Zinc Porphyrin Tweezer in Host–Guest Complexation: Determination of Absolute Configurations of Primary Monoamines by Circular Dichroism

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Abstract: A nonempirical exciton chirality circular dichroic (CD) method for determining the absolute configurations of primary monoamines with amino group directly linked to the stereogenic center is described. Conventional exciton chirality CD method cannot be applied to these compounds since they lack the two sites for attaching the interacting chromophores. This was solved by covalently linking the monoamine to a trifunctional bidentate carrier moiety **1**. Treatment of the carrier/monoamine conjugate with the porphyrin tweezer **4** consisting of two pentanediol-linked zinc porphyrins gives rise to 1:1 host–guest macrocyclic complexes that exhibit exciton-coupled CD spectra. The sign of the CD couplet can then be correlated with the absolute configuration of the monoamine as follows: a clockwise arrangement of the L, M, and S (large, medium, small) groups in the Newman projection of the monoamine with the amino group in the rear gives rise to a positive CD couplet, and vice versa; the assignments of L, M, S groups are based on conformational energies (*A* values). This method is applicable to cyclic and acyclic aliphatic amines, aromatic amines, amino esters, amides, and cyclic amino alcohols, and can be performed at the several microgram level.

Keywords: amines · circular dichroism · configuration determination · host–guest chemistry · zinc porphyrin tweezer

Introduction

The exciton chirality circular dichroic (CD) method, a nonempirical approach for absolute stereochemical determinations[1, 2] has been applied to a wide variety of compounds, such as polyols,[3] carbohydrates,[4–6] quinuclidines,[7, 8] hydroxy acids,[9–11] and others.[2] This method is based on the through-space exciton coupling between two or more chirally oriented chromophores which are usually introduced through derivatizations of functional groups present in the substrate. Therefore, unless a chromophore already exists in the molecule, the presence of at least two functional groups which can be transformed into chromophores is the prerequisite for applying this chiroptical method, that is, two attachment sites for chromophore(s) are necessary. This prerequisite, however, is not satisfied in some molecules to be studied, such as monoamines in which the amino function is the sole site for derivatization. However, the carrier molecule **1** described herein allows one to extend the exciton-coupled CD method to primary monoamines linked directly to a chiral center (Scheme 1). Derivatization of amine **2** with carrier **1** yields the carrier/monoamine conjugate **3**; binding of the conjugate **3** with porphyrin tweezer **4**[12] produces a 1:1 chiral macrocyclic host–guest complex **5** that exhibits exciton-coupled CD spectra reflecting the absolute configuration of monoamine **2**.

The stereochemistry of primary monoamines has been investigated by benzene chirality rules (aromatic amines),[13, 14] and CD induced by 1-indan-carboxylic acid,[15] benzoylbenzoic acid,[16–18] or polyacetylene carboxylic acid helices.[19, 20] These methods normally generate weak CD signals (CD amplitudes < 10, in many cases < 1), and require milligram quantities of sample.

Recently, we reported that the zinc porphyrin tweezer **4** can be used to determine the absolute configuration of diamines at the low microgram level.[12] Porphyrin tweezer **4** is capable of binding various acyclic chiral α,ω-diamines through zinc nitrogen coordination to form 1:1 macrocyclic host–guest complexes **6** (Figure 1). In the sterically more favored conformation of the complex, the small group at the stereogenic center of the guest molecule would be sandwiched between the two porphyrins, while the large group points outside; this orientation leads to a chiral twist between the two porphyrin effective transition moments[21] and a CD couplet with the sign determined by the chirality of the guest. The method can be extended to other compounds with two

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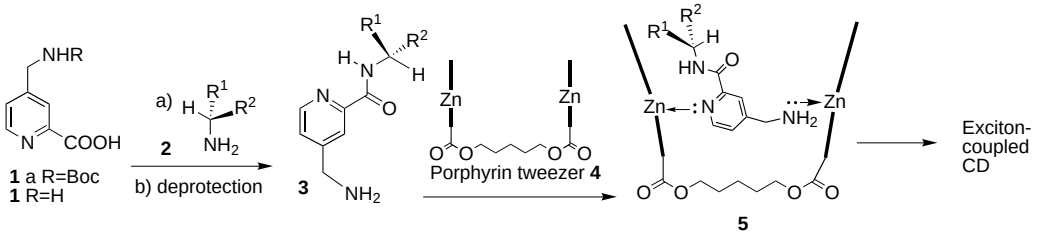


Scheme 1. Complex formation between carrier **1**/monoamine conjugate and porphyrin tweezer **4**.

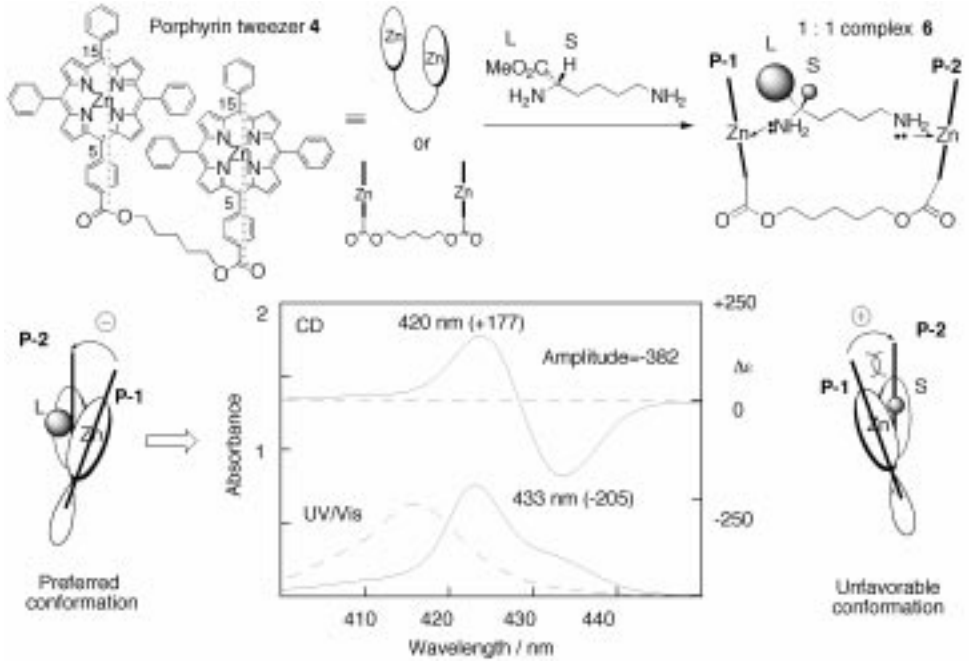


Figure 1. CD and UV/Vis spectra of the 1:1 macrocyclic complex **6** formed in *n*-hexane between porphyrin tweezer **4** host (dashed line shows the direction of the porphyrin effective transition moment μ) and a chiral diamine guest L-lysine methyl ester. CD amplitude denotes the difference between CD extrema (Cotton effects) in $\Delta\varepsilon$; either a positive or negative sign is assigned to it depending on whether the Cotton effect at longer wavelength is positive or negative (- - - - noncomplexed tweezer **4**, —— 1:1 complex **6**).

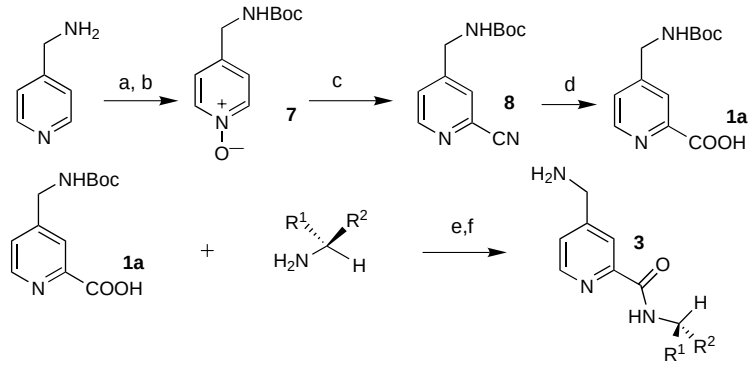
sites of attachment such as amino acids and amino alcohols by converting them into diamines via simple derivatizations with ethylene diamine and glycine, respectively.[12] This sensitive method requires less than 10 μg of both the host and the guest, and unlike the traditional exciton-coupled CD approach, the chromophores, that is zinc porphyrins, can be recycled as they are not covalently attached to the compounds of interest.

Bidentate carriers exemplified by **1** were developed in order to extend this tweezer method to primary monoamines with the amino group linked directly to stereogenic centers (Scheme 1). The angular arrangement of the two porphyrin rings in complex **5** gives rise to an exciton-coupled CD that reflects the absolute configuration of monoamine **2**.

Results and Discussion

The testing of several candidate compounds such as pyrazine carboxylic acid and 1,4-diamino- 2-benzoic acid showed that pyridine-4-aminomethyl-2-carboxylic acid **1** having the following attributes was suited to perform the role of the carrier molecule: i) presence of the carboxyl group to derivatize primary amines; ii) presence of the two nitrogen groups to bind to the tweezer; iii) presence of the pyridine nitrogen in the vicinity of the chiral center in the carrier/monoamine conjugate and a relatively rigid structure to reflect the chirality of the amine in the tweezer complex.

Carrier **1** was synthesized in high yield from commercially available compounds as shown in Scheme 2.[22] Boc protection of 4-aminomethylpyridine followed by 3-chloroperoxybenzoic acid (*m*CPBA) oxidation gave pyridine oxide **7**, which upon treatment with trimethylsilyl cyanide (TMSCN) and dimethylcarbamyl chloride gave pyridine-4-*N*-Boc-aminomethyl-2-nitrile (**8**);[23] this was then hydrolyzed to yield **1a** in the gram scale, overall 50% yield for



Scheme 2. Synthesis of the carrier **1a** and the carrier/monoamine conjugate **3**. a) $(Boc)_2O$, THF, TEA, room temperature, overnight (96%); b) *m*CPBA, CH_2Cl_2, room temperature, 12 h (82%); c) dimethylcarbamyl chloride, TMSCN, CH_2Cl_2, room temperature, 48 h (65%); d) NaOH, EtOH(aq), reflux, 24 h (quant.); e) BOP, DIPEA, THF, room temperature, 4h; f) 10% TFA/CH_2Cl_2, room temperature, 2 h (70–95%).

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the four steps. The coupling of **1a** with monoamines using benzotriaoyl-1-yloxytris(dimethylamino)phosphonium hexafluorophosphate (BOP)[24] as the coupling reagent under mild conditions followed by removal of the Boc group generated the carrier/monoamine conjugate in high yield. Although the coupling reaction was usually performed at the milligram scale, it was found that the conjugate could also be readily prepared with about 5 μg of the monoamine followed by HPLC purification to provide material sufficient for CD measurements (see Experimental Section).

Mixing of conjugate **10**, formed by carrier **1** and (*S*)-cyclohexylethylamine, with porphyrin tweezer **4** gave rise to a positive exciton CD couplet in a nonpolar solvent such as methylcyclohexane (MCH) as shown in Figure 2a.[25] Forty equivalents of the conjugate **3** was found out to be the optimum amount of the guest since this yielded maximum CD amplitudes (Figure 2b). CD spectra measured in other solvents, for example, hexane, benzene, toluene, methylene chloride, chloroform, and acetonitrile, disclosed that the CD amplitudes in hexane were similar to those in MCH, while they were much weaker or almost negligible in other solvents. The following CD measurements were performed in MCH.

A standard Job plot revealed a 1:1 stoichiometry for the binding between porphyrin tweezer **4** and the bidentate conjugate guest at low guest concentration (less than 20 equiv).[26] Formation of the 1:1 macrocyclic complex between porphyrin tweezer **4** and the bidentate conjugate guest is supported by changes in UV/Vis and CD spectra with different amounts of the guest (Figure 2). With increasing amounts of the guest such as conjugate **10** (0 to 200 equiv), the UV/Vis maxima is shifted from 416 nm (Figure 2b, 0 equiv curve) to 424 nm (saturated host, Figure 2b, 200 equiv curve) with the presence of an isosbestic point indicating a single-step transformation. The absorption maximum of the complex formed between a monoamine and porphyrin tweezer **4** is at 428 nm; in contrast that of the complex between the conjugate such as **10** and tweezer **4** is at 424 nm (complex **11** in Figure 2d). This apparent blue shift seen in the latter is most

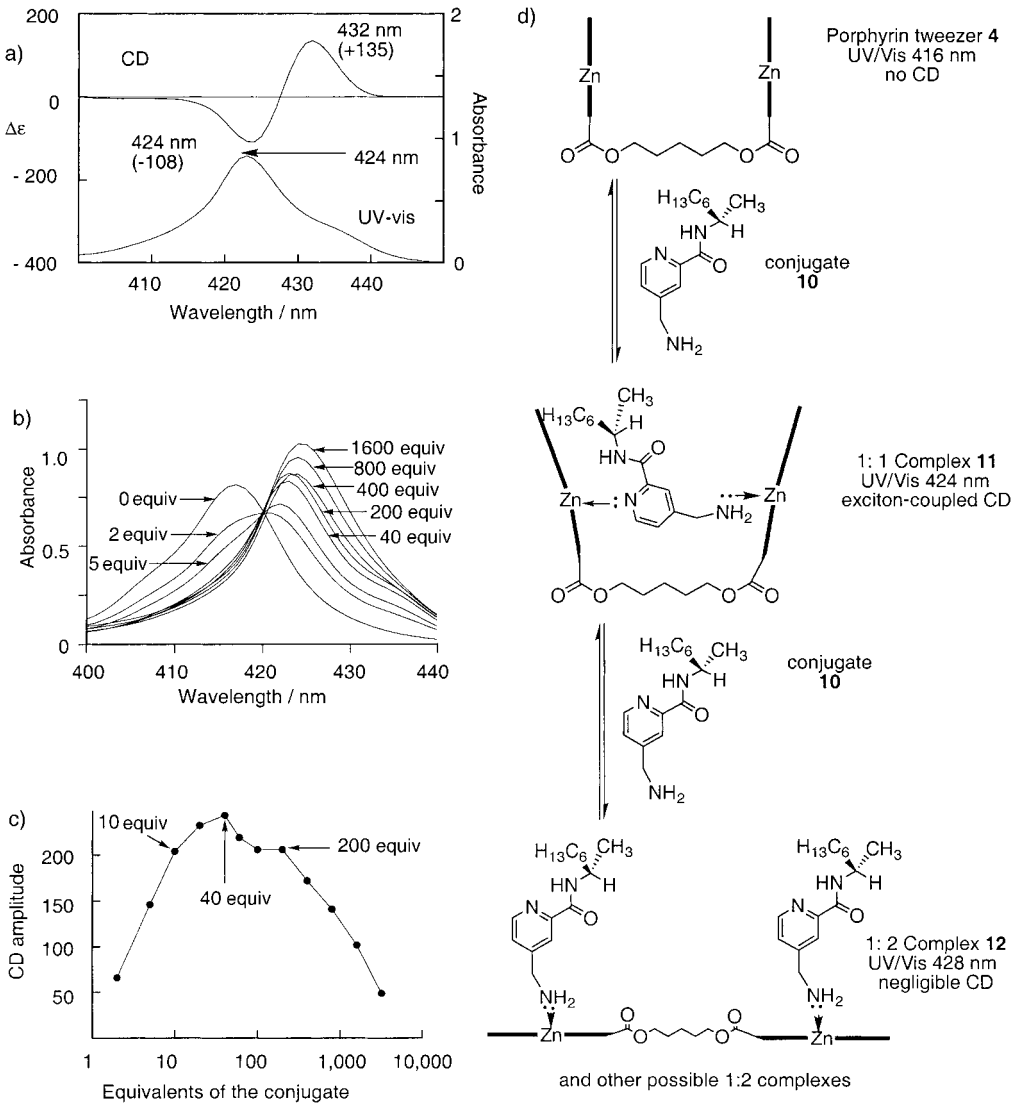

Figure 2. UV/Vis and CD spectra of porphyrin tweezer **4**/conjugate **10** complex with different concentrations of **10** in methylcyclohexane (MCH). (The tweezer concentration is kept constant at 1 μM in all cases). a) UV/Vis and CD spectra of **4**/**10** complex with 40 equiv of **10**. b) Change in UV/Vis spectrum with different equivalents of **10**. c) Change in CD amplitude with different equivalents of **10**. d) Schematic representation of the equilibria between porphyrin tweezer **4**, complex **11** (1:1 macrocyclic host–guest complex), and complex **12** (flexible 1:2 host–guest complexes).

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likely due to exciton coupling between the two nearby porphyrins held rigidly in a close to parallel orientation.[27–30] This clearly indicates the transition of the noncomplexed tweezer **4** to the 1:1 host–guest macrocyclic complex **11** (Figure 2b, 2d).[30–32] It is only after the guest concentration exceeds 200 equiv that UV/Vis maxima of the complex is shifted to longer wavelengths beyond 424 nm (Figure 2b, 400 equiv to 1600 equiv curves). This red shift of the maxima beyond 424 nm with no isosbestic point points an increase in the population of the flexible 1:2 host–guest complexes **12**.

The changes in the host–guest complex structures accompanying the addition of conjugate **10** to porphyrin tweezer **4** is also corroborated by changes in their CD spectra. As shown in Figure 2c, the CD amplitudes of the host–guest complex increase as the guest concentration increases from 2 to 10 equiv and reaches a maximum at 40 equiv, indicating formation of the 1:1 complex **11**. The CD amplitudes, while varying little between 10 to 200 equivalents of guest concentration, decrease above 200 equivalents (Figure 2c) suggesting an increase in the population of 1:2 complex **12** devoid of exciton coupling.[33–36] Forty equivalents of the guest was used as the optimal amount for the following CD investigations.

The principle by which the conjugate/porphyrin tweezer **5** complex yields an exciton-coupled CD spectrum with a specific sign is based on the steric differentiation of the three substituent groups at the chiral center by the two zinc porphyrins. Nonempirical assignments can be made if the spatial orientation of the two porphyrins could be predicted. This is attainable only if rotations around C_{pyr}–$C_{C=O}$ (bond I), $C_{C=O}$–NH (bond II), and HN–C_{chiral} (bond III) bonds of the conjugates are restricted (Figure 3). Molecular modeling of the conjugate[37] has yielded useful insights towards understanding the preferred conformations of these bonds. The conjugation favors a coplanar orientation of the carbonyl group to the pyridine ring. Moreover, possibly due to electrostatic repulsion, the *anti* carbonyl oxygen/pyridine nitrogen disposition is almost exclusively preferred by $\approx 30\ kJ\,mol^{-1}$ (Figure 3).[38–40] This is supported by the finding that all crystal structures of compounds bearing the pyridine-2-carboxamide moiety in the Cambridge Structural Database have the N_{pyr}–C–C=O projection angle close to 180° (Figure 4a). The preferred conformation around bond II is *s-trans* as shown in numerous cases[41–43] and in our calculations (Figure 3). The

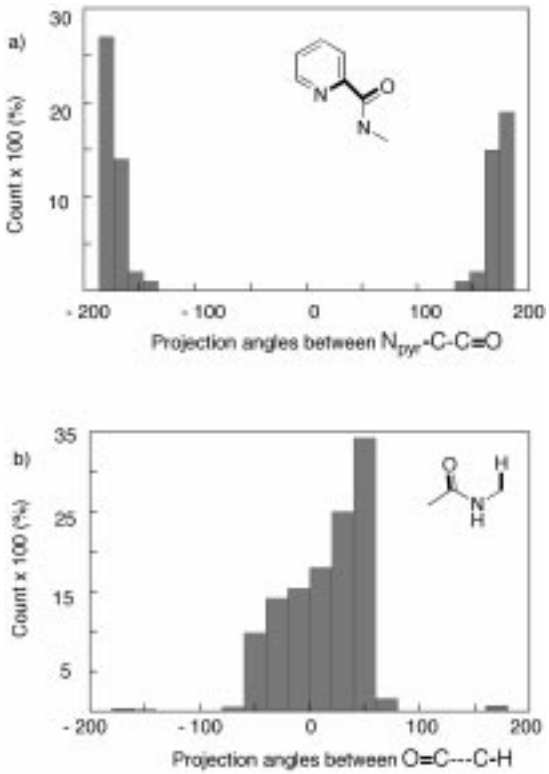


Figure 4. a) Projection angle (N_{pyr}–C–C=O) distribution in crystal structures of compounds containing pyridine-2-carboxamide in Cambridge Structural Database. b) Projection angle (O=C–C–H) distribution in crystal structures of compounds containing secondary amide in Cambridge Structural Database.

methine hydrogen at the chiral center prefers to be *syn* to the carbonyl by about $9\ kJ\,mol^{-1}$ in $CHCl_3$. Search of the Cambridge Structural Database for secondary amides also indicates that this *syn* conformation is more favorable, that is, the projection angles between the carbonyl and the methine hydrogen are normally small (Figure 4b). Thus it is clear that conformer I (Figure 3) is the most favored for the conjugate.

Due to the aforementioned conformational rigidity of the conjugate (Figure 3), it was assumed that a conformation similar to I was preferred for the conjugate in the host–guest complex as well. The correlation between sign of the exciton-coupled CD and the absolute stereochemistry of **10** can then be deduced as follows. The three substituents at the chiral center are assigned S (small), M

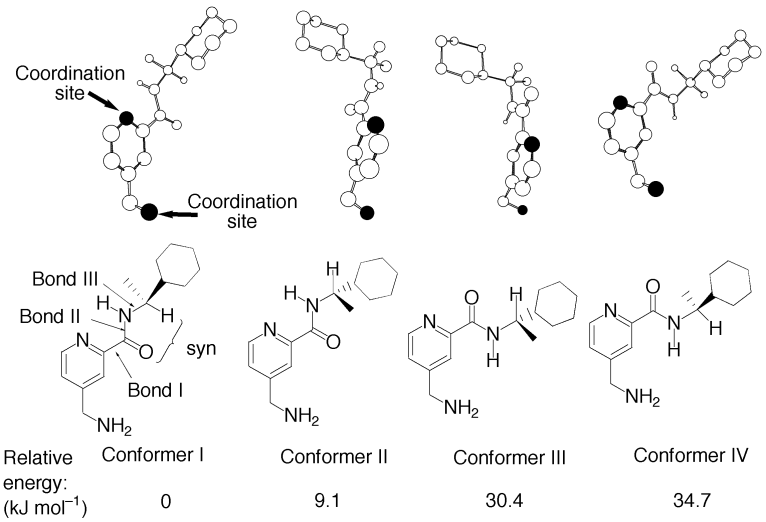


Figure 3. Four major types of conformers of conjugate **10** in $CHCl_3$ from Monte Carlo conformational searches using Amber* force field (MacroModel 6.0). (Most of hydrogen atoms are omitted for the sake of clarity.)

(medium), and L (large) according to their sizes, with hydrogen as S, methyl as M, and cyclohexyl ring as L. When the L, M, and S groups constitute a clockwise arrangement with the amino group in the rear as in the Newman projection for (*S*)-cyclohexylethylamine (Figure 5 and compound **10** in Table 1), the zinc porphyrin complexing with the pyridine nitrogen would prefer an approach from the side of the M group rather than the L group due to the unfavorable steric interactions with the L group. This leads to a clockwise twist between the two porphyrins, that is, a positive exciton-coupled CD spectrum, $\Delta\varepsilon + 135$ (432 nm)/-108 (424 nm), amplitude $+243$ (Figure 5).

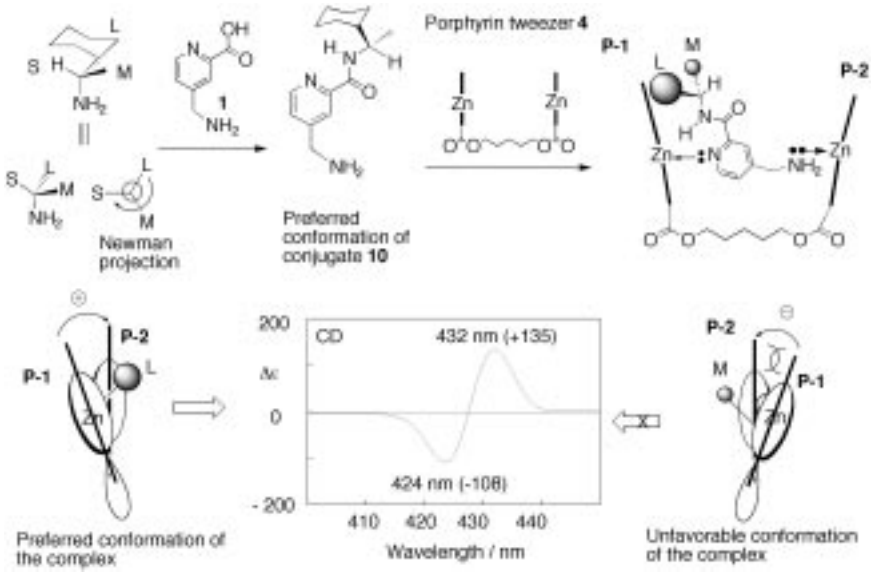
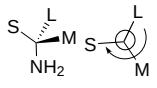
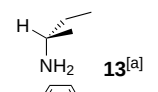
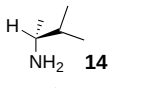
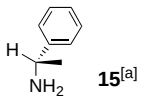
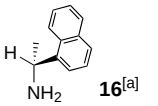
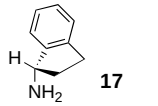
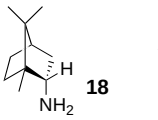
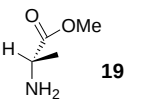
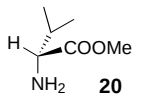
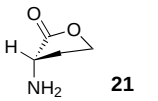
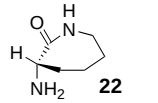
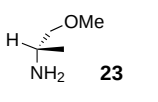
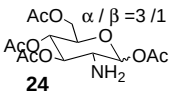
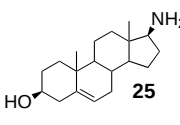
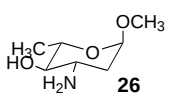
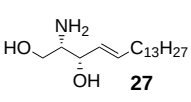


Figure 5. Conformations and CD spectrum of the complex formed by porphyrin tweezer **4** host and conjugate **10** guest in MCH.

For other primary monoamines conjugated with carrier **1** (compound **13** to **18**), as shown in Table 1, the absolute stereochemistry of the amines can be correlated with the sign of the exciton CD couplet. Namely, when the L, M, and S

Table 1. CD amplitudes of carrier **1**/monoamine conjugates and porphyrin tweezer **4** complex in MCH. All spectra were taken at room temperature with 40 equiv of the guest.

Parent amine	Schematic representation	Predicted sign	Δε	CD amplitude	Parent amine	Schematic representation	Predicted sign	Δε	CD amplitude
10[a]		positive	432 nm +135 424 nm -108	+243	**13**[a]		positive	432 nm +33 423 nm -31	+64
14		negative	432 nm -123 423 nm +97	-220	**15**[a]		positive	432 nm +78 423 nm -78	+156
16[a]		negative	433 nm -143 423 nm +106	-249	**17**		positive	435 nm +25 425 nm -13	+38
18		positive	431 nm +111 423 nm -86	+197	**19**		negative	431 nm -114 422 nm +84	-198
20		positive	431 nm +160 422 nm -126	+286	**21**		negative	433 nm -122 422 nm +107	-229
22		negative	432 nm -191 423 nm +173	-364	**23**		negative	432 nm -39 423 nm +27	-66
24		negative	432 nm -56 423 nm +52	-108	**25**		positive	432 nm +136 423 nm -110	+246
26		positive	431 nm +66 421 nm -60	+126	**27**		negative	438 nm -5 431 nm +16 421 nm +3	

[a] The enantiomer exhibited mirror image CD.

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groups are arranged in a clockwise fashion with the amino group in the rear in Newman projections, positive exciton-coupled CD spectra are observed, and vice versa. Even the small steric difference between methyl and ethyl groups (compound **13**) can be distinguished by porphyrin tweezer **4** which yields a positive exciton-coupled CD spectrum. The amplitudes of exciton-coupled CD spectra increase as the size of the L group increases from ethyl (**13**) to isopropyl (**14**) or from phenyl (**15**) to naphthyl (**16**). The smaller amplitudes of compound **17** compared to compound **15** is probably due to the fact that the phenyl L group is fused into a five-membered ring, therefore leading to a flatter molecule and less steric differentiation.

With substituent groups other than aliphatic groups and aromatic groups, the assignment of L and M groups becomes difficult. However, considerations based on conformational energies[44] expressed in *A* values[45, 46] turned out to be very useful to avoid ambiguities. For example, in the case of alanine derivative **19** the methyl carboxylate (*A* value = 5.0–5.4 kJ mol^{-1}) should be considered as M and the methyl group (*A* value = 7.28 kJ mol^{-1}) as L since the methyl *A* value is larger than that of the methyl carboxylate. This leads to a counterclockwise arrangement of the L, M, and S groups in **19**, and thus a negative exciton-coupled CD spectrum, $\Delta\varepsilon =$ − 114 (431 nm)/ + 84 (422 nm), amplitude − 198. The stereochemistry of valine derivative **20**, lactone **21**, and lactam **22** can be determined similarly by assigning the ester or amide groups as M. The CD amplitude of the Val derivative **20** is larger than that of Ala derivative **19** because the isopropyl group (*A* value = 9.25 kJ mol^{-1}) is larger than the methyl group (*A* value = 7.28 kJ mol^{-1}). Although the absolute stereochemistry of the amino acids can be determined as previously described,[12] the present method is preferred for amino esters (e.g. **19**–**21**) and amino amides (e.g. **22**), since it does not require hydrolysis to generate the free acid which could be accompanied by epimerization. (*S*)-1-Methoxy 2-propylamine derivative **23** yielded a CD spectrum with the predicted sign despite the small difference in conformational energies of M and L groups (*A* value = 7.20 kJ mol^{-1} for CH_2OMe vs. 7.28 kJ mol^{-1} for Me). Tetraacetyl glucosamine derivative **24** with multiple chiral centers also gave the predicted CD sign.

To further test the scope of the present method, chiral primary amines bearing free hydroxy groups were investigated. With molecules having hydroxy groups attached to a cyclic skeleton such as steroidal amine **25** and acosamine **26**, the absolute configuration at the amino center can be determined in a similar manner, namely, clockwise arrangement of L, M, and S groups gives positive exciton-coupled CD; presence of free hydroxy groups does not interfere with the determinations because they are locked in a cyclic system. In contrast, flexible acyclic monoamines containing hydroxy groups, such as L-*threo*-sphingosine derivative **27**, yielded complex CD spectra, presumably due to multiple conformations of the host–guest complexes. The current method is therefore not applicable to acyclic amino alcohols. However, the absolute configuration of such acyclic amino alcohols can be determined using other exciton-coupled CD approaches[12, 47] since they possess two sites of attachment.

Conclusion

A protocol utilizing zinc porphyrin tweezer **4** to determine the absolute stereochemistry of primary monoamines has been established. This method requires only microgram amounts of sample and can be applied to cyclic and acyclic aliphatic amines, aromatic amines, amino esters, amides, and cyclic amino alcohols. The stereochemistry of the monoamine can be readily determined from the sign of the exciton-coupled CD spectrum: a positive CD couplet corresponds to a clockwise arrangement of the L, M, and S groups in the Newman projection of the amine with amino group in the rear, while a negative couplet corresponds to a counterclockwise arrangement. Assignments of the M, L groups are based on their conformational energies (*A* values). Further studies on structures of carriers for secondary amines and alcohols are underway.

Experimental Section

Materials and general procedures: Anhydrous CH_2Cl_2 was dried over CaH_2 and distilled. Other solvents used for CD measurements were either Optima or HPLC grade. Unless otherwise noted, materials were obtained from commercial suppliers and were used without further purification. All reactions were performed in dried glassware under argon. Column chromatography was performed by using ICN silica gel (32–63 mesh). ^{1}H NMR spectra were obtained on Bruker DMX 300, 400 or 500 and are reported in parts per million (ppm) relative to the solvent resonances (δ), with coupling constants (*J*) in Hertz (Hz). Low-resolution and high-resolution FAB mass spectra were measured on a JEOL JMS-DX303 HF mass spectrometer using a glycerol matrix and Xe ionizing gas. ESI mass spectra were measured on a JEOL LC mate mass spectrometer. UV/Vis spectra were recorded on a Perkin-Elmer Lambda 40 spectrophotometer, and reported as λ_{max} [nm]. CD spectra were recorded on a JASCO J-720 spectropolarimeter, and reported as λ [nm] ($\Delta\varepsilon_{max}$ [L mol^{-1} cm^{-1}]).

General procedures for preparation of carrier 1/monoamine conjugate: To a solution of carrier **1a** (1 equiv) in THF (3 mL), BOP (1.2 equiv), diisopropylethylamine (DIPEA) (5 equiv), and the primary monoamine (0.95 equiv) were added. The solution was stirred overnight at room temperature. All the solvents were evaporated by a rotary evaporator and the remaining solid was dissolved in CH_2Cl_2 (10 mL). The solution was washed twice with aqueous $NaHCO_3$ (10 mL), and the organic layer was separated and dried with Na_2SO_4. The mixture was then separated by silica gel flash chromatography to yield the Boc-protected carrier/amine conjugate. The Boc group was removed by treatment with 10% trifluoroacetic acid (TFA) in CH_2Cl_2 (5 mL) at room temperature for two hours. Evaporation of all the solvents yielded the analytically pure carrier/amine conjugate.

Procedures for CD measurements: For a typical experiment, to prepare the amine solution, Na_2CO_3 (30 mg) was added to the solution of carrier **1a**/(*S*)-cyclohexylethylamine conjugate **10** (1 mg) in MeOH (0.2 mL). The solution was dried under a stream of argon and then on a high-vacuum pump (0.2 Torr) for 20 min. Anhydrous CH_2Cl_2 (1 mL) was added to yield a solution of **10** (2 mM). An aliquot of the amine solution (20 μL) was added to porphyrin solution (1 μM) in MCH prepared by addition of porphyrin tweezer **4** solution (0.1 mM) in anhydrous CH_2Cl_2 (10 μL) to MCH (1 mL) (this corresponds to about 1.6 μg of porphyrin tweezer **4** and 18 μg of conjugate **10**). The porphyrin/amine solution was shaken, then UV/Vis and CD spectra were recorded and corrected by background subtraction at 25 °C. The CD spectra were measured in millidegrees and normalized into $\Delta\varepsilon/\lambda$ [nm] units.

Procedures for obtaining the Job plot: Solutions of carrier **1a**/(*S*)-cyclohexylethylamine conjugate **10** (0.50 mM) in anhydrous CH_2Cl_2 (1 mL) and porphyrin tweezer **4** (0.1 mM) in anhydrous CH_2Cl_2 (1 mL) were prepared similarly as described above. Aliquots of the two solutions were mixed in

MCH (1 mL) to obtain twenty different solutions with the ratio (χ) of the host/(host + guest) concentrations ranging from 0.00 to 0.95 with 0.05 increments. The total concentration of the host and guest is kept constant at 3 μM in all solutions. The UV/Vis absorbance of these solutions at 417 nm was plotted against χ. Linear extrapolation of the absorbance measured near $\chi = 0$ and $\chi = 1$ resulted in two straight lines that intersected at the stoichiometric equivalence point where $\chi = 0.52$. This indicates that the stoichiometric ratio of the host and guest in the complex is 1:1.

4-[(*tert*-Butoxycarbonylamino)methyl]pyridine oxide (7): To a solution of 4-aminomethylpyridine (3.24 g, 30 mmol) in THF (20 mL) was added di-*tert*-butyl dicarbonate (6.48 g, 30 mmol) and triethylamine (1 mL). A lot of white precipitate was formed. After the mixture had been stirred at room temperature overnight, it was filtered and the light brown filtrate was concentrated to yield an oil-like liquid. Upon standing in air, it crystallized to yield 4-[(*tert*-butoxycarbonylamino)methyl]pyridine (6.0 g, 96%). To a solution of 4-[(*tert*-butoxycarbonylamino)methyl]pyridine (6.0 g, 29 mmol) in CH_2Cl_2 (50 mL), *m*CPBA (9.0 g, 30 mmol) was added. The solution was stirred at room temperature for 12 h and then washed with 0.5 N aqueous NaOH solution (10 mL). The aqueous layer was extracted with CH_2Cl_2 (10×20 mL) until no product was left in the aqueous phase. The organic layers were combined and purified by flash chromatography (9:1 CH_2Cl_2/MeOH) to yield **7** (5.3 g, 82%). ^{1}H NMR (300 MHz, CD_3OD): $\delta = 1.44$ (s, 9H; $C(CH_3)_3$), 4.27 (d, $J = 5.7$, 2H; CH_2), 7.44 (d, $J = 6.6$ Hz 2H), 8.27 (d, $J = 6.7$ Hz, 2H).

2-Cyano-4-[(*tert*-butoxycarbonylamino)methyl]pyridine (8): To a solution of **7** (2.0 g, 8.7 mmol) in CH_2Cl_2 (30 mL) under Ar was added TMSCN (1.44 mL, 11.3 mmol). After the mixture had been stirred for 5 min, dimethylcarbamyl chloride (0.94 mL, 9.5 mmol) was added. The solution was further stirred at room temperature for 48 h and washed with saturated aqueous $NaHCO_3$ solution (20 mL). The organic layer was dried with Na_2SO_4 and purified by flash chromatography (20:1 CH_2Cl_2/MeOH) to yield **8** (1.1 g, 53%). ^{1}H NMR (300 MHz, $CDCl_3$): $\delta = 1.47$ (s, 9H; $C(CH_3)_3$), 4.38 (d, $J = 6.2$ Hz, 2H; CH_2), 5.32–5.42 (br. s, 1H; NH), 7.44 (dd, $J = 0.7$, 5.1 Hz; 1H), 7.63 (d, $J = 0.7$ Hz; 1H), 8.65 (d, $J = 5.1$ Hz; 1H); MS (EI): *m/z*: $[M+H]^+$ 234.

4-[(*tert*-Butoxycarbonylamino)methyl]pyridine-2-carboxylic acid (1a): To a solution of **8** (1.1 g, 4.6 mmol) in EtOH (20 mL) was added 1N aqueous NaOH solution (5 mL). The solution was refluxed for 24 h and washed with CH_2Cl_2 (30 mL). The aqueous layer was acidified to about pH 6 and all the solvent was evaporated. The solid was then suspended in MeOH (20 mL) and filtered. The solvent of the filtrate was removed to yield **1a** (1.2 g, 100%). ^{1}H NMR (300 MHz, CD_3OD): $\delta = 1.45$ (s, 9H; $C(CH_3)_3$), 4.30 (s, 2H; CH_2), 5.32–5.42 (br. s, 1H; NH), 7.31 (d, $J = 5.0$ Hz, 1H), 7.92 (s, 1H), 8.47 (d, $J = 4.9$ Hz, 1H); ^{13}C NMR (75 MHz, CD_3OD): $\delta = 28.73$, 43.97, 80.42, 123.37, 124.40, 149.54, 152.10, 155.13, 158.39, 172.00; m.p. > 220 °C (decomp); MS (EI): *m/z*: $[M+H]^+$ 253; HR-FABMS of $C_{12}H_{16}O_4N_2K$: *m/z*: $[M+K]^+$ calcd 291.0747, found 291.0739.

Carrier 3/(*S*)-cyclohexylethylamine conjugate 10: (*S*)-Cyclohexylethylamine (2.6 mg, 20 μmol) was treated with carrier **1a** and then with TFA to yield the conjugate **10** (8.6 mg, 89%) according to the general procedures for conjugate synthesis. ^{1}H NMR (CD_3OD, 300 MHz): $\delta =$ 1.23 (d, $J = 6.19$ Hz, 3H; CH_3), 0.88–1.38, 1.42–1.58, 1.62–1.89 (m, 11H, C_6H_{11}), 3.88–3.98 (m, 1H, NHC*H*CH_3), 4.26 (s, 2H, CH_2NH$_2$TFA), 7.58 (d, $J = 4.96$ Hz, 1H), 8.15 (s, 1H), 8.69 (d, $J = 4.98$ Hz, 1H); MS (ESI): *m/z*: $[M+H]^+$ 262.2; HR-FABMS of $C_{15}H_{24}ON_3$: *m/z*: $[M+1]^+$ calcd. 262.1919, found 262.1925.

Procedures for the microgram-scale preparation of conjugate 10 and CD measurements: To a solution of carrier **1a** (10 mg, 40 μmol) in THF (1 mL) were added BOP (19mg, 44 equiv) and DIPEA (50 μL). The solution was stirred at room temperature for 10 min. An aliquot of this solution (5 μL) was added to a solution of (*S*)-cyclohexylethylamine (4.6 μg, 36 nmol) in THF (10 μL) in a 0.3 mL Wheaton V-Vial with a Spinvane magnetic stirring bar (both available from Aldrich). After the mixture had been stirred at room temperature overnight, all solvents were evaporated and the residue was treated with 10% TFA in CH_2Cl_2 (20 μL) for two hours. The conjugate (16 μg, 92% obtained from UV absorbance at 268 nm) was purified by reverse-phase HPLC (solvent system: 67% H_2O, 33% CH_3CN, 0.1% TFA; analytical C18 column; flow rate 1.3 mL min^{-1}; retention time: 4.2 min; monitored at 220 nm).

For CD measurements, the amine solution was prepared by dissolving the conjugate (16 μg) in MeOH (50 μL) with Na_2CO_3 (1 mg). The solvent was dried by a stream of argon and then on a high-vacuum pump (0.2 Torr) for 20 min. CH_2Cl_2 (40 μL) was added to the residue followed by a solution of the porphyrin tweezer **4** (1 μM) in MCH (1 mL). CD spectra of the porphyrin/amine solution were then recorded according to the general procedures with amplitudes within 10% of the values obtained by using the conjugate from milligram-scale synthesis.

Carrier 3/(*S*)-2-butylamine conjugate 13: (*S*)-2-Butylamine (4 mg, 55 μmol) was treated with carrier **1a**, and then with TFA to yield the conjugate **13** (18 mg, 75%) according to the general procedures for conjugate synthesis. ^{1}H NMR (CD_3OD, 300 MHz): $\delta = 0.94$ (t, $J = 7.40$ Hz, 3H; CH_3), 1.24 (d, $J = 6.63$ Hz, 3H; CH_3), 1.52–1.65 (m, 2H, CH_2CH$_3$), 3.95–4.09 (m, 1H; NHC*H*CH_3), 4.27 (s, 2H; CH_2NH$_2$TFA), 7.58 (d, $J =$ 4.96 Hz, 1H), 8.16 (s, 1H), 8.69 (d, $J = 4.94$ Hz, 1H).

Carrier 3/(*R*)-3-methyl 2-butylamine conjugate 14: (*R*)-3-Methyl 2-butylamine (4 mg, 46 μmol) was treated with carrier **1a** and then with TFA to yield the conjugate **14** (15 mg, 74%) according to the general procedures for conjugate synthesis. ^{1}H NMR (CD_3OD, 300 MHz): $\delta = 0.94$ (t, $J =$ 3.46 Hz, 3H; CH_3), 0.95 (d, $J = 3.48$ Hz, 3H; CH_3), 1.24 (d, $J = 6.75$ Hz, 3H; CH_3), 1.78–1.92 (m, 1H; C*H*$(CH_3)_2$), 3.86–4.02 (m, 1H; NHC*H*), 4.27 (s, 2H; CH_2NH$_2$TFA), 7.65 (d, $J = 4.96$ Hz, 1H), 8.16 (s, 1H), 8.69 (d, $J =$ 4.95 Hz, 1H); MS (ESI): *m/z*: $[M+H]^+$ 222.2.

Carrier 3/(*S*)-methylbenzylamine conjugate 15: (*S*)-Methylbenzylamine (4 mg, 33 μmol) was treated with carrier **1a** and then with TFA to yield the conjugate **15** (12 mg, 70%) according to the general procedures for conjugate synthesis. ^{1}H NMR (CD_3OD, 400 MHz): $\delta = 1.59$ (d, $J = 7.00$ Hz, 3H; CH_3), 4.25 (s, 2H; CH_2NH$_2$TFA), 5.22 (q, $J = 7.05$ Hz, 1H; NHC*H*), 7.20–7.27, 7.29–7.36, 7.38–7.42 (m, 5H; C_6H_5), 7.59 (d, $J = 4.96$ Hz, 1H), 8.13 (s, 1H), 8.60 (d, $J = 4.96$ Hz, 1H).

Carrier 3/(*R*)-1-naphthylethylamine conjugate 16: (*R*)-1-Naphthylethylamine (16 mg, 94 μmol) was treated with carrier **1a** and then with TFA to yield the conjugate **16** (38 mg, 75%) according to the general procedures for conjugate synthesis. ^{1}H NMR (CD_3OD, 400 MHz): $\delta = 1.73$ (d, $J =$ 6.90 Hz, 3H; CH_3), 4.24 (s, 2H; CH_2NH$_2$TFA), 6.06 (q, $J = 6.90$ Hz, 1H; NHC*H*), 7.42–7.52 (m, 4H; CH), 7.55–7.60 (m, 1H; CH), 7.62 (d, $J =$ 7.16 Hz, 1H; CH), 7.78 (d, $J = 8.20$ Hz, 1H; CH), 7.84–7.88 (m, 1H; CH), 8.12–8.19 (m, 2H; 2CH), 8.67 (d, $J = 4.98$ Hz, 1H); MS (ESI): *m/z*: $[M+H]^+$ 306.2.

Carrier 3/(*S*)-1-aminoindane conjugate 17: (*S*)-1-Aminoindane (21 mg, 160 μmol) was treated with carrier **1a** and then with TFA to yield the conjugate **17** (70 mg, 82%) according to the general procedures for conjugate synthesis. ^{1}H NMR (CD_3OD, 400 MHz): $\delta = 1.95–2.08$ (m, 1H; CH), 2.53–2.62 (m, 1H; CH), 2.88–2.95 (m, 1H; CH), 3.02–3.12 (m, 1H; CH), 4.28 (s, 2H; CH_2NH$_2$TFA), 5.55–5.62 (m, 1H; NHC*H*COO), 7.14–7.28 (m, 4H; CH), 7.60 (d, $J = 4.90$ Hz, 1H), 8.17 (s, 1H), 8.65 (d, $J =$ 4.91 Hz, 1H); MS (ESI): *m/z*: $[M+H]^+$ 268.2; HR-FABMS of $C_{16}H_{17}ON_3K$: *m/z*: $[M+K]^+$ calcd. 306.1009, found 306.1004.

Carrier 3/(*R*)-bornylamine conjugate 18: (*R*)-Bornylamine (15 mg, 94 μmol) was treated with carrier **1a** and then with TFA to yield the conjugate **18** (45 mg, 88%) according to the general procedures for conjugate synthesis. ^{1}H NMR (CD_3OD, 400 MHz): $\delta = 0.85$ (s, 3H; CH_3), 0.94 (s, 3H; CH_3), 1.03 (s, 3H; CH_3), 1.05–1.14 (m, 1H; CH), 1.32–1.44 (m, 2H; 2CH), 1.63–1.74 (m, 2H; 2CH), 1.78–1.88 (m, 1H; CH), 2.34–2.44 (m, 1H; CH), 4.27 (s, 2H; CH_2NH$_2$TFA), 4.38–4.47 (m, 1H; C*H*NH), 7.65 (d, $J = 4.70$ Hz, 1H), 8.18 (s, 1H), 8.73 (d, $J = 4.75$ Hz, 1H); MS (ESI): *m/z*: $[M+H]^+$ 288.2.

Carrier 3/(*S*)-alanine methyl ester conjugate 19: (*S*)-Alanine methyl ester hydrochloride (13 mg, 93 μmol) was treated with carrier **1a** and then with TFA to yield the conjugate **19** (33 mg, 73%) according to the general procedures for conjugate synthesis. ^{1}H NMR (CD_3OD, 400 MHz): $\delta = 1.52$ (d, $J = 7.24$ Hz, 3H; CH_3), 3.75 (s, 3H; CO_2CH_3), 4.27 (s, 2H; CH_2NH$_2$TFA), 4.68 (q, $J = 7.29$ Hz, 1H; C*H*CH_3), 7.62 (d, $J = 4.89$ Hz, 1H), 8.16 (s, 1H), 8.72 (d, $J = 4.96$ Hz, 1H); MS (ESI): *m/z*: $[M+H]^+$ 238.1; HR-FABMS of $C_{11}H_{16}O_3N_3$: *m/z*: $[M+1]^+$ calcd. 238.1192, found 238.1186.

Carrier 3/(*R*)-valine methyl ester conjugate 20: (*R*)-Valine methyl ester trifluoroacetate (23 mg, 94 μmol) was treated with carrier **1a** and then with

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TFA to yield the conjugate **20** (36 mg, 70%) according to the general procedures for conjugate synthesis. ^{1}H NMR (CD_3OD, 300 MHz): $\delta = 0.99$ (s, 3H; CH_3), 1.01 (s, 3H; CH_3), 2.20–2.38 (m, 1H; C*H*(CH_3)$_2$), 3.76 (s, 3H; CO_2CH_3), 4.28 (s, 2H; CH_2NH$_2$TFA), 4.53–4.62 (m, 1H; C*H*CH(CH_3)$_2$), 7.65 (dd, $J = 1.72$, 4.99 Hz, 1H), 8.18 (d, $J = 1.72$ Hz, 1H), 8.73 (d, $J = 4.96$ Hz, 1H).

Carrier 3/(*S*)-α-amino-γ-butyrolactone conjugate 21: (*S*)-α-Amino-γ-butyrolactone hydrobromide (18 mg, 96 μmol) was treated with carrier **1a** and then with TFA to yield the conjugate **21** (38 mg, 86%) according to the general procedures for conjugate synthesis. ^{1}H NMR (CD_3OD, 400 MHz): $\delta = 2.42–2.53$ (m, 1H; C*H*CH$_2$), 2.58–2.65 (m, 1H; C*H*CH$_2$), 4.27 (s, 2H; CH_2NH$_2$TFA), 4.32–4.38 (m, 1H; CHOCO), 4.45–4.53 (m, 1H; CHOCO), 4.85 (dd, $J = 9.31$, 11.01 Hz, 1H; NHC*H*COO), 7.62 (d, $J = 4.90$ Hz, 1H), 8.16 (s, 1H), 8.71 (d, $J = 4.94$ Hz, 1H); MS (ESI): *m/z*: $[M+H]^+$ 236.1.

Carrier 3/L-α-amino-ε-caprolactam conjugate 22: L-α-Amino-ε-caprolactam (13 mg, 94 μmol) was treated with carrier **1a** and then with TFA to yield the conjugate **22** (36 mg, 75%) according to the general procedures for conjugate synthesis. ^{1}H NMR (CD_3OD, 400 MHz): $\delta = 1.34–1.45$ (m, 1H; CH), 1.55–1.65 (m, 1H; CH), 1.82–1.94 (m, 2H; 2CH), 1.96–2.13 (m, 2H; 2CH), 3.25–3.40 (d, $J = 9.80$ Hz, 1H; NHC*H*CO), 4.27 (s, 2H; CH_2NH$_2$TFA), 7.65 (d, $J = 4.85$ Hz, 1H), 8.18 (s, 1H), 8.69 (d, $J = 4.86$ Hz, 1H); MS (ESI): *m/z*: $[M+H]^+$ 263.2; HR-FABMS of $C_{13}H_{19}O_2N_4$: *m/z*: $[M+1]^+$ calcd. 263.1508, found 263.1508.

Carrier 3/(*S*)-1-methoxy 2-propylamine conjugate 23: (*S*)-1-Methoxy 2-propylamine (4.5 mg, 51 μmol) was treated with carrier **1a** and then with TFA to yield the conjugate **23** (16 mg, 72%) according to the general procedures for conjugate synthesis. ^{1}H NMR (CD_3OD, 300 MHz): $\delta = 1.27$ (d, $J = 6.78$ Hz, 3H; CH_3), 3.38 (s, 3H; OCH_3), 3.42–3.53 (m, 2H; CH_2OCH$_3$), 4.27 (s, 2H; CH_2NH$_2$TFA), 4.24–4.35 (m, 1H; NHC*H*), 7.58 (d, $J = 4.93$ Hz, 1H), 8.17 (s, 1H), 8.69 (d, $J = 4.93$ Hz, 1H).

Carrier 3/tetraacetyl D-glucosamine conjugate 24: Tetraacetyl D-glucosamine hydrochloride (10 mg, 21 μmol) was treated with carrier **1a** and then with TFA to yield the conjugate **24** (12 mg, 71%) according to the general procedures for conjugate synthesis. ^{1}H NMR (CD_3OD, 400 MHz): $\delta = 1.91$, 2.05, 2.09, 2.19 (4s, 12H; 4CH_3), 4.05–4.12 (m, 1H; CH), 4.17–4.25 (m, 1H; CH), 4.27 (s, 2H; CH_2NH$_2$TFA), 4.53–4.62 (m, 1H; CH), 5.18–5.28 (m, 1H; CH), 5.42–5.55 (m, 1H; CH), 6.04 (d, $J = 8.77$ Hz, 0.25H, β anomeric proton), 6.22 (d, $J = 3.63$ Hz, 0.75H, α anomeric proton), 7.62 (d, $J = 4.95$ Hz, 1H), 8.14 (s, 1H), 8.69 (d, $J = 4.90$ Hz, 1H); MS (ESI): *m/z*: $[M+H]^+$ 482.2; HR-FABMS of $C_{21}H_{27}O_{10}N_3K$: *m/z*: $[M+K]^+$ calcd. 520.1334, found 520.1340.

Carrier 3/5-androsten-17β-amino-3β-ol conjugate 25: 5-Androsten-17β-amino-3β-ol (15 mg, 52 μmol) was treated with carrier **1a** and then with TFA to yield the conjugate **25** (32 mg, 95%) according to the general procedures for conjugate synthesis. ^{1}H NMR (CD_3OD, 400 MHz): $\delta = 0.82$, 1.02 (2s, 6H; 2CH_3), 1.08–1.88, 1.92–2.05, 2.11–2.30 (m, 20H), 3.48–3.58 (m, 1H; C*H*OH), 4.02–4.12 (m, 1H; C*H*NH), 4.28 (s, 2H; CH_2NH$_2$TFA), 5.38 (d, $J = 5.15$ Hz, 1H; CH), 7.38 (d, $J = 4.95$ Hz, 1H), 8.09 (s, 1H), 8.52 (d, $J = 4.90$ Hz, 1H).

Carrier 3/methyl L-acosamine conjugate 26: Methyl L-acosaminide hydrochloride (9 mg, 45 μmol) was treated with carrier **1a** and then with TFA to yield the conjugate **26** (20 mg, 93%) according to the general procedures for conjugate synthesis. ^{1}H NMR (CD_3OD, 500 MHz): $\delta = 1.28$ (d, $J = 4.85$ Hz, 3H; CH_3), 1.82–1.88 (m, 1H; CH), 2.06–2.14 (m, 1H; CH), 3.18–3.25 (m, 1H; CH), 3.35 (s, 3H; OCH_3), 3.66–3.74 (m, 1H; CH), 4.25 (s, 2H; CH_2NH$_2$TFA), 4.31–4.38 (m, 1H; CH), 4.71 (d, $J = 2.95$ Hz, 1H; OC*H*OCH$_3$), 7.58 (d, $J = 4.95$ Hz, 1H), 8.14 (s, 1H), 8.69 (d, $J = 5.01$ Hz, 1H); MS (ESI): *m/z*: $[M+H]^+$ 296.2.

Carrier 3/L-*threo*-sphingosine conjugate 27: L-*threo*-Sphingosine (2 mg, 6.7 μmol) was treated with carrier **1a** and then with TFA to yield the conjugate **27** (3.7 mg, 83%) according to the general procedures for conjugate synthesis. ^{1}H NMR (CD_3OD, 500 MHz): $\delta = 0.89$ (t, $J = 6.86$ Hz, 3H; CH_3), 1.19–1.40 (m, 22H), 1.95–2.05 (m, 2H; CH), 3.65–3.72, 3.74–3.80 (m, 2H, CH_2OH), 4.02–4.12 (m, 1H; NHC*H*CH$_2$OH), 4.25 (s, 2H; CH_2NH$_2$TFA), 4.38–4.42 (m, 1H; NHCHC*H*OH), 5.48–5.52 (m, 1H; C*H*CHCH$_2$), 5.70–5.79 (m, 1H; CHC*H*CH$_2$), 7.58 (d, $J = 4.95$ Hz, 1H), 8.14 (s, 1H), 8.68 (d, $J = 4.96$ Hz, 1H).

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