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Synthesis of Some 2,2′:6′,2′′-Terpyridines Disubstituted in Positions 6 and 6′′ with Head-to-Tail Oriented Amino Acids and Dipeptides: A Simple Entry to a Reversible Inducer of Folding in Amino Acid Sequences

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The 2,2′:6′,2′′-terpyridine scaffold has been identified as a conformationally discrete structural element potentially capable of inducing reversible folding in substituents, attached through suitable spacers to its 6,6′′-positions, by metal complexation/decomplexation or by protonation/deprotonation. The synthesis of some terpyridine–amino acids and terpyridine–dipeptide conjugates is described. The assembly of these conjugates has been achieved by connecting NH_2- and CO_2H-protected glycine, alanine, and valine residues or antiparallel oriented AlaGly/GlyAla chains to the terpyridine scaffold through phenylacetylene spacers. Preliminary experiments showed that upon addition of Zn^{2+} to the amino acid substituted *transoid* terpyridine systems, folded *cisoid* complexes were formed. Also, bis(protonation) of the dipeptide-substituted system resulted in the formation of a folded adduct. Reversibility of the folding process was shown by Zn^{2+} removal with triethylamine or deprotonation with aqueous ammonia.

Introduction

Conformational control represents an important tool for the rational design of functional molecules. In this line, the development of artificial elements capable of inducing a folding motif in conformationally mobile derivatives is the subject of a continuous research effort.[1] This is especially true in the case of peptides, whose functional properties largely depend on their three-dimensional structures. Accordingly, there is a great deal of interest in the synthesis of molecules capable of inducing folding in a peptide chain.[2]

The vast majority of the reported examples of peptide folders (generally turn mimics) are based on fully rigid or conformationally locked scaffolds, both natural (mostly obtained from amino acids and their derivatives) and unnatural (derived from ad-hoc synthesized molecules).[3] Much less popular, but equally relevant, are *reversible* folding inducers, that is, scaffolds existing in discrete conformations capable of forcing attached peptide chains to fold upon application of a chemical signal and to unfold upon signal removal.[4]

We reasoned that a valuable addition to the existing arsenal of reversible folding inducers could be represented by a properly modified terpyridine scaffold, because this would be capable of promoting the reversible conformational change as the result of both metal complexation/decomplexation and protonation/deprotonation. The latter possibility seemed particularly attractive, because the examples of foldamers whose conformation depends on the acidity of the medium are rare and have never been described in combination with amino acids or peptides.[5] Here, we wish to report the synthesis of some 2,2′:6′,2′′-terpyridines unsymmetrically functionalized at positions 6,6′′ with NH_2- and CO_2H-protected amino acids or antiparallel oriented dipeptide sequences. Experiments describing reversible isomerization of these scaffolds by metal complexation/decomplexation or protonation/deprotonation are also reported.

Results and Discussion

6,6′′-Disubstituted 2,2′:6′,2′′-terpyridines attracted our attention as a scaffold that can adopt discrete conformations for several reasons. It is well known[6] that 2,2′:6′,2′′-terpyridine (tpy) exists in the unfolded *transoid* conformation **1a** (Scheme 1) to minimize repulsion between the pyridine nitrogen lone pairs. Isomerization to the folded *cisoid* disposition **1b** can be achieved by metal complexation or by bis(protonation). While metal complexation has been extensively studied in a variety of contexts,[6] isomerization by protonation has been less frequently investigated. It has been shown that, in the presence of strong acids (HCl, HBr, HI, CF_3SO_3H, $HClO_4$, CF_3CO_2H) tpy undergoes two suc-

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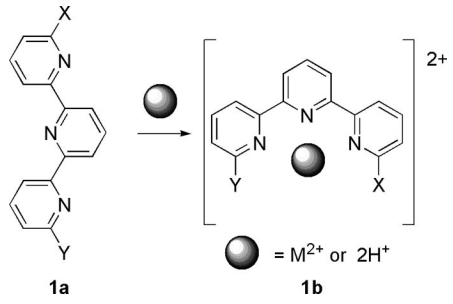
cessive protonations occurring at the nitrogen atoms of the outer rings.[7] Upon the first protonation, tpyH$^+$ adopts a *cisoid* conformation around the biaryl bond connecting the protonated and the central pyridine ring, while the remaining biaryl bond keeps its *transoid* arrangement.[7b] The second protonation completes the *transoid*-to-*cisoid* isomerization to afford conformation **1b**, as demonstrated by a number of crystallographic and spectroscopic studies.[7c,7d] Further addition of acid does not result in protonation of the free nitrogen atom,[7d] and thus, even in the presence of excess acid, only tpyH$_2^{2+}$ is formed. Remarkably, it has been demonstrated that bis(protonation) and metal complexation lead to adducts of very similar electronic structure, as determined by their UV spectra.[7d]

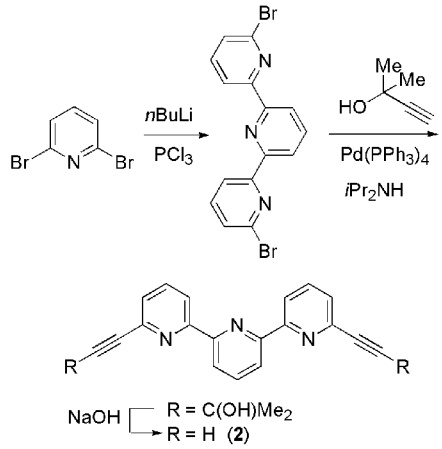


Scheme 1. *transoid* (**1a**) and *cisoid* (**1b**) conformations of a unsymmetrically 6,6′′-disubstituted 2,2′:6′,2′′-terpyridine.

Selection of the tpy skeleton was also suggested by the fact that the introduction of different substituents at the 6,6′′-positions, indicated by X and Y in Scheme 1, should be possible.[6] In the context of developing a peptide folder, one can think of functionalizing one of these positions with a residue capable of connecting to the nitrogen atom of an amino acid, and the other position with a group that can react with an amino acid carboxy group. Very importantly, this would allow the attachment of antiparallel-directed peptide chains onto the tpy skeleton.

It was also decided to separate the site of attachment of the carboxy and amino functionalities from the core of the tpy skeleton with a suitable spacer in order to avoid that the amino acid chains could fold back over the core of the tpy. The spacer selection followed two main criteria. First, we reasoned that the ideal spacer should feature a linear and rigid topology to avoid the introduction of other elements of conformational mobility on the system and to ensure that the structural information present on the tpy could effectively be transmitted to the attached residues. Secondly, the spacer should be readily assembled through a short and simple synthesis allowing the sequential insertion of the different functionalities. With these goals in mind, a 4-substituted phenylacetylene moiety was selected as the spacer. For synthetic convenience, it was decided to introduce first the ethynyl groups on the tpy nucleus and then use Sonogashira chemistry for the sequential introduction of the differently substituted phenyl rings on the triple bond.

To accomplish this design, 6,6′′-diethynyl-2,2′:6′,2′′-terpyridine (**2**) was prepared in three steps starting from commercially available 2,6-dibromopyridine (Scheme 2). Reaction of the latter with *n*BuLi and PCl_3 at low temperature afforded 6,6′′-dibromo-2,2′:6′,2′′-terpyridine (60% yield).[8] Pd-catalyzed coupling with 2-methyl-3-butyn-2-ol (97% yield),[9] followed by reaction with NaOH in refluxing toluene (77% yield),[10] led to **2** in 45% overall yield.



Scheme 2. Synthesis of 6,6′′-diethynyl-2,2′:6′,2′′-terpyridine (**2**).

Commercially available 4-iodobenzoic acid and 4-iodoaniline were then connected to suitably protected glycine, alanine, and valine residues through amide bond with their amino or carboxy functions, respectively, to afford iodobenzenes **3a**–**c** and **4a**–**c** in good yields (Figure 1; see the Supporting Information for details of their synthesis).

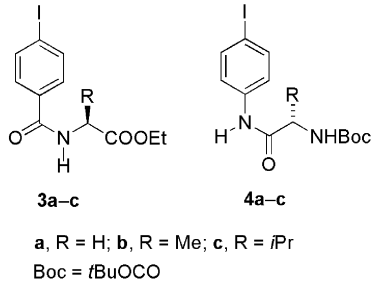
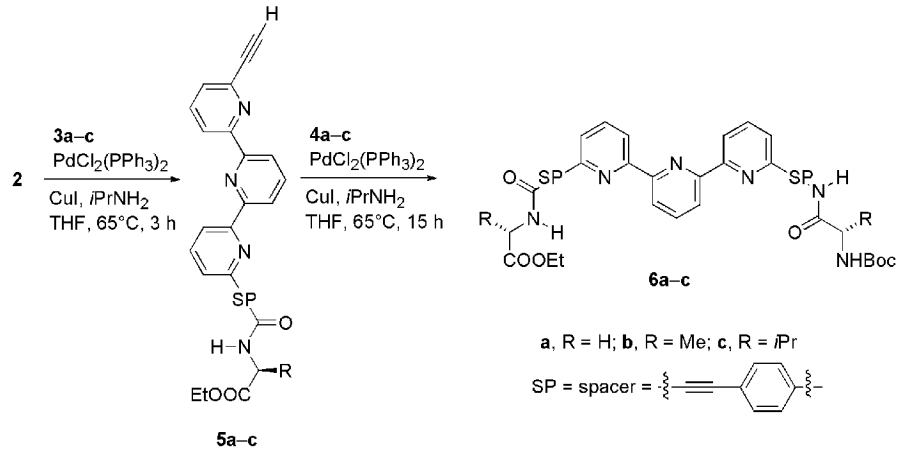


Figure 1. Structures of amino acid derived iodobenzenes **3a**–**c** and **4a**–**c**.

With these compounds in hand, the crucial unsymmetric functionalization of tpy–bis(acetylene) **2** by Sonogashira reaction was investigated. After extensive experimentation, it was found that monofunctionalization of tpy could satisfactorily be accomplished by controlling the reaction stoichiometry. Thus, reaction[11] of 1.5 mol equiv. of tpy **2** with 1.0 mol equiv. of glycine derivative **3a** carried out in the presence of [$PdCl_2(PPh_3)_2$] (0.03 mol equiv.) and CuI (0.1 mol equiv.) in a refluxing THF/diisopropylamine (1.5:1) mixture (0.1 M solution, 3 h) afforded the monoaddition product **5a** in 65% isolated yield. About 50% of the unreacted **2** could be recovered during the chromatographic purification of **5a** and recycled (Scheme 3). Very limited



Scheme 3. Synthesis of terpyridines **5a**–**c** and **6a**–**c**.

amounts (<5%) of bis(substituted) adduct were obtained. Reaction of product **5a** (1.0 molequiv.) with iodobenzene **4a** (1.5 molequiv.) under the same conditions reported above but for a longer time (15 h) allowed to isolate adduct **6a** in 51% yield (33% overall). By a similar reaction sequence 6,6′′-disubstituted tpy **6b** and **6c** were obtained via **5b** and **5c** in 30 and 36% overall yield, respectively, from **2**, thus showing that also sterically hindered amino acids could be connected to the tpy scaffold by this procedure. It must be noted that the introduction of the *N*-Boc protected amino acid residue was performed as the second step to expose the products containing the Boc group to only one chromatographic purification, to which they proved to be unstable.

The synthesis of a tpy derivative featuring two antiparallel oriented dipeptides was then addressed. In designing a derivative suitable for folding by both complexation and protonation, the protecting group at the N-terminal amino acid was changed from the acid-labile Boc to the more stable acetyl group. Accordingly, dipeptides **7** and **8** (Figure 2, see the Supporting Information for details of their synthesis) were prepared and connected to 6,6′′-diethynyl-2,2′:6′,2′′-terpyridine (**2**) by using the reaction sequence described in Scheme 4.

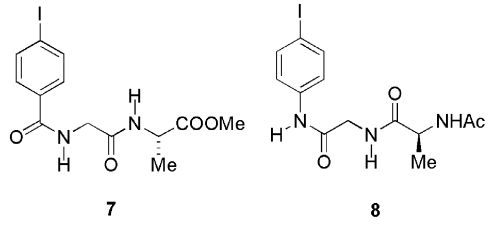
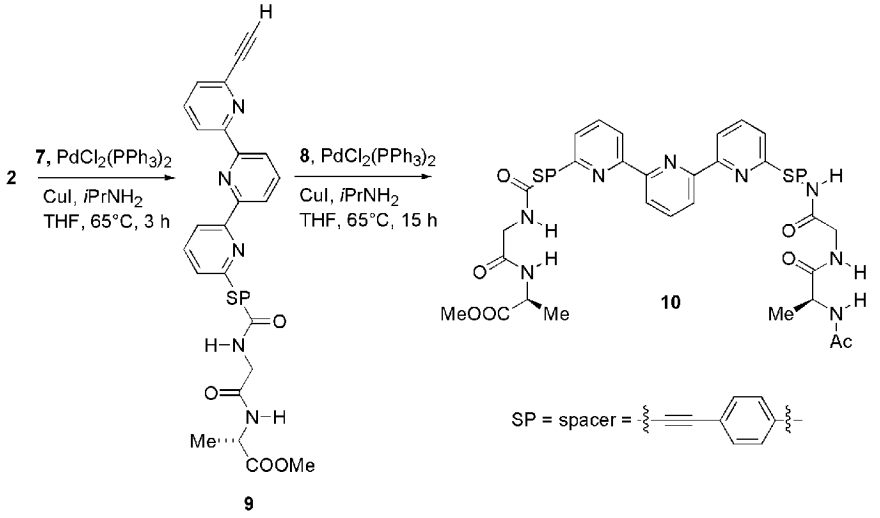


Figure 2. Structures of dipeptide-derived iodobenzenes **7** and **8**.

By reaction of **2** (1.6 molequiv.) with iodobenzene **7** (1.0 molequiv.) adduct **9** was obtained in 65% isolated yield. Reaction of **9** (1.0 molequiv.) with iodobenzene **8** (1.5 molequiv.) afforded the disubstituted tpy **10** in 43% isolated yield. The 28% overall yield showed that our synthesis did not suffer from the increasing size of the chains attached to the iodobenzene ring employed in the Sonoga-



Scheme 4. Synthesis of terpyridines **9** and **10**.

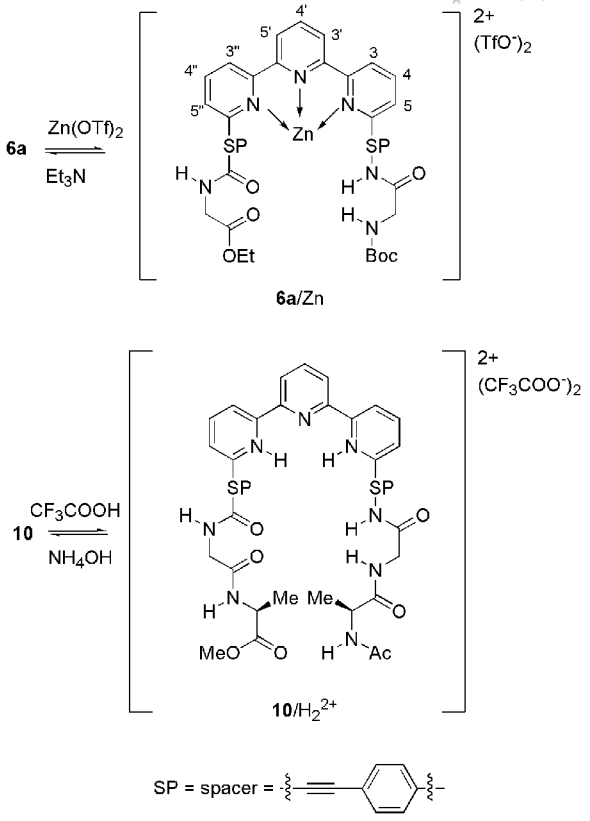
shira coupling, and seemed flexible enough to prepare derivatives featuring peptide residues of different structures and lengths.

With adducts **6** and **10** in hand, the compatibility of the amino acid substituents with the conditions required for *transoid*-to-*cisoid* isomerization of the terpyridine scaffold was then studied. As mentioned above, such isomerization can be induced by metal complexation and protonation. On the basis of literature examples,[6,7d,12] complexation with Zn^{II} salts was attempted. These salts are known to react with terpyridines to form 1:1 adducts.[6,7d,12] By addition of 1.1 mol-equiv. of $Zn(OTf)_2$[13] to a solution of terpyridine **6a** in $CDCl_3$ at room temperature, a yellow complex was obtained. The expected[12] marked shift of some of the ^1H and ^{13}C NMR signals of the tpy nucleus were observed upon complexation. These included: downfield shifts by up to 0.39 ppm for 4-H, 4′-H, and 4′′-H signals; downfield shifts by up to 4.2 ppm for C-4, C-4′, and C-4′′ signals; and upfield shifts by up to 0.37 ppm for 3-H, 3′-H, 5′-H and 3′′-H signals (see Scheme 5 for numbering). In addition, the 3-H/3′-H distance of 2.60 Å, obtained from NOESY experiments by using the 4-H/5-H distance of 2.46 Å as internal reference, strongly suggested that in the **6a**/Zn complex the tpy nucleus had indeed adopted the expected *cisoid* conformation. It is also interesting to note that the chemical shift variations in the signals of the protected amino acid moieties were generally rather small, being ≤ 0.2 ppm for the H and ≤ 2 ppm for the C signals. This can be taken as an indication that the amino acid residues did not offer competitive sites of chelation for the Zn^{2+} cation.

Isomerization of tpy **6a** by protonation was also attempted. However, when trifluoroacetic acid was added, extensive removal of the Boc protecting group was observed. Attempts to minimize Boc removal by the use of a weaker proton source such as acetic acid, resulted only in partial protonation, leading to a mixture of protonated and unprotonated species.

Complexation of **10** with $Zn(OTf)_2$ in a variety of solvents (CD_2Cl_2, $CDCl_3$, [D_8]THF) led to poorly soluble yellow complexes, thus preventing NMR analysis of the adduct. However, when protonation of **10** was carried out by addition of trifluoroacetic acid (0.1 mmol) to a suspension of this compound (0.025 mmol) in CD_3CN (0.75 mL) a clear, bright yellow solution was obtained. A single species could be detected by ^1H and ^{13}C NMR spectroscopy. This showed variations in the chemical shift of the tpy signals, fully consistent with the formation of the *cisoid* tpy **10**/H_2^{2+} (see Scheme 5 for numbering). For instance, downfield shifts ranging from 0.25 to 0.51 ppm and from 2.3 to 4.5 ppm were observed for 4-H, 4′-H, 4′′-H signals and for C-4, C-4′, C-4′′ signals, respectively. Also in this case, the 3-H/3′-H and 5′-H/3′′-H distances measured at 2.66 Å by NOESY experiments suggested that the protonated adduct has indeed adopted the expected *cisoid* conformation.

The protonation of **10** also resulted in variations for some of the signals of the dipeptide chains. The most relevant involved those of the methylene protons of the glycine residues which were isochronous in compound **10** and became anisochronous in **10**/H_2^{2+}, giving rise to AB systems. This change was regarded as a possible indication that some restriction of the conformational freedom of the peptide chains had occurred. This effect could be due, at least in part, to the formation of interchain hydrogen bonds. However, no other indication of the occurrance of this process could be obtained, and investigation in this sense was delayed to future studies.[14]



Scheme 5. Reversible complexation of **6a** and protonation of **10**.

Having demonstrated the folding properties of a properly modified tpy scaffold carrying amino acid and dipeptide residues, we turned our attention to show the reversible nature of the folding inducer. To this end, a solution of the **6a**/Zn complex in chloroform was treated with an excess of triethylamine at room temperature for 1 h (Scheme 5). Aqueous workup allowed to isolate tpy **6a**, identical to the original material by ^1H NMR spectroscopy in quantitative yield. Similarly, a suspension of adduct **10**/H_2^{2+} in dichloromethane was treated with excess 28% aqueous ammonium hydroxide at room temperature for 1 h (Scheme 5). Addition of a few drops of methanol to the mixture, followed by separation of the organic phase and solvent evaporation afforded compound **10**, identical to the original material by ^1H NMR spectroscopy and optical rotation in quantitative yield. These experiments showed the reversibility of the tpy-based folding inducer.

Conclusions

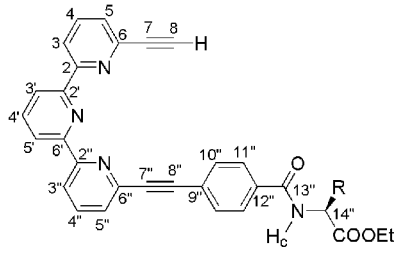
Unsymmetrically 6,6′′-disubstituted 2,2′:6′,2′′-terpyridine has been identified as a conformationally discrete scaffold potentially capable of inducing a reversible folding motif into an amino acid sequence. The folding inducer has been obtained by connecting NH_2- and CO_2H-protected glycine, alanine, and valine residues or antiparallel oriented AlaGly/GlyAla chains to the terpyridine through phenylacetylene spacers. Upon addition of Zn^{2+} to the glycine-substituted systems, a folded *cisoid* complex was formed. Also bis(protonation) of the dipeptide-substituted system with trifluoroacetic acid resulted in the formation of the folded *cisoid* adduct. The reversible nature of the folding inducer was demonstrated by isomerization of **6a**/Zn to **6a** by metal removal with triethylamine, and deprotonation of **10**/H_2^{2+} to **10** with aqueous ammonia. Future work will focus on the synthesis of a water-soluble terpyridine-based folding inducer and the attachment of peptide residues to this scaffold that are more prone than AlaGly/GlyAla to form interchain hydrogen bonds when the scaffold is in its folded conformation.

Experimental Section

Materials: All commercially available reagents including dry solvents were used as received, with the exception of dichloromethane (DCM), that was distilled from calcium hydride, and of diisopropylamine, that was distilled from KOH pellets. Organic extracts were dried with sodium sulfate, filtered, and concentrated under vacuum by using a rotary evaporator. Nonvolatile materials were dried under high vacuum. Reactions were monitored by thin-layer chromatography on pre-coated Merck silica gel 60 F254 plates and visualized either by UV light or by staining with a solution of cerium sulfate (1 g) and ammonium heptamolybdate tetrahydrate (27 g) in water (469 mL) and concentrated sulfuric acid (31 mL). Flash chromatography was performed on Fluka silica gel 60.

Methods: The ^1H and ^{13}C NMR spectra were acquired with a Bruker AMX 300 or Avance 500 spectrometer. All experiments were carried out at room temperature (30 °C). $^{13}C\{^1H\}$ NMR spectra were obtained by using Waltz decoupling and were exponentially multiplied to give 0.8 Hz line broadening before Fourier transformation. The 2D NOESY experiments were recorded by using standard Bruker software sequences, with a 1024 × 1024 data matrix and 256 increments of 80 scans each in phase-sensitive mode, with a relaxation delay of 4.0 s and a mixing time (τ_m) of 1.5 s. All 2D experiments were acquired with a Bruker inverse 5 mm *z*-gradient probe. The 90° pulse widths were 6.6 μs and 12.83 μs for ^1H and ^{13}C, respectively. The gradient was shaped by a waveform generator and amplified by a Bruker B-AFPA-10 amplifier. A sinusoidal gradient of 1 ms length and a recovery time of 0.1 ms was used. The 2D COSY spectra were recorded with a 1024 × 1024 data matrix and 512 increments of 1 scan each, in magnitude mode, with a relaxation delay of 5.0 s and a 1:1 gradient combination. The HMQC and HMBC spectra were recorded by using standard Bruker software sequences inv4gs and inv4gslplrnd, respectively. The following acquisition parameters were applied in both experiments: spectral widths in f_1 (^{13}C) and f_2 (^1H) dimensions 20000 Hz and 4000 Hz, respectively, a 1024 × 1024 data matrix, 256 time increments of 560 scans each and a 5:3:4 gradient combination. Chemical shifts are expressed in ppm and referenced to tetramethylsilane or to the solvent resonance resulting from incomplete deuteration. Data are reported as follows: chemical shift, multiplicity (s = singlet, d = doublet, t = triplet, q = quartet, br. = broad, m = multiplet), coupling constants (Hz), integration, and assignment. Optical rotations were obtained with a Perkin–Elmer 241 instrument at room temperature. All melting points are uncorrected and were obtained with a Büchi B 540 melting point apparatus.

Synthesis of Adducts 5a–c. General Procedure: A stirred solution of tpy **2** (281 mg, 1.0 mmol) and (4-iodobenzoyl)amino acid ethyl ester **3** (0.625 mmol) in a mixture of diisopropylamine (26 mL) and dry THF (37 mL) was degassed with a nitrogen stream for 10 min. To this solution CuI (12 mg, 0.0625 mmol) and $[PdCl_2(PPh_3)_2]$ (13 mg, 0.0188 mmol) were added, and the mixture was heated to 80 °C under a positive pressure of nitrogen for 3 h. The dark brown solution was then concentrated under vacuum, and the resulting residue was purified by flash chromatography with a DCM/MeOH (98:2) mixture as eluant to afford the products as orange solids. See Figure 3 for NMR numbering.



5a, R = H; **5b**, R = Me; **5c**, R = *i*Pr

Figure 3. Numbering for adducts **5a**–**c**.

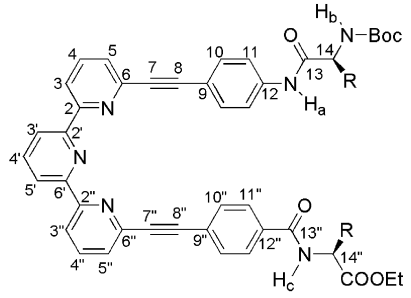
Adduct **5a** (197 mg) was obtained in 65% yield; m.p. 137–138 °C. IR (chloroform): $\tilde{\nu}$ = 3282, 1736, 1660 cm^{-1}. ^1H NMR ($CDCl_3$): δ = 1.35 (t, *J* = 7.1 Hz, 3 H, CH_3 of Et group), 3.21 (s, 1 H, 8-H), 4.27 (d, *J* = 4.9 Hz, 2 H, 14′′-H), 4.30 (q, *J* = 7.1 Hz, 2 H, CH_2 of Et group), 6.73 (br. t, *J* = 4.9 Hz, 1 H, NH_c), 7.55 (d, *J* = 8.0 Hz, 1 H, 5-H), 7.61 (d, *J* = 7.8 Hz, 1 H, 5′′-H), 7.74 (A part of an AB system, *J* = 8.2 Hz, 2 H, 10′′-H), 7.85 (t, *J* = 8.0 Hz, 1 H, 4-H), 7.87 (B part of an AB system, *J* = 8.2 Hz, 2 H, 11′′-H), 7.90 (t, *J* = 7.8 Hz, 1 H, 4′′-H), 7.99 (t, *J* = 7.8 Hz, 1 H, 4′-H), 8.55 (d, *J* = 7.8 Hz, 2 H, 3′-H and 5′-H), 8.60 (d, *J* = 7.8 Hz, 1 H, 3′′-H), 8.63 (d, *J* = 8.0 Hz, 1 H, 5-H) ppm. ^{13}C NMR ($CDCl_3$): δ = 14.0 (CH_3 of Et group), 41.9 (C-14′′), 61.8 (CH_2 of Et group), 76.8 (C-8), 83.0 (C-7), 87.8 (C-8′′), 91.1 (C-7′′), 120.7 (C-3′′), 121.0 (C-5), 121.8 (C-3′ and C-5′), 126.0 (C-9′′), 127.1 (C-11′′), 127.5 (C-3 and C-5′′), 132.3 (C-10′′), 133.8 (C-12′′), 137.0 (C-4 and C-4′′), 138.0 (C-4′), 142.0 (C-2), 142.4 (C-6′′), 154.5 (C-2′ and C-6′), 156.7 (C-6 and C-2′′), 166.6 (C-13′′), 170.0 (*C*O_2Et) ppm. $C_{30}H_{22}N_4O_3$ (486.5): calcd. C 74.06, H 4.56, N 11.52; found C 74.29, H 4.69, N 11.29.

Adduct **5b** (188 mg) was obtained in 60% yield; m.p. 200 °C (dec). $[a]_D$ = +95.3 (*c* = 0.86, in chloroform). IR (chloroform): $\tilde{\nu}$ = 3432, 3302, 1736, 1654 cm^{-1}. ^1H NMR ($CDCl_3$): δ = 1.36 (t, *J* = 7.1 Hz, 3 H, CH_3 of Et group), 1.58 (d, *J* = 7.1 Hz, 3 H, CH_3 of alanine residue), 3.24, (s, 1 H, 8-H), 4.30 (q, *J* = 7.1 Hz, 2 H, CH_2 of Et group), 4.30 (q, *J* = 7.1 Hz, 1 H, 14′′-H), 6.83 (br. d, *J* = 7.1 Hz, 1 H, NH_c), 7.57 (d, *J* = 7.8 Hz, 1 H, 5-H), 7.63 (d, *J* = 7.8 Hz, 1 H, 5′′-H), 7.75 (part A of an AB system, *J* = 8.1 Hz, 2 H, 10′′-H), 7.87 (t, *J* = 7.8 Hz, 1 H, 4-H), 7.88 (part B of an AB system, *J* = 8.1 Hz, 2 H, 11′′-H), 7.89 (t, *J* = 7.6 Hz, 1 H, 4′′-H), 8.00 (t, *J* = 7.6 Hz, 1 H, 4′-H), 8.57 (d, *J* = 7.6 Hz, 2 H, 5′-H, 3′-H), 8.63 (d, *J* = 7.8 Hz, 1 H, 3′′-H), 8.64 (d, *J* = 7.8 Hz, 1 H, 3-H) ppm. ^{13}C

NMR ($CDCl_3$): δ = 14.1 (CH_3 of Et group), 18.7 (CH_3 of alanine residue), 48.7 (C-14′′), 61.7 (CH_2 of Et group), 76.6 (C-8), 83.1 (C-7), 87.9 (C-8′′), 91.1 (C-7′′), 120.7 (C-3′′), 121.0 (C-5), 121.8 (C-3′ and C-5′), 125.9 (C-9′′), 127.1 (C-11′′), 127.5 (C-3 and C-5′′), 132.2 (C-10′′), 134.0 (C-12′′), 137.0 (C-4 and C-4′′), 137.9 (C-4′), 141.7 (C-2), 142.4 (C-6′′), 154.5 (C-2′), 154.6 (C-6′), 156.6 (C-6), 156.7 (C-2′′), 165.9 (C-13′′), 173.2 (CO_2Et) ppm. $C_{31}H_{24}N_4O_3$ (500.6): calcd. C 74.38, H 4.83, N 11.19; found C 74.59, H 5.00, N 11.05.

Adduct **5c** (215 mg) was obtained in 65% yield; m.p. 191–193 °C. IR (chloroform): $\tilde{\nu}$ = 3300, 1735, 1650 cm^{-1}. ^1H NMR ($CDCl_3$): δ = 1.05 (d, J = 6.8 Hz, 3 H, CH_3 of *i*Pr), 1.07 (d, J = 6.8 Hz, 3 H, CH_3 of *i*Pr), 1.34 (t, J = 7.1 Hz, 3 H, CH_3 of Et group), 2.30 (m, 1 H, CH of *i*Pr), 3.25 (s, 1 H, 8-H), 4.26 (q, J = 7.1 Hz, 2 H, CH_2 of Et group), 4.78 (dd, J = 6.0, 7.0 Hz, 1 H, 14′′-H), 6.73 (d, J = 6.0 Hz, 1 H, NH_c), 7.54 (d, J = 7.6 Hz, 1 H, 5-H), 7.64 (d, J = 7.6 Hz, 1 H, 5′′-H), 7.75 (part A of an AB system, J = 8.4 Hz, 2 H, 10′′-H), 7.88 (part B of an AB system, J = 8.4 Hz, 2 H, 11′′-H), 7.92 (t, J = 7.6 Hz, 1 H, 4′′-H), 8.01 (t, J = 7.6 Hz, 1 H, 4′-H), 8.59 (d, J = 7.6 Hz, 1 H, 5′-H), 8.63 (d, J = 7.6 Hz, 2 H, 3-H, 3′′-H), 8.64 (d, J = 7.6 Hz, 1 H, 3′-H) ppm. ^{13}C NMR ($CDCl_3$): δ = 14.2 (CH_3 of Et group), 17.9 (CH_3 of *i*Pr), 19.0 (CH_3 of *i*Pr), 31.7 (CH of *i*Pr), 57.5 (C-14′′), 61.5 (CH_2 of Et group), 77.0 (C-8), 83.0 (C-7), 88.8 (C-8′′), 91.5 (C-7′′), 120.8 (C-3 and C-3′′), 121.9 (C-5′ and C-3′), 126.0 (C-9′′), 127.1 (C-11′′), 127.6 (C-5 and C-5′′), 132.3 (C-10′′), 134.0 (C-12′′), 137.1 (C-4), 137.2 (C-4′′), 138.0 (C-4′), 142.0 (C-6′′), 142.5 (C-6), 154.5 (C-2′′), 155.5 (C-2′ and C-6′), 157.0 (C-2), 167.0 (C-13′′), 172.0 (CO_2Et) ppm. $C_{33}H_{28}N_4O_3$ (528.6): calcd. C 74.98, H 5.34, N 10.60; found C 75.11, H 5.45, N 10.35.

Synthesis of Adducts 6a–c. General Procedure: A stirred solution of tpy **5** (0.45 mmol) and Boc-amino acid *N*-(4-iodophenyl)amide **4** (0.70 mmol) in a mixture of diisopropylamine (30 mL) and dry THF (37 mL) was degassed with a nitrogen stream for 10 min. To this solution CuI (10 mg, 0.047 mmol) and $[PdCl_2(PPh_3)_2]$ (8 mg, 0.014 mmol) were added, and the mixture was heated to 80 °C under a positive pressure of nitrogen for 15 h. Upon cooling, a brown solid had formed, which was removed by filtration. The filtrate was then concentrated under vacuum, and the resulting residue was purified by flash chromatography with a DCM/MeOH (98:2) mixture as eluant to afford the product as an orange solid. See Figure 4 for NMR numbering.



6a, R = H; **6b**, R = Me; **6c**, R = *i*Pr

Figure 4. Numbering for adducts **6a**–**c**.

Adduct **6a** (169 mg) was obtained in 51% yield; m.p. 222–223 °C. IR (nujol): $\tilde{\nu}$ = 3348, 1740, 1690, 1665 cm^{-1}. ^1H NMR ($CDCl_3$): δ = 1.35 (t, J = 7.0 Hz, CH_3 of Et group), 1.51 (s, 9 H, CH_3 of *t*Bu group), 3.93 (d, J = 5.8 Hz, 2 H, 14-H), 4.20–4.35 (m, 4 H, 14′′-H, CH_2 of Et group), 5.30 (br. t, J = 5.8 Hz, 1 H, NH_b), 6.75 (br. s, 1 H, NH_c), 7.55–7.65 (m, 6 H, 10-H, H11, 5-H, 5′′-H), 7.74 (part A of an AB system, J = 8.2 Hz, 2 H, 10′′-H), 7.86 (part B of an AB system, J = 8.2 Hz, 2 H, 11′′-H), 7.87 (t, J = 7.8 Hz, 1 H, 4-H), 7.90 (t, J = 7.8 Hz, 1 H, 4′′-H), 7.99 (t, J = 7.8 Hz, 1 H, 4′-H), 8.49 (br. s, 1 H, NH_a), 8.58 (d, J = 7.8 Hz, 3 H, 3-H, 3′-H, 5′-H), 8.62 (d, J = 7.8 Hz, 1 H, 3′′-H) ppm. ^{13}C NMR ($CDCl_3$): δ = 14.0 (CH_3 of Et group), 28.3 (CH_3 of *t*Bu group), 42.0 (C-14′′), 45.9 (C-14), 61.8 (CH_2 of Et group), 81.2 (quaternary C of *t*Bu group), 87.5 (C-8′′), 88.8 (C-7 and C-8), 91.0 (C-7′′), 119.0 (C-9), 119.4 (C-11), 120.3 (C-3), 120.7 (C-3′′), 121.8 (C-3′ and C-5′), 126.0 (C-9′′), 127.1 (C-11′′), 127.3 (C-5′′), 127.5 (C-5), 132.3 (C-10′′), 133.0 (C-10), 133.7 (C-12′′), 137.0 (C-4′′), 137.1 (C-4), 138.0 (C-12 and C-4′), 142 (C-6′′), 143.0 (C-6), 155.0 (C-2′ and C-6′), 156.8 (CO_2*t*Bu), 157.0 (C2 and C-2′′), 166.3 (C-13′′), 168.0 (C-13), 170.2 (CO_2Et) ppm. $C_{43}H_{38}N_6O_6$ (734.8): calcd. C 70.28, H 5.21, N 11.44; found C 70.30, H 5.44, N 11.61.

Adduct **6b** (172 mg) was obtained in 50% yield; m.p. 237 °C. $[a]_D$ = +11.5 (c = 0.15, in chloroform). IR (nujol): $\tilde{\nu}$ = 3297, 1738, 1695, 1662 cm^{-1}. ^1H NMR ($CDCl_3$): δ = 1.34 (t, J = 7.0 Hz, 3 H, CH_3 of Et group), 1.46 (d, J = 7.1 Hz, 3 H, CH_3CH of *N*-Boc-protected alanine), 1.50 (s, 9 H, CH_3 of *t*Bu group), 1.56 (d, J = 7.1 Hz, 3 H, CH_3CH of alanine Et ester), 4.27 (q, J = 7.1 Hz, 2 H, CH_2 of Et group), 4.34 (br. q, J = 7.0 Hz, 2 H, 14-H), 4.80 (q, J = 7.1 Hz, 2 H, 14′′-H), 5.10 (br. d, J = 7.0 Hz, 1 H, NH_b), 6.88 (d, J = 7.0 Hz, 1 H, NH_c), 7.55 (d, J = 7.8 Hz, 1 H, 3-H), 7.58 (AB system, J = 8.3 Hz, 4 H, 10-H, 11-H), 7.61 (d, J = 7.8 Hz, 1 H, 5′′-H), 7.72 (part A of an AB system, J = 8.3 Hz, 2 H, 10′′-H), 7.85 (part B of an AB system, J = 8.3 Hz, 2 H, 11′′-H), 7.86 (t, J = 7.8 Hz, 1 H, 4-H), 7.89 (t, J = 7.8 Hz, 1 H, 4′′-H), 7.98 (t, J = 7.8 Hz, 1 H, 4′-H), 8.56 (d, J = 7.8 Hz, 1 H, 5-H), 8.59 (d, J = 7.8 Hz, 2 H, 3′-H, 5′-H), 8.62 (d, J = 7.8 Hz, 2 H, 3′′-H), 8.81 (br. s, 1 H, NH_a) ppm. ^{13}C NMR ($CDCl_3$): δ = 14.2 (CH_3 of Et group), 17.3 (CH_3CH of *N*-Boc-protected alanine), 18.6 (CH_3CH of alanine Et ester), 28.3 (CH_3 of *t*Bu group), 48.7 (C-14′′), 50.9 (C-14), 61.7 (CH_2 of Et group), 81.0 (quaternary C of *t*Bu group), 87.9 (C-8′′), 88.65 (C-7), 89.0 (C-8), 91.1 (C-7′′), 117.8 (C-12), 118.6 (C-9), 119.4 (C-11), 120.2 (C-5), 120.7 (C-3′′), 121.8 (C-3′ and C-5′), 125.8 (C-9′′), 127.1 (C-11′′), 127.3 (C-5′′), 127.5 (C-3), 132.2 (C-10′′), 132.9 (C-10), 134.0 (C-12′′), 137.0 (C-4 and C-4′′), 138.0 (C-4′), 142.4 (C-6′′), 143.0 (C-2), 154.6 (C-6′), 154.7 (C-2′), 156.5 (CO_2*t*Bu), 156.7 (C-6 and C-2′), 167.0 (C-13′′), 171.0 (C-13), 174.0 (CO_2Et) ppm. $C_{45}H_{42}N_6O_6$ (762.9): calcd. C 70.85, H 5.55, N 11.02; found C 70.80, H 5.41, N 11.29.

Adduct **6c** (203 mg) was obtained in 55% yield; m.p. 220 °C. $[a]_D$ = +10.9 (c = 0.23, in chloroform). IR (nujol): $\tilde{\nu}$ = 3273, 1738, 1695, 1662 cm^{-1}. ^1H NMR (CD_3CN): δ = 1.02 (d, J = 7.0 Hz, 6 H, CH_3 of *i*Pr group of *N*-Boc-protected valine), 1.08 (d, J = 7.0 Hz, 6 H, CH_3 of *i*Pr group of valine Et ester), 1.34 (t, J = 6.9 Hz, 3 H, CH_3 of Et group), 1.49 (s, 9 H, CH_3 of *t*Bu group), 2.30 (m, 2 H, CH of *i*Pr groups), 4.01 (dd, J = 7.0 Hz and 6.0, 1 H, 14-H), 4.26 (AB system, J = 6.9 Hz and 2.6, 2 H, CH_2 of Et group), 4.80 (dd, J = 7.0 Hz and 4.0, 1 H, 14′′-H), 5.10 (br. d, J = 6.0 Hz, 1 H, NH_b), 6.70 (d, J = 4.0 Hz, 1 H, NH_c), 7.59 (d, J = 7.8 Hz, 1 H, 3-H), 7.61 (AB system, J = 7.0 Hz, 4 H, 10-H, 11-H), 7.63 (d, J = 7.8 Hz, 1 H, 5′′-H), 7.79 (A part of an AB system, J = 8.5 Hz, 2 H, 10′′-H), 7.85 (B part of an AB system, J = 8.5 Hz, 2 H, 11′′-H), 7.87 (t, J = 7.8 Hz, 1 H, 4-H), 8.08 (t, J = 7.8 Hz, 1 H, 4′-H), 8.25 (br. s, 1 H, NH_a), 8.58 (d, J = 7.8 Hz, 1 H, 5-H), 8.60 (d, J = 7.8 Hz, 2 H, 3′-H and 5′-H), 8.63 (d, J = 7.8 Hz, 1 H, 3′′-H) ppm. ^{13}C NMR (CD_3CN): δ = 14.2 (CH_3 of Et group), 18.0 (one CH_3 of *i*Pr group of valine Et ester), 19.0 (one CH_3 of *i*Pr group of valine Et ester), 19.1 (one CH_3 of *i*Pr group of *N*-Boc-protected valine), 19.5 (one CH_3 of *i*Pr group of *N*-Boc-protected valine), 28.3 (CH_3 of *t*Bu

group), 30.5 (CH of *i*Pr group of *N*-Boc-protected valine), 31.7 (CH of *i*Pr group of valine Et ester), 57.5 (C-14′′), 61.3 (C-14), 61.4 (CH_2 of Et group), 81.0 (quaternary C of *t*Bu group), 87.5 (C-8′′), 89.5 (C-7 and C-8), 91.0 (C-7′′), 118.6 (C-9), 119.5 (C-11), 120.9 (C-5 and C-3′′), 122.1 (C-3′ and C-5′), 126.0 (C-9′′), 127.1 (C-11′′), 127.3 (C-3 and C-5′′), 132.3 (C-10′′), 133.2 (C-10), 134.5 (C-12′′), 137.4 (C-4 and C-4′′), 138.0 (C-12 and C-4′), 142.5 (C-6′′), 143.0 (C-2), 155.2 (C-2′ and C-6′), 156.8 (*C*O_2*t*Bu), 157.0 (C-6 and C-2′′), 166.8 (C-13′′), 170.0 (C-13), 172.0 (*C*O_2Et) ppm. $C_{49}H_{50}N_6O_6$ (819.0): calcd. C 71.86, H 6.15, N 10.26; found C 71.57, H 5.99, N 10.53.

Synthesis of 6a/Zn: To a stirred solution of tpy **6a** (ca. 10 mg) in 1 mL of $CDCl_3$, 1.1 molequiv. of $Zn(OTf)_2$ was added, and the yellow mixture was stirred at room temperature under nitrogen overnight. The crude mixture was analyzed by NMR spectroscopy. The relevant chemical shift differences are reported in Table S1 (see Supporting Information).

Synthesis of Adduct 9: A stirred solution of tpy **2** (281 mg, 1.0 mmol) and compound **7** (244 mg, 0.625 mmol) in a mixture of diisopropylamine (26 mL) and dry THF (37 mL) was degassed with a nitrogen stream for 10 min. To this solution CuI (12 mg, 0.0625 mmol) and $[PdCl_2(PPh_3)_2]$ (13 mg, 0.0188 mmol) were added, and the mixture was heated to 80 °C under a positive pressure of nitrogen for 3 h. The dark brown solution was then concentrated under vacuum, and the resulting residue was purified by flash chromatography with a DCM/MeOH (95:5) mixture as eluant to afford the product as an orange solid (221 mg, 65% yield); m.p. 185 °C (dec). $[\alpha]_D$ = –18.5 (*c* = 0.1, in chloroform). IR (chloroform): $\tilde{\nu}$ = 3302, 3284, 1741, 1660 cm^{-1}. ^1H NMR ($CDCl_3$): δ = 1.50 (d, *J* = 7.1 Hz, 3 H, 17′′-H), 3.23 (s, 1 H, 8-H), 3.81 (s, 3 H, 19′′-H), 4.23 (d, *J* = 4.7 Hz, 2 H, 14′′-H), 4.67 (q, *J* = 7.2 Hz, 1 H, 16′′-H), 6.74 (br. d, *J* = 7.2 Hz, 1 H, NH_e), 7.10 (br. t, *J* = 4.7 Hz, 1 H, NH_d), 7.57 (d, *J* = 7.4 Hz, 1 H, 5-H), 7.63 (d, *J* = 7.4 Hz, 1 H, 5′′-H), 7.75 (part A of an AB system, *J* = 8.1 Hz, 2 H, 10′′-H), 7.80–7.90 (m, 4 H, 4-H, 4′′-H, 11′′-H), 7.98 (t, *J* = 7.4 Hz, 1 H, 4′-H), 8.57 (d, *J* = 7.8 Hz, 2 H, 3′-H and 5′-H), 8.63 (d, *J* = 7.4 Hz, 1 H, 3-H), 8.64 (d, *J* = 7.4 Hz, 1 H, 3′′-H) ppm. ^{13}C NMR ($CDCl_3$): δ = 18.3 (C-17′′), 43.5 (C-14′′), 48.3 (C-16′′), 52.6 (C-19′′), 76.8 (C-8), 83.1 (C-7), 87.8 (C-8′′), 91.2 (C-7′′), 120.7 (C-3), 121.0 (C-3′′), 121.8 (C-3′ and C-5′), 126.1 (C-9′′), 127.2 (C-5 and C-5′′), 127.5 (2 C-11′′), 132.3 (2 C-10′′), 133.6 (C-12′′), 137.0 (C-4 and C-4′′), 137.9 (C-4′), 141.7 (C-6), 142.4 (C-6′′), 154.5 (C-2′ and C-6′), 156.6 (C-2), 156.7 (C-2′′), 166.9 (C-13′′), 168.2 (C-15′′), 173.5 (C-18′′) ppm (see Figure 5 for NMR numbering). $C_{32}H_{25}N_5O_4$ (543.6): calcd. C 70.71, H 4.64, N 12.88; found C 70.54, H 4.66, N 13.02.

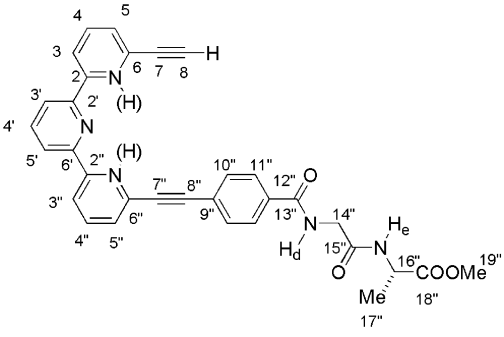


Figure 5. Numbering for adduct **9**.

Synthesis of Adduct 10: A stirred solution of tpy **9** (204 mg, 0.36 mmol) and compound **8** (220 mg, 0.562 mmol) in a mixture of diisopropylamine (24 mL) and dry THF (30 mL) was degassed with a nitrogen stream for 10 min. To this solution CuI (8 mg, 0.038 mmol) and $[PdCl_2(PPh_3)_2]$ (8 mg, 0.0112 mmol) were added, and the mixture was heated to 80 °C under a positive pressure of nitrogen for 15 h. Upon cooling, a brown solid had formed, which was removed by filtration. The solid residue was washed with diethyl ether and DCM and purified by crystallization from MeOH to afford the product as an orange-brown solid (125 mg, 43% yield); m.p. 275 °C (dec). $[\alpha]_D$ = –7.5 (*c* = 0.16, in DMSO). IR (nujol): $\tilde{\nu}$ = 3289, 1742, 1636 cm^{-1}. ^1H NMR (CD_3CN): δ = 1.36 (d, *J* = 7.2 Hz, 3 H, 17-H), 1.38 (d, *J* = 7.2 Hz, 3 H, 17′′-H), 2.03 (s, 3 H, 19-H), 3.70 (s, 3 H, 19′′-H), 3.92 (AB system, *J* = 6.2 Hz and 17.0, 2 H, 14-H), 4.03 (AB system, *J* = 5.8 Hz and 16.0, 2 H, 14′′-H), 4.12 (dq, *J* = 4.7 Hz and 7.2, 1 H, 16-H), 4.45 (q, *J* = 7.2 Hz, 1 H, 16′′-H), 5.40 (br. s, 1 H, NH_c), 7.00 (br. s, 1 H, NH_e), 7.25 (t, *J* = 6.2 Hz, 1 H, NH_b), 7.46 (t, *J* = 5.8 Hz, 1 H, NH_d), 7.63 (part A of an AB system, *J* = 8.3 Hz, 2 H, 10-H), 7.69 (d, *J* = 7.7 Hz, 1 H, 5-H), 7.75 (d, *J* = 7.0 Hz, 1 H, 5′′-H), 7.78 (part A of an AB system, *J* = 8.4 Hz, 1 H, 10′′-H), 7.88 (part B of an AB system, *J* = 8.3 Hz, 2 H, 11-H), 7.94 (part B of an AB system, *J* = 8.4 Hz, 2 H, 11′′-H), 8.00 (t, *J* = 7.7 Hz, 1 H, 4-H), 8.04 (t, *J* = 7.0 Hz, 1 H, 4′′-H), 8.13 (t, *J* = 7.8 Hz, 1 H, 4′-H), 8.53 (d, *J* = 7.8 Hz, 2 H, 3′-H and 5′-H), 8.67 (d, *J* = 7.7 Hz, 1 H, 3-H), 8.71 (d, *J* = 7.0 Hz, 1 H, 3′′-H), 8.94 (br. s, 1 H, NH_a) ppm. ^{13}C NMR (CD_3CN): δ = 17.5 (C-17′′), 18.1 (C-17), 23.0 (C-19), 42.7 (C-14′′), 43.4 (C-14), 48.0 (C-16′′), 49.3 (C-16), 52.2 (C-19′′), 88.3 (C-8′′), 88.8 (C-7), 89.4 (C-8), 91.1 (C-7′′), 116.1 (C-9), 119.6 (2 C-11), 120.8 (C-3), 121.2 (C-3′′), 121.8 (C-3′ and C-5′), 124.6 (C-9′′), 128.3 (2 C-11′′ and C-5′′), 128.5 (C-5), 132.2 (2 C-10′′), 133.0 (2 C-10), 135.0 (C-12′′), 138.6 (C-4′′), 138.7 (C-4), 140.4 (C-12 and C-4′) 142.1 (C-6′′), 142.7 (C-6), 154.6 (C-2′), 154.7 (C-6′), 156.0 (C-2′′), 156.1 (C-2), 166.1 (C-13′′), 168.7 (C-13), 169.2 (C-15), 170.3 (C-18), 173.5 (C-18′′ and C-15′′) ppm (see Figure 6 for NMR numbering). $C_{45}H_{40}N_8O_7$ (804.9): calcd. C 62.68, H 5.01, N 13.92; found C 62.55, H 4.89, N 14.07.

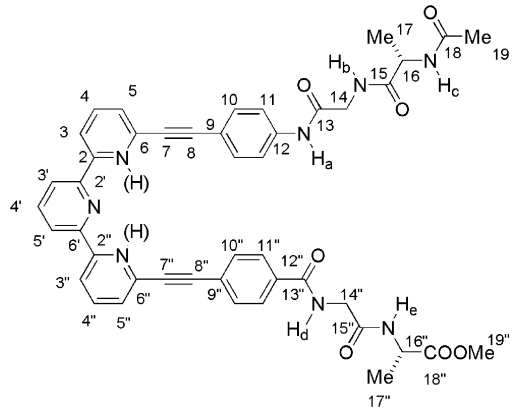


Figure 6. Numbering for adduct **10**.

Protonation of Adduct 10: Protonation of **10** was carried out by adding trifluorocacetic acid (0.1 mmol) to a suspension of this compound (0.025 mmol) in CD_3CN (0.75 mL). A clear, bright yellow solution was obtained, which was analyzed by NMR spectroscopy. Relevant chemical shift differences are collected in Tables S2 and S3 (see Supporting Information).

Supporting Information (see footnote on the first page of this article): Experimental procedures and spectral and analytical data for compounds **3a**–**c**, **4a**–**c**, **7**, and **8**; chemical shifts for **6a**/Zn (Table S1) and **10**/H_2^{2+} (Tables S2 and S3).

Acknowledgments

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