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 antifungal 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-2-carboxylate derivatives. For the synthesis of **1**, nitroethane was condensed with 2-methoxy-1-napthaldehyde to give **2**, which was reacted with isocyanoacetate **3**[6] 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, (±)-**1b** was transesterified with benzyl alcohol, and the resulting (±)-**1c** was hydrogenolysed to yield (±)-**1a**, which was esterified[7] with (*R*)-phenethyl alcohol. Upon crystallization of the diastereoisomeric 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 ($\Delta G^{\ddagger}$) about the pyrrole–naphthalene bond was evaluated to be 25 kcal mol^{-1} at 25 °C.[8]

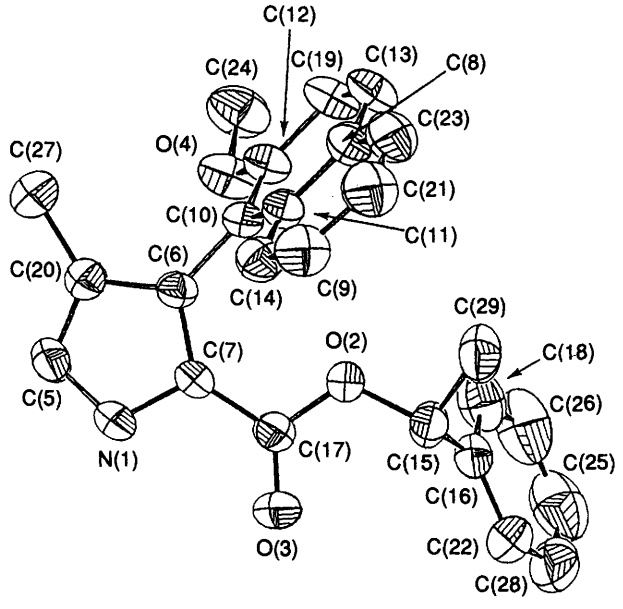
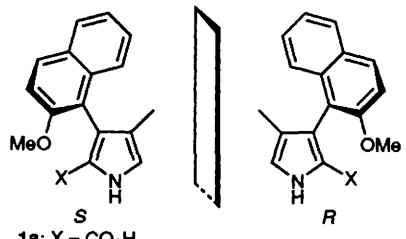


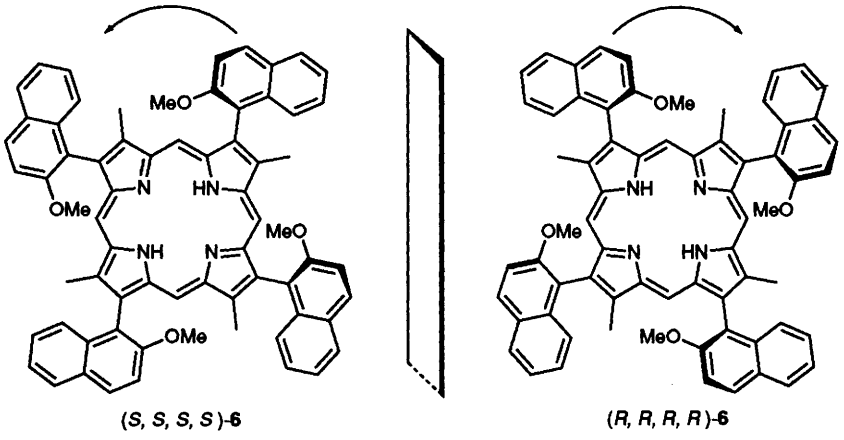
Fig. 1 ORTEP view of (*R*)-phenethyl (*S*)-4-methyl-3-(2'-methoxy-1'-naphthyl)pyrrole-2-carboxylate [(*SR*)-**1d**]. A selected bond distance (Å) and dihedral angles (deg): C(6)–C(10); 1.49(4), C(7)–C(6)–C(10)–C(12); 115.58, C(6)–C(7)–C(17)–O(2); 1.52.

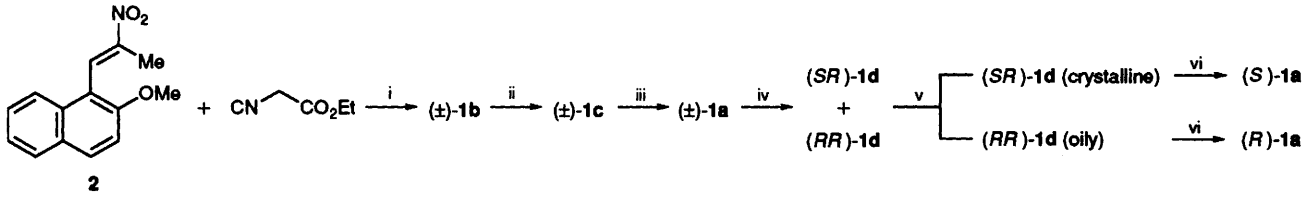


1a; X = CO_2H
1b; X = CO_2Et
1c; X = CO_2CH_2Ph
(*SR*)-**1d**; (*S*)-**1** with X = CO_2-(*R*)-CHMePh
(*RR*)-**1d**; (*R*)-**1** with X = CO_2-(*R*)-CHMePh

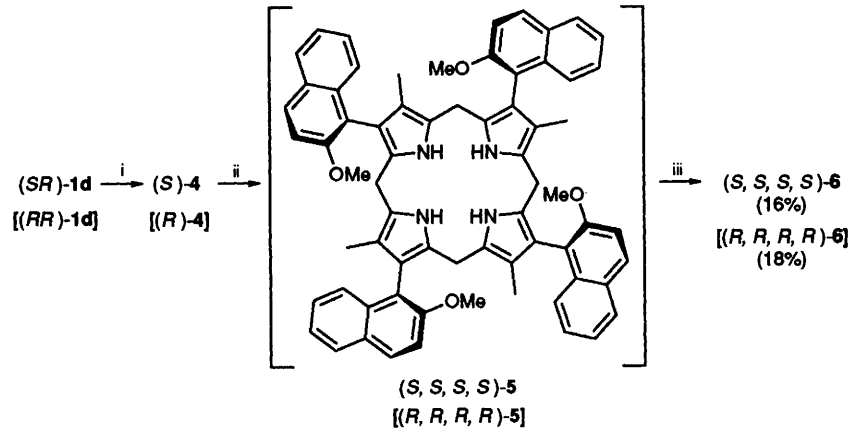
4; X = CH_2OH

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 **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 ^{1}H 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 (±)-**1c** was CD-silent as expected, and actually the mixture of four possible atropisomers, as observed by TLC and ^{1}H NMR.‖ Thus, the porphyrins derived





Scheme 1 *Reagents and conditions*: i, DBU (83%); ii, Na/$PhCH_2OH$ (89%); iii, H_2/Pd-C (96%); iv, (*R*)-PhCH(Me)OH/2-Br-1-ethylpyridinium BF_4^- (91%); v, Cryst., (*SR*)-**1d** [26% based on (±)-**1a**]/Column Chromato., (*RR*)-**1d** [28% based on (±)-**1a**]; vi, H_2/Pd-C



Scheme 2 *Reagents*: i, $LiAlH_4$; ii, Cl_3CCO_2H; 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.

The present work was partly supported by Grant-in-Aid No. 05209206 for Scientific Research on Priority Area from the Ministry of Education, Science and Culture, Japan. We acknowledge Professor K. Saigo for technical guidance for X-ray crystallography.

Received, 19th October 1993; Com. 3/06255D

Footnotes

† A 4.6 × 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 g cm^{-3}; Z = 4. A total of 2078 reflections (maximum 2θ 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 μmol 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_f = 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 $CDCl_3$, 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)].

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