# THE INFLUENCE OF ALLYLIC OXYGEN ON THE CD OF SKEW DIENES

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**Abstract**—The CD of eight compounds each containing a conjugated diene system is discussed. In five of these the sign of the Cotton effect attributable to the lowest energy diene absorption band is at variance with the sign predicted by the rules relating sign to diene helicity. Each of the five compounds incorporates one or more oxygen substituents (hydroxyl, methoxyl, (1-carboxyvinyl)oxy) allylic to the diene system. If its is assumed that the helicity of the system O—C—C=C— may have a larger influence on the CD than the helicity of the diene system itself, these results are consistently explained.

Two GENERALIZATIONS linking optical rotatory properties to absolute molecular geometry are the rules relating the sign of the high-intensity Cotton effect associated with the lowest energy electronic transition of the cisoid[1,2] or transoid[3] conjugated diene chromophore to the helical sense of the diene system. Right-handed and left-handed helicity correspond, respectively, to positive and negative Cotton effects. The relationships are illustrated in Fig. 1.
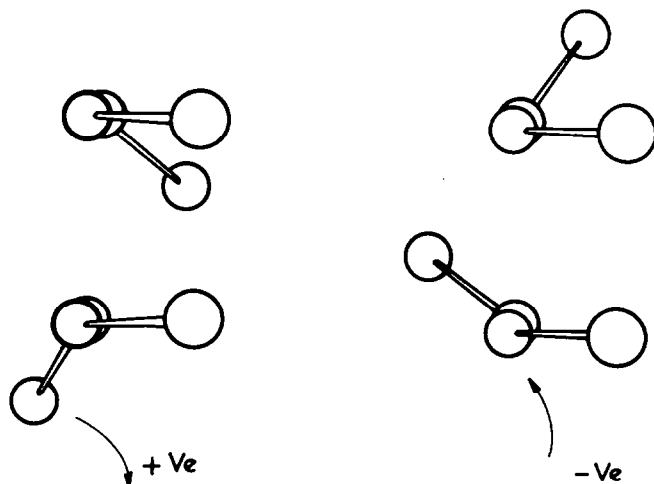


FIG 1. The relationship between helical sense and CD sign in cisoid and transoid skew-dienes

Several apparent exceptions to these rules have been observed, for most of which explanations have been proposed. Thus, laevopimaric acid[2, 4, 5] is required to adopt the folded form. I. in order to accommodate both the ORD and the chemical evidence relating to its absolute configuration, and α-phellandrene, II, must exist as a mixture of the two possible conformers at ordinary temperatures[4, 6] that with the quasi-axial isopropyl group having the larger influence on the CD. The results of low-temp. studies[7, 8, 9] are compatible with this. Pyrocalciferol (10α-ergosterol), III, and isopyro-calciferol (9β-ergosterol), IV, are opposite in configuration both at C9 and C10 but produce almost identical Cotton effect curves.[1, 10] In Dreiding models of III and IV the diene systems appear to be planar and repulsions between hydrogens at C1 and C11[1] or relief of other non-bonded interactions[10] are invoked to account for the helicity, right-handed in both, necessary to fit these molecules to the rule.
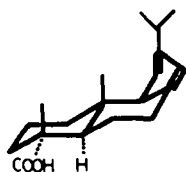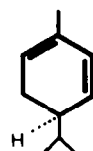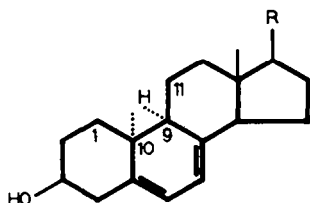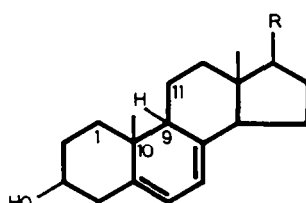


In a paper summarising work relating to the cisoid rule in 1965[2] other examples are listed in which, a priori, either skew-sense is equally possible (occidentalol, palustric acid) or in which the diene appears almost planar (thebaine) in a Dreiding model. In the same place a warning is given that application of the rule to heteroannular cisoid dienes should be held in abeyance, although no results from such compounds were included. Hence the statement,[2] ". . . the cisoid diene rule correctly predicts the sign of Cotton effect and CD band in every compound investigated thus far", might have been more accurately phrased. It would be true to say, however, that the rule could be reconciled to the observed sign in almost every compound examined. This was also true for transoid dienes[3] where only one intractable exception, Δ[6, 8(14), 22]-ergostatriene-3β-ol-acetate,

was found among the eight compounds considered. Both rules have proved to be useful generalisations and have been successfully applied in several cases.[11]

However, an exception which could not be explained in conformational terms appeared to be presented by gliotoxin, V, the absolute molecular geometry of which was established by X-ray structure analysis.[12, 13] From a consideration[14] of the CD spectra of V and one of its derivatives a CD band in gliotoxin was deduced to occur near 260 nm with $\Delta\varepsilon \simeq +10$, appropriate in energy, sign and magnitude to the lowest frequency transition of a cisoid diene with righ-handed helicity. The X-ray study had shown the diene skew-sense to be left-handed. It was suggested[14] that this contradiction of the rule must reflect the influence of peripheral asymmetry on the diene. Ziffer et al.[15] examined other possibilities. They found the ORD spectra of gliotoxin in the solid state and in MeCN solution to be essentially the same and in agreement as to sign with the previously reported CD curve in dioxan. They therefore concluded that the molecular conformation determined for the crystalline solid by X-ray analysis must be retained in solution. However, they found that dethiogliotoxin, VI, exhibited negative CD of moderate intensity in the diene region with a peak, $\Delta\varepsilon\simeq-2\cdot6$, at 265 nm and a shoulder, $\Delta\varepsilon\simeq-2\cdot2$, at 254 nm. One, but not necessarily both, of these features they ascribed to the diene transition, thus reconciling rule and sign if it were assumed that the conformation of the 1,3-cyclohexadiene moiety remained the same in VI as in V. They suggested that the positive CD in the diene region deduced for V[14] might result from a composite diene-disulphide transition.

While this suggestion has received acceptance[11] and cautious acceptance[16] from two reviewers, it has not seemed convincing to two of the present authors. One reason for doubt is the remoteness in space between the diene and disulphide systems in V, rendering improbable the orbital overlap necessary for a composite transition to occur. Secondly, one may doubt the possibility claimed[15] for strong interaction between nearly degenerate transitions of the diene, "at about 270 mµ", and the disulphide, "at about 280 mµ", since a disulphide transition in this region is unlikely. The relationship between dihedral angles in disulphides and the wavelengths at which the lowest energy transitions occur has been clearly demonstrated by Barltrop et al.[17] and in gliotoxin, dihedral angle 14°,[14] this transition is almost certainly responsible for the negative CD at 340 nm.[14] There are also excellent reasons to suppose[14] that a second disulphide transition is implicated in the very intense negative CD peak at 233 nm. The first and second disulphide peaks in brugine[18] where the disulphide dihedral angle is $\simeq27°$[19, 20] occur at 325 nm and 230 nm respectively. Further, the diene bands near 270 nm in the UV spectra of V and VI are almost identical in position and intensity[14] so that no postulated contribution in this region from disulphide absorption can be justified.



$\underline{\text{V}}$                $\underline{\text{VI}}$

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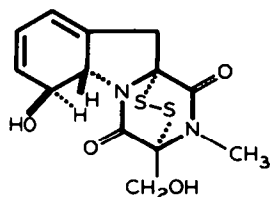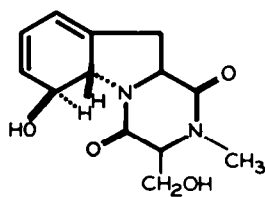
Since it seemed to us that the gliotoxin problem was not resolved, we have sought other examples which appear not to obey the diene rules and which are not subject to conformational uncertainties. The absolute stereochemistry of schelhammerine[21] has been determined by X-ray analysis[22] and this compound has been converted to schelhammeridine, the absolute stereochemistry of which, VII, is thus also defined.[21] The two epimeric alcohols, VIII and IX, are obtained[23] by mild acid hydrolysis of VII. The CD spectra of all three compounds are reproduced in Fig 2.
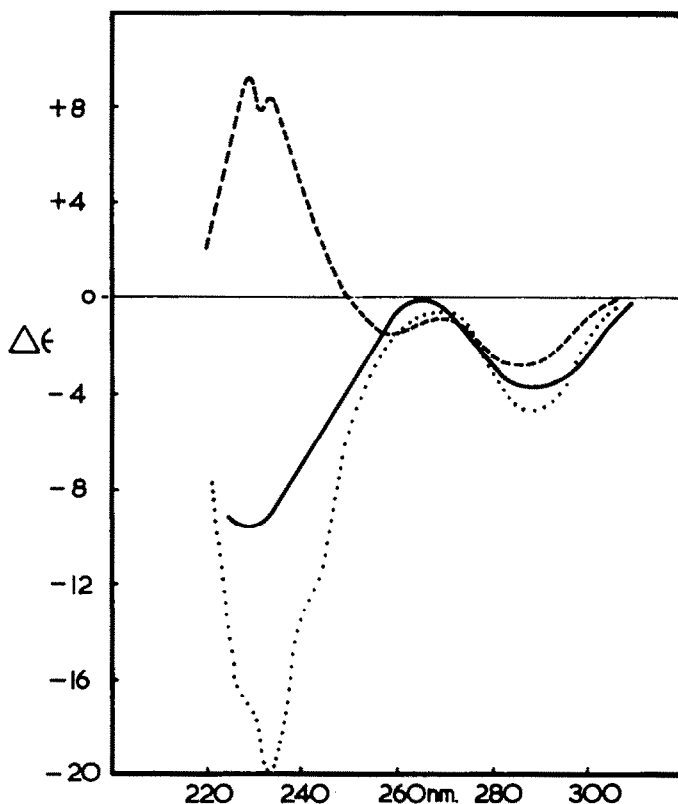


FIG 2. The CD, $10^{-3}$ M in MeOH, of VII ————; VIII · · · ·; IX – – – –

The CD spectra of a number of other schelhammera bases have been determined[24] and these all show the low amplitude peaks, near 245 nm and 290 nm, characteristic[25, 26] of the methylenedioxyphenyl chromophore in such systems. Only the three diene-containing compounds, VII, VIII and IX, exhibit CD maxima in the 230–235 nm region. In the UV spectra the lowest energy diene absorption occurs at 234 nm in VII, 233 nm in VIII and 227 nm in IX.[23] The intense CD bands, therefore, undoubtedly have their origin in the transoid diene system.
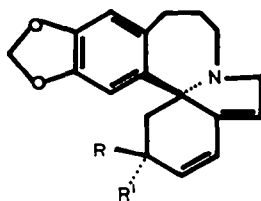
| | R | R' |
|---|---|---|
| **VII** | OMe | H |
| **VIII** | OH | H |
| **IX** | H | OH |

Examination of Dreiding models shows that the conformational freedom of these molecules is limited and that in all possible forms the diene chromophore retains left-handed helicity. Thus, the sign of the diene CD in IX is in conflict with the diene rule and, since IX differs from VIII only in the configuration at the C atom bearing the OH group, this configuration must hold the key to the conflict. It is reasonable, then, to examine the dissymmetric spatial relationship between the substituent at this centre and the diene. This may be done in the following way. The hydroxyl oxygen, the asymmetric carbon to which it is attached and the two carbons linked by the nearer double bond of the diene may be regarded as forming a helical system. In VII and VIII this grouping has the same left-handed helicity as the diene itself, but in IX the helicity is right-handed, in opposition to that of the diene. To account for the observed CD it must then be supposed that, in IX, the effect of the oxygen-containing helix is the dominant one, or, expressed otherwise, that the allylic oxygen, spatially disposed as it is in IX, has a larger influence on the sign of the diene band than the helicity of the diene itself.

We may note that in gliotoxin, V, the cyclohexadiene ring bears a OH substituent allylic to the diene and that here, too, the oxygen-containing helix is opposed in sense to the diene helix.

Further evidence comes from four 1,3-cyclohexadiene carboxylic acids with allylic oxygens. The structure, absolute configuration and conformation in $D_2O$ of chorismic acid, X, were established by Edwards and Jackman.[27] This compound in water, unionized or as the di-anion, exhibits a negative Cotton effect in the diene region, Fig. 3, yet the helical sense of the diene is right-handed. While the same Cotton effect in ORD curves was observed both by Edwards and Jackman[27] and independently by Weiss,[28] no comment has hitherto appeared on its conflict with the diene rule. More recently, three compounds related to chorismic acid have become available. These are the 5,6-dihydroxy-1,3-cyclohexadiene-2-carboxylic acid, XI, termed "3,4-dihydro-3,4-dihydroxybenzoic acid" or 3,4-DHDHB, the absolute configuration of which has been determined by degradation to (−) tartaric acid;[29] the isomeric 2.3-DHDHB. XII[30]
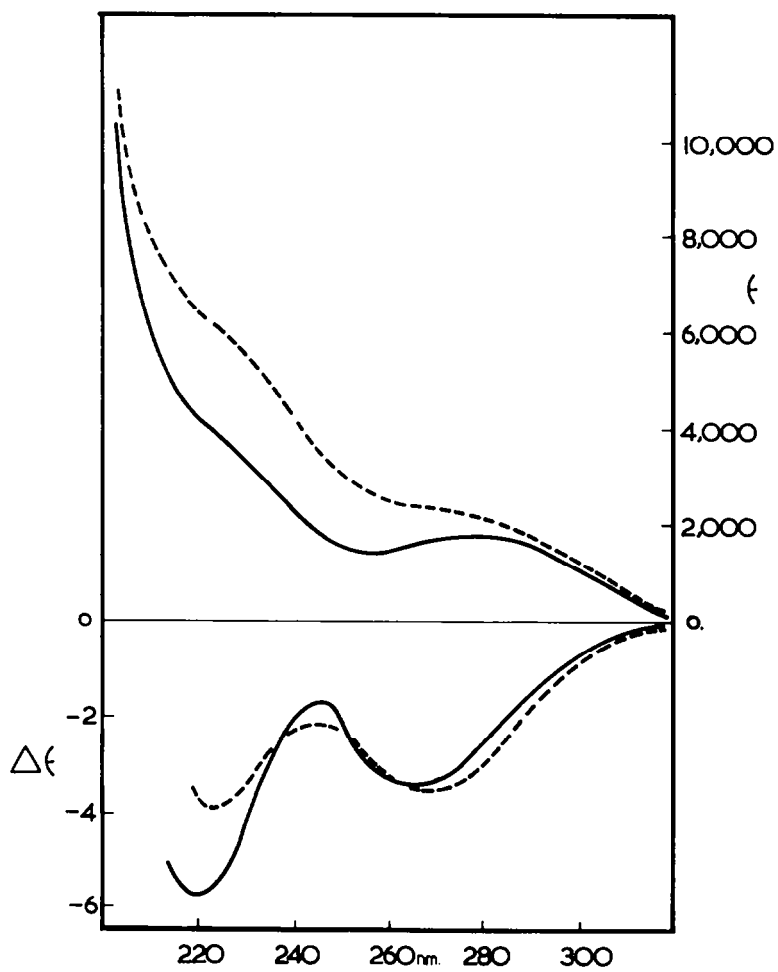
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and isochorismic acid, XIII.[31] The absolute configurations of XII and XIII have also been established and that of X confirmed by degradations to (+)- or (−) tartaric acid.[32] The ORD and CD of XI, XII and XIII in water are recorded in Figs 4, 5, 6 and 7. The ORD of X, XI, XII and XIII at concentrations of c. $5 \times 10^{-2}$ M in dimethylsulphoxide



X     R = C COOH
              ‖
              CH₂

XI     R = H

XII     R = H

XIII     R = C COOH
              ‖
              CH₂

(DMSO) have also been determined. In every case the sign of the diene Cotton effect was the same as in water and magnitudes at extrema were within 20% of the aqueous solution values.

In DMSO, as in water, the OH and (l-carboxyvinyl)oxy substituents of X are quasi-equatorial,[29, 33] hence the helicity of the diene is right-handed. Similarly in XI the two OH substituents in DMSO are quasi-equatorial[29] and the diene skew-sense is right-handed. However, both compounds, Figs 3, 4 and 5, exhibit negative Cotton effects of moderate intensity near 270 nm, corresponding to the lowest energy diene bands in the UV spectra. The ionisation states of the carboxyl groups have little effect on the positions or intensities of these first CD bands. Chorismic acid, X, has a second negative Cotton effect near 220 nm, Figs 3 and 4, corresponding to a shoulder in the UV absorption, with $\varepsilon_{max} = 4700$ and 7100 (225 nm) in the acid and the di-anion respectively. Presumably this feature has its origin in the (l-carboxyvinyl)oxy side chain, since the CD intensity varies markedly between the acid and the di-anion and since no shoulder is observed in the UV absorption curve of 3,4-DHDHB, XI. The CD curve of XI, however, Fig. 5, contains a shoulder at 240 nm, possibly arising from a low intensity UV transition of the conjugated carboxyl group. CD from the same source in X may be hidden by the negative band near 220 nm.

Both X and XI contain two allylic oxygen substituents. If the helices formed by each of these with its adjacent double bond are considered, it is seen that both are left-handed and in opposition to the skew-sense of the diene itself. Here, too, if it is supposed that the influence on the diene CD of the dissymmetrically disposed allylic oxygens is larger than that of the diene helix itself, then the observations are accounted for.

Isochorismic acid, XIII, was not available for CD study, but its ORD curve in water is closely similar to that of XII, Fig. 6. The CD spectra of XII and its anion both contain a single, intence, positive peak which is little affected by the state of ionisation, Fig. 7.

In DMSO, the oxygens substituent to the 6-membered ring are trans diquasi-axial in both XII[30, 33] and XII,[31] hence, the diene possesses right-handed helicity in both

Fig 3. The CD and UV absorption in water of X, $1 \cdot 2 \times 10^{-3}$ M ————; the di-anion of X, $3 \cdot 5 \times 10^{-4}$ M — — — —

Fig 4. The ORD in water of X, $5 \times 10^{-4}$ M ————; XI, $3 \times 10^{-4}$ M – – – –

FIG 5  The CD and UV absorption in water of XI, $10^{-3}$ M ————; the anion of XI, $5 \times 10^{-4}$ M — — — —

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FIG 6. The ORD in water of XII, $3 \times 10^{-4}$ M ————; XIII, $4 \times 10^{-4}$ M – – – –

FIG 7. The CD in water of XII, $10^{-3}$ M ————; the anion of XII, $5 \times 10^{-4}$ M – – – –

compounds. There is no conflict with the diene rule. Here, the helices formed by the allylic oxygens and their adjacent double bonds are also right-handed and may be considered to reinforce the effect on the CD sign of the diene helicity. Possibly the intensities of the observed Cotton effects reflect this reinforcement.

It has been noted, however, that the conformation of XII is solvent-dependent.[30, 33] In CDCl$_3$ containing 10% DMSO the two OH groups are trans diquasi-equatorial and the skew-sense of the diene is left-handed. For this reason we have examined the CD of XII in pure DMSO, in CHCl$_3$ containing 50% DMSO and in CHCl$_3$ containing 10% DMSO. In the mixed solvents there was some reduction in the height of the CD peak, which could not be accurately assessed owing to difficulties in handling small quantities of sample and solvents, but in all solutions the CD band remained strongly positive. The conformation-change was detected by NMR for which solutions were more concentrated, c. 0·2M, than is normally appropriate for CD. However, at these concentrations, while the solutions were opaque at the wavelength of the band centre, the beginning of the circularly dichroic absorption could be observed. It was positive. Further confirmation was obtained from ORD determinations on $5 \times 10^{-2}$M solutions in DMSO and in CHCl$_3$ containing 10% DMSO, each of which showed the first extremum of a strong positive Cotton effect near 300 nm.

After critical re-examination of the NMR evidence from which the solvent-dependent inversion in conformation of the cyclo-hexadiene ring was deduced,[30, 33] we are convinced that it does, indeed, occur. We, therefore, conclude that this inversion of helicity in the diene system is not mirrored by a change in sign of the Cotton effect associated with the lowest energy diene transition, hence, the CD of XII in CHCl$_3$ containing 10% DMSO provides another example of violation of the diene rule. It may be rationalised as before. The helices formed by the allylic oxygens and their adjacent double bonds remain right-handed despite the conformation-change and are now in opposition to the helicity of the diene. Since the Cotton effect remains positive, their combined effect must be supposed to be greater than that of the diene helix itself.

To summarize thus far: in five of the compounds we have examined the diene rules are transgressed. All contain oxygen substitutents allylic to the diene system. One, IX, may be compared to its rule-obeying epimer, VIII, from which it differs only in the location in space of its allylic oxygen. We conclude that the spatial relationship, in IX, between the allylic oxygen and the diene, changes the sign of the lowest energy diene CD band, from that predicted by the diene rule to its opposite. We find that similar spatial relationships exist between allylic oxygen and diene in the other four compounds, V, X, XI and XII. We conclude that the effect may be general.

Some further points require mention. V, X, XI and XII are cisoid diene compounds IX is transoid, so the effect would appear to apply to both types.

In V, IX*, X and XI, also in XII in CHCl$_3$ − 10% DMSO, that is, in all cases where the diene rules are violated, the allylic oxygens are quasi-equatorial. Whether or not quasi-axial allylic oxygen would have a similar influence is, as yet, unknown.

There appears to be little difference between the effects of allylic OH and allylic (1-carboxyvinyl)oxy substituents, Figs 3–7. While Fig 2 reveals a large difference in

* The referee has drawn our attention to the structure of erythristemine (*Chem. Comm.* 391,1970) which is analogous to IX, in which an α-methoxyl corresponding to the α-hydroxyl of IX is in quasi-equatorial orientation. The NMR spectra of our ref. 23 show the α-hydroxyl of IX to be quasi-equatorial, correcting our initial assumption that it would be quasi-axial as are the β-methoxyl and β-hydroxyl of VII and VIII.

intensity between the diene CD of VII and VIII, this may be due to conformational adjustment rather than to an intrinsic difference between allylic OH and OMe. Therefore, we can do no more than note the differences and similarities as the oxygen substituents vary. Both V and IX contain nitrogen in allylic linkage to the dienes. Whether this, too, affects the diene CD cannot be determined on present evidence.

It is possible to suggest a way in which the conflicting results from gliotoxin, V[14] and dethiogliotoxin, VI[15] may be reconciled. In V the allylic OH group is quasi-equatorial.[12, 13] If removal of the disulphide bridge to form VI caused some conformational readjustment such that the diene skew-angle increased, the dihedral angle of the oxygen-containing helix would also increase. The first angular change would increase the negativity of the CD band,[34] the second would bring the allylic oxygen closer to co-planarity with the nearer double bond of the diene and, thus, closer to what is a nodal surface for both orbitals involved in the $\pi \rightarrow \pi^*$ transition concerned. This would reduce the opposing positive effect of the allylic substituent. While this is purely speculative since the molecular geometry of VI is not accurately known, we mention it to show that the observed CD of VI does not necessarily imply a contradiction to the influence of allylic oxygen which we suggest exists.

We have used the phrase, "oxygen-containing helix", merely as a convenient means of designating the dissymmetric spatial relationship between the allylic oxygen and the diene. It implies nothing as to the mode of interaction between substituent and chromophore, about which we cannot yet comment.

It is natural to consider the influence of allylic oxygen on the CD of chromophores other than the dienes. One such is the isolated carbon–carbon double bond in a dissymmetric environment. Mills' rule,[35] which has proved widely applicable, states that all alcohols derived from XIV are more laevorotatory than their epimers, XV. Thus, the

$$\underline{XIV} \qquad \underline{XV}$$
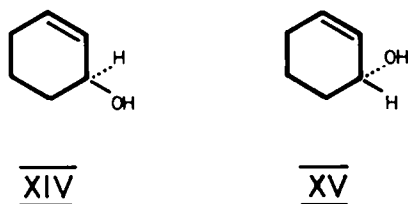
oxygen-containing helices of XIV and XV operate in the same sense as in the dienes. Scott and Wrixon[36] have observed that allylic oxygenated substituents exhibit behaviour which is the inverse in sign from that predicted by the symmetry rule which they propose for chiral olefins. Examination shows this behaviour to be equivalent to that described here for the dienes. Scott and Wrixon suggest that it may form the physical basis for Mills' rule, as had already been implied by Legrand and Viennet.[37] Our results, we believe, tend to reinforce and extend the suggestion.

## EXPERIMENTAL

ORD and CD curves were measured, at ambient temperatures, with a Carey Model 60 spectropolarimeter and a Roussel-Jouan Dichrograph Model A, 1961. Some preliminary ORD results were obtained

using a Perkin-Elmer Spectropolarimeter, P22. A Beckman DK2A far-UV instrument was used for measurements of UV absorption. Cells with fused silica windows, 0·5–10 nm path lengths, were used throughout.

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