-**1** complex, and $\Delta\Delta G°_{COOMe}$ was –0.45 kcal/mol for the aminoethanol–(+)-**1** complex (Table 2). Although these stabilization energies seem to be small, it should be noted that repulsive energies ranging between +0.5 and +1.0 kcal/mol are observed for all the D-amino acid esters (Table 2). If the steric repulsion energy between (+)-**1** and D-Ser–OBzl can be assumed to be comparable to those observed for D-Ala–OMe and D-Val–OMe, the additional attractive interaction between the CH_2CO_2Me group and Ser–OBzl would amount to –0.6 to –1.1 kcal/mol. This attractive interaction may be attributable to hydrogen bonding between the OH group of the serine side chain and the CH_2CO_2Me group of (+)-**1**. In the above discussion, we assumed that the enantioselectivities are ascribed to the differences in recognition energies of the CH_2CO_2Me groups.[33] Similar discussions are also possible on the assumption that the enantioselectivities are ascribed to the differences in recognition energies of the OH groups of host (+)-**1**. These thermodynamic analyses demonstrate that interactions depicted in Figure 2 are operating in the present chiral recognition.

The binding behavior of Ser–OBzl and aminoethanol to the reference hosts is also consistent with the above discussions that attractive interactions between the CH_2CO_2Me groups of the host and the OH groups of the guest exist. The attractive energies between the CH_2CO_2Me groups of host and the OH groups of the guests can be calculated from $-RT\ln(K(3)/K(4))$, and those between the OH groups of host and the C=O groups of the guests, from $-RT\ln(K(2)/K(4))$. The free energies thus estimated were (**2**)OH···O=C(Ser), –0.92 kcal/mol; (**3**)C=O···HO(Ser), –0.37 kcal/mol; (**2**)OH···OH(aminoethanol), –0.36 kcal/mol; (**3**)C=O···HO(aminoethanol), –0.45 kcal/mol. These attractive interactions may be attributable to hydrogen bonding interaction. The fact that the (**2**)OH···O=C(Ser) interaction is stronger than the (**3**)C=O···HO(Ser) interaction may indicate that the geometry for the latter hydrogen bond is not optimum. Contributions from entropy changes associated with changes in the internal rotation of the guest may also be important because the formation of the latter hydrogen bond would freeze more C–C bond rotations. Internal rotation of the host CH_2CO_2Me group on forming the hydrogen bond to Ser–OBzl also makes contributions to the entropy changes upon complexation.

B. ^{1}H NMR Studies on the Binding. The ^{1}H NMR chemical shift displacements of the signals of host (+)-**1** upon binding of L- (or D-) Ala–OMe and Leu–OMe in $CDCl_3$ at 25 °C were measured at various concentrations of amino acid esters. The complexation-induced shifts ($\Delta\delta_{sat}$) were evaluated and summarized in Figure 3. The values of $\Delta\delta_{sat}$ were largest for the OH proton. The downfield shifts of the OH protons can be ascribed to the hydrogen bonding to the guest carbonyl group. Other protons whose chemical shifts are affected are meso protons, the protons of the CH_2 and the CH_3 group of the CH_2CO_2Me groups, and 2- (or 18-) ethyl protons further from the phenyl group. In Figure 4 are shown the differences between $\Delta\delta_{sat}$ of the L-enantiomer and the D-enantiomer ($\Delta\Delta\delta = \Delta\delta_{sat}(D) - \Delta\delta_{sat}(L)$). This value ($\Delta\Delta\delta$) can be taken as a measure of the chiral interaction. The largest difference in $\Delta\Delta\delta$ was observed for the CH_3 group of the CH_2CO_2Me group of host (+)-**1** for both guests, Ala–OMe and Leu–OMe. The CH_2 group of the CH_2CO_2Me

(33) The relative magnitudes of these terms are $|\Delta G°_{Zn}| > |\Delta\Delta G°_{OH}| > |\Delta\Delta G°^{L}_{COOMe}|$ for L-amino acid esters and $|\Delta G°_{Zn}| > |\Delta\Delta G°_{OH}| \approx |\Delta\Delta G°^{D}_{COOMe}|$ for D-amino acid esters. Therefore, in the case of D-amino acid esters, the magnitude of the hydrogen bonding energy is comparable to that of the steric repulsion energy and the assumption that the hydrogen bonding interaction observed for host **2** was the same as that observed for host (+)-**1** does not hold. In this case, explicit separation between the hydrogen bonding energy and steric the repulsion energy is difficult.

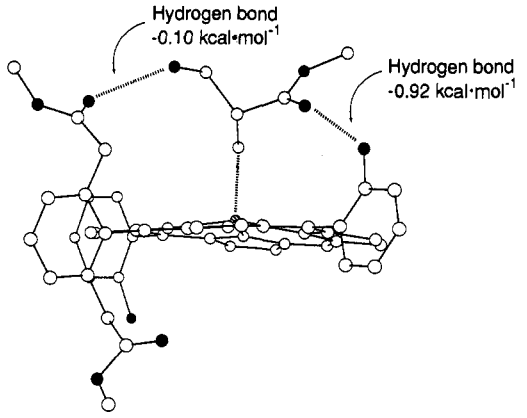


Figure 5. Proposed structure of the (+)-**1**–D-Ser–OBzl complex. The geometry was optimized by the PM3 method[34] for a simplified structure in which the ethyl groups at the β-positions of pyrroles in host (+)-**1** were replaced with hydrogen and the benzyloxy group of Ser–OBzl was replaced with a methoxy group. In the figure, all hydrogen atoms are omitted for clarity. The hydrogen bonding energies within CO_2Me(host)···HO(Ser) and OH(host)···O=C(Ser) were calculated by use of $-RT$ ln (K(3)/K(4)) and $-RT$ ln (K((+)-1)/K(3)), respectively.

group was also affected much and in the opposite direction. These observations are consistent with the mechanism in Figure 2, where chiral differentiation was assumed to originate from the interaction between the third recognition group (CH_2CO_2Me) of the host and the side chain group of the guest. The values of $\Delta\Delta\delta$ for the 3- (or 17-) ethyl groups are larger than those for the 2- (or 18-) ethyl groups. This suggests that the chirality-dependent interaction is present between the OH of the phenyl group of the host and the C=O group of the guest, since the ethyl groups closer to the OH groups are more affected.

C. Mechanism of Chiral Recognition. The observed selectivities of hosts **1**–**4** would allow us to discuss the conformation of the host–guest complexes and the mechanism of chiral recognition. We observed that the CH_2CO_2Me groups of host (+)-**1** served a repulsive function for L-Ser–OBzl and an attractive function for D-Ser–OBzl. This dual function of the third recognition group may be made possible by the simultaneous two-point fixation of the guest through the metal coordination within ((+)-**1**)Zn···NH_2-(Ser) and the hydrogen bonding interaction within ((+)-**1**)-OH···O=C(Ser). These selectivities of host (+)-**1** strongly suggest that the D-amino acid side chain is in close proximity to the CH_2CO_2Me group by two-point fixation, whereas the L-amino acid side chain is directed away from the CH_2CO_2Me group. Therefore, in the case of the (+)-**1**–D-Ser–OBzl complex, the side chain group of serine comes close to the CH_2CO_2Me group. The stabilization by the CH_2CO_2Me group can be ascribed to the hydrogen bonding interaction between the OH group of Ser–OBzl and the C=O group of the host. Complementary three-point fixation in the D-Ser–OBzl–(+)-**1** complex is shown in Figure 5, where the geometry was optimized by semiempirical molecular orbital calculations. We can assume that the conformation of the complexes between other guests and host (+)-**1** is similar to that of the complex between Ser–OBzl and host (+)-**1** because these conformations are consistent with the observed enantioselectivities. For example, in the case of the Leu–OMe–(+)-**1** complex, in order to form hydrogen bond between the OH group of the host and the C=O group of the guest, the side chain group of the D-amino acid ester needs to be directed toward the CH_2CO_2Me groups in the D-isomer–(+)-**1** complex, whereas it needs to be directed away from the CH_2CO_2Me group in the L-isomer–(+)-**1** complex as schematically shown in Figure 6. Thus steric repulsion will be smaller for L-guest, leading to a preference for the L-guest as observed for host (+)-**1**. By assuming these

(34) MOPAC Version 6.0: Stewart, J. J. P. *QCPE Bull.* **1989**, *9*, 10. Revised as Version 6.02 by T. Hirano and M. Okada.

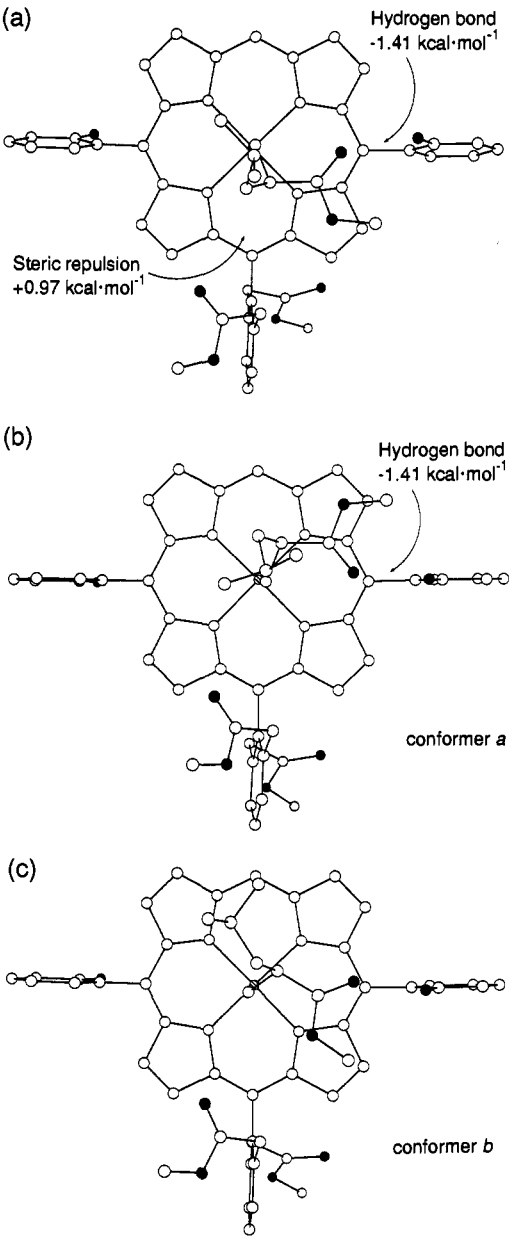


Figure 6. Schematic representation of the (a) (+)-**1**–D-Leu–OMe complex, (b) (+)-**1**–L-Leu–OMe complex (conformer a), and (c) (+)-**1**–L-Leu–OMe complex (conformer b). The geometry was optimized by the PM3 method[34] for a simplified host (+)-**1** in which the ethyl groups at the β-positions of pyrroles in host (+)-**1** were replaced with hydrogen. In conformer a, the carbonyl group of the guest is closer to the host $C_6H_4(CH_2CO_2CH_3)_2$ group than the methoxy group of the guest, while in conformer b, the methoxy group of the guest is closer.

conformations, the enantioselectivity of host (+)-**1** can be consistently understood for all the amino acid esters examined. On the basis of these observations, we suggest that (+)-**1** has (*S*,*S*) and (−)-**1** has (*R*,*R*) configuration (Figure 1).

Other evidence supporting the above proposed mechanism of chiral recognition is that there is a correlation between chiral recognition energy and hydrogen bonding energy. Figure 7 shows that the chiral recognition energies ($|\Delta G°$((+)-**1**, L) − $\Delta G°$((+)-**1**, D)|) were correlated to the hydrogen bonding energy ($-\Delta\Delta G°_{OH}$) between the OH group of the host and the C=O group of the guest. The chiral recognition energies increased with increasing hydrogen bonding energy ($-\Delta\Delta G°_{OH}$). The correlation coefficient ρ between the two energies was 0.76 for all data included and 0.95 if Phe–OMe and Ser–OBzl were excluded. In the case of phenylalanine, the aryl–aryl interaction operates in the host–guest complex, and this additional interaction may complicate

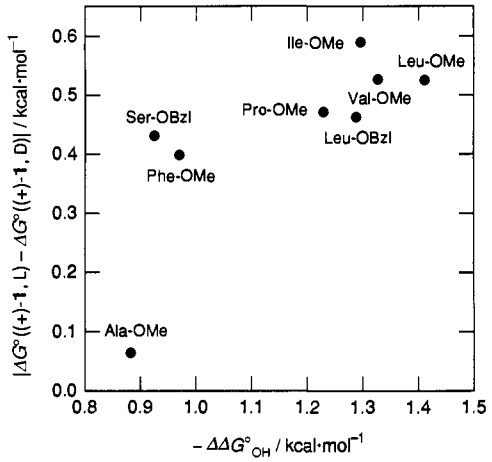


Figure 7. Correlation between the hydrogen bonding energy ($-\Delta\Delta G^\circ_{OH}$) and the chiral recognition energy ($|\Delta G^\circ((+)\text{-}1, L) - \Delta G^\circ((+)\text{-}1, D)|$).

the host–guest conformation. In a similar host–guest system, circular dichroism and thermodynamic studies indicated that the conformation of the complexes between aromatic amino acid esters and a porphyrin host was perturbed due to the aryl–aryl interaction.[32] If Phe–OMe and Ser–OBzl can be excluded, the correlation is good. On the other hand, poor correlation (ρ = 0.25) was found between the chiral recognition energy and the coordination energy ($-\Delta G^\circ_{Zn}$).[35] These observations indicate that hydrogen bonding is a driving force for the chiral recognition. The above correlation implies that the magnitude of the first recognition ($-\Delta G^\circ_{Zn}$, metal coordination) is relatively unimportant and the magnitude of the second recognition ($-\Delta\Delta G^\circ_{OH}$, hydrogen bonding) is important for the chiral recognition. This may be the direct consequence that the rotation of the guest along the Zn–N axis should be restricted for the chiral recognition to occur.

Conclusions

A trifunctional porphyrin was designed and prepared as a chiral recognition host for amino acid esters. The pyrrylmethanol method was used to prepare the porphyrin with C_2 symmetry regiospecifically. The chiral host (+)-**1** exhibited enantioselective binding of amino acid esters. In order to clarify the roles of three recognition groups (Zn, OH, and CH_2CO_2Me groups), reference hosts lacking some of the recognition groups were also prepared. Binding experiments indicated that the Zn ion and the OH groups stabilized the host–guest complex via coordination and hydrogen bonding interactions, respectively. The third recognition group, the CH_2CO_2Me groups, acted as a minor steric repulsive site for L-amino acid esters, as a major steric repulsive site for D-amino acid esters, and as an attractive site for D-Ser–OBzl. We suggest that these changes in recognition interactions caused by the two-point fixation of the guest through coordination and hydrogen bonding can account for the enantioselectivity and substrate selectivity observed for host **1**.

Experimental Section

General Procedures. ^{1}H NMR spectra were obtained using either a JEOL GX-400 spectrometer, a JEOL A-500 spectrometer, or a JEOL JNM FX 90Q FT NMR spectrometer, and chemical shifts are reported relative to internal Me_4Si. IR spectra were recorded on a Bio-rad FTS-7 FT-IR spectrometer. UV–vis spectra were recorded on either a Hitachi U-3410 spectrometer or a Hewlett-Packard 8452 diode array spectrophotometer with a thermostated cell compartment. Circular dichroism spectra were recorded on a JASCO J-600 spectropolarimeter with a thermostated cell compartment. Mass spectra were obtained with a JEOL JMS DX-300 mass spectrometer. High-resolution mass spectra were obtained with a JEOL JMS SX-102A instrument. High-performance liquid chromatography (HPLC) was performed on a Waters Model 6000 instrument with a Waters 600E system controller and a Tosoh UV-8010 detector. Thin layer chromatography (TLC) was performed on either Merck Kieselgel 60 F_{254} or DC-Alufolien Aluminiumoxid 60 F_{254} neutral (Typ E). Association constants between hosts **1**–**4** and amino acid esters were determined by UV–vis spectrophotometric titration at 15 °C in $CHCl_3$. $CHCl_3$ was Spectrosol purchased from Dojindo Laboratories, which contains *ca.* 1% ethanol. Amino acid esters were distilled before titration experiments. Details of the titration were reported before.[32] Molecular orbital calculations were carried out on a Silicon Graphics IRIS Indigo XS 24 workstation.

Materials. 3,4-Diethylpyrrole (**5**) was prepared by decarboxylation of 3,4-diethylpyrrole-2,5-dicarboxylic acid.[36] 2-Methyl-1,3-benzenedicarboxylic acid (**11**) was prepared by methylation of 1,3-dicyanobenzene (**9**) with lithium diisopropylamide (LDA) and methyl iodide in THF,[19] followed by saponification in aqueous potassium hydroxide.[20] Serine benzyl ester was prepared by a reported procedure.[36] Ether and THF were distilled from sodium, and dichloromethane was distilled from CaH_2. Ag^I_2O was purchased from Wako Pure Chemicals Industries. (*R*)- and (*S*)-1-Phenylethylamine (1-PhEtNH$_2$) were purchased from Nacalai tesque.

3,4-Diethyl-2-(2-methoxybenzoyl)pyrrole (6). A solution of 3,4-diethylpyrrole (**5**) (8.76 g, 71.2 mmol) in toluene (100 mL) was added dropwise to 1.8 M ethylmagnesium bromide in dry ether (45 mL) over a period of 1.5 h under Ar in an ice bath in the dark, and the mixture was stirred at room temperature for 2 h. The resulting Grignard reagent was added to a solution of *o*-methoxybenzoyl chloride (15.71 g, 92.1 mmol) in toluene (100 mL) at −50 °C over 1.5 h. After the addition, stirring was continued for 1 h, followed by the addition of saturated NH_4Cl (40 mL). The mixture was stirred for 1 h at room temperature. The organic layer was isolated, washed with aqueous NaCl (40 mL), and dried over K_2CO_3. Evaporation of the solvent and separation by column chromatography on silica gel ($CHCl_3$) afforded 12.04 g (46.8 mmol, 66%) of a pale yellow powder **6**. Recrystallization from MeOH gave pale yellow crystals: mp 95.0–96.5 °C; TLC R_f 0.35 (SiO_2, $CHCl_3$:ethyl acetate = 20:1); ^{1}H NMR ($CDCl_3$, 90 MHz) δ 0.90 (t, J = 9 Hz, 3H, CH_2CH_3), 1.18 (t, J = 9 Hz, 3H, CH_2CH_3), 2.30 (q, J = 9 Hz, 2H, CH_2CH_3), 2.47 (q, J = 9 Hz, 2H, CH_2CH_3), 3.80 (s, 3H, OCH_3), 6.83 (d, J = 3 Hz, 1H, α-H), 6.9–7.5 (m, 4H, phenyl-H), 9.03 (br s, 1H, NH); IR (KBr, cm^{-1}) 3282 (NH, s), 2965 (w), 2932 (w), 2873 (w), 2835 (w), 1598 (C=O, s), 1494 (w), 1458 (w), 1403 (s), 1288 (w), 1242 (m), 1170 (w), 1111 (w), 1023 (w); MS *m/z* 257 (M^+, 100), 242 ($M^+ - CH_3$, 82), 135 (M^+ – pyrrole), 122 (M^+ – anisoyl, 29). Anal. Calcd for $C_{16}H_{19}O_2N\cdot{}^1/_3(MeOH\cdot H_2O)$: C, 71.59; H, 7.72; N, 5.11. Found: C, 71.64; H, 7.84; N, 5.01.

(3,3′,4,4′-Tetraethyl-5,5′-bis(2-methoxybenzoyl)-2,2′-dipyrryl)-methane (7). A solution of **6** (8.56 g, 33.3 mmol) in ethanol (40 mL) and concentrated hydrochloric acid (9 mL) was heated at 40 °C, and dimethoxymethane (17 mL) was added. After the solution was heated at 40 °C for 3 h, another portion of dimethoxymethane (8 mL) was added and the mixture was heated for 3 h. After evaporation of the solvent, the dark brown residue was redissolved in $CHCl_3$ (90 mL). The chloroform layer was washed with saturated aqueous $NaHCO_3$ (90 mL) and saturated aqueous NaCl (60 mL) and dried over Na_2SO_4. Evaporation of the solvent and separation by repeated column chromatography (SiO_2, hexane: ethyl acetate = 2:1) afforded orange crystals of **7** (5.64 g, 10.7 mmol, 64%). Recrystallization from MeOH afforded pale yellow crystals: mp 170.5–171.5 °C; TLC R_f 0.18 (SiO_2, $CHCl_3$:ethyl acetate = 20:1); ^{1}H NMR ($CDCl_3$, 90 MHz) δ 0.87 (t, J = 9 Hz, 6H, CH_2CH_3), 1.04 (t, J = 9 Hz, 6H, CH_2CH_3), 2.24 (q, J = 9 Hz, 4H, CH_2CH_3), 2.40 (q, J = 9 Hz, 4H, CH_2CH_3), 3.78 (s, 6H, OCH_3), 3.92 (s, 2H, CH_2), 6.9–7.5 (m, 8H, phenyl-H), 9.00 (br s, 2H, NH); IR (KBr, cm^{-1}) 3300 (NH, m), 3207 (w), 2965 (w), 2928 (w), 2869 (w), 1607 (C=O, s), 1554 (s), 1489 (m), 1427 (s), 1370 (w), 1293 (m), 1250 (m), 1187 (w), 1159 (w), 1114 (w), 1055 (w), 1023 (w); MS *m/z* 526 (M^+, 15), 391 (3), 270 (12), 135 (100). Anal. Calcd for $C_{33}H_{38}O_4N_2$: C, 75.03; H, 7.39; N, 5.34. Found: C, 75.26; H, 7.27; N, 5.32.

(35) We should examine the correlation between the chiral recognition energy and $\Delta\Delta G^\circ_{Zn}$ instead of ΔG°_{Zn}. To evaluate $\Delta\Delta G^\circ_{Zn}$, the reference host for host **4** is needed, which is difficult to find. Even if we use the free base of **4** as a reference host, the binding constant of the free base of **4** and L-Leu–OMe in $CHCl_3$ is too weak to determine. We assume that $\Delta\Delta G^\circ_{Zn}$ is approximately equal to ΔG°_{Zn}. This approximation can be justified if the binding constant between a host without zinc and a guest is negligibly small. It should be noted that ΔG°_{Zn} involves the large entropy term $-T(\Delta S_{trans} + \Delta S_{rot})$.

(36) Eisner, U.; Lichtarowicz, A.; Linstead, R. P. *J. Chem. Soc.* **1957**, 733.
(37) Koehn, P. V.; Kind, C. A. *Arch. Biochem. Biophys.* **1965**, *111*, 614.

(3,3',4,4'-Tetraethyl-5,5'-bis(α-hydroxy-2-methoxybenzyl)-2,2'-dipyrryl)methane (8). To a stirred solution of **7** (1.04 g, 1.98 mmol) in ethanol (35 mL) was added $NaBH_4$ (0.7 g, 18.5 mmol), and stirring was continued under Ar at room temperature in the dark for 28 h. Then another portion of $NaBH_4$ (0.5 g, 13.2 mmol) was added, and stirring was continued under Ar for 19 h. The progress of the reaction was monitored by TLC (neutral alumina, $CHCl_3$:ethyl acetate = 20:1). After the reaction mixture was concentrated under reduced pressure, water (50 mL) was added. The mixture was extracted with ether (50 mL × 3), and the ether layer was dried over K_2CO_3. Evaporation of the solvent afforded an orange foam 1.05 g, (1.98 mmol, 100%). The product was air sensitive and can be stored at −20 °C under Ar for 2–3 weeks. The product was used for the next reaction without purification: MS *m/z* 512 ($M^+ - H_2O$, 89), 496 ($M^+ - 2OH$, 54).

Dimethyl 2-Methyl-1,3-benzenediacetate (13). A solution of 2-methyl-1,3-benzenedicarboxylic acid (**11**) (37.7 g, 0.21 mol) in pyridine (1.15 mL) and $SOCl_2$ (115 mL, 1.6 mol) was stirred at 45 °C for 1 h and then refluxed for 16 h. After excess $SOCl_2$ was distilled off, distillation at a reduced pressure (95–109 °C, 0.2 mmHg) afforded 2-methyl-1,3-benzenedicarbonyl dichloride (**12**) as a pale yellow solid, 43.3 g (200 mmol, 96%): mp 89–92 °C; ^1H NMR ($CDCl_3$, 90 MHz) δ 2.67 (s, 3H, CH_3), 7.58 (t, *J* = 9 Hz, 1H, phenyl-H), 8.28 (d, *J* = 9 Hz, 2H, phenyl-H); IR (KBr, cm^{-1}) 3085 (w), 1767 (C=O, s), 1570 (w), 1436 (w), 1386 (w), 1282 (w), 1237 (w), 1176 (w), 1076 (m).

To 0.38 M diazomethane in ether (410 mL) was added dropwise 2-methyl-1,3-benzenedicarbonyl dichloride **12** (8.73 g, 40 mmol) in dry ether (200 mL). The nitrogen gas was evolved, and pale yellow precipitates were formed soon. The reaction mixture was stirred at room temperature for 12.5 h. Evaporation of the ether gave the diazoketone as a pale yellow solid. The diazoketone was dissolved in MeOH (60 mL). The solution was heated at 50 °C and $Ag^1{}_2O$ (0.152 g, 0.66 mmol) was added. Three portions of $Ag^1{}_2O$ (0.076 g, 0.33 mmol) were added over 1.5 h. The reaction mixture was filtered through Celite (545) while it was hot. Recrystallization from MeOH afforded 4.97 g (21 mmol, 53%) of **13** as colorless needles: mp 102–103 °C; TLC R_f 0.25 (SiO_2, $CHCl_3$); ^1H NMR ($CDCl_3$, 90 MHz) δ 2.25 (s, 3H, CH_3), 3.70 (s, 10H, $CH_2CO_2CH_3$), 7.18 (s, 3H, phenyl-H); IR (KBr, cm^{-1}) 3002 (w), 2953 (w), 2848 (w), 1727 (C=O, s), 1456 (m), 1427 (m), 1353 (m), 1262 (w), 1208 (s), 1166 (s); MS *m/z* 236 (M^+, 47), 205 ($M^+ - OCH_3$, 13), 177 ($M^+ - CO_2CH_3$, 100), 18 ($M^+ - 2CO_2CH_3$, 30). Anal. Calcd for $C_{13}H_{16}O_4$: C, 66.09; H, 6.83. Found: C, 65.79; H, 6.85.

Dimethyl 2-(Bromomethyl)-1,3-benzenediacetate (14). A solution of **13** (8.24 g, 34.9 mmol) in CCl_4 (170 mL) was cooled in a constant temperature bath at 20 °C and irradiated with 500-W light while Br_2 (7.32 g, 45.75 mmol) in CCl_4 (62 mL) was added dropwise over 4.6 h. The progress of the reaction was monitored by ^1H NMR. After the reaction was complete, the solution was washed with saturated aqueous $NaHCO_3$ (40 mL) and saturated aqueous NaCl (80 mL) and dried over Na_2SO_4. Evaporation of the solvent and repeated separation on column chromatography (SiO_2, $CHCl_3$) yielded colorless crystals of **14**, 5.85 g (18.6 mmol, 53%). Recrystallization from ether gave colorless needles: mp 56.0–57.0 °C; TLC R_f 0.28 (SiO_2, $CHCl_3$); ^1H NMR ($CDCl_3$, 90 MHz) δ 3.72 (s, 6H, CO_2CH_3), 3.80 (s, 4H, $CH_2CO_2CH_3$), 4.68 (s, 2H, CH_2Br), 7.28 (s, 3H, phenyl-H); IR (KBr, cm^{-1}) 3011 (w), 2960 (w), 1714 (C=O, s), 1587 (w), 1434 (w), 1463 (m), 1008 (w); MS *m/z* 316, 314 (M^+, 2), 257, 255 ($M^+ - CO_2CH_3$), 235 (M^+ − Br, 100), 176 (M^+ − Br, CO_2CH_3, 16), 117 (M^+ − Br, $2CO_2CH_3$, 12). Anal. Calcd for $C_{13}H_{15}O_4Br$: C, 49.54; H, 4.80; Br, 25.35. Found: C, 49.82; H, 4.81; Br, 24.72.

Dimethyl 2-Formyl-1,3-benzenediacetate (15). Dimethyl sulfoxide (Me_2SO, 27 mL) was deaerated by bubbling with Ar for 1 h, and the Me_2SO was added to **14** (1.35 g, 4.30 mmol) and $NaHCO_3$ (3.09 g, 36.8 mmol). The mixture was heated at 100 °C under Ar with vigorous stirring for 7 min. The reaction mixture was then immediately cooled in an ice bath, poured into saturated aqueous NaCl (100 mL), and extracted with ether (100 mL × 1, 50 mL × 2). The ether layer was combined and dried over Na_2SO_4. Evaporation of the solvent gave colorless crystals of **15**, 957 mg (3.83 mmol, 89%). Recrystallization from ether afforded colorless crystals: mp 114.5–116.0 °C; TLC R_f 0.32 (SiO_2, $CHCl_3$:ethyl acetate = 20:1); ^1H NMR ($CDCl_3$, 90 MHz) δ 3.75 (s, 6H, CO_2CH_3), 4.05 (s, 4H, $CH_2CO_2CH_3$), 7.25–7.6 (m, 3H, phenyl-H), 10.55 (s, 1H, CHO); IR (KBr, cm^{-1}) 3002 (w), 2957 (w), 2785 (w), 1724 (C=O, s), 1590 (w), 1449 (w), 1352 (m), 1261 (w), 1211 (m), 1170 (m), 1033 (w); MS *m/z* 250 (M^+, 25), 219 ($M^+ - OCH_3$, 67), 191 ($M^+ - CO_2CH_3$), 177 ($M^+ - CH_2CO_2CH_3$, 60), 162 (M^+ − CHO, CO_2CH_3, 57), 104 ($M^+ - 2CH_2CO_2CH_3$, 23). Anal. Calcd for $C_{13}H_{14}O_5$: C, 62.39; H, 5.64. Found: C, 62.13; H, 5.75.

Dimethyl 2-(Bis(2-pyrryl)methyl)-1,3-benzenediacetate (16). A solution of aldehyde **15** (0.928 g, 3.71 mmol) in MeOH (50 mL) was added slowly to a solution of *p*-toluenesulfonic acid monohydrate (0.709 g, 3.65 mmol) and a large excess of distilled pyrrole (12 mL, 147 mmol) in MeOH (28 mL) over 1 h at room temperature in the dark. After the addition, the reaction mixture was poured into saturated aqueous NaCl (100 mL). The mixture was extracted with ether (100 mL × 3), and the ether layer was dried over Na_2SO_4. Evaporation of the solvent and excess pyrrole and repeated column chromatographic separation (SiO_2, $CHCl_3$) afforded a pale yellow solid **16**, 0.924 g (2.52 mmol, 68%). Recrystallization from ether afforded a pale green powder: mp 120.0–120.5 °C; TLC R_f 0.35 (SiO_2, $CHCl_3$:ethyl acetate = 20:1); ^1H NMR ($CDCl_3$, 90 MHz) δ 3.62 (s, 6H, CO_2CH_3), 3.70 (s, 4H, $CH_2CO_2CH_3$), 5.83 (s, 1H, CH), 5.97 (m, 2H, β-H), 6.13 (m, 2H, β-H), 6.73 (m, 2H, α-H), 7.10–7.30 (m, 3H, phenyl-H), 8.73 (br s, 2H, NH); IR (KBr, cm^{-1}) 3389 (NH, s), 3004 (w), 2948 (w), 1719 (C=O, s), 1554 (w), 1430 (m), 1341 (m), 1249 (m), 1208 (m), 1159 (m), 1107 (w), 1033 (w), 1005 (w); MS *m/z* 366 (M^+, 100), 335 ($M^+ - OCH_3$, 13), 307 ($M^+ - CO_2CH_3$, 11), 234 (M^+ − 2pyrrole, 4). Anal. Calcd for $C_{21}H_{22}O_4N_2$: C, 68.84; H, 6.05; N, 7.65. Found: C, 68.68; H, 6.01; N, 7.68.

[*trans*-5,15-Bis(2-methoxyphenyl)-10-{2,6-bis((methoxycarbonyl)-methyl)phenyl}-2,3,17,18-tetraethylporphyrinato]zinc(II) (17) and Its Cis Atropisomer (18). A solution of $Zn(OAc)_2$ (0.204 g, 0.928 mmol) in propionic acid (36 mL) was heated at 95 °C. A heated solution of pyrrylmethanol **8** (0.476 g, 0.897 mmol) and dipyrromethane **16** (0.299 g, 0.817 mmol) in 1,2-dichloroethane (8.1 mL) was added quickly. The solution turned dark red immediately and was stirred for 1 h at 95 °C in the dark. The propionic acid was distilled off at room temperature. The repeated column chromatography (SiO_2, $CHCl_3$:ethyl acetate = 20:1) afforded trans- and cis zinc complexes. The total yield was 82.5 mg (0.09 mmol, 11%). Recrystallization from CH_2Cl_2–MeOH afforded purple crystals. **17**: mp >300 °C; TLC R_f 0.57 (SiO_2, $CHCl_3$:ethyl acetate = 20:1); ^1H NMR ($CDCl_3$, 400 MHz) δ 1.27 (t, *J* = 7.6 Hz, 6H, CH_2CH_3), 1.89 (t, *J* = 7.6 Hz, 6H, CH_2CH_3), 2.80 (s, 6H, CO_2CH_3), 2.98–3.21 (m, 4H, CH_2CH_3), 3.16 (s, 4H, $CH_2CO_2CH_3$), 3.62 (s, 6H, OCH_3), 4.03 (q, *J* = 7.6 Hz, 4H, CH_2CH_3), 7.27–7.90 (m, 11H, phenyl H), 8.49 (AB q, *J* = 4.66 Hz, 2H, β-H), 8.54 (AB q, 2H, *J* = 4.66 Hz, 2H, β-H), 10.13 (s, 1H, meso-H); FAB MS (*m*-nitrobenzyl alcohol matrix) *m/z* 917 (M^+); UV–vis ($CHCl_3$) λ_{max} (log ε) 421 (5.56), 549 (4.30), 570 (sh, 3.67). **18**: mp >300 °C; TLC R_f 0.42 (SiO_2, $CHCl_3$:ethyl acetate = 20:1); ^1H NMR ($CDCl_3$, 400 MHz) δ 1.27 (t, *J* = 7.6 Hz, 6H, CH_2CH_3), 1.89 (t, *J* = 7.6 Hz, 6H, CH_2CH_3), 2.69 (s, 3H, CO_2CH_3), 2.86 (s, 3H, CO_2CH_3), 3.03–3.17 (m, 4H, CH_2CH_3), 3.14 (s, 2H, $CH_2CO_2CH_3$), 3.18 (s, 2H, $CH_2CO_2CH_3$), 3.62 (s, 6H, OCH_3), 3.99–4.09 (m, 4H, CH_2CH_3), 7.26–7.88 (m, 11H, phenyl H), 8.48 (AB q, *J* = 4.66 Hz, 2H, β-H), 8.54 (AB q, *J* = 4.66 Hz, 2H, β-H), 10.13 (s, 1H, meso-H); FAB MS (*m*-nitrobenzyl alcohol matrix) *m/z* 917 (M^+); UV–vis ($CHCl_3$) λ_{max} (log ε) 420 (5.52), 548 (4.26), 572 (sh, 3.38).

The free bases of **17** and **18** were obtained by treating **17** and **18** with 10% HCl and recrystallized from CH_2Cl_2–MeOH: mp 272–273 °C; TLC R_f 0.68 (SiO_2, $CHCl_3$:ethyl acetate = 20:1); UV–vis ($CHCl_3$) λ_{max} (log ε) 415.5 (5.43), 510.9 (4.27), 535.5 (sh, 3.50), 582.9 (3.80). Anal. Calcd for $C_{54}H_{54}O_6N_4 \cdot CH_3OH$: C, 74.47; H, 6.59; N, 6.32. Found: C, 74.57; H, 6.51; N, 6.17.

[*trans*-5,15-Bis(2-hydroxyphenyl)-10-{2,6-bis((methoxycarbonyl)methyl)phenyl}-2,3,17,18-tetraethylporphyrinato]zinc(II) (1) and Its Cis Atropisomer (19). The methoxy derivative **17** (43.5 mg, 0.047 mmol) was dissolved in dry CH_2Cl_2 (2.2 mL) under Ar. The solution was cooled to −40 °C, and 1 M BBr_3 in CH_2Cl_2 (0.75 mL) was added. The reaction mixture was allowed to warm up slowly over 3 h to room temperature and stirred for 3 h. The solution was cooled to −20 °C, and MeOH (0.68 mL) was added. Saturated aqueous $NaHCO_3$ was added, and the mixture was extracted with CH_2Cl_2. The organic layer was washed with water and dried over Na_2SO_4, and the solvent was evaporated. Purification by column chromatography (SiO_2, $CHCl_3$:ethyl acetate = 10:1) afforded 27 mg (0.033 mmol, 69.5%) of the free base porphyrin. The free base porphyrin was dissolved in $CHCl_3$ and refluxed with zinc acetate-saturated MeOH. Evaporation of the solvent and extraction with CH_2Cl_2, followed by chromatographic separation on silica gel ($CHCl_3$:ethyl acetate = 10:1) gave the zinc complex **1**. **1**: TLC R_f 0.61 (SiO_2, $CHCl_3$:ethyl acetate = 5:1); ^1H NMR ($CDCl_3$, 400 MHz) δ 1.32 (t, *J* = 7.6 Hz, 6H, CH_2CH_3), 1.90 (t, *J* = 7.6 Hz, 6H, CH_2CH_3), 2.89 (s, 6H, $CH_2CO_2CH_3$), 3.09–3.20 (m, 8H, CH_2CH_3, $CH_2CO_2CH_3$), 4.04 (q, *J* = 7.6 Hz, 4H, CH_2CH_3), 4.90 (br s, 2H, OH), 7.27–7.94 (m, 11H, phenyl H), 8.54 (AB q,

J = 4.58 Hz, 2H, β-H), 8.62 (AB q, J = 4.58 Hz, 2H, β-H), 10.18 (s, 1H, meso-H); FAB MS (*m*-nitrobenzyl alcohol matrix) *m/z* 889 (M^+); UV–vis ($CHCl_3$) λ_{max} (log ε) 422 (5.43), 551 (4.15), 579 (sh, 3.39); high-resolution mass spectrum (HRFAB MS) of the free base of **1** (*m*-nitrobenzyl alcohol matrix) *m/z* calcd for $C_{52}H_{51}O_6N_4$ 827.3809, found 827.3823 (+1.7 ppm).

Compound **19** was also prepared in a similar manner from **18**. Compounds **18** and **19** can also be prepared by cleaving the methyl ether of a mixture of **17** and **18**, followed by the column chromatographic separation. **19**: TLC R_f 0.24 (SiO_2, $CHCl_3$:ethyl acetate = 5:1); ^1H NMR ($CDCl_3$, 400 MHz) δ 1.31 (t, J = 7.6 Hz, 6H, CH_2CH_3), 1.90 (t, J = 7.6 Hz, 6H, CH_2CH_3), 2.87 (s, 3H, $CH_2CO_2CH_3$), 2.88 (s, 3H, $CH_2CO_2CH_3$), 3.07 (s, 2H, $CH_2CO_2CH_3$), 3.12–3.16 (m, 4H, CH_2CH_3), 3.19 (s, 2H, $CH_2CO_2CH_3$), 4.03 (q, J = 7.6 Hz, 4H, CH_2CH_3), 4.94 (br s, 2H, OH), 7.26–7.95 (m, 11H, phenyl H), 8.60 (AB q, J = 2.5 Hz, 2H, β-H), 8.61 (AB q, 2H, J = 2.5 Hz, 2H, β-H), 10.17 (s, 1H, meso-H); FAB MS (*m*-nitrobenzyl alcohol matrix) *m/z* 889 (M^+, 100).

(Bis(2-pyrryl)methyl)benzene (20). Compound **20** was prepared by a procedure similar to that described for **16**. The product was purified by repeated column chromatography (SiO_2, $CHCl_3$). Recrystallization from ether gave a white solid **20**, 0.706 g (3.18 mmol, 36.5%): mp 102–103 °C; TLC R_f 0.33 (SiO_2, $CHCl_3$); ^1H NMR ($CDCl_3$, 90 MHz) δ 5.50 (s, 1H, CH), 5.93 (m, 2H, β-H), 6.17 (m, 2H, β-H), 6.72 (m, 2H, α-H), 7.20–7.33 (m, 5H, phenyl-H), 7.98 (br s, 2H, NH); IR (KBr, cm^{-1}) 3345 (NH, s), 3134 (w), 3092 (w), 3058 (w), 2860 (w), 1554 (w), 1490 (w), 1456 (w), 1411 (w), 1315 (w), 1260 (w), 1181 (w), 1107 (w); MS *m/z* 222 (M^+, 100), 156 (M^+ – pyrrole, 32), 145 (M^+ – benzene, 54). Anal. Calcd for $C_{15}H_{14}N_2$: C, 81.05; H, 6.35; N, 12.60. Found: C, 81.31; H, 6.21; N, 12.76.

2-Benzoyl-3,4-diethylpyrrole (21). This compound was prepared in a manner similar to that for **6**. Yield = 4.84 g (71%) of **21**. Recrystallization from hexane afforded pale yellow prisms: mp 54.0–55.5 °C; TLC R_f 0.30 (SiO_2, hexane:ether = 5:1); ^1H NMR ($CDCl_3$, 90 MHz) δ 1.0 (t, 3H, CH_2CH_3), 1.2 (t, 3H, CH_2CH_3), 2.5 (dq, 4H, CH_2CH_3), 6.8 (d, 1H, α-H), 7.3–7.8 (m, 5H, phenyl-H), 8.8 (br s, 1H, NH); IR (KBr, cm^{-1}) 3268 (NH, s), 3181 (sh), 1608 (C=O), 1562 (w); MS *m/z* 227 (M^+). Anal. Calcd for $C_{15}H_{17}ON$: C, 79.26; H, 7.54; N, 6.16. Found: C, 79.25; H, 7.61; N, 6.19.

(3,3′,4,4′-Tetraethyl-5,5′-dibenzoyl-2,2′-dipyrryl)methane (22). This compound was prepared from **21** in 76% yield: mp 66.0–73.0 °C; TLC R_f 0.20 (SiO_2, $CHCl_3$:ethyl acetate = 20:1); ^1H NMR ($CDCl_3$, 90 MHz) δ 0.93 (t, 6H, CH_2CH_3), 1.07 (t, 6H, CH_2CH_3), 2.50 (dq, 8H, CH_2CH_3), 3.97 (s, 2H, CH_2), 7.3–7.6 (m, 10H, phenyl-H), 9.30 (br s, 2H, NH); IR (KBr, cm^{-1}) 3281 (NH), 1595 (C=O, s), 1560 (m); MS *m/z* 466 (M^+). Anal. Calcd for $C_{31}H_{34}O_2N_2$: C, 79.79; H, 7.34; N, 6.00. Found: C, 79.51; H, 7.35; N, 5.84.

(3,3′,4,4′-Tetraethyl-5,5′-bis(α-hydroxybenzyl)-2,2′-dipyrryl)methane (23). This compound was prepared in a manner similar to that for **8** from **22**. The reduction with $NaBH_4$ was finished in 12 h: MS *m/z* 434 ($M^+ - 2H_2O$).

***[trans*-5,15-Bis(2-methoxyphenyl)-2,3,17,18-tetraethyl-10-phenylporphyrinato]zinc(II) (24) and Its Cis Atropisomer (25).** This complex was prepared in a manner similar to that for **17** and **18**. **24**: yield 4%; TLC R_f 0.50 (SiO_2, $CHCl_3$); ^1H NMR ($CDCl_3$, 400 MHz) δ 1.25 (t, J = 9 Hz, 6H, CH_2CH_3), 1.90 (t, J = 9 Hz, 6H, CH_2CH_3), 3.15 (q, J = 9 Hz, 4H, CH_2CH_3), 3.65 (s, 6H, OCH_3), 4.05 (q, J = 9 Hz, 4H, CH_2CH_3), 7.65–8.25 (m, 13H, phenyl-H), 8.66 (AB q, J = 4.5Hz, 2H, β-H), 8.82 (AB q, J = 4.5Hz, 2H, β-H), 10.18 (s, 1H, meso-H); FAB MS (*m*-nitrobenzyl alcohol matrix) *m/z* 773 (M^+). **25**: yield 4%; TLC R_f 0.15 (SiO_2, $CHCl_3$); FAB MS (*m*-nitrobenzyl alcohol matrix) *m/z* 773 (M^+).

***[trans*-5,15-Bis(2-hydroxyphenyl)-2,3,17,18-tetraethyl-10-phenylporphyrinato]zinc(II) (2) and Its Cis Atropisomer (26).** This complex was prepared in a manner similar to that for **1**. **2**: TLC R_f 0.40 (SiO_2, $CHCl_3$:ethyl acetate = 20:1); ^1H NMR ($CDCl_3$, 90 MHz) δ 1.33 (t, J = 9 Hz, 6H, CH_2CH_3), 1.93 (t, J = 9 Hz, 6H, CH_2CH_3), 3.20 (q, J = 9 Hz, 4H, CH_2CH_3), 4.10 (q, J = 9 Hz, 4H, CH_2CH_3), 4.90 (br s, 2H, OH), 7.65–8.25 (m, 13H, phenyl-H), 8.78 (AB q, J = 4.5Hz, 2H, β-H), 8.90 (AB q, J = 4.5Hz, 2H, β-H), 10.25 (s, 1H, meso-H); FAB MS (*m*-nitrobenzyl alcohol matrix) *m/z* 745 (M^+); UV–vis ($CHCl_3$) λ_{max} (log ε) 419 (5.58), 546 (4.29), 573 (sh, 3.62); HRFAB MS of the free base of **2** (*m*-nitrobenzyl alcohol matrix) *m/z* calcd for $C_{46}H_{43}O_2N_4$ 683.3386, found 683.3368 (–2.6 ppm). **26**: TLC R_f 0.16 (SiO_2, $CHCl_3$: ethyl acetate = 20:1); FAB MS (*m*-nitrobenzyl alcohol matrix) *m/z* 745 (M^+); UV–vis ($CHCl_3$) λ_{max} (log ε) 418 (5.33), 545 (4.07), 570 (sh, 3.48).

[2,3,17,18-Tetraethyl-10-{2,6-bis((methoxycarbonyl)methyl)phenyl}-5,15-diphenylporphyrinato]zinc(II) (3). This complex was prepared in a manner similar to that for **17** and **18**. Column chromatographic separation (SiO_2, $CHCl_3$) and recrystallization from CH_2Cl_2–hexane afforded **3**: yield 17.5%; mp 258-262 °C; TLC R_f 0.30 (SiO_2, CH_2Cl_2); ^1H NMR ($CDCl_3$, 90 MHz) δ 1.25 (t, J = 9 Hz, 6H, CH_2CH_3), 1.90 (t, J = 9 Hz, 6H, CH_2CH_3), 2.90 (s, 6H, CO_2CH_3), 3.00 (q, J = 9 Hz, 4H, CH_2CH_3), 3.20 (s, 4H, $CH_2CO_2CH_3$), 4.08 (q, J = 9 Hz, 4H, CH_2CH_3), 7.58–8.23 (m, 13H, phenyl-H), 8.55 (AB q, 4H, β-H), 10.25 (s, 1H, meso-H); FAB MS (*m*-nitrobenzyl alcohol matrix) *m/z* 857 (M^+); UV–vis ($CHCl_3$) λ_{max} (log ε) 423 (5.57), 551 (4.28), 582 (sh, 3.45); HRFAB MS of the free base of **3** (*m*-nitrobenzyl alcohol matrix) *m/z* calcd for $C_{52}H_{51}O_4N_4$ 795.3910, found 795.3942 (+4.0 ppm).

(2,3,17,18-Tetraethyl-5,10,15-triphenylporphyrinato)zinc(II) (4). This complex was prepared in a manner similar to that for **17** and **18**. Column chromatographic separation (SiO_2, hexane:$CHCl_3$ = 1:3) and recrystallization from CH_2Cl_2–hexane afforded **4**: yield 8.6%, mp >300 °C; TLC R_f 0.28 (SiO_2, $CHCl_3$:hexane = 1:1); ^1H NMR ($CDCl_3$, 90 MHz) δ 1.30 (t, J = 9 Hz, 6H, CH_2CH_3), 1.95 (t, J = 9 Hz, 6H, CH_2CH_3), 3.05 (q, J = 9Hz, 4H, CH_2CH_3), 4.10 (q, J = 9 Hz, 4H, CH_2CH_3), 7.75–8.30 (m, 15H, phenyl-H), 8.70 (AB q, J = 4.5 Hz, 2H, β-H), 8.90 (AB q, J = 4.5 Hz, 2H, β-H), 10.30 (s, 1H, meso-H); FAB MS (*m*-nitrobenzyl alcohol matrix) *m/z* 713 (M^+); UV–vis ($CHCl_3$) λ_{max} (log ε) 416 (5.54), 544 (4.23), 576 (sh, 3.40); HRFAB MS of the free base of **4** (*m*-nitrobenzyl alcohol matrix) *m/z* calcd for $C_{46}H_{43}N_4$ 651.3488, found 651.3480 (–1.2 ppm).

Acknowledgment. This work was supported by a Grant-in-Aid for Specially Promoted Research (No. 04101003) from the Ministry of Education, Science, and Culture, Japan. We thank Kazuo Tanaka (JEOL) for the measurement of high resolution mass spectra.