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Highly Selective Chlorosulfonation of Tris(pentafluorophenyl)corrole as a Synthetic Tool for the Preparation of Amphiphilic Corroles and Metal Complexes of Planar Chirality

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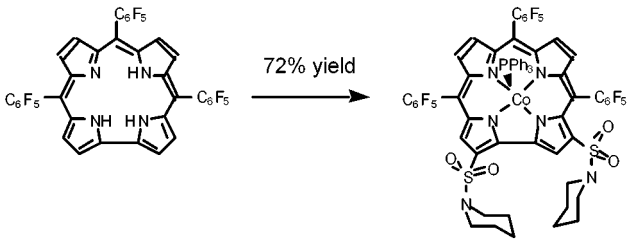
ABSTRACT



The chlorosulfonation of tris(pentafluorophenyl)corrole proceeds with an extremely high selectivity as to afford one out of 139 possible isomers in very high yield. The bis-chlorosulfonated corrole is an excellent precursor to the planar-chirality (triphenylphosphine)cobalt(III) complex (fully characterized by X-ray crystallography) and to the amphiphilic bis-sulfonic acid derivative, both the first of their kind.

Porphyrins, phthalocyanines, and related macrocycles are extensively investigated in many applications, among them photodynamic therapy and catalysis.[1] The most promising candidates for selective association to tumor cells are amphiphilic derivatives,[2] and chiral metal complexes are of prime importance for the utilization in asymmetric catalysis.[3] Both structural types present a significant synthetic challenge because of the high symmetry of the most common precursors, tetraarylporphyrins and phthalocyanine.[4] On the other hand, the less symmetric corroles could be very useful candidates for the above-mentioned purposes. However, this potential was not explored until most recently because of the nonavailability of simple synthetic methodologies for the preparation of corroles.[5] This situation is now experiencing a highly significant change due to the discoveries of practical syntheses of *meso*-aryl-substituted corroles.[6] The most important one so far appears to be tris(pentafluorophenyl)-

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(1) (a) Sternberg, E. D.; Dolphin, D.; Bruckner, C. *Tetrahedron* **1998**, *54*, 4151. (b) Sessler, J. L.; Weghorn, S. J. *Expanded, Contracted, & Isomeric Porphyrins*; Pergamon: Oxford, 1997. (c) *Metalloporphyrins Catalyzed Oxidations*; Montanari, F., Casella, L., Eds.; Kluwer Academic Publishers: Dordrecht, 1994.

(2) Bonnett, R. *Chem. Soc. Rev.* **1995**, *24*, 19.

(3) Collman, J. P.; Zhang, X.; Lee, V. J.; Uffelman, E.; Brauman, J. I. *Science* **1993**, *261*, 1404.

(4) Lindsey, J. S. In *The Porphyrin Handbook, Vol. I*; Kadish, K. M., Smith, K. M., Guilard, R., Eds.; Academic Press: New York, 2000; Chapter 2, pp 45−118.

(5) Paolesse, R. In *The Porphyrin Handbook, Vol. II*; Kadish, K. M., Smith, K. M., Guilard, R., Eds.; Academic Press: New York, 2000; Chapter 11, pp 201−232.

(6) (a) Gross, Z.; Galili, N.; Saltsman, I. *Angew. Chem., Int. Ed.* **1999**, *38*, 1427. (b) Paolesse, R.; Jaquinod, L.; Nurco, D. J.; Mini, S.; Sagone, F.; Boschi, T.; Smith, K. M. *Chem. Commun.* **1999**, 1307. (c) Cho, W.-S.; Lee, C.-H. *Tetrahedron Lett.* **2000**, *41*, 697. (d) Gryko, D. T. *Chem. Commun.* **2000**, 2243. (e) Briñas, R. P.; Brückner, C. *Synlett* **2001**, 442.

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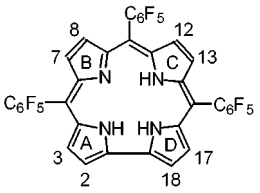
Scheme 1. Numbering System of **1**



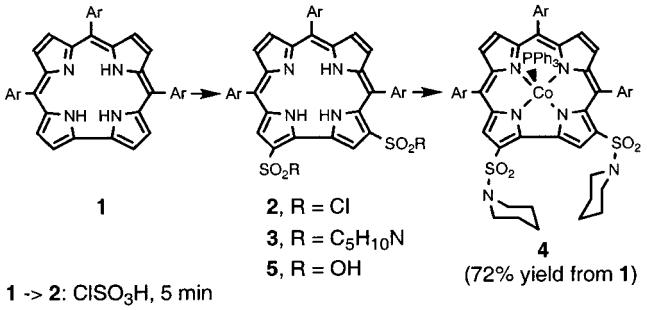
corrole (**1** in Scheme 1):[6a] its metal complexes are excellent catalysts for various organic reactions,[7] a water-soluble derivative of **1** has a large affinity to cancer cells,[8] chiral derivatives of **1** are easily prepared,[9] and **1** and many of its metal complexes have been characterized by X-ray crystallography.[7c,10] Another advantage of **1** is that its NMR spectra are very easily analyzed, not at least because the C_6F_5 substituents can be sensed by ^{19}F NMR and do not interfere with the ^1H NMR spectra.

The presence of β-pyrrole CH's in *meso*-arylcorroles opens up the opportunity for relatively straightforward skeleton modification, which in porphyrins has been used for reactivity-tuning of the metal complexes in catalysis (the so-called third-generation metalloporphyrins).[11] Since a large body of information for both β-pyrrole and *meso*-aryl-substituted corroles indicates that they are much more electron-rich than porphyrins,[7c,12] it suggests that electrophilic activation of corroles should be quite straightforward. This was proven true for β-pyrrole-substituted corroles,[5] as well as in two most recent reports about the bromination of all β-pyrrole CH's in *meso*-aryl-substituted corroles.[13,14] In both latter cases, attempts to isolate significant amounts of partially brominated corroles have failed so far. This is not very surprising, since the number of possible partially brominated isomers is exceedingly large. In fact, the relatively low symmetry (C_{2v} at most) of corroles raises the number of possible products to 140 (1 nonbrominated, 4 mono-, 16 bis-, 28 tris-, 42 tetra-, 28 penta-, 16 hexa-, 4 hepta-, and 1 octa-brominated). Accordingly, we have sought for a different electrophilic reagent that upon the first substitution will induce a more significant electronic effect for deactivation of the corrole skeleton for further reaction.

Relying on the extensive literature about porphyrins and on the strong deactivation by nitro substituents,[15] we have first attempted the nitration of **1** and several metal complexes thereof. Although the reactions were more selective than bromination, the overall yields were quite low because of the oxidative reaction conditions (these results will soon been reported). The next reagent that was examined was chlorosulfonic acid, which in porphyrins is used for aromatic electrophilic substitution of the *meso*-aryl groups without attacking the macrocycle[16] and in phthalocyanines for nonselective chlorosulfonation of the benzopyrrole moieties.[17] The working hypothesis was that the C_6F_5 groups in **1** will be inert, while the electron-rich corrole might be reactive enough.

This approach appeared to be highly fruitful indeed (Scheme 2). Thus, **1** was quantitatively transformed into

Scheme 2. Selective Chlorosulfonation of **1** and Its Further Transformations



products by dissolving it in a minimal amount of chlorosulfonic acid followed by evaporation of the reagent after 5 min. Furthermore, NMR analysis of the crude reaction mixture (not shown) revealed quantitative transformation of **1** into only one major product (**2**). Without any purification, the crude reaction mixture was treated with piperidine to afford **3** (immediate and quantitative reaction). Metalation of **3** by cobalt acetate, followed by addition of triphenylphosphine, afforded the (triphenylphosphine)cobalt(III) complex of **2** (**4** in Scheme 2). Postponing any purification procedures to the last synthetic step allowed the isolation of pure **4** in 72% yield, based on **1**.[18,19]

Elucidation of the structure of **4** was quite straightforward. Its MS revealed two sulfonamido groups, which could be

(7) (a) Gross, Z.; Simkhovich, L.; Galili, N. *Chem. Commun.* **1999**, 599. (b) Gross, Z.; Golubkov, G.; Simkhovich, L. *Angew. Chem., Int. Ed.* **2000**, *39*, 4045. (c) Simkhovich, L.; Mahammed, A.; Goldberg, I.; Gross, Z. *Chem. Eur. J.* **2001**, *7*, 1041.

(8) Aviezer, D.; Cotton, S.; David, M.; Segev, A.; Khaselev, N.; Galili, N.; Gross, Z.; Yayon, A. *Cancer Res.* **2000**, *60*, 2973.

(9) Gross, Z.; Galili, N. *Angew. Chem., Int. Ed.* **1999**, *38*, 2366.

(10) (a) Gross, Z.; Galili, N.; Simkhovich, L.; Saltsman, I.; Botoshansky, M.; Blaser, D.; Boese, R.; Goldberg, I. *Org. Lett.* **1999**, *1*, 599. (b) Bendix, J.; Gray, H. B.; Golubkov, G.; Gross, Z. *Chem. Commun.* **2000**, 1957. (c) Simkhovich, L.; Galili, N.; Saltsman, I.; Goldberg, I.; Gross, Z. *Inorg. Chem.* **2000**, *39*, 2704. (d) Meier-Callahan, A. E.; Gray, H. B.; Gross, Z. *Inorg. Chem.* **2000**, *39*, 3605. (e) Mahammed, A.; Goldberg, I.; Gross, Z. *Chem. Eur. J.* **2001**, *7*, 4259.

(11) (a) Mansuy, D. *Coord. Chem. Rev.* **1993**, *125*, 129. (b) Gross, Z.; Simkhovich, L. *Tetrahedron Lett.* **1998**, *39*, 8171.

(12) (a) Erben, C.; Will, S.; Kadish, K. M. In *The Porphyrin Handbook, Vol. II*; Kadish, K. M., Smith, K. M., Guilard, R., Eds.; Academic Press: New York, 2000; Chapter 12, pp 233−300.(b) Bendix, J.; Dmochowski, I. J.; Gray, H. B.; Mahammed, A.; Simkhovich, L.; Gross, Z. *Angew. Chem., Int. Ed.* **2000**, *39*, 4048.

(13) Paolesse, R.; Nardis, S.; Sagone, F.; Khoury, R. G. *J. Org. Chem.* **2001**, *66*, 550.

(14) Golubkov, G.; Bendix, J.; Gray, H. B.; Mahammed, A.; Goldberg, I.; DiBilio, A. J.; Gross, Z. *Angew. Chem., Int. Ed.* **2001**, *34*, 2132.

(15) Palacio, M.; Mansuy-Mouries, V.; Loire, G.; Barch-Ozett, K.; Leduce, P.; Barkigia, K. M.; Fajer, J.; Battion, P.; Mansuy, D. *Chem. Commun.* **2000**, 1907.

(16) Rocha Gonsalves, A. M. A.; Johnson, R. A. W.; Pereira, M. M.; SantAna, A. M. P.; Serra, A. C.; Sobral, A. J. F. N. *Heterocycles* **1996**, *43*, 829.

(17) Gregory, P. *J. Porphyrins Phthalocyanines* **2000**, *4*, 432.

assigned as being attached to carbons 2 and 17 (see Scheme 1) via the analysis of its ^{1}H and ^{19}F NMR spectra (Figure 1). First, symmetrical substitution, i.e., one that will retain

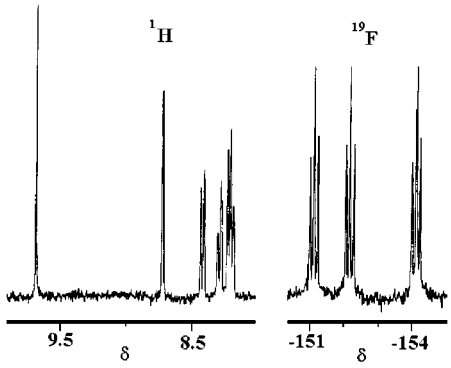


Figure 1. ^{1}H NMR (β-pyrrole CH) and ^{19}F NMR (*p*-F only) spectra of **4**.

the C_2 axis present in **1**, is easily ruled out by the clear observation of three different C_6F_5 rings. The same conclusion may be reached from the ^{1}H NMR spectrum of **4**, which displays two singlets and four doublets rather than one singlet and two doublets. Second, we have noted that the ^{1}H NMR spectra of nonsubstituted **1** and all its diamagnetic metal complexes consist of two sets of β-pyrrole CH doublets with different *J*-coupling constants. On the basis of a comparison to porphyrins and 2,2′-bipyrroles, the CH's that display larger coupling constants (J = 4.5−5.0 Hz) are confidently assigned to pyrroles B and C and those with J = 3.9−4.3 Hz to pyrroles A and D (Scheme 1).[10e,20] The fact that the coupling constants of all four doublets in the ^{1}H NMR spectrum of **4** display large *J*-coupling constants indicates that the chlorosulfonation of **1** took place selectively at the directly joined pyrrole rings of **1** (A and D in Scheme 1). Concluding, **4** was confidently identified as the (triphenylphosphine)cobalt(III) complex of the nonsymmetrically substituted 2,17-bis-sulfonatopiperidine-5,10,15-tris(pentafluorophenyl)corrole.

It is important to note that the corrole plane in **2** and **3** is their sole symmetry element and that it is lost upon metalation (unless the metal is coordinated by two identical axial ligands), i.e., **4** is a complex with metal-centered chirality (planar chirality).[21] This phenomenon, as well as further substantiation of the spectroscopic analysis, is clearly manifested via X-ray crystallography of **4** (Figure 2).[22] The

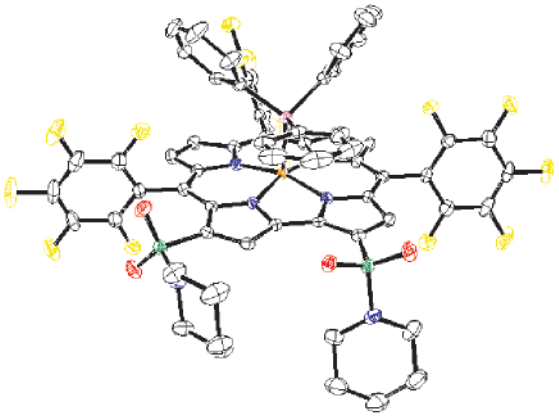


Figure 2. Hydrogen-atoms-omitted ORTEP view of **4**.

crystals are racemic, containing equal amounts of the enantiomeric species. They also contain 2.5 equiv of benzene as a crystallization solvent that fills the intermolecular sites

(18) **Synthesis of 2:** 80 mg of **1** (100 μmol) and 2 mL of chlorosulfonic acid (30 mmol) were stirred at 25 °C for 5 min, after which the reaction mixture was cooled by an ice bath and treated with small ice chips (5−10 mg, caution!). The product was obtained via the addition of 20 mL of distilled water and CH_2Cl_2 (the CH_2Cl_2 solution was washed three times with distilled water) and evaporation. **2** was obtained in quantitative yield, in about 97% purity (see ref 19): ^{1}H NMR (200 MHz, $CDCl_3$) δ = 9.44 (s, 1H), 8.95 (s, 1H), 8.60 (d, J = 5.0 Hz, 1H), 8.50 (d, J = 5.0 Hz, 1H), 8.41 (d, J = 5.0 Hz, 1H), 8.18 (d, J = 5.0 Hz, 1H); ^{19}F NMR (188 MHz, $CDCl_3$) δ = −137.5 (d, J = 21.1 Hz, 4F), −138.3 (d, J = 18.1 Hz, 2F), −149.6 (t, J = 21.31, 1F), −150.1 (t, J = 21.21, 2F), −160.0 (m, 4F), −161.6 (m, 2F); MS (DCI$^-$) *m*/*z* (%) 991.8 (5) [M$^-$], 892 (20) [M$^-$ − SO_2Cl]. **Synthesis of 3:** a solution of **2** and piperidine (8 equiv) in CH_2Cl_2 (20 mL) was stirred for 30 min. The solution was washed twice with a solution of HCl (2 M) and then with distilled water. The solvent was evaporated and **3** was obtained in quantitative yield: ^{1}H NMR (200 MHz, $CDCl_3$) δ = 9.50 (s, 1H), 8.83 (s, 1H), 8.64 (d, J = 4.9 Hz, 1H), 8.58 (d, J = 4.9 Hz, 1H), 8.47 (d, J = 4.9 Hz, 1H), 8.32 (d, J = 4.9 Hz, 1H), 3.27 (m, 8H), 1.5−2.0 (m, 12H); ^{19}F NMR (188 MHz, $CDCl_3$) δ = −137.5 (d, J = 21.1 Hz, 4F), −138.3 (d, J = 18.1 Hz, 2F), −149.6 (t, J = 21.3 Hz, 1F), −150.1 (t, J = 21.0 Hz, 2F), −160.0 (m, 4F), −161.6 (m, 2F); MS (DCI$^-$) *m*/*z* (%) 1090.1 (100) [M]$^-$. **Synthesis of 4:** a solution of **3** and $Co(OAc)_2 \cdot 4H_2O$ (4 equiv) in pyridine (10 mL) was refluxed for 1 h. The solvent was evaporated, and the residue was dissolved in 10 mL of CH_2Cl_2. At this stage, PPh_3 (4 equiv) was added and the residue was passed through a column of silica with CH_2Cl_2 as eluent. After recrystallization from benzene/heptane, **4** was obtained in 72% yield based on **1** (102 mg, 72 μmol). X-ray quality crystals of **4** were obtained by slow recrystallization from a mixture of benzene/heptane: ^{1}H NMR (200 MHz, benzene-d_6) δ = 9.64 (s, 1H), 8.68 (s, 1H), 8.37 (d, J = 5.0 Hz, 1H), 8.24 (d, J = 5.0 Hz, 1H), 8.14 (t, J = 4.7 Hz, 2H), 6.64 (dt, J^1 = 2.4 Hz, J^2 = 7.5 Hz, 3H), 6.46 (dt, J^1 = 2.8 Hz, J^2 = 7.4 Hz, 6H), 4.71 (dd, J^1 = 7.5 Hz, J^2 = 11.7 Hz, 6H), 3.51 (t, J = 5.0 Hz, 4H), 3.1 (m, 4H), 1.46 (m, 4H), 1.27 (m, 2H), 1.01 (m, 4H), 0.63 (m, 2H); ^{19}F NMR (188 MHz, benzene-d_6) δ = −137.0 (dd, J^1 = 24.5 Hz, J^2 = 6.8 Hz, 1F), −137.4 (dd, J^1 = 17.9 Hz, J^2 = 6.8 Hz, 1F), −137.9 (m, 2F), −138.6 (dd, J^1 = 28.8 Hz, J^2 = 6.8 Hz, 1F), −139.5 (dd, J^1 = 24.5 Hz, J^2 = 6.8 Hz, 1F), −151.0 (t, J = 21.5, 1F), −152.2 (t, J = 21.5, 1F), −154.1 (t, J = 21.5, 1F), −161.0 (m, 4F), −164.2 (m, 2F); UV/vis (CH_2Cl_2) λ_{max} (ϵ(M^{-1} cm^{-1})) = 314 (20 000), 382 (43 000), 410 (44 000), 564 (16 000), 606 (15 000); MS (DCI$^-$) *m*/*z* (%) 1145.8 (4) [M − PPh_3]$^-$, 999 (100) [M − PPh_3, −$SO_2NC_5H_{10}$]$^-$.

(19) Careful chromatographic treatment of the recrystallization solution of **4** allowed the isolation of another minor product (3% yield), which was identified as a bis-substituted isomer with C_{2v} symmetry (either 2,18- or 3,17-bis-sulfonatopiperidine-5,10,15-tris(pentafluorophenyl)corrole): ^{1}H NMR (200 MHz, benzene-d_6) δ = 9.05 (s, 2H), 8.34 (d, J = 4.9 Hz, 2H), 8.20 (d, J = 4.9 Hz, 2H), 6.61 (dt, J^1 = 2.3 Hz, J^2 = 7.5 Hz, 3H), 6.40 (dt, J^1 = 2.7 Hz, J^2 = 7.9 Hz, 6H), 4.71 (dd, J^1 = 7.5 Hz, J^2 = 11.7 Hz, 6H), 3.17 (m, 8H), 1.28 (m, 8H), 1.08 (m, 4H); ^{19}F NMR (188 MHz, benzene-d_6) δ = −136.7 (d, J = 24.7 Hz, 2F), −137.2 (d, J = 25.0 Hz, 2F), −137.7 (d, J = 21.8 Hz, 1F), −139.7 (d, J = 23.4 Hz, 1F), −152.2 (t, J = 21.7, 1F), −154.3 (t, J = 21.3, 2F), −161.3 (m, 4F), −164.2 (m, 2F).

(20) Farnier, M.; Soth, S.; Fournari, P. *Can. J. Chem.* **1976**, *54*, 1083.

(21) Blackburg, B. K.; Davies, S. G.; Whittacker, M. In *Stereochemistry of Organometallic and Inorganic Compounds*, Vol. 3; Bernal, I., Ed.; Elsevier: Amsterdam, 1989; p 141.

(22) Complex **4** ($C_{65}H_{41}CoF_{15}N_6O_4PS_2 \cdot 2^1/_2C_6H_6$; M_r = 1604.33) crystallized in the monoclinic space group *C*2/*c* with a = 36.2430(3), b = 15.9160(2), and c = 28.5150(4) Å, β = 119.906(1)°, V = 14258.4(3) Å^3, Z = 8, T = 110 K, ρ_{calc} = 1.495 g.cm^{-3}, μ(Mo Kα) = 0.42 mm^{-1}, 13464 unique reflections, R_1 = 0.055 for 9744 observations with $F_o > 4\sigma(F_o)$, R_1 = 0.085 (R_w = 0.160) for all the unique data.

within the crystal lattice. The crystallographic analysis revealed that the 23-membered corrole macrocycle is roughly planar, the deviations of the individual atoms from its mean plane not exceeding 0.10 Å. The Co ion in the ring center is five-coordinate and imparts a domed structure. It deviates 0.32 Å from the mean corrole plane toward the axial triphenylphosphine ligand. The corresponding bond lengths of Co−N and Co−P are 1.867−1.874(3) Å and 2.225(1) Å, respectively. To facilitate this effective bonding, the four pyrrole nitrogens are pulled out slightly (by about 0.07 Å) from the 19-membered all-carbon framework, toward the metal ion. As commonly observed, the pentafluorophenyl substituents are oriented nearly perpendicular to the corrole ring. Noteworthy in this context are the conformational aspects of the 1-piperidinesulfonate groups. While the two piperidine rings are characterized by similar chair structures, they differ in their relative orientation with respect to the core macrocycle. The S−N bond of the residue attached to C2 is perpendicular to the corrole plane, which places its piperidine ring in a sterically unhindered area on the opposite side of the corrole to that occupied by the triphenylphosphine ligand. On the other hand, in view of the closer proximity to one of the pentafluorophenyl substituents, the S−N bond of the residue attached to C17 lies in the plane of the corrole, and its heterocyclic ring is directed away from the neighboring aromatic moiety (and toward the free space outside the C1−C19 bond) to avoid collision.

A different utilization of **2** was hydrolysis of the chlorosulfonate moieties, easily achieved by its treatment with boiling water.[23] The resulting bis-sulfonic acid derivative **5** (obtained in 71% yield, based on **1**) is the first of its kind in corrole chemistry. Its novelty relative to other related macrocycles is by virtue of the control of the number of $-SO_3H$ moieties and their precise locations and the easily achieved amphiphilicity. This is in contrast to the sulfonation (or chlorosulfonation plus hydrolysis) of teraarylporphyrins and phthalocyanines, which results in nonamphiphilic tetrasulfonic acid derivatives.[16,17] Furthermore, the substitutions on peripheral benzo groups in phthalocyanines are usually not regioselective. In fact, the disulfonated aluminum phthalocyanine has actually been shown to be a mixture of at least eight isomers.[24] Other advantageous features of **5** are its high water solubility and that the characteristic intense fluorescence of **1** is retained.

Concluding, we have demonstrated that the highly selective functionalization of β-pyrrole-unsubstituted corroles can be used for the easy preparation of amphiphilic derivatives and to complexes with metal-centered chirality. These novel compounds are currently examined in several applications.

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(23) **Synthesis of 5:** a suspension of **2** in 20 mL of water was refluxed for 12 h. The solution was filtered and evaporated to dryness to provide **5** in 71% yield based on **1** (68 mg, 71 μmol): ^{1}H NMR (200 MHz, CD_3OD) δ = 9.68 (br s, 1H), 9.14 (d, J = 4.8 Hz, 1H), 8.98 (d, J = 4.8 Hz, 1H), 8.90 (br s, 1H), 8.86 (d, J = 4.8 Hz, 1H), 8.84 (d, J = 4.8 Hz, 1H); ^{19}F NMR (188 MHz, CD_3OD) δ = −137.5 (d, J = 20.3 Hz, 2F), −137.8 (d, J = 19.6 Hz, 4F), −149.8 (t, J = 20.3, 1F), −150.8 (t, J = 20.1, 1F), −152.1 (t, J = 19.4, 1F), −160.3 (m, 2F), −160.8 (m, 2F), −163.1 (m, 2F); UV/vis (buffer solution, pH 7.00) λ_{max} (ϵ(M^{-1} cm^{-1})) = 414 (71 000), 430 (62 000), 588 (15 000), 620 (27 000).

(24) Bishop, S. M.; Khoo, B. J.; MacRobert, A. J.; Simpson, M. S. C.; Phllips, D.; Beeby, A. *J. Chromatogr.* **1993**, *646*, 345.