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ASSIGNMENT OF RELATIVE AND ABSOLUTE CONFIGURATION OF ACYCLIC POLYOLS AND AMINOPOLYOLS BY CIRCULAR DICHROISM - TRENDS FOLLOW FISCHER'S SUGAR FAMILY TREE

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Abstract: Reference CD curves (measured in methylcyclohexane) of a homologous series of 1,2-polyols up to pentols derivatized as anthroates at 1-OH and *p*-methoxycinnamates at the remaining hydroxyl groups show a systematic trend that greatly simplifies assignments of relative and absolute configurations. The same trend also holds for the corresponding 1-aminopolyols, but not for 2-aminopolyols.

REFERENCE CD CURVES OF 1,2- TO 1,2,3,4,5-POLYOL BICHROMOPHORIC DERIVATIVES

The "bichromophoric" exciton chirality method[1] utilizes two different types of exciton chromophores which have been selectively introduced into two different types of hydroxyls, providing "fingerprint" CD curves, as exemplified in numerous reference curves prepared in the pyranoside series.[2] While only limited numbers of known natural products (aside from carbohydrates) contain 1,2,3-triol, 1,2,3,4-tetrol, or 1,2,3,4,5-pentol moieties, many could provide these hydroxylated derivatives upon degradation, particularly upon ozonolysis and reduction. We have applied the concept of selective "bichromophoric" derivatization to acyclic 1,2-polyols in which a terminal primary hydroxyl and remaining secondary hydroxyls are converted into the 9-anthroate and *p*-methoxycinnamates, respectively.[3] The same technique was applied to acyclic 1-aminopolyols up to 2,3,4,5,6-pentols where the CD spectra were compared with those of corresponding polyol

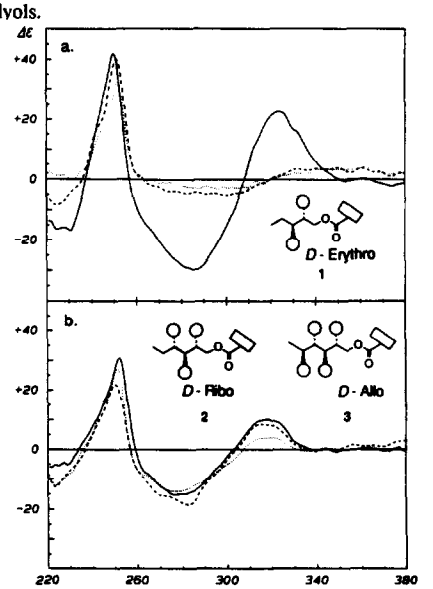


Fig. 1. CD spectra of D-erythro **1** (dotted), D-ribo **2** (dashed) and D-allo **3** (solid): (a) in acetonitrile, (b) in methylcyclohexane.

Dedicated to Carl Djerassi on the occasion of his seventieth birthday

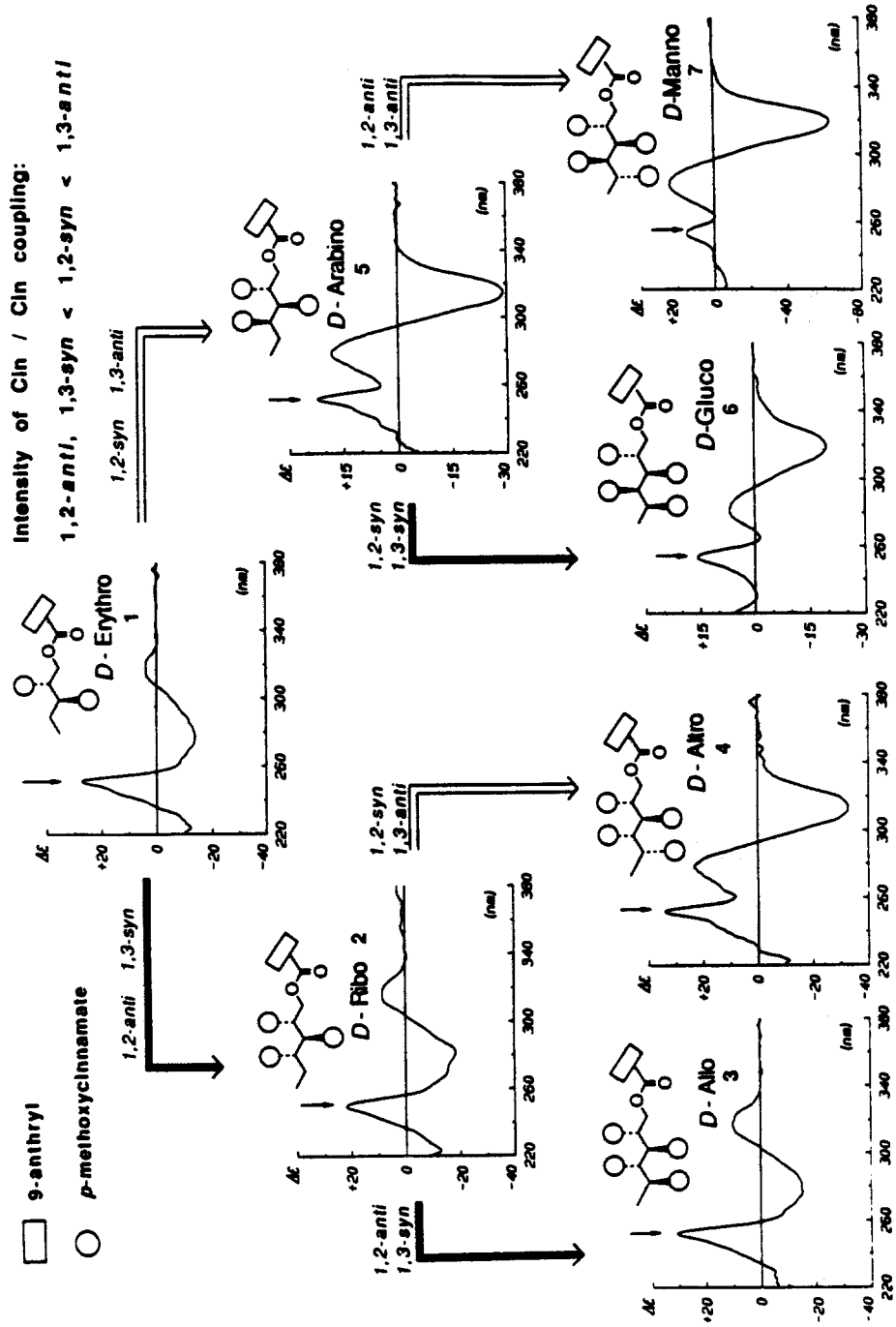


Fig. 2. CD spectra of derivatized polyols. D-erythro series, in methylcyclohexane.

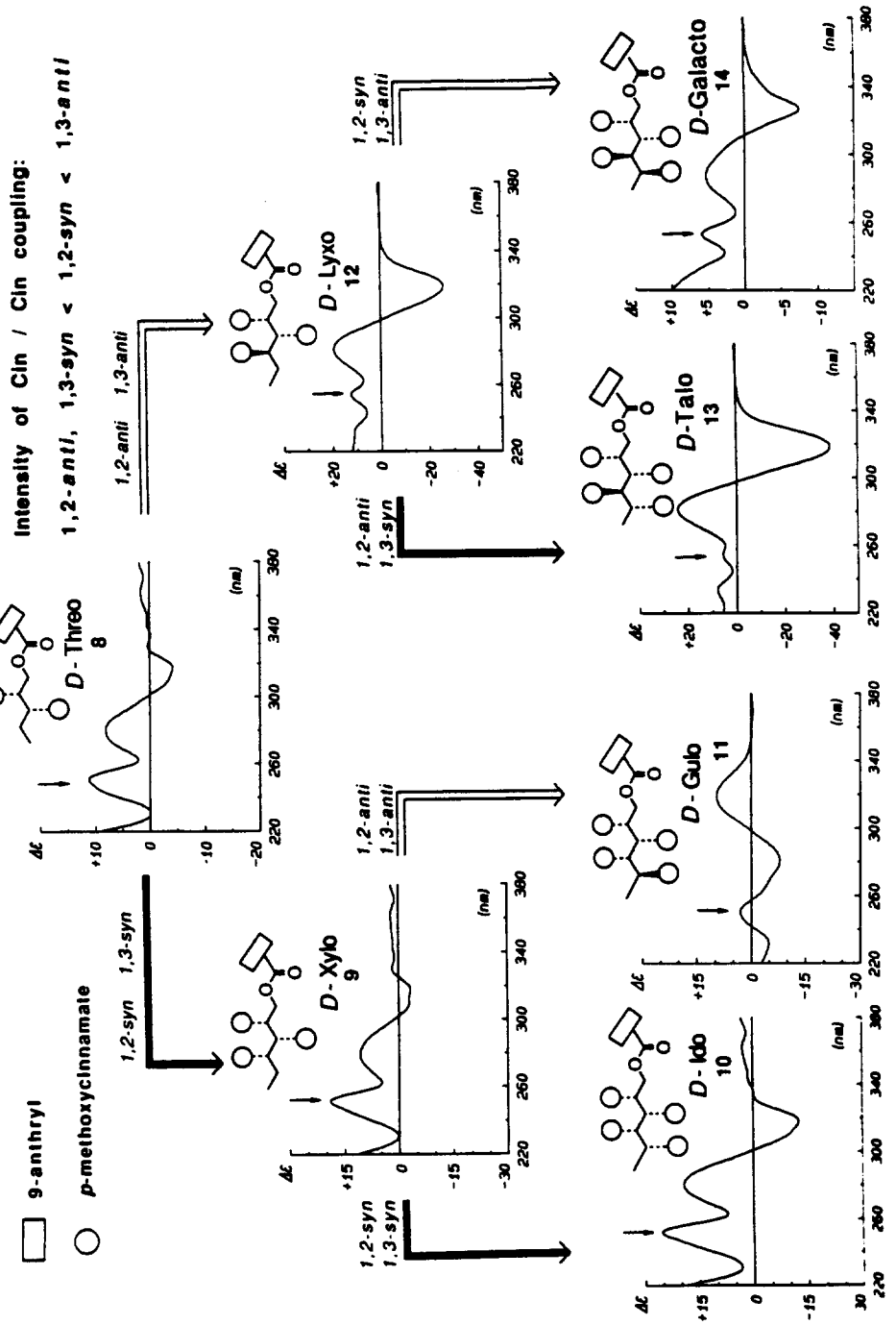


Fig. 3. CD spectra of derivatized polyols, D-threo series, in methylcyclohexane.

anthroate/ *p*-methoxycinnamates.[4] However, the similarity of the two acyclic sets, i.e., 1,2-polyols and 1,2-aminopolyols, was not sufficient in acetonitrile, the common solvent for the exciton chirality method.[1-3] Comparisons of the two series became satisfactory when the solvent was changed to the nonpolar methylcyclohexane (MC).[4]

It turns out that MC is a superior solvent for the 1,2-polyol acylates as well. As shown in Fig. 1, considerable differences exist in CD spectra measured in the two solvents; consequently, no generality was obvious upon comparison of a series of 1,2-polyol acylate spectra in acetonitrile.[3] In contrast, remeasurement of the entire set up to pentol acylates in MC has disclosed important general trends which follow Fischer's sugar family tree, illustrated in Figs. 2 , 3 and Table 1. This is not surprising since the flexible conformations of the lipophilic acyclic ester series should maintain far more uniformity and not be affected much by the chain length in the nonpolar solvent MC. These reference curves can be used for analyzing the CD spectra of 1-amino-1,2-polyol acylates as well.

The bichromophorically derivatized triols, tetrols and pentols of the erythro and threo series show the following common trends in the "fingerprint" CD curves:

(i) In all spectra, the sign of the 253 nm CE, originating from the sharp anthroate absorption at 253 nm (ε 142,200), defines the configuration at C-2 in cases where it is seen clearly (arrows in Fig. 2 and 3).

(ii) The filled and unfilled bent arrows, leading to the next higher homolog connect spectra which have, respectively, more similar and less similar shapes in the CD spectra around 300 nm with its precursor polyol. Thus, the spectra of **1** and **2** are more similar than **1** and **5**.

Table 1 CD spectra of model acyclicpolyols of D-configuration in methylcyclohexane

Compounds	CD, λ_{ext} nm ($\Delta\varepsilon$)	Compounds	CD, λ_{ext} nm ($\Delta\varepsilon$)
erythro **1**	319(+4.1) 278(-14.0) 252(+27.2) 224(-12.1)	threo **8**	318(-4.2) 280(+8.0) 251(+11.2)
ribo **2**	315(+8.4) 282(-18.3) 250(+21.9) 223(-12.7)	xylo **9**	318(-3.2) 280(+10.7) 252(+18.9)
allo **3**	318(+10.2) 277(-15.1) 252(+30.8)	ido **10**	318(-12.6) 280(+19.1) 253(+25.3)
altro **4**	313(-32.7) 278(+23.3) 252(+34.1)	gulo **11**	319(+9.5) 281(-7.9) 251(+2.9)
arabino **5**	315(-29.0) 278(+18.4) 252(+22.4)	lyxo **12**	319(-26.1) 281(+19.4) 254(+12.6) 230sh(+11.3)
gluco **6**	319(-19.4) 281(+6.9) 254(+15.9) 207(+12.6)	talo **13**	318(-38.7) 281(+24.3) 253(+5.7) 233 (+8.0)
manno. **7**	320(-63.0) 283(+24.4) 254(+15.5) 223(-6.2)	galacto **14**	327(-7.5) 287(+5.7) 254(+5.9)

These trends can be rationalized as follows. The extent of exciton coupling of two cinnamates on extended zig-zag chains (and the torsional angle between the two chromophores) are as follows: close to nil in 1,3-*syn* (zero angle) and 1,2-*anti* (180° angle) < weak in 1,2-*syn* (60°) < strong in 1,3-*anti* (60°).[5] Pairs connected by filled arrows are extended by 1,2-*anti* / 1,3-*syn* cinnamates which only have a minor effect on the CD, or by 1,2-*syn* / 1,3-*syn* which may exert a weak effect. In contrast, pairs connected by unfilled

arrows are all extended by a 1,3-*anti* cinnamate (strong interaction); furthermore, some pairs are extended by a 1,2-*syn* cinnamate as well. As a result of these interrelations, changes seen in the CD spectra in going from one polyol to its next higher homolog can be classified into 4 groups, I~IV, ranging from small or no changes to large changes.

Class I: very similar; 1,2-*anti* and 1,3-*syn* extensions. **1/2, 2/3, 12/13.**

Class II: slightly different; 1,2-*syn* and 1,3-*syn* extensions. **5/6, 8/9, 9/10.**

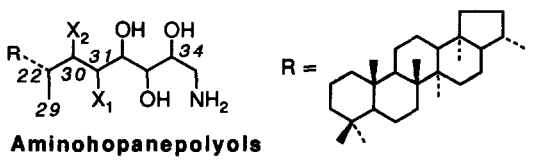
Class III: different; 1,2-*anti* and 1,3-*anti* extensions. **5/7, 8/12, 9/11.**

Class IV: very different; 1,2-*syn* and 1,3-*anti* extensions. **1/5, 2/4, 12/14.**

In addition to the difference in shapes of respective CD curves, note the differences in intensities. The CD curves displayed in Figs. 2 and 3 thus not only show a general and rational trend that facilitates their analysis but also represent characteristic fingerprints. This selective bichromophoric derivatization with two types of exciton coupling chromophores makes it possible to assign configurations to four contiguous chiral centers from a single fingerprint CD spectrum.[6]

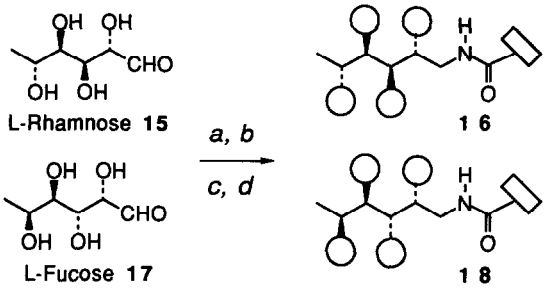
APPLICATION OF POLYOLS REFERENCE CD CURVES FOR STEREOCHEMISTRY ASSIGNMENT OF 1-AMINOPOLYOLS

The general trends summarized in the previous section can be extended to assign the absolute stereochemistry of natural aminopolyols, such as those comprising the acyclic side-chain of the aminobacteriohopanoids.[7] Since the first discovery of hopanoids in sedimentary rocks,[8] more than 200 individual members of this family have been isolated.[9] Determination of the configuration of the acyclic side-chain of the hopanoid bacterial lipids, however, is by no means a trivial problem.



Aminohopanepolyols

X_1=X_2=H, aminotriol; X_1=OH, X_2=H, aminotetrol
X_1=X_2=OH, aminopentol



Scheme 1. *a.* $NH_4OAc/NaBH_3CN/MeOH$, reflux; *b.* 9-anthroyl tetrazole/Et_3N/DMF; *c. p*-methoxy-cinnamoyl imidazole/ DBU/MeCN.

From the similar exciton coupling of O-acylate and N-acylate of conformationally rigid and simple acyclic diols and aminoalcohols,[10] it was possible that the reference curves generated from polyols might be applicable to acyclic

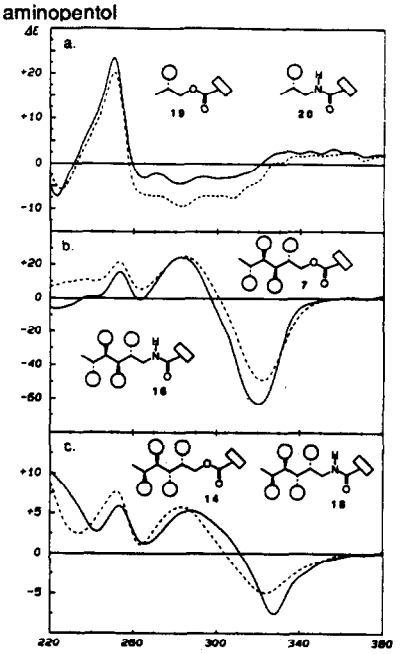


Fig.4. CD curves in MC of: (a) **19** (solid) and **20** (dotted); (b) **7** (solid) and **16** (dotted); (c) **14** (solid) and **18** (dotted).

1-aminopolyols as well. Starting from the 6-deoxyaldoses, L-rhamnose **15** and L-fucose **17**, we synthesized and converted the corresponding 1-aminopolyols into the bichromophoric derivatives **16** and **18** (see Scheme 1). The CD curves (Figure 4), indeed, of 1-aminopolyol derivatives **16, 18** and **20** exhibited in the nonpolar methylcyclohexane a remarkable similarity with these of the polyol analogues D-Manno **7**, D-Galacto **14** and (S)-**19**[3b], respectively. These similarities suggested the CD exciton chirality method combined with the reference curves generated from acyclic polyols should provide a powerful spectroscopic tool to assign the stereochemistry of acyclic 1-aminopolyols as well.

Fig. 5 shows the superimposed CD spectra of the bichromophorically derivatized aminobacteriohopanetriol **21** and aminobacteriohopanetetrol **22** as well as those of the corresponding polyol derivatives, i.e. the enantiomers of **2** (L-ribo), **3** (L-allo) and **4** (L-altro). As discussed above, the strong 253 nm CE mainly reflects the stereochemistry at C-2, while the CE in the 260-340 nm region is governed by the cinnamate-cinnamate couplings of the derivatized secondary hydroxyl groups. The close resemblence between CD curves of aminotriol derivative **21** and L-ribo derivative **2** in Fig 5a is in good agreement with the side-chain absolute stereochemistry of this aminopolyol determined previously by chemical synthesis[11] and NMR spectroscopy. Fig. 5b shows the CD curves of aminotetrol derivative **22** and of the model allo and altro pentols of L-configurations, i.e. the enantiomers of **3** and **4**. The almost superimposable CD curves of L-allo and aminotetrol derivative **22** was used for assigning in a staigthforward manner the stereochemistry of **22** as being identical to L-allo , namely 31R, 32R, 33S, 34S.[4]

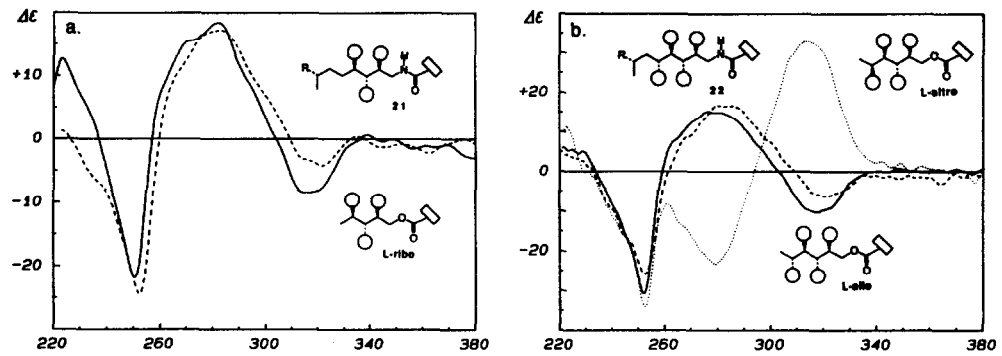


Fig. 5. CD curves in MC of: (a) **21** (dashed) and L-ribo (solid); (b) **22** (dashed), L-allo (solid) and L-altro (dotted). The curves for L-ribo, L-allo and L-altro are plotted as a miror image of **2**,**3** and **4** of D-series.

The configurational determination of the aminopentol cannot be carried out using the same strategy as for the aminotriol and aminotetrol due to the lack of reference CD spectra of hexols. However, the general trends observed in the CD spectra of model polyols reveal the possibility of assigning the absolute configuration of polyols and aminopolyols having a polyol moiety longer than the references. Fig 6 depicts the CD curves of partially derivatized aminopentol and L-allo. The similar shape between these two derivatives establishes that the configuration of C-31/34 of aminopentol is also L-allo. The curve of the pentacinnamate

prepared by acylating C-30 with the more powerful acylating agent *p*-methoxycinnamoyltetrazole is similar to its partially derivatized precursor; 30-OH must thus be *anti* to the adjacent 31-OH. This determines the configuration of the aminopentol to be 30R, 31R, 32R, 33S, 34S.[4]

Thus, it has been shown that a clearcut general trend exists in the CD of bichromophorically derivatized acyclic 1,2-polyols and 1-aminopolyols when measured in methylcyclohexane, and that under favorable conditions, this general trend can be utilized to determine the absolute configuration of acyclic polyols for which no reference curves exist. However, it should be noted that this general trend is not applicable to 2-aminopolyols; this aspect, important for determining configurations of sphingosines for example, is currently under study.

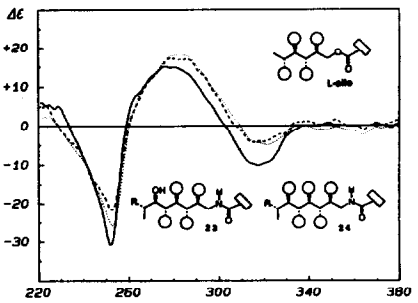


Fig.6. CD curves in MC of L-allo (solid), **23** (dotted) and **24** (dashed).

EXPERIMENTAL

Unless otherwise noted, reagents were purchased from Aldrich Chemical Company. FAB-MS was obtained using a JOEL JMS-DX 303 HF mass spectrometer. Proton NMR spectra were recorded using either a Varian VXR 200, a Varian VXR 300 or a Varian VXR 400 spectrometer. Chemical shifts are reported in parts per million on the δ scale relative to TMS as determined by trace monoprotiosolvent as an internal standard: $CDCl_3$ (7.24 ppm), CD_3CN (1.93 ppm), and CD_3OD (4.78 ppm). Coupling constants were determined by first order analysis. HPLC purifications were performed using a Rainin Rabbit HP pump system and an SP 8490 dual wavelength detector. The HPLC column was packed with YMC 5μ silica gel. All chromatography solvents were HPLC grade. CD spectra were measured either with a JASCO J-500 CD spectrometer equipped with a data processor or with a J-720 CD spectrometer. For the CD data manipulation software developed in house was employed.

Preparation of 1-aminopolyols bichromophoric derivatives 16, 18 and 20.

a. To a solution of 0.5 g (2.7 mmol) 6-deoxy aldose in MeOH (10 ml) was added 0.18 g (3.3 mmol) NH_4Cl and 0.21 g (3.3 mmol).$NaCNBH_3$. The mixture was heated to 50°C for 2 hr then cooled to r.t. The white precipitate was washed with MeOH (3x5 ml) to give the desired product (30-40%) which was used without further purification.

6-Deoxy-1-amino-D-mannitol ^1H NMR (D_2O): 3.56-3.79 (m, 3 H), 3.45 (dd, 1.3, 8.0 Hz, 1 H) 3.20 (dd, 3.2, 13.2 Hz, 1 H), 2.84 (dd, 9.1, 13.2 Hz, 1 H), 1.16 (d, 6.6 Hz, Me)

6-Deoxy-1-amino-D-galactitol ^1H NMR (D_2O): 4.08 (ddd, 1.4, 3.2, 9.6 Hz, 1 H, H-1), 3.87 (dq, 1.4, 6.6 Hz, 1 H, H-5), 3.47 (dd, 1.4, 9.5 Hz, 1 H, H-1), 3.36 (dd, 1.5, 9.5 Hz, 1 H, H-1'), 3.13 (dd, 3.2, 9.6 Hz, 1 H, H-3), 3.05 (dd, 1.4, 9.6 Hz, 1 H, H-4), 1.03 (d, 6.6 Hz, 3 H, Me).

b. To ~50 mg of model aminopolyol in dry DMF at r.t. was added 1.2 eq. of 9-anthroyl tetrazole and a few drops of triethylamine.The mixture was stirred at r.t. for 1 hr. After removing DMF at reduced pressure, the

crude 9-anthroyl tetrazole was subject to flash chromatography on silica gel (5-7% MeOH in CH_2Cl_2) to afford the desired anthroamide in 85-95% yield.

6-Deoxy-1-anthramide-D-mannitol ^{1}H NMR (CD_3OD): 8.49 (s, 1 H), 8.08-7.96 (m, 4 H), 7.48-7.39 (m, 4 H), 3.94-3.88 (m, 1 H, H-2), 3.81 (dd, 1.3, 8.2 Hz, 1 H, H-3), 3.78-3.69 (m, 3 H, H-5, H-1's), 3.52 (dd, 1.3, 7.9 Hz, 1 H, H-4), 1.21 (d, 6.7 Hz, Me).

6-Deoxy-1-anthramide-D-galactitol ^{1}H NMR (CD_3OD) : 8.49 (s, 1 H), 8.04-7.98 (m, 4 H), 7.52-7.44 (m, 4 H), 4.24-4.12 (m, 1 H, H-2), 4.09-4.01 (m, 2 H, H-1's), 3.94 (dq, 1.8, 6.6 Hz, 1 H, H-5), 3.63 (dd, 1.7, 9.0 Hz, 1 H, H-3), 3.40 (dd, 1.8, 9.0 Hz, 1 H, H-4), 1.10 (d, 6.6 Hz, 3 H, Me).

(2S)-1-Anthramide-2-hydroxy-propane was prepared following precedure *b*. except CH_2Cl_2 was used instead of DMF. ^{1}H NMR ($CDCl_3$): 8.48 (s, 1 H), 8.03-7.92 (m, 4 H), 7.52-7.41 (m, 4 H), 6.52 (m, 1 H, -NH), 4.10 (m, 1 H, H-3), 3.79 (ddd, 3.1, 6.6, 13.9 Hz, H-2), 3.43 (ddd, 5.5, 7.7, 13.9 Hz, 1 H, H-1's), 1.26 (d, 6.31 Hz, Me).

c. Subsquent treatment of the anthramide obtained from step *b*. with freshly prepared *p*-methoxycinnamoyl imidazole (1.2 eq)./ DBU in acetonitrile at r.t. for 4 hr provided the final aminopolyol bichromophoric derivatives after flash chromatograpy (25% EtOAc in hexane) in 80-90% yield.

6-Deoxy-D-mannitol 1-anthramide-2,3,4,5-tetra-*p*-methoxycinnamate (16) ^{1}H NMR ($CDCl_3$): 8.51 (s, 1 H), 8.04-7.98 (m, 4 H), 7.73, 7.62, 7.59 (d's, 16.0 Hz, 3 x 1 H), 7.52-7.41 (m, 11 H), 7.27 (d, 8.8 Hz, 2 H), 6.92-6.86 (m, 6 H), 6.75 (d, 8.7 Hz, 2 H), 6.43, 6.38, 6.34, 6.12 (d's, 16 Hz, 4 x 1 H), 5.81 (dd, 3.0, 6.9 Hz, 1 H, H-3), 5.60 (m, 1 H, H-2), 5.52 (dd, 3.0, 6.2 Hz, 1 H, H-4), 5.25 (dq, 6.2, 6.4 Hz, 1 H, H-5), 4.01 (m, 2 H, H-1's), 3.79 (bs, 12 H, OMe's), 3.52 (dd, 1.36, 7.93 Hz, 1 H), 1.27 (d, 6.4 Hz, Me).
CD (in MC): 322 (-49.0), 283 (+24.8), 253 (+21.4).

6-Deoxy-D-galactitol 1-anthramide 2,3,4,5-tetra-*p*-methoxycinnamate (18). ^{1}H NMR ($CDCl_3$): 8.49 (s, 1 H), 8.02 and 7.96 (d's, 8.6 Hz, 2 x 2 H), 7.67, 7.63, and 7.52 (d's, 16.0 Hz, 3 x 1 H), 7.5-7.31 (m, 11 H), 7.16 (d, 8.8 Hz, 2 H), 6.92-6.82 (m, 8 H), 6.41, 6.34, 6.22, and 6.01 (d's, 16.0 Hz, 4 x 1 H), 5.74 (dd, 2.9, 8.3 Hz, 1 H, H-3), 5.62 (m, 1 H, H-2), 5.49 (dd, 2.9, 8.3 Hz, 1 H, H-4), 5.31 (dq, 2.9, 6.5 Hz, 1 H, H-5), 4.12-4.01 (m, 2 H, H-1's), 3.81-3.74 (bs, 12 H, OMe's), 1.16 (d, 6.5 Hz, 3 H, Me).
CD (in MC): 323 (-4.9), 283 (+5.8), 252 (+7.7).

(2S)-1-Anthramide-2-*p*-methoxycinnamate-propane (20) ^{1}H NMR ($CDCl_3$): 8.48 (s, 1 H), 8.08-7.96 (m, 4 H), 7.62 (d, 16.0 Hz, 1 H), 7.48-7.39 (m, 4 H), 7.43 (d, 8.8 Hz, 2 H) 6.87 (d, 8.8 Hz, 2 H), 6.39 (m, 1 H, -NH), 6.28 (d, 16.0 Hz, 1 H), 5.38 (m, 1 H, H-2), 3.93 (m, 2 H, H-1's), 3.83 (s, 3 H, OMe), 1.48 (d, 6.4 Hz, Me).
CD (in MC): 380 (+2.4), 363 (+2.8), 307 (-7.6), 283 (-9.4), 251 (+20.3).

Preparation of the aminohopanepolyol bichromophoric derivatives 21-24.

In a micro glass tube (2x30mm) were placed aminopolyol (aminotriol ~30 μg, aminotetrol ~50 μg, aminopentol ~120 μg), 2 eq of anthroyltetrazole, 2 μl Et_3N and 15 μl of DMF. After the tube was sealed under N_2, the reaction was carried out at 70°C for 30 min with occasionally shaking. Then the reaction, the tube was opened and 2 ml Et_2NH was added to destroy excess anthroyltetrazole. Evaporation of the solvent gave the desired compound which was used without further purification. The crude anthramide was treated with excess *p*-methoxycinnamoylimidazole and DBU in acetonitrile at r.t. for 4 hr provided the corresponding tricinnamate

and tetracinnamate derivatives of aminotriol and aminotetrol, respectively. In the aminopentol case, however, instead of the pentacinnamate derivative, the major product was partially derivatized tetracinnamate. An extention of the reaction time or an increase of the temperature did not result in any further change. The pentacinnamate derivative was isolated only when a more reactive derivatization reagent, *p*-methoxycinnamoyltetrazole and a stronger base, NaH were employed. After HPLC purifcation the derivatives **21-24** were characterized by FAB-MS and submitted to CD measurements.

34-Anthramide-31,32,33-tri-*p*-methoxycinnamate hopanetriol (21) FAB-MS *m/z* 1230 (M^+).
CD (in MC): 362 (-2.2), 344 (-1.2), 320 (-4.2), 282 (+17.2), 251 (-24.4).

35-Anthramide-31,32,33,34-tetra-*p*-methoxycinnamate hopanetetrol (22) FAB-MS *m/z* 1406 (M^+).
CD (in MC): 363 (-3.2), 321 (-6.3), 285 (+16.6), 252 (-25.7).

36-Anthramide-32,33,34,35-tetra-*p*-methoxycinnamate hopanepentol (23) FAB-MS *m/z* 1422 (M^+).
CD (in MC) : 363 (-2.3), 320 (-4.9), 284 (+18.2), 252 (-25.7).

36-Anthramide-31,32,33,34,35-penta-*p*-methoxycinnamate hopanepentol (24) FAB-MS *m/z* 1582 (M^+).
CD (in MC): 352 (+1.6), 314 (-4.2), 286sh (+17.1), 278 (+17.4), 252 (-21.6).

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