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# Synthesis of a Chiral 3,3'-Di-*tert*butyl-2,2'-bipyrrole

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**Summary.** Diethyl 3,3'-di-*tert*-butyl-4,4'-dimethyl-2,2'-bipyrrole-5,5'-dicarboxylate was synthesized in four steps from ethyl 3,5-dimethyl-1*H*-pyrrole-2-carboxylate. The CH<sub>2</sub> hydrogens of the ethyl ester groups of the former are diastereotopic in the <sup>1</sup>H-NMR, consistent with axial chirality of the bipyrrole and restricted rotation about the 2,2'-bipyrrole bond, due to the *tert*-butyl groups. An X-ray structure of the crystalline target compound shows the pyrrole rings are twisted out of coplanarity by 84.5°.

Keywords. Pyrrole; Axial chirality; Spectroscopy.

# Introduction

Although bipyrroles [1, 2] are found widely in nature, from anti-tumor agents [3] to seabird eggs [4], prior to approximately 15 years ago they were the subject of interest directed mainly toward indigoid dyes, the tripyrrole prodigiosin [5], the corrin vitamin  $B_{12}$  [6], and the oligopyrrole conducting polymers [7, 8]. More recently, the prodigiosin group has received renewed interest [9] in connection with anti-cancer properties, and new classes of conjugated cyclic oligomers [10-15] have been synthesized and are under study as therapeutic agents in photodynamic therapy, as ionophores, and as radiation sensitizers, *inter alia*. Curiously, and in contrast to the well-studied atropisomeric stereochemistry of biaryls [16], there are only two known optically active bipyrroles (Fig. 1): a 1,1'-bipyrrole, resolved in 1931 [17] and a 2,2'-bipyrrole resolved in 1953 [18]. The pyrrole rings are thus not co-planar. Molecular orbital calculations [19] and photoelectron spectroscopy [20] support a conformation with orthogonal pyrrole rings in the parent 1,1'-bipyrrole. In contrast the parent unsubstituted 2,2'-bipyrrole was shown to adopt the *anti-periplanar* (ap) conformation in the crystal [21, 22]; whereas, ab *initio* calculations indicate a (gas phase) *anti-clinal* (ac) global minimum with the N-2-2'-N' torsion angle ( $\phi \sim 148^\circ$ , or 12–16 kJ/mole more stable than the syn*clinal* local minimum ( $\phi \sim 46^{\circ}$ ) [22–25].

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Fig. 1. A 1,1'-bipyrrole (left) and a 2,2'-bipyrrole (right) that have been resolved into enantiomers



**Fig. 2.** (Top) Enantiomeric 2,2'-bipyrroles interconverting by  $180^{\circ}$  rotation about the 2–2' bond. The absolute configurations are denoted by *S* and *R*. The enantiomeric interconversion shown passes through a coplanar conformation (either *ap* or *sp*), and with sufficiently large substituents at C(3)/C(3') the *ap* and *sp* conformers represent barriers to interconverting *R* and *S* enantiomers. (Bottom) A biphenyl with *o,o'-tert*-butyl groups that prevent interconversion of *R* and *S* enantiomers (Ref. [26]), and the target bipyrrole of this work

The bipyrrole molecular framework presents an intriguing system for the study of axial chirality [16]. Of particular interest to us are bipyrroles that are potentially resolvable into enantiomers due to restricted rotation about the bond connecting the two pyrrole rings (Fig. 2). Two bulky "ortho" tert-butyl groups, one on each pyrrole ring, might be expected to restrict rotation and generate resolvable, axially chiral bipyrroles, as has been reported [26] for biphenyl (Fig. 2). In the latter, the two ortho tert-butyl groups gave a remarkably stable, resolvable axially-chiral biphenyl that was not racemized even in boiling pyridine or boiling aqueous alkali. In the current work, we have identified **5** as a suitable target for synthesis and study. Based on the stereochemical studies of the di-tert-butyl biphenyl, we expect that **5** should exhibit restricted rotation about the 2,2′ bond.

# **Results and Discussion**

# Synthetic Aspects

2,2'-Bipyrroles appear in literature much more frequently than other bipyrrole isomers, although they generally appear late and infrequently in the first half of



Scheme 1. (a) *t*-BuOAc/MeNO<sub>2</sub>/conc H<sub>2</sub>SO<sub>4</sub>; (b) SO<sub>2</sub>Cl<sub>2</sub>/Et<sub>2</sub>O; (c) aq. acetone; (d)  $I_2/KI/aq$ . NaHCO<sub>3</sub>; (e) Cu powder/xylene/140°C

the 20<sup>th</sup> century. Successful directed syntheses began to appear in the 1950s, usually by an Ullman-type coupling of 2-iodopyrroles [1, 2, 18, 27], although other coupling methods, e.g., FeCl<sub>3</sub>, have been used [1]. However, tert-butyl-2,2'-bipyrroles are unknown, and it was not clear whether an Ullmann-type copper-catalyzed self-coupling of the precursor iodopyrrole 4 proposed in Scheme 1 could overcome the considerable steric hindrance imposed by the *tert*-butyls. Iodopyrrole **4** has not been reported in literature, but its precursor *tert*-butylpyrrole 2 has been synthesized previously by  $H_2SO_4$ -catalyzed reaction of 1 in acetic acid with *tert*-butyl acetate [28]. We synthesized pyrrole 1, reported previously [29], in 40% yield and converted it to 2 by *tert*-butylation [28] in similar yield. We noted that 2 was contaminated by 2,4-dimethylpyrrole. Attempts to reduce the amount of contamination and improve the yield of 2 by reaction of 1 with tert-butyl chloride catalyzed by anhydrous  $SnCl_4$  (in  $CH_2Cl_2$ ) of AlCl<sub>3</sub> (in  $CS_2$ ) were unsuccessful. However, changing the solvent from acetic acid to nitromethane gave 2 with lesser amounts of 2,4-dimethylpyrrole by-product, which could be removed by allowing the total crude reaction product to air oxidize for 1-2 days followed by passing a dichloromethane solution of the mixture through a thin pad of TLC silica gel. Fractional crystallization then afforded pure 2 in 40–50% yield, with recovered mother liquors containing a mixture of 1 and 2. The 5-iodo substituent was introduced by reaction of the 5-carboxylic acid 3 in bicarbonate with  $I_3^-$  according to established procedures [27, 30]. To prepare 3, tert-butylpyrrole ester 2 was reacted in standard fashion [31] with  $SO_2Cl_2$  to trichlorinate the 5-methyl group, which was hydrolyzed smoothly in aqueous acetone to afford carboxylic acid 3. A by-product found following the iodination reaction, ethyl 4-chloro-5-iodo-3methylpyrrole-2-carboxylate (detected by GC-MS) apparently originates from adventitious de-tert-butylation of 2 during SO<sub>2</sub>Cl<sub>2</sub> treatment and replacement by chlorine, because 2 was pure and free from any traces of ethyl 3,5-dimethylpyrrole-2-carboxylate contamination.

Coupling iodopyrroles to give bipyrroles by the *Ullmann* reaction typically uses copper bronze or copper powder. In 1963, it had been shown that the reaction proceeds smoothly in N,N-dimethylformamide (*DMF*) with less deiodinated monopyrrole by-product, *e.g.*, diethyl

5-iodo-3-methylpyrrole-2,4-dicarboxylate gave a 61% yield of bipyrrole after reaction at room temperature for 2 hours [32]. Other unhindered  $\alpha$ -iodo-pyrroles were shown to couple smoothly in warm *DMF* [27], which became the solvent of choice for coupling ethyl 3-ethyl-5-iodo-4-methylpyrrole-2-carboxylate (*DMF*, 140°C, 1 h, 50% yield) [33], diethyl 5-iodo-3-phenylpyrrole-2,4-dicarboxylate (*DMF*, refl., 9 h, 44%) [30], and ethyl 3,4-diethyl-5-iodopyrrole-2-carboxylate (*DMF*, 110°C, 3 h, 40%) [34]. Despite the improvement, 2,2'-bipyrrole formation has typically been plagued by low yields and tedious isolations [32, 35]. Protection of the pyrrole nitrogens as *tert-BOC* derivatives signaled another important achievement for the coupling of  $\alpha$ -iodo-pyrroles, with higher yields in *DMF* and easier isolation, *e.g.*, ethyl 3-ethyl-5-iodo-4-methyl-1-(*tert*-butoxy-carboxylate gave a 78% yield in hot *DMF* [35].

Even with more sterically hindered pyrroles, *e.g.*, ethyl 3,5-dimethyl-4-iodopyrrolecarboxylate, the *Ullmann* reaction using copper bronze in hot *DMF* served well in producing the bipyrrole (diethyl 2,2',4,4'-tetramethyl-3,3'-bipyrrole-5,5'-dicarboxylate, *DMF*, reflux 1 h 25%) [27]. In contrast, with hot acetic acid used as solvent [36], only the deiodinated monopyrrole ester was isolated [27]. Our attempts to couple the more sterically hindered iodopyrrole **4** in *DMF* or acetic acid to bipyrrole **5** were unsuccessful and led only to deiodination of **4**, along with unreacted **4**. Attempts to couple the deiodinated monopyrrole using oxidative coupling methods: anhydrous ferric chloride or potassium ferricyanide [1, 37] were unsuccessful. However, changing the solvent to (hot) xylene [38] afforded an acceptable yield (34%) of **5**. In addition to **5**, a minor by-product (0–5%, molecular weight 416) was isolated and shown spectroscopically to be an *N*,2'-bipyrrole, diethyl 3',4-di-*tert*-butyl-3,4'-dimethyl-*N*,2'bipyrrole-2,5'-dicarboxylate.

# Structure and Conformation

A crystal of bipyrrole **5**, suitable for X-ray crystallographic analysis, was grown from  $CH_2Cl_2$ /hexane. Examination of its X-ray structure (Fig. 3) shows clearly that the two pyrrole rings are not coplanar but lie nearly orthogonal. The N-2-2'-N' dihedral angle is found to be 84.5°, in the *sc* conformation found in the



Fig. 3. Structural drawing of bipyrrole 5, showing the atom numbering scheme (50% probability ellipsoids) as observed in its crystal structure

crystal. Molecular mechanics calculations predict a dihedral angle of  $84.5^{\circ}$  for the gas phase global energy minimum *sc* conformation of **5**, an unexpected coincidence that suggests crystal packing forces do not distort the energy-minimum conformation. (In contrast, molecular mechanics calculations [39] of the parent unsubstituted 2,2'-bipyrrole predict a planar structure, as found in the crystal [21, 22].) Molecules of **5** of the same helicity are organized into parallel ribbons in the crystal, with N–H····O=C hydrogen bonds connecting adjacent ribbons of opposite helicity.

The bond lengths and bond angles found in **5** are quite similar to those reported for a dipyrrylmethane, 5,5'-diethylcarbonyl-3,3',4,4'-tetraethyldipyrrol-2-ylmethane [40]. The C(3)–C(4) bond of **5** is slightly (0.17 Å) longer than in the latter, and the N–C(5) bond length is slightly shorter (0.27 Å). The internal pyrrole ring angle C(2)–C(3)–C(4) is  $1.5^{\circ}$  smaller in **5**.

# Structure and Spectroscopy

The <sup>13</sup>C NMR of **5** correlates nicely with its structure and is consistent with that observed for the monopyrole precursors **3** and **4**, with the necessary changes at what will become C(2) in **5**. Similarly, the <sup>1</sup>H NMR spectra show good correlation. The UV spectra of **5** and **7** are similar, showing an intense ( $\varepsilon = 30000$ ) absorbance near 288 nm and a shoulder near 250 nm (Fig. 4). The profile of the UV spectrum of **5** closely matches that of monopyrrole **2** ( $\varepsilon = 18500$  near  $\lambda_{max} = 284$  nm, shoulder near 250 nm), but broadening of the main band and shoulder in **5** suggest possible exciton coupling between the two orthogonal pyrrole chromophores.



**Fig. 4.** UV spectrum of  $10^{-5}$  M **5** in ethanol at  $23^{\circ}$ C



Scheme 2. (a) NaOH/EtOH; (b) SOCl<sub>2</sub>/CHCl<sub>3</sub>; (c) CH<sub>3</sub>CH<sub>2</sub>C\*H (CH<sub>3</sub>)CH<sub>2</sub>OH/Et<sub>3</sub>N

## Atropisomerism

Nonplanar 2,2'-bipyrroles are intrinsically chiral, with enantiomeric conformations interconverting by rotation about the C(2)-C(2') bond through planar conformations (Fig. 2). When the barrier to interconversion is raised sufficiently, the interconversion rate is slowed and the enantiomers are, in principle, separable. The phenomenon is well-represented in studies of biphenyls and other biaryls, and it has been observed with two bipyrroles. With free rotation about the C(2)-C(2')bond of 5 greatly reduced by the presence of the C(3) and C(3') tert-butyls, one might expect to observe its atropisomers. Axial chirality in 5 was detected by <sup>1</sup>H NMR, where diastereotopic hydrogen from the  $CH_2$  group of the ethyl ester(s) were seen. By changing from the ethyl ester to the 2(S)-methylbutyl group (Scheme 2), the bipyrrole 7 has both a chiral center and a chiral axis. If free rotation about the C(2)-C(2') bond is restricted, bipyrrole 7 is thus a mixture of (R,S) and (R,R) diastereomers. In the <sup>13</sup>C NMR spectrum of 7, signal doubling is observed for the methyl group (16.83/16.88 ppm) on the ester methine carbon and the ester methylene group (26.44/26.39 ppm), as well as for pyrrole ring carbon 5 (126.47/126.85 ppm). However, attempts to separate the diastereomers of 7 by GC, TLC, or fractional crystallization were unsuccessful. And a crystal structure of carefully crystallized 7 showed the presence of both diastereomers.

## **Experimental**

#### General

All nuclear magnetic resonance (NMR) spectra were recorded in CDCl<sub>3</sub> unless otherwise indicated on a GE GN-300 or Varian Unity Plus spectrometer operating at a <sup>1</sup>H proton frequency of 300 MHz or 500 MHz, respectively. Chemical shifts are reported in  $\delta$  ppm referenced to the residual CHCl<sub>3</sub> <sup>1</sup>H signal at 7.26 ppm and CDCl<sub>3</sub> <sup>13</sup>C signal at 77.00 ppm. A *J*-modulated spin-echo experiment was used to obtain <sup>13</sup>C NMR signal's multiplicity. UV spectra were recorded in ethanol on a Perkin Elmer Lambda 12 spectrophotometer, and infrared spectra were obtained on a Perkin-Elmer Spectrum BX FT-IR spectrophotometer from KBr pellets. Gas chromatography-mass spectrometry analyses were carried out on a Hewlett-Packard 5890A capillary gas chromatograph (30 m DB-1 column) equipped with a Hewlett-Packard 5970 mass selective detector. Analytical thin layer chromatography was carried out on J.T. Baker silica gel IB-F plates (Merck, 125 µm layer). Silica gel 70–230 mesh was employed for column chromatography. Radial chromatography was carried out on Merck Silica Gel PF<sub>254</sub> with gypsum preparative layer grade, using a Chromatotron (Harrison Research, Inc., Palo Alto, CA). Melting points were determined on a Mel-Temp capillary apparatus and are uncorrected. Combustion analyses were carried out by Desert Analytics, Tucson, AZ, and the data were within  $\pm 0.3\%$ 

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from the calculated values. Commercial reagents and HPLC grade solvents (Aldrich or Fisher) were dried and purified following standard procedures [20]. (S)-(-)-2-Methyl-1-butanol (*prim.* active amyl alcohol,  $[\alpha]^{23} = -5.8^{\circ}$  (neat) was from Aldrich Chemical Co. The starting ethyl 3,5-dimethyl-1*H*-pyrrole-2-carboxylate (1) was synthesized as previously described [1, 2]. The Cu bronze powder was Cu for organic synthesis (29,258-3 Cat. no.) from Aldrich Chemical Co.

#### *Ethyl-4-tert-butyl-3,5-dimethyl-1H-pyrrole-2-carboxylate* (2)

10g (0.06 mol) of ethyl 3,5-dimethyl-1*H*-pyrrole-2-carboxylate (**1**) were suspended in 20 cm<sup>3</sup> of nitromethane and 16.2 cm<sup>3</sup> (2 eq.) of *tert*-butyl acetate. 1 cm<sup>3</sup> of conc. H<sub>2</sub>SO<sub>4</sub> was added, with stirring, then the temperature was raised to 75°C, and the mixture was stirred for 4 h (during which **1** dissolved). The progress of the reaction was monitored by TLC (eluent: CH<sub>2</sub>Cl<sub>2</sub>). After cooling, sufficient CH<sub>2</sub>Cl<sub>2</sub> was added to keep the pyrrole dissolved. The solution was washed with H<sub>2</sub>O, sat. aq. NaHCO<sub>3</sub>, and H<sub>2</sub>O, then dried over anhydrous Na<sub>2</sub>SO<sub>4</sub>. The solvent was evaporated, and the dry crystalline solid (*approx.* 10 g) was left exposed to air for 1–2 days, during which it turned red. The solid was dissolved in dichloromethane and filtered through a pad of silica gel to remove the red-black polypyrrole. The almost colorless eluent was evaporated, and the desired product **2** was isolated by fractional crystalization using methanol. The mother liquor, containing a mixture of **1** and **2** can be recycled in a subsequent *tert*-butylation reaction. Yield: 6.6 g (49%); mp: 109–110°C (Ref. [28] 108–110°C); <sup>1</sup>H NMR:  $\delta = 1.30$  (3H, t, J = 7.0 Hz), 1.36 (9H, s), 2.36 (3H, s), 2.50 (3H, s), 4.28 (2H, q, J = 7.0 Hz), 8.20 (1H, br) ppm; <sup>13</sup>C NMR:  $\delta = 13.68$  (3-CH<sub>3</sub>), 14.82 (CH<sub>3</sub>CH<sub>2</sub>), 16.60 (5-CH<sub>3</sub>), 33.19 (*t*BuC), 31.98 (*t*BuCH<sub>3</sub>), 55.77 (CH<sub>2</sub>), 117.22 (C-2), 127.74 (C-3 or C-5), 128.04 (C-4), 128.87 (C-3 or C-5), 161.00 (C-2) ppm; MS: m/z (%) = 223 (M<sup>+•</sup>, 21), 208 (54), 178 (8), 162 (100), 91 (5).

# 4-tert-Butyl-3-methyl-5-iodo-1H-pyrrole-2-carboxylate (4; C<sub>12</sub>H<sub>18</sub>INO<sub>2</sub>)

6.0 g of *tert*-Butylpyrrole **2** (27 mmol) were dissolved in 200 cm<sup>3</sup> of diethyl ether, then 12.7 g of SO<sub>2</sub>Cl<sub>2</sub> (7.64 cm<sup>3</sup>, 94.5 mmol) were added dropwise. The reaction mixture was stirred at room temperature for 24 h and evaporated to dryness. To the residue, a solution of 120 cm<sup>3</sup> of acetone and 60 cm<sup>3</sup> of H<sub>2</sub>O was added, and the solution was heated at reflux for 45 min. The acetone was removed, and the mixture was extracted with CH<sub>2</sub>Cl<sub>2</sub> until no suspension remained. The combined extracts were evaporated to dryness, taken with 250 cm<sup>3</sup> of diethyl ether and extracted with 350 cm<sup>3</sup> of 10% aq. NaHCO<sub>3</sub>. The combined aqueous extracts were carefully acidified with conc. HCl: water = 1:1 to give **3** as a white precipitate. It was unstable toward decarboxylation and was used directly in the next step. Yield: 3.1 g (46%); <sup>1</sup>H NMR (CDCl<sub>3</sub>):  $\delta$  = 1.38 (3H, t, *J* = 7.3 Hz), 1.50 (9H, s), 2.57 (3H, s), 4.35 (2H, q, *J* = 7.3 Hz), 9.70 (br) ppm; (d<sub>6</sub>-DMSO):  $\delta$  = 1.23 (3H, t, *J* = 7.2 Hz), 1.33 (9H, s), 2.30 (3H, s), 41.8 (2H, q, *J* = 7.2 Hz), 10.77 (1H, s), 13.55 (1H, br) ppm; <sup>13</sup>C NMR (d<sub>6</sub>-DMSO):  $\delta$  = 12.79 (4-CH<sub>3</sub>), 14.21 (CH<sub>3</sub>CH<sub>2</sub>), 31.17 (tBuCH<sub>3</sub>), 32.83 (tBu-C), 59.63 (CH<sub>2</sub>), 119.58 (C-2), 123.89 (C-5), 124.63 (C-4), 133.99 (C-3), 160.51 (ester C=O), 163.82 (COOH) ppm.

Mono-acid **3** (3.11 g, 12.3 mmol) and NaHCO<sub>3</sub> (3.62 g, 43.1 mmol) in 9 cm<sup>3</sup> of 95% ethanol and 16 cm<sup>3</sup> of H<sub>2</sub>O were stirred at 70–75°C. A solution of 3.75 g of I<sub>2</sub> (14.7 mmol) and 6.13 g of KI (36.9 mmol) in 45 cm<sup>3</sup> of H<sub>2</sub>O was added as fast as it was decolorized. The reaction mixture was poured into ice water. A waxy solid formed and was extracted into  $3 \times 80$  cm<sup>3</sup> of CH<sub>2</sub>Cl<sub>2</sub>. The combined CH<sub>2</sub>Cl<sub>2</sub> extracts were dried over anhydrous Na<sub>2</sub>SO<sub>4</sub> and evaporated to afford 3.4 g (82%) of crude product, which was purified by extraction by hexane and radial chromatography on silica gel using ethylacetate:*n*-hexane = 3:97 (*v*/*v*) as eluent afforded the desired iodopyrrole **4**. Yield: 2.14 g (63%); mp: 83–85°C; IR:  $\bar{\nu}$  = 3295, 2958, 1672, 1226, 1096 cm<sup>-1</sup>; <sup>1</sup>H NMR:  $\delta$  = 1.35 (3H, t, *J* = 7.0 Hz), 1.44 (9H, s), 2.54 (3H, s), 4.30 (2H, q, *J* = 7.0 Hz), 8.66 (1H, br) ppm; <sup>13</sup>C NMR:  $\delta$  = 13.92 (3-CH<sub>3</sub>), 14.74 (CH<sub>3</sub>CH<sub>2</sub>), 32.00 (*t*Bu-CH<sub>3</sub>), 33.00 (*t*Bu-C), 60.35 (CH<sub>2</sub>), 67.27 (C-5), 124.60 (C-2), 127.23 (C-3), 134.88 (C-4), 160.60 (C=O) ppm; MS: *m/z* (%) = 335 (M<sup>+•</sup>, 34), 320 (71), 274 (100), 147 (11), 91 (8).

## Diethyl 3,3'-di-tert-butyl-4,4'-dimethyl-2,2'-bipyrrole-5,5'-dicarboxylate (5; C<sub>24</sub>H<sub>36</sub>N<sub>2</sub>O<sub>4</sub>)

To 2.51 g of iodopyrrole **4** (7.5 mmol) dissolved in 10 cm<sup>3</sup> of dry xylene were added 2.86 g of Cu powder (45 mmol, 6 eq.), and the mixture was heated in a sealed tube at 140°C for 2 days. After cooling, the Cu was removed by filtration through celite, which was washed well with CHCl<sub>3</sub>. The organic filtrates were washed with 25 cm<sup>3</sup> of 1 *M* HCl and Na<sub>2</sub>S<sub>2</sub>O<sub>3</sub>, then H<sub>2</sub>O. After drying over anhydrous Na<sub>2</sub>SO<sub>4</sub>, the solvents were removed, and the resulting solid was purified by radial chromatography using CH<sub>3</sub>OH:CH<sub>2</sub>Cl<sub>2</sub> = 2:98 (v/v) as eluent and crystallized from CH<sub>2</sub>Cl<sub>2</sub>/n-hexane to give 450 mg (1st crop) + 82 mg (2nd crop) of **5**. Yield: 528 mg (34%); mp: 291–2°C (sealed capillary); UV (ethanol):  $\lambda_{max}(\varepsilon) = 286$  (34700), 250 (sh, ~16400) nm; IR:  $\bar{\nu} = 3288$ , 2952, 1665, 1223, 1094 cm<sup>-1</sup>; <sup>1</sup>H NMR:  $\delta = 1.20$  (9H, s), 1.34 (3H, dd, J = 6.85, 7.30 Hz), 2.53 (3H, CH<sub>3</sub>), 4.27 (1H, dq, J = 10.96, 6.85 Hz), 4.32 (1H, dq, J = 10.96, 7.30 Hz), 8.52 (1H, br) ppm; <sup>13</sup>C NMR:  $\delta = 13.46$  (CH<sub>3</sub>CH<sub>2</sub>), 14.73 (C-4,4' CH<sub>3</sub>), 31.10 (*t*Bu-CH<sub>3</sub>), 32.85 (*t*Bu-C), 60.22 (CH<sub>2</sub>), 119.65, 123.88, 126.76, 1330.10, 161.62 (C=O) ppm; MS: m/z (%) = 416 (M<sup>+•</sup>, 55), 345 (100), 299 (47), 253 (50), 225 (9), 155 (16), 147 (7), 57 (18).

## Disobutyl 3,3'-di-tert-butyl-4,4'-dimethyl-2,2'-bipyrrole-5,5'-dicarboxylate (7; C<sub>30</sub>H<sub>48</sub>N<sub>2</sub>O<sub>4</sub>)

220 mg of bipyrrole **5** (0.529 mmol) were suspended in 20 cm<sup>3</sup> of 95% ethanol and to this mixture was added 180 mg (4.5 mmol) of NaOH in 6 cm<sup>3</sup> of H<sub>2</sub>O. The mixture was heated at reflux with stirring, until the ester dissolved. After cooling, the reaction mixture was evaporated to dryness, and the residue was dissolved in 20 cm<sup>3</sup> of H<sub>2</sub>O and acidified with conc HCl:H<sub>2</sub>O = 1:1) to afford a white precipitate, which was collected by filtration and dried to give diacid **6**, which was used directly in the next step. Yield: 185 mg (96%); decpt. 260°C; <sup>1</sup>H NMR (d<sub>6</sub>-DMSO):  $\delta$  = 1.11 (9H, *t*Bu-CH<sub>3</sub>), 2.42 (3H, CH<sub>3</sub>), 11.02 (H, s), 11.92 (1H, s) ppm; <sup>13</sup>C NMR (d<sub>6</sub>-DMSO):  $\delta$  = 13.57 (CH<sub>3</sub>), 30.86 (*t*Bu-CH<sub>3</sub>), 32.56 (*t*Bu-C), 119.16, 124.83, 124.98, 131.23, 163.05 (CO) ppm.

33.2 mg of diacid **6** (0.0922 mmol) were suspended in 7 cm<sup>3</sup> of CHCl<sub>3</sub> to which 0.1 cm<sup>3</sup> (>6 eq.) of SOCl<sub>2</sub> was then added. The stirred mixture was heated at reflux until it was clear. Then the reaction mixture was evaporated, and the residue was dissolved in CHCl<sub>3</sub> and re-evaporated. The residue was dissolved in 3 cm<sup>3</sup> of CH<sub>2</sub>Cl<sub>2</sub>, and 30 mm<sup>3</sup> (~3 eq.) of (*S*)-(-)-2-methyl-1-butanol were added along with ~60 mm<sup>3</sup> (~4 eq.) of triethylamine. The mixture was stirred for 1 h at room temperature, then the solvent was evaporated and the residue redissolved in CH<sub>2</sub>Cl<sub>2</sub>. The CH<sub>2</sub>Cl<sub>2</sub> solution was washed with 10% aq. HCl, then water, and it was dried over anhydrous Na<sub>2</sub>SO<sub>4</sub>. The solid, after evaporation, was purified by radial chromatography on silica gel using CH<sub>2</sub>Cl<sub>2</sub> as eluent to afford diester **7**. Yield: 39 mg (85%); mp: 209–210°C; IR:  $\bar{\nu}$  = 3294, 2961, 1664, 1235, 1100 cm<sup>-1</sup>; UV (ethanol):  $\lambda_{max}(\varepsilon)$  = 285 (29000), 250 (sh, ~15000) nm; <sup>1</sup>H NMR:  $\delta$  = 0.95 (6H, t, *J* = 7.3 Hz), 0.976 (3H, d, *J* = 6.8 Hz), 0.980 (3H, d, *J* = 6.8 Hz), 1.21 (18H, s), 1.3 (2H, m), 1.5 (2H, m), 1.8 (2H, m), 2.55 (6H, s), 4.1 (4H, m), 9.55 (2H, br, NH) ppm; <sup>13</sup>C NMR:  $\delta$  = 11.50, 13.60, 16.83, 16.86, 26.39, 26.43, 31.11, 32.85, 34.55, 69.00, 119.74, 123.95, 126.47, 133.05, 161.93 ppm; MS: *m/z* (%) = 501 (M + 1, 33), 500 (M<sup>+•</sup>, 100), 429 (37), 359 (53), 313 (22), 309 (34), 271 (16), 270 (13), 269 (29), 267 (38), 227 (12), 71 (18), 57 (49).

#### X-ray Structure and Solution

Crystals of bipyrrole **5** were grown from  $CH_2Cl_2/n$ -hexane. Suitable crystals were coated with epoxy cement, mounted on a glass fiber and placed on a Siemens P4 diffractomer. Unit cell parameters were determined by least squares analysis of 3614 reflections with 1591 independent ones (R(int) = 0.0357). The data were corrected for *Lorentz* and polarization effects. Crystal data are given in Table 1. Scattering factors and corrections for anomalous dispersion were taken from a standard source [37].

Calculations were performed using Siemens SHELXTL PLUS, version 5.03, system of programs refining on  $F^2$ . The structure was solved by direct methods in the chiral space group,  $C_2/c$ . The unit cell contains an ordered array of the molecule with short N to O(1) #1 contacts. The handedness of the molecule shown in Fig. 3 is therefore arbitrarily chosen.

Formula weight Crystallized from	416.5 CH <sub>2</sub> Cl <sub>2</sub> /hexane
Crystal size [mm <sup>3</sup> ]	295 0.18 × 0.28 × 0.24
Crystal size [iiiii ]	$0.16 \times 0.38 \times 0.24$
	$C_{24}H_{36}N_2O_4$
space group	C2/C
Z Call dimensional	4 - 22 700(2) Å
Cen dimensions:	a = 23.700(3) A
	b = 10.2800(10)  A
	c = 11.136(2)  A
	$\alpha = 90^{-1}$
	$\beta = 112.250(10)^{2}$
	$\gamma = 90^{\circ}$
C	$V = 2511.1(6) \text{ A}^2$
Calc, density $d_x [mg/m^2]$	1.102
Data collection range	$3.5 < 2\theta < 50^{\circ}$
Theta range for data collection	1.86 to 22.50°
Scan type/scan range	$\omega/1.2^{\circ}$
Index ranges	$-25 \le h \le 25, -1 \le k \le 11, -11 \le 1 \le 11$
Reflections collected	3614
Independent reflections	1591 $[R(int) = 0.0357]$
Completeness to theta $= 22.50^{\circ}$	97.4%
Absorption correction	Empirical
Max. and min. transmission	0.8059 and 0.7648
Refinement method	Full-matrix least squares on $F^2$
Data/restraints/parameters	1591/0/142
Goodness-of-fit on $F^{2a}$	1.065
$R_1$ , $^{\mathrm{b}} w R_2^{\mathrm{c}} (I > 2\sigma(I))$	$R_1 = 0.0701, wR_2 = 0.1795$
R indices (all data)	$R_1 = 0.1082, wR_2 = 0.2154$
Extinction coefficient	0.011(2)
Largest diff. peak and hole	0.323 and $-0.260 \text{ e.Å}^{-3}$
F (000)	904
$\mu$ (MoK $\alpha$ ), mm <sup>-1</sup>	0.074
Radiation $(\lambda, \dot{A})$	0.71073
Transm. factors:	1.7648-0.8059

 Table 1. Crystallographic data for bipyrrole 5

 $\overline{a \ w^{-1} = [\sigma^2(F_o^2) + (aP)^2 + bP]} \text{ where } P = (F_o^2 + wF_c^2)/3. \text{ Goodness of Fit (GOOF),} [\Sigma[w(F_o^2 - F_c^2)^2]/(M - N)]^{0.5} \text{ where } M \text{ is the number of reflections and } N \text{ is the number of parameters refined}$  $\overline{b} \ R_1 = \Sigma ||Fo| - |Fc||/\Sigma|Fo|$ 

<sup>b</sup>  $R_1 = \Sigma ||Fo| - |Fc|| / \Sigma |Fo|$ <sup>c</sup>  $wR_2 = [\Sigma [w(F_o^2 - F_c^2)^2] / \sigma [w(F_o^2)^2]]^{0.5}$ 

All non-hydrogen atoms (Table 2) were refined with anisotropic thermal parameters. The data were corrected using a riding model derived from psi scans. Hydrogen atom positions were calculated using a riding model with a C–H distance fixed at 0.96 Å and a thermal parameter 1.2 times the host carbon atom.

Tables of anisotropic displacement parameters, isotropic displacement parameters, atomic coordinates, bond angles and bond lengths for bipyrrole **5** have been deposited at the Cambridge Crystal-lographic Data Center (CCDC No. 191399).

	х	у	Ζ	U(eq)
N(1)	324(1)	1613(3)	1434(3)	51(1)
C(2)	288(2)	2403(4)	2380(3)	44(1)
O(1)	648(2)	151(4)	-279(4)	115(2)
O(2)	1525(1)	1181(3)	279(3)	81(1)
C(3)	845(2)	3061(4)	2945(3)	44(1)
C(4)	1217(2)	2629(4)	2269(3)	45(1)
C(5)	876(2)	1740(4)	1339(3)	48(1)
C(31)	1029(2)	4024(4)	4067(3)	53(1)
C(32)	1209(2)	5325(5)	3647(5)	86(2)
C(33)	1572(2)	3475(5)	5216(4)	85(2)
C(34)	532(2)	4302(5)	4567(5)	89(2)
C(41)	1860(2)	3008(4)	2492(4)	62(1)
C(51)	996(2)	952(4)	383(4)	62(1)
C(53)	1674(3)	435(6)	-669(7)	120(2)
C(54)	1775(5)	1139(7)	- 1549(9)	206(5)

**Table 2.** Atomic coordinates (×10<sup>4</sup>) and equivalent isotropic displacement parameters ( $\mathring{A}^2 \times 10^3$ ) for bipyrrole **5**. *U*(eq) is defined as one third of the trace of the orthogonalized *U*<sup>ij</sup> tensor

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