The Axially Dissymmetric Pyrrole as a Novel Chiral Building Block: Synthesis, Characterization and Application to the First 'Predetermined' Synthesis of a Chiral Atropisomeric Porphyrin with Molecular Asymmetry

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The first axially dissymmetric pyrroles, 4-methyl-3-(2'-methoxy-1'-naphthyl)pyrrole-2-carboxylates **1**, were synthesized, characterized by X-ray crystallography and circular dichroism analysis, and applied to the first 'predetermined' synthesis of a chiral atropisomeric porphyrin with molecular asymmetry, (*R*,*R*,*R*,*R*)- and (*S*,*S*,*S*,*S*)-2,7,12,17-tetramethyl-3,8,13,18-tetrakis(2'-methoxy-1'-naphthyl)porphyrin

Pyrroles are interesting compounds both synthetically and biologically. They have been utilized as synthetic precursors for porphyrins,¹ bile pigments,¹ and conductive polymers,² and as components for organic reagents.³ Some naturally occurring antibiotics such as netropsin and distamycin involve peptide-linked oligopyrrole units, which are capable of recognizing the intricate structure of DNA.⁴ Furthermore, certain types of halogenopyrroles are known to exhibit activities as antifungual antibiotics.⁵ We report here the synthesis, X-ray crystallography, and circular dichroism of the first axially dissymmetric pyrroles **1**.

The axially chiral pyrroles 1 exploited here are pyrrole-2carboxylate derivatives. For the synthesis of 1, nitroethane



Fig. 1 ORTEP view of (R)-phenethyl (S)-4-methyl-3-(2'-methoxy-1'-naphthyl)pyrrole-2-carboxylate [(SR)-1d]. A selected bond distance (Å) and dihedral angles (deg): C(6)-C(10); 1.49(4), C(7)-C(6)-C(10)-C(12); 115.58, C(6)-C(7)-C(17)-O(2); 1.52.



was condensed with 2-methoxy-1-napthaldehyde to give 2, which was reacted with isocyanoacetate 36 to afford racemic 1b (Scheme 1). Although the antipodes of 1b are directly separable by chiral HPLC,[†] the resolution is much enhanced by crystallization of the diastereoisomeric (R)-phenethyl ester derivative 1d. Thus, (\pm) -1b was transesterified with benzyl alcohol, and the resulting (\pm) -1c was hydrogenolysed to yield (\pm) -1a, which was esterified⁷ with (R)-phenethyl alcohol. Upon crystallization of the diastereoisometric mixture [(SR)-+ (RR)-1d] in EtOH, white crystals were formed, which were identified as pure (SR)-1d. ‡ Chromatography of the residue on silica gel with benzene-ether (99:1) as eluent allowed the isolation of pure (RR)-1d as oily substance. The S-configuration about the pyrrole-naphthalene bond in (SR)-1d was established by X-ray crystallography (Fig. 1),§ where the naphthalene ring is twisted by 115.58° relative to the pyrrole ring. (SR)-1d and (RR)-1d were hydrogenolysed respectively to give the antipodes of the carboxylic acid (S)-1a and (R)-1a, whose circular dichroism (CD) spectra were perfect mirror images to each other. At the maximum ultraviolet absorption band of 1a (231 nm), the (S)-antipode exhibited an intense positive CD band, while the (R)-antipode showed a negative one. The rotation about the pyrrole-naphthalene bond is considerably restricted: the ethyl ester [(S)-1b] did not racemize at all at 100 °C for 4 h in dichlorobenzene, and even at 130 °C only 11% of (S)-1b was configurationally inverted under similar conditions. From the thermal racemization profile of 1b,¶ the rotational barrier (ΔG^{\ddagger}) about the pyrrole– naphthalene bond was evaluated to be 25 kcal mol⁻¹ at 25 °C.8

The axially dissymmetric pyrroles 1 are of wide potential utility as chiral building blocks. As an example, 1 was applied to the first 'predetermined' synthesis of a chiral atropisomeric porphyrin $\hat{\mathbf{6}}$ with molecular asymmetry. Although several types of chiral porphyrins with molecular asymmetry constructed in the porphyrin skeletons^{9,10} have so far been exploited, all of them are formed as racemates, and the resolution requires tedious effort for optimizing chiral HPLC. For this reason, absolute configurations of such chiral porphyrins have never been defined except one example.¹¹ The target chiral porphyrin 6 has C_4 symmetry owing to the syn orientation of all the 2'-methoxy-1'-naphthyl groups together with the alternate arrangement of the two different pyrrole- β substituents along the periphery of the porphyrin plane. The synthetic pathway to 6 (Scheme 2)⁶ involves reduction of 1d to the corresponding alcohol 4, which was converted to the porphyrinogen 5 followed by oxidation. The porphyrins formed from (SR)-1d and (RR)-1d provided identical ¹H NMR spectra to each other, where all the signals were reasonably assigned to the single atropisomeric structure of 6 with all the 2'-methoxy-1'-naphthyl substituents pointing up or down. Furthermore, the CD spectra of these two porphyrins were again perfect mirror images to each other, where a new CD band with the same sign as that characteristic of the parent 1a (230 nm) appeared at the Soret region of 6 (409 nm). In sharp contrast, the porphyrin derived from (\pm) -1c was CD-silent as expected, and actually the mixture of four possible atropisomers, as observed by TLC and ¹H NMR. Thus, the porphyrins derived

+ (S)-1a

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Scheme 1 Reagents and conditions: i, DBU (83%); ii, Na/PhCH₂OH (89%); iii, H₂/Pd-C (96%); iv, (R)-PhCH(Me)OH/2-Br-1-ethylpyridinium BF₄⁻ (91%); v, Cryst., (SR)-1d [26% based on (±)-1a]/Column Chromato., (RR)-1d [28% based on (±)-1a]; vi, H₂/Pd-C



Scheme 2 Reagents: i, LiAlH4; ii, Cl₃CCO₂H; iii, Chloranil

from (SR)-1d and (RR)-1d are respectively the (S, S, S, S)- and (R, R, R, R)-antipodes of 6, where the configuration of the naphthylpyrrole moiety is perfectly retained.

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Footnotes

- † A 4.6 \times 250 mm column (Chiralcell OD, Daicel) was used with hexane-EtOH (98:2) as eluent at a flow rate of 1.0 ml min⁻¹, detection; 280 nm, t_R : 13 min for (R)-1b and 17 min for (S)-1b.
- ‡ The diastereoisomeric purity was determined by the ¹H NMR signal due to the OMe group (δ 3.75 and 3.88 for (SR)- and (RR)-1d, respectively).

§ Crystal data for (SR)-1d: orthorhombic; $P2_12_12_1$; a = 11.930(1), b =23.183(2), c = 7.4286(9) Å; $D_{calc} = 1.25 \text{ g cm}^{-3}$; Z = 4. A total of 2078 reflections (maximum 20 of 130°) were collected at room temperature on a Mac Science MXC18 diffractometer using the 2θ-ω scan method. The structure was solved by direct methods (SHELXS 86) and refined with 1947 reflections ($|F_0| > 3\sigma$), GOF = 2.13, R = 0.054, Rw = 0.059. Atomic coordinates, bond lengths and angles and thermal parameters have been deposited at the Cambridge Crystallographic Data Centre. See Information for Authors, Issue No. 1.

¶ A dichlorobenzene solution of (S)-1a (3.2 μ mol dm⁻³) was heated at 115, 130, and 145 °C, and the changes in enantiomeric excess versus time were monitored by chiral HPLC.

|| TLC of (S, S, S, S)-6 and (R, R, R, R)-6 using benzene-ether (4:1) as eluent provided a single spot $(R_t = 0.56)$, while the porphyrin from (R,S)-1c gave four spots [0.56 (weak), 0.66, 0.75, 0.83 (intense)]. In the ¹H NMR spectra in CDCl₃, both (S,S,S,S)-6 and (R,R,R,R)-6 gave a single OMe signal at δ 3.86 ppm, while for the porphyrin from (R,S)-1c multiple OMe signals were observed [δ 3.67 (major), 3.74, 3.76 (major), 3.77, 3.86 (minor)].

References

- 1 The Porphyrins, ed. D. Dolphin, Academic, NY, 1977. 2 T. A. Skotheim, Handbook of Conducting Polymers, Marcel Dekker, NY, 1986.
- Y. Joh and Y. Kotake, Macromolecules, 1970, 3, 337; M. Anez, G. Uribe, L. Mendoza and R. Contreras, Synthesis, 1981, 214.
- 4 D. S. Sigman and C. B. Chen, Annu. Rev. Biochem., 1990, 59, 207.

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- 5 T. Nogami, Y. Shigehara, N. Matsuda, Y. Takahashi, H. Naganawa, H. Nakamura, M. Hamada, Y. Muraoka, T. Takita, Y. Iitaka and T. Takeuchi, J. Antibiotics, 1990, 43, 1192.
- 6 N. Ono, H. Kawamura, M. Bougauchi and K. Maruyama, *Tetrahedron*, 1990, **46**, 7483.
- 7 K. Saigo, M. Usui, K. Kikuchi, E. Shimada and T. Mukaiyama, Bull. Chem. Soc. Jpn., 1977, 50, 1863.
- M. Oki, Applications of Dynamic NMR Spectroscopy to Organic Chemistry, VCH, NY, 1985.
 H. Kubo, T. Aida, S. Inoue and Y. Okamoto, J. Chem. Soc.,
- 9 H. Kubo, T. Aida, S. Inoue and Y. Okamoto, J. Chem. Soc., Chem. Commun., 1988, 1015; K. Konishi, T. Sugino, T. Aida and S. Inoue, J. Am. Chem. Soc., 1991, 113, 6487; K. Konishi, K. Miyazaki, T. Aida and S. Inoue, J. Am. Chem. Soc., 1990, 112, 5639; K. Konishi, K. Nishida, K. Oda, K. Nishida, T. Aida and S. Inoue, J. Am. Chem. Soc., 1992, 114, 1313; L.-C. Chiang, K. Konishi, T. Aida and S. Inoue, J. Chem. Soc., Chem. Commun., 1992, 254; H. Diekman, C. K. Chang and T. G. Traylor, J. Am.

Chem. Soc., 1971, 93, 4068; A. R. Battersby, D. G. Buckley, S. G. Hartley and M. D. Turnbull, J. Chem. Soc., Chem. Commun., 1976, 879; H. Ogoshi, K. Saita, K. Sakurai, T. Watanabe, H. Toi and Y. Aoyama, Tetrahedron Lett., 1986, 27, 6365; T. Mizutani, T. Ema, T. Tomita, Y. Kuroda and H. Ogoshi, J. Chem. Soc., Chem. Commun., 1993, 520; Y. Kuroda, Y. Kato, T. Higashioji and H. Ogoshi, Angew. Chem., Int. Ed. Engl., 1993, 32, 723.

- 10 Some chiral porphyrins having axially dissymmetric side groups or straps with defined configurations have been reported, which are however conceptually different from 6, since the chiral centres are present outside the porphyrin skeletons: J. T. Groves and R. S. Mayers, J. Am. Chem. Soc., 1983, 105, 5791; S. O'Malley and T. Kodadek, J. Am. Chem. Soc., 1989, 111, 9116; Y. Naruta, F. Tani, N. Ishihara and K. Maruyama, J. Am. Chem. Soc., 1991, 113, 6865.
- 11 K. Konishi, Y. Takahata, T. Aida, S. Inoue and R. Kuroda, J. Am. Chem. Soc., 1993, 115, 1169.