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Determining Absolute Configuration in Flexible Molecules: A Case Study

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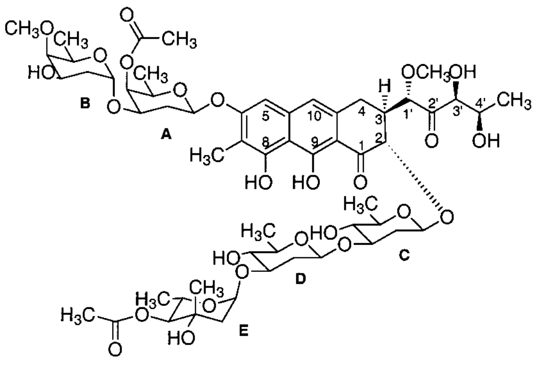
Abstract: Assigning absolute configuration of molecules continues to be a major problem. Determining absolute configuration in conformationally flexible systems is challenging, even for experts. Here, we present a case study in which we use a combination of molecular modeling, solution NMR, and X-ray crystallography to illustrate why it is difficult to use solution methods alone for configuration assignment. For the case examined, a comparison of calculated and experimental optical rotatory dispersion (ORD) data provides the most straightforward way to assign the absolute configuration.

Introduction

The two most common methods for determining absolute configuration in solution are the circular dichroism (CD) exciton chirality method, pioneered by Nakanishi and Harada,[1] and NMR analysis of diastereomeric esters, first introduced by Mislow[2] and later developed by Mosher[3] and others.[4] In the course of synthesizing analogues of the antitumor antibiotic Chromomycin A_3 (**1**, CRA_3),[5] we prepared **2** (Scheme 1) as a racemic mixture and performed a kinetic resolution using *Pseudomonas fluorescens* lipase (PFL).[5c] Prior to carrying products **3** and **4** forward, we needed to determine their absolute configurations. The common methods gave contradictory results, (*R*) from the CD method and (*S*) from the NMR method for **3**. In an attempt to resolve this issue, we compared the calculated and experimental optical rotatory dispersion (ORD) data for "aglycone" **3** and found the results to agree with the (*S*) configuration determined using Mosher ester analysis.[6] Subsequently, single-crystal X-ray diffraction studies of bis(bromobenzoate) **5** unambiguously established the configuration as (*S*) (Figure 1). Below, we discuss unforeseen difficulties that preclude the reliable application of the CD exciton chirality method for the absolute configuration assignment of **3** and **4**. We suggest that computational techniques have reached the point where the comparative ORD method rivals other solution methods for determining absolute configuration.



Chromomycin A_3
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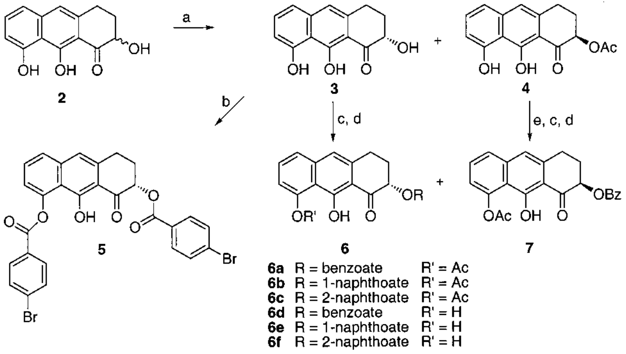
Scheme 1



[a] PFL, vinyl acetate, rt, 4 h (53%). [b] *p*-Bromobenzoyl chloride (2 equiv), *N*-methylimidazole (3 equiv), 2:1 CH_2Cl_2/propylene oxide, rt, 30 min (60%). [c] Acetyl chloride (1 equiv), *N*-methylimidazole (0.2 equiv), 2:1 CH_2Cl_2/propylene oxide, rt, 2.5 h (74%). [d] Acyl chloride, *N*-methylimidazole, 2:1 CH_2Cl_2/propylene oxide, rt, 2 h (50−70%). [e] PFL, 50 mM phosphate buffer, pH = 7, rt, overnight (40%).

Results and Discussion

Intending to use the exciton chirality method to assign the configuration of **3** and **4**, we converted **3** and **4** to benzoate esters **6a** and **7**, respectively (Scheme 1). The CD exciton chirality method requires knowing the relative orientation of the two chromophores. NMR coupling constants for the H2 protons of **6a** and **7** were 12.5 and 5.1 Hz, consistent with a conformation in which the benzoate is equatorial. On the basis of the assumption that the methine hydrogen was *syn*-coplanar

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(1) (a) Harada, N.; Nakanishi, K.; Tatsuoka, S. *J. Am. Chem. Soc.* **1969**, *91*, 5896−5898. (b) Harada, N.; Nakanishi, K. *Cicular Dichroic Spectroscopy-Exciton Coupling in Organic Stereochemistry*; University Science Books: Mill Valley, CA, 1983. (c) Berova, N.; Nakanishi, K. *Exciton Chirality Method: Principles and Applications*, 2nd ed.; Berova, N., Nakanishi, K., Woody, R. W., Eds.; Wiley-VCH: New York, 2000, pp 337−382.

(2) (a) Raban, M.; Mislow, K. *Tetrahedron Lett.* **1965**, *48*, 4249−4253. (b) Raban, M.; Mislow, K. *Top. Stereochem.* **1967**, *2*, 199−230. (c) Lewis, R. A.; Korpiun, O.; Mislow, K. *J. Am. Chem. Soc.* **1967**, *89*, 4786−4787.

(3) Dale, J. A.; Mosher, H. S. *J. Am. Chem. Soc.* **1973**, *95*, 512−519.

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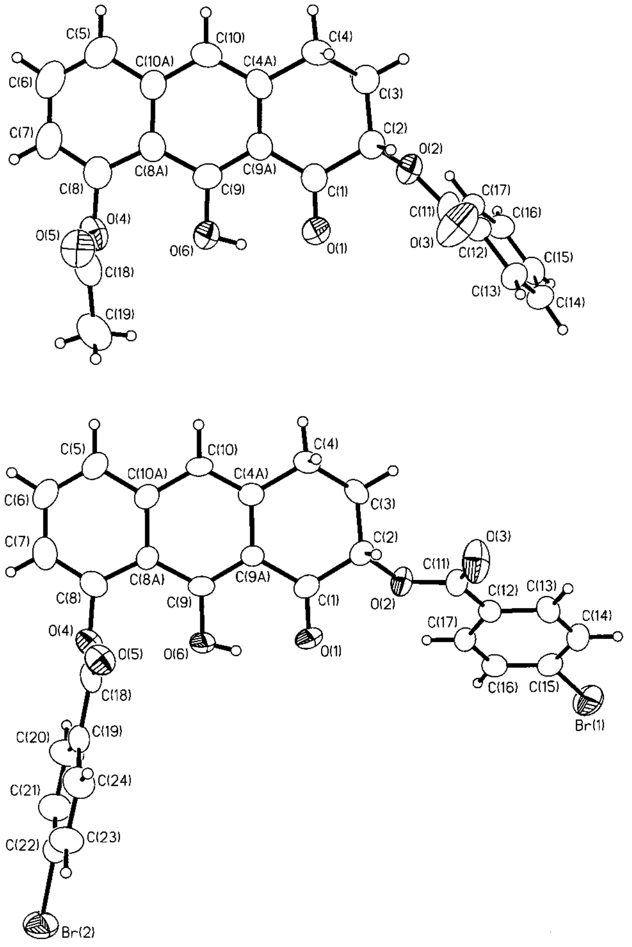


Figure 1. X-ray structures of **6a** (top) and **5** (bottom). Thermal ellipsoids have been drawn at the 50% probability level.

to the benzoate carbonyl,[7] **6a** and **7** would be predicted to give very weak exciton split Cotton effects,[1c] the sign of which should reflect the absolute configuration. As shown in Figure 2, benzoate ester **6a** gave rise to a negative exciton couplet (263 nm, $\Delta\epsilon = -20.7$), which led to an initial assignment of (*R*), and the enantiomeric ester **7** gave the opposite pattern and an assignment of (*S*).[5c] Mosher ester analysis predicted the opposite configurations, calling the CD assignments into question. We had already been concerned about the intensity of the CD signals for **6a** and **7**, which were stronger than expected. Naphthoate esters can be used in place of benzoate esters for the CD method, and because they have higher extinction coefficients, they are expected to give more intense signals. Therefore, we constructed the naphthoate esters **6b**,**c** and measured their CD spectra (Figure 2). The CD couplet for the 2-naphthoate derivative (**6c**) had the same shape as that for **6a**, but the signal intensity was smaller rather than larger. The 1-naphthoate derivative (**6b**) gave a spectrum with a barely detectable Cotton effect of the opposite sign to that of **6c**. Determination of absolute configuration from the sign of the exciton couplet, in this case, reached a borderline where subtle conformational effects complicated the assignment.

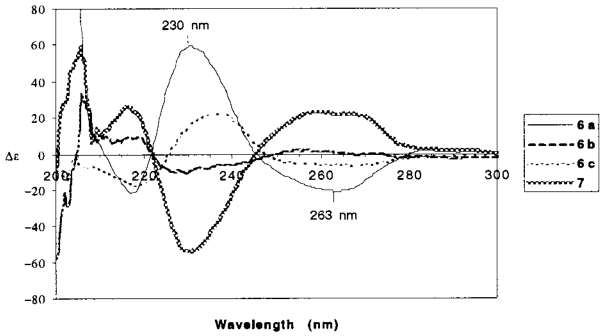
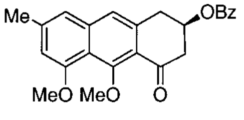


Figure 2. Circular dichroism spectra of compounds **6a**−**c** and **7** in methanol.

The CD method for determining absolute configuration is undeniably useful for many systems,[8] but our experience highlights some of its limitations.[9] To use it effectively, one must know the orientation of the two chromophores with respect to each other, which in turn requires having a conformationally homogeneous molecule, or at least a molecule in which the CD spectrum reflects the dominant conformation. Although compounds **3** and **4** would appear to be relatively rigid and, thus, ideally suited for the CD method, a conformational analysis of several ester derivatives of **3** using four different computational methods shows that this is not the case (Table 1). For example, there are several distinct low-energy conformations within 1.5 kcal/mol for the benzoate ester **6d**. The orientations of the benzoate group with respect to the tricyclic core are quite different in the various conformations (Figure 3). Because the relative orientation of the chromophores determines the sign and magnitude of the CD, and because it would be predicted to be positive for some conformations and negative for others, the experimental CD spectrum is simply the population-weighted average spectrum.



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In 1994, Endo and Naoki[10] used the CD method to assign the configuration of closely related compound **8** as (*R*). In that case, NMR analysis showed that the C3 ester was axial. Our

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[4] (a) Trost, B. M.; Belletire, J. L.; Godleski, S.; McDougal, P. G.; Balkovec, J. M. *J. Org. Chem.* **1986**, *51*, 2370−2374. (b) Ohtani, I.; Kusumi, T.; Kashman, Y.; Kakisawa, H. *J. Am. Chem. Soc.* **1991**, *113*, 4092−4096. (c) Latypov, S. K.; Seco, J. M.; Quinoa, E.; Riguera, R. *J. Am. Chem. Soc.* **1998**, *120*, 877−882.

[5] (a) Silva, D. J.; Kahne, D. E. *J. Am. Chem. Soc.* **1993**, *115*, 7962−7970. (b) Silva, D. J.; Robert Goodnow, J.; Kahne, D. *Biochemistry* **1993**, *32*, 463−471. (c) Silva, D. J.; Kraml, C. M.; Kahne, D. *J. Am. Chem. Soc.* **1994**, *116*, 2641−2642. (d) Silva, D. J.; Kraml, C. M.; Kahne, D. *Bioorg. Med. Chem.* **1994**, *2*, 1251−1259.

[6] The (*R*,*R*)-, (*R*,*S*)-, (*S*,*R*)-, (*S*,*S*)-α-methoxy-α-trifluoromethylphenylacetate esters of **6** and **7** were synthesized using the commercially available acyl chlorides, using the same conditions as in Scheme 1d, and analyzed according to ref 4b.

[7] See ref 1c and (a) 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. (b) Lightner, D. A.; Gurst, J. E. *Organic Conformational Analysis and Stereochemistry from Circular Dichroism*; Wiley-VCH: New York, 2000, pp 423−456.

[8] For conformationally homogeneous systems, the CD method has shown tremendous utility, specifically for assignment of carbohydrates. See (a) Wiesler, W. T.; Berova, N.; Ojika, M.; Meyers, H. V.; Chang, M.; Zhou, P.; Lo, L. C.; Niwa, M.; Takeda, R.; Nakanishi, K. *Helv. Chim. Acta* **1990**, *73*, 509−551. (b) Akritopoulou-Zanze, I.; Nakanishi, K.; Stepowska, H.; Grzeszczyk, B.; Zamojski, A.; Berova, N. *Chirality* **1997**, *9*, 699−712.

[9] For a detailed explanation of other limitations see: (a) Person, R. V.; Monde, K.; Humpf, H.-U.; Berova, N.; Nakanishi, K. *Chirality* **1995**, *7*, 128−135. For other cases where the CD method could not be applied see: (b) Chisholm, J. D.; Golik, J.; Krishnan, B.; Matson, J. A.; Vranken, D. L. V. *J. Am. Chem. Soc.* **1999**, *121*, 3801−3802. (c) Hattori, T.; Sakurai, K.; Koike, N.; Miyano, S.; Goto, H.; Ishiya, F.; Harada, N. *J. Am. Chem. Soc.* **1998**, *120*, 9086−9087. (d) Alcaraz, L.; Macdonald, G.; Ragot, J. P.; Lewis, N.; Taylor, R. J. K. *J. Org. Chem.* **1998**, *63*, 3526−3527. (e) Capon, R. J.; MacLeod, J. K. *Tetrahedron* **1988**, *44*, 1637−1650.

[10] Endo, M.; Naoki, H. *Tetrahedron* **1980**, *36*, 2449−2452.

Table 1. Calculated Energies of Conformations of Benzoate and Naphthoate Esters of **6**

	computational method			
cmpd/conformation	MMFF	AM1	HF/6-31G(d)	B3LYP/6-31G(d)
		Benzoate Ester		
6d/A (≈ X-ray of **6a**)	0.00[a]	−137.28[b] (0.00)[a]	−1178.92732[c] (0.00)[a]	−1186.04124[c] (0.00)[a]
6d/B (≈ X-ray of **5**)	−0.51	−137.13 (0.15)	−1178.92658 (0.46)	−1186.04071 (0.33)
6d/C	1.40	−135.88 (1.40)	−1178.92514 (1.37)	−1186.03942 (1.14)
6d/D	0.39	−135.96 (1.32)	−1178.92488 (1.53)	−1186.03874 (1.57)
6d/E	3.85	−133.91 (3.37)		
6d/F	14.91	−130.93 (6.35)		
		1-Naphthoate Ester		
6e/e1-st-anti2[d]	0.11	−116.72 (0.00)		
6e/e2-st-anti2	0.00	−116.71 (0.01)		
6e/e1-st-syn2	0.31	−116.50 (0.22)		
6e/e1-st-anti1	0.51	−116.32 (0.40)		
6e/e2-st-anti1	0.84	−115.99 (0.73)		
6e/e2-st-syn1	1.44	−115.48 (1.24)		
6e/e1-st-syn1	0.89	−115.31 (1.41)		
6e/a2-st-anti2	1.82	−115.23 (1.49)		
6e/e3-st-anti2	0.63	−115.22 (1.50)		
6e/e3-st-anti1	0.88	−115.03 (1.69)		
6e/e3-st-syn1	0.69	−115.02 (1.70)		
6e/a2-st-anti1	2.45	−115.02 (1.70)		
6e/a2-st-syn2	1.96	−114.76 (1.96)		
6e/e3-st-syn2	1.34	−114.18 (2.54)		
		2-Naphthoate Ester		
6f/e1-st-syn[d]	0.55	−118.63 (0.00)		
6f/e1-st-anti	0.52	−118.57 (0.06)		
6f/e2-st-syn	0.01	−118.54 (0.09)		
6f/e2-st-anti	0.00	−118.40 (0.23)		
6f/a2-st-syn	1.94	−117.34 (1.29)		
6f/e3-st-syn	0.96	−117.29 (1.34)		
6f/e3-st-anti	0.92	−117.26 (1.37)		
6f/a2-st-anti	1.95	−117.18 (1.45)		
6f/a3-st-syn	4.43	−115.27 (3.36)		
6f/a3-st-anti	4.39	−115.24 (3.39)		
6f/e1-sc-syn	15.23	−112.28 (6.35)		
6f/e1-sc-anti	15.28	−112.06 (6.57)		

[a] Relative energies (kcal/mol) of benzoate derivative **6d** are referenced to the X-ray conformation of **6a**. [b] Enthalpy of formation in kcal/mol. [c] Energy in au (1 au = 627.503 kcal/mol). [d] For the conformations of the naphthoate esters, the calculated conformations are enumerated in the following way: (1) for the orientation about the C(2)−O(2) bond (see Figure 1), there are three potential axial (a1, a2, a3) and three potential equatorial (e1, e2, e3) conformations; (2) the configuration about O(2)−C(11) is nearly always s-trans (st), but a few s-cis minima were located (sc); (3) the naphthoate may be oriented so that its distal ring is either syn or anti to the carbonyl group, and in the case of the 1-naphthoates, there are potentially two syn (syn1, syn2) and two anti (anti1, anti2) conformations, because of steric conflicts between the peri substituents. The conformational searches for the naphthoates were not exhaustive.

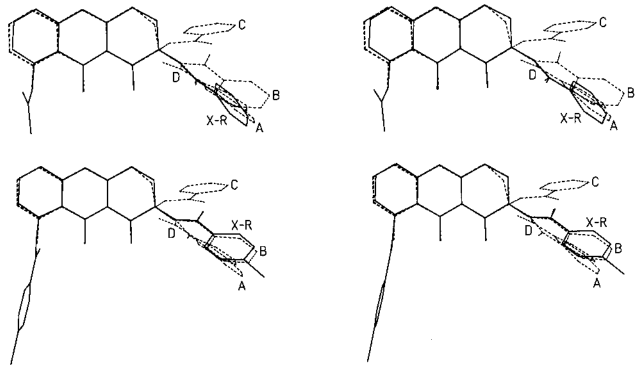

Figure 3. Stereoviews of the X-ray structures of **6a** (top) and **5** (bottom) overlaid with the four low energy conformations calculated using the B3LYP/6-31G(d) method.

modeling studies show an accessible axial orientation of the benzoate in **6d** (C, Table 1). Although this orientation would likely occupy less than 10% of the total population, on the basis of the energy calculations, it would result in a more intense exciton couplet, because of a more favorable angle between the chromophores. This more intense signal would dominate the weaker CD signals contributed by the equatorial conformations. This would largely account for the observed spectrum. Additional calculations have shown that the distribution of conformations varies, depending on the substituents, even for closely related series **6d**−**f** (Table 1), a result consistent with our finding that the CD signal can change in unexpected and unpredictable ways when the ester chromophore is varied (**6a**−**c**, Figure 2).

Although it was not possible to determine the absolute configuration of **3** and **4** using the CD method, we were able to obtain X-ray structures of bis(bromobenzoate) compound **5** as well as **6a** (Figure 1). The crystal structure of **5** established that the configuration of **3** is (*S*). The crystal structures also confirmed that there are at least two accessible conformations in which the orientations of the benzoates with respect to the aglycones are dramatically different. For example, **5** crystallized in what was calculated to be the second lowest energy conformation (B, Table 1), with a torsion angle of −27.9° for H(2)−C(2)−O(2)−C(11). Compound **6a** crystallized in the lowest energy conformation (A, Table 1), with a torsion angle of +21.0°. These conformations would give rise to CD signals of opposite sign, highlighting the importance of knowing the relative populations of these and all other conformations prior

Table 2. Computed Rotation Angles for (*S*)-**3** Using MM2*/6-31G at Three Wavelengths

	Boltzmann-averaged angles, deg		
		DALTON	
wavelength, nm	CADPAC	non-London	London
589	−39.4	−40.9	−66.2
578	−40.9	−42.5	−68.9
546	−45.8	−47.8	−77.0

to assigning the chirality of ester derivatives of **3** by the exciton chirality method.

The question arises as to how one might determine the configuration of **3** or some similarly flexible system if one could not obtain crystals. The ideal method for assigning absolute configuration would be one that does not require derivatization. Derivatization adds steps, can be complicated by incompatible functionality in the molecule or steric congestion at the reaction center, and introduces the possibility of epimerization.[4a] Furthermore, methods that require derivatization, including the CD method and the Mosher ester method, make assumptions about the disposition of the derivative that must be valid in order to assign the configuration correctly.[11] In the past, optical rotatory dispersion (ORD), which does not require derivatization, was sometimes used to establish absolute configuration.[12] ORD, however, was limited to compounds closely related to a model compound for which an experimental ORD spectrum was available *and* for which the absolute configuration had been independently established. These limitations were severe. However, recent advances in computational methods now make it possible to use ORD to establish absolute configuration reliably. Experimental ORD spectra can simply be compared to ORD spectra calculated from a Boltzmann-weighted set of geometries of the structure in question, as determined by computational methods.[13] In the present case, the experimentally determined optical rotation for **3** at an incident wavelength of 589 nm ($[\alpha]_D$) was −69 (*c* 0.1, $CHCl_3$). The calculated rotation at this wavelength, in the dynamic field approximation, was −66, in excellent agreement with experiment. The agreement between calculated and experimental values was found to be excellent at 578 and 546 nm as well (Table 2; experimental values were −72 and −88, respectively).

One could also use a similar approach for the calculation of the CD spectrum.[14] However, in the present case, the tricycle **3** has only two possible conformations, but the benzoate ester has at least six, and the naphthoates **6e**,**f** have at least a dozen each (Table 1). Simulation of the CD spectrum of each of the esters would require the Boltzman-weighted summations of the calculated CD spectra of each of the many accessible conformations. The many conformational degrees of freedom introduced by the addition of the ester derivatives complicates the computational analysis.[15] For the present case, ORD is a better choice, because there are many fewer conformations and the calculations are simpler.

Conclusions

A large portion of the chiral compounds for which one might want to determine absolute configuration possess some degree of conformational flexibility. Our experience shows that even a small degree of flexibility can complicate assignment of absolute configuration by CD, if the relative orientation of interacting chromophores is affected. The solution is to use calculations to take this flexibility into account. Ab initio calculations of optical rotation angles based on a Boltzmann-weighted set of geometries can be accomplished quickly for most small and medium sized molecules. In cases where experimental ORD data cannot be obtained because of insufficient material, then the CD microscale exciton chirality method becomes a useful alternative, because the drawbacks to derivatization are more than compensated for by the enhancement in sensitivity. Again, however, it is essential to compare the experimental CD spectrum to that calculated from a Boltzmann-weighted set of geometries in order to make the correct assignment.

Experimental Section

General Methods. Unless otherwise stated, all chemicals were purchased from Aldrich or Sigma and used without further purification. Methylene chloride was distilled from calcium hydride under dry argon. All reactions were carried out under argon atmosphere with freshly distilled solvents under anhydrous conditions, unless otherwise noted.

Analytical thin-layer chromatography (TLC) was performed using silica gel 60 F254 precoated plates (0.25 mm thickness) with a fluorescent indicator. The developed plates were examined under shortwave UV light. Preparative TLC was performed using 20 cm × 20 cm 1000 μm silica gel GF plates from Analtech, Inc.

NMR spectra were recorded on a Varian Inova 500 Fourier transform NMR spectrometer. Chemical shifts (δ) are reported in parts per million (ppm) downfield from tetramethylsilane (TMS). Coupling constants (*J*) are reported in hertz (Hz). Multiplicities are abbreviated as follows: singlet (s), doublet (d), triplet (t), quartet (q), multiplet (m), doublet of doublets (dd), and broad singlet (bs).

CD spectra were recorded on a JASCO-810 spectropolarimeter driven by a JASCO V500/FP-750 data analysis program for Windows. The CD spectra were measured in millidegrees and normalized to $\Delta\epsilon$ [L mol^{-1} cm^{-1}]/λ [nm] units.

(*S*)-2,8-(*O*)-Bis(bromobenzoyl)-2,8,9-trihydroxy-3,4-dihydro-1(2*H*)-anthracenone (5). Residual water was removed from **3** (20 mg, 82 μmol) by azeotropic distillation with toluene. Compound **3** was then dissolved in CH_2Cl_2 (1.5 mL) and propylene oxide (0.75 mL). Bromobenzoyl chloride (54 mg, 155 μmol) and *N*-methylimidazole (20 μL, 250 μmol) were added, and the reaction was stirred at room temperature for 30 min. The reaction mixture was diluted with CH_2Cl_2 and poured into a solution of 0.1 N HCl (5 mL). The organic layer was washed with saturated aq $NaHCO_3$ (2 × 5 mL), dried over Na_2SO_4, and concentrated in vacuo. The residue was purified by preparative TLC (1:15:85 HOAc/EtOAc/toluene) to give 30 mg (60%) of **5**: R_f 0.78 (1/25/75 HOAc/EtOAc/toluene); ^1H NMR ($CDCl_3$, 500 MHz) δ 13.94 (s, 1H), 8.10 (d, *J* = 8.5 Hz, 2H), 7.97 (d, *J* = 8.5 Hz, 2H), 7.63 (m, 6H), 7.19 (dd, *J* = 6.4, 2.1 Hz, 1H), 7.16 (s, 1H), 5.84 (dd, *J* = 12.5, 5.2 Hz, 1H), 3.24 (m, 2H), 2.50 (m, 1H), 2.42 (m, 1H).

General Conditions for 6a−c and 7. Residual water was removed from either (*R*)- or (*S*)-2,8,9-trihydroxy-3,4-dihydro-1(2*H*)-anthracenone

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[11] For limitations of the Mosher ester method see ref 4b and Seco, J. M.; Quiñoá, E.; Riguera, R. *Tetrahedron: Asymmetry* **2000**, *11*, 2781−2791.

[12] Eliel, E. L.; Wilen, S. H. *Stereochemistry of Organic Compounds*; Wiley: New York, 1994; pp 991−1118.

[13] (a) Kondru, R. K.; Wipf, P.; Beratan, D. N. *J. Am. Chem. Soc.* **1998**, *120*, 2204−2205. (b) Kondru, R. K.; Wipf, P.; Beratan, D. N. *Science* **1998**, *282*, 2247−2250. (c) Polavarapu, P. L. *Mol. Phys.* **1997**, *91*, 551−554. (d) Stephens, P. J.; Devlin, F. J.; Cheeseman, J. R.; Frisch, M. J.; Mennucci, B.; Tomasi, J. *Tetrahedron: Asymmetry* **2000**, *11*, 2443−2448. (e) Furche, F.; Ahlrichs, R.; Wachsmann, C.; Weber, E.; Sobanski, A.; Vögtle, F.; Grimme, S. *J. Am. Chem. Soc.* **2000**, *122*, 1717−1724. (f) de Meijere, A.; Khlebnikov, A. F.; Kostikov, R. R.; Kozhushkov, S. I.; Schreiner, P. R.; Wittkopp, A.; Yufit, D. S. *Angew. Chem., Int. Ed. Engl.* **1999**, *38*, 3474−3479.

[14] Comparison of experimental and calculated circular dichroism spectra has been used recently as well. See Dong, J.-G.; Guo, J.; Akritopoulou-Zanze, I.; Kawamura, A.; Nakanishi, K.; Berova, N. *Chirality* **1999**, *11*, 707−721 and references therein.

[15] Improvements in the accuracy of CD calculations continue to be made. See for example: Furche, F.; Ahlrichs, R.; Wachsmann, C.; Weber, E.; Sobanski, A.; Vögtle, F.; Grimme, S. *J. Am. Chem. Soc.* **2000**, *122*, 1717−1724.

(23 mg, 94 μmol) by azeotropic distillation with toluene. The compound was then dissolved in CH_2Cl_2 (1.6 mL) and propylene oxide (0.8 mL). Acetyl chloride (7 μL, 98 μmol) and 15 μL (19 μmol) of a 10% solution of *N*-methylimidazole in CH_2Cl_2 were added. The reaction was stirred at room temperature for 2.5 h, then diluted with CH_2Cl_2, and poured into a solution of 0.1 N HCl. The organic layer was washed with saturated aq $NaHCO_3$ (5 mL), dried over Na_2SO_4, and concentrated in vacuo. The residue was purified by preparative TLC (1/25/75 HOAc/EtOAc/toluene) to give 20 mg (74%) of 8-(*O*)-acetyl-2,8,9-trihydroxy-3,4-dihydro-1(2*H*)-anthracenone: R_f 0.23 (1/25/75 HOAc/EtOAc/toluene).

Residual water was removed from either (*R*)- or (*S*)-8-(*O*)-acetyl-2,8,9-trihydroxy-3,4-dihydro-1(2*H*)-anthracenone (15 mg, 52 μmol) by azeotropic distillation with toluene. The compound was then dissolved in CH_2Cl_2 (1.5 mL) and propylene oxide (0.8 mL). Acyl chloride (2.5 equiv) and *N*-methylimidazole (2.5 equiv) were added, and the reaction mixture was stirred at room temperature for 2 h. It was then diluted with CH_2Cl_2 and poured into a solution of 0.1 N HCl. The organic layer was washed with saturated aq $NaHCO_3$ (5 mL), dried over Na_2SO_4, and concentrated in vacuo. The residue was purified by preparative TLC to give product in yields from 50−70%.

8-(*O*)-Acetyl-2-(*O*)-benzoyl-2,8,9-trihydroxy-3,4-dihydro-1(2*H*)-anthracenone ((*S*)-6a) and ((*R*)-7). R_f 0.68 (1/25/75 HOAc/EtOAc/toluene); ^1H NMR ($CDCl_3$, 500 MHz) δ 14.24 (s, 1H), 8.16 (d, $J = 8.0$ Hz, 2H), 7.60 (m, 3H), 7.50 (t, $J = 7.7$ Hz, 2H), 7.14 (s, 1H), 7.07 (dd, $J = 6.0$, 2.4 Hz, 1H), 5.90 (dd, $J = 12.5$, 5.1 Hz, 1H), 3.24 (m, 2H), 2.52 (m, 1H), 2.43 (m, 1H), 2.38 (s, 3H); ^{13}C NMR ($CDCl_3$, 500 MHz) δ 199.29, 170.52, 166.03, 164.15, 149.31, 140.05, 137.70, 133.62, 131.04, 130.21, 129.74, 128.71, 125.84, 119.73, 117.47, 111.54, 73.94, 29.04, 27.98, 21.39 (20 of 21 expected resonances observed); MS *m*/*z* (ion, % relative intensity) 390 (M^+, 4), 105 ($M - C_{16}H_{13}O_5$, 100).

(*S*)-8-(*O*)-Acetyl-2-(*O*)-(1-naphthoyl)-2,8,9-trihydroxy-3,4-dihydro-1(2*H*)-anthracenone (6b). R_f 0.63 (1/25/75 HOAc/EtOAc/toluene); ^1H NMR ($CDCl_3$, 500 MHz) δ 14.29 (s, 1H), 9.00 (d, $J = 8.8$ Hz, 1H), 8.34 (dd, $J = 7.3$, 1.1 Hz, 1H), 8.08 (d, $J = 8.1$ Hz, 1H), 7.92 (d, $J = 8.1$ Hz, 1H), 7.67 (t, $J = 7.8$ Hz, 1H), 7.58 (m, 4H), 7.15 (s, 1H), 7.08 (dd, $J = 5.9$, 2.6 Hz, 1H), 6.03 (dd, $J = 12.6$, 5.3 Hz, 1H), 3.27 (m, 2H), 2.58 (m, 1H), 2.48 (m, 1H), 2.40 (s, 3H); ^{13}C NMR ($CDCl_3$, 500 MHz) δ 199.47, 170.55, 166.89, 164.17, 149.32, 140.07, 137.72, 134.07, 133.99, 131.68, 131.05, 130.89, 128.78, 128.17, 126.77, 126.54, 126.06, 125.86, 124.78, 119.75, 117.51, 111.60, 73.97, 29.91, 29.13, 28.10, 21.42 (27 of 27 expected resonances observed); MS *m*/*z* (ion, % relative intensity) 440 (M^+, 6), 155 ($M - C_{16}H_{13}O_5$, 100).

(*S*)-8-(*O*)-Acetyl-2-(*O*)-(2-naphthoyl)-2,8,9-trihydroxy-3,4-dihydro-1(2*H*)-anthracenone (6c). R_f 0.64 (1/25/75 HOAc/EtOAc/toluene); ^1H NMR ($CDCl_3$, 500 MHz) δ 14.26 (s, 1H), 8.73 (s, 1H), 8.16 (dd, $J = 8.6$, 1.6 Hz, 1H), 8.00 (d, $J = 8.1$ Hz, 1H), 7.94 (d, $J = 8.8$ Hz, 1H), 7.91 (d, $J = 8.4$ Hz, 1H), 7.60 (m, 4H), 7.15 (s, 1H), 7.07 (dd, $J = 5.9$, 2.6 Hz), 5.97 (dd, $J = 12.5$, 5.1 Hz, 1H), 3.26 (m, 2H), 2.57 (m, 1H), 2.49 (m, 1H), 2.38 (s, 3H); ^{13}C NMR ($CDCl_3$, 500 MHz) δ 199.35, 170.53, 166.20, 164.17, 149.32, 140.06, 137.72, 135.99, 132.73, 131.87, 131.05, 129.70, 128.69, 128.53, 128.02, 126.95, 125.85, 125.61, 119.74, 117.49, 111.58, 74.08, 29.11, 28.01, 21.40 (25 of 27 expected resonances observed); MS *m*/*z* (ion, % relative intensity) 440 (M^+, 5), 155 ($M - C_{16}H_{13}O_5$, 100).

Computational Studies. Molecular mechanics calculations (MMFF[16]) and semiempirical molecular orbital calculations (AM1[17]) were performed by using the SPARTAN[18] program package (Version 5.0), and its built-in default thresholds for wave function and gradient convergence were employed. All ab initio [HF/6-31G(d)[19]] and hybrid density functional [B3LYP/6-31G(d)[20−22]] calculations were performed by using GAUSSIAN 98,[23] again employing the default convergence criteria. The function OFIT in Siemens SHELXTL[24] was used to determine the best fit of the experimental and calculated geometries and the deviations of the atomic positions.

Calculation of Optical Rotatory Dispersion. Two independent ab initio methods were used to compute the electric-dipole−magnetic-dipole polarizability (**G′**) tensor that is responsible for specific rotation angles. The first method used the static-field approximation[25] implemented in CADPAC,[26] and the second method computed the **G′** tensor at the frequency of incident light, using both gauge-dependent and gauge-independent (London) atomic orbitals.[27] The latter dynamic method is implemented in DALTON.[28] It is important to note that computed angles using CADPAC are origin dependent; however, they often provide reliable estimates if the origin is chosen at the center of mass of the molecule. The specific rotation angle (measured at the sodium D line), in units of degrees $[\mathrm{dm}\ (\mathrm{g/mL})]^{-1}$, is $[\alpha]_D = 1.343 \times 10^{-4}\beta\bar{\upsilon}^2(n^2 + 2)/3MW$, with β in units of bohr,^{4} MW, the molar mass, in g/mole, and $\bar{\upsilon}$, the frequency of the sodium D line, in cm^{-1}. The parameter β is related to the electric-dipole−magnetic-dipole polarizability tensor $\mathbf{G'}_{\alpha\beta}$. For further details of the theoretical methodology, see ref 29.

For our ORD calculations on **3**, we obtained unique low-energy conformations from Monte Carlo conformational searches using the Macromodel[30] program with the MM2* force field[31] using the chloroform continuum solvent model. The specific rotation angles were computed using the geometries of the conformations generated using the Monte Carlo search.[32] These angles were Boltzmann-weighted and summed to obtain the final specific rotation angle. The second- and third-lowest energy conformations for **3** were 4.4 and 13.9 kJ/mol higher in energy than the lowest energy conformation. Accordingly, the two lowest energy conformations of **3** dominated the Boltzmann sum both in the static- and dynamic-field methods using the CADPAC and DALTON programs, respectively (Table 2).

X-ray Crystallographic Analysis of (*S*)-2,8-(*O*)-Bis(bromobenzoyl)-2,8,9-trihydroxy-3,4-dihydro-1(2*H*)-anthracenone (5). Formula $C_{28}H_{18}Br_2O_6$; orthorhombic, space group $P2_12_12$, $a = 14.4086$ (3) Å, $b = 35.6380$ (6) Å, $c = 5.6490$ (1) Å, $V = 2900.73$ (9) Å^3, $Z = 4$. A pale yellow plate from benzene cut to dimensions of 0.05 mm × 0.24 mm × 0.25 mm was used for intensity measurements at 200(2) K with a Nonius Kappa CCD diffractometer and Mo Kα radiation ($\lambda = 0.71073$ Å). A total of 22 119 reflections ($\theta_{max} = 24.99°$) were indexed, integrated, and corrected for Lorentz and polarization effects (using the programs DENZO and SCALEPACK[33]); a Gaussian face-indexed absorption correction was applied using SHELXTL[24] to give 5096

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(16) Halgren, T. A. *J. Comput. Chem.* **1996**, *17*, 490−519.

(17) Dewar, M. J. S.; Zoebisch, E. G.; Healy, E. F.; Stewart, J. J. P. *J. Am. Chem. Soc.* **1985**, *107*, 3902−3909.

(18) *SPARTAN*, version 5.0; Wavefunction, Inc.: Irvine, CA, 1997.

(19) Hehre, W. J.; Radom, L.; Schleyer, P. v. R.; Pople, J. A. *Ab Initio Molecular Orbital Theory*; John Wiley & Sons: New York, 1986; pp 63−100.

(20) Becke, A. D. *J. Chem. Phys.* **1993**, *98*, 5648−5652.

(21) Lee, C.; Yang, W.; Parr, R. G. *Phys. Rev. B* **1988**, *37*, 785−789.

(22) Miehlich, B.; Savin, A.; Stoll, H.; Preuss, H. *Chem. Phys. Lett.* **1989**, *157*, 200−206.

(23) Frisch, M. J.; Trucks, G. W.; Schlegel, H. B.; Scuseria, G. E.; Robb, M. A.; Cheeseman, J. R.; Zakrzewski, V. G.; Montgomery, J. A., Jr.; Stratmann, R. E.; Burant, J. C.; Dapprich, S.; Millam, J. M.; Daniels, A. D.; Kudin, K. N.; Strain, M. C.; Farkas, O.; Tomasi, J.; Barone, V.; Cossi, M.; Cammi, R.; Mennucci, B.; Pomelli, C.; Adamo, C.; Clifford, S.; Ochterski, J.; Petersson, G. A.; Ayala, P. Y.; Cui, Q.; Morokuma, K.; Malick, D. K.; Rabuck, A. D.; Raghavachari, K.; Foresman, J. B.; Cioslowski, J.; Ortiz, J. V.; Baboul, A. G.; Stefanov, B. B.; Liu, G.; Liashenko, A.; Piskorz, P.; Komaromi, I.; Gomperts, R.; Martin, R. L.; Fox, D. J.; Keith, T.; Al-Laham, M. A.; Peng, C. Y.; Nanayakkara, A.; Gonzalez, C.; Challacombe, M.; Gill, P. M. W.; Johnson, B.; Chen, W.; Wong, M. W.; Andres, J. L.; Gonzalez, C.; Head-Gordon, M.; Replogle, E. S.; Pople, J. A.; *Gaussian 98*, revision A.7; Gaussian, Inc.: Pittsburgh, PA, 1998.

(24) Sheldrick, G. M. *SHELXTL*, version 5; Siemens Analytical X-ray Instruments: Madison, WI, 1996.

(25) Amos, R. D. *Chem. Phys. Lett.* **1982**, *87*, 23.

(26) Amos, R. D.; Rice, J. E. *The Cambridge Analytic Derivative Package*, issue 6.3; 1997.

(27) (a) London, F. *J. Phys. Radium* **1937**, *8*, 397. (b) Bak, K. L.; Jørgensen, P.; Helgaker, T.; Ruud, K. *Faraday Discuss.* **1994**, *99*, 121.

(28) (a) Helgaker, T.; Jensen, H. J. A.; Olsen, J.; Ruud, K.; Anderson, A. T.; Bak, K. L.; Bakken, V.; Christiansen, O.; Dahle, P.; Dalskov, E. K.; Enevoldsen, T.; Fernandez, B.; Heiberg, H.; Hettema, H.; Jonsson, D.; Kirpekar, S.; Kobayashi, R.; Koch, H.; Mikkelsen, K. V.; Norman, P.; Packer, P.; Saue, T.; Taylor, P. R.; Vahtras, O. *Dalton, an Ab Initio Electronic Structure Program*, release 1.0; 1997. (b) Olsen, J.; Jørgensen, P. *J. Chem. Phys.* **1985**, *82*, 3235.

unique reflections ($R_{\mathrm{int}} = 0.0615$). The structure was solved by direct methods and refined by full-matrix least-squares on F^2 (SHELXTL). Non-hydrogen atoms were refined anisotropically; hydrogen atoms were included with a riding model and refined isotropically. The refinement converged to $R(F) = 0.0317$, $wR(F^2) = 0.0590$, and $S = 1.041$ for 3866 reflections, with $I > 2\sigma(I)$, $R(F) = 0.515$, $wR(F^2) = 0.0635$, and $S = 0.963$ for 5096 unique reflections, 383 parameters, and 0 restraints.

X-ray Crystallographic Analysis of (*S*)-8-(*O*)-Acetyl-2-(*O*)-benzoyl-2,8,9-trihydroxy-3,4-dihydro-1(2*H*)-anthracenone (6a). Formula $C_{23}H_{18}O_6$; orthorhombic, space group $P2_12_12_1$, $a = 5.8916$ (5) Å, $b = 13.181$ (2) Å, $c = 23.488$ (3) Å, $V = 1824.1$ (4) Å^3, $Z = 4$. A yellow needle from benzene cut to dimensions 0.02 mm × 0.05 mm × 0.32 mm was used for intensity measurements at 200(2) K with a Nonius Kappa CCD diffractometer and Mo Kα radiation ($\lambda = 0.71073$ Å). A total of 11 030 reflections ($\theta_{\max} = 18.80°$) were indexed, integrated, and corrected for Lorentz and polarization effects (using the program DENZO); the data were scaled and merged (SCALEPACK) to give 1426 unique reflections ($R_{\mathrm{int}} = 0.137$). The structure was solved by direct methods and refined by full-matrix least-squares on F^2 (SHELXTL). Non-hydrogen atoms were refined anisotropically; hydrogen atoms were included with a riding model and refined isotropically. The refinement converged to $R(F) = 0.0617$, $wR(F^2) = 0.0950$, and $S = 1.186$ for 1243 reflections with $I > 2\sigma(I)$, $R(F) = 0.0763$, $wR(F^2) = 0.0999$, and $S = 1.145$ for 1426 unique reflections, 264 parameters, and 270 restraints.

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(29) The expression for the optical rotational angle, ϕ, in radians, is

$$\phi = 4\pi N\beta\omega^2(n^2+2)/3c^2 \tag{1}$$

where

$$\beta = -\omega^{-1}(\mathbf{G}'_{xx} + \mathbf{G}'_{yy} + \mathbf{G}'_{zz})/3 \tag{2}$$

$\mathbf{G}'_{ii}$ are the diagonal elements of the electric−magnetic polarizability tensor, N is the number of molecules per unit volume, n is the refractive index of the medium, and c is the speed of light. The specific rotation angle (measured at the sodium D line), in units of degrees[dm (g/mL)]$^{-1}$, is

$$[\alpha]_D = 1.343 \times 10^{-4}\beta\bar{\nu}^2(n^2 + 2)/3\mathrm{MW} \tag{3}$$

with β in units of bohr.[4] MW is the molar mass in g/mole, and $\bar{\nu}$ the frequency of the sodium D line in cm^{-1}. From $[\alpha]_D$, the molar rotation is defined as $[M]_D = [\alpha]_D\mathrm{MW}/100$. We calculate $\mathbf{G}'_{\alpha\beta}$ for the full molecule using

$$\mathbf{G}'_{\alpha\beta} = -2\sum_{e\neq g}\frac{\omega\ \mathrm{Im}[\langle\Psi_g^{(0)}|\mu_\alpha|\Psi_e^{(0)}\rangle\langle\Psi_e^{(0)}|m_\alpha|\Psi^{(0)}{}_g\rangle]}{\omega_{eg}^2 - \omega^2} \tag{4}$$

Here, g and e denote the ground and excited states, respectively, $\omega_{eg} = \omega_e - \omega_g$ is the associated excitation frequency, and μ_α and m_α are the electric-dipole and magnetic-dipole operators oriented along the α-axes. To avoid the explicit sum-over-states expression for the electric-dipole−magnetic-dipole polarizability tensor, Amos applied the static-field approximation. In this regime, eq 4 is simplified ($\omega^2 \ll \omega_{jn}{}^2$) to

$$\omega^{-1}\mathbf{G}'_{\alpha\alpha} = -2\sum_{e\neq g}\frac{\mathrm{Im}[\langle\Psi_g^{(0)}|\mu_\alpha|\Psi_e^{(0)}\rangle\langle\Psi_e^{(0)}|m_\alpha|\Psi^{(0)}{}_g\rangle]}{\omega_{eg}^2} \tag{5}$$

(30) Mohamadi, F.; Richards, N. G. J.; Guida, W. C.; Liskamp, R.; Caufield, C.; Chang, G.; Hendrickson, T.; Still, W. C. *J. Comput. Chem.* **1990**, *11*, 440.

(31) Pettersson, I.; Liljefors, T. In *Reviews in Computational Chemistry*; Lipkowitz, K. B., Boyd, D. B., Eds.; VCH: New York, 1996; Vol. 9, p 167.

(32) The lowest energy conformers obtained by Monte Carlo sampling were minimized at every step and compared to see if the newly obtained structure was duplicated. If so, the duplicated structure was ignored. Only unique structures were retained. Low energy structures were usually chosen from a Monte Carlo sampling of 3000 conformations; each new conformation was minimized using a 3000 step energy minimization iteration method forcing all the newly found structures to be fully relaxed.

(33) Otwinowski, Z.; Minor, W. *Methods Enzymol.* **1997**, *276*, 307−326.