2-Propanol was added to quench the excess Jones reagent followed by 10 mL of ether. The solution was filtered and the filtrate washed twice with saturated sodium sulfate. The crude product was purified by chromatography using 8:1 ether/acetone to afford 0.043 g (64%) of **16** as a white solid: mp 131-132 °C; 300-MHz ^{1}H NMR ($CDCl_3$) δ 1.02 (d, 3 H, J = 5.4 Hz), 1.9-2.1 (m, 4 H), 2.1 (s, 3 H), 2.3-2.45 (m, 1 H), 2.6-2.8 (m, 1 H), 2.9-3.05 (m, 1 H), 3.99-4.29 (AB q, 2 H, J = 6.9 Hz), 5.05 (m, 1 H); ^{13}C NMR, δ 11.85, 20.71, 30.85, 36.78, 38.58, 48.17, 67.16, 81.85, 83.64, 170.93, 176.67; IR (film) 3490, 2980, 1765, 1740, 1370, 1230 cm^{-1}; HRMS for $C_{11}H_{16}O_5$, calcd 228.099 78, found 228.099 28.

6-(Hydroxymethyl)-6-hydroxy-7-methyl-2-oxabicyclo[3.3.0]octan-3-one (5). Compound **16** (0.09 g, 0.39 mmol) was dissolved in 1 mL of methanol. Potassium carbonate (0.01 g, 0.08 mmol) was added and the solution stirred for 3 h. Ethyl acetate (5 mL) was added and the resulting solution filtered. The solvent was removed to afford 0.05 g (66%) of **5**, which was a light yellow oil and used without purification: 300-MHz ^{1}H NMR, δ 0.98 (d, 3 H, J = 5.5 Hz), 1.8-2.5 (m, 6 H), 2.7-2.9 (m, 1 H), 2.9-3.0 (m, 1 H), 3.5-3.8 (AB q, 2 H, J = 11 Hz), 5.1 (m, 1 H); IR (film) 3470, 2980, 1760, 1180, 1020, cm^{-1}; HRMS for $C_9H_{14}O_4$, calcd 186.089 21, found 186.089 51.

9-Hydroxysemperoside (17). Compound **5** (0.035 g, 0.113 mmol) was dissolved in 1 mL of ether. Sodium hydride (0.015 g, 0.37 mmol) and ethyl formate (0.027 g, 0.37 mmol) were added, and the solution was refluxed for 3 h. The solution was acidified with 0.5 N hydrochloric acid and stirred for 1 h. The reaction was poured into 10 mL of ether, and the water layer was removed. The product was purified by chromatography using 1:2 hexane/ethyl acetate to afford 0.008 g (35%) of **17** as a white solid: 300-MHz ^{1}H NMR ($CDCl_3$) δ 1.1 (d, 3 H, J = 6.3 Hz), 1.75-2.20 (m, 4 H), 2.65 (br s, 1 H), 2.99 (s, 2 H), 3.51 and 3.97 (AB q, 2 H, J = 11.7 Hz), 5.03 (m, 1 H), 5.58 (s, 1 H); MS, m/e 97, 108, 149, 166, 183, 196, 213, 214; HRMS, m/e for $C_{10}H_{14}O_5$ (M^+) calcd 214.084 13, found 214.083 80; HRMS, m/e for $C_{10}H_{12}O_4$ ($M^+ - H_2O$), calcd 196.0735, found 196.0742. No authentic sample was available. However, our NMR matched up peak for peak with the NMR spectrum listed in ref 12.

Registry No. 2, 110309-28-9; (±)-α-**4**, 123594-34-3; (±)-β-**4**, 123671-85-2; (±)-**5**, 123594-35-4; (±)-**6**, 120584-50-1; (±)-**7**, 123594-36-5; (±)-**8**, 123594-37-6; (±)-α-**9**, 123594-38-7; (±)-β-**9**, 123671-82-9; (±)-α-**10**, 123594-39-8; (±)-β-**10**, 123671-88-5; (±)-**11**, 123594-40-1; (±)-α-**12**, 123594-41-2; (±)-β-**12**, 123671-83-0; (±)-α-**13**, 123594-42-3; (±)-β-**13**, 123671-84-1; (±)-α-**14**, 123594-43-4; (±)-β-**14**, 123671-81-8; (±)-α-**14** (X = CH_2OH), 123594-45-6; (±)-β-**14** (X = CH_2OH), 123671-86-3; (±)-**16**, 123594-44-5; (±)-**16** α-lactol, 123594-46-7; (±)-**1b** β-lactol, 123671-87-4; (±)-**17**, 123671-80-7; (±)-3-acetoxycyclohexene, 76704-31-9.

Relative and Absolute Configurational Assignments of Acyclic Polyols by Circular Dichroism. 1. Rationale for a Simple Procedure Based on the Exciton Chirality Method

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Abstract: A general procedure for assigning multiple stereocenters in acyclic polyols is presented. Relative and absolute stereochemistry of 1,2,3-triols, 1,2,3,4-tetrols, and 1,2,3,4,5-pentols can be assigned by circular dichroism (CD) after a simple, two-step derivatization with exciton-coupling chromophores. Selective 9-anthroylation of primary hydroxyls followed by per-*p*-methoxycinnamoylation of secondary hydroxyls affords "bichromophoric" derivatives, the CD spectra of which are *characteristic and predictable for each stereochemical pattern.* A complete set of reference curves for empirical assignment of configuration in these polyols is presented. Accurate simulations of the CD spectra by summation of pairwise interchromophoric interactions demonstrate the nonempirical basis of the "bichromophoric" exciton chirality method. Full conformational analyses for all derivatives allows for rational interpretation of the manner in which the various stereoisomers give rise to the characteristic CD spectra. Applications to other hydroxylation patterns are discussed.

The assignment of stereochemistry in acyclic polyols remains a difficult task. The emergence of many highly stereoselective synthetic techniques, such as Sharpless epoxidation,[1] has facilitated assignment by trial-and-error syntheses of possible stereoisomers. However, the number of structures elucidated by time-consuming syntheses indicates the distinct lack of spectroscopic methodology in this area. Methods for assigning relative configuration in 1,3-polyols by NMR have recently emerged,[2-5] yet of the over 200 1,3-polyhydroxylated polyene macrolides known,[6] only mycoticin A and B[7] have been fully assigned since the X-ray crystallographic elucidation of amphotericin B.[8]

In polyols with contiguous hydroxylation, relative configuration can be deduced by using a combination of ^{1}H NMR J values and NOE's for one or more cyclic derivatives, preferably with comparisons to model compounds.[9] However, the use of coupling constant data alone has often proven unreliable, as illustrated by stereochemical studies of palytoxin by Moore et al.[10] Deduction of relative stereochemistry by ^{1}H NMR analysis was straightforward for chiral centers included in rings but not for those in acyclic regions of the molecule due to conformational uncertainties. Seven errors in these regions led to 12 misassigned chiral centers, as elucidated by the synthetic work of Kishi and co-workers.[11]

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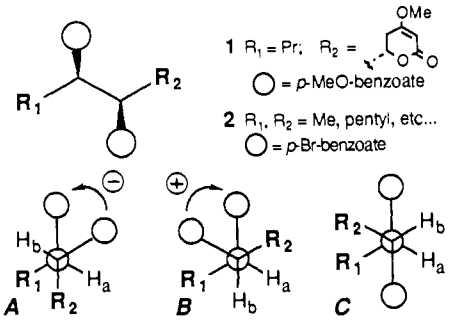
A detailed ^1H NMR study of several acetylated alditols has confirmed the difficulties in using coupling constants to assign relative stereochemistry.[12] More recently, vicinal coupling constants have been accurately predicted for alditol peracetates by using molecular mechanics and a modified Karplus equation.[13] While this approach appears promising for future structural studies, the extensive computation involved may limit its utility to simple systems.

The exciton chirality method for CD spectroscopic determination of stereochemistry[14] has been most extensively applied in molecules with rigid rings, but applications to simple acyclic systems have also proven successful.[15] Absolute configuration in acyclic allylic[16] and propargylic[17] alcohols is easily determined by CD of the corresponding bromobenzoates.[18] Application of the dibenzoate chirality rule to assign configuration in an acyclic diol was first demonstrated for hydroxypestalotin.[19] On the basis of the observed coupling constant of 6.0 Hz between the two methine protons (H_a and H_b) of its dianisoate derivative **1**, it was determined that they must be predominantly trans to one another, as in rotamer A. The absolute configuration was correctly[20]



assigned as shown on the basis of the negative dianisoate coupling observed in the CD spectrum. Similar applications to acyclic diols, aminoalcohols, and diamines have been noted.[21-23] Harada has

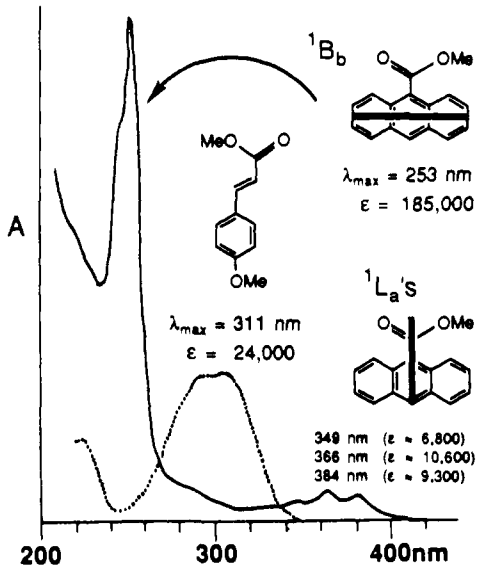


Figure 1. UV absorption spectra and associated transitions of 9-anthroate and *p*-methoxycinnamate chromophores (not shown to scale).

confirmed the generality of this method for a number of acyclic diols, i.e., **2**.[24] The dibenzoate chirality rule has also been applied to acyclic 1,3-diols.[24,25]

The "bichromophoric" exciton chirality method utilizes *two different types of exciton chromophores* which have been *selectively introduced to two different types of hydroxyls*, providing "fingerprint" CD curves.[26-28] This approach is the basis for a highly sensitive CD spectroscopic variation of oligosaccharide methylation analysis, in which free hydroxyls are derivatized with one type of chromophore, and, after glycosidic cleavage, liberated hydroxyls are derivatized with a second, red-shifted chromophore. The identities, linkage patterns, and absolute configurations of the resulting sugar subunits are indicated by their characteristic CD spectra. Furthermore, we have shown that the CD curves of such multichromophoric derivatives reflect the additive effects of all pairwise degenerate and nondegenerate interchromophoric interactions, and thus can be accurately predicted.[26,27]

Here we apply this concept of selective "bichromophoric" derivatization to acyclic polyols in which a terminal primary hydroxyl may be differentiated from secondary hydroxyls at chiral centers. While only limited numbers of known natural products (aside from carbohydrates) contain 1,2,3-triol,[29] 1,2,3,4-tetrol,[30,31] or 1,2,3,4,5-pentol[32] moieties, many could provide these hydroxylated derivatives upon degradation, particularly upon ozonolysis and reduction. The alkene diol moiety, i.e., **3**, occurs in palytoxin,[10] hydroxylated fatty acid derivatives,[33-36] and many other natural

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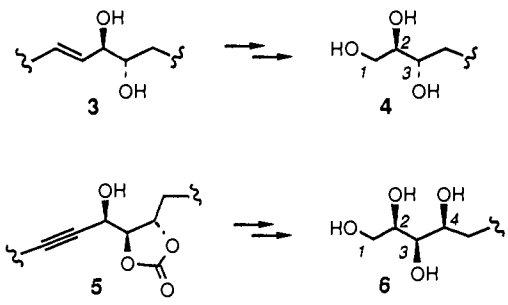


products[37] and could be easily converted to the 1,2,3-triol **4** for CD configurational studies. Analogously, tetrol **6** could be derived from alkene triols[36,38] and a variety of other natural products, such as **5**.[39]

A simple procedure for assigning both relative and absolute configuration in acyclic 1,2,3-triols was recently reported.[40] Selective 9-anthroylation of primary hydroxyls followed by per-*p*-methoxycinnamoylation of secondary hydroxyls provides characteristic CD spectra for each possible stereoisomer.

We report here that this CD spectroscopic method can similarly be used to assign the three chiral centers in 1,2,3,4-tetrols and even four centers in 1,2,3,4,5-pentols. The "fingerprint" CD curves obtained are rationally interpreted by considering the additive effects of pairwise interchromophoric exciton couplings which occur in the conformations indicated by ^{1}H NMR analyses. The demonstrated ability to accurately predict these CD spectra reflects the nonempirical basis of the method and its applicability to natural products with other hydroxylation patterns.

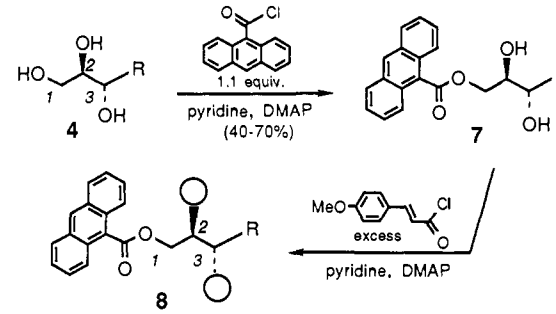
Results and Discussion

The bichromophoric exciton chirality method requires two different chromophores with well-separated absorption maxima.[26-28] Here we have utilized the 9-anthroate and *p*-methoxycinnamate esters. The absorption spectra of these two chromophores are shown in Figure 1. The two chromophores have complementary absorption regions: the λ_{max} of 9-anthroate (253 nm) corresponds to a minima of *p*-methoxycinnamate and vice versa. In addition to its strongly absorbing ^1B_b band at 253 nm (ϵ 185 000),[41] the anthroate also has a strong shoulder at 245 nm (ϵ 100 000) and three ^1L_a bands (349, 366, 384 nm) which are red-shifted to the cinnamate chromophore. Coupling of these minor transitions with the methoxycinnamate transition provides additional structure to the CD spectra in the 350–380-nm region.

The 9-anthroate chromophore was employed for derivatization of the terminal, primary hydroxyl for two reasons.[28] First, it has been shown[42] that the magnitude of exciton coupling is proportional to ϵ^2. Thus, the very high extinction coefficient of anthroate and the sharpness of this transition (Figure 1) insures that a strong, clear Cotton effect (CE) will be observed at 253 nm upon exciton coupling with chromophores at the secondary hydroxyls. This is important in acyclic systems because conformational averaging significantly reduces the observed $\Delta\epsilon$ in comparison to rigid systems. Second, the 9-anthroyl group may be selectively introduced to primary hydroxyls.[43] Furthermore, the anthroate esters are highly fluorescent (365 nm active), and this facilitates easy purification on a small scale.

The *p*-methoxycinnamate chromophore (λ_{max} 311 nm, ϵ 24 000) was employed for derivatization of the remaining secondary hydroxyls at chiral centers. The energy of the major cinnamate transition is close enough to that of the major anthracene transition to allow for efficient anthracene/cinnamate exciton coupling, and yet it is red-shifted enough such that the CEs resulting from degenerate cinnamate/cinnamate (C/C) coupling will be observable in a distinct region of the CD spectrum.[26] This is in accord with previous studies which have indicated an optimal λ_{max} separation of 60 nm when two types of exciton chromophores are simultaneously employed.[26-28]

Triol Derivatives. All acyclic polyols were obtained stereochemically pure from D-aldoses as either dithioacetals[44] or hydrazinolysis products.[45] Treatment with 9-anthroyl chloride[46] afforded the 1-*O*-(9-anthroate) esters, i.e., **7**. Subsequent treatment of monoesters **7** with excess *p*-methoxycinnamoyl chloride[47] gave the 1-*O*-(9-anthroate) 2,3-di-*O*-*p*-methoxycinnamates **8**. The CD spectra of five such erythro derivatives having identical stereochemistry are shown in Figure 2a.



The spectra of these erythro derivatives reflect the additive effects of two anthracene/cinnamate pairwise interactions, as shown in Figure 2b. The 1,2-anthracene/cinnamate interaction (represented by the derivatized (*S*)-1,2-propanediol (**9**)) makes the greatest contribution to the strong positive CE at 253 nm. The 1,3-anthracene/cinnamate coupling (represented by the derivatized (*S*)-1,3-butanediol (**10**)) makes an additional positive contribution. Additional CEs in the 350–380 region are also observed. Conformational analysis has revealed the relative geometries between anthracene and cinnamate transitions, providing a physical model which predicts the signs and intensities of the 253 nm and 350–380 nm CEs.[48] The sum of these two spectra (**9** + **10**) accurately simulates spectra of erythro derivatives shown in Figure 2a. Most erythro derivatives show no appreciable Cotton effects due to cinnamate/cinnamate (C/C) coupling, which, when observed, gives rise to Davydov-split bisignate curves with extrema at 287 and 322 nm.[26]

For conformational analysis of acyclic sugar derivatives by ^{1}H NMR, it has been generally assumed that coupling constants of <4 Hz represent protons having predominantly a gauche (60°) orientation, while coupling constants of >7 Hz indicate a trans (180°) orientation of the vicinal protons.[49,50] Additional con-

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(47) Prepared from the acid and thionyl chloride (1.2 equiv) in refluxing benzene (2 h). Benzene and excess reagent were removed in vacou, and distillation in a sublimation apparatus (140°C/0.1 mmHg) afforded the pure acid chloride.

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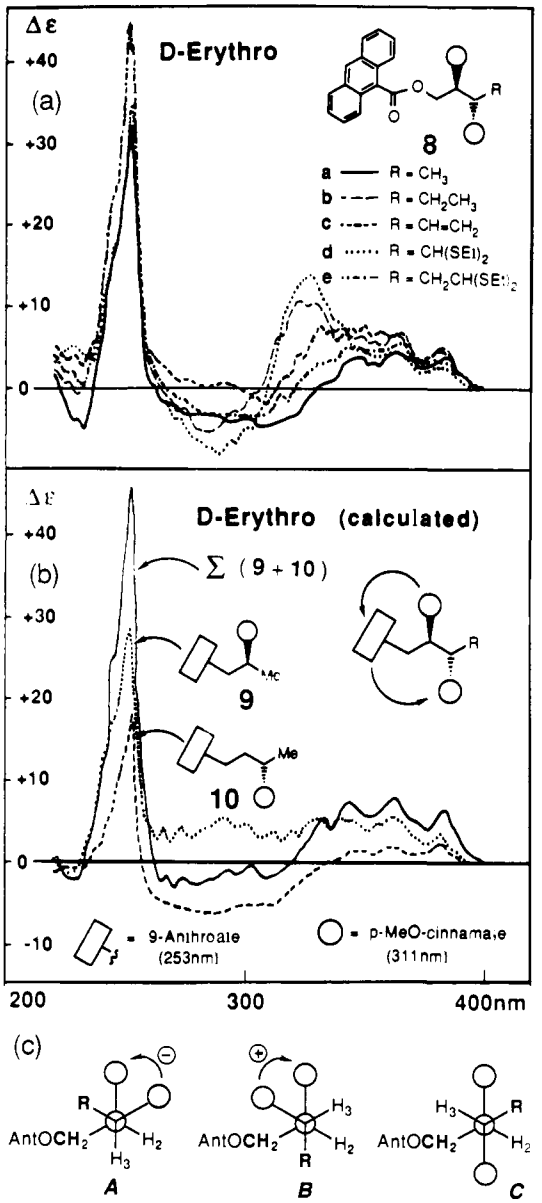

Figure 2. Circular dichroic spectra of "bichromophorically derivatized" D-erythro 1,2,3-triols **8**: (a) Reference curves for empirical assignment of relative and absolute configuration. (b) Simulated curve from summation of 1,2- and 1,3-anthracene/cinnamate pairwise interactions represented by **9** and **10**, respectively. (c) Three C-2/C-3 rotamers dictating minimal net cinnamate/cinnamate exciton coupling.

formational information can be obtained from the CD spectra. To best correlate NMR and CD data, all measurements were recorded in the same solvent (acetonitrile) as solvent-dependent conformational differences could be expected. Thus, both NMR and CD data have been utilized to determine major and minor conformations, with the purpose of rationally interpreting the manner in which the various stereoisomers give rise to distinctive CD curves. Additionally, we have examined how varying the alkyl substituent affects both the NMR and the CD and have correlated these changes with shifts in conformational equilibria.

Consideration of the three possible rotamers around C-2/C-3 (Figure 2c) reveals that two (A and B) are energetically similar but have opposite exciton chiralities, while a third (C) exhibits no chirality between the cinnamate chromophores. The $J_{2,3}$ of 4.6 Hz in **8a–c** (Table I) indicates an equilibrium of gauche and anti orientations between H-2 and H-3, with gauche orientations

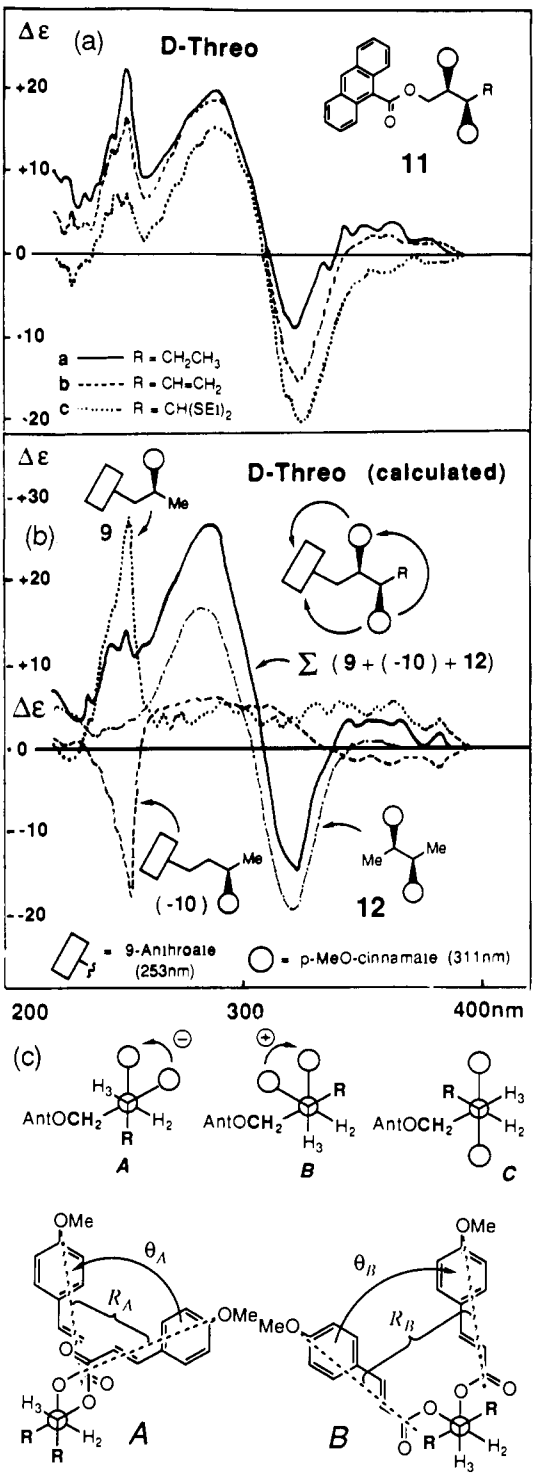

Figure 3. CD spectra of D-threo triol derivatives **11**. (a) Reference curves for empirical assignment. (b) Simulated curve (Σ) from summation of 1,2- and 1,3-anthracene/cinnamate and 2,3-cinnamate/cinnamate pairwise interactions represented by **9**, **–10**, and **12**, respectively. (c) Three C-2/C-3 rotamers dictating net negative cinnamate/cinnamate exciton coupling. The negative exciton chirality of rotamer A dominates owing to its shorter interchromophoric distance ($R_A < R_B$) and its optimal dihedral angle ($\theta_A \sim 70°$) between transitions (represented as dotted lines).

(A and/or B) favored. The lack of any observable C/C coupling in these derivatives indicates that A and B are equally populated, the negative exciton chirality of A cancelling with the positive coupling of B. Thus, on the basis of NMR and CD, there is roughly an equal proportion of the three C-2/C-3 rotamers in these erythro derivatives. For erythro derivative **8d**, however, a positive C/C couplet indicates that in this derivative, B > A. The $J_{2,3}$ of 6.5 Hz indicates an increased proportion of rotamer C, which

(50) (a) Blanc-Muesser, M.; Defaye, J.; Horton, D. *Carbohydr. Res.* **1980**, *87*, 71–86. (b) Horton, D. *Pure Appl. Chem.* **1975**, *42*, 301–325. (c) Defaye, J.; Gagnaire, D.; Horton, D.; Muesser, M. *Carbohydr. Res.* **1972**, *21*, 407–416. (d) Horton, D.; Wander, J. D. *Carbohydr. Res.* **1969**, *10*, 279–288.

Table I. Partial ^1H NMR Data (CD_3CN) of Anthroate Percinnamates for Conformational Analysis and Correlation

	no.	H1[a]	J1-2	H1'[a]	J1'-2	J1-1'	H2[b]	J2-3	H3[c]	J3-4	H4[d]	J4-5	H5[e]	Ha[f]
erythro	**8a**	4.95	3.7	4.87	6.4	12.1	5.54	4.6	5.33					6.32
	8b	4.95	3.6	4.88	6.5	12.1	5.55	4.6	5.28					6.34
	8c	4.90	5.1	4.90	5.1		5.62	4.6	5.71					6.36
	8d	5.10	3.0	4.84	5.2	12.3	5.84	6.5	5.68					6.33
	8e	4.94		4.86	(secondary multiplet)		5.60		5.66					6.31
threo	**11a**	4.93	3.3	4.75	6.6	12.1	5.59	4.5	5.30					6.26
	11b	4.96	3.3	4.77	6.6	12.1	5.64	5.7	5.74					6.30
	11c	5.12	3.7	4.71	4.6	12.4	5.92	5.6	5.64					6.14
ribo	**13a**	5.08	2.8	4.86	6.3	12.3	5.70	6.0	5.53	4.7	5.36			6.33
	13b	5.12	2.8	4.87	6.5	12.3	5.70	5.5	5.53	5.0	5.27			6.33
	13c	5.12	2.7	4.85	5.5	12.3	5.65	6.0	5.60	4.5	5.74			6.35
	13d	5.10	2.6	4.93	6.9	12.2	5.77	4.4	5.93	6.3	5.70			6.32
arabino	**14a**	5.03	2.9	4.81	5.6	12.3	5.66	7.1	5.48	3.5	5.40			6.33
	14b	5.02	2.8	4.80	5.3	12.3	5.60	6.7	5.54	3.3	5.33			6.35
	14c	5.04	2.8	4.82	5.2	12.4	5.65	7.1	5.59	3.9	5.75			6.34
	14d	4.99	3.6	4.80	5.9	12.2	5.64	6.0	6.00	3.4	5.59			6.32
xylo	**15a**	5.00	3.4	4.71	6.0	12.1	5.72	4.7	5.52	4.7	5.35			6.20
	15b	5.04	3.2	4.74	5.6	12.2	5.68	5.3	5.61	4.1	5.31			6.18
	15c	5.03	3.6	4.71	5.6	12.1	5.67	4.7	5.62	5.3	5.73			6.12
	15d	5.00	3.7	4.74	5.9	12.1	5.85	3.9	6.06	5.8	5.63			6.17
lyxo	**16a**	4.98	3.7	4.77	6.4	12.0	5.83	3.6	5.50	5.9	5.31			6.19
	16b	4.97	4.0	4.74	6.3	12.0	5.77	3.2	5.50	5.9	5.25			6.14
	16c	4.99	3.7	4.76	6.2	12.0	5.80	3.4	5.56	6.0	5.65			6.16
	16d	5.02	4.3	4.75	6.3	11.8	5.82	1.8	5.93	6.8	5.67			6.12
allo	**17**	5.14	2.8	4.97	6.4	12.3	5.86	4.9	5.77	5.3	5.62	5.3	5.36	6.26
altro	**18**	5.13	2.7	4.92	6.3	12.2	5.72	4.9	5.68	6.1	5.54	3.7	5.42	6.26
gluco	**19**	5.03	3.2	4.84	5.7	12.3	5.60	6.4	5.72	3.8	5.57	5.3	5.26	6.20
manno	**20**	5.07	3.2	4.82	5.4	12.3	5.62	6.9	5.82	2.9	5.56	6.0	5.27	6.12
gulo	**21**	5.05	3.4	4.78	5.0	12.3	5.65	5.3	5.87	3.1	5.53	6.0	5.20	6.02
ido	**22**	5.06	3.8	4.76	5.3	12.2	5.67	4.7	5.78	5.0	5.55	4.6	5.31	6.13
galacto	**23**	5.05	4.3	4.68	5.5	12.0	5.70	2.3	5.76	8.3	5.54	2.8	5.31	6.00
talo	**24**	5.06	4.2	4.75	5.9	12.0	5.82	2.9	5.73	6.8	5.56	4.8	5.28	6.12

[a] Splitting patterns for footnote *a–e*: dd. [b] ddd. [c] dd or multiplet (8a,b,e and 11a). [d] dd or multiplet (13–16a,b). [e] dq. [f] Most upfield cinnamate vinylic H, 16.0 Hz doublet (chemical shifts are often diagnostic of stereochemical class).

Table II. CD Data of Bichromophoric Triol and Tetrol Derivatives ($\Delta\epsilon$, CH_3CN)

	no.	253 nm	287 nm	322 nm	362 nm
erythro	**8a**	+31	−3	−3	+5
	8b	+45	−5	+11	+7
	8c	+42	0	+4	+8
	8d	+34	−8	+14	+5
	8e	+44	−4	0	+5
threo	**11a**	+24	+21	−9	+4
	11b	+17	+20	−15	+2
	11c	+8	+15	−20	0
ribo	**13a**	+52	−4	0	+6
	13b	+41	−9	0	+4
	13c	+39	−14	+10	+3
	13d	+47	−16	+22	+6
arabino	**14a**	+26	+21	−22	+4
	14b	+18	+18	−26	+3
	14c	+20	+17	−28	+2
	14d	+38	+26	−25	+5
xylo	**15a**	+23	+15	−4	+4
	15b	+24	+6	−15	+1
	15c	+17	−5	0	+2
	15d	+21	−13	+26	+3
lyxo	**16a**	+7	+29	−28	+2
	16b	−6	+20	−31	0
	16c	−1	+25	−29	0
	16d	0	+31	−39	+1

results from a decreased proportion of A.[51]

The CD spectra of the corresponding threo derivatives with identical stereochemistry at C-2 (*R*)[52] are shown in Figure 3a. These spectra are characterized by a strong negative C/C couplet and a smaller, yet still positive CE at 253 nm which results from the 1,3-interaction (**−10**, Figure 3b) subtracting from the dominant 1,2-interaction **9** (Figure 3b). The intensity of the 253 nm CE varies with alkyl substitution in threo derivatives.[53] The 2,3-cinnamate/cinnamate coupling in D-threo derivatives is represented by the (*R,R*)-2,3-butanediol dimethoxycinnamate (**12**, Figure 3b), and summation of these three spectra [Σ(**9** + (**−10**) + **12**)] nicely simulates the characteristic D-threo curves (compare Figure 3a).

The strong negative C/C couplet is attributed to rotamer A (Figure 3c) as in earlier studies described above. The $J_{2,3}$ of 4.6 Hz for **11a**, however, indicates that rotamer A, in which H-2 and H-3 are trans, is not predominant, and yet the CD spectrum is still dominated by its negative exciton chirality. While rotamers A and B have opposite chiralities, rotamer A possesses an interchromophoric geometry which gives rise to stronger exciton coupling. This is due to two factors. Coupling amplitude is proportional to $1/R^2$, where R is the distance between the coupling transitions,[14] and this distance is shorter in A than in B[54] (see bottom Figure 3c). Coupling amplitude is also strongly dependent upon the dihedral angle θ between the two transitions. Calculations have shown coupling amplitude to be at a maximum when $\theta \sim 70°$, and zero when $\theta = 0$ and 180°.[14,55] This factor also favors rotamer A as the more important contributor to the CD spectrum owing to its near ideal dihedral angle. A greater proportion of rotamer A in derivatives **11b** and **11c** is indicated by $J_{2,3}$ of 5.7 and 5.6 Hz, respectively. As expected, this increases the amplitude of the 287/322 nm C/C couplet in the CD.

(51) This decrease in A with concommitant increase in C is due to an unfavorable 1,3-steric interaction between anthroate (in favored gg C-1/C-2 rotamer) and the bulky $-CH(SEt)_2$ group which occurs in A. See ref 48.

(52) (*R,S*) configurational assignment can vary with alkyl substituent: While all the triols, tetrols, and pentols derived from D-aldoses have *R* configuration at C-2, note that the 1,2-diol derivative **9** with identical stereochemistry at C-2 is designated *S*.

(53) We have found that this variation is due to the degree to which the various derivatives adopt a minor yet very strongly coupling conformation in which the anthroate and the C-3 cinnamate are stacked. See ref 48.

(54) As indicated by CPK models. The esters are expected to adopt the s-trans conformation with the carbonyl groups oriented toward their respective carbinyl H's, in accordance with spectroscopic (ref 14) and crystallographic evidence. See: (a) Bocelli, G.; Grenier-Loustalot, M. F. *Acta Crystallogr.* **1983**, *C39*, 633–636 and 636–638. (b) Lichtenthaler, F. W.; Sakakibara, T.; Oeser, E. *Carbohydr. Res.* **1977**, *59*, 47–61.

(55) Harada, N.; Chen, S.-M. L.; Nakanishi, K. *J. Am. Chem. Soc.* **1975**, *97*, 5345.

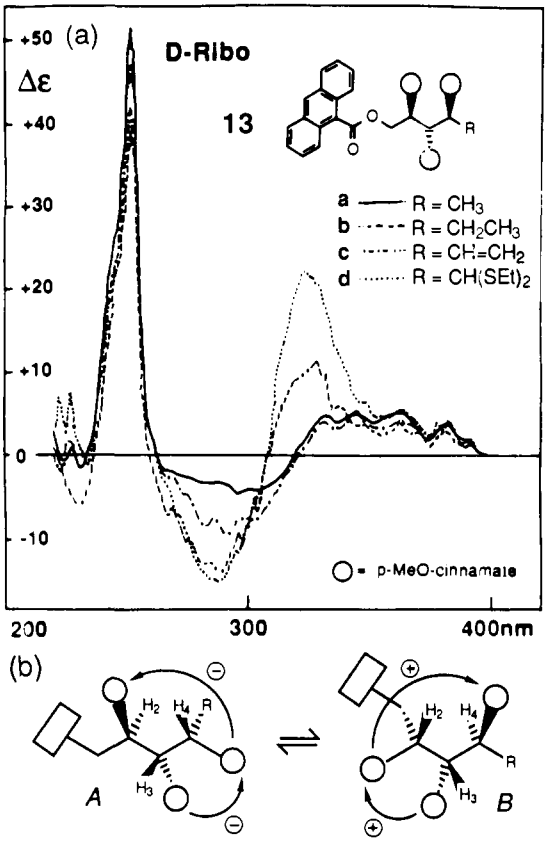

Figure 4. (a) CD spectra of four 1,2,3,4-tetrol derivatives with D-ribo stereochemistry and different alkyl substituents (R). (b) Major "sickle" conformations and their corresponding exciton chiralities in D-ribo derivatives as determined by NMR analysis.

Tetrols. Extensive conformational studies by Horton of acetylated acyclic sugar derivatives contributed to the generalization that an extended "zigzag" arrangement of the carbon chain is favored unless this would result in a parallel 1,3-interaction between syn periplanar acyloxy substituents.[50] Such an unfavorable steric interaction is alleviated by formation of one or more bent ("sickle") conformations. Such is the case for D-ribo tetrol derivatives **13** (Figure 4), in which the C-4 and C-2 cinnamates are syn. The two terminal chiral centers (C-2 and C-3) have D-erythro stereochemistry, and the similarity of the erythro and ribo CD spectra reflects this relationship. While all exhibit an intense positive 253 nm CE, C/C coupling ranges from nil (**13a**) to strong positive (**13d**). This is due to an equilibrium between the two sickle conformations A and B (Figure 4b), as indicated by the intermediate $J_{2,3}$'s and $J_{3,4}$'s of 4.5–6.0 Hz (**13a–c**). The two conformations have opposite C/C exciton chiralities which cancel one another, except in the case of **13d**, which shows a strong positive C/C couplet. This indicates a predominance of B, and the values of $J_{2,3}$ (4.4 Hz) and $J_{3,4}$ (6.3 Hz) support this conclusion. The increased steric bulk of the alkyl group can be better accomodated by B, in which the alyl group adopts the extended chain position.

The CD curves of the analogous four D-arabino derivatives **14** are characterized by a positive 253 nm CE of medium intensity and a strong negative CC couplet (Figure 5). A single, extended conformation predominates, as indicated by the values of $J_{2,3}$ (6.0–7.1 Hz) and $J_{3,4}$ (3.4–3.9 Hz). The negative exciton chirality between the C-2 and C-4 cinnamates accounts for the strong CE's at 287/322 nm. Harada's study of acyclic dibenzoates indicated that 1,3-interactions were stronger than 1,2-interactions,[24] and we have found the same trend for acyclic dicinnamates: the coupling in (*R*,*R*)-2,4-pentanediol dimethoxycinnamate ($\Delta\epsilon_{287nm}$ = +26, $\Delta\epsilon_{322nm}$ = −44) is roughly double that in the vicinal dicinnamate **12** (Figure 3b). Thus, the negative C/C couplets in the CD's of D-arabino derivatives (**14**, Figure 5) reflect the additive effects of the large negative 2,4- and smaller positive 3,4-dicinnamate pairwise interactions.

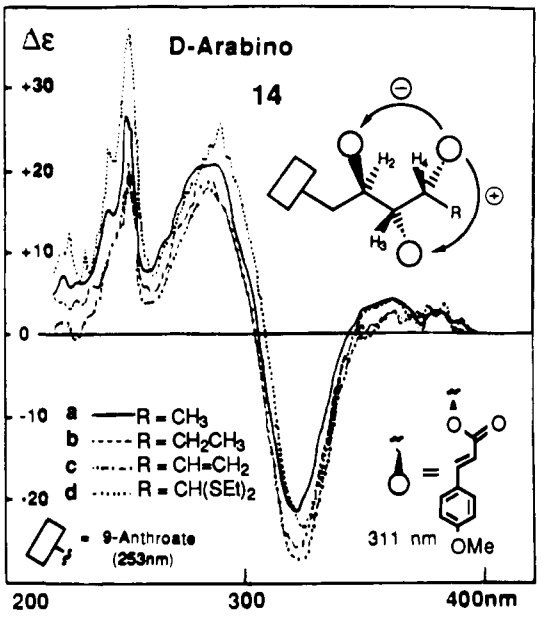

Figure 5. CD spectra of tetrol derivatives with D-arabino stereochemistry.

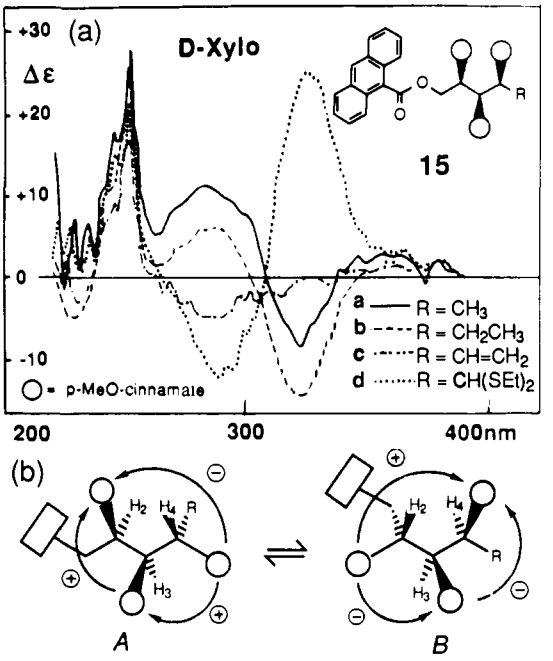

Figure 6. (a) CD spectra of four tetrol derivatives with D-xylo stereochemistry with varying alkyl substituents. Note that the variable spectral pattern in *this* series requires that any tetrol derivative with unknown configuration be compared to those derivatives with the most similar alkyl group, i.e., the curve of an unknown having a C-5 methylene should be compared to the curves of **13b–16b**. (b) Major "sickle" conformations and their corresponding exciton chiralities in D-xylo derivatives as determined by NMR analysis. Conformation A, with a net positive exciton chirality, dominates in **15d**, while conformation B, with a net negative exciton chirality, dominates in **15a,b**.

When using the tetrol CD spectra as reference curves for empirical assignments, the curves with the alkyl substituent which best matches the unknown should be compared. For example, derivatives with an extended series of methylenes[30,31] should be compared to the derivatives in which R = CH_2CH_3 (**13b**, **14b**, **15b**, and **16b**), while derivatives with alkyl branching at C-5 should be compared to the dithioacetal derivatives (**13d**, **14d**, **15d**, and **16d**). This is important in D-xylo tetrol derivatives **15**, which exhibit marked variations dependent upon the alkyl group (Figure 6). In these derivatives, an unfavorable 1,3-interaction between syn cinnamates is alleviated by two sickle conformations (A and B, Figure 6b). The equilibrium between A and B is strongly

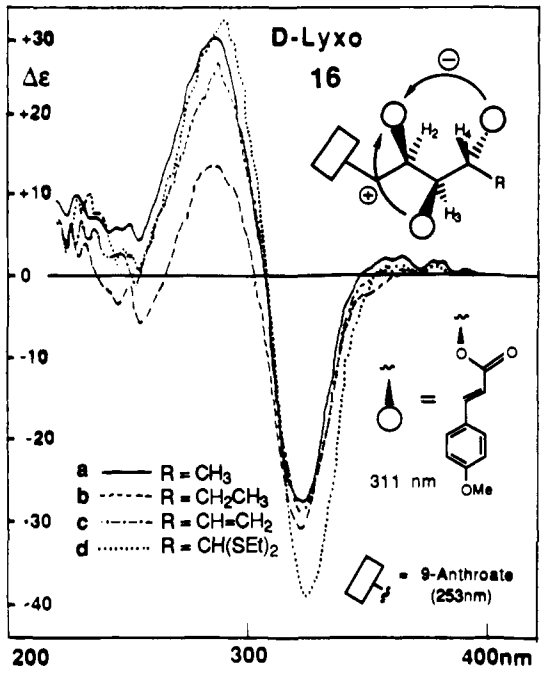

Figure 7. CD spectra of tetrol derivatives with D-lyxo stereochemistry.

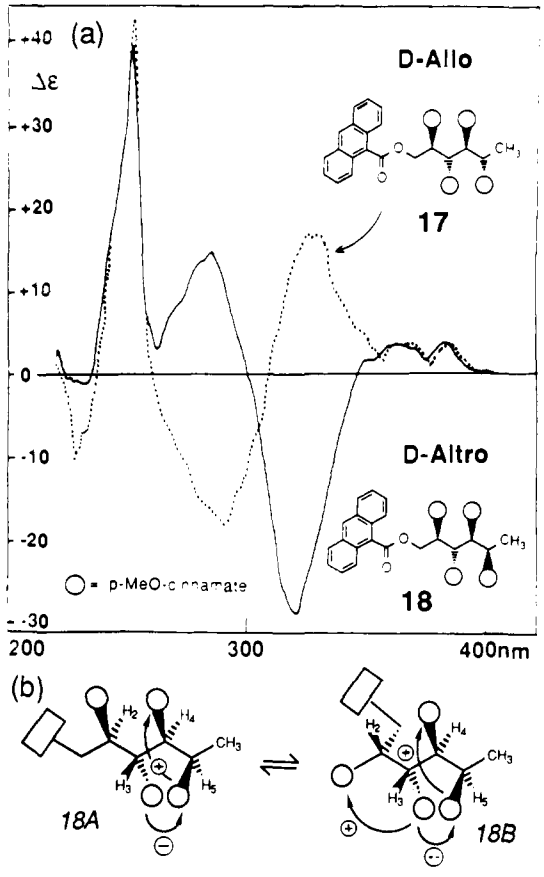

Figure 8. (a) CD spectra of 1,2,3,4,5-pentol derivatives with D-allo and D-altro stereochemistry. (b) Major conformations and their corresponding pairwise exciton chiralities of D-altro derivative **18**, as determined by NMR: extended ("zigzag") conformation **18A** and bent ("sickle") conformation **18B**.

affected by the alkyl group (R). Conformation A predominates in **15d** as indicated by values of $J_{2,3}$ (3.9 Hz) and $J_{3,4}$ (5.7 Hz), and its expected net positive C/C chirality is reflected in the CD curve. Alternatively, conformation B is prefered in **15b** as indicated by values of $J_{2,3}$ (5.3 Hz) and $J_{3,4}$ (4.1 Hz). The small negative C/C couplet exhibited by this derivative is in accord with that predicted for the B conformation.

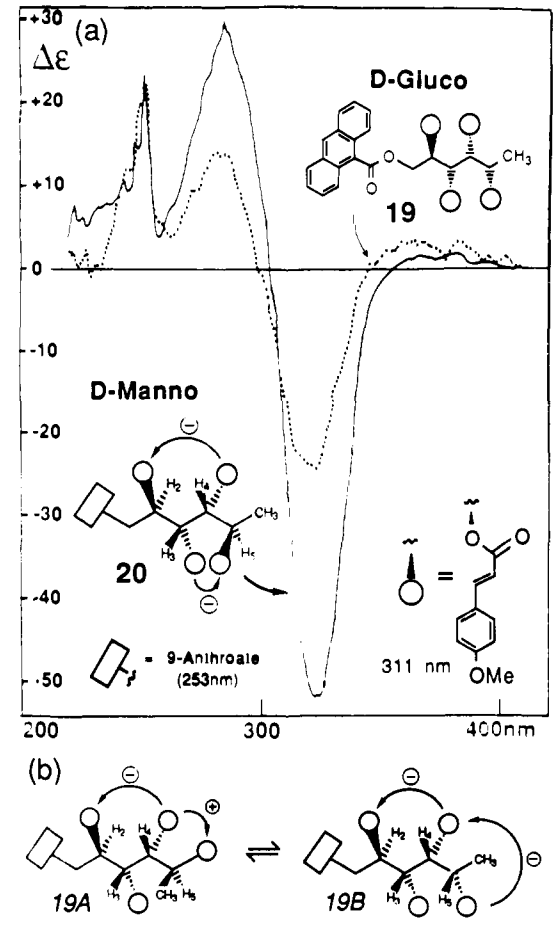

Figure 9. (a) CD spectra of 1,2,3,4,5-pentol derivatives with D-gluco and D-manno stereochemistry. (b) Major conformations of D-gluco derivatives **19**, as determined by NMR: bent ("sickle") conformation **19A** and extended ("zigzag") conformation **19B**. The net negative C/C coupling in both derivatives is indicated by the signs of the pairwise interactions.

In the D-lyxo tetrol derivatives **16**, a very strong negative C/C couplet dominates the CD spectra (Figure 7). An extended zigzag conformation is preferred, indicated by the values of $J_{2,3}$ (3.2–3.6 Hz) and $J_{3,4}$ (5.9–6.0 Hz) for **16a–c**. For **16d**, the predominance of the extended conformation is even greater, as indicated by the more extreme values of $J_{2,3}$ (1.8 Hz) and $J_{3,4}$ (6.8 Hz) and the larger negative C/C couplet in the CD spectrum. As in the case of the arabino derivatives, this effect is attributed to the negative exciton chirality between the C-2 and C-4 cinnamates. A striking feature of the lyxo spectra is the very small positive and sometimes negative 253 nm CE.[53]

Pentols. The bichromophoric derivatives of the eight diastereomeric 1-deoxyhexitols[56] also exhibit distinctive and predictable CD spectra. The conformational dispositions of the pentol derivatives can be correlated with those discussed above for tetrol derivatives. This follows the concept of homomorphology, introduced by Horton in an NMR study of acyclic aldohexose derivatives.[50a] The results of our conformational analyses in the pentol series are in accord with the findings of Horton and others. Homomorphological relationships are indicated not only by similarities in NMR J values (see Table I) but are directly reflected in the CD spectra.

The CD curves of the D-allo and D-altro derivatives, both of which have the identical ribo stereochemistry at C-2,3,4, are shown

(56) This conventional carbohydrate numbering has not been used in the text or the tabulated NMR data (Table I). For continuity in comparing NMR data of the various triol, tetrol, and pentol derivatives and for relevance to natural products (i.e., ref 31) the position of the primary hydroxyl has been designated C-1. (By conventional carbohydrate nomenclature, this is C-4 in tetrose derivatives, C-5 in pentose derivatives, and C-6 in hexose derivatives. Conventional numbering has been employed in the Supplementary Material.)

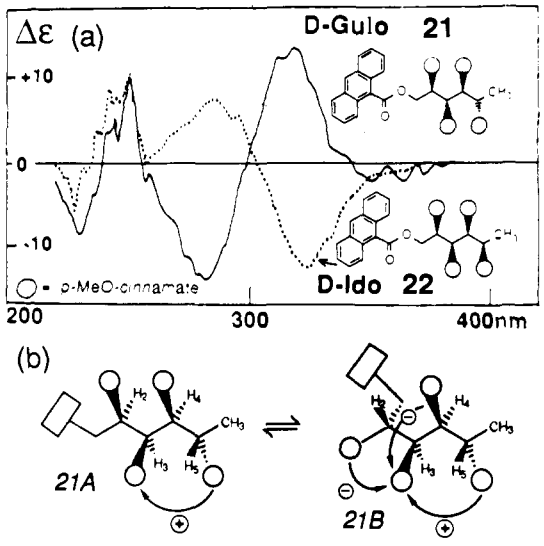

Figure 10. (a) CD spectra of 1,2,3,4,5-pentol derivatives with D-gulo and D-ido stereochemistry. (b) Major conformations of D-gulo derivative **21**, as determined by NMR: extended ("zigzag") conformation **21A** and bent ("sickle") conformation **21B**.

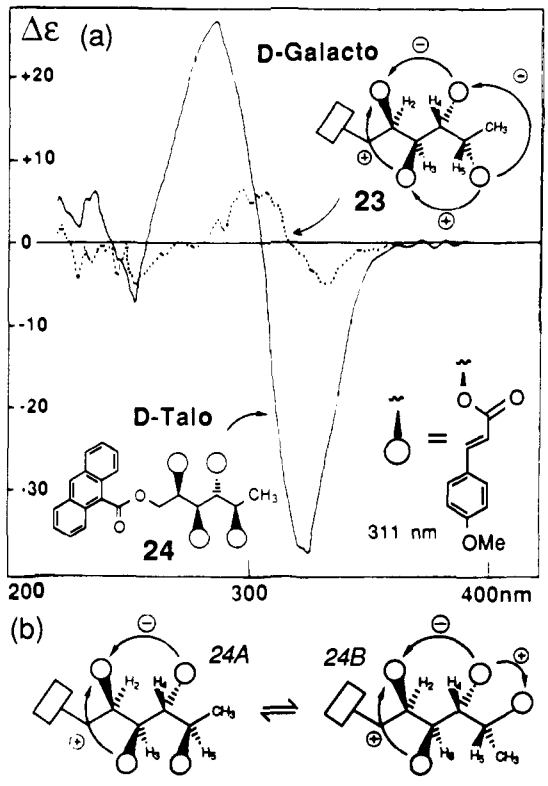

Figure 11. (a) CD spectra of 1,2,3,4,5-pentol derivatives with D-galacto and D-talo stereochemistry. (b) Major conformations of D-talo derivative **24**, as determined by NMR: extended ("zigzag") conformation **24A** and bent ("sickle") conformation **24B**.

in Figure 8. As in the ribo derivatives, the 253 nm CE is very intense. The configuration at C-5 has little effect upon the intensity of this CE, owing to the distance between the anthroate at C-1 and the cinnamate at C-5. This is a general result found for the entire series of pentol derivatives (see Figures 9–11).

Extensive conformational mixing in the D-allo derivative **17** is indicated by the intermediate values of $J_{2,3}$, $J_{3,4}$, and $J_{4,5}$ (4.9–5.3 Hz). This is due to rotation about all of these bonds to alleviate the two parallel 1,3-dicinnamate interactions. The allo derivative has ribo configuration not only in the C-2,3,4 segment but also in the C-3,4,5 segment as well. The CD spectrum of allo derivative **17** is nearly identical with that of the ribo derivative **13d**, directly reflecting the homomorphological relationship.

The D-altro derivative **18** has only one unfavorable 1,3-syn interaction, and this is alleviated by rotation about the C-2/C-3 bond ($J_{2,3}$ 4.9 Hz) to result in an equilibrium favoring sickle conformation (**18B**) over the extended conformation (**18A**, Figure 8b). The arabino configuration between C-3,4,5 gives rise to an extended conformation in this region, as indicated by the predominantly trans orientation of H-3 and H-4 ($J_{3,4}$ = 6.1 Hz) and gauche orientation of H-4 and H-5 ($J_{4,5}$ = 3.7 Hz). It follows that the CD spectrum shows negative C/C coupling similar to the arabino derivatives (Figure 5). This net negative chirality reflects the dominant contribution of the pairwise interaction between cinnamates at position 3 and 5. Thus, while allo and altro derivatives differ by only a single chiral center, the 287/322 CE's differentiate between the two in a predictable manner.

The D-gluco and D-manno derivatives, which share the same D-arabino stereochemistry at C-2,3,4 exhibit identical 253 nm CE's ($\Delta\epsilon$ +23, Figure 9), the intensity of which is typical for arabino derivatives. The C-1,2,3,4 segment of gluco derivative **19** is homomorphic with arabino derivatives and adopts the extended conformation. The cinnamate at C-5 is syn to that at C-3, and the 1,3-parallel interaction between cinnamates in extended conformation **19B** is relieved by rotation about the C-4/C-5 bond to give sickle conformation **19A** (Figure 9b). The CD spectrum of gluco derivative **19** is nearly identical with that of arabino derivative **14a**, once again reflecting a familial relationship.

In manno derivative **20**, no parallel 1,3-interactions are present, and a single extended conformation predominates, as indicated by NMR ($J_{2,3}$ = 6.9 Hz, $J_{3,4}$ = 2.9 Hz, and $J_{4,5}$ = 6.0 Hz). The CD spectrum shows an intense negative C/C couplet resulting from the additive effects of two 1,3-pairwise interactions with negative chirality (C-2/C-4 and C-3/C-5 cinnamate pairs, Figure 9).

The remaining four pentol derivatives **21–24** share D-threo stereochemistry at C-2 and C-3, and this is reflected by the smaller intensities of their corresponding 253 nm CE's (Figures 10 and 11). The D-gulo (**21**) and D-ido (**22**) derivatives have the identical stereochemistry (D-xylo) at their first three centers, and this relationship is once again indicated by the equal intensities of their 253 nm CE's (Figure 10). As shown in Figure 10b, the gulo derivative exists in two conformations, one with the carbon chain extended (**21A**) and a second sickle conformation (**21B**) resulting from rotation about the C-2/C-3 bond. NMR indicates that a fair proportion of extended conformation **21A** exists ($J_{2,3}$ = 5.3 Hz, $J_{3,4}$ = 3.1 Hz, and $J_{4,5}$ = 6.0 Hz), suggesting that the syn 1,3-parallel interaction between C-2 and C-4 cinnamates is not as energetically unfavorable as in the case with acetates.[49,50] The parallel 1,3-dicinnamate orientation may be partially stabilized relative to parallel 1,3-diacetates by aryl/aryl attraction. The positive exciton chirality between C-3 and C-5 cinnamates gives rise to the positive C/C couplet in the CD spectrum; however, the intensity of this couplet is reduced by negative C/C interactions which exist in the sickle conformation (**21B**, Figure 10b).

As in the case of allo stereochemistry, two unfavorable parallel 1,3-interactions in D-ido derivative **22** result in extensive conformational mixing as indicated by the intermediate values of $J_{2,3}$, $J_{3,4}$, and $J_{4,5}$ (4.6–5.0 Hz). The CD spectrum shows a small negative C/C couplet (Figure 10) and bears similarities to spectra of xylo derivatives **15a,b** (Figure 6) and threo derivatives **11**.

The D-galacto and D-talo derivatives (**23** and **24**) differ only in the configuration of the chiral center at C-5, and yet their CD spectra distinguish the two quite dramatically (Figure 11). The small negative 253 nm CEs reflect their shared D-lyxo stereochemistry at C-2,3,4. Small negative 253 nm CE's were observed in lyxo derivatives **16b** and **16c**, while in the other D-lyxo derivatives this CE was nil (**16d**) or slightly positive (**16a**).[53]

D-Galacto derivative **23** was found to adopt the extended conformation exclusively, as indicated by the extreme values of $J_{2,3}$, $J_{3,4}$, and $J_{4,5}$ (2.3, 8.3, and 2.8 Hz, respectively). The CD spectrum shows very little C/C coupling resulting from the cancelling effects of two 1,3-pairwise interactions with opposite chirality (C-2/C-4 and C-3/C-5 cinnamate pairs) and two 1,2-interactions also with opposite chirality (C-2/C-3 and C-4/C-5

cinnamate pairs, Figure 11). In contrast, the CD of talo derivative **24** exhibits a very strong negative C/C couplet, owing to the dominant contribution of the C-2/C-4 cinnamate pair. The C-1,2,3,4 segment is homomorphic with lyxo derivatives, as indicated by similar J's (see Table I) and reflected in the CD spectra. The parallel 1,3-interaction between C-3 and C-5 cinnamates in the extended conformation **24A** is alleviated in sickle conformation **24B**, and the intermediate value of $J_{4,5}$ (4.8 Hz) indicates an equilibrium between these two forms (Figure 11b).

From comparisons of the entire series of triol, tetrol, and pentol diastereomers, a generalization concerning the homomorphological relationships may be drawn. The differences between related triol and tetrol derivatives or between tetrol and pentol derivatives are due to the addition of a contiguous cinnamate to the carbon chain. When this results in a parallel 1,3-interaction with an existing center, the effect of the additional cinnamate upon the CD spectrum will be minimal. For example, the cinnamate at C-5 in talo derivative **24** results in little change over the parent lyxo derivative spectra. This is due not only to the fact that syn 1,3-dicinnamates have no exciton chirality when parallel (C-3 and C-5 in **24A** Figure 11b), but because rotation about the C-4/C-5 bond to relieve the unfavorable 1,3-interaction results in a sickle conformation in which the C-5 cinnamate is extended away from the rest of the molecule (**24B**, Figure 11b). Thus, the C-1,2,3,4 segment of the molecule maintains the same conformation as in the case without the additional cinnamate at C-5 (i.e., lyxo), and a similar CD spectrum results. By analogy to this example, the erythro/ribo, ribo/allo, arabino/gluco, threo/xylo, and xylo/ido similarities are also explained.

Other Hydroxylation Patterns. The same approach may be applied to 1,3-("skipped") polyols with primary hydroxyl ends. For example, the absolute configuration of a derivatized 1,2,4-triol is indicated by the sign of the 253 nm CE owing to the 1,2-anthroate/cinnamate coupling (i.e., **9**, Figure 2b). We have seen above in the pentol derivatives that anthroate interaction with distant C-4 cinnamates is negligible. Relative configuration in a 1,2,4-triol derivative is indicated by the C/C coupling which is minimal in erythro (2,4-syn) but very strong in threo (2,4-anti) derivatives, indicating absolute stereochemistry as well in this latter case.[24,25] The same analysis may be applied to 1,3,5-triols, only in this case the 1,3-anthroate/cinnamate interaction (**10**, Figure 2b, or **-10**, Figure 3b) is considered to determine absolute stereochemistry. In skipped polyols with numerous stereocenters,[6-8] the sign of the 253 nm CE would indicate absolute stereochemistry of the cinnamoylated stereocenter nearest to the terminal anthroate.

Conclusion

A simple method for simultaneous assignment of relative and absolute stereochemistry of acyclic polyols which have primary hydroxyl termini has been presented. This circular dichroism technique is based on the nonempirical exciton chirality method which has been previously applied to assign one or two stereocenters in acyclic diols. Selective "bichromophoric" derivatization with two types of exciton coupling chromophores represents a significant advance in that four contiguous chiral centers may be assigned from a single CD spectrum.

We recently demonstrated that the CD curves of multichromophoric derivatives reflect the additive effects of all pairwise degenerate and nondegenerate interchromophoric interactions.[26] We have applied this principle of pairwise additivity here, together with ^{1}H NMR conformational analysis, to show the predictable nature of these "fingerprint" CD spectra.

The practical advantages of this CD method include its exceptional ease and its minimal material requirement. The derivatives here were prepared in sufficient quantity for characterization and full ^{1}H NMR assignment. The NMR resonances are well separated and in many cases diagnostic of relative stereochemistry (see Table I). However, the *CD spectra are routinely recorded on 20 nmol or less*, and thus the method is amenable to microscale structure determination beyond the range of NMR. Derivatization and purification on a microscale is facilitated by the strongly fluorescent anthroate ester.

The "bichromophoric" exciton chirality method[26-28] is a powerful spectroscopic technique for systems with multiple chiral centers. Its successful application to cyclic as well as acyclic carbohydrate derivatives suggests further application to skipped 1,3-polyols, amino polyols, and other natural products. We are currently examining a range of applications to structural studies.

Experimental Section

^{1}H NMR spectra were recorded on a Brucker WM250 operated at 250 MHz in CD_3CN (anthroate percinnamates), $CDCl_3$ (triol and tetrol intermediates), or CD_3OD (pentol intermediates). UV measurements (acetonitrile) were performed on a Perkin-Elmer 320 UV spectrophotometer. CD spectra (acetonitrile) were recorded from 420–220 nm on a JASCO 500A spectropolarimeter driven by a JASCO DP500N data processor (1-cm cell, ambient temperature).

General Procedure. The acyclic sugar derivatives were treated with 1.1 equiv of 9-anthroyl chloride in dry pyridine (1–2 mL) with a small amount of DMAP (acylation catalyst).[57] After stirring overnight under N_2, the reaction mixture was frozen (to prevent bumping), and pyridine was removed in vacou (1 mmHg) upon warming. The crude reaction mixture was purified directly without workup by flash chromatography[58] ($MeOH/CH_2Cl_2$, 2:98 for triol derivatives; 3:97 for tetrol derivatives; 5:95 for pentol derivatives. Flash chromatography was preferable to preparative TLC purification, which resulted in poor recovery.) The fluorescent (365 nm active) monoesters, i.e., **7**, were obtained in 40–60% unoptimized yield. Subsequent treatment with excess *p*-methoxycinnamoyl chloride in this same manner afforded the anthroate percinnamate derivatives after flash chromatography (CH_2Cl_2, for triol, tetrol derivatives; $MeOH/CH_2Cl_2$, 1:199 for pentol derivatives) in high yield.

All anthroate intermediates and final peracylated derivatives were characterized by ^{1}H NMR with full assignment of sugar protons. These resonances and coupling constants are of diagnostic value and are listed in Table I for correlative purposes. Prior to UV and CD measurements, all samples were purified by HPLC (EtOAc–hexane, 3:7; 5 μm YMC SiO_2 gel; 2 mL/min; 311 nm UV detection). UV measurements were performed on 5–15 μM acetonitrile solutions, the concentrations of which were determined on the basis of the following approximate extinction coefficients: anthroate monocinnamates ϵ_{311nm} = 28 400; anthroate dicinnamates ϵ_{311nm} = 49 400; anthroate tricinnamates ϵ_{311nm} = 72 400, anthroate tetracinnamates ϵ_{311nm} = 93 400. While extinction coefficients vary slightly depending upon configuration and alkyl substitution, these average values should always be used for the sake of consistency. Relative intensities of the 253 and 311 nm UV maxima varied according to chromophore ratios: anthroate monocinnamates $A_{253nm}/A_{311nm} \sim 4$; anthroate dicinnamates $A_{253nm}/A_{311nm} \sim 2.6$–$2.9$; anthroate tricinnamates $A_{253nm}/A_{311nm} \sim 2$; anthroate tetracinnamates $A_{253nm}/A_{311nm} \sim 1.5$. CD spectra of these acetonitrile solutions were recorded from 420–220 nm at a sensitivity of 2m°/cm and normalized to 10 μM for comparison purposes. Tabulated data for triol and tetrol derivatives is recorded in Table II.

Acyclic Sugar Derivatives. Diethyl mercaptals of D-tetroses, D-pentoses, and 2-deoxy-D-ribose were prepared by standard procedures[44] and were purified by flash chromatography ($MeOH/CH_2Cl_2$, 3:47 to 4:46).

The remaining acyclic polyols were conveniently obtained by subjecting the entire series of D-aldoses to the hydrazinolysis conditions of Williams (48 h reflux in anhydrous hydrazine),[45] from which 1-deoxyalditols, 1,2-dideoxyalditols, and the corresponding 1-alkenes are obtained in various proportions. Catalytic hydrogenation of the mixtures converted alkenes to 1,2-dideoxyalditols, which were separated from 1-deoxyalditols by flash chromatography ($MeOH/CH_2Cl_2$ gradient, 3:47 to 6:44 for triol/tetrol separation; 6:44 to 9:41 for tetrol/pentol separation). Alternatively, tetrol/pentol mixtures could be directly subjected to anthroylation after which separation of the fluorescent monoesters was greatly simplified.

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Supplementary Material Available: Preparations and complete ^{1}H NMR data for all intermediates and peracylated derivatives (15 pages). Ordering information is given on any current masthead page.

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