

## Synthesis and chiroptical property of $C_2$ -symmetric cyclohexapyrrole

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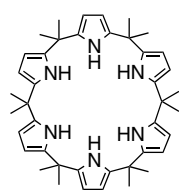
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**Abstract**—Condensation reaction of *gem*-dimethyldipyrromethane-5,5'-dicarbinol and 4,4'-dimethyl-3,3'-di-*iso*-butyl-2,2'-bipyrrole under the catalysis by trifluoroacetic acid gave a hexapyrrolic macrocycle **6** in 15% yield after DDQ oxidation. X-ray crystallography of **6** shows that three parts of highly planar dipyrromethene unit are assembled by two  $sp^3$  hybridized *gem*-dimethyl carbon bridges and one direct linking at the pyrrole  $\alpha$ -positions, leading to  $C_2$  molecular symmetry. The complexation of **6** with (*S*)-(+)- and (*R*)-(–)-mandelic acid induced a CD Cotton effect at 461 and 650 nm.

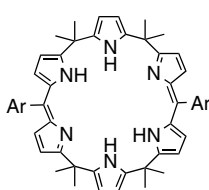
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Hexapyrrolic macrocycles with bridging  $sp^3$  carbon(s) have been synthesized and their unique structures with interrupted  $\pi$ -electron conjugation are in contrast to those of fully conjugated hexaphyrins.<sup>1–3</sup> Depending on the substitution pattern of the six bridging  $sp^3$  carbons and pyrrole  $\beta$ -positions, calix[6]pyrrole changes its shape from a hexagonal disc-like structure to a trigo-

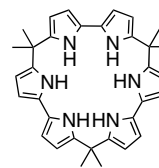
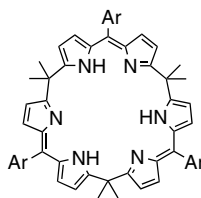
contrast to these structures and functions, this Letter focuses on the new aspect of cyclohexapyrrole with bridging  $sp^3$  carbons. A new cyclohexapyrrole having  $C_2$  molecular symmetry is described with its application to supramolecular chirogenesis where optically active carboxylic acid regulates the chiral conformation of the macrocycle.<sup>4</sup>



calix[6]-  
pyrrole



calix[6]phyrins



calix[3]-  
bipyrrole

nal cone structure and a hexagonal column-like structure.<sup>1</sup> Calix[6]phyrins with a combination of  $sp^3$  and  $sp^2$  bridging carbons and calix[3]bipyrrole with a little bit smaller cavity size have unique structural features.<sup>2,3</sup> Some of these cyclohexapyrroles are drawing great attention because of their anion binding properties. In

The acid catalyzed condensation reactions between 2,2'-bipyrrole and dipyrromethane-5,5'-dicarbinol have been reported to give corrole and octaphyrin(1.1.1.0.1.1.1.0) after oxidative work-up.<sup>5</sup> We examined here a similar [2+2]-type cyclization of 4,4'-dimethyl-3,3'-di-*iso*-butyl-2,2'-bipyrrole **1** and *gem*-dimethyldipyrromethane-5,5'-dicarbinol **2**, which generated isocorrole and the higher homologues after DDQ oxidation. The presence of alkyl substituents at the 2,2'-bipyrrole  $\beta$ -positions and at the dipyrromethane central position in our case significantly changed the distribution and yield of the cyclooligomers in comparison with

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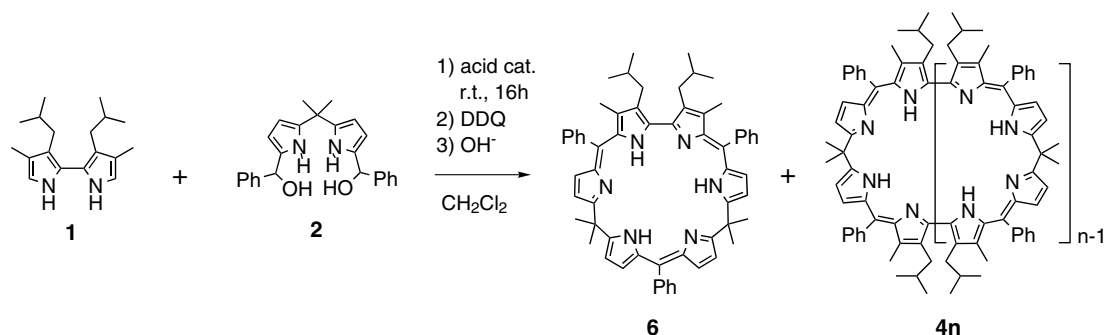
the previous works.<sup>5</sup> If scandium triflate ( $\text{Sc}(\text{OTf})_3$ ) or trifluoroacetic acid (TFA) was used as an acid catalyst in  $1 \text{ mmol dm}^{-3}$  concentration with reactant concentration of  $30 \text{ mmol dm}^{-3}$ , isocorrole **4**, cyclooctapyrrole **8**, and the higher homologues **12**, **16**, **20**, **24**, **28** were obtained in ca. 50% total yields as shown in Table 1 (runs 1 and 2). Here, we used a much smaller amount of catalyst and solvent in comparison with the literature reaction where a 25% yield of octaphyrin(1.1.1.0.1.1.1.0) was obtained using a  $10 \text{ mmol dm}^{-3}$  concentration of  $\text{Yb}(\text{OTf})_3$  with a  $2.5 \text{ mmol dm}^{-3}$  reactant concentration.<sup>5a</sup> The product distribution and yield in these reactions of **1** and **2** are similar to those observed in the reaction of **1** and bis(azafulvene) **3**, a doubly dehydrated product from **2**.<sup>6</sup> However, the present acidic reaction conditions gave rise to cyclohexapyrrole **6**<sup>7</sup> that was absent in the reaction of **1** and **3** under neutral conditions.

Increasing the amount of TFA from 0.033 M equiv ( $1 \text{ mmol dm}^{-3}$ ) to 0.22 M equiv ( $7 \text{ mmol dm}^{-3}$ ) caused the formation of **6** in 15% yield with the complete disappearance of the higher homologues (Table 1, run 3). Since **6** is made of one bipyrrrole and two *gem*-dimethyldipyrrylmethanes, 1:2 molar ratio of **1** and **2** in the reactant composition was expected to give a better yield of **6**. However, this was not the case and the yield of **6** was significantly decreased (Table 1, run 4). Therefore, it seems unlikely that the hexapyrrole- $\alpha,\omega$ -dicarbinol (**A**) may lead to **6** by the acid catalyzed release of benzaldehyde followed by the dehydration as shown in Scheme 1. The pyrrolylphenylmethyl cation intermediates (**B**) produced during the acid catalyzed decomposition of the big cyclooligopyrroles or long chain oligopyrroles may lead to **6**. This protonolysis reaction of the  $C_{\text{meso}}-C_{\text{pyrrole-}\alpha}$  bond is known to give rise to the scrambled macrocycles in the porphyrinoid synthesis,<sup>8</sup> and seems to promote the transformation to **6** in the present case under the strongly acidic reaction conditions.

The X-ray crystallography of **6**<sup>9</sup> shows that three dipyrrylmethene units are assembled by two  $\text{sp}^3$  hybridized *gem*-dimethyl carbon bridges and one direct linking at the pyrrole  $\alpha$ -positions, which leads to a beautiful  $C_2$ -symmetric molecular shape (see Fig. 1). The  $C_2$  rotational axis passes through C(15) and the midpoint of the bipyrrrole 2,2'-bond C(1)–C(1A). The torsion angles N(1)–C(4)–C(5)–C(6) and C(4)–C(5)–C(6)–N(2), which are diagnostic of the planarity of the N(1)–C(5)–N(2) dipyrrylmethene unit, are  $0.58^\circ$  and  $2.39^\circ$ . The corresponding torsion angles N(3)–C(14)–C(15)–C(14A) and C(14)–C(15)–C(14A)–N(3A) for the N(3)–C(15)–N(3A) dipyrrylmethene are  $2.95^\circ$  and  $2.95^\circ$ . Two dipyrrylmethene units are connected by a hinge-like bipyrrrole 2,2'-bond with the N(1)–C(1)–C(1A)–N(1A) torsion angle of  $54.51^\circ$ . The mean plane of each dipyrrylmethene was defined by 11  $\text{sp}^2$  atoms and the angles between these three dipyrrylmethene mean planes are  $98.29^\circ$ ,  $98.29^\circ$ , and  $58.93^\circ$ . These highly planar dipyrrylmethene units indicate that **6** is almost free from the ring strain of the macrocycle and the conformational freedom of the macrocycle is limited.

A pair of methyl doublets at 0.76 and 0.70 ppm due to the *iso*-butyl group and a pair of methyl singlets at 1.77 and 1.54 ppm due to the *gem*-dimethyl group were observed in the  $^1\text{H}$  NMR in tetrachloroethane- $d_2$  at  $20^\circ\text{C}$ . Since the latter signals were coalesced at  $90^\circ\text{C}$ , the interconversion between the enantiomeric forms of **6** is taking place on the NMR time scale. The energy barrier ( $\Delta G_{363}^\ddagger$ ) for the racemization estimated on the basis of the coalescence temperature and the chemical shift difference between the *gem*-dimethyl signals is  $76 \text{ kJ mol}^{-1}$ . This barrier is in the range where optical resolution is not easy. The major UV–vis band of **6** appears at an intermediate wavelength (453 nm) between **4** (420 nm) and **8** (541 nm) and it shifted to 457 nm on protonation. A broad visible region band of **6** centered at 611 nm was shifted to 714 nm at the same time by

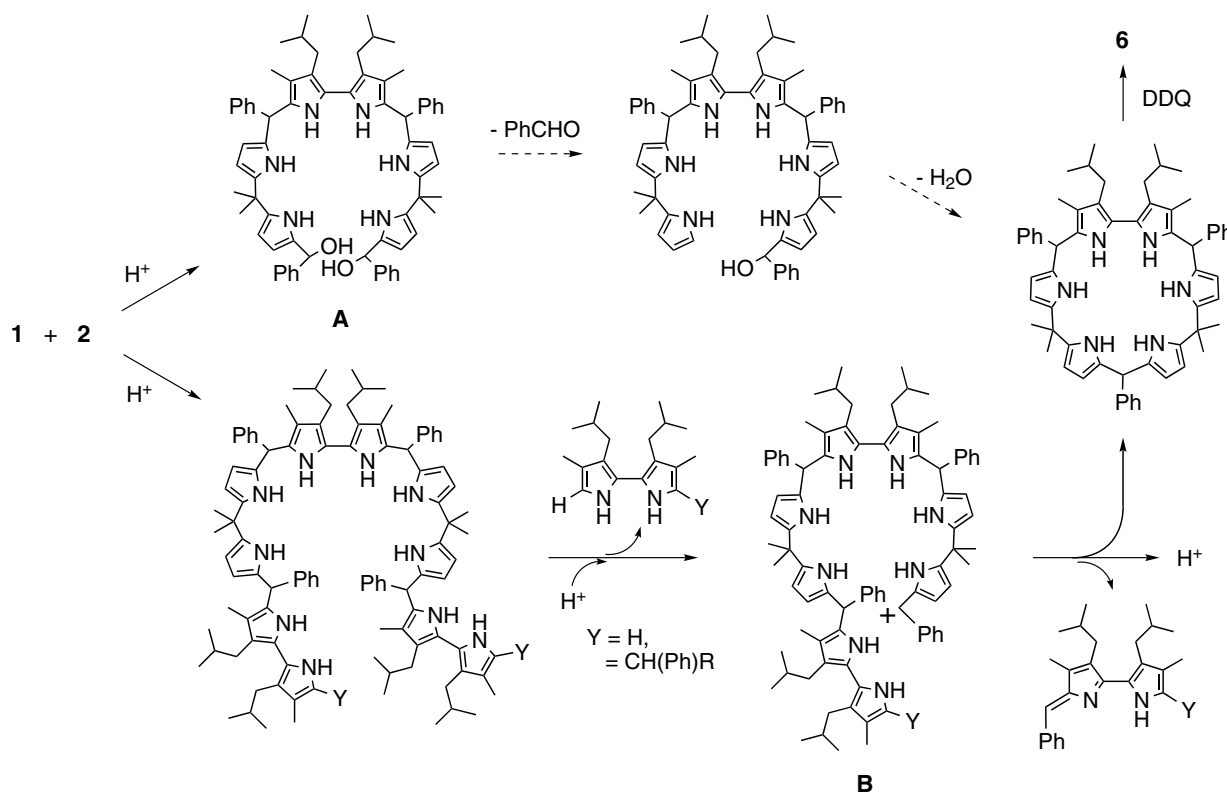
Table 1. Synthesis of cyclopolypyrroles **6** and **4n** ( $n = 1-7$ )



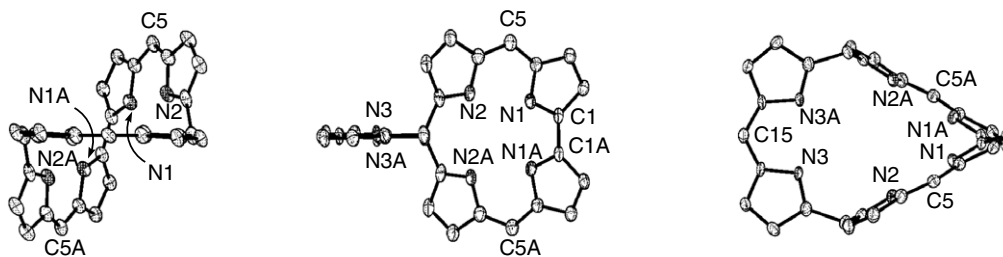
Run	Catalyst	Molar ratio <sup>a</sup>		Yield (%)			
		cat./1	2/1	6	4	8	12–28 <sup>b</sup>
1	$\text{Sc}(\text{OTf})_3$	0.034	1.0	2.1	7.6	25.1	21.1
2	TFA	0.033	1.0	tr	4.6	12.4	28.5
3	TFA	0.22	1.0	15.1	5.3	—	—
4	TFA	0.25	2.0	3.2	1.1	—	—

<sup>a</sup> The concentration of **1** is in the range of  $0.027-0.032 \text{ mol dm}^{-3}$ .

<sup>b</sup> The sum of higher homologues **12**, **16**, **20**, **24**, and **28**.



**Scheme 1.** Plausible mechanism for formation of **6**.

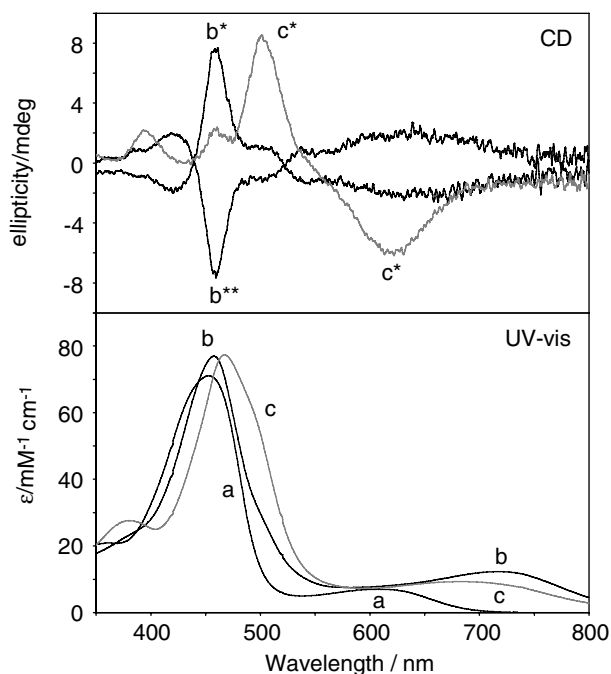


**Figure 1.** ORTEP drawings of **6** with a numbering scheme: a front view (left), a side view (center), and a top view (right). Peripheral substituents are omitted for clarity. N(1A), N(2A), N(3A), C(1A), and C(5A) are at equivalent positions ( $-x, y, 0.5 - z$ ) of N(1), N(2), N(3), C(1), and C(5), respectively.

protonation as seen in Figure 2 (lines a and b). While the CD spectrum of free base **6** in  $CH_2Cl_2$  solution ( $1.1 \times 10^{-5}$  mol  $dm^{-3}$ ) is silent, addition of (*S*)-(+)-mandelic acid (200 equiv) in methanol solution ( $1.65 \times 10^{-1}$  mol  $dm^{-3}$ ) induced a positive CD Cotton signal at 461 nm and a negative CD Cotton signal at around 650 nm (Fig. 2, line b\*). A mirror image CD spectrum was observed by using (*R*)-(-)-mandelic acid (Fig. 2, line b\*\*). These observations clearly indicate that the carbon center asymmetry of the carboxylic acid induced the axis asymmetry of **6** by the complex formation. The further UV-vis spectral change was observed by adding more amount of (*S*)-(+)-mandelic acid. A shoulder band at 500 nm increased and a broad visible region band shifted to 685 nm at the addition of 3300 equiv of (*S*)-(+)-mandelic acid (Fig. 2, line c), when the 461 nm CD band almost disappeared and new CD bands at 393 (positive), 501 (positive), and 620 (nega-

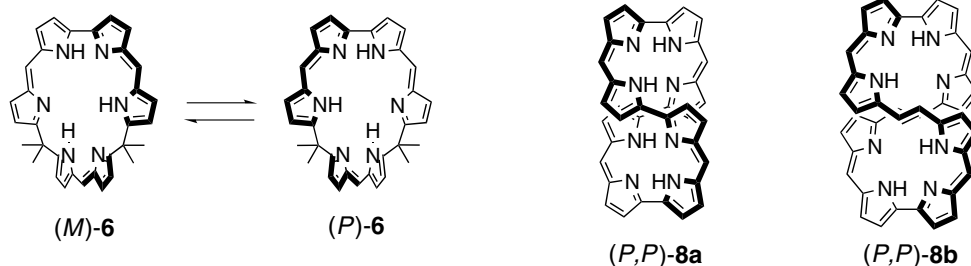
tive) nm (Fig. 2, line c\*) appeared. This indicates that the polyprotonation of **6** does not change the helicity of the  $\pi$ -conjugated tetrapyrrolic moiety.

The intensity of the CD Cotton effect is dependent on the diastereoselectivity in the complexation of **6** with the mandelic acid. We have recently reported that the induced CD bands appear at 630–650 nm for 2,3,6,7,11,12,15,16,20,21,24,25,29,30,33,34-hexadecaethyl-9,18,27,36-tetraphenyl[32]octaphyrin(1.0.1.0.1.0.1.0) **8a** upon the addition of various optically active carboxylic acids.<sup>4</sup> This phenomenon may be applied to the direct determination of the absolute configuration of optically active carboxylic acids. The induced CD bands seem to originate from the helical chirality in the  $\pi$ -conjugated tetrapyrrolic moiety in **8a**. In fact, Vogel and co-workers separated the [36]octaphyrin(2.1.0.1.2.1.0.1) free base **8b** having a similar  $\pi$ -conjugated tetrapyrrolic moiety into



**Figure 2.** UV-vis (bottom) spectra of **6** ( $1.1 \times 10^{-5}$  mol dm $^{-3}$ ) in CH $_2$ Cl $_2$  (3 ml) (a); adding MeOH (40  $\mu$ l) and (*S*)-(+)-mandelic acid (200 equiv) (b); adding MeOH (200  $\mu$ l) and (*S*)-(+)-mandelic acid (3300 equiv) (c). The CD (top) spectra of **6** in the presence of 200 equiv (b\*) and 3300 equiv (c\*) of (*S*)-(+)-mandelic acid; in the presence of 200 equiv of (*R*)-(-)-mandelic acid (b\*\*).

enantiomers and observed a negative CD Cotton effect at 630 nm for (*P,P*)-**8b**.<sup>10</sup> The same helical  $\pi$ -conjugated tetrapyrrolic moiety is present in **6**. The CD Cotton effects based on helical chirality in the  $\pi$ -conjugated tetrapyrrolic moiety have been known for biliverdins, bilindiones, and bilinones.<sup>11</sup> In addition, exciton coupling between the non-conjugated dipyrromethene units in **6** causes CD Cotton effects.<sup>12</sup> A similar exciton coupling between dipyrrolic units was used to empirically explain the sign of CD Cotton effects observed for bilirubins and double-helicate metal complexes of bis(dipyrromethenes).<sup>13</sup> The left-handed chirality (–) is expected for the relative orientations of the electric dipole transition moments of a couple of dipyrromethene chromophores connected by an sp $^3$  carbon bridge in the case of (*P*)-**6**. Although correlation between the stereochemistry of the mandelic acid complex of **6** and the sign of the CD Cotton effect has remained unknown at present, the molecular framework of **6** illustrates appropriate molecular design for inducing simple CD response to chiral guest molecules.



In summary, we have found that the condensation of 2,2'-bipyrrole and *gem*-dimethyldipyrromethane-5,5'-dicarbinol afforded a novel cyclohexapyrrole under strongly acidic conditions. X-ray crystallography of the cyclohexapyrrole showed a C $_2$ -symmetric molecular structure. Since the pyrrole NH protons are not in a convergent arrangement, compound **6** may not be appropriate for an anion binding host. However, this unusual C $_2$ -symmetric cyclohexapyrrole can be applied to a chirality sensing device as illustrated by the CD signal induction in the visible region by optically active carboxylic acid. The scope and limitation of this novel chirality probe is now extensively studied in our laboratory.

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### Supplementary data

Supplementary data associated with this article can be found, in the online version, at [doi:10.1016/j.tetlet.2007.01.004](https://doi.org/10.1016/j.tetlet.2007.01.004).

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7. Trifluoroacetic acid (5.2  $\mu\text{g}$ , 0.046 mmol) was added to a dry  $\text{CH}_2\text{Cl}_2$  (18 ml) solution of 4,4'-dimethyl-3,3'-di-*iso*-butyl-2,2'-bipyrrrole **1** (58.1 mg; 0.213 mmol) and *gem*-dimethyldipyrromethane-5,5'-dicarbinol **2** (81.7 mg; 0.211 mmol) and the mixture was stirred for 16 h at room temperature under argon. DDQ (134 mg, 0.589 mmol) was then added to the reaction mixture and stirring was continued for additional 2 h at room temperature. The resulting blue-green solution was passed through Celite that was washed with  $\text{CH}_2\text{Cl}_2$  and then with acetone. The organic solution was evaporated and the residue was dissolved in  $\text{CH}_2\text{Cl}_2$ . The combined organic solution was shaken with 2% aqueous  $\text{HClO}_4$  solution, water, and 0.5% aqueous NaOH solution, sequentially. The organic layer was separated, dried over  $\text{Na}_2\text{SO}_4$ , and evaporated to dryness. The residue was chromatographed on  $\text{Al}_2\text{O}_3$  (activity II–III). The first green band was eluted with  $\text{CH}_2\text{Cl}_2$  to give isocorrole **4** in 5.3% yield. The second green band was eluted with  $\text{CH}_2\text{Cl}_2$ -acetone 100:1 and recrystallization from  $\text{CH}_2\text{Cl}_2$ -methanol gave **6** in 15.1% yield. UV-vis ( $\lambda_{\text{max}}$  nm (log  $\epsilon$ ) in  $\text{CH}_2\text{Cl}_2$ ) 453 (4.85), 611 (3.84).  $^1\text{H}$  NMR ( $\delta$ -value in  $\text{CDCl}_3$ ) 14.0 (br, 2H, NH); 13.3 (br, 1H, NH); 7.52–7.30 (m, 15H, *meso*-Ph-H); 6.46, 6.40, 6.38, 6.01 (d  $\times$  4, 2H  $\times$  4,  $J = 4.3$  Hz,  $\beta$ -py-H); 2.34 (m, 4H,  $-\text{CH}_2\text{CHMe}$ ); 1.86 (s, 6H,  $\beta$ -py- $\text{CH}_3$ ); 1.61, 1.39 (s  $\times$  2, 6H  $\times$  2, *gem*- $\text{CH}_3$ ); 1.70 (m, 2H,  $-\text{CH}_2\text{CHMe}$ ); 0.83, 0.75 (d  $\times$  2, 6H  $\times$  2,  $J = 6.6$  Hz,  $-\text{CH}_2\text{CHMe}_2$ ). ESI-MS (found/calcd for  $\text{C}_{61}\text{H}_{62}\text{N}_6 + \text{H}^+$ ) 879.48/879.51. Anal. Calcd for  $\text{C}_{61}\text{H}_{62}\text{N}_6$ : C, 83.37; H, 7.11; N, 9.56. Found: C, 83.33; H, 7.05; N, 9.59.
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9. Recrystallization from  $\text{CH}_2\text{Cl}_2$ /hexane gave crystals of **6**. Crystal data:  $\text{C}_{61}\text{H}_{62}\text{N}_6$ ,  $M = 879.17$ , monoclinic, space group  $C2/c$ ,  $a = 12.146(2)$ ,  $b = 22.439(6)$ ,  $c = 20.212(4)$  Å,  $\beta = 97.953(4)^\circ$ ,  $V = 5456(2)$  Å $^3$ ,  $Z = 4$ ,  $D_{\text{calc}} = 1.070$  Mg/m $^3$ ,  $\mu(\text{MoK}\alpha) = 0.063$  mm $^{-1}$ ,  $T = 90(2)$  K, crystal size  $0.30 \times 0.20 \times 0.10$  mm. A total of 5506 unique reflections were collected ( $3.6^\circ < 2\theta < 54.4^\circ$ ) using graphite-monochromated MoK $\alpha$  radiation. The structure was solved by the direct method using a SHELX97 package. Four hundred and thirty-five parameters were refined with all non-hydrogen atoms anisotropically. All hydrogen atoms were found on a difference Fourier map and refined.  $R_1 = 0.0752$ ,  $wR_2 = 0.1662$  for 3046 reflections with  $I > 2.00\sigma(I)$ ;  $R_1 = 0.1468$ ,  $wR_2 = 0.2016$  for all data. GOF (on  $F^2$ ) = 1.020. CCDC reference number 632014.
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