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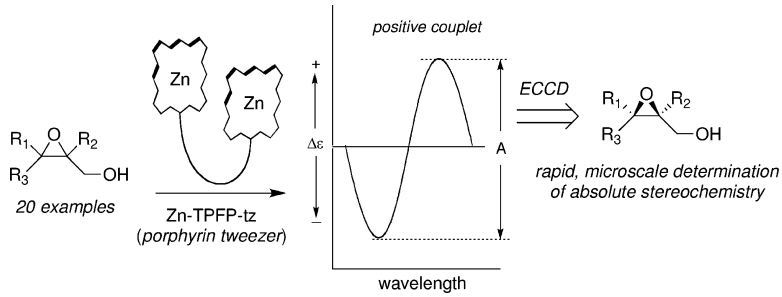

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Prompt Determination of Absolute Configuration for Epoxy Alcohols via Exciton Chirality Protocol

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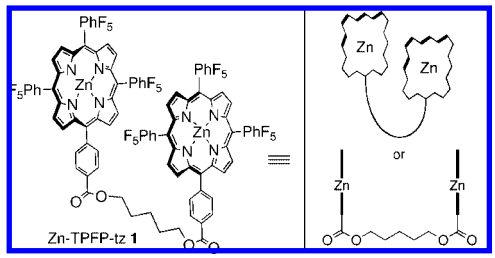
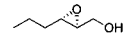
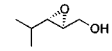
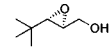
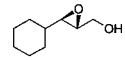
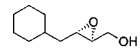
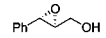
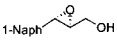
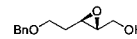
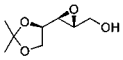
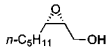
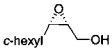
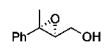
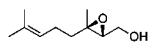
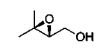
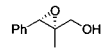
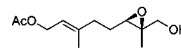
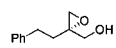
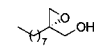
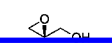
Chiral epoxy alcohols are invaluable building blocks in organic synthesis and are encountered in many biologically active natural products. Assignment of absolute configuration of chiral epoxy alcohols relies heavily on Mosher ester analysis[1,2] of the corresponding ring opened diol or established empirical mnemonics developed for different asymmetric epoxidation strategies.[3−7] The former approach requires derivatization, which is inconvenient especially when only a limited amount of substrate is available. Moreover, in many cases the absolute stereochemistry cannot be unambiguously assigned until several diastereomers are synthesized.[8,9] As important as chiral epoxy alcohols are in synthetic organic chemistry, there is no direct method for the assignment of their absolute stereochemistry. We describe here a microscale, nonempirical, expedient protocol to determine the absolute configuration of chiral epoxy alcohols without the need for any derivatization.



It was envisaged that the use of the porphyrin tweezer, utilized previously to assign the absolute stereochemistry of families of different chiral organic molecules such as diamines and amino alcohols, could also lead to a successful strategy for assignment of chirality for epoxy alcohols.[10,11] Central to the success of this route would be the use of a porphyrin tweezer capable of efficient binding with the epoxy alcohol. Recently, we have introduced the use of the highly Lewis acidic porphyrin tweezer **1**[11] featuring a strong binding affinity for hydroxyl groups and demonstrated its ability to bind 1,2,3,4-diepoxybutane. Indication of strong binding can be demonstrated from the binding affinity of epoxy alcohols with Zn-TPFP-tz **1** (K_{assoc} of **7** with **1** is 2.88×10^4 M^{-1}, which is comparable to that of vicinal diols;[12] see Supporting Information, SI). In light of the latter observations, Zn-TPFP-tz **1** was examined for configurational assignment of epoxy alcohols via the Exciton Coupled Circular Dichroism (ECCD) protocol.[13−15] To our delight, prominent bisignate CD signals (ECCD) at the Soret region were observed upon complexation of Zn-TPFP-tz **1** with a large number of chiral epoxy alcohols at micromolar concentrations.

As shown in Table 1, the (2*S*,3*S*) *trans*-disubstituted epoxy alcohols (**2**, **4**, and **6**−**8**) resulted in negative ECCD spectra while positive signals were observed for (2*R*,3*R*) substrates (**9** and **10**). The correlation between substrate chirality and the sign of ECCD is illustrated in Figure 1a in which two binding interactions occur between the OH group and the epoxide oxygen with the zincated porphyrins. It is assumed that the binding of **P1**, the porphyrin bound to the epoxidic oxygen, occurs opposite the largest substituent on the epoxide. Since **P2** is bound to the alcohol, invariably this will be the largest group such that **P1** and **P2** avoid steric clash with each other. Since the lone pairs on the epoxidic oxygen are geometrically fixed due to the rigid nature of the epoxide ring, steric relief of **P1** is through rotation/sliding of the porphyrin ring to avoid the largest substituent on the epoxide that

Table 1. ECCD Data of 2,3-Epoxy Alcohols in Hexane[a]

	Epoxy Alcohol	Predicted Sign	λ nm, (△ε)	A
2 **2*S*,3*S***		*neg*	423 (-60) 412 (+45)	-105
3 **2*S*,3*S***		*neg*	Complex CD	
4 **2*S*,3*S***		*neg*	423 (-117) 412 (+89)	-206
5[b] **2*R*,3*R***		*pos*	Complex CD	
6[c] **2*S*,3*S***		*neg*	422 (-27) 413 (+31)	-58
7[b] **2*S*,3*S***		*neg*	423 (-55) 410 (+62)	-117
8 **2*S*,3*S***		*neg*	423 (-65) 411 (+56)	-121
9[d] **2*R*,3*R***		*pos*	424 (+29) 412 (-17)	+46
10 **2*R*,3*R***		*pos*	420 (+45) 411 (-49)	+94
11 **2*S*,3*R***		*pos*	423 (+34) 411 (-31)	+65
12 **2*S*,3*R***		*pos*	423 (+40) 411 (-27)	+67
13 **2*R*,3*S***		*neg*	423 (-46) 411 (+24)	-70
14 **2*R*,3*S***		*neg*	423 (-66) 411 (+46)	-112
15 **2*S*,3*S***		*neg*	424 (-152) 411(+111)	-263
16 **2*R*,3*R***		*pos*	426 (+41) 418 (-20)	+61
17 **2*R***		*pos*	424 (+105) 412 (-63)	+168
18[c] **2*S*,3*S***		*neg*	425 (-10) 413 (+12)	-22
19 **2*R*,3*R***		*pos*	422 (+71) 413 (-72)	+143
20 **2*S***		*pos*	423 (+101) 410 (-73)	+174
21 **2*S***		*pos*	424 (+90) 411 (-65)	+155
22[e]			No ECCD	

[a] Tweezer/substrate ratio - 1:40 unless otherwise indicated. [b] The enantiomer showed mirror image CD spectrum. [c] Tweezer/substrate ratio - 1:200. [d] Tweezer/substrate ratio - 1:100, 2 μM tweezer concentration at 0 °C was used for all measurements.

10.1021/ja805058t CCC: $40.75

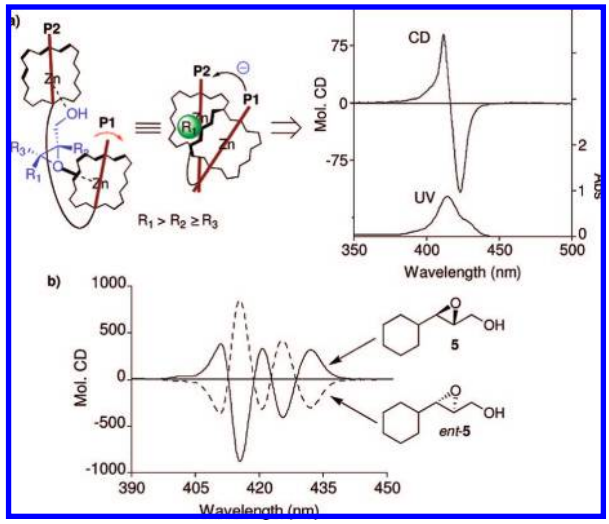


Figure 1. (a) Proposed complexation pattern between tweezer **1** and epoxy alcohol. Negative ECCD spectrum was obtained for compound **4**; (b) enantiomeric ECCD of **5** and ***ent*-5** (40 equiv) in hexane exhibiting complex CD.

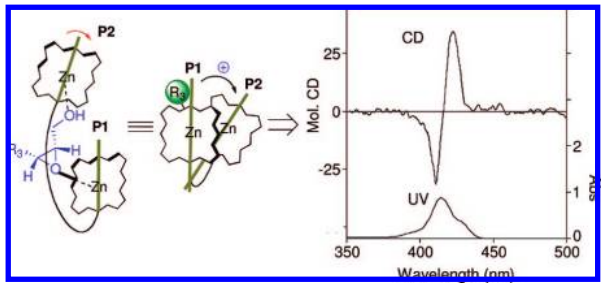


Figure 2. Proposed complexation pattern between tweezer **1** and *cis*-epoxy alcohol. Positive ECCD spectrum was obtained for **11**.

faces **P1**. In case of *trans*-disubstituted epoxy alcohols ($R_2 = R_3 =$ H) depicted in Figure 1a, **P1** slides away from R_1 in preference for the smaller hydrogen atom, thus generating the energetically favored complex in which the two chromophores are twisted in a counterclockwise fashion. Consequently, a negative ECCD spectrum is observed for (2*S*,3*S*) *trans*-disubstituted substrates. Interestingly, compounds **3** and **5** exhibited complex CD patterns with a fairly high amplitude when 1−100 equiv of guests were added (Figure 1b).[16] This unique behavior was observed only in chiral epoxides with α-branched aliphatic substituents (see SI for further discussion). Although the following statement is based on observation and has no theoretical basis, we have noticed that the sign of the first CE for the complex CD spectra is the same as the sign of the anticipated ECCD.

With *cis*-disubstituted epoxy alcohols complexed with tweezer, **P1** (assuming it also coordinates with the lone pair *anti* to the hydroxyl bound **P2**) faces no steric bias since both R_1 and R_2 are hydrogen atoms. The steric interaction between **P2** and R_3 would drive **P2** away from R_3, leading to a clockwise twist of the two porphyrins relative to each other (Figure 2), and hence a positive ECCD signal is expected for (2*S*,3*R*) *cis*-disubstituted substrates. This was indeed observed experimentally (**11**−**14**). It is instructive to note that **14** yields a strong ECCD signal despite its fairly low optical purity (22% *ee*, see SI for correlation of %ee with amplitude of ECCD).[17]

Next, we turned our attention to trisubstituted epoxy alcohols (**15**−**19**), which upon complexation with Zn-TPFP-tz **1** resulted in CD spectra that could be rationalized by the binding model depicted in Figure 1a. For both 2,3,3 ($R_2 =$ H) and 2,2,3 ($R_3 =$ H) trisubstituted substrates, **P1** slides away from the bulky R_1 group in a similar manner as was described for *trans*-disubstituted substrates to minimize steric clash. The resultant counterclockwise helicity results in a negative ECCD spectrum for 2*S*,3*S* substrates (**15**, **18**). Accordingly, positive signals would reflect 2*R*,3*R* configuration (**16**, **19**). It should be noted that, with 2,3,3-trisubstituted olefins, the nature of R_3 is inconsequential, since **P1** is bound away from R_3 and undergoes steric differentiation between R_1 and the hydrogen atom (positioned at R_2 in Figure 1a). Conversely, with 2,2,3-trisubstituted olefins, both R_1 and R_2 face **P1**, and thus steric differentiation is governed by their relative sizes. In examples listed in Table 1 (**18** and **19**) R_1 is larger than R_2, thus leading to the observed ECCD spectra.

2,2-Disubstituted epoxy alcohols ($R_1 = R_3 =$ H), with R_2 facing **P1** should also lead to predictable ECCD spectra based on the fact that **P1** would slide away from R_2 toward the H atom (R_1 in Figure 1a). This is indeed observed, as the anticipated sign of the ECCD for **20** and **21** matches the experimentally observed data (**20** and **21** bearing 2*S* configuration yield positive ECCD, resulting from steric discrimination between R_2 (*n*-octyl group or $PhCH_2CH_2-$) and R_1 (H)). In contrast, epoxy alcohol **22** did not yield an observable ECCD. This is not surprising since there are no steric determinants that orient **P1** and **P2** relative to each other.

In summary, we have demonstrated the facile determination of absolute configurations for 2,3-epoxy alcohols with various substitution patterns utilizing Zn-TPFP-tz **1** devoid of any derivatization in a microscale fashion requiring only micrograms of substrate via the nonempirical ECCD methodology. We are presently exploring the extension of this methodology to epoxy alcohols bearing a chiral hydroxyl group.

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Supporting Information Available: Synthesis of epoxy alcohols and general procedures for CD measurements. Determination of K_{assoc} for complexation of **7** with tweezer **1**. This material is available free of charge via the Internet at http://pubs.acs.org.

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(11) Li, X. Y.; Tanasova, M.; Vasileiou, C.; Borhan, B. *J. Am. Chem. Soc.* **2008**, *130*, 1885–1893.
(12) The binding constant for a typical diol with **1** in hexane is 1.52×10^5 M^{-1}.
(13) Harada, H.; Nakanishi, K. *Circular Dichroic Spectroscopy: Exciton Coupling in Organic Stereochemistry*; University Science Books: Mill Valley, CA, 1983.
(14) Nakanishi, K.; Berova, N.; Woody, R. W. *Circular Dichroism: Principles and Applications*; VCH: New York, 1994.
(15) Zn-TPP-tz used previously for absolute stereodetermination of diamines was examined; however, it failed to yield ECCD spectra with a number of epoxy alcohols, presumably due to its weak binding with the substrate.
(16) Similar ECCD signal was obtained for **5** in hexane, methylcyclohexane, and isooctane while no CD was detected in benzene, toluene, CH_3CN, and CH_2Cl_2.
(17) Substrates **11** (67% *ee*), **12** (56% *ee*), **13** (65% *ee*), and **21** (72% *ee*) with low optical purity also rendered prominent ECCD.

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