Chiral Recognition of Cyclic α-Hydroxyketones by CD-Sensitive Zinc Tetraphenylporphyrin Tweezer

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Dedicated to Professor Piero Salvadori, Pisa, on the occasion of his 70th birthday.

ABSTRACT A combined chemical/chiroptical microscale protocol for the determination of absolute configurations of cyclic α-hydroxyketones is described. The hydroxyl group in cyclic α-hydroxyketones is converted into (3-aminopropylamino)acetate ($NH_2CH_2CH_2CH_2NHCH_2COOR$), or more generally, according to a newly developed protocol, into (3-hydroxypropylamino)acetate group ($HOCH_2CH_2CH_2NHCH_2COOR$). The resultant conjugated compound forms a 1:1 host–guest complex with a dimeric zinc porphyrin tweezer, which exhibits exciton-coupled bisignate CD spectrum centered around the 420-nm porphyrin Soret band due to induced helicity between the two porphyrins in the complex. The absolute configurations of the α-stereogenic center is then determined by comparison of the sign of the observed CD exciton couplet of the complex with that of the preferred porphyrin twist predicted by the Merck Molecular Force Field (MMFFs) method. *Chirality 17:305–315, 2005.*

KEY WORDS: α-hydroxyketones; circular dichroism; exciton chirality; porphyrin tweezer; host–guest complexation

Chiral cyclic α-hydroxyketones are frequently found in bioactive compounds and are also important building blocks for the syntheses of complex chiral compounds including natural products and pharmaceutically important compounds,[1–8] e.g., HIV protease inhibitors, such as indinovir (Crixivan), which has been used in controlling the progression of AIDS in HIV-infected patients since 1996.[9–13] However, due to the fast emergence of resistant viral strains of HIV,[14,15] second-generation analogues with improved potency against resistant strains and improved pharmacokinetic profiles are needed. The Merck Research Laboratories synthesized compound **I,** which showed superior properties versus indinovir and was chosen as a developmental candidate (Chart 1).[16–18] The synthesis of non-racemic amino chromanol fragment **II** has presented a synthetic challenge and several synthetic routes to **II** have been identified via the chiral non-racemic hydroxyketone **III.**[19]

Many synthetic methods have been developed for the preparation of chiral α-hydroxyketones,[19–22] and their absolute configurations have been determined by stereoselective reactions,[23,24] by spectroscopic methods such as Mosher methods,[19] or by comparison of optical rotation/CD with known compounds.[25,26] Although these methods have been used in various specific cases, they are not general enough to be applicable to all α-hydroxyketones, such as closely related hydroxyketones that Merck synthesized as part of this program. For example, in at least one case an assignment was tentatively made based on similar retention times by chiral HPLC. In addition, configurational analysis has been hampered by various difficulties.[27,28] In the application of the dibenzoate chirality method, reduction of α-hydroxyketones to 1,2-diols is required. However, this reduction frequently produces cis and trans diol mixtures, thus necessitating further stereochemical assignments.[22,29]

In the following we describe studies aimed at developing a combined chemical/chiroptical protocol for configurational assignments of cyclic α-hydroxyketones by application of the exciton-coupled CD method based on chiral recognition by dimeric zinc porphyrin host **1.** As typical ketones, we chose five cyclic α-hydroxyketones, (*S*)- α-hydroxychromanone **2,** (*R*)-hydroxytetralone **3,** (*R*)- α-hydroxybenzosuberone **4,** (*R*)- α-hydroxycyclohexanone **5,** and (*R*)- α-hydroxycycloheptanone **6,** which were synthesized by Sharpless asymmetric dihydroxylation of the corresponding ketones (Chart 2).[19]

In the conventional application of the exciton method, the substrate should contain at least two covalently attached chromophores. More recently, a supramolecular approach based on chiral exciton coupling between porphyrin chromophores has been developed. It is based

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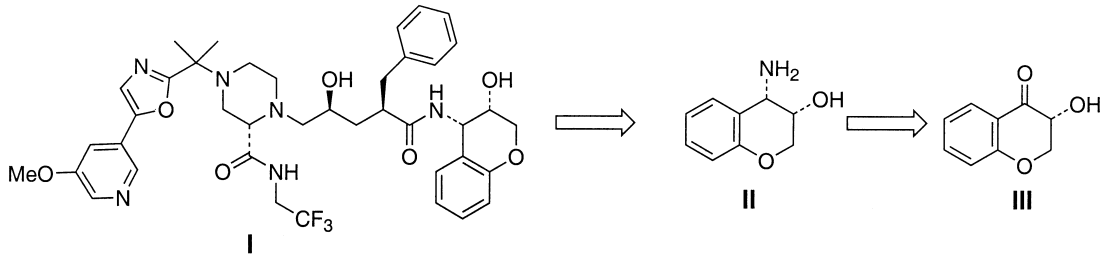


Chart 1.

on a 1:1 complex formation between a chiral substrate linked to an achiral bidentate carrier (guest) and an achiral zinc tetraphenylporphyrin molecular tweezer **1** (host). Because the complexation proceeds in a stereocontrolled manner, it favors 1:1 host–guest complexes that adopt a preferred porphyrin–porphyrin twist. The latter leads to a strong induced CD exciton couplet in the porphyrin Soret band region which is diagnostic for the absolute configuration assignment of the chiral substrate.[30–37] In the following an improved method is described that allows the stereochemical determination of cyclic α-hydroxyketones **2–6** by usage of an improved carrier molecule (Scheme 1).

MATERIALS AND METHODS

General

High-resolution FABMS was performed on a JMS-110/110 tandem mass spectrometer (JMS, Tokyo, Japan) using a *m*-nitrobenzyl alcohol (*m*-NBA) matrix. ^{1}H NMR spectra were recorded on a Bruker DPX-300 (300 MHz; Bruker, Billerica, MA) spectrometer in $CDCl_3$ or CD_3OD. Chemical shifts are reported in ppm relative to Me_4Si (0.0 ppm) or CD_2HOD (3.3 ppm). Data are reported as follows: (s) singlet, (d) doublet, (t) triplet, and (m) multiplet; coupling constants are in Hz; integration. The CD spectra, recorded on a JASCO-810 spectrophotometer, were converted into $\Delta\varepsilon_{max}$ [l mol^{-1} cm^{-1}]/λ [nm] units. The zinc tetraarylporphyrin tweezer (**1**) is commercially available from TCI (Portland, OR, catalogue no. P1364).

Computational Section

Molecular modeling calculations were performed as described earlier[33,34,36,37] with the following modification: (i) sampling of all the structures was adopted within 15 kJ/mol instead of 10 kJ/mol of the lowest-energy conformer over 1,000 fully optimized steps, (ii) the distance checks for primary alcohol O–Zn were set to 2.4 ± 0.5 Å,[38] and (iii) the dihedral angles around the stereogenic center [Hα–Cα–O–C(=O) dihedral] of the guest, α-hydroxyketone derivatives, were locked in order to find the lowest-energy conformations within a limited calculation time.[39,40] After all the calculations (3,000 times), the most stable conformers within a 15-kJ/mol energy window were analyzed using the Boltzmann distribution based on energy difference.

Synthesis of (3-Aminopropylamino)acetate Derivatives

Preparation of di-BOC-protected diaminopropionic acid and methods **A** and **B** are described in ref. 31.

Synthesis of *2-*(*N-tert*-Butoxycarbonyl-3-(*tert*-butyldimethylsilyloxy)propylamino)acetic acid is reported in the Supplemental Material.

Synthesis of (3-Hydroxypropylamino)acetate Derivatives

Typical procedure of method C. To a solution of cyclic α-hydroxyketone **2** (5.3 mg, 33 μmol) in CH_2Cl_2 (2 ml) were added bromoacetyl bromide (20 μl, 230 μmol) and triethylamine (100 μl, 1.0 mmol). The reaction mixture was stirred for 30 min. After the solvent had been removed, the residue was purified by preparative TLC (SiO_2) developed with *n*-hexane/ethyl acetate (2:1) to give bromoacetate derivative **8** (6.2 mg, 66%). To a solution of bromoacetate **8** (6.2 mg, 22 μmol) in THF (1.0 ml) was added sodium carbonate (3.0 mg, 28 μmol) followed by 3-aminopropanol (3.6 mg, 48 μmol). The reaction mixture was stirred for 30 min and purified by silica gel column chromatography (ethyl acetate/methanol, 5:1) to give conjugate **2b** (5.0 mg, 81%).

Typical procedure of method D. To a solution of cyclic α-hydroxyketone **2** (4.0 mg, 24 μmol) in CH_2Cl_2 (1.0 ml) were added{*tert*-BOC-[3-(*tert*-butyldimethylsilanyloxy)propyl]amino}acetic acid (17 mg, 49 μmol), EDC (11 mg, 58 μmol), and DMAP (5.0 mg, 41 μmol). The reaction mixture was stirred for 12 h at room temperature

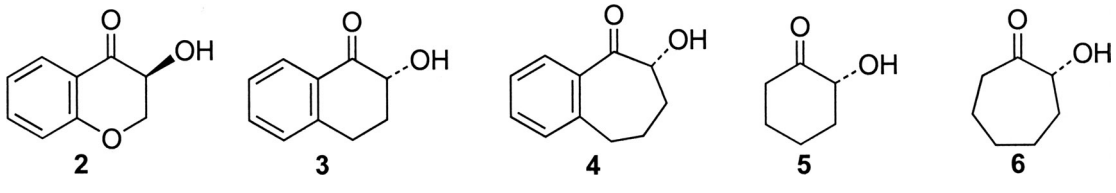
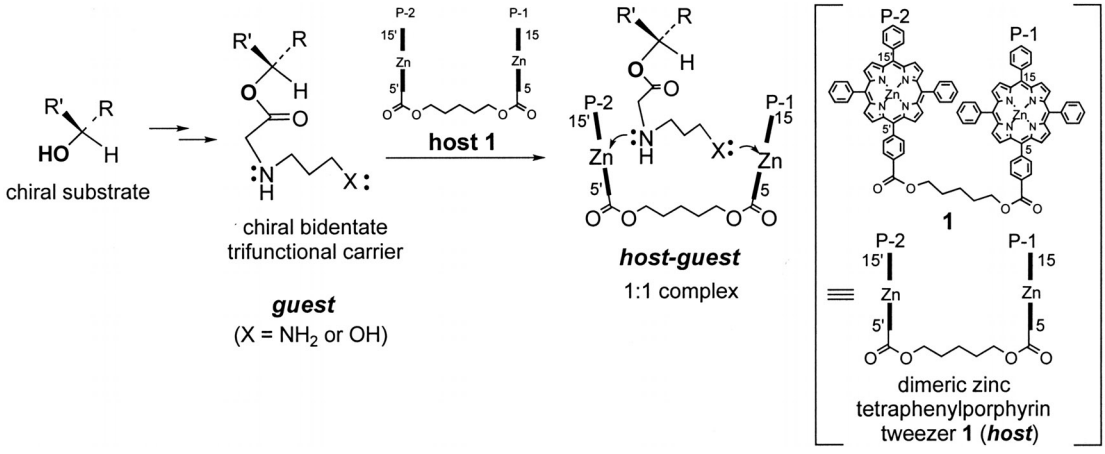


Chart 2.



Scheme 1.

and then concentrated in vacuo. The crude product was purified by preparative TLC (SiO_2) with *n*-hexane/ethyl acetate (1:1) to give protected conjugate **11** (8.3 mg, 70%). To a solution of **11** (8.3 mg, 17 μmol) in CH_2Cl_2 (1.0 ml) was added TFA (100 μl) and stirred for 3 h at room temperature. The solvent and excess TFA were then removed under reduced pressure to give TFA salt **12** (6.6 mg). The salt was neutralized with sodium carbonate (10 mg) in methanol (1.0 ml). After removal of methanol in vacuo, conjugate **2b** was used in the complexation with the zinc porphyrin tweezer without any further purification.

Hydroxyconjugate 2b. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.87 (dd, *J* = 7.9, 1.7 Hz, 1 H), 7.50 (ddd, *J* = 7.7, 7.3, 1.7 Hz, 1 H), 7.06 (ddd, *J* = 7.9, 7.3, 0.9 Hz, 1 H), 6.99 (dd, *J* = 8.2, 0.5 Hz, 1 H), 5.71 (dd, *J* = 11.8, 5.6 Hz, 1 H), 4.58 (dd, *J* = 11.2, 5.6 Hz, 1 H), 4.41 (dd, *J* = 11.8, 11.2 Hz, 1 H), 3.80 (t, *J* = 5.3 Hz, 2 H), 3.59 (s, 1 H), 3.58 (S, 1 H), 2.92 (t, *J* = 5.8 Hz, 2 H), 1.73 (tt, *J* = 5.8, 5.3 Hz, 2 H); HRFABMS *m/z* 280.1163 $[M + H]^+$, calcd. for $C_{14}H_{18}O_5N$, 280.1185.

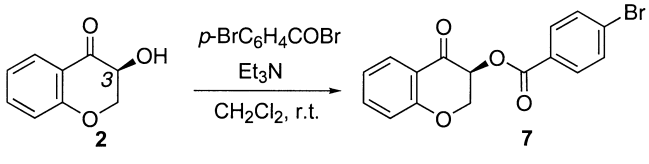
Hydroxyconjugate 3b. ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.00 (dd, *J* = 7.8, 1.1 Hz, 1 H), 7.51 (ddd, *J* = 7.5, 7.4, 1.1 Hz, 1 H), 7.33 (dd, *J* = 7.8, 7.5 Hz, 1 H), 7.26 (d, *J* = 7.8 Hz, 1 H), 5.60 (dd, *J* = 12.8, 5.4 Hz, 1 H), 3.85 (t, *J* = 5.3 Hz, 1 H), 3.68 (s, 1 H), 3.67 (s, 1 H), 3.3-3.0 (m, 2 H), 3.03 (t, *J* = 5.8 Hz, 2 H), 2.48–2.24 (m, 2 H), 1.82 (tt, *J* = 5.8, 5.3 Hz, 2 H); HRFABMS *m/z* 278.1396 $[M + H]^+$, calcd. for $C_{15}H_{20}O_4N$, 278.1392.

Hydroxyconjugate 4b. ^{1}H NMR (300 MHz, CD_3OD) δ 7.65 (d, *J* = 7.7 Hz, 1 H), 7.48 (dd, *J* = 7.7, 7.3 Hz, 1 H), 7.34–7.28 (m, 2 H), 5.61 (dd, *J* = 11.2, 5.8 Hz, 1 H), 4.17 (s, 2 H), 3.71 (t, *J* = 5.7 Hz, 2 H), 3.23 (t, *J* = 5.5 Hz, 2 H), 3.18–2.97 (m, 2 H), 2.33 (m, 1 H), 2.22 (m, 1 H), 2.08–1.74 (m, 4 H); HRFABMS *m/z* 292.1554 $[M + H]^+$, calcd. for $C_{16}H_{22}O_4N$, 292.1549.

Hydroxyconjugate 5b. ^{1}H NMR (300 MHz, CD_3OD) δ 5.38 (dd, *J* = 11.8, 6.6 Hz, 1 H), 4.11 (s, 2 H), 3.71 (t, *J* = 5.0 Hz, 2 H), 3.23 (t, *J* = 5.5 Hz, 2 H), 2.54–2.34 (m, 2 H), 2.22–2.09 (m, 2 H), 1.96–1.70 (m, 6 H); HRFABMS *m/z* 230.1400 $[M + H]^+$, calcd. for $C_{11}H_{20}O_4N$, 230.1392.

Hydroxyconjugate 6b. ^{1}H NMR (300 MHz, CD_3OD) δ 5.47 (dd, *J* = 9.1, 5.5 Hz, 1 H), 4.07 (s, 2 H), 3.70 (t, *J* = 5.8 Hz, 2 H), 3.22 (t, *J* = 7.2 Hz, 2 H), 2.68 (ddd, *J* = 16.4, 5.4, 5.3 Hz, 1 H), 2.34 (ddd, *J* = 16.4, 5.4, 5.3 Hz, 1 H), 2.23–2.10 (m, 2 H), 1.95–1.70 (m, 8 H); HRFABMS *m/z* 244.1550 $[M + H]^+$, calcd. for $C_{12}H_{22}O_4N$, 244.1549.

Aminoconjugate 3a. ^{1}H NMR (300 MHz, CD_3OD) δ 7.94 (dd, *J* = 8.3, 1.4 Hz, 1 H), 7.58 (ddd, *J* = 7.5, 7.4, 1.3 Hz,



Scheme 2.

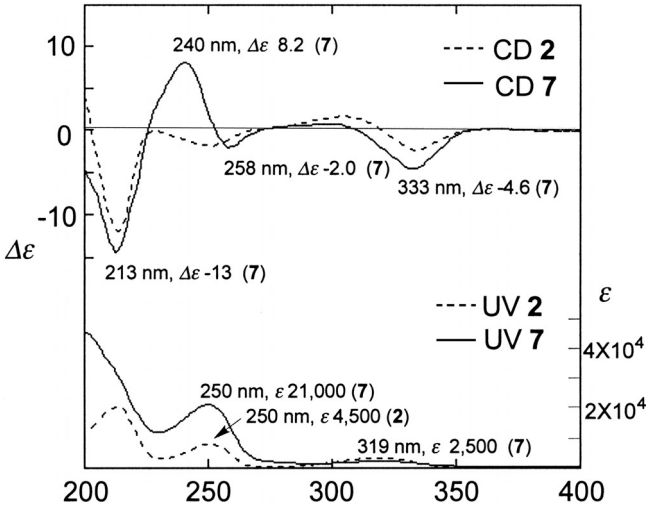


Fig. 1. CD and UV spectra of **2** and **7** in MeCN (6.8×10^{-5} M).

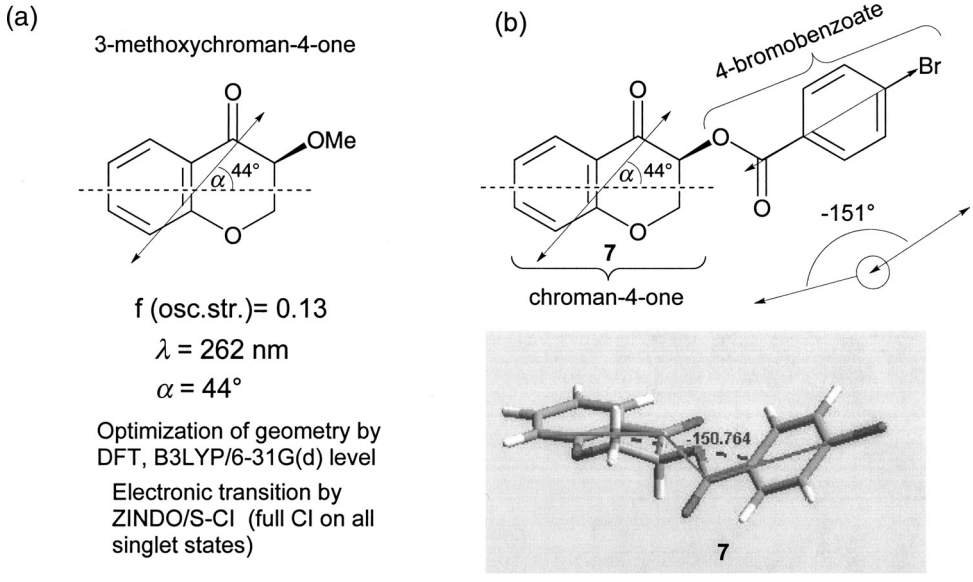


Fig. 2. (**a**) Electric transition dipole moment (↔) of 3-methoxychroman-4-one calculated by ZINDO/S-CI. (**b**) Dihedral angle between electric transitions dipole moments in the lowest conformation of compound **7.**

1 H), 7.38–7.34 (m, 2 H), 5.75 (dd, J = 14.6, 5.3 Hz, 1 H), 4.21 (s, 2 H), 3.44–3.14 (m, 4 H), 3.08 (dd, J = 7.8, 7.7 Hz, 2 H), 2.53–2.45 (m, 1 H), 2.33 (ddd, J = 12.6, 12.6, 4.9 Hz, 1 H), 2.13 (m, 2 H); HRFABMS m/z 277.1569 $[M + H]^+$, calcd. for $C_{15}H_{21}O_3N_2$, 277.1552.

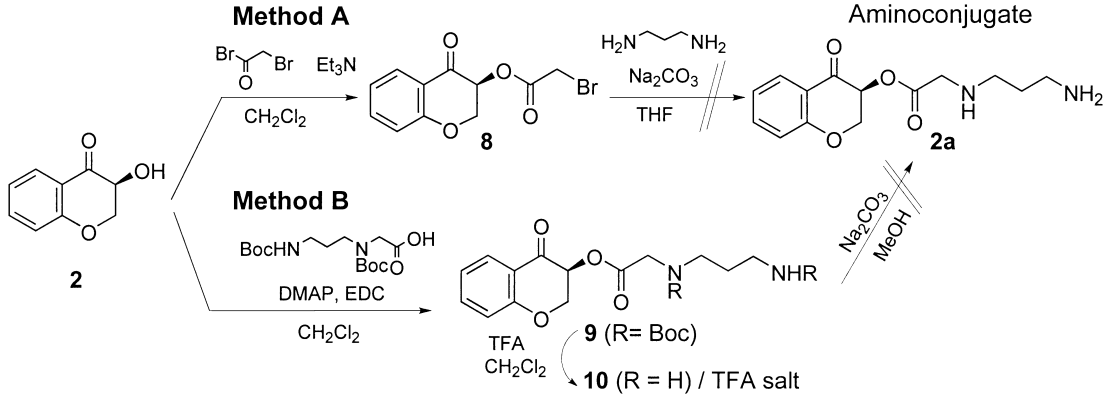
Aminoconjugate 4b. ^{1}H NMR (300 MHz, CD_3OD) δ 7.66 (dd, J = 8.0, 1.6 Hz, 1 H), 7.49 (ddd, J = 7.5, 7.3, 1.5 Hz, 1 H), 7.35–7.31 (m, 2 H), 5.62 (dd, J = 11.2, 5.9 Hz, 1 H), 3.21–3.16 (m, 2 H), 3.11–3.03 (m, 4 H), 2.38–2.15 (m, 4 H), 2.14–1.97 (m, 3 H), 1.92–1.75 (m, 1 H); HRFABMS m/z 291.1714 $[M + H]^+$, calcd. for $C_{16}H_{23}O_3N_2$, 291.1709.

Preparation of Host/Guest Complex for CD Measurement

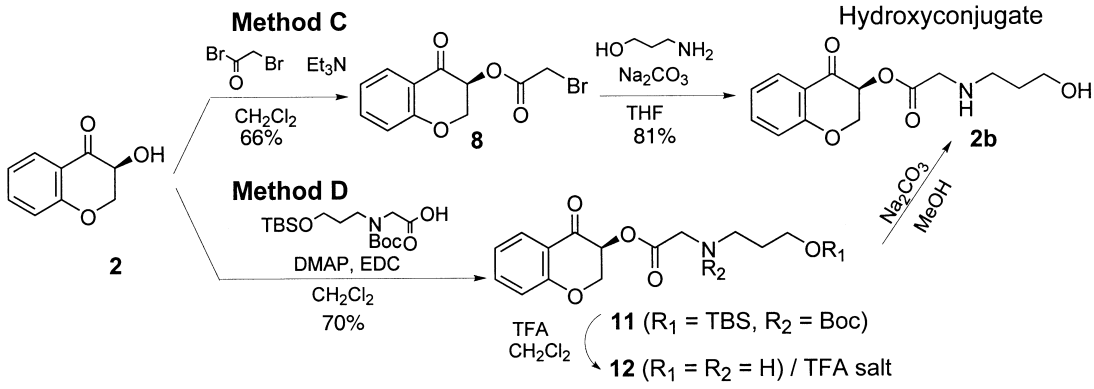
Porphyrin tweezer **1** solution, 0.1 mM in anhydrous CH_2Cl_2 (10 μl), was added to methylcyclohexane (MCH) (1 ml). The exact concentration of the diluted tweezer **1** solution was determined by UV from the known ε value of the Soret band in methylcyclohexane (ε = 640,000 l mol^{-1} cm^{-1}). To this solution was added 3 mM **2b** in anhydrous CH_2Cl_2 (10 μl). This solution was shaken, and UV and CD spectra were then recorded at room temperature and corrected by background subtraction. The CD spectra were measured in millidegrees and normalized into [l mol^{-1} cm^{-1}]/λ [nm] units.

RESULTS AND DISCUSSION

The aim of this paper is first to test the applicability of the conventional exciton chirality method to α-hydroxyketones and, second, to develop a more general protocol based on the porphyrin tweezer approach. For this purpose, we first attempted to apply the conventional approach of the exciton chirality method, namely, chromophoric derivatization of a functional group close to the stereogenic center, i.e., the 3-OH. Compound **2** was converted into its *p*-bromobenzoate **7** (λ = 244 nm, ε =19,500 in EtOH) (Scheme 2). However, as shown in



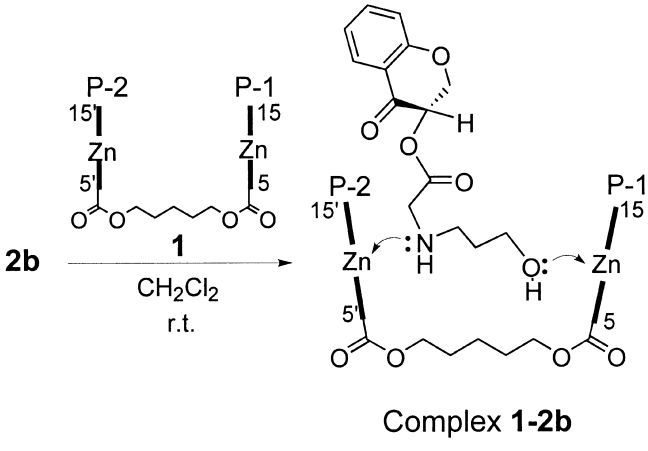
Scheme 3.



Scheme 4.

Figure 1, benzoate **7** gave only a weak and ill-defined CD couplet at 258 nm ($\Delta\varepsilon = -2.0$) and 240 nm ($\Delta\varepsilon = +8.2$). A comparison with the CD of the original **2** (Fig. 1, dotted line) shows that it is impossible to interpret this very weak couplet between the chromanone (λ =250 nm, ε = 4,500 in MeCN) and *p*-bromobenzoate chromophores. In order to analyze this weak CD couplet we performed ZINDO/S-Cl calculation of 3-methoxychroman-4-one, which showed the electric transition dipole around 262 nm to be oriented as depicted in Figure 2a. Furthermore, the dihedral angle between this dipole and that 4-bromobenzoate CT band in the optimized conformation of **7** found by MMFFs conformational search in chloroform (Fig. 2b) was calculated to be circa −151°. Thus, although the weak couplet between 258 nm ($\Delta\varepsilon = -2.0$) and 240 nm ($\Delta\varepsilon = +8.2$) originates from a negative exciton couplet between the two electric transition dipoles, its low intensity precludes application in configurational analysis.

In order to overcome the restriction due to such unsuitable CD coupling orientation between interacting dipoles, we chose the host–guest chiral recognition approach using dimeric zinc porphyrin tweezer **1** (λ = 417 nm, ε = 640,000, methylcyclohexane) (Scheme 1).[30–34] As shown in Scheme 3, it was attempted to convert α-hydroxyketone **2** into its bifunctional ester conjugate **2a** according to methods **A** and **B.**[31] In method **A,** alcohols are converted into bromoacetyl derivatives followed by reaction with diaminopropane to give aminoconjugate **2a.** Advantages of method **A** are that all reagents are commercially available and that the reactions are fast. The disadvantage, however, is that it is not applicable to compounds that are sensitive under basic conditions, due to the strong basicity of diaminopropane. On the other hand, in method **B,** di-BOC-protected diaminopropane ester is reacted with the hydroxyketone, followed by deprotection and neutralization to give the aminoconjugate. Although di-BOC-protected diaminopropionic acid has to be prepared, the aminoconjugate **10** is obtained under milder conditions. However, attempts to neutralize the TFA salt resulted in aminolysis, thereby regenerating the starting α-hydroxyketone **2** instead of the desired conjugate **2a** ("aminoconjugate"). With method **A,** the intermediate α-bromomethyl acetate **8** survived treatment with sodium carbonate in THF, but addition of



Scheme 5.

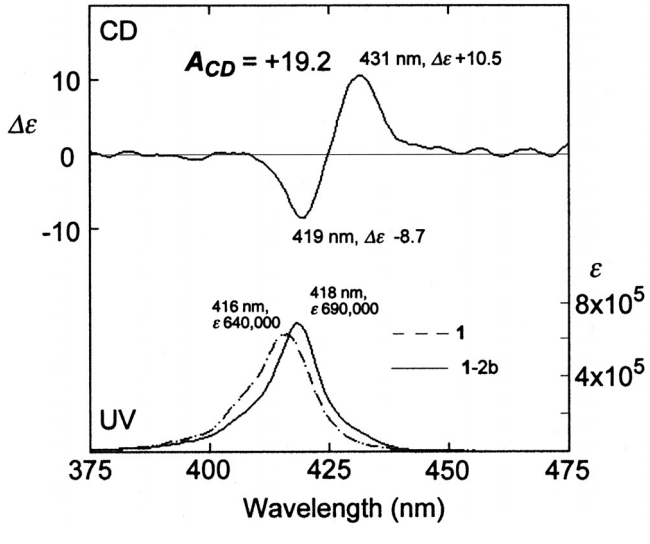
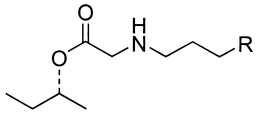
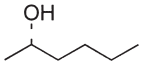
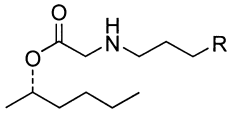
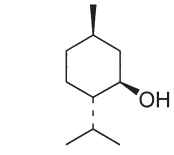
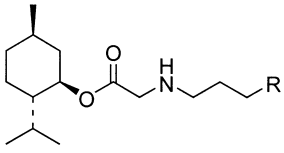
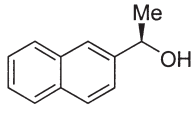
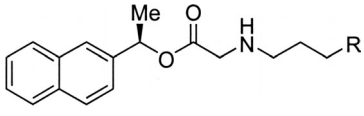


Fig. 3. CD and UV spectra of complex **1–2b** (c = 1.1 × 10^{-6} M in MCH).

TABLE 1. Predicted CD exciton chirality and observed CD amplitude (A_{CD}) of the complexes between zinc porphyrin tweezer 1 and conjugate compounds (13a–16a and 13b–16b)

Parent alcohol	Predicted CD exciton chirality (MMFFs)	Conjugate compound	R = NH_2 Preparation method A A_{CD}	R = OH Preparation method C A_{CD}
 (*S*)-**13**	Negative		**13a** −17	**13b** −17
 (*S*)-**14**	Positive		**14a** +40	**14b** +44
 (1*R*,2*S*,5*R*) -**15**	Negative		**15a** −494	**15b** −317
 (*R*)-**16**	Negative		**16a** −202	**16b** −198

1,3-diaminopropane resulted in its immediate decomposition to α-hydroxyketone **2.** With method **B,** TFA salt **9** was obtained as a stable compound, but neutralization with sodium carbonate in methanol also gave the α-hydroxyketone **2.** In both cases, the ester bonds in **8** and **9** are readily cleaved by inter- or intramolecular aminolysis which is well-documented as general base-catalysis arising from the 1,3-diaminopropane moiety.[41,42] Therefore we examined the employment of milder conjugates that are capable of coordinating with the zinc of the tweezer molecule, to prevent undesirable aminolysis.

Although oxygen nucleophilicity is weaker than that of nitrogen, it is known that coordination occurs between the substrate that contains a methyl ether oxygen and the zinc ion in the porphyrin.[38,43] Thus the (3-hydroxypropylamino)acetyl group $HOCH_2CH_2CH_2NHCH_2CO$- was

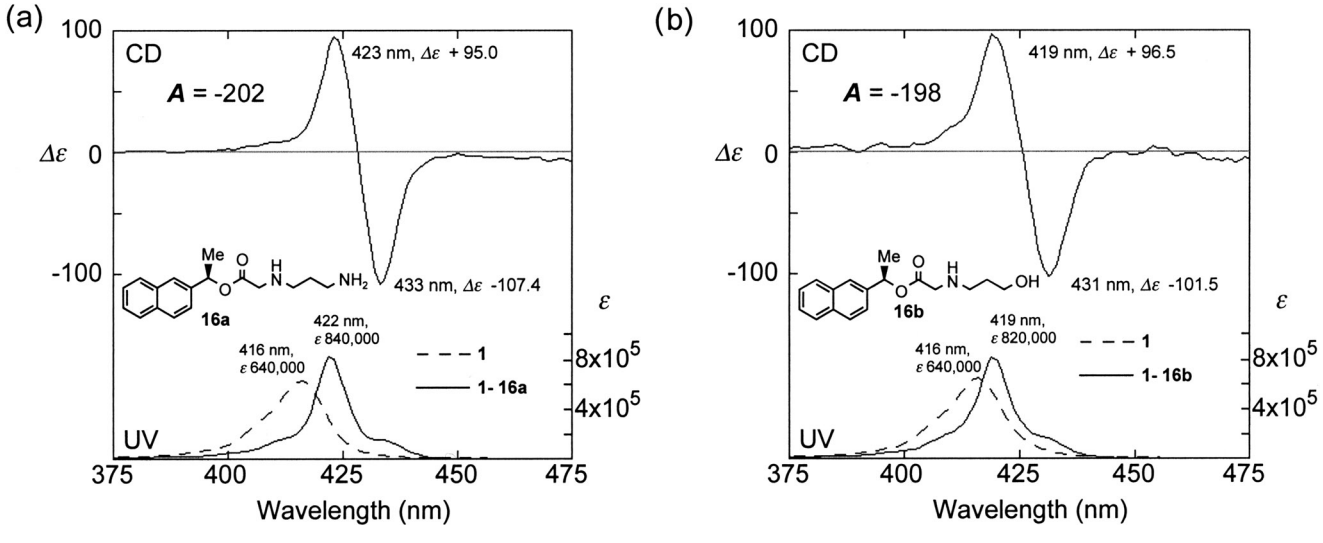


Fig. 4. (**a**) CD and UV spectra in MCH of the complex between the zinc tweezer and (**a**) conjugate **16a** ($c = 1.3 \times 10^{-6}$ M) and (**b**) conjugate **16b** ($c = 1.3 \times 10^{-6}$ M).

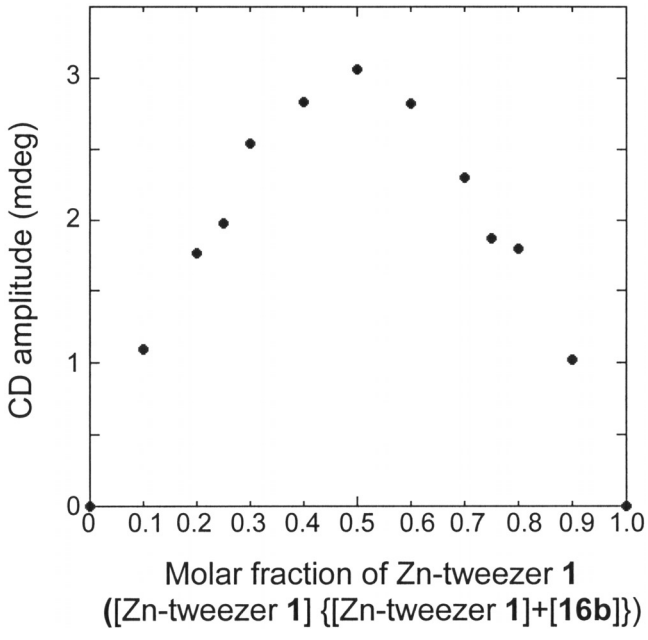
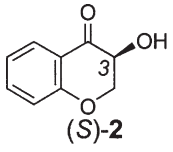
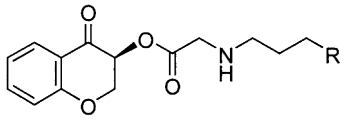
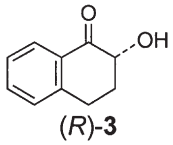
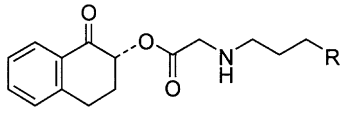
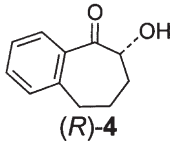
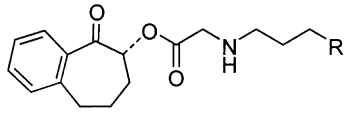
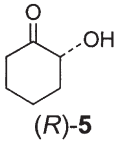
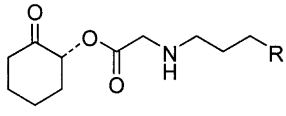
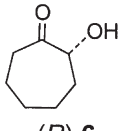
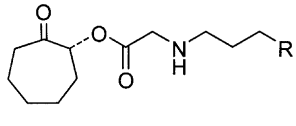


Fig. 5. Job plot for the complexation of Zn tweezer **1** with **16b.** The total concentration of two components was 10 μM in MCH, with the molar fraction varying from 0 to 1.

tested as a new carrier moiety to produce "hydroxyconjugate" **2b** (Scheme 4). First, we applied method **C**, where 3-aminopropane is used instead of diaminopropane (see method A). An advantage of method **C** is that no racemization occurs because of the rapid formation of bromoacetate **8.** Addition of 3-aminopropanol to bromoacetate **8** in THF gave the desired products **2b** without ester bond hydrolysis. Method D was also tested. In this case, the carrier hydroxypropylamino moiety was introduced to give **11,** which was deprotected to TFA salt **12** and subsequently neutralized to yield the desired compound **2b.** Thus, both methods yielded the desired compound **2b.** The conjugate **2b** was then subjected to complexation with zinc porphyrin tweezer host **1,** giving rise to complex **1–2b** (Scheme 5). As shown in Figure 3, complex **1–2b** exhibited a clear-cut positive exciton couplet at 431 nm ($\Delta\varepsilon$ = +10.5) and 419 nm ($\Delta\varepsilon$ = −8.7), amplitude A_{CD} = +19.2. Furthermore, formation of the 1:1 complex between zinc porphyrin tweezer **1** and bidentate conjugate guest **2b** is supported by the shift of the broad UV/vis peak from 416 nm to the sharper 418 nm absorption (Fig. 3).[30]

Because complex **1–2b** and those of **13b–16b** are a new type of host/guest complexes involving coordination between zinc and a primary alcohol function,

TABLE 2. Predicted CD exciton chirality and observed CD amplitude (A_{CD}) of the complexes between zinc porphyrin tweezer 1 and conjugate compounds (2a–6a and 2b–6b)

Parent alcohol	Predicted CD exciton chirality (MMFFs)	Conjugate compound	R = NH_2 Preparation method B A_{CD}	R = OH Preparation method D A_{CD}
 (*S*)-**2**	Positive		**2a** —	**2b** +19.2
 (*R*)-**3**	Negative		**3a** −283	**3b** −149
 (*R*)-**4**	Negative		**4a** −180	**4b** −175
 (*R*)-**5**	Positive		**5a** —	**5b** +137
 (*R*)-**6**	Positive		**6a** —	**6b** +42.8

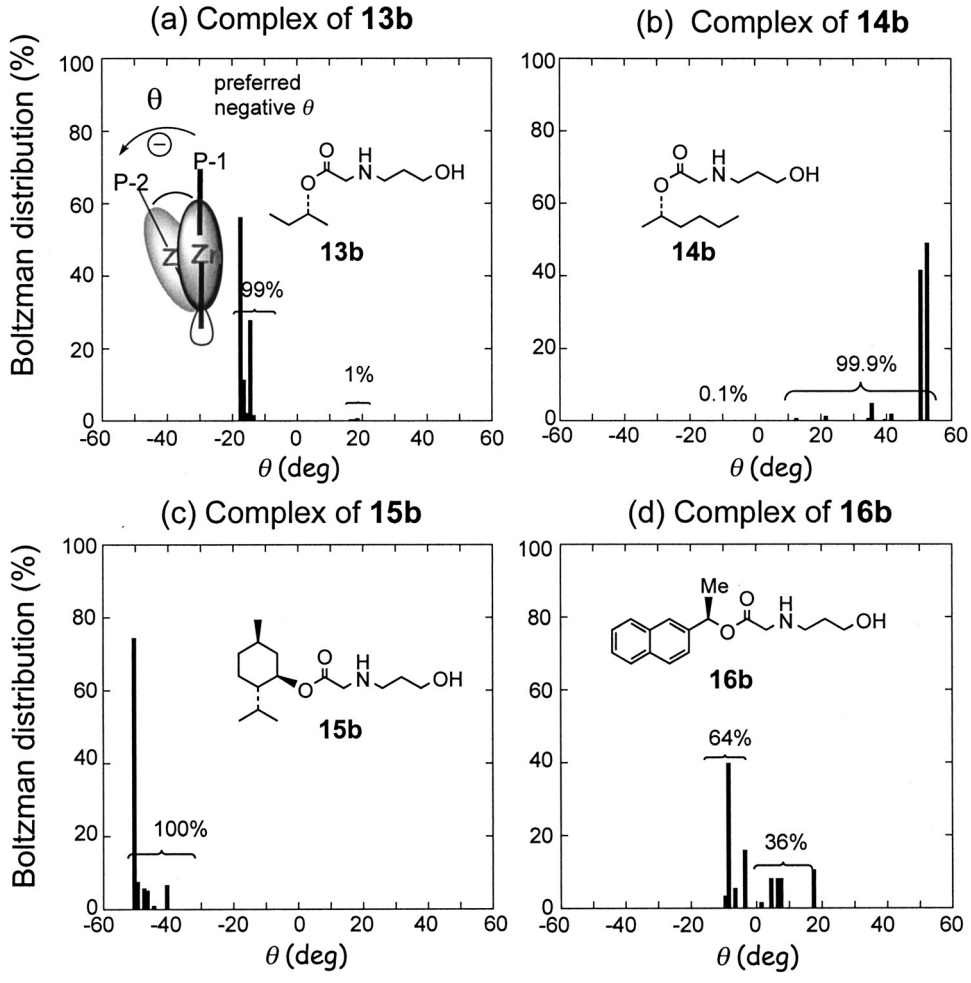


Fig. 6. Boltzmann distribution of θ values of the MC/MMFF calculated host–guest complex within 15 kJ/mol (3.6 kcal/mol) of the lowest-energy conformation for various conjugate (**13b–16b**).

their CD data were compared with those of conventional aminoconjugates **13a–16a** (Table 1). As shown, the sign of exciton-coupled CD and amplitudes (A_{CD}) of each set, aminoconjugates **13a–16a** and the corresponding hydroxyconjugates **13b–16b** were in good agreement. Note that in both cases of **1–13a** and **1–13b,** the zinc porphyrin tweezer recognizes even the subtle difference between methyl and ethyl groups (A_{CD} = −17). Although

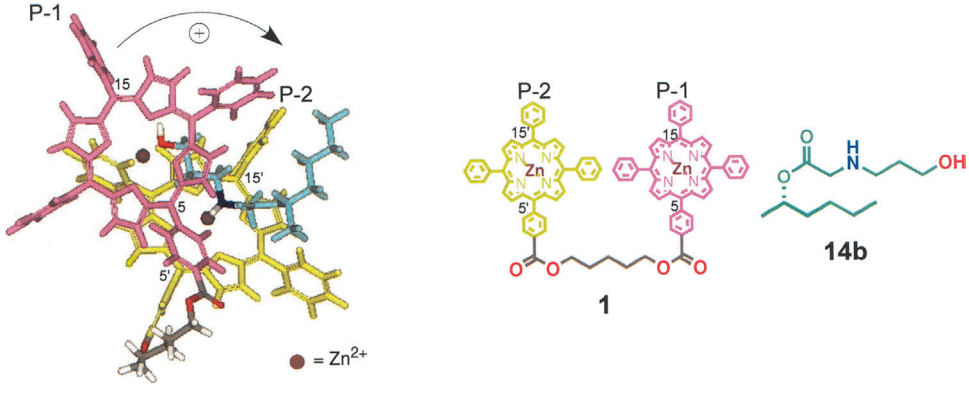


Fig. 7. Front view of the most probable structure of complex **1–14b** calculated by MC/MMFFs. Complex **1–14b** was colored as follows: (pink) Zn-porphyrin (P-1) bound with primary alcohol; (yellow) Zn-porphyrin (P-2) bound with secondary amine; hydroxyconjugate **14b** is sky blue except for the primary alcohol (red) and secondary amine (dark blue).

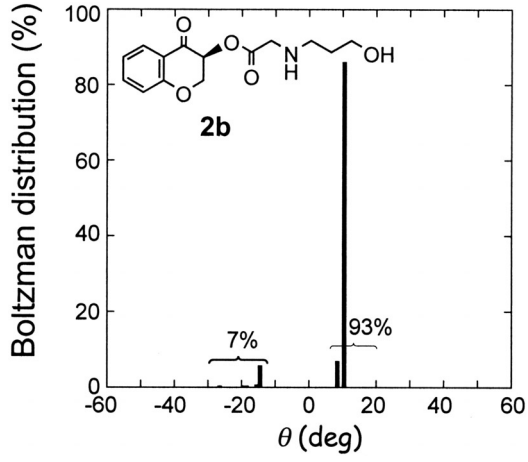


Fig. 8. Boltzmann distribution of θ values of the MC/MMFFs calculated host–guest complex within 15 kJ/mol (3.6 kcal/mol) of the lowest-energy conformation for conjugate **2b**.

the UV/vis shift upon complexation in the hydroxyconjugate, from 416 to 419 nm, is smaller than that of the aminoconjugate, 416 and 422 nm, respectively, the conformations of complexes between zinc porphyrin tweezer **1** and amino conjugates **13a–16a** are expected to be similar to those of hydroxyconjugates **13b–16b** (Fig. 4).

The Job plot performed for complex **1–16b,** where the relation between CD amplitude and molar fraction exhibited a maximum at molar fraction 0.5, suggests a 1:1 complexation between **1** and **16b** as previously reported for other tweezer complexes[33,34] (Fig. 5).

After successful testing of hydroxyconjugates of model compounds **13b–16b,** the new conjugate system was applied to cyclic α-hydroxyketones (**3–6**), the conjugates being prepared according to methods shown in Table 2; in all cases, the hydroxyconjugates exhibited clear exciton CD. Interestingly, the negative exciton couplets of benzo-condensed cyclic α-hydroxyketones **3** and **4** opposite those of the corresponding cyclic α-hydroxyketones **5** and **6** (see below).

We also attempted to prepare the aminoconjugates of **3–6.** With aminoconjugates **3a** and **4a,** the A_{CD} was similar to those of the corresponding hydroxyconjugates **3b** and **4b;** however, the aminoconjugates of **5** and **6** could not be prepared.

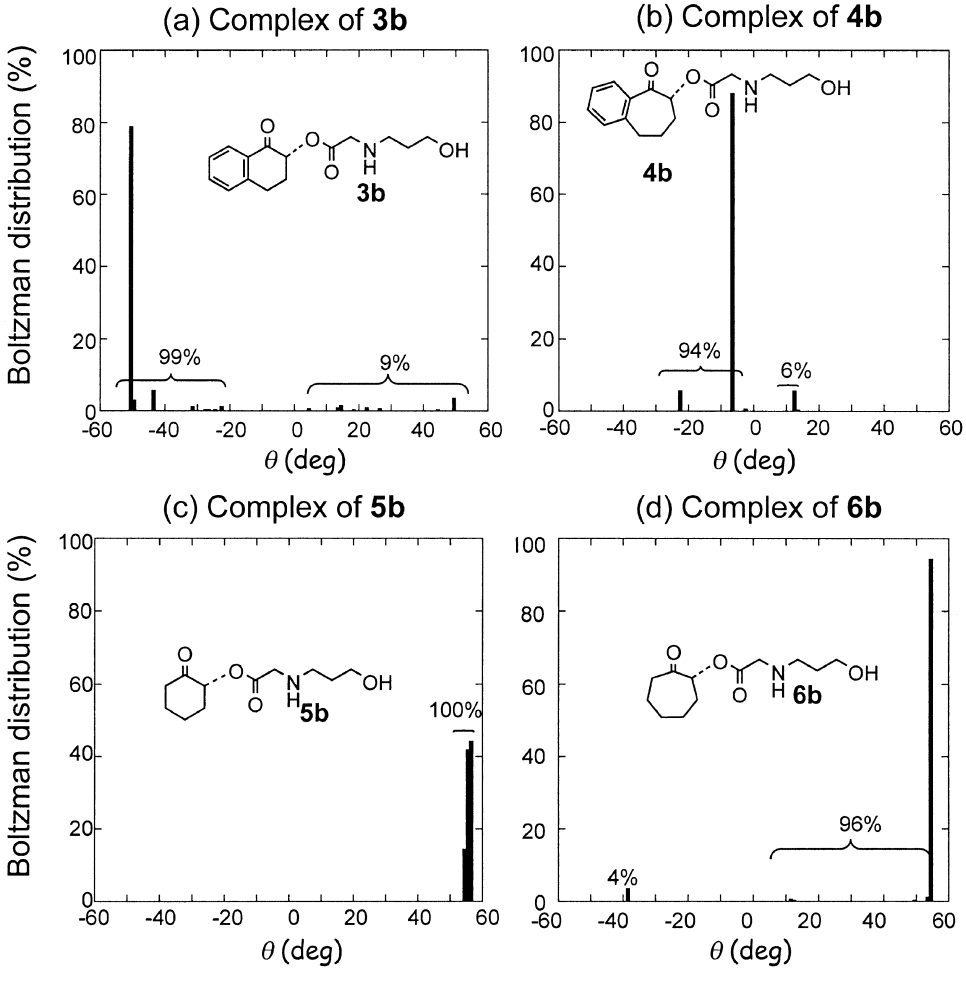


Fig. 9. Boltzmann distribution of θ values of the MC/MMFF calculated host–guest complex within 15 kJ/mol (3.6 kcal/mol) of the lowest-energy conformation for various conjugates (**3b–6b**).

In previous studies, the assignment of absolute configurations from the observed CD couplet of the tweezer complex were mostly based on the relative steric sizes of the substituents at the stereogenic center, where the larger group protrudes from binding pocket while the medium group is clamped inside.[30–32] However, in more complicated cases, this approach is not applicable. The Monte Carlo (MC) conformational search/Merck Molecular Force Field (MMFFs) molecular modeling[44] approaches developed more recently for predicting the porphyrin helicity in more sterically complicated substrates was found to be more favorable for α-hydroxyketone as well.[33,35–37]

MMFFs calculations were thus performed in order to predict the porphyrin helicity in the complexes. As shown in Figure 6, the Boltzmann distribution of conformation with preferred porphyrin helicity (θ) of the complex was in good agreement with the observed sign of exciton-coupled CD. For example, the Boltzmann distribution of complex **1–13b** shows that 99% of the preferred conformations of complex **1–13b** adopt negatively arranged porphyrins (Fig. 6a), leading to a negative sign of the exciton-coupled CD, which is in agreement with the observed CD (Table 1). The lowest-energy conformation of complex **1–14b** is shown in Figure 7. Here the butyl group protrudes from the porphyrin sandwich to give a complex with positive helicity between the two porphyrin transition moments, 5–15 (P-1) and 5′–15′ (P-2).[40]

Similarly, the Boltzmann distribution of helicity (θ) between porphyrins in the complex **1–2b** was calculated using MMFFs. In agreement with experimental results shown in Figure 3, the calculation predicted a positive helicity (θ) between porphyrins in complex **1–2b** (Fig. 8). Furthermore, in complexes between hydroxyconjugate (**3b–6b**) and zinc porphyrin tweezer, the helicity based on MMFFs calculations also correctly predicted the observed results (Fig. 9).

Although the predicted porphyrin helicity by molecular modeling is in agreement with the observed CD exciton chirality, additional conformational studies aimed at clarification of the opposite interporphyrin helicity of **3a,b** vs. **5b** and of **4a,b** vs. **6b** are underway.

As mentioned above, in order to apply this method to α-hydroxyketones of unknown configurations, we prefer to make hydroxyconjugates according to **method D** and determine the configuration by comparison between the observed exciton coupled CD of the corresponding complex molecule and the results of the MMFFs calculations.

CONCLUSION

An efficient procedure for determination of absolute configurations of chiral cyclic α-hydroxyketones has been developed. The use of the (3-hydroxypropylamino)acetyl moiety as an improved carrier over the (3-aminopropylamino)acetyl moiety yields hydroxyconjugates that complex with the zinc porphyrin tweezer. This further extends the applicability of the tweezer method to cyclic α-hydroxycarbonyl systems for which there exists no general method. The absolute configurations of resulting complexes can be determined from both the observed CD sign and from the predicted porphyrin helicity, as calculated by the Merck Molecular Force Field (MMFFs) method.

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