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5,10,15-Tris(*o*-aminophenyl) Corrole (TAPC) as a Versatile Synthon for the Preparation of Corrole-Based Hemoprotein Analogs

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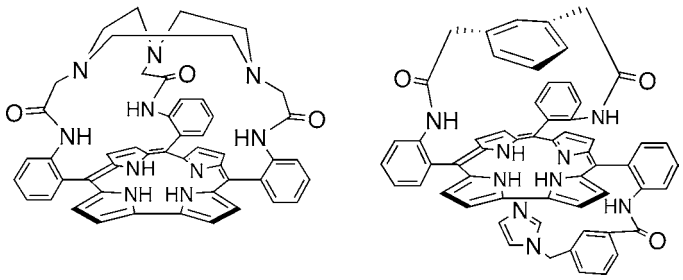
ABSTRACT



The atropisomers of 5,10,15-tris(*o*-aminophenyl) corrole (α*β*α, αα*β*, and ααα) are metastable at room temperature as a result of the low rotational barrier of the *o*-aminophenyl pickets adjacent to the bipyrrole moiety. Atropisomer enrichment of TAPC was required for the preparation of picket fence, triazacyclononane-capped, and trisimidazole-ααα-corroles. A racemic $\alpha_2\beta$ model of *cis*-A_2B geometry was also obtained by linking two *cis* anilines with a short strap and inserting an imidazole tail on the opposite face of TAPC.

Numerous synthetic methods have been recently developed for constructing the corrole macrocycle.[1a−g] As a result, the properties of their metal complexes have been studied in many fields.[2a−g] The main ligands that have been studied are tris(pentafluorophenyl) corrole (tpfc, Gross),[1] triazacorrole (corrolazine, Cz, Goldberg)[1d,2c,2d] and also alkyl- and aryl-substituted corroles (Kadish and Guilard).[2e−g] The unusual properties of these trianionic ligands prompted us to revisit some of the results obtained with porphyrin-based hemoprotein analogs[3] using their corrole counterparts. The study of mono- and bimetallic corrole-based hemoprotein analogs (Hb, CcO, P450) requires a corrole synthon that would have the functions suitable to allow covalent linkage of various distal and/or proximal superstructures. We have

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(2) (a) Gross, Z.; Gray, H. *Adv. Synth. Catal.* **2004**, *346*, 165. (b) Gross, Z.; Golubkov, G.; Simkhovich, L. *Angew. Chem., Int. Ed.* **2000**, *39*, 4045. (c) Ramdhanie, B.; Telser, J.; Caneschi, A.; Zakharov, L. N.; Rheingold, A. L.; Goldberg, D. P. *J. Am. Chem. Soc.* **2004**, *126*, 2515. (d) Mandimutsira, B. S.; Ramdhanie, B.; Todd, R. C.; Wang, H. L.; Zareba, A. A.; Czemuszewicz, R. S.; Goldberg, D. P. *J. Am. Chem. Soc.* **2002**, *124*, 15170. (e) Kadish, K. M.; Ou, Z. P.; Shao, J. G.; Gros, C. P.; Barbe, J. M.; Jérôme, F.; Bolze, F.; Burdet, F.; Guilard, R. *Inorg. Chem.* **2002**, *41*, 3990. (f) Kadish, K. M.; Shao, J. G.; Ou, Z. P.; Gros, C. P.; Bolze, F.; Barbe, J. M.; Guilard, R. *Inorg. Chem.* **2003**, *42*, 4062. (g) Barbe, J. M.; Canard, G.; Brandes, F.; Jérôme, F.; Dubois, G.; Guilard, R. *Dalton Trans.* **2004**, *8*, 1208.

(3) (a) Collman, J. P.; Gagne, R. R.; Halbert, T. R.; Marchon, J.-C.; Reed, C. A. *J. Am. Chem. Soc.* **1973**, *95*, 7868. (b) Collman, J. P.; Bröring, M.; Fu, L.; Rapta, M.; Schwenniger, R.; Straumanis, A. *J. Org. Chem.* **1998**, *63*, 8082. (c) Collman, J. P.; Bröring, M.; Fu, L.; Rapta, M.; Schwenniger, R. *J. Org. Chem.* **1998**, *63*, 8084. (d) Collman, J. P.; Decréau, R. A.; Costanzo, S. *Org. Lett.* **2004**, *6*, 1033. (e) Collman, J. P.; Sunderland, C.; Boulatov, R. *Inorg. Chem.* **2002**, *41*, 2282. (f) Collman, J. P.; Boulatov, R.; Sunderland, C. J. In *The Porphyrin Handbook*; Academic Press: Boston, 2003; Vol. 11, Chapter 63, pp 1−49. (g) Collman, J. P.; Gagne, R. R.; Reed, C. A.; Halbert, T. R.; Lang, G.; Robinson, W. T. *J. Am. Chem. Soc.* **1975**, *97*, 1427.

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chosen 5,10,15-tris(*o*-aminophenyl) corrole (TAPC, **1**), the corrole counterpart of 5,10,15,20-tetrakis(*o*-aminophenyl) porphyrin TAPP that has been widely used for the constructions of various superstructured porphyrins over the past 30 years.[3] Herein we disclose the synthesis of TAPC (**1**) and

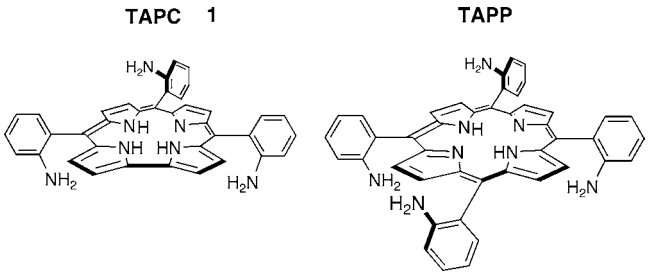


Figure 1. 5,10,15-Tris(*o*-aminophenyl) corrole (TAPC, **1**, αβα atropisomer shown) and 5,10,15,20-tetrakis(*o*-aminophenyl) porphyrin (TAPP, αβαβ atropisomer shown).

its use as a versatile synthon for the construction of the following free base hemoprotein corrole analogs: picket fence (**2**), triazacyclononane (TACN)-capped (**3**), trisimidazole picket (**4**), and *cis*-strapped tailed (**5**) corroles. Corroles **2**, **3**, and **5** are to be used as myoglobin models, whereas **3** and **4** would be used as CcO analogs. The effect of the axial ligand on the properties of several metallocorroles will be studied with **5**, which bears an imidazole tail covalently attached to the "proximal" face. Moreover **5** is chiral, and the chirality is triggered by linking two *cis* anilines in **1**. This is in contrast with the *trans*-strapped corrole reported by Rose, where the chirality relies on introducing a chiral molecule onto the corrole precursor,[4e] but it is reminiscent of Gross's approach forming chiral *N*-alkylated corroles from two achiral precursors.[4i] Compound **5** is the first reported imidazole-tailed corrole. The synthesis of **1** starts from tris-*o*-nitrophenylcorrole, synthon **6,** which was previously reported by Paolesse.[1b] A modification of his method gives **6** in up to 10% yield. [5a] It consisted of scaling up the reaction by up to 22 times, changing the reaction time,[5b] slightly

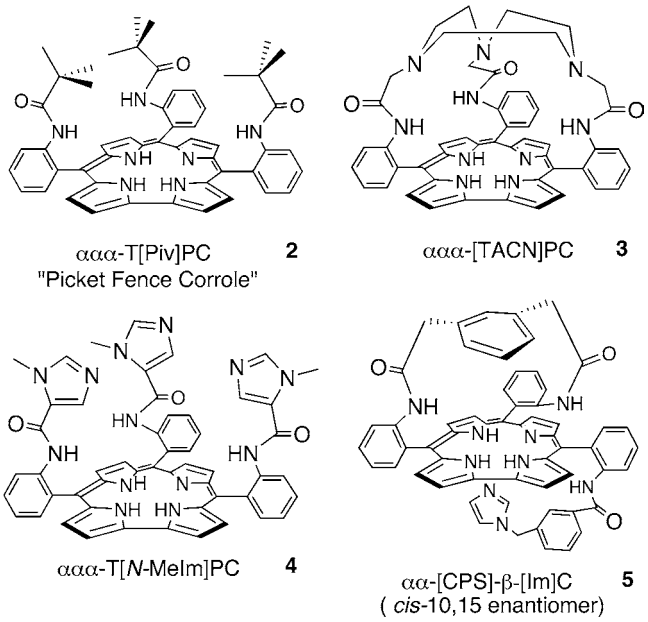
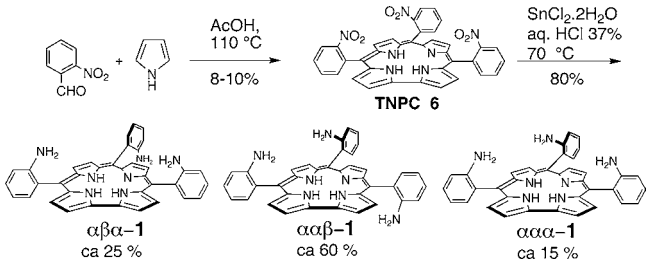


Figure 2. Corrole targets: picket fence (**2**), TACN-capped (**3**), trisimidazole (**4**), and *cis*-strapped-tailed (**5**) corroles.

raising the concentration of the reagents, and purifying by chromatography.[5c] The reduction of **6** to tris(*o*-aminophenyl) corrole (TAPC) **1** is achieved in 80% yield by treatment with 9 equiv $SnCl_2 \cdot 2H_2O$ in HCl at 70 °C in an opened vessel, followed by neutralization and extraction with ethyl acetate. An estimate of the ratios αβα:ααβ:ααα of the TAPC atropisomers was ca. 0.25:0.60:0.15.[6a,b] These ratios change with

Scheme 1. Synthesis of TAPC **1**



the polarity and the temperature of solvents.[6c] Unlike porphyrin TAPP, chromatography separation was not entirely satisfactory for the isolation of pure TAPC atropisomers, because they equilibrate in solution (for example, the original αβα:ααβ:ααα ratio is restored in solution (at low concentration) within 15 min at ca. 40 °C or within 1 h at room temperature, several hours at 0 °C, and several days at −20

(4) (a) Collman, J. P.; Lee, V. J.; Zhang, X.; Ibers, J. A. *J. Am. Chem. Soc.* **1993**, *115*, 3834. (b) Collman, J. P.; Lee, V. J.; Kellen-Yuen, C. J.; Zhang, X.; Ibers, J. A.; Brauman, J. I. *J. Am. Chem. Soc.* **1995**, *117*, 692. (c) Collman, J. P.; Wang, Z.; Straumanis, A.; Quelquejeu, M.; Rose, E. *J. Am. Chem. Soc.* **1999**, *121*, 460. (d) Collman, J. P.; Zhang, X. M.; Lee, V. J.; Uffelman, E. S.; Brauman, J. I. *Science* **1993**, *261*, 1404. (e) Andrioletti, B.; Rose, E. *J. Chem. Soc., Perkin Trans. 1* **2002**, 715. (f) Kubo, H.; Aida, T.; Inoue, S.; Okamoto, Y. *Chem. Commun.* **1988**, 1015. (g) *Inorg. Chem.* **1998**, *37*, 2009. (h) Muzzi, C. M.; Medforth, C. J.; Smith, K. M.; Jia, S.-L.; Shelnutt, J. A. *Chem. Commun.* **2000**, 131. (i) Gross, Z.; Galili, N. *Angew. Chem., Int. Ed.* **1999**, *38*, 2366.

(5) (a) The initial workup described by Paolesse using filtration and crystallization is used to separate TNPP from TNPC, but somehow a significant amount of TNPC is lost in the process. We prefer to isolate as much corrole as possible and separate the porphyrin at the later stage of atropisomer enrichment after TNPC reduction, allowing easy separation of α_3-TAPC from α_4-TAPP. (b) We previously demonstrated that corroles decompose after a long time spent at high temperature: Collman, J. P.; Decréau, R. A. *Tetrahedron Lett.* **2003**, *44*, 1207. (c) We revisited the original TNPP synthesis: TNPP was originally worked up by filtration and washing, and the filtrates were discarded.[3a,g] Here we decided to keep these filtrates and to work them up as in ref 5a. We found that, together with TNPP obtained in 13% yield, TNPC was also found in up to 1.5−3% yield, reminiscent to the story of another corrole obtained as side product in the porphyrin synthesis.[5d] (d) Rose, E.; Kossanyi, A.; Quelquejeu, M.; Soleil-havoup, M.; Duwavran, F.; Bernard, N.; Lecas, A. *J. Am. Chem. Soc.* **1996**, *118*, 1567.

°C).[6c] Because of the isomerization, NMR characterization of the individual atropisomers of **1** (or of the other *o*-aminophenyl corrole **9**) could not be achieved.

Calculation with CAChe (PM3 procedure) gives insights concerning the rotational barrier of differently substituted pickets in corroles **1**, **2**, and **7** (Table 1). In TAPC **1**, the barrier to rotation of the *meso*-picket 5 and 15 (*cis* to the bipyrrole unit) is 11−14 kcal/mol, whereas it is 23.8 kcal/mol for the *meso*-picket 10 (*trans* to the bipyrrole), as it is for the aminophenyl pickets in the porphyrin analog TAPP (22.3 kcal/mol). Spontaneous rotation at room temperature is thus attributed to pickets 5 and 15, whereas the *meso*-phenyl 10 is more porphyrin-like and would rotate more slowly. Interestingly, it was found in the theoretical analysis that the barrier to rotation of the *meso*-aminophenyl picket 5 is higher when the picket rotates toward the pyrrole opposite to the bipyrrole moiety (14.8 kcal/mol), and slightly lower when it rotates toward the bipyrrole moiety (11.1 kcal/mol). This might be explained by less steric hindrance on the bipyrrole side. The calculation of the heat of formation of the atropisomers of **1** shows that the most stable atropisomer is αα*β* (248.1 kcal/mol), followed by α*β*α and ααα (247.3 kcal/mol), which agrees with their TLC profile. The same calculation carried out with pivalamido- and bromoacetamido-corroles **2** and **7** showed values similar to those of TAPP and other porphyrins.[7a−c]

Table 1. Calculated Free Energy of Rotation (Δ*G*, kcal/mol) of *ortho*-Substituted *meso*-Phenyl Rings in Various Corroles and Comparison with Porphyrin TAPP

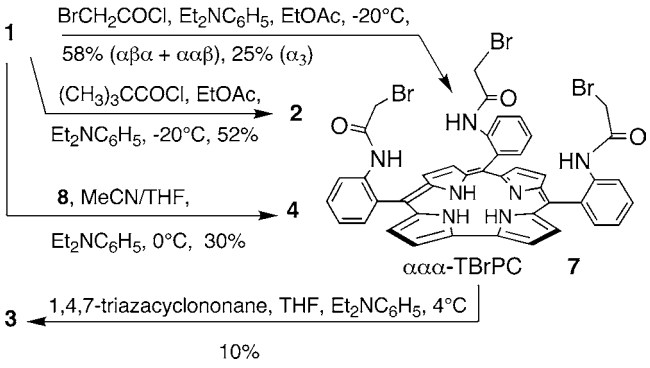
meso-phenyl	TAPC (**1**)	TBrPC (**7**)	TpivPC (**2**)	TAPP
5, 15- (a)	11.1	19.9	36.3	22.3
5, 15- (b)	14.8	39.6	39.1	
10-	23.8	39.0		22.3

[a] Using CAChe (PM3 method, 1 label). For 5- and 15-*meso*-phenyls, rotation takes place toward (a) or opposite to (b) the bipyrrole moiety.

Because of the α_3 geometry in models **2**−**4**, preliminary enrichment of TAPC in the α_3 atropisomer was required. This was carried out by adsorbing a statistical mixture of TAPC atropisomers (α*β*α, αα*β*, ααα) on silica and heating in toluene/hexane under N_2.

This procedure is similar to the method previously developed with porphyrins.[3b,8] This resulted in nearly quantitative conversion into α_3, with little decomposition after 10 min. In the event of a sample contaminated with the porphyrin (TAPP), a longer heating time on silica was required in order to convert all of the porphyrin into α_4-TAPP, which is easy to separate from the corrole because of the porphyrin's greater polarity.[6b] To overcome the low rotational barrier of aminopickets, α_3-TAPC **1** was handled at −20 °C. Isolated α_3-TAPC **1** was reacted immediately at −20 °C with an excess of acyl chlorides in the presence of base to give α_3-T[Piv]PC (or PFC or **2**) and α_3-TBrPC **7** in 52% and 25% yield, respectively. Similarly α_3-T[*N*-MeIm]-PC **4** was obtained in 30% yield from the reaction of **1** and reported *N*-methyl imidazole acyl chloride **8**.[3e] Compounds **2**, **3**, and **7** were sufficiently stable at room temperature to allow chromatographic separation without rotation, as predicted by the calculation.[6c] If a large excess of base and acyl chloride was used, reversible *N*-acylation of the inner nitrogen occurred during the synthesis of **7**, which was recovered by washing with Na_2CO_3, as *N*-acylated corroles are labile.[9a] Moreover, the separation and isolation of each atropisomer (α*β*α, αα*β*, and ααα) was possible with **7**, **4**, and **2**.

Scheme 2. Synthesis of ααα-Corroles: Picket Fence (**2**), TACN-Capped (**3**), and Trisimidazole (**4**) Corroles



Prior derivatization of the amines in **1** giving **7** was required for preparing TACN-capped corrole **3**. Bromoacetamides are efficient linkers for appending superstructures under mild conditions,[3d,10] which is a prerequisite for the fast-rotating pickets in the corroles. Low-temperature conditions (4 °C) were used for the preparation of **3** because even the bromoacetamide pickets rotate at room temperature (20% rotation after 16 h). The reaction of α_3-TBrPC **7** with 1,4,7-triazacyclononane at 4 °C gave the TACN-capped corrole **3** in 10% yield.

Linking two *cis*-anilines with diacyl chloride straps has been reported in porphyrin chemistry.[3g,4] Calculation using

(6) (a) The concept of atropisomers in a corrole was previously introduced by us with the tris(*o*-trifluoromethylphenyl) corrole.[5b] (b) The α*β*α-, αα*β*-, and ααα-TAPC atropisomers are more polar than the corresponding α*β*α*β*-, αα*ββ*-, and ααα*β*-TAPP atropisomers. However αααα-TAPP is more polar than ααα-TAPC. α*β*α-TAPC and αα*β*-TAPC have much closer R_f values (0.57 and 0.53, respectively) than α*β*α*β*-TAPP and αα*ββ*-TAPP (0.75 and 0.62, respectively). A TLC profile is given in Supporting Information. (c) Moreover the rotation appears to be dependent on the concentration of TAPC but does not seem to be induced by light irradiation.

(7) (a) Schrijvers, R.; Vanduk, M.; Sanders, G. M.; Sudholter, E. J. R. *Rec. Trav. Chim. Pays-Bas* **1994**, *113*, 351. (b) Eaton, S. S.; Eaton, G. R. *J. Am. Chem. Soc.* **1977**, *99*, 6594. (c) Dirks, J. W.; Underwood, G.; Matheson, J. C.; Gust, D. *J. Org. Chem.* **1979**, *44*, 2551.

(8) Lindsey, J. *J. Org. Chem.* **1980**, *45*, 5215.

(9) (a) Broadhurst, M. J.; Grigg, R.; Shelton, G.; Johnson, A. W. *J. Chem. Soc., Perkin Trans. 1* **1972**, 143. (b) Saltsman, I.; Goldberg, I.; Gross, Z. *Tetrahedron Lett.* **2003**, *44*, 5669.

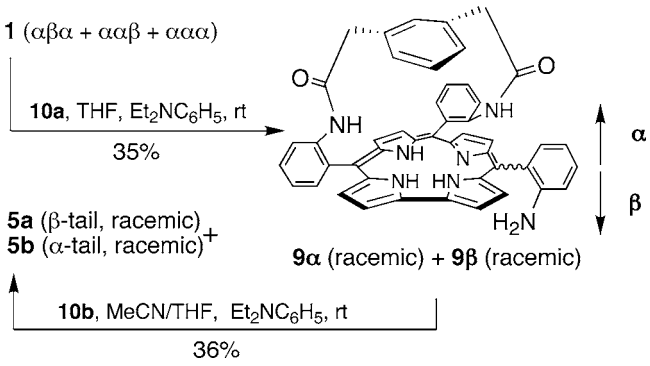
(10) (a) Other previously reported linkers, such as chloroacetamido,[3b] and Michael acceptors[3b] were not considered here because high temperatures are required for reaction, which would rotate the picket on the opposite face, preventing reaction and leading to oligomer formation, nor was isocyanato[10b] useful since phosgene was shown to react with inner NH.[9b] (b) Collman, J. P.; Wang, Z.; Straumanis, A. *J. Org. Chem.* **1998**, *63*, 2424.

CACHe showed that the average distance between two *cis*-anilines in **1** is 7.33 Å, and thus we picked *m*-phenylene diacyl chloride **10a**.[11a−c] Contrary to the preparation of models **2**−**4** where low temperatures are mandatory to preserve the α_3-geometry in **1**, the synthesis of $\alpha_2\beta$-corroles **5** and **9** could be carried out at room temperature using a TAPC statistical mixture of atropisomers, because the most abundant atropisomer is $\alpha_2\beta$. Under appropriate dilution (3.5 mM) and injection rate of the strap (20 mL/h), a 35% yield of the *cis*-strapped corrole **9** was obtained. The mixture of α and β atropisomers in **9** was easily separated from the side products and unreacted starting material by chromatography over neutral alumina. However, the individual atropisomers could not be separated because of the same reason found in **1** (spontaneous rotation of *meso*-pickets 5 and 15). Compound **9** was reacted with the acyl chloride imidazole **10b**[3c] to give the tailed corrole **5** in 80% yield. Because of the chirality of **5**, the methylene protons of the tail are diastereotopic. Contrary to **1** and **9**, the separation of α and β atropisomers in **5** is straightforward using chromatography because rotation is no longer possible. However the separation of the enantiomers **5a** and **5b** by HPLC using a ChiralCel OD column (previously reported for the enantiomer separation of chiral corrole and porphyrins)[4a−d,i,9b] is still being investigated.[12] PM3 calculation shows that the distal phenyl strap and the corrole are nearly coplanar. This might explain why the strap ^{1}H NMR signals are shifted upfield (ca. 7 ppm for the aromatic proton *meta* to the CH_2), which is one of the first reports of the strong ring current induced by a corrole.[13a,b] It is also worth mentioning that the substitution pattern obtained by linking two *cis*-anilines led to the first report of corroles having a *cis*-A_2B geometry (**5** and **9**), in contrast to the *trans*-A_2B geometry reported and developed by Gryko.[1c] Overall, TAPC and its derivatives display less chemical stability and are more photosensitive than porphyrins or other corroles such as **6** or tpfc, and their stability during chromatography becomes an important issue.

The TAPC synthon opens a window to the chemistry of super-structured corroles for various applications in biomimetic chemistry. Despite the low rotational barrier of the *o*-aminophenyl pickets 5 and 15, an easy access to a large fraction of $\alpha\alpha\beta$ and $\alpha\alpha\alpha$ atropisomers of **1** is possible. This was accomplished using a statistical mixture containing ca. 60−70% of the $\alpha\alpha\beta$ atropisomer or from the enrichment of the $\alpha\alpha\alpha$ atropisomer followed by storage at low temperature. However, the $\alpha\beta\alpha$ corrole atropisomer could only be obtained after derivatization of TAPC.[14a]

These successful syntheses are being followed by introducing the appropriate method and examining these derivatives as functional hemoprotein models.

Scheme 3. Synthesis of Chiral $\alpha\alpha\beta$ Corrole **5**



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Supporting Information Available: Detailed experimental procedures; ^{1}H NMR, ^{13}C NMR, MS, UV−vis spectra and HPLC chromatograms of new compounds **1**−**7** and **9**. This material is available free of charge via the Internet at http://pubs.acs.org.

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(11) (a) The longer distance between the two acyl chlorides is 6.50 Å (CACHe, PM3). (b) For comparison, the shortest distance between *trans*-anilines is 9.61 Å. (c) Shorter linkers such as *m*-isophthaloyl chloride led to a corrole that decomposed under the conditions employed for column chromatography. Similarly, the *trans* isomer of **9** obtained in very low yield is very unstable and decomposes rapidly on silica. It means that the distortion of the corrole that results from either *cis*- or *trans*-strapping with short linkers leads to very unstable corroles.

(12) Two fractions (elution times 12.1 and 13.1 min) have been isolated and characterized by MS and UV−vis and are currently being characterized by ^{1}H NMR and CD spectroscopies.

(13) Other examples of corrole-induced ring currents on various axially ligated bases to Co and Rh corroles: (a) Collman, J. P.; Wang, H. J. H.; Decréau, R. A.; Eberspacher, T. A.; Sunderland, C. J. *Chem. Commun.* **2005**, in press; (b) Mahammed, A.; Giladi, I.; Goldberg, I.; Gross, Z. *Chem. Eur. J.* **2001**, *7*, 4259. (c) Saltsman, I.; Simkhovich, L.; Balazs, Y.; Goldberg, I.; Gross, Z. *Inorg. Chim. Acta* **2004**, *357*, 3038.

(14) (a) An attempt to obtain enriched $\alpha\beta\alpha$- and $\alpha\alpha\beta$-TAPC atropisomers by adapting a method developed by Rose et al.[12b,c] did not work with **1**. (b) Rose, E.; Cardonpilotaz, A.; Quelquejeu, M.; Bernard, N.; Kossanyi, A.; Desmazieres, B. *J. Org. Chem.* **1995**, *60*, 3919. (c) Rose, E.; Quelquejeu, M.; Pochet, C.; Julien, N.; Kossanyi, A.; Hamon, L. *J. Org. Chem.* **1993**, *58*, 5030.