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Quantitative Definition of Exciton Chirality and the Distant Effect in the Exciton Chirality Method

Nobuyuki Harada,[1] Sow-mei Lai Chen, and Koji Nakanishi*

Contribution from the Department of Chemistry, Columbia University, New York, New York 10027. Received January 29, 1975

Abstract: The circular dichroism spectra (CD) of a series of steroidal glycol bis(*p*-dimethylaminobenzoates) have been measured and quantitatively calculated in order to clarify the distant effect in the exciton chirality method. An excellent agreement has been found between the experimental and theoretical curves. Theoretical calculations have shown that the intensity of the split Cotton effect is maximal at a dihedral angle of ca. 70°, and is inversely proportional to r^2 (where r is interchromophoric distance). This coupled Cotton effect is still observable for remote dibenzoates such as the 1,8-glycol dibenzoate (**10**) and hence should be useful for configurational studies of a variety of natural products. Taylor expansion of eq 9 representing the split CD Cotton effect gives $R_{ij} \cdot (\mu_{i0a} \times \mu_{j0a}) V_{ij}$ as a quantitative definition of exciton chirality for two interacting identical chromophores. The imbalance between the first and second apparent Cotton effects was found to originate from the asymmetrical pattern of the corresponding electronic absorption band.

There are two nonempirical methods for determining absolute configurations; one is the Bijvoet method of X-ray crystallography which is universally employed for various compounds, and the other is the optical method based on Davydov-split CD Cotton effects, which is applicable to compounds having more than two chromophores. The latter method has been studied extensively in the fields of biopolymers,[2] inorganic complexes,[3] physical chemistry,[4,5] as well as in organic chemistry.[6,7] Because of its nonempirical nature the method is more reliable than other empirical rules put forward for various organic chromophores.

We have proposed the exciton chirality method based on the dipole–dipole coupling mechanism and have determined the absolute configurations of various natural products.[7,8] A more quantitative treatment of coupled Cotton effects observed in steroidal glycol bis(*p*-dimethylaminobenzoate) systems[7,9] is given below together with experimental data for the purpose of clarifying the distant effect in practical applications of the exciton chirality method. Provided the angle between the electric transitions of two interacting chromophores does not change, the amplitudes of split CD curves are inversely proportional to the square of interchromophoric distances. On the other hand, in vicinal dibenzoates a maximum amplitude is expected at an interchromophoric angle of ca. 70°. A quantitative definition of exciton chirality is also described in this paper.

Theoretical Calculations

According to the molecular exciton theory,[10] when N identical chromophores possessing strong $\pi \rightarrow \pi^*$ transitions ($0 \rightarrow a$) interact with each other, the excitation wave number σ_k to the kth excited level of the whole system is represented by eq 1, where σ_0 is the excitation wave number

$$\sigma_k - \sigma_0 = \sum_{i=1}^{N} \sum_{j \neq i}^{N} C_{ik} C_{jk}^* V_{ij} \qquad (1)$$

of the isolated noninteracting chromophore, C_{ik} and C_{jk}^* are coefficients of the corresponding kth wave function, and

V_{ij} is the transition dipole interaction energy between two chromophores i and j.

Similarly, the kth rotational strength R^k due to the exciton coupling mechanism is

$$R^k = \pi \sigma_0 \sum_{i=1}^{N} \sum_{j \neq i}^{N} C_{ik} C_{jk}^* \mathbf{R}_j \cdot (\mu_{j0a} \times \mu_{i0a}) \qquad (2)$$

where $\mathbf{R}_j$ is the distance vector from the origin to chromophore j, and μ_{i0a} and μ_{j0a} are electric transition moment vectors of groups i and j. If we take the real wave function for the N-mer and combine the two terms of $\mathbf{R}_j \cdot (\mu_{j0a} \times \mu_{i0a})$ and $\mathbf{R}_i \cdot (\mu_{i0a} \times \mu_{j0a})$, the following origin-independent formula of rotational strength is obtained

$$\sigma_k - \sigma_0 = 2 \sum_{i=1}^{N} \sum_{j>i}^{N} C_{ik} C_{jk} V_{ij} \qquad (3)$$

$$R^k = -\pi \sigma_0 \sum_{i=1}^{N} \sum_{j>i}^{N} C_{ik} C_{jk} \mathbf{R}_{ij} \cdot (\mu_{i0a} \times \mu_{j0a}) \qquad (4)$$

where $\mathbf{R}_{ij}$ is the interchromophoric distance vector from i to j, and V_{ij} (expressed in cm^{-1} unit) is approximated as follows

$$V_{ij} = \mu_{i0a} \mu_{j0a} R_{ij}^{-3} (e_i \cdot e_j - 3(e_i \cdot e_{ij})(e_j \cdot e_{ij})) \qquad (5)$$

where e_i, e_j, and e_{ij} are unit vectors of μ_{i0a}, μ_{j0a}, and $\mathbf{R}_{ij}$, respectively.
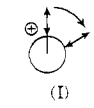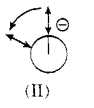
Next, if a Gaussian distribution is approximated for the component CD Cotton effects, the curve of the kth Cotton effect is formulated as

$$\Delta \epsilon(\sigma)^k = \Delta \epsilon_{max}^k \exp\{-((\sigma - \sigma_k)/\Delta \sigma)^2\} \qquad (6)$$

where $\Delta \epsilon_{max}^k$ is the maximum value of the Cotton effect, and $\Delta \sigma$ is the standard deviation of the Gaussian distribution. On the other hand, the kth experimental rotational strength R^k is expressed by

$$R^k = 2.296 \times 10^{-39} \int_0^{\infty} \Delta \epsilon(\sigma)^k / \sigma \, d\sigma =$$

$$(2.296 \times 10^{-39}/\sigma_k) \int_0^{\infty} \Delta \epsilon(\sigma)^k \, d\sigma \text{ (cgs unit)} \qquad (7)$$

Table I. Definition of Exciton Chirality for a Binary System

	Qualitative definition	Quantitative definition	Cotton effect
Positive chirality	(I)	$R_{ij} \cdot (\mu_{ioa} \times \mu_{joa}) V_{ij} > 0$	Positive 1st and negative 2nd Cotton effects
Negative chirality	(II)	$R_{ij} \cdot (\mu_{ioa} \times \mu_{joa}) V_{ij} < 0$	Negative 1st and positive and Cotton effects
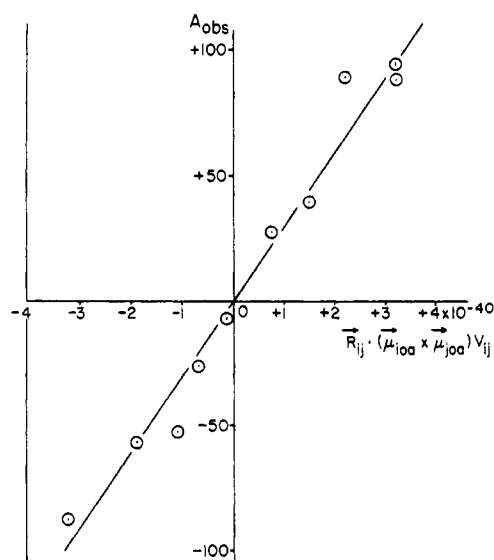
Figure 1. The linear relation between A_{obsd} and exciton chirality $R_{ij} \cdot (\mu_{i0a} \times \mu_{j0a}) V_{ij}$.

Substitution of eq 6 into 7 and integration gives

$$R^k = 2.296 \times 10^{-39} \sqrt{\pi} \, \Delta\epsilon_{max}{}^k \Delta\sigma/\sigma_k \qquad (8)$$

where σ_k can be replaced by σ_0 because $\sigma_k \approx \sigma_0$. From eq 6 and 8, the calculated CD curve of a whole system is derived as follows

$$\Delta\epsilon(\sigma) = \frac{\sigma_0}{2.296 \times 10^{-39}\sqrt{\pi}\Delta\sigma} \sum_{k=1}^{N} R^k \times$$

$$\exp\left\{ -\left(\frac{\sigma - \sigma_k}{\Delta\sigma} \right)^2 \right\} \qquad (9)$$

where $\sigma_k - \sigma_0$ and R^k are calculable by eq 3 and 4, respectively.

A Taylor expansion[10] of eq 9 against $\sigma_k/\Delta\sigma$ around $\sigma_0/\Delta\sigma$ simplifies the equation in the following manner. Namely, the first term vanishes because of the sum rule,

$$\sum_{k=1}^{N} R^k = 0$$

while the expanded second term becomes

$$\Delta\epsilon(\sigma) = \frac{2\sigma_0}{2.296 \times 10^{-39}\sqrt{\pi}\Delta\sigma} \exp\left\{ -\left(\frac{\sigma - \sigma_0}{\Delta\sigma} \right)^2 \right\} \times$$

$$\left(\frac{\sigma - \sigma_0}{\Delta\sigma} \right) \sum_{k=1}^{N} R^k \left(\frac{\sigma_k - \sigma_0}{\Delta\sigma} \right) \qquad (10)$$

On the other hand, higher terms, e.g., the third term which is formulated as follows

$$\Delta\epsilon(\sigma) = \frac{\sigma_0}{2.296 \times 10^{-39}\sqrt{\pi}\Delta\sigma} \exp\left\{ -\left(\frac{\sigma - \sigma_0}{\Delta\sigma} \right)^2 \right\} \times$$

$$\left\{ 2\left(\frac{\sigma - \sigma_0}{\Delta\sigma} \right)^2 - 1 \right\} \sum_{k=1}^{N} R^k \left(\frac{\sigma_k - \sigma_0}{\Delta\sigma} \right)^2 \qquad (11)$$

can be neglected because $(\sigma_k - \sigma_0)/\Delta\sigma \ll 1$.[11] Substitution of eq 3 and 4 into 10 gives

$$\Delta\epsilon(\sigma) = \frac{4\sqrt{\pi}\sigma_0{}^2}{2.296 \times 10^{-39}\Delta\sigma^2}\left(\frac{\sigma_0 - \sigma}{\Delta\sigma} \right) \times$$

$$\exp\left\{ -\left(\frac{\sigma_0 - \sigma}{\Delta\sigma} \right)^2 \right\} \sum_{k=1}^{N} \left\{ \sum_{i=1}^{N} \sum_{j>i}^{N} C_{ik}C_{jk} \times \right.$$

$$\left. R_{ij} \cdot (\mu_{i0a} \times \mu_{j0a}) \right\} \left\{ \sum_{i=1}^{N} \sum_{j>i}^{N} C_{ik}C_{jk}\bar{V}_{ij} \right\} \qquad (12)$$

This is the expanded CD equation for the N-mer; the coefficients C_{ik} and C_{jk}, which depend on the geometry of chromophores, can be obtained by solving the secular equation of the Nth order.

In binary systems, the excited state is split into two levels, α and β, as a result of transition dipole interaction. Coefficients for α-state, $1/2^{1/2}$ and $-1/2^{1/2}$, and for β-state, $1/2^{1/2}$ and $1/2^{1/2}$, are independent of the mutual geometry of two chromophores. Therefore eq 12 is further simplified as

$$\Delta\epsilon(\sigma) = \underbrace{\frac{2\sqrt{\pi}\sigma_0{}^2}{2.296 \times 10^{-39}\Delta\sigma^2}\left(\frac{\sigma_0 - \sigma}{\Delta\sigma} \right)\exp\left\{ -\left(\frac{\sigma_0 - \sigma}{\Delta\sigma} \right)^2 \right\}}_{A}$$

$$\times \underbrace{R_{ij} \cdot (\mu_{i0a} \times \mu_{j0a}) V_{ij}}_{B} \qquad (13)$$

where σ_0 and $\Delta\sigma$ are obtainable from the electronic spectrum of the corresponding chromophore. Equation 13 expressing the split Cotton effects of dimers shows that term B, $R_{ij} \cdot (\mu_{i0a} \times \mu_{j0a}) V_{ij}$, which is calculable from the mutual configuration of two transition point dipoles, determines the sign and amplitude of the coupled Cotton effects.

Figure 1 shows that a linear relation holds between A_{obsd} ($A = \Delta\epsilon_1 - \Delta\epsilon_2$) and the exciton chirality $R_{ij} \cdot (\mu_{i0a} \times \mu_{j0a}) V_{ij}$ for various steroid bis(p-dimethylaminobenzoates) (Table II). Thus it is reasonable to take the term $R_{ij} \cdot (\mu_{i0a} \times \mu_{j0a}) V_{ij}$ as the quantitative definition of exciton chirality in a system having two interacting and identical chromophores.

Actual measurements of numerous dibenzoates and other compounds of known absolute configurations containing two interacting chromophores[7,8] (see also data described below) have shown that in unit I (Table I) where the two interacting electric transition dipoles constitute a clockwise

Table II. Calculated and Observed CD Cotton Effects of Bis(p-dimethylaminobenzoates) of Various Steroid Glycols and Interchromophoric Distance R_{ij}

Entry	Compd[a]	$\Delta\epsilon(\lambda, nm)$ (calcd) Conformer I	Conformer II	$\Delta\epsilon_{calcd}$, nm[b]	A_{calcd}[c]	$\Delta\epsilon_{obsd}$, nm	A_{obsd}[c]	Solvent[d]	R_{ij}, Å
1	5α-Cholestane-2β,3β-	+64.0 (323)		+64.0 (323)	+92.5	+61.7 (320)	+94.8	E	8.1
		−28.5 (296)		−28.5 (296)		−33.2 (295)			
2	5α-Cholestane-2α,3α-	+64.0 (323)		+64.0 (323)	+92.5	+61.3 (321)	+88.4	E	8.1
		−28.5 (296)		−28.5 (296)		−27.1 (295)			
3	Cholest-5-ene-3β,4β-	−64.0 (323)		−64.0 (323)	−92.5	−57.8 (321)	−93.4	E	8.1
		−28.5 (296)		+28.5 (296)		+35.6 (295)			
4	5α-Cholestane-3β,6β	−40.0 (324)	−34.4 (323)	−37.2 (323)	−54.5	−37.6 (320)	−56.8	10% D–E	9.9
		+18.8 (295)	+15.7 (294)	+17.3 (295)		+19.2 (295)			
5	5α-Cholestane-3β,6α-	+40.0 (323)	+48.5 (323)	+44.3 (323)	+64.5	+59.2 (319)	+89.3	20% D–E	9.5
		−18.3 (296)	−22.0 (295)	−20.2 (295)		−30.2 (294)			
6	5α-Cholestane-3β,7α-	+31.0 (323)	+28.0 (323)	+29.5 (323)	+43.0	+28.5 (320)	+39.8	E	10.6
		−14.0 (295)	−13.0 (295)	−13.5 (295)		−11.3 (295)			
7	5α-Cholestane-3β,7β-	−5.2 (323)	0.0	−2.6 (323)	−3.8	−2.8 (321)	−7.1	E	12.4
		+2.3 (295)	0.0	−1.2 (295)		+4.3 (300)			
8	5α-Androstane-3β,11β-	+11.0 (323)	+19.0 (323)	−15.0 (323)	+21.8	+18.8 (320)	+27.5	10% D–E	11.4
		−5.0 (296)	−8.6 (295)	+6.8 (295)		−8.7 (294)			
9	5α-Pregnane-3β,11α-	−18.5 (324)	−25.2 (323)	−21.9 (323)	−32.1	−35.0 (320)	−52.7	E	10.3
		+8.5 (295)	+11.8 (295)	+10.2 (295)		+17.7 (295)			
10	D-Homo-5α-androstane-3β,15β-	−12.0 (323)	−15.7 (324)	−13.9 (323)	−20.4	−20.4 (319)	−26.4	E	12.8
		+5.5 (295)	+7.4 (295)	+6.5 (295)		+6.0 (291)			

[a] Positions of p-dimethylaminobenzoyloxy groups follow compound name. [b] Except of entries 1, 2, and 3, $\Delta\epsilon_{calcd}$ is the average value of two rotational conformers I and II around the 3β–C–O bond (Figure 6). [c] $A = \Delta\epsilon_1 - \Delta\epsilon_2$. [d] E, ethanol; D, dioxane.

twist (defined as positive), the sign of the first split Cotton effect at longer wavelength is positive.

This is in agreement with the sign of the term $\mathbf{R}_{ij}\cdot(\mu_{i0a} \times \mu_{j0a})V_{ij}$ described above; furthermore, there is excellent agreement between the experimental and calculated CD extrema (see Figures 8-10), and it is these aspects which make the exciton chirality method a simple and nonambiguous means for determining absolute configurations. In a few rare cases, however, depending on the geometry of the molecule, the Newman projection such as unit I does not lead to clearcut predictions of chirality; in such cases the term $\mathbf{R}_{ij}\cdot(\mu_{i0a} \times \mu_{j0a})V_{ij}$ should be calculated.

Term B of eq 13 can be modified as follows

$$\text{term } B = D_{i0a}D_{j0a}R_{ij}^{-2}\mathbf{e}_{ij}\cdot(\mathbf{e}_i \times \mathbf{e}_j) \times$$
$$(\mathbf{e}_i\cdot\mathbf{e}_j - 3(\mathbf{e}_i\cdot\mathbf{e}_{ij})(\mathbf{e}_j\cdot\mathbf{e}_{ij})) \quad (14)$$

where D_{i0a} and D_{j0a} are transition dipole strengths of groups i and j, respectively. This equation indicates that *the Cotton effect amplitude is inversely proportional to the square of interchromophoric distance* provided the remaining angular part is the same. Furthermore, in α-glycol dibenzoate systems, when the calculated amplitude is plotted against the dihedral angle between the two transition moments (or the two C–O bonds) a curve having its extremum around 70° is obtained (Figure 2).[12] Thus, *the Cotton effect sign is unchanged 0 through 180° with an extremum at ca. 70°*.

Term A of eq 13 represents a curve similar in shape to an ORD anomalous dispersion curve; the shape depends only on the nature of the employed chromophore, namely, the positions of two extrema are expected to be constant irrespective of the mutual configuration of the two chromophores. As seen in Table II, the observed and calculated extrema are thus both located within a very narrow wavelength spread, a feature which is of diagnostic value for detection of split CD Cotton effects.

In many cases, the actual CD curve shows a conspicuous imbalance in the shape of two Cotton effects;[8,13] i.e., the first Cotton effect is sharper and stronger than the second Cotton effect. This phenomenon is unexpected if one considers the equality of rotational strengths of the two excited states, α and β: $R^\alpha = \frac{1}{2}\pi\sigma_0\mathbf{R}_{ij}\cdot(\mu_{i0a} \times \mu_{j0a})$ and $R^\beta = -\frac{1}{2}\pi\cdot$
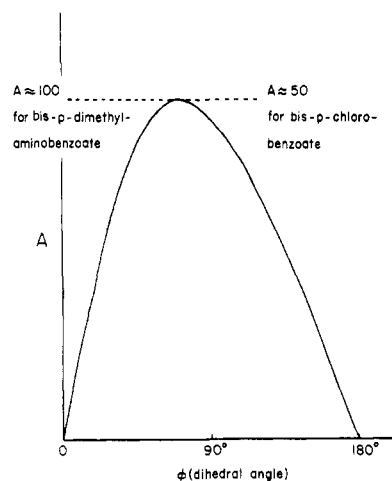

Figure 2. Relation between dihedral angle and CD amplitude $A(\Delta\epsilon_1 - \Delta\epsilon_2)$ of vicinal bis(para-substituted benzoates).

$\sigma_0\mathbf{R}_{ij}\cdot(\mu_{i0a} \times \mu_{j0a})$. This imbalance of the two apparent Cotton effects cannot be satisfactorily explained by assuming a Gaussian distribution. Therefore, instead, we adopted the actual pattern of the corresponding uv band for the shape of component CD Cotton effects.

This choice is reasonable because, in the case of coupled Cotton effects due to the exciton chirality mechanism, the magnetic transition moment, which is one of the factors responsible for the rotational strength, originates from the coupled electric moment, i.e., uv excitation. The uv transition naturally reflects the other factor, the electric transition moment, as well.

In general, *the experimental uv band* plotted against wavelength is asymmetric; namely, the longer wavelength side is steeper, while the shorter wavelength side is broader. This tendency is further emphasized by plotting the uv spectra against wave number. The summation of two such curves of opposite signs separated by the Davydov split $2V_{ij}$, and representing the two states α and β, affords a sharp first and a broad second Cotton effect (Figure 3).

Numerical Calculations for Steroidal Dibenzoates

In the following systematic studies on the distance dependency of the split Cotton effect $\Delta\epsilon$ values, the steroidal nu-
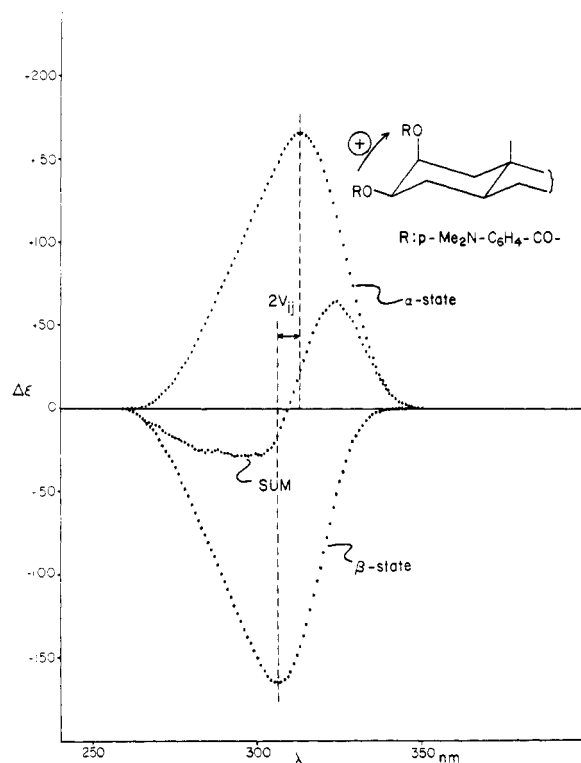
Figure 3. Summation of two asymmetric component CD curves gives an asymmetric resultant curve; the example is for 5α-cholestane-2β,3β-diol bis(p-dimethylaminobenzoate). The two component CD curves are derived from experimental uv curves, and hence the summation curve is not smooth.
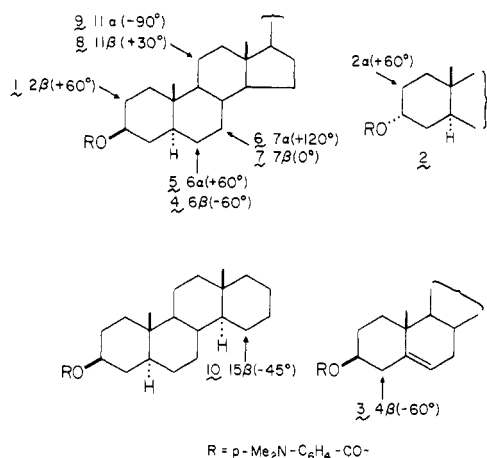

Figure 4. Numerals in parentheses denote dihedral angles between the two C–O bonds of diols.

cleus was chosen for obvious reasons that the skeleton is rigid and that a number of simple diols were available (Figure 4). All diols carry one of the hydroxyl functions at C-3. As a model for the distant 1,8-glycol, a 3β,15β-diol having a six-membered D-homo ring was chosen. This was to avoid complications arising from a five-membered ring, which is flexible and has bond lengths and angles differing from six-membered rings.

We have chosen the p-dimethylaminobenzoate group as the chromophore because the strong uv intensity of its intramolecular charge transfer band along the long axis at 309 nm[14] leads to strong coupled Cotton effects.[15] Furthermore, the long wavelength location of the band at 309 nm (see Figure 8) facilitates theoretical treatments; it presumably overlaps with the short axis B_{2u} transition but the con-
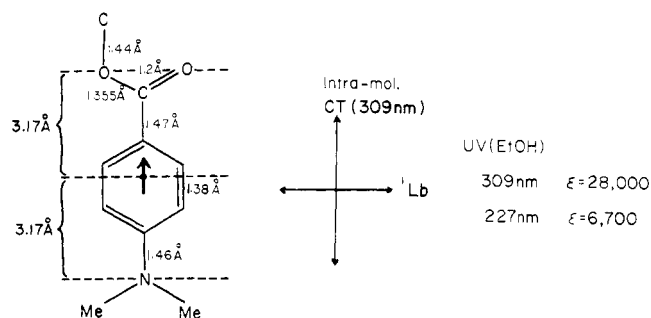

Figure 5. Location and direction of the transition point dipole in p-dimethylaminobenzoate chromophore.
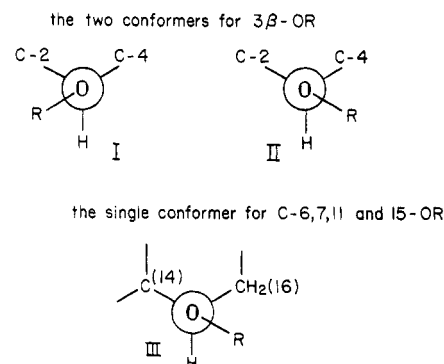

Figure 6. Conformation of the benzoate group OR.

tribution of the latter has been neglected because of its low uv intensity.

In the present calculation, we have assumed that the point dipole is located at the midpoint between the N and O–O distance as shown in Figure 5. The coordinates for the point dipole were computed by assuming that the steroid skeleton adopts an ideal chair conformation,[16] and that each benzoyloxy group adopts the most stable staggered conformation. For the benzoate groups adjacent to ring junctions, only one conformation in which it is trans to the ring junction C–H was considered (Figure 6, III). However, in the case of 3β-benzoate which is flanked by two CH_2 moieties, two staggered conformers I and II (Figure 6) were taken into consideration and the arithmetic average of the two sets of $\Delta\epsilon$'s (e.g., Figure 9, curves calcd I and calcd II) was calculated for the values listed in Table II. In the case of vicinal dibenzoates (**1, 2, 3**), it was assumed that both benzoate moieties adopt only one conformation in which they were pointed away from each other (e.g., Figure 8).

The actual numerical calculation of coordinates of a point dipole is exemplified for the 6α-benzoate group as follows: (i) set the plane A which contains the benzoate plane and C-5, and C-6 atoms and place x and y axes in this plane (Figure 7); (ii) calculate the local coordinates of atoms C-5, C-6, ethereal oxygen, and C-7 and the point dipole against x, y, and z axes, then estimate the distance between the point dipole and each atom, respectively; (iii) set the other plane B which contains C-3, C-4, C-5, C-6, and C-7 atoms and place X, Y axes in this plane and obtain the principal coordinates of C-5, C-6, ethereal oxygen, and C-7 against the X, Y, Z axes; and (iv) this gives four second-order equations of three unknown parameters, X_i, Y_i, Z_i. The principal coordinates of the point dipole i, X_i, Y_i, Z_i, are thus computable.

The absolute value of the electric transition length $|\mathbf{r}|$ = $|\boldsymbol{\mu}|/e$ was estimated from the uv spectra of the corresponding bis(p-dimethylaminobenzoate). The experimental dipole strength D which is theoretically expressed as D =
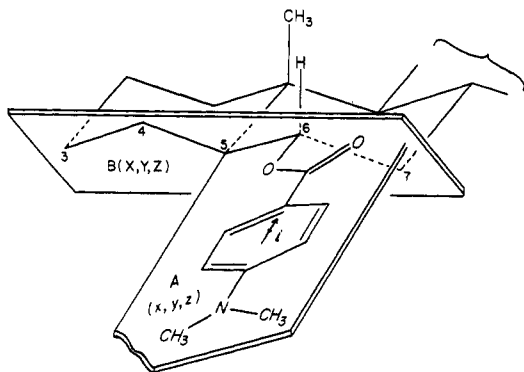
Figure 7. Estimations of the principal coordinates of a point dipole i, X_i, Y_i, Z_i.

$e^2|\mathbf{r}|^2$ is related to the molecular extinction coefficient ϵ as follows.

$$D = 0.9184 \times 10^{-38} \int_0^\infty \epsilon(\sigma)/\sigma \, d\sigma \quad \text{(cgs unit)} \quad (15)$$

The numerical integration of the actual uv spectrum curve gave $|\mathbf{r}| = 1.156 \, \text{Å}.$[17]

The interaction energy V_{ij} in each compound was computed by using the point dipole approximation and varies from 353.8 cm^{-1} for compound **1** to 44.2 cm^{-1} for compound **10**. The rotational strengths were also computed by eq 4; for example, for compound **1**, $R^\beta = -0.457 \times 10^{-37}$ cgs unit.

The component CD curve is expressed by

$$\Delta\epsilon(\sigma)^k = \Delta\epsilon_{max}{}^k f(\sigma + \sigma_0 - \sigma_k) \quad (16)$$

where $\Delta\epsilon_{max}{}^k$ is the maximum value of the kth Cotton effect, and $f(\sigma)$ is the function describing the shape of a component CD Cotton effect curve and is adopted from the uv spectra. Then, the rotational strength as expressed by eq 7 becomes

$$R^k = 2.296 \times 10^{-39} \Delta\epsilon_{max}{}^k \int_0^\infty f(\sigma)/\sigma \, d\sigma \quad (17)$$

where $f(\sigma + \sigma_0 - \sigma_k)$ is approximated to be $f(\sigma)$ because of the small value of $\sigma_0 - \sigma_k$. From eq 16 and 17, the following expression for a component CD Cotton effect curve is derived.

$$\Delta\epsilon(\sigma)^k = \frac{R^k}{2.296 \times 10^{-39} \int_0^\infty f(\sigma)/\sigma \, d\sigma} \times$$
$$f(\sigma + \sigma_0 - \sigma_k) \quad (18)$$

The integration part in (18) is numerically calculable from the uv data, while R^k is theoretically calculable from eq 4.

In the case of dimers, the composite CD curve is expressed by summation of the two component Cotton effects α and β, $\Delta\epsilon(\sigma) = \Delta\epsilon(\sigma)^\alpha + \Delta\epsilon(\sigma)^\beta$, and these two Cotton effects are separated by the so-called Davydov split $2V_{ij}$ (Figure 3). Figure 8 shows the calculated and observed CD curves of 5α-cholestane-$2\beta,3\beta$-diol bis(p-dimethylaminobenzoate) (**1**). This compound exhibits a weak negative Cotton effect around 225 nm besides the coupled Cotton effects. The position, amplitude, and shape of the calculated split-Cotton effects are in excellent agreement with the observed.

From the formula $R = (2.296 \times 10^{-39}/\sigma_0) \int_0^\infty \Delta\epsilon(\sigma) \, d\sigma$, the apparent rotational strengths of first and second Cotton effects of **1** can be calculated to be $R_{first} = +0.821 \times 10^{-38}$ and $R_{second} = -0.821 \times 10^{-38}$ cgs unit. Therefore, although the shapes of two apparent Cotton effects are uneven, the criterion of equality of two rotational strengths,
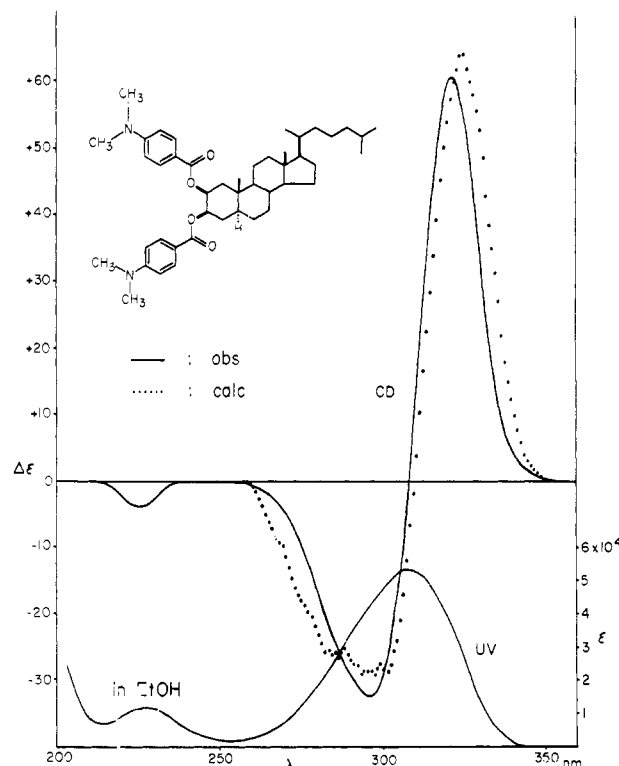

Figure 8. The uv and calculated and observed CD spectra of 5α-cholestane-$2\beta,3\beta$-diol bis(p-dimethylaminobenzoate). The calculated curve is the same as that shown in Figure 3.

R_{first} and R_{second}, is strictly satisfied. This criterion is met satisfactorily for the observed Cotton effects as well: $R_{first} = +0.756 \times 10^{-38}$, $R_{second} = -0.696 \times 10^{-38}$ cgs unit. Thus the imbalance in the shape of two apparent Cotton effects originates from the asymmetrical distribution of vibrational factors in the corresponding electronic excitation.

The Steroid Dibenzoates and Results

We first attempted to prepare D-homo-5α-androstane-$3\beta,15\beta$-diol (**19**) starting from the readily available conjugate adduct (15β-methoxyl) of methanol[18] to 3β-hydroxy-5α-androst-15-en-17-one (**11**).[19] However, this route had to be abandoned after carrying it through to 15β-methoxy-D-homo-5α-androstan-3β-ol (Scheme I, **18** with 15β-OMe instead of 15β-OCH$_2$Ph) when demethylation of the methoxy ether function failed with a variety of reagents, i.e., boron tribromide,[20] boron trifluoride etherate–acetic anhydride,[21] mixed sulfonic–carboxylic anhydride,[22] and anhydrous chromium trioxide–acetic acid (Fieser reagent).[23]

The 15-alkoxyl function was therefore replaced by the benzyloxyl group (Scheme I). Since the objective was to obtain the diol **19** for CD studies no particular attention was given to optimize reaction conditions. In contrast to the facile conjugate addition of methanol, which occurred in high yield with mild base catalyst, that of benzyl alcohol required the strong base benzyl alkoxide. The ^{1}H NMR coupling constants of 15- and 16-protons, 15-H 4.15 ppm (t, $J = 5.5$ Hz), 16-H 2.70 (d, $J = 19$ Hz) and 2.30 (dd, $J = 19$ and 5.5 Hz), are very similar to those of the above mentioned methoxyl analog, 15-H 3.92 ppm (dt, $J = 1$ and 5.5 Hz), 16-H 2.63 (dd, $J = 19$ and 1 Hz) and 2.33 (dd, $J = 19$ and 5.5 Hz), which has an established the C/D $trans$-15β-methoxy structure.[18] The values of this cyclopentanone moiety would have differed considerably if the configurations of the methoxyl and benzyloxyl derivatives were not identical.

Reduction of the cyanohydrin **13** with lithium aluminum

Scheme I
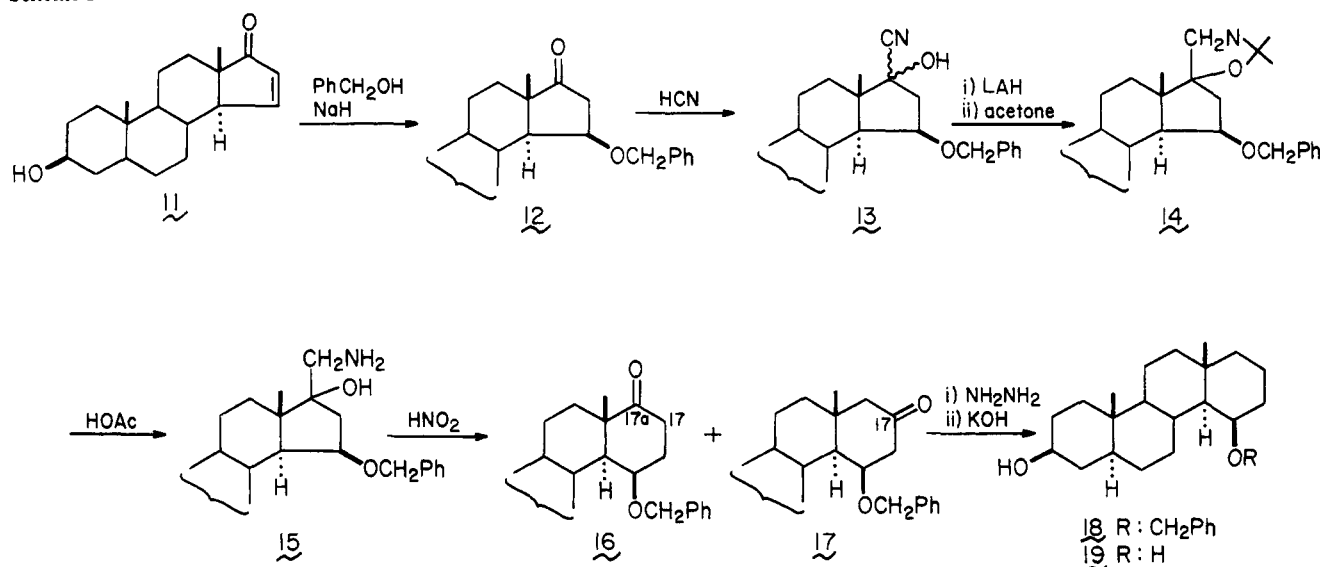
hydride led to formation of insoluble complexes between the metal and resulting hydroxyamine,[24] and an overnight extraction with chloroform–methanol mixture (9:1) gave only a very poor yield. However, extraction of the aluminum complexes with acetone in a Soxhlet apparatus improved the yield and efficiency through formation of the spirooxazolidine 14,[25] from which the hydroxyamine 15 could be regenerated with acid. Ring enlargement gave a mixture of D-homo-17a ketone (16) (major) and D-homo-17 ketone (17); the mixture was reduced by the Huang-Minlon procedure to 15β-benzyloxy-D-homo-5α-androstan-3β-ol (18), which was debenzylated to the desired D-homo-5α-androstane-3β,15β-diol (19).

5α-Pregnane-3β,11α-diol (cf 9) and 5α-androstane-3β,11β-diol (cf 8) were obtained by Huang-Minlon reduction of 3β,11α-dihydroxy-5α-pregnan-20-one (5 mg)[26] and 3β,11β-dihydroxy-5α-androstan-17-one (15 mg), respectively.

All bis(p-dimethylaminobenzoates) were prepared by reacting the diols with freshly prepared p-dimethylaminobenzoyl chloride in pyridine.

Table II summarizes the calculated and observed results for the ten bis(p-dimethylaminobenzoates). The calculated values are in good agreement with the observed values including the unevenness of the first and second Cotton effects (Figure 8). As mentioned earlier, it has been assumed that the benzoate groups in vicinal dibenzoates 1, 2, and 3 adopt only one conformation and hence there is only one theoretical curve (Figure 8). For the other benzoates 4–10 there are two sets of theoretical data (see Table II and Figures 9 and 10).

It is seen that the positions of the two split Cotton effects are fixed around 323 (calcd) and 320 nm (obsd) for the first extrema and around 295 (calcd) and 295 nm (obsd) for the second extrema. This effect is easily understood by considering eq 13; namely, term A which determines the shape of curves only contains parameters $\Delta\sigma$ and σ_0 of the uv spectra, and therefore locations of the two apparent Cotton effects are independent of the mutual configuration of the two chromophores.

Figure 9 shows the observed and calculated split CD curves for the remote 1,8-dibenzoate 10; the two calculated curves correspond to the two conformations I and II (Figure 6) of the 3-benzoate group. It is seen that in spite of an interchromophoric distance (distance between the two point dipoles of the 3β- and 15β-benzoates) of 12.8 Å, the ampli-

tudes $A_{calcd} = -20.4$ and $A_{obsd} = -26.4$ are quite significant, and therefore the exciton chirality method should be applicable to even more distant binary systems; as mentioned above, the amplitude is inversely proportional to the square of the interchromophoric distance.

The 3β,7β-dibenzoate (7) (Figure 10) is worthy of comment. The two C–O bonds are diequatorial with a dihedral angle of 0° (Figure 4) and hence an unsplit CD curve, i.e., summation of two independent CD curves with like or unlike signs centered at ca. 309 nm, might have been expected. However, although definitely much weaker than that of the 7α-epimer 6, $A_{obsd} = +39.8$, the experimental A_{obsd} nevertheless had a value of −7.1. This phenomenon can be qualitatively accounted for by assuming the 3-benzoate to adopt the two conformations I and II (Figure 6). Conformation I leads to calculated curve I (Figure 10). On the other hand, when the 3-benzoate adopts conformation II, the 3- and 7-benzoates are disposed symmetrically with respect to the plane encompassing C-5/C-10/C-19 (Figure 10), and hence the resultant CD curve "calcd II" is nil. Summation of the two calculated curves leads to a reasonable agreement with experimental data.

As shown in Figure 11, the observed A values fall within reasonable distances from the ideal linear relationship expected for a plot of A_{obsd} vs. A_{calcd}.

It is notable that the present theoretical treatment based on molecular geometry and experimental uv data reproduces the coupled Cotton effects of binary systems. Although the present data are only for dibenzoate systems, it is clear that similar treatment should hold for interactions between other chromophores, e.g., enone–benzoate,[8,27] and others,[7] including relatively remote groups.[29]

Experimental Section

Spectral data were determined on the following instruments: NMR, Varian Associates T60 and HA-100; mass spectrum, Jeol MS-07; uv, Cary 15 spectrophotometer; CD, JASCO J-40 spectropolarimeter.

The CD data given in the following are those of the extrema and zero line intersections.

15β-Benzyloxy-3β-hydroxy-5α-androstan-17-one (12). Benzyl alcohol (2 ml) was added to sodium hydride (from 0.2 g of 50% oil dispersion). This fresh solution was added to an ice–salt cold solution of 3β-hydroxy-5α-androst-15-en-17-one (11) (400 mg) in the minimum amount of benzyl alcohol (0.8 ml, ca. 5 equiv). The mix-
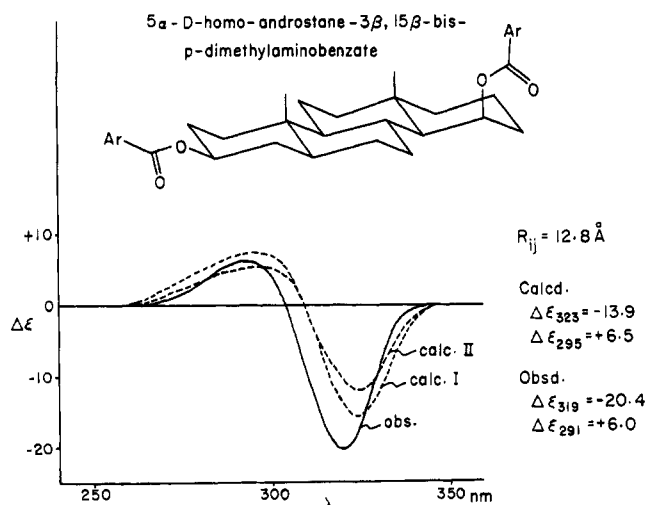
Figure 9. Coupled Cotton effect of a remote dibenzoate system (1,8-glycol), D-homo-5α-androstane-3β,15β-diol bis(p-dimethylaminobenzoate) (10).

Figure 10. Calculated and observed Cotton effects of 5α-cholestane-3β,7β-diol bis(p-dimethylaminobenzoate) (7). Conformer I (calcd I) has a weak negative chirality, while conformer II (calcd II) has nil chirality.

ture was stirred for 3 hr during which it warmed gradually to room temperature. The resulting pale yellow solution was worked by pouring into water and extracted with ether. The dried residue was purified twice by preparative TLC (silica gel–3% 2-propanol in hexane) to give an oily product (340 mg): yield 62%; mass spectrum (30 eV, 100°) m/e 396 (M$^+$); NMR (CDCl$_3$) δ 0.87 (s, 19-H), 1.17 (s, 18-H), 2.30 (dd, J = 19 Hz, 5.5, 16α-H), 2.70 (d, J = 19 Hz, 16β-H), 3.60 (broad m, 3α-H), 4.15 (t, J = 5.5 Hz, 15α-H), 4.34 and 4.57 (AB q, J = 12 Hz, OCH$_2$Ph), 7.28 (s, Ph).

15β-Benzyloxy-3β,17-dihydroxy-5α-androstane-17-carbonitrile (13). Potassium cyanide (3.0 g) was added to the solution of ketone **12** (190 mg) in 15 ml of ethanol. To the ice-cooled solution, glacial acetic acid (2.8 ml) was added dropwise and stirred for 1 hr at 0°, and for an additional 2 hr at room temperature. The mixture was poured into ice-water and kept in a refrigerator for 1 hr. The white precipitate was collected, washed with water, and dried: yield 130 mg (65%); ir (KBr) 3250, 2200 cm^{-1}; NMR (CDCl$_3$) δ 0.83 (s, 19-H), 1.08 (s, 18-H), 4.22 and 4.48 (AB q, J = 11.5 Hz, OCH$_2$Ph), 7.23 (s, Ph).

15β-Benzyloxy-3β-hydroxy-D-homo-5α-androstan-17a-one (16) and -17-one (17). The solution of crude cyanohydrin **13** (120 mg) in anhydrous ether (10 ml) was added dropwise to the suspension of LiAlH$_4$ (150 mg) in ether and stirred at room temperature for 30 min and a further 30 min at 40°. After addition of water, and removal of ether by blowing nitrogen, the aqueous suspension was mixed with 4 ml of 10% aqueous sodium carbonate solution. The white precipitate was collected, washed with water, dried, and transferred to a Soxhlet apparatus. After refluxing with 100 ml of acetone for 2 hr, the acetone solution was concentrated to dryness to give the oxazolidine (**14**); mass spectrum (10 eV, 110°) m/e 467 (M$^+$).

The crude oxazolidine was stirred with 5 ml of 50% aqueous acetic acid for 30 min. The mixture was poured into 5 ml of water and extracted with ether to remove the nonbasic impurities. The ether layer was washed with 2 ml of water twice, and the combined aqueous layer was subjected to Tiffenau ring enlargement without further purification.

To the present aqueous solution, 5 ml of acetic acid was added and cooled in an ice–salt bath. Sodium nitrite powder (0.2 g) was added very slowly, and the solution was allowed to warm to room temperature and stirred for 2 hr. After extracting with ether and washing with water, the dried residue was chromatographed on silica gel (5 g) and eluted with 3% 2-propanol in hexane to give 20 mg of an oily mixture of 17a ketone **16** and 17 ketone **17**: yield 17% from cyanohydrin **13**; mass spectrum (30 eV, 100°) m/e 410 (M$^+$); NMR (CDCl$_3$) δ 0.84 (s, 19-H), 1.32 and 1.27 (two s, 18-H), 3.57 (broad m, 3α-H), 3.86 (m, $W_{1/2}$ = 8, 15α-H), 4.37 and 4.71 (AB q, J = 12 Hz, OCH$_2$Ph), 7.3 (s, Ph).

15β-Benzyloxy-D-homo-5α-androstan-3β-ol (18). The mixture of D-homoandrosterone **16** and **17** (20 mg) in diethylene glycol (15 ml) and hydrazine hydrate (1 ml) was heated at 100° for 30 min
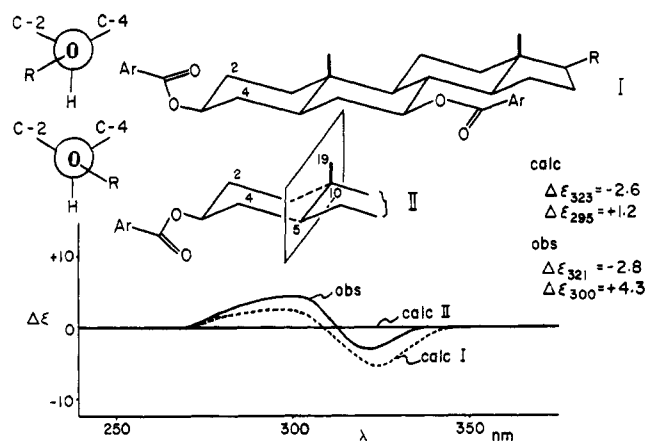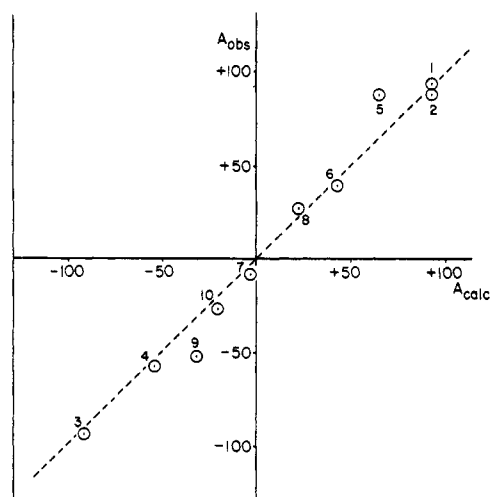

Figure 11. Comparison of calculated and observed A values of bis(p-dimethylaminobenzoates) listed in Table II: (- - -) expected.

under a stream of nitrogen. Potassium hydroxide (1 g) was added and the temperature was raised to 200° with distillation of water and excess hydrazine. After 3 hr at 200°, the cooled mixture was poured into water, extracted with ether, and washed with water and brine. The dried residue was purified by silica gel chromatography and eluted with 3% 2-propanol in hexane to give 15 mg of compound **18**; yield 78%; mass spectrum (75 eV, 130°) m/e 396 (M$^+$); NMR (CDCl$_3$) δ 0.83 (s, 19-H), 1.08 (s, 18-H), 4.2 and 4.6 (AB q, J = 12 Hz, OCH$_2$Ph), 7.3 (s, 5 H, Ph).

D-Homo-5α-androstane-3β,15β-diol (19). Benzyl ether (**18**) (15 mg) in 2 ml of acetic acid was catalytically reduced over 10% Pd-C at room temperature. The reaction mixture was filtered through celite and the dried residue was crystallized from 8% 2-propanol in hexane: yield 10 mg (90%); mp 191–193°; mass spectrum (12 eV, 130°) m/e 306 (M$^+$); NMR (CDCl$_3$) δ 0.87 (s, 19-H), 1.08 (s, 18-H), 3.57 (broad m, $W_{1/2}$ = 20, 3α-H), 4.12 (m, $W_{1/2}$ = 7, 15α-H).

p-Dimethylaminobenzoyl Chloride.[28] The solution of 1.6 g of oxalyl chloride in 3 ml of dry benzene was added slowly to the mixture of 2.5 g of potassium p-dimethylaminobenzoate and 10 ml of benzene at 0°, stirred at room temperature for 20 min, and then refluxed for 1 hr. After cooling, removal of potassium chloride by filtration and concentration precipitated p-dimethylaminobenzoyl chloride, mp 146–148°.

D-Homo-5α-androstane-3β,15β-diol Bis(p-dimethylaminobenzoate) (10). The mixture of D-homo-5α-androstane-3β,15β-diol (**19**) (8 mg) and excess p-dimethylaminobenzoyl chloride in 0.5 ml of dry pyridine was heated at 80° for 4 hr. After complete removal of pyridine in vacuo, the residue was purified by preparative TLC (silica gel–3% ethyl acetate in benzene) to give pure dibenzoate **10**

(17 mg, yield 99%), mp 285–286° (from ethyl acetate): mass spectrum (75 eV, 200°) m/e 600 (M$^+$); NMR (CDCl$_3$) δ 0.86 (s, 19-H), 1.25 (s, 18-H), 3.05 and 3.07 (two s, 12 H, N-methyl), 4.86 (broad m, $W_{1/2}$ = 20, 3α-H), 5.38 (m, $W_{1/2}$ = 7, 15α-H), 6.67 and 6.72 (two d, 4 H, J = 9), 7.91 and 7.97 (two d, 4 H, J = 9 Hz); uv (EtOH) λ_{max} 310 nm (ϵ 55,800); CD (EtOH) $\Delta\epsilon_{319}$ = −20.4, $\Delta\epsilon_{305}$ = 0, $\Delta\epsilon_{291}$ = +6.0.

The other steroid glycol bis(p-dimethylaminobenzoates) were prepared by similar methods. Each product was purified twice by preparative TLC and then recrystallized twice from ethyl acetate. When the amount of sample was limited (1–2 mg), recrystallization was performed in small test tubes, and the excess solvent was allowed to evaporate at room temperature very slowly.

5α-Cholestane-2β,3β-diol bis-p-dimethylaminobenzoate (1): mp 226–228°; mass spectrum (200°, 75 eV) m/e 698 (M$^+$); uv (EtOH) λ_{max} 307 nm (ϵ 54,300); CD (EtOH), $\Delta\epsilon_{320}$ = +61.7, $\Delta\epsilon_{307}$ = 0, $\Delta\epsilon_{295}$ = −33.2.

5α-Cholestane-2α,3α-diol bis(p-dimethylaminobenzoate) (2): mp 235–237°; NMR (CDCl$_3$), δ 0.67 (s, 18-H), 1.0 (s, 19-H), 3.05 and 3.1 (two s, 12 H, N-CH$_3$), 5.2 (broad m, 2β-H), 5.48 (broad m, 3β-H), 6.53 and 6.72 (two d, 4 H, J = 9 Hz), 7.77 and 8.00 (two d, 4 H, J = 9 Hz); uv (EtOH) λ_{max} 308 nm (ϵ 51,200); CD (EtOH), $\Delta\epsilon_{321}$ = +61.3, $\Delta\epsilon_{308}$ = 0, $\Delta\epsilon_{295}$ = −27.1.

Cholest-5-ene-3β,4β-diol bis(p-dimethylaminobenzoate) (3): mp 203°; NMR (CDCl$_3$) δ 0.68 (s, 18-H), 1.27 (s, 19-H), 3.0 and 3.7 (two s, 12 H, N-CH$_3$), 5.06 (broad m, 3α-H), 5.85 (m, 4α-H), 6.0 (m, 6-H), 6.58 and 6.7 (two d, 4 H, J = 9 Hz), 7.78 and 8.0 (two d, 4 H, J = 9 Hz); uv (EtOH) λ_{max} 308 nm (ϵ 53,200), λ_{max} 227 nm (ϵ 13,400); CD (EtOH), $\Delta\epsilon_{321}$ = −57.8, $\Delta\epsilon_{308}$ = 0, $\Delta\epsilon_{295}$ = +35.6.

5α-Cholestane-3β,6β-diol bis(p-dimethylaminobenzoate) (4): mp 196–200°; NMR (CDCl$_3$) δ 3.03 and 3.07 (two s, 12 H, N-CH$_3$), 5.04 (m, 3α-H), 5.20 (m, 6α-H), 6.62 and 6.73 (two d, 4 H, J = 9 Hz), 7.90 and 8.00 (two d, 4 H, J = 9 Hz); uv (EtOH) λ_{max} 309 nm (ϵ 53,300), λ_{max} 228 nm (ϵ 12,100); CD (10% dioxane in EtOH) $\Delta\epsilon_{320}$ = −37.6, $\Delta\epsilon_{307}$ = 0, $\Delta\epsilon_{295}$ = +19.2.

5α-Cholestane-3β,6α-diol bis(p-dimethylaminobenzoate) (5): mp 270–272°; NMR (CDCl$_3$) δ 0.67 (s, 18-H), 0.98 (s, 19-H), 3.0 (s, 12 H, N-CH$_3$), 4.88 (broad m, 3α and 6β-H), 6.60 and 6.61 (two d, 4 H, J = 9 Hz), 7.88 and 7.91 (two d, 4 H, J = 9 Hz); uv (EtOH), λ_{max} 310 nm (ϵ 57,500); CD (20% dioxane in EtOH) $\Delta\epsilon_{319}$ = +59.2, $\Delta\epsilon_{307}$ = 0, $\Delta\epsilon_{294}$ = −30.2.

5α-Cholestane-3β,7α-diol bis(p-dimethylaminobenzoate) (6): NMR (CDCl$_3$) δ 0.67 (s, 18-H), 0.93 (s, 19-H), 3.03 and 3.07 (two s, 12 H, N-CH$_3$), 4.92 (broad m, 3α-H), 5.13 (m, 7β-H), 6.67 and 6.73 (two d, 4 H, J = 9), 7.93 and 8.00 (two d, 4 H, J = 9 Hz); uv (EtOH) λ_{max} 310 nm (ϵ 55,700), λ_{max} 227 nm (ϵ 14,300); CD (EtOH) $\Delta\epsilon_{320}$ = +28.5, $\Delta\epsilon_{307}$ = 0, $\Delta\epsilon_{295}$ = −11.3.

5α-Cholestane-3β,7β-diol bis(p-dimethylaminobenzoate) (7): mp 225–227°; NMR (CDCl$_3$) δ 0.73 (s, 18-H), 1.0 (s, 19-H), 3.05 (s, 12 H, N-CH$_3$), 4.7 (broad m, 2 H, 3α and 7α-H), 6.7 (d, 4 H, J = 9 Hz), 7.94 (d, 4 H, J = 9 Hz); uv (EtOH) λ_{max} 310 nm (ϵ 60,700), λ_{max} 227 nm (ϵ 14,800); CD (EtOH) $\Delta\epsilon_{321}$ = −2.8, $\Delta\epsilon_{312}$ = 0, $\Delta\epsilon_{300}$ = +4.3.

5α-Androstane-3β,11β-diol bis(p-dimethylaminobenzoate) (8): mp 262–263°; NMR (CDCl$_3$) δ 0.88 (s, 18-H), 1.01 (s, 19-H), 3.05 and 3.07 (two s, 12 H, N-CH$_3$), 4.90 (broad m, 3α-H), 5.67 (broad m, $W_{1/2}$ = 9, 11α-H), 6.7 and 6.74 (two d, J = 9 Hz, 4 H), 7.97 and 8.03 (two d, J = 9 Hz, 4 H); uv (EtOH) λ_{max} 310 nm (ϵ 59,200), λ_{max} 227 nm (ϵ 14,000); CD (10% dioxane in EtOH) $\Delta\epsilon_{320}$ = +18.8, $\Delta\epsilon_{307}$ = 0, $\Delta\epsilon_{294}$ = −8.7.

5α-Pregnane-3β,11α-diol bis(p-dimethylaminobenzoate) (9): mp 250°; mass spectrum (250°, 30 eV) m/e 614 (M$^+$); uv (EtOH) λ_{max} 310 nm (ϵ 54,000); CD (EtOH) $\Delta\epsilon_{320}$ = −35.0, $\Delta\epsilon_{308}$ = 0, $\Delta\epsilon_{295}$ = +17.7.

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