

# Chiral Recognition by CD-Sensitive Dimeric Zinc Porphyrin Host. 1. Chiroptical Protocol for Absolute Configurational Assignments of Monoalcohols and Primary Monoamines

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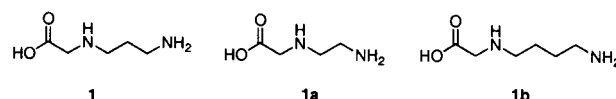
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**Abstract:** A general microscale protocol for the determination of absolute configurations of primary amino groups or secondary hydroxyl groups linked to a single stereogenic center is described. The chiral substrates are linked to the achiral trifunctional bidentate carrier molecule (3-aminopropylamino)acetic acid (**1**,  $\text{H}_2\text{NCH}_2\text{CH}_2\text{CH}_2\text{NHCH}_2\text{COOH}$ ) and the resultant conjugates are then complexed with dimeric zinc porphyrin host **2** giving rise to 1:1 host/guest sandwiched complexes. These complexes exhibit exciton-coupled bisignate CD spectra due to stereodifferentiation leading to preferred porphyrin helicity. Since the chiral sense of twist between the two porphyrins in the complex is dictated by the stereogenic center of the substrate, the sign of the couplet determines the absolute configuration at this center. The twist of the porphyrin tweezer in the complex can be predicted from the relative steric sizes of the groups flanking the stereogenic center, such that the bulkier group protrudes from the complex sandwich. In certain  $\alpha$ -hydroxy esters and  $\alpha$ -amino esters, electronic factors and hydrogen bonding govern the preferred conformation of the complex, and hence the CD spectra.

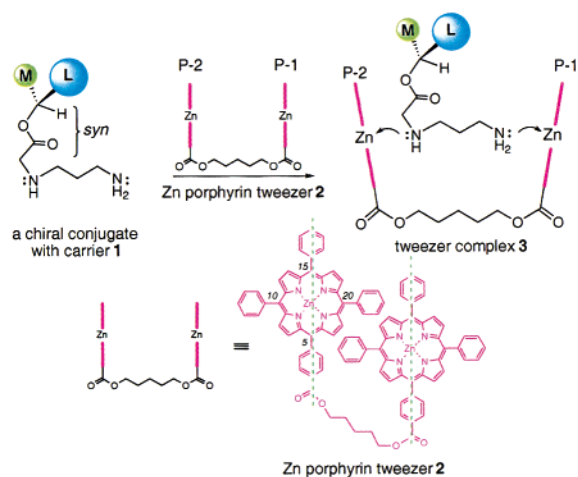
## Introduction

The configurational assignment of substrates containing primary amino groups or secondary hydroxyl groups linked to a single stereogenic center is a challenging task. Since many of these substrates exhibit important biological activities and often are available only in limited amounts, determination of their absolute configurations is of academic as well as of practical importance. In the following, we have developed a chemical/chiroptical method that allows the microscale determination of absolute configuration of such substrates. Namely, the substrate is derivatized with carrier **1** (Figure 1) to give an ester or amide. As outlined in Figure 2, treatment of these esters or amides with a CD sensitive dimeric zinc porphyrin host, referred to as tweezer **2**,<sup>1–3</sup> yields complex **3**, which exhibits intense exciton-coupled CD reflecting their absolute configurations.

The assignment of absolute configurations of primary monoamines and secondary monoalcohols by chiroptical spectroscopy is mostly based on empirical and semiempirical CD sector and helicity rules, and thus in contrast to methods based on exciton-coupled CD, the Cotton effects (CE) are smaller and milligram quantities of sample are often required.<sup>4</sup> Benzene sector rules



**Figure 1.** The three aliphatic diamino carrier molecules for derivatization of chiral monoamines and monoalcohols.



**Figure 2.** Complexation of a chiral conjugate of carrier **1** with zinc porphyrin tweezer **2**; the broken line in structure **2** depicts the orientation of the effective electric transition moment. Upon treatment of tweezer **2** with the conjugate, the primary amino group of the carrier moiety coordinates with the zinc in P-1, and this is followed by coordination of the *sec*-amino group to the zinc in P-2 to yield tweezer complex **3**; the helicity between the two porphyrin rings is dictated by the absolute configuration of the substrate and affords an exciton-coupled CD (see Figure 5).

have been forwarded for benzyl carbinols and aryl carbinamines<sup>5</sup> while the induced CE of chiral monoamines were used in their

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acid–base complexes with benzoylbenzoic acid<sup>6</sup> and poly((4-carboxyphenyl)acetylene).<sup>7</sup> The stereochemistry of secondary monoalcohols has been investigated by induced CD of their complexes with Rh<sub>2</sub>(OCOCF<sub>3</sub>)<sub>4</sub>,<sup>8</sup> copper hexafluoroacetylacetonate,<sup>9</sup> and the optical rotation and CD of their 2,4-dinitrobenzenesulfonyl derivatives.<sup>10</sup>

The most widely used method for configurational assignments of both secondary monoalcohols<sup>11,12</sup> and monoamines<sup>13</sup> is the Mosher NMR method and its modified versions which are based on the ring current effect of the introduced aryl moiety. The original protocol requires derivatization of the chiral alcohol or amine with both (*R*)- and (*S*)-enantiomers of a chiral aromatic acid, such as  $\alpha$ -methoxy- $\alpha$ -(trifluoromethyl)phenylacetic acid (MTPA),  $\alpha$ -methoxyphenylacetic acid (MPA), or other auxiliary reagent, and measurement of the  $\Delta\delta^{S,R}$  values for the protons flanking the alcoholic and amino functions. The Mosher NMR method has also found some of its most sensitive applications in using <sup>19</sup>F- and <sup>13</sup>C-NMR spectroscopy.<sup>11</sup> Recently, this method has undergone considerable progress in terms of introducing new auxiliary reagents<sup>14</sup> and novel procedures<sup>15</sup> that require the preparation of only one of the two chiral esters or amides. Despite such improvements there are cases<sup>12,16</sup> where the Mosher method cannot be applied with certainty due to either the lack of protons on one side of the molecule or the small  $\Delta\delta^{S,R}$  values that approach the limits of experimental error. The required amount of sample is also a restriction in Mosher's method since milligram quantities are usually needed, especially

if both derivatives of the chiral amine or alcohol have to be prepared and measured.

In the following we describe a microscale method for determining the absolute configurations of secondary monoalcohols and primary monoamines in which the hydroxyl and amino groups are linked to the stereogenic center. It is an extension of the conventional exciton chirality method. Since the presence of two or more chirally oriented chromophores is a prerequisite for the exciton chirality method,<sup>17,18</sup> it cannot be applied directly to compounds in which the hydroxyl or amino group is the only site available for the introduction of a chromophore. Application to such compounds requires either a chromophore already present in the substrate, such as  $\alpha$ -aryl-substituted alcohols<sup>19</sup> or allylic alcohols,<sup>20</sup> or employment of a host molecule as a sensitive bichromophoric CD reporter group.<sup>3,21</sup>

In recent years porphyrins and zinc porphyrins have attracted widespread attention as reporter groups with multifaceted properties for structural studies by CD spectroscopy.<sup>22</sup> The chromophore 5-(carboxyphenyl)-10,15,20-triphenylporphyrin<sup>22</sup> has an intense red-shifted Soret band at ca. 414 nm and propensity to undergo intramolecular  $\pi$ – $\pi$  stacking in a stereocontrolled manner. This renders it a versatile and powerful reporter group in configurational assignments of various substrates with a single stereogenic center, e.g. acyclic diamines and amino alcohols,<sup>23</sup> diols,<sup>24,25</sup> and  $\alpha$ -hydroxy acids.<sup>26</sup> In another protocol, two zinc tetraphenylporphyrin residues were linked by a pentanediol spacer.<sup>1</sup> The resulting zinc porphyrin tweezer **2** (Figure 2), an achiral CD reporter "receptor", was capable of binding various chiral acyclic  $\alpha,\omega$ -diamines through zinc–amine coordination that resulted in formation of 1:1 macrocyclic host/guest complexes.<sup>1</sup> The stereoselective complexation gave rise to one clearly preferred porphyrin helicity, represented by an exciton-coupled CD in the porphyrin spectral region with signs controlled by the absolute configuration of the bound diamine. It was subsequently found that this zinc porphyrin tweezer **2** also forms complexes with conjugate **7a** (Scheme 1) prepared from primary monoamines **4a** and carrier **5** (the *N*-Boc protected form of the trifunctional bidentate carrier<sup>3</sup> molecule **6**). In such cases, the preferred porphyrin helicity of the resultant complex **8a** was also dictated by the relative steric size of substituents attached to the stereogenic center. The stereodifferentiation between the large and medium groups, R<sub>1</sub>

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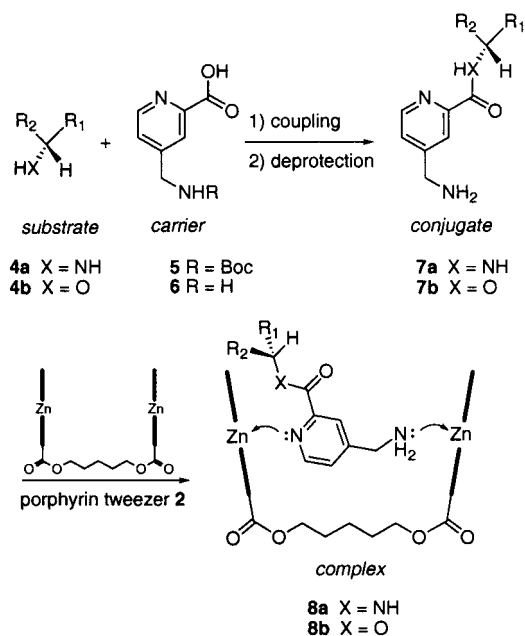
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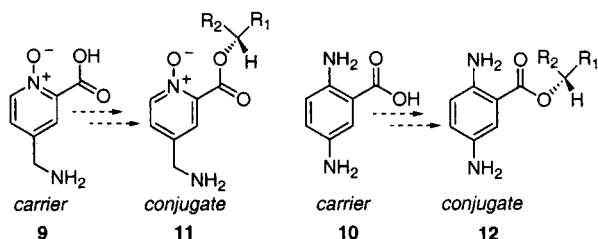
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**Scheme 1.** Formation of Complex **8** from Tweezer **2** and Conjugates **7** Prepared from Chiral Monoamines **4a**, Mono Alcohols **4b**, and Carrier **6** (the Boc protected carrier **5** is employed in the synthesis)

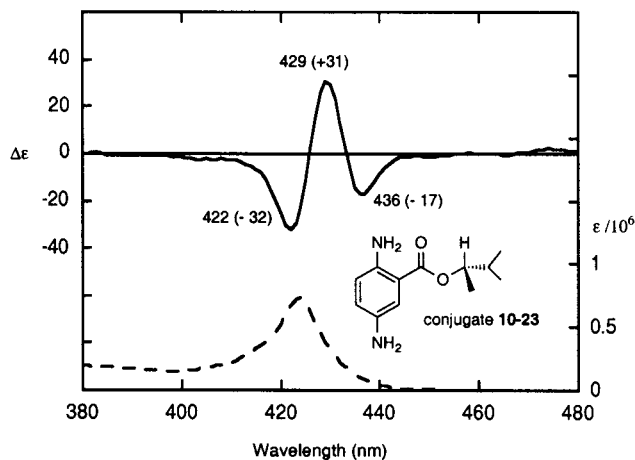


**Scheme 2.** Unsited Carriers and Their Alcohol Conjugates (see Supporting Information for synthesis)



and  $R_2$ , respectively, led to a preferred chiral sense of twist between the two interacting porphyrins that gave rise to a positive or negative exciton couplet reflecting the relative steric bulk. This procedure is applicable to both acyclic and cyclic aromatic amines, aliphatic amines, and amino esters and can be performed at the low microgram level.<sup>3</sup> However, the method cannot distinguish between hydrogen and deuterium since the stereoselectivity is based on relative steric size and not relative mass.

Extension of this method to secondary monoalcohols **4b** would be intriguing and desirable, since it could become a general microscale method where its application would not require any preexisting CD chromophore in the hydroxyl-containing substrate. The conjugates of secondary monoalcohols **4b** with this carrier molecule **6** were first studied to check the applicability. The UV–VIS spectra of zinc porphyrin tweezer complexes with the monoalcohol conjugates **7b** were almost identical with those prepared from monoamine conjugates **7a** (Scheme 1). However, none of these complexes **8b** gave distinctive CD couplets in the solvents tested, most likely due to the lack of conformational rigidity of esters compared to amides. This led to the design of two further carriers **9** and **10** (Scheme 2). In the pyridine oxide conjugates **11**, the increased electronic repulsion between the negatively charged oxygen of the pyridine oxide and the carbonyl oxygen was supposed to reduce the conformational flexibility of the alcohol conjugates. Similarly, in the case of the *p*-phenylenediamine conjugate **12**,



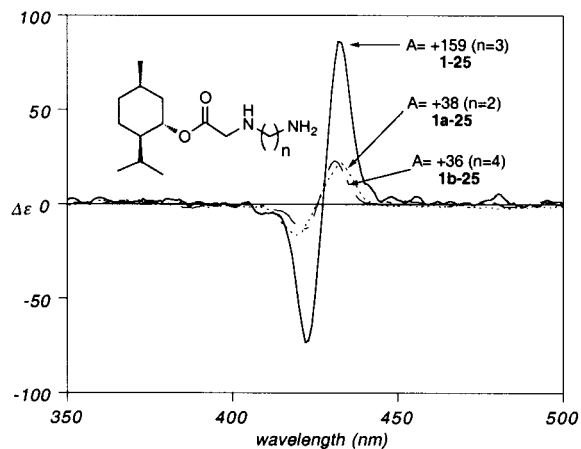
**Figure 3.** UV–VIS and CD spectra of conjugate **10-23** complexed with porphyrin tweezer **2** in methylcyclohexane at room temperature (conjugate **10-23** is the definition for the ester formed between carrier **10** and chiral alcohol substrate **23**; see Table 1).

the intramolecular hydrogen bond between the amino group and the carbonyl oxygen was also considered to make its conformation less flexible. The complexes between tweezer **2** and pyridine oxide alcohol conjugates **11** indeed gave exciton-coupled CD spectra in nonpolar solvents but their signs could not be correlated unambiguously with the absolute configuration of the alcohols. The complexes from tweezer **2** and conjugates **12** also exhibited distinctive CD spectra in methylcyclohexane and hexane; however, usually three Cotton effects were observed (see Figure 3). Such multiple Cotton effects are most likely due to overlapping CD couplets of various conformers. In addition, their intensities were relatively small and did not increase when the substrate substituents at the stereogenic center were made bulkier. The use of carriers **9** and **10** was thus abandoned.

Most likely, in the alcohol conjugates **7b** (Scheme 1), **11** and **12** (Scheme 2), the aromatic moieties restrict the conformational freedom of the complexing nitrogens. This suggests that when complexation occurs between the carrier nitrogens and the zinc porphyrin, conformation of the amide and ester moieties might be different before and after binding so that the complexes do not reflect the subtle differences stemming from the substituents surrounding the stereogenic center. On the other hand, in the case of conjugates formed between monoamines **4a** and carrier **6** (Scheme 1), the rigid amide bond gave rise to a major conformer, so that signs of the CD couplets could be correlated with the absolute configurations.<sup>3</sup> Obviously this is not the case with conjugates formed between alcohols and the three carriers **6**, **9**, and **10**. The more flexible ester bonds do not impart sufficient conformational rigidity; hence overlapping CD couplets arising from multiple conformers render the interpretations difficult or impossible.

## Results and Discussion

**Selection of Carrier 1 (Figure 1).** The search for a different type of carrier molecule has highlighted some important attributes to be considered. First, it should be an achiral molecule containing two amino nitrogens with sufficient Lewis basicity to bind to the tweezer zinc atoms and an additional carboxyl group to couple to alcohols or amines. Second, when linked to the substrate (monoalcohol or amine) the carrier molecule should lead to a bidentate conjugate where the stereogenic center is in close proximity to the nitrogen of the secondary amine, which upon coordination to zinc adopts a chirality controlled by the



**Figure 4.** CD spectra of conjugates **1-25**, **1a-25**, and **1b-25** prepared from (+)-isomenthol **25** and carriers **1**, **1a**, and **1b** (Figure 1) with varying chain lengths, in methylcyclohexane, respectively; carrier **1** gives the highest amplitude.

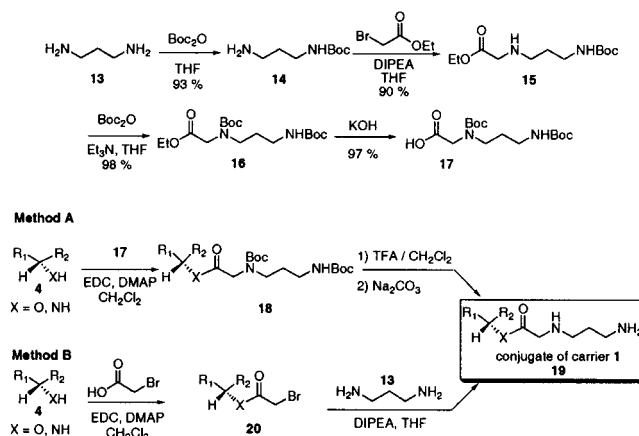
absolute configuration of the stereogenic center in the substrate. It was also expected that if the carrier molecule contains a flexible diaminoalkyl chain, this would allow the conjugate to be sandwiched between the host tweezer without noticeable conformational distortion in the substrate. Moreover, an optimal fit between the pentanediol bridge and the two porphyrin rings in tweezer **2** should yield intense CD amplitudes.<sup>27</sup> The CD amplitude is taken as the difference in  $\Delta\epsilon$  of the split extrema; the sign is defined positive when the first Cotton effect (longer wavelength) is positive and vice versa (see Table 1).

Such considerations led to the design of (3-aminopropyl-amino)acetic acid (**1**), (2-aminoethylamino)acetic acid (**1a**), and (4-aminobutylamino)acetic acid (**1b**) carrier molecules (Figure 1). The conjugates of (1*S*,2*R*,5*R*)-(+)-isomenthol (**25**, Table 1) with these three carriers, **1-25**, **1a-25**, and **1b-25**, were prepared and their CD spectra were measured after complexation to tweezer **2** (Figure 4). While all three complexes gave desired bisignate curves, that of conjugate **1-25** provided the highest amplitude (+159). The addition or removal of a methylene group in **1**, as in **1a-25** and **1b-25**, resulted in smaller CD amplitudes, +36 and +38, respectively, demonstrating that the trimethylene chain in **1** represents the optimal distance between the two nitrogens complexing with the zinc atoms of tweezer **2**.

#### Conjugate Synthesis and Complexation with Tweezer **2**.

The formation of a bidentate conjugate between carrier **1** and a chiral monoalcohol or monoamine prior to complexation with the zinc porphyrin tweezer **2** was performed by two independent routes (Scheme 3). Method A involved the use of the diBoc protected carrier molecule **17**, which was synthesized from 1,3-diaminopropane (**13**) in four steps, via intermediates **14**, **15**, and **16** in 85% overall yield. Chiral secondary monoalcohols or primary monoamines **4** were then directly linked to the diBoc protected carrier molecule **17** in the presence of 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide (EDC) and 4-(dimethylamino)pyridine (DMAP). This was followed by removal of the Boc protecting groups with 20% TFA in dichloromethane to afford the TFA salt of conjugate **19**. The latter was converted to its free amine with  $\text{Na}_2\text{CO}_3$  before complexation to tweezer **2**. In method B, conjugate **19** was prepared in two steps with

#### Scheme 3. Synthesis of diBoc Protected Carrier Molecule **17**<sup>a</sup>



<sup>a</sup> Methods A and B: Derivatization of chiral alcohols/amines with (3-aminopropylamino)acetic acid.

no protecting groups to yield the product as the free amine, ready for complexation with the porphyrin tweezer. The chiral alcohol or amine **4** is first reacted with bromoacetic acid in the presence of EDC/DMAP, and then the resultant bromoester **20** is treated with an excess of 1,3-diaminopropane (**13**) to afford the free amine of conjugate **19**.

While method A gives conjugates in excellent yields and is applicable to most chiral alcohols, it is not suited for some benzylic alcohols where deprotection by TFA can also cleave the ester bond. Method B is thus preferred for benzylic monoalcohols. In the case of chiral amines, both methods can be used to yield amine conjugates in quantitative yields. Thirty equivalents of the resulting monoalcohol or monoamine conjugate was added to ca. 1  $\mu\text{M}$  solution of porphyrin tweezer **2** and UV/CD were measured in dichloromethane and methylcyclohexane. It was feasible to form the conjugate with as little as 50  $\mu\text{g}$  of chiral substrate followed by the use of a pipet column for purification prior to UV/CD measurements (see Experimental Section).

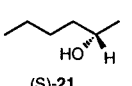
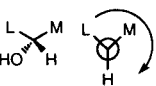
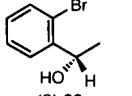
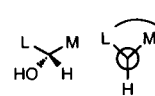
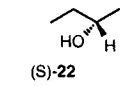
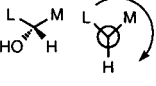
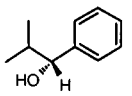
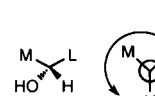
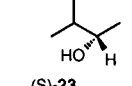
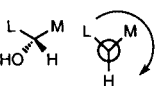
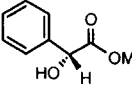
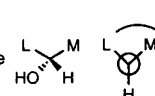
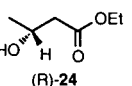
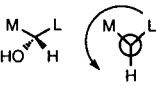
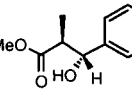
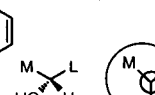
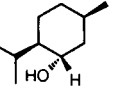
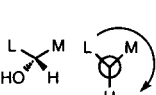
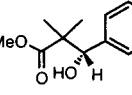
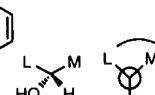
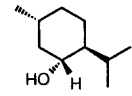
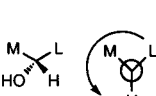
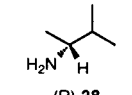
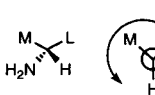
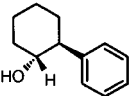
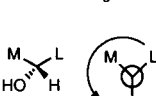
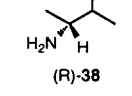
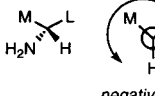
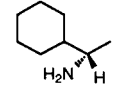
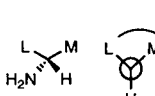
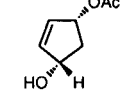
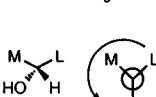
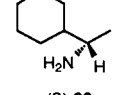
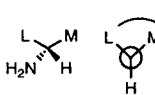
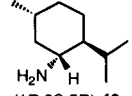
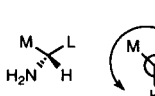
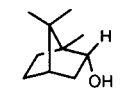
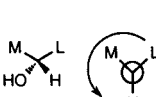
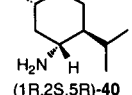
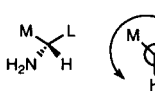
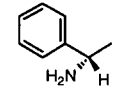
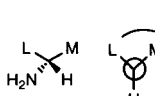
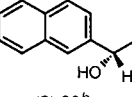
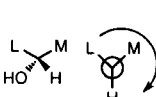
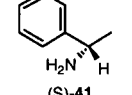
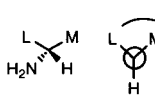
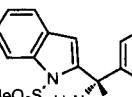
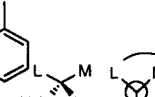
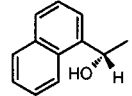
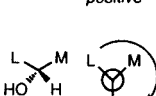
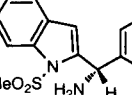
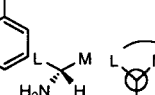
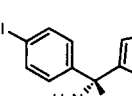
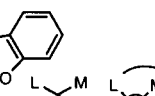
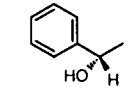
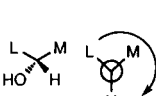
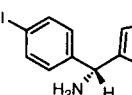
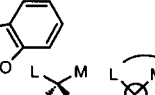
**Helicity of the Bisporphyrin Complex.** Figure 5 depicts conjugate **1-30** and its CD spectrum with porphyrin tweezer **2** in methylcyclohexane. In this conjugate, the methine hydrogen of the ester is syn coplanar with the carbonyl oxygen (see also Figure 2, complex **3**)<sup>17,28</sup> and this in turn defines the orientation of the naphthyl and methyl groups. It was found that the addition of conjugate **1-30** to achiral porphyrin tweezer **2** leads to the formation of a 1:1 host-guest tweezer complex (see the following paper) via coordination of amine nitrogens in **1-30** to the zinc atoms of porphyrins P-1 and P-2 in tweezer **2**.<sup>29</sup> The zinc in porphyrin P-1 coordinates with the terminal primary amino group. The P-2, however, approaches the secondary amino group from the side of the less bulky group (M) (see also Figure 2) giving rise to a stable configuration of the nitrogen, which is governed by the chirality of the stereogenic center in the substrate. This stereoselection leads to the most stable conformer **I** (Figure 5) in which the “less bulky group” (M) at the stereogenic center is sandwiched between P-1 and P-2 while the “bulkier group” (L) is pointing out and away from the P-2 porphyrin ring (Figure 2). In this preferred conformation

(27) (a) Hayashi, T.; Nonoguchi, M.; Arya, T.; Ogoshi, H. *Tetrahedron Lett.* **1997**, *38*, 1603–1606. (b) Schneider, H.-J.; Wang, M. *J. Org. Chem.* **1994**, *59*, 7464–7472. (c) Crossley, M. J.; Mackay, L. G.; Try, A. C. *J. Chem. Soc., Chem. Commun.* **1995**, 1925–1927.

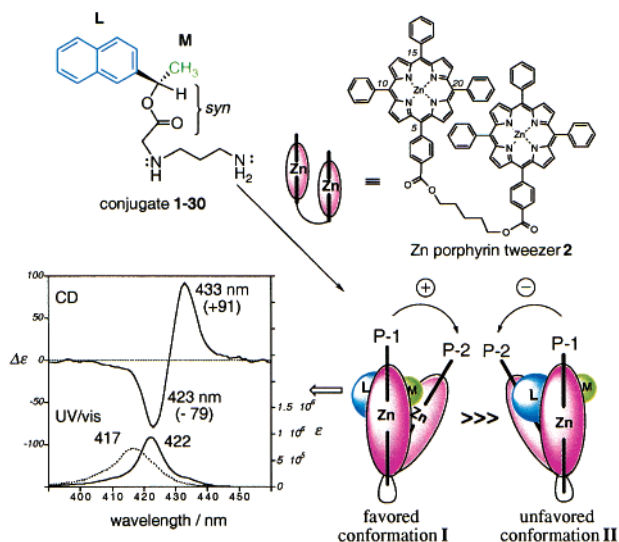
(28) Jeffrey, G. A.; Sundaralingam, M. In *Advances in Carbohydrate Chemistry and Biochemistry*; Tipson, R. S., Horton, D., Eds.; Academic Press: Orlando, FL, 1985; Vol. 43, pp 204–272.

(29) In Tweezer **2**, P-1 and P-2 are indistinguishable; however, in the complex of **2** and conjugate **1-30**, P-1 refers to the porphyrin close to the terminal amine, and P-2 refers to the porphyrin close to the secondary amine.

**Table 1.** Structures and Schematic Representations of Chiral Substrates (alcohols and amines) and CD Data of Their Conjugates with Carrier **1** after Complexation with Tweezer **2**<sup>a</sup>

chiral substrate	CD Couplet predicted	method solvent	$\lambda / \Delta\epsilon$	$A_{CD}$ amplitude observed	chiral substrate	CD Couplet predicted	method solvent	$\lambda / \Delta\epsilon$	$A_{CD}$ amplitude observed
<b>Alcohols</b>									
		A	MCH 435 nm +20 423 nm -20	+40			B	MCH 432 nm +68 422 nm -59	+127
(S)-21	positive		CH <sub>2</sub> Cl <sub>2</sub> 435 nm +13 424 nm -15	+28	(S)-33	positive		CH <sub>2</sub> Cl <sub>2</sub> 434 nm +60 423 nm -49	+109
		A	MCH 427 nm +10 416 nm -3	+13			B	MCH 434 nm -67 423 nm +68	-135
(S)-22	positive		CH <sub>2</sub> Cl <sub>2</sub> no distinctive CD		(R)-34	negative		CH <sub>2</sub> Cl <sub>2</sub> 435 nm -36 424 nm +16	-52
		A	MCH 432 nm +25 421 nm -26	+51			A	MCH 432 nm +42 422 nm -30	+72
(S)-23	positive		CH <sub>2</sub> Cl <sub>2</sub> no distinctive CD		(R)-35	positive		CH <sub>2</sub> Cl <sub>2</sub> 435 nm +38 422 nm -27	+65
		A	MCH 432 nm -27 421 nm +23	-50			A	MCH 433 nm -60 422 nm +61	-121
(R)-24	negative		CH <sub>2</sub> Cl <sub>2</sub> 433 nm -22 421 nm +21	-43	(2S,3R)-36	negative		CH <sub>2</sub> Cl <sub>2</sub> 434 nm -18 423 nm +29	-47
		B	MCH 432 nm +86 422 nm -73	+159			A	MCH 432 nm +17 423 nm -2	+19
(1S,2R,5R)-25	positive		CH <sub>2</sub> Cl <sub>2</sub> 435 nm +4 419 nm -23	+84	(S)-37	positive		CH <sub>2</sub> Cl <sub>2</sub> 435 nm -15 424 nm +15	-30
		B	MCH 432 nm -270 422 nm +224	-494	<b>Amines</b>				
(1R,2S,5R)-26	negative		CH <sub>2</sub> Cl <sub>2</sub> 433 nm -164 423 nm +142	-306			A	MCH 433 nm -42 422 nm +38	-80
		B	MCH 435 nm -188 424 nm +156	-344			A	CH <sub>2</sub> Cl <sub>2</sub> 435 nm -25 423 nm +34	-59
(1R,2S)-27	negative		CH <sub>2</sub> Cl <sub>2</sub> 436 nm -179 425 nm +170	-349			B	MCH 434 nm +158 423 nm -124	+282
		A	MCH 428 nm -6 421 nm +6	-12			B	CH <sub>2</sub> Cl <sub>2</sub> 435 nm +104 424 nm -78	+182
(1R,3S)-28	negative		CH <sub>2</sub> Cl <sub>2</sub> 434 nm -13 423 nm +13	-26			B	MCH 434 nm -224 424 nm +195	-419
		B	MCH 432 nm -11 421 nm +20	-31			B	CH <sub>2</sub> Cl <sub>2</sub> 435 nm -139 425 nm +129	-268
(1S,2R,4S)-29	negative		CH <sub>2</sub> Cl <sub>2</sub> no distinctive CD				B	MCH 434 nm +130 424 nm -110	+240
		B	MCH 433 nm +91 423 nm -79	+170			B	CH <sub>2</sub> Cl <sub>2</sub> 435 nm +78 423 nm -62	+140
(S)-30 <sup>b</sup>	positive		CH <sub>2</sub> Cl <sub>2</sub> 434 nm +63 424 nm -59	+122			A	MCH 430 nm +43 420 nm -39	+82
		B	MCH 435 nm +98 424 nm -84	+182			A	CH <sub>2</sub> Cl <sub>2</sub> 433 nm +30 422 nm -26	+56
(S)-31	positive		CH <sub>2</sub> Cl <sub>2</sub> 436 nm +85 425 nm -66	+151			A	MCH 428 nm +31 418 nm -20	+51
		B	MCH 433 nm +83 423 nm -84	+167			A	CH <sub>2</sub> Cl <sub>2</sub> 430 nm +22 420 nm -18	+40
(S)-32	positive		CH <sub>2</sub> Cl <sub>2</sub> 435 nm +66 424 nm -59	+125	(R)-43	positive			

<sup>a</sup> The predicted CD couplet is based on relative steric sizes or conformational A values of substituents. For synthetic Methods A and B see Scheme 3. <sup>b</sup> Enantiomer of (S)-30 exhibited an enantiomeric CD spectrum.

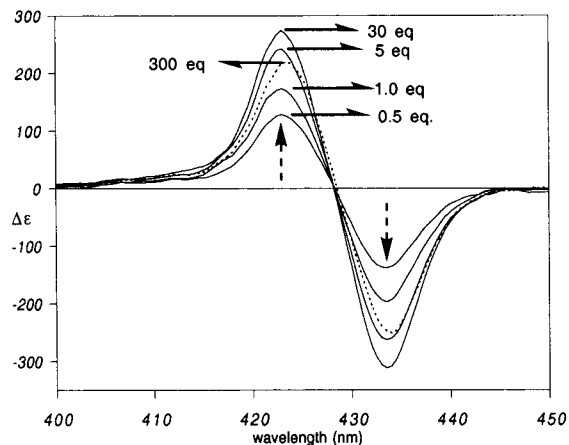


**Figure 5.** Complex formation between conjugate **1-30** and tweezer **2** leads to two conceivable conformations with opposite sense of twists. The predominant conformation **I**, the one in which the L (larger) group is protruding away from the P-1/P-2 sandwich, gives rise to a typical CD couplet representing the sense of twist between the two porphyrins and hence the absolute configuration at the stereogenic center; the dashed curve in the UV represents tweezer **2** prior to complexation. Spectra were measured in methylcyclohexane.

**I**, supported by NMR ROESY and anisotropic porphyrin ring current effects on M and L groups (following paper), porphyrins P-1 and P-2 adopt a predicted positive helicity resulting from the clockwise arrangement of their effective electric transition moments which run alongside the C-5–C-15 axis<sup>25</sup> of the zinc tetraphenylporphyrin (Figure 2). Thus the overriding positive twist between the transition moments in conformer **I** leads to a positive CD couplet, which is in full agreement with the observed positive CD couplet with  $A_{CD} = +170$ .

While measurements of CD spectra of conjugate **1-30** after complexation in dichloromethane, hexane, chloroform, acetonitrile, and toluene resulted in varying amplitudes, they all gave the same CD sign, i.e., a positive exciton couplet. Since hexane, methylcyclohexane, and dichloromethane gave the highest amplitudes, all other tweezer complexes were measured in these solvents. The CD data were generally recorded in 1  $\mu$ M solutions of tweezer **2** with 30 equiv of the conjugates. A titration of tweezer **2** with 0.5 to 300 equiv of conjugate **1-26** is shown in Figure 6. A substantial increase in the CD amplitude is observed up to 5 equiv of the conjugate, the slight increase being continued up to 30 equiv (Figure 6); half of the maximal amplitude was attained even with 0.5 equiv of conjugate **1-26**. Above 40 equiv, the CD amplitude gradually decreases most likely due to the formation of a 1:2 host–guest complex in which the chiral twisted conformation of the tweezer is disrupted.<sup>3</sup>

**Analysis of Representative Chiral Substrates.** The CD data for monoalcohols and monoamines with previously established absolute configurations, in both methylcyclohexane and dichloromethane, are given in Tables 1 and 2. The schematic representations depict the substituents attached to the stereogenic center that leads to the prediction of the CD couplet sign. If the hydroxyl or amino group is placed in the rear, as shown, the clockwise arrangement of L, M, and hydrogen results in a positive CD couplet, and vice versa. The absolute sense of twist between the porphyrin electric transition moments and hence the sign of the exciton-coupled CD is dependent on whether



**Figure 6.** CD titration curves of porphyrin tweezer **2** with 0.5–300 equiv of conjugate **1-26** in hexane.

the P-2 porphyrin of tweezer **2** coordinates to the secondary amine nitrogen from the direction of the M or the L group (Figures 2 and 5). The preferred conformer determines the sign of the CD couplet and hence the observed CD exciton chirality reveals the absolute configuration of the substrate.

The assignment of M and L to substituents at the stereogenic center is thus critical for predicting the sign of the CD couplet. The sign and intensity of the CD couplet depend on the degree of stereoselection between the conformers with opposing porphyrin helicity (Figure 5). While steric considerations play an important role in conformational analysis, it should be emphasized that factors other than steric bulk, such as electronic interactions, hydrogen bonding, and rotational degrees of freedom, cannot be ignored. The conformer that predominates is a result of these interrelated factors that often sway in opposite directions. We therefore performed a systematic study of the factors that may be encountered and their effects on the predominant conformation aided by Molecular Modeling calculations.<sup>30</sup> To clarify the concept and applicability of the method, the chiral substrates investigated were classified into two general categories: namely, L/M assignments based on the relative steric bulk of substituents derived from *A* values (Table 1) and L/M assignments based on the overriding electronic factors studied by molecular modeling (Table 2).

**A. L/M Based on Relative Steric Bulk.** In chiral alcohols **21** to **37** and chiral amines **38** to **43** presented in Table 1, the hydroxyl and amino functions are attached to stereogenic centers carrying aliphatic and/or aromatic substituents. In such substrates, the L and M substituents can be distinguished on the basis of conformational energy differences for the cyclohexane model, or so-called *A* values (kcal/mol) defined by Winstein and Holness,<sup>31</sup> and later described by Elie<sup>32</sup> and Bushweller,<sup>33</sup> and more recently by Lightner.<sup>34</sup> Even in cases where the difference between the two R groups is subtle, such as in alcohol **22** where R groups are methyl (*A* value of 1.74) and ethyl (*A* value of 1.79), the tweezer **2** complex of conjugate **1-22** reflects

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**Table 2.** Structures and Schematic Representations of Chiral Substrates (alcohols and amines) and CD Data of Their Conjugates with Carrier **1** after Complexation with Tweezer **2**<sup>a</sup>

chiral substrate	CD Couplet predicted	method	solvent	$\lambda / \Delta\epsilon$	$A_{CD}$ amplitude observed	chiral substrate	CD Couplet predicted	method	solvent	$\lambda / \Delta\epsilon$	$A_{CD}$ amplitude observed
<b>Alcohols</b>						<b>Amines</b>					
		B	MCH	432 nm +19 423 nm -25	+44			B	MCH	435 nm -80 424 nm +62	-142
			CH <sub>2</sub> Cl <sub>2</sub>	435 nm +20 425 nm -12	+32				CH <sub>2</sub> Cl <sub>2</sub>	434 nm -35 424 nm +25	-60
		B	MCH	435 nm -61 425 nm +51	-112			B	MCH	436 nm +59 426 nm -28	+87
			CH <sub>2</sub> Cl <sub>2</sub>	436 nm -51 427 nm +56	-117				CH <sub>2</sub> Cl <sub>2</sub>	436 nm +28 423 nm -21	+49
		A	MCH	432 nm +85 422 nm -76	+161			A	MCH	434 nm -77 423 nm +59	-136
			CH <sub>2</sub> Cl <sub>2</sub>	434 nm +44 422 nm -26	+70				CH <sub>2</sub> Cl <sub>2</sub>	434 nm -22 424 nm +20	-42
		A	MCH	433 nm +99 421 nm -90	+189			A	MCH	432 nm -23 422 nm +11	-34
			CH <sub>2</sub> Cl <sub>2</sub>	434 nm +60 424 nm -34	+94				CH <sub>2</sub> Cl <sub>2</sub>	434 nm -14 427 nm +10	-24
		A	MCH	434 nm +45 422 nm -42	+87			A	MCH	431 nm -50 421 nm +54	-104
			CH <sub>2</sub> Cl <sub>2</sub>	435 nm +26 424 nm -23	+49				CH <sub>2</sub> Cl <sub>2</sub>	433 nm -7 424 nm +10	-17
		A	MCH	435 nm -60 422 nm +35	-95						
			CH <sub>2</sub> Cl <sub>2</sub>	no distinctive CD							

† The actual CD measurement was carried out with the (S)-50 enantiomer and the data for (R)-50, derived from its enantiomer, is only shown since it was used in molecular modeling for comparison purposes with the alcohol analog (R)-44.

L\* and M\* refer to apparent relative sizes, large and medium respectively, imposed by electronic factors.

<sup>a</sup> The predicted CD couplet is based on electronic factors, i.e., mainly H-bonding and lone pair electron repulsion, which exerts an apparent large and medium effect on the substituent. For synthetic Methods A and B see Scheme 3.

this difference in accordance with *A* values. Replacement of the ethyl with an isopropyl, as in **23**, or a pentyl group, as in **21**, consistently resulted in an enhanced stereodifferentiation and hence larger CD amplitudes of the same sign. In **1-24** the sign of the CD couplet is opposite in agreement with the *M* and *L* sequence.

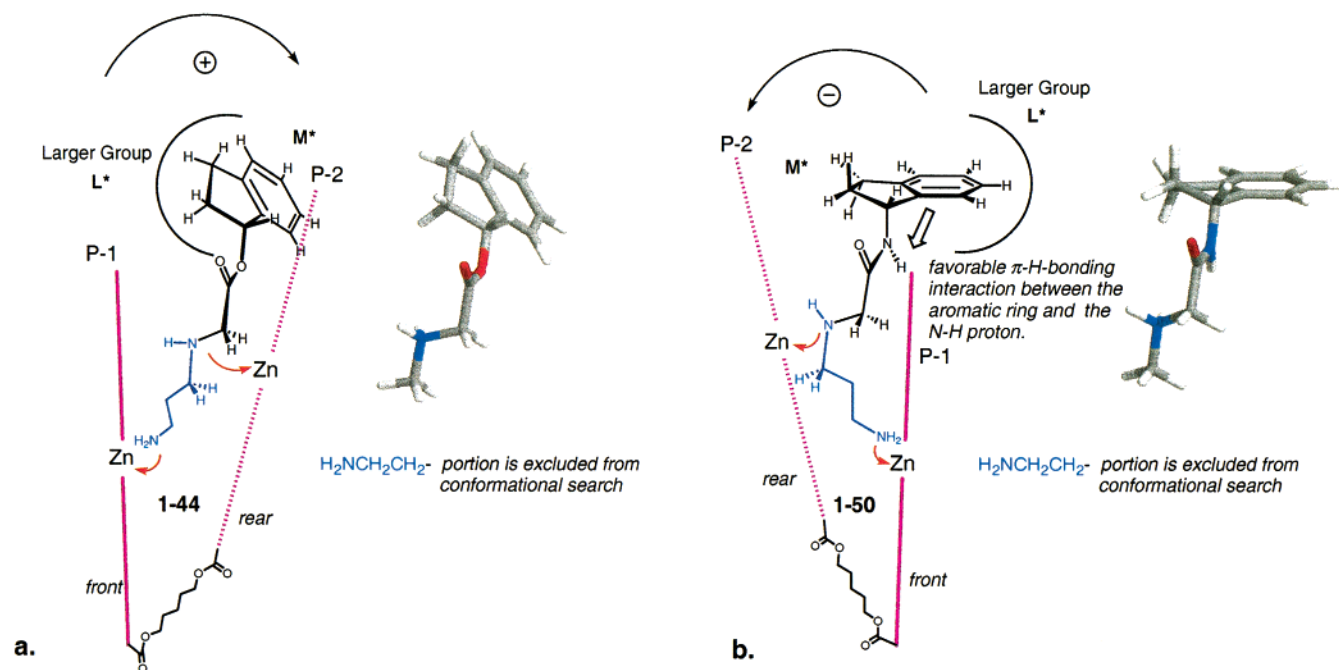
Monoalcohols with multiple stereogenic centers (**25-29**) also showed CD signs consistent with the absolute configuration of the carbon bearing the hydroxyl group. In diastereomers isomenthol **25** and menthol **26** with CD couplets of opposite signs, the substantially smaller amplitude of isomenthol **25** derives from the axial orientation of the C-5 methyl group which adds to the bulk of the *M* side, resulting in decreased stereorecognition. The conjugates **1-26** and **1-27** gave intense CD couplets where the porphyrin host had to differentiate between the isopropyl (*A* value of 2.21) vs hydrogen, in **1-26**, and the phenyl (*A* value of 2.8) vs hydrogen, in **1-27**, flanking the secondary OH group. In alcohol **28**, a saturated methylene at the  $\alpha$  position and an acetoxyl group at the  $\beta$  position are larger than the double bond. In alcohol **29**, a quaternary carbon is assigned *L* while the methylene is assigned *M*.

Due to the red-shifted Soret band of tweezer **2** at ca. 420 nm, this method is also applicable to substrates which inherently contain a chromophore, e.g. a phenyl or a naphthyl, that absorb below 300 nm, thus interference of such shorter wavelength transitions with the porphyrin is excluded. In benzylic alcohols (**30-37**) the aromatic rings are assigned *L* in accordance with

the conformational energy *A* values. The CD amplitudes in **31**, **32**, and **34** also reflect the bulk of the aromatic group. Alcohol **36** is, in a sense, comparable to alcohol **34** with a carbomethoxyl in place of a methyl and hence results in an identical sign with comparable amplitude. However, the introduction of an additional  $\alpha$ -methyl group, as in alcohol **37**, results in two groups of comparable steric size and the tweezer complex gives opposite signs in methylocyclohexane and dichloromethane; thus alcohol **37** clearly represents a borderline case.

The tweezer **2** complexes of the conjugates prepared from amines **38** to **43** with carrier **1** gave exciton-coupled CD with identical signs and comparable amplitudes to the ones measured as conjugates of carrier **6** (Scheme 1).<sup>3</sup> Amines **38** to **40** are analogous to alcohols **21** to **26** in which the substituents are simply aliphatic groups, and hence follow the same trend in *M* and *L* assignments. The opposite configuration of amines **38** and **39** is reflected in their opposite CD signs, while the amplitudes reflect the size difference between isopropyl and cyclohexyl groups. The CD couplet sign of menthylamine **40** is the same as its alcohol analogue **26**, and the amplitudes are also comparable. Amine **41** is comparable to its alcohol analogue **32**, possessing an identical CD sign but a larger amplitude, most likely due to the increased rigidity of the amide in its conjugate compared to the ester in the alcohol conjugate of **32**. In amine **43** the *p*-chlorophenyl group is larger than the benzofuran ring.

Thus for aliphatic/benzylic alcohols and amines, the steric bulk of the *M* and *L* groups, predictable based on cyclohexane



**Figure 7.** (a) The complex formed from tweezer **2** and conjugate **1-44**. The stick model represents the optimal conformation (obtained from an MM2 Monte Carlo conformational search) of partial conjugate **1-44** lacking the  $\text{H}_2\text{NCH}_2\text{CH}_2-$  tail before complexation with tweezer **2**; the coplanarity of the phenyl and carbonyl groups leads to the  $\text{M}^*$  assignment for the phenyl ring. (b) The complex formed from tweezer **2** and conjugate (*R*)-**1-50**. The stick model represents the optimal conformation of partial conjugate **1-50** (without the  $\text{H}_2\text{NCH}_2\text{CH}_2-$  tail) before complexation with tweezer **2**; due to the  $\pi$ -H-bonding between the amide N-H hydrogen and the aromatic ring, the phenyl adopts a conformation perpendicular to the carbonyl group, thus making it  $\text{L}^*$ .

conformational  $A$  values,<sup>32,33</sup> appears to be the main factor in determining their recognition and hence the predicted CD couplet.

**B. L/M Based on Electronic Factors.** The chiral alcohols **44** to **49** and chiral amines **50** to **54** presented in Table 2 represent cases in which electronic factors override the effect of relative steric bulk. Unlike alcohols, the conjugates of amines contain an amide NH capable of H-bonding, and when such bonds are present, this could lead to opposite L/M assignments for alcohols and amines as shown in Table 2. The L and M assignments in these cases do not directly reflect the steric bulk, i.e., cannot be derived from conformational  $A$  values, but instead refer to substituents that behave as if they are larger (or smaller) due their electronic effect on the overall conformation. Therefore we employ the use of an asterisk as in  $\text{M}^*$  and  $\text{L}^*$ , where  $\text{M}^*$  refers to the group that is pointing toward P-2, while  $\text{L}^*$  refers to the group that is pointing away from P-2, due to factors other than steric bulk.

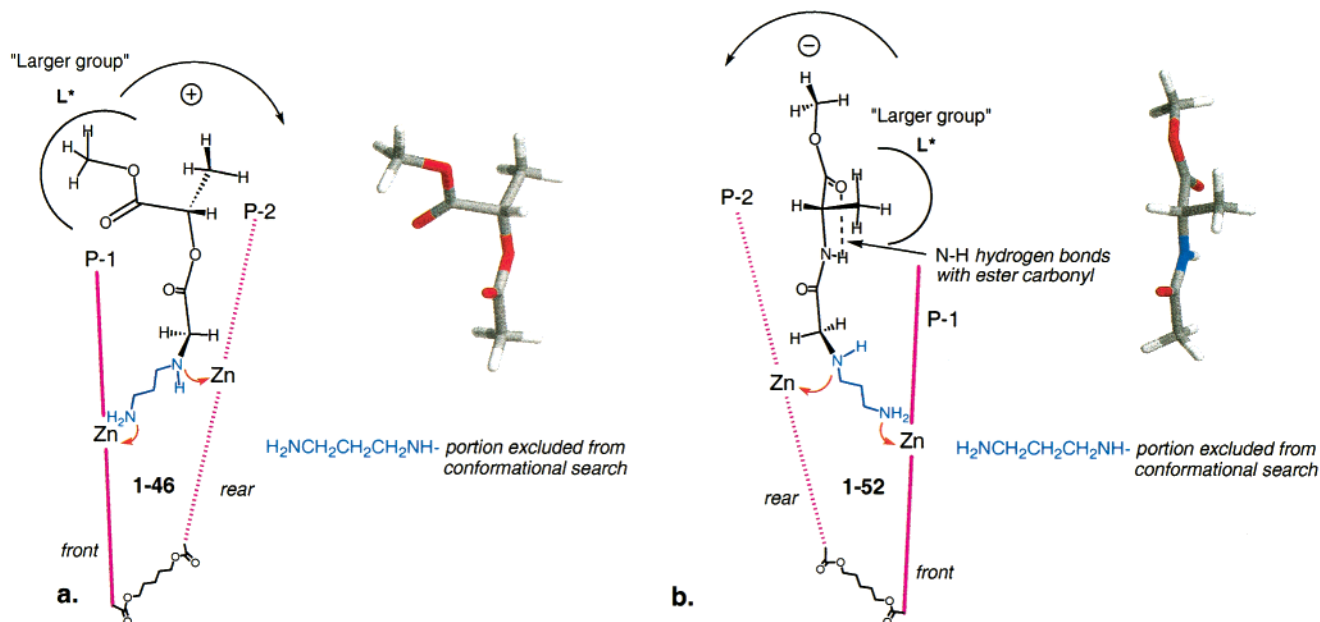
In contrast to alcohol **32** and amine **41**, in bicyclic benzylic alcohols **44/45** and amines **50/51**, the  $A$  values of substituents do not reflect their actual steric bulk because rotation of the phenyl moiety is restricted. The overall steric demand of such substituents was clarified through molecular modeling of the conjugate prior to complexation. An MM2 Monte Carlo conformational search on MacroModel<sup>30</sup> 7.0 was performed with a "partial" conjugate **1-44** lacking the flexible  $\text{CH}_2\text{CH}_2\text{NH}_2$  chain (Figure 7). The truncated conjugate was used to reduce the number of potential conformers to those of interest, mainly focusing on the orientation of the carrier's carbonyl with respect to the methine proton. The most stable conformation of partial conjugate **1-44** is shown in Figure 7a. It is clear that the phenyl ring is almost in the plane of the carrier carbonyl and hence has less steric demand on P-2. In this case, the ester group adopts a conformation in which the projection angle between the

carrier's carbonyl and the benzylic methine proton, which in other cases is usually *syn*-coplanar, is found to be  $+51^\circ$ . The other conformers obtained from the conformational search that predominantly gave structures with phenyl protruding from the side were at least 0.63 kcal/mol higher in energy. This corresponds to a stereodifferentiation of the preferred conformer by a factor of 3:1 (data not shown). Therefore in **44** and **45** the methylenes flanking the stereogenic center have a *larger apparent size*, hence  $\text{L}^*$ , compared to the phenyl moiety which lies more or less parallel to P-2. The introduction of a methylene group into the aliphatic ring in **44**, i.e. **45**, results in a larger CD amplitude as the aliphatic ring size is further increased.

In the amine analogues of **44** and **45**, i.e., **50** and **51**, the presence of N-H, a hydrogen bond donor, favors a conformation where the substituents adopt an orientation leading to different  $\text{M}^*/\text{L}^*$  assignments. An MM2 Monte Carlo conformational search of the partial conjugate **1-50** (lacking  $\text{CH}_2\text{CH}_2\text{NH}_2$ ) revealed that in its most stable conformer, the N-H proton of the amide is partially overlapping with the aromatic ring, probably due to  $\pi$ -hydrogen bonding (Figure 7b). This type of hydrogen bonding has been observed in other similar cases<sup>35</sup> where the hydrogen bond donor is also two atoms away from the aromatic moiety. The optimal projection angle between the carrier's carbonyl and the benzylic methine proton was calculated to be  $+29^\circ$  (see Figure 7b). This angle difference ( $+51^\circ$  in analogue **44**), along with the difference in the conformation of the cyclopentene ring, renders the phenyl group to protrude to the side almost perpendicular to the carrier's carbonyl; this is contrary to analogue **44** (Figure 7a). Thus the P-2 porphyrin

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**Figure 8.** (a) The complex formed from tweezer **2** and conjugate **1-46**. The stick model represents the optimal conformation (obtained from an AMBER Monte Carlo conformational search) of partial conjugate **1-46** lacking the  $\text{H}_2\text{NCH}_2\text{CH}_2\text{CH}_2\text{NH}$ - tail before complexation with tweezer **2**; the protruding methyl ester group is assigned  $\text{L}^*$ . (b) The complex formed from tweezer **2** and conjugate **1-52**. The stick model represents the optimal conformation (obtained from an AMBER Monte Carlo conformational search) of partial conjugate **1-52** lacking the  $\text{H}_2\text{NCH}_2\text{CH}_2\text{CH}_2\text{NH}$ - tail before complexation with tweezer **2**; due to the hydrogen bonding between the amide  $\text{N-H}$  and the ester carbonyl, the ester becomes the  $\text{M}^*$  group in this case.

ring avoids approaching from the phenyl side, hence the  $\text{L}^*$  assignment. This is also supported by the fact that an additional methylene group in **51** increases the steric demand of  $\text{M}^*$ , hence diminishing the stereodifferentiation, thus resulting in a smaller CD amplitude. It should be noted that this change from the five-membered-ring **50** to the six-membered-ring **51** causes, as expected, an opposite trend in the CD amplitude as compared to the alcohol analogues **44** and **45**. The conformer in which the  $\text{N-H}$  proton is not interacting with the aromatic ring was found to be 3.1 kcal/mol higher in energy (data not shown).

The remaining chiral alcohols **46** to **49** and amines **52** and **54** (except for **53**) all contain one aliphatic substituent and one ester group that can behave as an H-bond acceptor. Surprisingly, experimental results show that in alcohols it is the ester function that is the  $\text{L}^*$  group, whereas in amines the ester function is the  $\text{M}^*$  group (Table 2). Amine **53** has a methoxyl group that is also an H-bond acceptor and hence is treated as an ester group. The effect of the H-bond in the amine cases was studied by molecular modeling to evaluate its effective relative steric demand (Figure 8). The alcohols (which are esters in their conjugates with carrier **1**) lacking such H-bonding properties were also modeled for comparison purposes. The truncated conjugate of **1-46** (lacking the  $\text{NHCH}_2\text{CH}_2\text{CH}_2\text{NH}_2$  chain) was modeled via a Monte Carlo conformational search in the solvent  $\text{CHCl}_3$  using the AMBER force field. This resulted in a preferred conformation that would lead to positive porphyrin helicity upon complex formation with tweezer **2**. Namely in the conformer shown in Figure 8a, the aliphatic methyl group is in the plane of the carrier carbonyl and with a carbonyl–methine projection angle of  $+46^\circ$ . This leaves the ester group protruding from the side (hence  $\text{L}^*$ ). This conformational result was also supported by X-ray crystallographic data of similar esters.<sup>36</sup> Alternate

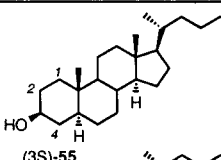
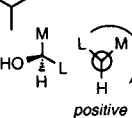
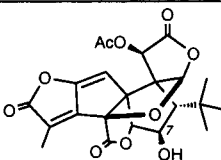
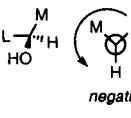
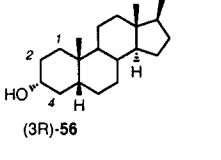
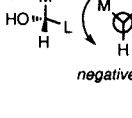
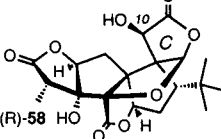
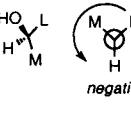
conformers (not shown) that would have resulted in negative porphyrin helicity were at least 2.4 kcal/mol higher in energy. Another contributing electronic factor that needs to be considered is the potential electronic repulsion that may take place between the partially negative ester carbonyl oxygen and the  $\pi$ -electrons of the P-2 porphyrin ring. This favors the orientation in which the ester/lactone groups are pointing away from the P-2 porphyrin ring. In all four cases **46** to **49**, the P-2 porphyrin ring avoids approach from the side of the ester. Therefore in alcohol cases **46** and **47**, where one of the substituents is an ester and the other one is a methyl or isopropyl, the former will have the effect of the “larger” group pointing away from P-2, and hence is given the assignment  $\text{L}^*$ . Lactones **48** and **49** also follow the same trend, with P-2 avoiding complexation from the side of the ester group.

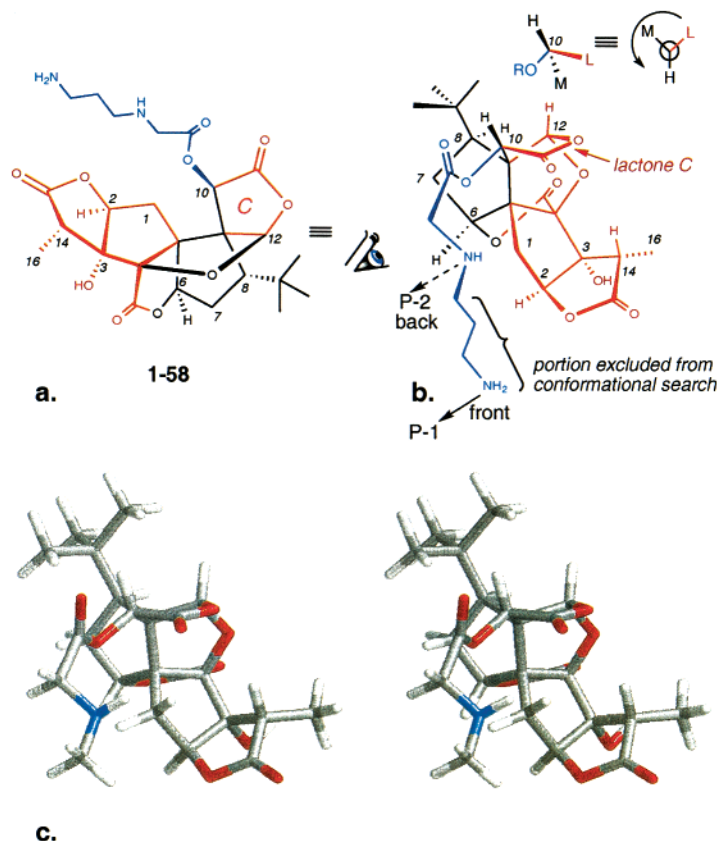
In the amine substrates **52** to **54**, the amide  $\text{N-H}$  proton engages in H-bonding to the methoxyl oxygen in **53** and to the ester carbonyl oxygen in **52** and **54**, as shown for **52** in Figure 8b. This type of H-bonding has been well studied and encountered in X-ray crystallographic<sup>37</sup> data of similar compounds. This was also confirmed by molecular modeling calculations using the AMBER force field and the Monte Carlo conformational search tool in solvent  $\text{CHCl}_3$ . In the most stable conformer of partial conjugate **1-52** (lacking the  $\text{NHCH}_2\text{CH}_2\text{CH}_2\text{NH}_2$ ), the carbonyl of the ester group, the amide  $\text{N-H}$  proton, and the carbonyl of the amide are all coplanar due to the hydrogen bond between  $\text{N-H}$  and the ester carbonyl (Figure 8b). The projection angle between the carrier amide carbonyl and methine hydrogen was  $-43^\circ$ . This orients the ester group (or the methoxyl in **53**) into the plane of the amide carbonyl which ultimately makes the aliphatic chain protrude to the side (hence  $\text{L}^*$ ). The alternate conformer in which the ester carbonyl

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**Table 3.** Structures and Schematic Representations of Some Chiral Natural Products and CD Data of Their Conjugates with Carrier **1** after Complexation with Tweezer **2**

chiral substrate	CD Couplet predicted	solvent	$\lambda / \Delta\epsilon$	$A_{CD}$ amplitude observed	chiral substrate	CD Couplet predicted	solvent	$\lambda / \Delta\epsilon$	$A_{CD}$ amplitude observed
 (3S)-55	 positive	hexane	433 nm +21 423 nm -14	+35	 (R)-57	 negative	MCH	no CD was obtained	
		CH <sub>2</sub> Cl <sub>2</sub>	433 nm +9 425 nm -8	+17			CH <sub>2</sub> Cl <sub>2</sub>	434 nm -35 424 nm +37	-72
 (3R)-56	 negative	MCH	433 nm -46 424 nm +39	-85	 (R)-58	 negative	MCH	433 nm -28 422 nm +22	-50
		CH <sub>2</sub> Cl <sub>2</sub>	435 nm -18 424 nm +33	-51			CH <sub>2</sub> Cl <sub>2</sub>	435 nm -26 423 nm +25	-51

**Figure 9.** (a) Conventional representation of ginkgolide A **58** conjugate with carrier **1**. (b) The same structure presented in Figure 9a oriented in a fashion to overlap with the stereo stick models in part c and to divide the cage molecule into two halves along the 10-oxygen function and 10-H. The larger and smaller halves are shown in red (L) and black (M), respectively. (c) Stereoview of the optimal conformation of partial conjugate **1-58** (lacking the H<sub>2</sub>NCH<sub>2</sub>CH<sub>2</sub>- tail) before complexation with tweezer **2** obtained from an AMBER Monte Carlo conformational search, emphasizing the orientation of the conjugate carbonyl relative to the ginkgolide cage.

and the N-H are not H-bonded and thus with the ester group protruding was 1.24 kcal/mol higher in energy. Moreover, since the N-H proton diminishes the electron density on the carbonyl via hydrogen bonding, the electronic repulsion between the ester carbonyl and P-2, observed in the conjugates of alcohols **46** to **49**, may not play a dominant role in amino compounds **52** to **54**.

It should be noted that the ester-containing substrates (Table 2) were included in the study mainly for probing the applicability of the method. However, since these substrates in fact contain two functional groups, their absolute configuration can be readily determined by the conventional exciton chirality method; i.e., after hydrolysis of the ester and lactone groups, the  $\alpha$ -hydroxy

or  $\alpha$ -amino acids can be derivatized to the corresponding porphyrins derivatives<sup>26</sup> giving rise to exciton-coupled CD.

**C. Application Extended to Complex Natural Products.** The configurational assignment protocol has been applied to more complex compounds of biological relevance, **55** to **58**, Table 3. While in all previous cases the sign of the CD couplet was dictated by the "size" of the groups next to the stereogenic center, i.e., the  $\alpha$ -position, this is not the case with cholestanols **55** and **56**. In these steroids, the alcohol function is flanked by two methylene groups at C-2 and C-4, but as C-1 is also a methylene while C-5 is at the ring juncture, the C-5 side becomes the larger group, L. Therefore in the case of **56** with the hydroxyl pointing away from the viewer, the counterclock-

wise relationship among L, M, and H predicts a negative exciton-coupled CD. In steroid **55**, however, the opposite 3-hydroxyl configuration gives the opposite sign for the exciton-coupled CD. In the caged ginkgolide molecules, dianhydroginkgolide C 10-monoacetate<sup>38</sup> **57** and ginkgolide A **58**, assignments of L and M to the moieties flanking the 7- and 10-hydroxyls, respectively, require a more thorough examination of the three-dimensional structure.

In ginkgolide **57** (Table 3), an imaginary divider along the 7-hydroxyl will show that the right-hand side, i.e., the *tert*-butyl side, is smaller in size (hence M) than the diene side (hence L). With ginkgolide A **58** (Figure 9), the case is much less obvious since the 10-OH is somehow buried in the cage of the molecule, which is more concave in nature than **57** due to the absence of the two double bonds. A Monte Carlo conformational search, using an AMBER force field, of the ginkgolide partial conjugate **1-58** (lacking CH<sub>2</sub>CH<sub>2</sub>NH<sub>2</sub>) shows that lactone C lies perpendicular to the rest of the cage and that the lactone side (also containing the rest of the molecule shown in red in Figure 9a,b) is much larger than the quaternary carbon bearing the *tert*-butyl group (see also the stereoview in Figure 9c) and hence the lactone side is assigned L. This assignment is dependent on the projection angle between the ester carbonyl and the methine proton 10-H, calculated to be  $-27^\circ$  in the most stable conformer. Therefore in conjugate **1-58**, the L assignment reflects not only the steric size of the directly attached lactone C but also the entire moiety shown in red in Figure 9b. Ginkgolides are rigid molecules and hence molecular modeling calculations give only a small number of possible conformers. All the other conformers obtained from the search that were within 2.4 kcal/mol showed similar projection angles ranging from  $-27^\circ$  to  $-35^\circ$ , and led to the same L and M assignment and hence a negative exciton-coupled CD of its tweezer **2** complex. These L and M assignments in ginkgolide conjugates **1-57** and **1-58** also corroborate those of conjugates **1-46** to **1-49**.

## Conclusion

A microscale procedure based on the CD exciton chirality method has been developed for the determination of absolute configurations of monoalcohols and primary monoamines. Conventional exciton chirality methods cannot be applied to such substrates due to the lack of required two sites for chromophoric derivatization. This new protocol takes advantage of host/guest complexation between chiral substrate and bichromophoric zinc porphyrin host as a CD reporter group. The method is applicable to alcohols and amines carrying aliphatic groups and/or aromatic groups. The substrate is derivatized with carrier **1**, the resultant conjugate complexed with tweezer **2**, and the CD spectrum is measured. A clockwise relationship of L, M, and H groups of the substrate denotes a positive CD couplet, and vice versa; the L (large) and M (medium) assignments are based on the conformational *A* values. Although there are other CD methods available for the configurational assignments of  $\alpha$ -hydroxy and  $\alpha$ -amino esters, an attempt has been made to extend this method to this class of substrates as well. This has led to further clarification of additional electronic factors that govern the L and M assignments. Furthermore, NMR analysis and molecular modeling (see succeeding paper) can lead to independent L/M assignments of substituents which is critical for interpreting the CD data and determining absolute configurations, thus extending the protocol to more complicated cases.

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## Experimental Section

Zinc porphyrin tweezer **2** is commercially available from TCI (Japan).<sup>39</sup>

**Preparation of Conjugates 19. Method A: via diBoc Reagent 17.** To a solution of secondary alcohol/primary monoamine (15  $\mu$ mol) and **17** (18.5  $\mu$ mol) in anhydrous CH<sub>2</sub>Cl<sub>2</sub> (5 mL) were added EDC (20.4  $\mu$ mol) and DMAP (0.2 equiv) with stirring for 1 h at 0 °C and overnight at room temperature. The mixture was then washed with NaHCO<sub>3</sub> and brine and dried over Na<sub>2</sub>SO<sub>4</sub>. Subsequent purification by flash chromatography afforded the diBoc protected conjugate **18**. Deprotection was carried out by dissolving **18** in CH<sub>2</sub>Cl<sub>2</sub> (2 mL) followed by the addition of TFA (0.4 mL). After being stirred at room temperature for 2 h, the solution was evaporated and dried in vacuo to give conjugate **19** as its TFA salt. This protocol was successful with microscale amounts of alcohol as low as 0.35  $\mu$ mol which is equivalent to 55  $\mu$ g in the case of (*S*)-(-)-isomenthol **25**.

**Method B: via Bromoacetate 20.** To a solution of secondary alcohol/primary monoamine (10  $\mu$ mol) and bromoacetic acid (2 equiv) in CH<sub>2</sub>Cl<sub>2</sub> (5 mL) were added EDC (2 equiv) and DMAP (0.2 equiv) with stirring at 0 °C for 1 h and then stirring overnight at room temperature. The mixture was then washed with NaHCO<sub>3</sub> and brine and dried over Na<sub>2</sub>SO<sub>4</sub>. Subsequent purification by flash chromatography afforded bromoacetate derivative **20**. To a solution of 1,3-diaminopropane **13** (10 equiv) and diisopropylethylamine (DIPEA) (0.1 equiv) in THF (3 mL) was added a solution of **20** (1 equiv) in THF (1 mL) dropwise and with stirring for 1 h at 0 °C and overnight at room temperature. After evaporation of the solvent, the remaining residue was dissolved in CH<sub>2</sub>Cl<sub>2</sub> (15 mL) and washed three times with brine until **13** could no longer be detected by TLC. The organic layer was dried over Na<sub>2</sub>SO<sub>4</sub> and evaporated to yield conjugate **19** as the free diamine.

**General Procedure for Milligram Scale Preparation of Host–Guest Complexes for Measurement of CD. Preparation of Tweezer 2 Complex of 1-35.** In a typical experiment, a 1  $\mu$ M tweezer **2** solution was prepared by the addition of a 10  $\mu$ L aliquot of tweezer **2** (0.1 mM in anhydrous CH<sub>2</sub>Cl<sub>2</sub>) to 1 mL of CH<sub>2</sub>Cl<sub>2</sub>. The exact concentration of the diluted tweezer **2** solution was determined by UV from the known  $\epsilon$  value of the Soret band in CH<sub>2</sub>Cl<sub>2</sub> ( $\epsilon = 890\,000\text{ L mol}^{-1}\text{ cm}^{-1}$ ). The free amine solution of conjugate **1-35** (1.8 mg, 3.54  $\mu$ mol) was prepared from its TFA salt after the addition of 0.5 mL of MeOH followed by solid Na<sub>2</sub>CO<sub>3</sub> (10 mg). The solvent (MeOH) was then dried under a stream of argon followed by placement under high vacuum (0.2 Torr) for 20 min. Anhydrous CH<sub>2</sub>Cl<sub>2</sub> (1 mL) was then added to yield the free amine solution of conjugate **1-35** (3.54 mM). An aliquot of 10  $\mu$ L of the latter solution (ca. 30 equivalents) was added to the prepared porphyrin tweezer **2** solution to afford tweezer **2**/conjugate **1-35** host–guest complex. The UV/VIS and CD spectra were recorded at 25 °C and corrected for background. The CD spectra were recorded on JASCO-720 and JASCO-810 spectropolarimeter driven by a JASCO V500/FP-750 analysis program for Windows. The CD spectra were measured in millidegrees and normalized into  $\Delta\epsilon_{\text{max}} [\text{L mol}^{-1}\text{ cm}^{-1}]/\lambda$  [nm] units. In the UV spectra, the red shift of the tweezer Soret band indicated that complexation took place.

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(39) The synthesis of the zinc porphyrin tweezer **2** was first accomplished in our laboratories (see ref 1) and is now commercially available from TCI, Japan. Address: Tokyo Kasei Kogyo Co., Ltd., 3-1-13 Nihonbashi-Honcho, Chuo-Ku, Tokyo 103-0023, Japan. (TCI America, 9211 North Harbortgate Street, Portland, OR 97203.)

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**Supporting Information Available:** Materials and general procedures, syntheses of **14** to **17**, carrier **9**, and conjugates **11** and **12**; <sup>1</sup>H NMR and MS data of conjugates **1-21** to **1-58**, **10-23**, **1a-25**, **1b-25**, diBoc conjugates **17-21** to **17-24**, **17-28**, **17-32**, **17-35** to **17-39**, **17-42**, **17-43**, **17-46** to **17-49**, **17-52** to **17-**

**58**, bromoacetates of **25** to **27**, **29** to **31**, **33**, **34**, **44**, **45**, and bromoacetamides of **39** to **41**, **51**; synthetic schemes for conjugates **11** and **12**, and CD data of their tweezer **2** complexes; and CD measurements of the tweezer **2** complex of conjugate **1-30** in different solvents (PDF). This material is available free of charge via the Internet at <http://pubs.acs.org>.

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