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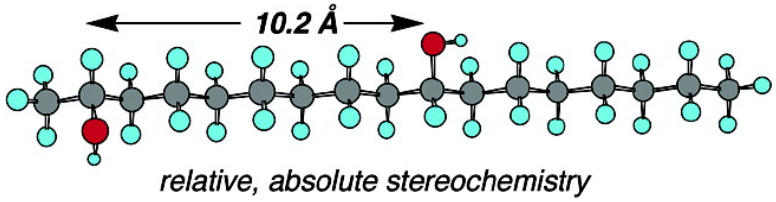

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Long-Range Stereo-Relay: Relative and Absolute Configuration of 1,*n*-Glycols from Circular Dichroism of Liposomal Porphyrin Esters

John B. MacMillan and Tadeusz F. Molinski*

Department of Chemistry, One Shields Avenue, University of California, Davis, California 95616

Received April 19, 2004; E-mail: tfmolinski@ucdavis.edu

Long-chain natural product lipids, bearing multiple hydroxyl substituents (e.g. caylobolide A, **1**, from the cyanobacterium *Lyngbya majuscula*)[1] are often encountered in natural products polyketides and glycolipids and exemplify a particularly difficult problem in stereochemical determination—how to relate the relative configurations of two or more isolated stereogenic centers.

Polyketides may contain segments that embody 1,3-, 1,5-, or even 1,7-glycols. Successful approaches to solving 1,2- and 1,3-glycol configurations[2] include ^{13}C NMR analysis of the corresponding 1,3-glycol acetonides,[2a] exciton coupling CD (ECCD) of dibenzoates (or other aryl carboxylates) of 1,2- and 1,3-glycols,[2c,d] NMR-based *J*-based analysis of ^{1}H−^{1}H and ^{1}H−^{13}C coupling constants,[2e] and the proposed "universal NMR database"[2f−h] that addresses stereochemistry through least-difference analysis of ^{13}C NMR chemical shifts ($\Delta\delta$). The latter methods have powerful advantages but rely upon adequate NMR signal dispersion and reliable chemical shift assignments. Within acyclic chains or macrocylic polyketides, OH groups separated by four or more C−C bonds are effectively "insulated" from each other as stereogenic elements and do not convey configurational information from their NMR or CD spectral properties. For example, unlike 1,2-dibenzoates,[3] the CD spectra of acyclic 1,5-glycol diarylcarboxylate esters in isotropic solution show only baseline signal.

A solution to the problem resides in pre-alignment of the long chains by imposing partial ordering within lipid bilayers (Figure 1) to allow nonaveraged orientations of the chromophore charge-transfer electronic dipole moments. We describe herein long-range transmission of stereochemical information within 1,*n*-glycol lipids (where $n = 5,7$, and 9) that gives relative *and* absolute configurations of glycol molecules from interpretation of ECCD of their derived porphyrin carboxylate diesters within submicrometer liposomes.

A model study served to demonstrate the proof of principle. C_2 symmetric enantiomeric glycols, (*R*,*R*)-**2** and (*S*,*S*)-**3** (>99% ee), were prepared from (*R*)-1,2-epoxypentane (*R*)-**4** and (*S*)-**4**, respectively, through double C2-alkylation of 1,3-dithiane (*t*-BuLi), followed by removal of the dithiane (Raney Ni) (see Supporting Information). The *meso*-isomer, **5**, was separated from the mixture obtained by double addition of *n*-propylmagnesium bromide to pentane-1,5-dinitrile followed by reduction of the resultant 4,8-diketone.[4]

Three arylcarboxylate chromophores, commonly used in configurational analysis by ECCD, were chosen for initial examination (Figure 2, X = OH) 2-naphthoic acid (***a***, λ_{max} 234 nm, ϵ 58000), and two red-shifted chromophores, 7-(diethylamino)coumarin-3-carboxylic acid (***b***, λ 540 nm, ϵ 80000)[5] and 4-(10,15,20-triphenylporphyrin-5-yl)-benzoic acid (TPP, ***c***, λ_{max} 418 nm, ϵ 350000).[6b] Stereoisomers, **2**, **3**, and **5** were acylated with either the free carboxylic acid ***a***−***c*** (5 equiv, glycol, DCC, DMAP, CH_2Cl_2) or the corresponding *N*-acylimidazole (glycol, DBU, CH_3CN) to obtain the diesters **2a**−**c**, **3c**, and **5c** which were purified by HPLC.

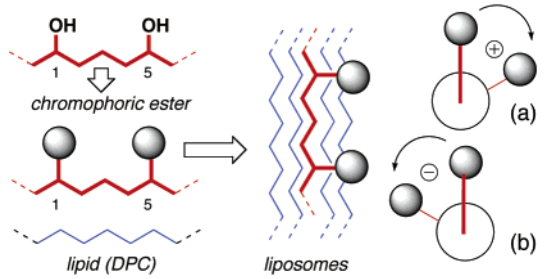

Figure 1. Ordering of long-chain bis-arylcarboxylate esters of 1,5-glycols in liposomes. (a) Sign of bisignate CD of 1,5-glycol arylcarboxylate esters: *positive* for 1,5-(*R*,*R*), (b) *negative* for 1,5-(*S*,*S*).

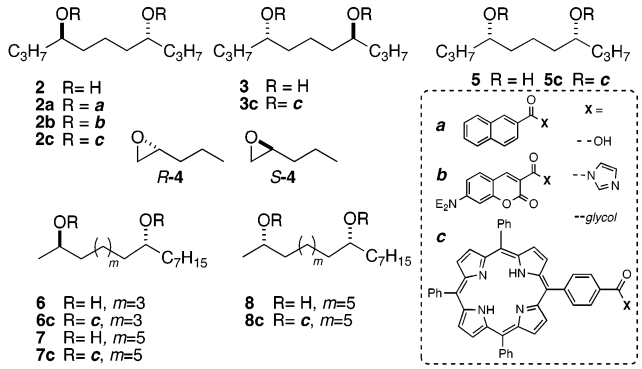

Figure 2. Model glycols, esters, and chromophores for ECCD.

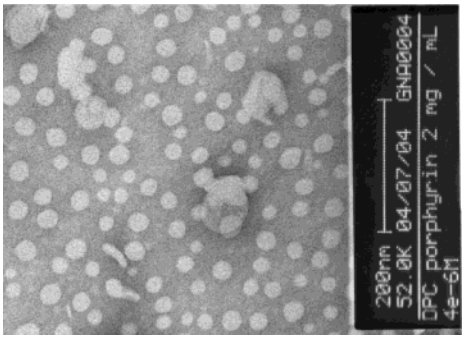

Figure 3. TEM image of liposomes containing (*R*,*R*)-**2c**. Scale bar = 200 nm (mean liposome diameter $\phi = 26 \pm 5.1$ nm).[8]

Liposomal glycol bis-TPP esters were formulated according to a procedure developed for the purpose of this work.[7] Transmission electron microscopy (TEM) of the product (Figure 3) revealed highly uniform, unilamellar liposomes of narrow size distribution ($\phi = 26 \pm 5.1$ nm).[8]

Measurement of the CD of (*R*,*R*)-**2a**-**c** in MeOH or (*R*,*R*)-**2a**-**b** in liposomes gave only baseline spectra; however, the CD spectrum of (*R*,*R*)-**2c** in liposomes (Figure 4a) showed a strong positive bisignate signal due to exciton coupling [λ_{max} 430 nm ($\Delta\epsilon$ +27),

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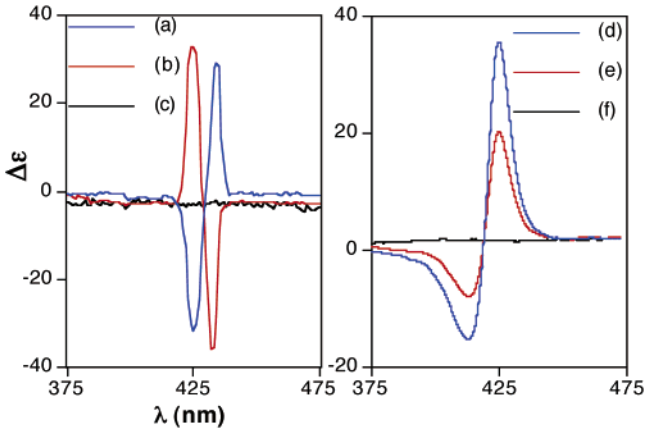

Figure 4. CD spectra of TPP glycol esters in DPC liposomes (2 mg/mL, 1,2-distearoyl-*sn*-glycero-3-phosphocholine). (a) (*R*,*R*)-**2c**, (b) (*S*,*S*)-**3c**, (c) *meso* ester **5c** ($c = 1 \times 10^{-6}$ M), (d) (*R*,*R*)-**6c**, (e) (*R*,*R*)-**7c**, and (f) pseudo-*meso* (*S*,*R*)-**8c** ($c = 6.5 \times 10^{-7}$ M).

413, (−25), *A* value[3c] = max − min = 52]. The enantiomer, (*S*,*S*)-**3c**, gave a bisignate CD spectrum of opposite sign and magnitude [λ 413 nm ($\Delta\epsilon$ −34); 429 nm, $\Delta\epsilon$ +31, $A = 65$) while the CD spectrum of *meso*-**5c** ester showed only baseline signal.

The signs of the bisignate CD spectra of liposomal TPP glycol diesters (*R*,*R*)-**5c** and (*S*,*S*)-**5c** correlate with the helicity predicted from consideration of the extended conformation of the lipid chain (Figure 1a,b)[9] and the well-known dependence of the signs of bisignate CD spectra with the absolute helicity of the electric transition dipole moments of coupled chromophores.[3c] The ECCD of (*R*,*R*)-**5c** showed a nonlinear concentration dependence above $c = 10$ μM; optimal concentration appears to be ≤ 1 μM. As has been noted by Nakanishi and co-workers,[6a,b] TPP diol esters provide very high extinctions and good $\Delta\epsilon/\epsilon$ ratios which, in the present case, leads to excellent sensitivity (limit of detection ∼40 pmol).

The distance dependence of liposomal ECCD in TPP diesters of acyclic 1,*n*-glycols was briefly examined. Diastereomeric glycols **6** ($n = 7$) and **7** ($n = 9$) have the two OH groups disposed *anti*- ("pseudo-C_2" symmetric), while in **8** ($n = 9$) they are *syn*- ("pseudo-*meso*"). The CD spectra of (*R*,*R*)-**6c** and **7c**, (Figure 3b) exhibited strong positive bisignate curves[13] with *A* values ($A = 51$ and 27, respectively) that diminish roughly linearly with *n* and the interatomic distance between the ester oxygens (∼10 Å for $n = 9$, Supporting Information). Again, the pseudo-*meso* (**8c**) showed only baseline signal. Assuming linearity beyond $n = 9$, extrapolation of the *A* versus *n* plot suggests that the limiting distance for ECCD detection should occur at $n = 13$ (∼15 Å, Chem3D model).

The present work demonstrates *transmission of stereochemical information across extraordinary atomic distances (8 C−C bonds) in liposomal acylic diol esters*. This method will find use in critical stereochemical determinations of hydroxylated long-chain natural product polyketides.

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Supporting Information Available: Preparation of model glycols, ^{1}H and ^{13}C NMR and MS of compounds, graphs of ECCD concentration dependence and distance dependence of *A* values. This material is available free of charge via the Internet at http://pubs.acs.org.

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(4) All new compounds gave satisfactory ^{1}H and ^{13}C NMR and HRMS spectra. Reduction of 4,8-undecanedione ($NaBH_4$, MeOH) gave diastereomeric glycols, which were separated by prep. HPLC (5 μ silica, Microsorb, 10 mm × 250 mm, 1:9 *i*-PrOH/hexane) to give pure (±)-**2** (R_t = 12.7 min, identified by co-injection with authentic (+)-**2**) and *meso*-**5** (R_t 14.3 min) (See Supporting Information).

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(7) A solution of TPP ester and DPC (2 mg/mL) in $CHCl_3$ was "shell-evaporated" in a 50-mL round-bottom flask. Distilled H_2O (2 mL) was added and the flask sonicated (∼60 s). The crude liposome preparation was twice heated (60 °C) and cooled to room temperature, then repeatedly extruded (×21) through a 100-nm membrane filter secured between two gastight 0.5-mL syringes (Liposofast, Avestin, Canada) to give unilamellar liposomes (see Figure 3).

(8) Uniform liposomes of a diameter ($\phi = 26 \pm 5.1$ nm) smaller than the λ_{max} of TPP excitation (λ 418 nm) greatly reduce loss of CD signal from non-Rayleigh light scattering. CD of 1,5-glycol TPP esters in micelles (aq. 1-*O*-octyl glycoside) or 2D-liquid crystals gave inferior results.

(9) We cannot exclude secondary effects, e.g. $\pi-\pi$ stacking of porphyrin rings.

(10) Methyl carbinols **6**−**8** were prepared from (*R*)-1,2-epoxynonane (>99% ee). Epimeric C2 carbinol mixtures of **6**−**8** were resolved by lipase-catalyzed acetylation (Novozym 435,[12] vinyl acetate, CH_3CN). The separated product diacetates and unreacted (2*S*) alcohols were converted into stereomerically pure glycols by ammoniolysis (NH_3, MeOH). (>99% de by Mosher's analysis) (see Supporting Information).

(11) CD (**6c**): λ 426 nm ($\Delta\epsilon$ +36), 415 (−15). CD (**7c**): 426 ($\Delta\epsilon$ +20), 415 (−7).

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(13) Bis-TPP esters of rigid dimeric sterol diol scaffolds have been shown to exhibit comparable ECCD at separations of ∼18 Å.[6a]

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