$\Delta\epsilon_F/\epsilon_F$ directly as a function of wavelength.[15] This method has been successful in CD calculations of polynucleotides.[16] The equation is

$$\frac{\Delta\epsilon_F}{\epsilon_F} = -\frac{2\pi}{\lambda}\frac{\sum_i \sum_{j\neq i} \phi_i \mathrm{Im} A_{ij} \mathbf{R}_{ij} \cdot \mathbf{e}_i \times \mathbf{e}_j}{\sum_i \sum_{j\neq i} \phi_i \mathrm{Im} A_{ij} \mathbf{e}_i \cdot \mathbf{e}_j} \qquad (22)$$

$$A_{ij} = \left[\frac{\delta_{ij}}{\alpha_i(\lambda)} + G_{ij}\right]^{-1}$$

where λ is the wavelength and $\mathbf{R}_{ij}$ is the distance between groups i and j. A_{ij} is the inverse of a matrix which has wavelength dependent complex polarizabilities, $\alpha_i(\lambda)$, on the diagonal and interaction terms ($G_{ij} = V_{ij}/|\mu_i||\mu_j|$) off the diagonal. Unit vectors $\mathbf{e}_i$ and $\mathbf{e}_j$ specify the directions of the one-dimensional polarizability tensors corresponding to each transition. The real and imaginary parts of the polarizability correspond to the refraction and absorption of the transition. Note that each transition is weighted by its effective fluorescence quantum yield, ϕ_i. The effective quantum yield characterizes the relative contribution of each transition to the measured fluorescence. It can take into account energy transfer and different efficiencies of detection for different fluorophores in the system.

The fluorescence quantum yield weighting of the transitions is particularly interesting for nonrigid molecules. The usual CD measures the average over all conformations; FDCD measures the average over fluorescent conformations. Comparison of the two measurements will allow a better assessment of what conformations are present in the molecules.

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Studies in the Chiroptical Properties of Selenoamino Acids[1]

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Abstract: The circular dichroism (CD) spectra of four selenium-containing amino acids were investigated and compared with those of their sulfur and methylene analogues. In the region 190–250 nm, positive Cotton effects of carboxyl and selenide (or sulfide) chromophores always correlate with L (= *S*) or L,L (= *S*,*S*) absolute configurations. The additive nature of such Cotton effects was demonstrated by a "difference curve" method, which permits the chiroptical properties of the Se (or S) chromophore to be determined. Results suggest that the C–Se–C selenide chromophore has three optically active transitions in the near uv range at approximately 225, 210, and 195–200 nm. The absolute configuration of natural (+)-selenocystathionine has been established spectroscopically to be L,L (= *S*,*S*), in agreement with enzymatic results.

Selenoamino acids first attracted interest during the latter part of the 1930's when it was shown that a cattle disease known as "alkali disease", found in parts of the United States, was closely connected with the selenium content of the soil, that plants were capable of accumulating selenium, and that the selenium so incorporated occurred in the protein fraction of the plants.[3,4] Selenoamino acids were isolated from the plant material[5] and proved to be highly toxic.[6]

These findings led to the synthesis of selenoamino acids by Fredga[7] and by Zdansky.[8] Walter and Roy[9] have reviewed the selenopeptides and selenoproteins, an undiscovered territory only a decade ago.

Optically active selenocystathionine (**2**) has been isolated from plant material[10,11] and was found to possess biological effects. Its absolute configuration was assigned as L on the basis of the lack of reactivity with D-amino acid oxidase.[11] However, the selenium compound could have inhibited the enzyme.

Since no chiroptical studies of selenoamino acids have been made, we decided to investigate this subject. Among the physical methods used for obtaining information on chiroptical properties, the technique of circular dichroism (CD) measurement is the most efficient since it gives precise data on the chirality of specific transitions. The acids under investigation contain two chromophores which absorb in the near-uv region: COOH and C–Se–C. References on simple carboxyl absorption indicate that the n $\rightarrow$ π^* transition occurs at approximately 210 nm and a $\pi \rightarrow \pi^*$ transition below 190 nm.[12] However, few literature references exist for the C–Se–C selenide chromophore. The solution spectrum (hexane) of diethylselenide[13] reveals an absorption band at 250 nm (ϵ_{max} 50). In the similarly constituted dialkyl sulfides, the C–S–C sulfide chromophore has recently been shown[14,15] to have several electronic transitions between 198 and 255 nm. The n $\rightarrow$ σ^* transitions of the C–Se–C chromophore may therefore be

Table I. Intensity and Position of Cotton Effects of Amino Acids Used in CD Studies[a]

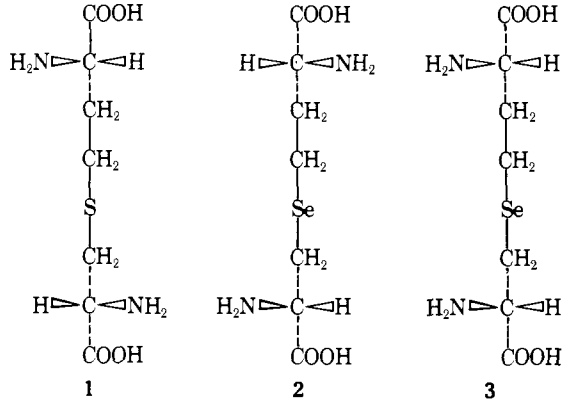
Compd	[θ]	λ_{max}, nm
L-(+)-Selenomethionine (**5b**)	5480	206
L-(+)-Selenolanthionine (**4b**)	3580	220
	8420	200
D-(−)-Selenocystathionine (**2**)	−9990	201
D-(+)-Alloselenocystathionine (**3**)	4440	216
L-(+)-Cysteine (**6a**)	5130	208
L-(−)-*S*-Methylcysteine (**6b**)	5130	223
	2320	205 (sh)
L-(+)-Methionine (**5a**)	4060	205
L-(+)-Lanthionine (**4a**)	9220	217.5
L-(+)-Cystathionine (**1**)	6050	217.5
	9160	200
L-(+)-2-Aminobutyric acid (**7a**)	3150	207.5
L-(+)-2-Aminovaleric acid (**7b**) (norvaline)	3900	207.5
L-(+)-2-Aminocaproic acid (**5c**) (norleucine)	3880	207.5
L,L-(+)-α,ε-Diaminopimelic acid (**4c**)	6850	204
(+)-Selenocystathionine (natural product)	11290	200

[a] All compounds were measured in 0.2 N HCl except (+)-selenocystathionine (natural product) and L,L-(+)-α,ε-diaminopimelic acid which were measured in 0.1 N HCl.

expected to occur in the same region as the n → π* transition of COOH.

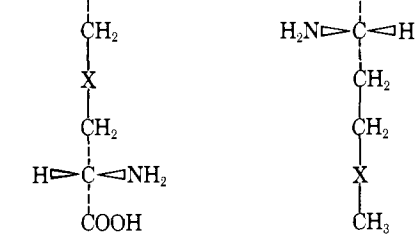
Results and Discussion

We studied the CD properties of the following optically active selenoamino acids: selenocystathionine (**2**) and its allo diastereomer **3**, selenolanthionine (**4b**), and selenomethionine



1 **2** **3**

(**5b**). In order to have a better understanding of the experimental results, we also carried out measurements on the corresponding sulfur analogues cystathionine (**1**), lanthionine (**4a**), methionine (**5a**), and cysteine (**6a**) and its *S*-methyl derivative **6b** and on their methylene analogues α,ε-diaminopimelic acid (**4a**) and 2-aminobutyric (**7a**), -valeric (**7b**), and



4a, X = S
b, X = Se
c, X = CH_2

5a, X = S
b, X = Se
c, X = CH_2

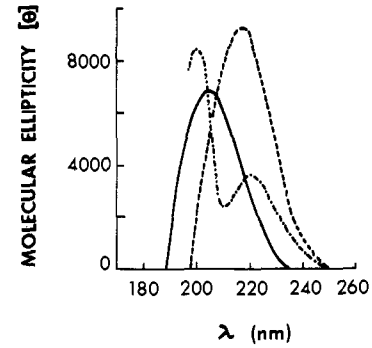
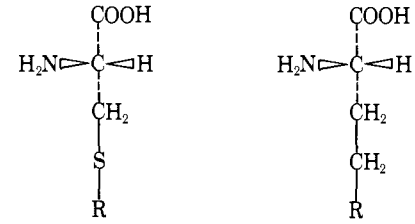


Figure 1. CD spectra of L-(+)-lanthionine·2HCl (**4a**) (- - -), L-(+)-selenolanthionine·2HCl (**4b**) (- · -), and L,L-(+)-α,ε-diaminopimelic acid·2HCl (**4c**) (—).



6a, R = H
b, R = CH_3

7a, R = H
b, R = CH_3

-caproic (**5c**) acids. The position of the CD maxima and the corresponding ellipticity values are given in Table I for all compounds. It was observed that selenoamino acids, like other amino acids,[16] exhibit a red shift of the CD when the pH changes from the alkaline to the acidic region; all CD data were therefore recorded at pH 1 in aqueous solution as the hydrochloride salts. This also establishes standard conditions for comparing chiroptical contributions from the COOH chromophore in different molecules, since protonation of the amino group abolishes any contribution from the n → σ* transition of free NH_2. Unlike some acids which have S attached directly to the asymmetric center,[17] the compounds shown in Table I exhibit relatively simple CD spectra. In the 190–250-nm region, where contributions from COOH and S–C or Se–C are both present, positive Cotton effects are always related to *S* (= L) or *S,S* (= L,L) configurations. This permits the assignment of absolute configuration of new selenium- or sulfur-containing amino acids (Table I). Even in a molecule containing two asymmetric centers of opposite configuration, e.g., D-alloselenocystathionine (**3**), the absolute configuration at each chiral center can be determined by the difference curve method which will be discussed in the following sections.

The CD spectrum of L-selenolanthionine·2HCl (**4b**) is shown in Figure 1. Of the four selenoamino acids measured, this is the only one which exhibits a complex CD curve, suggesting that there are at least two Cotton effects present, at 200 and 220 nm, respectively. Present knowledge of the electronic states of selenium-containing compounds is very limited, whereas sulfur and carboxyl transitions have been well studied. Since sulfur and selenium are both group 6 elements, it is informative to compare the chiroptical behavior of L-selenolanthionine (**4b**) with that of its sulfur analogue, L-lanthionine (**4a**) (Figure 1).

Jung et al.[16] recorded the CD spectra of several sulfur-containing amino acids and investigated their pH and temperature dependence. They reported, and our measurements confirm, that the CD of L-lanthionine at pH 1 consists of a broad positive band centered at 218 nm, regarded as a superposition of two bands, the shorter wavelength band being attributed to the carboxyl transition and the higher wavelength portion belonging to a sulfur transition. In view of recent re-

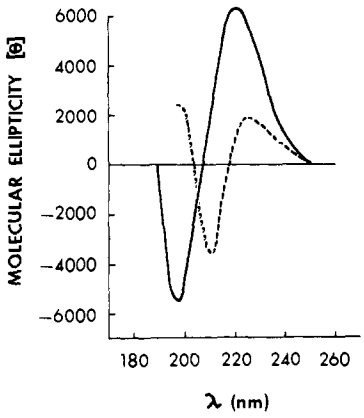


Figure 2. CD difference curves for L-(+)-lanthionine·2HCl (**4a**) and L,L-(+)-α,ε-diaminopimelic acid·2HCl (**4c**) (—) and L-(+)-selenolanthionine·2HCl (**4b**) and L,L-(+)-α,ε-diaminopimelic acid·2HCl (**4c**) (- - -).

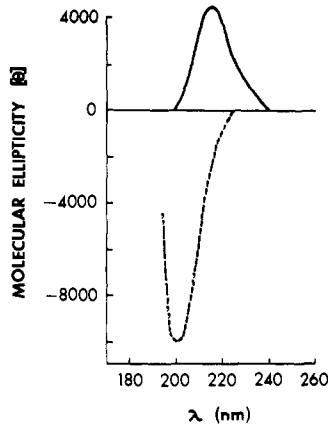


Figure 3. CD spectra of D-(−)-selenocystathionine·2HCl (**2**) (- - -) and D-(+)-alloselenocystathionine·2HCl (**3**) (—).

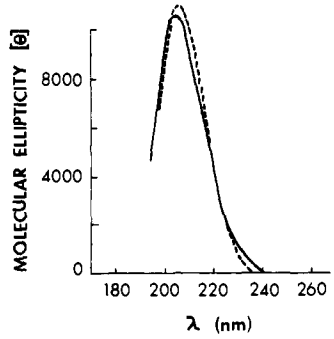


Figure 4. CD spectrum of L-(+)-selenomethionine·HCl (**5b**) multiplied by two (- - -) and CD difference curve for D-(+)-alloselenocystathionine·2HCl (**3**) and D-(−)-selenocystathionine·2HCl (**2**) (—).

ports[14,15] that there are at least three optically active transitions present in compounds containing the C–S–C (sulfide) chromophore, it was possible that the conclusion of Jung et al. was oversimplified. A CD measurement on L,L-α,ε-diaminopimelic acid (**4c**), which is the methylene analogue of L-lanthionine (**4a**), showed a simple positive CD maximum as a narrow band centered at 204 nm (Figure 1). Since the methylene group shows no uv or CD contribution between 185 and 250 nm, the difference between the CD spectra of **4a** and **4c** was replotted as shown in Figure 2 and represents the chiroptical contribution due to the C–S–C sulfide chromophore. The difference curve shows a negative CD at 197 nm and a positive CD at 223 nm. These results are in excellent agreement with Salvadori's report[14] of transitions at 201–210 nm (negative), 229–230 nm (positive), and 246–250 nm (small negative) for open-chain sulfides of the *S* configuration, when the difference in the solvents used is taken into consideration. Our measurements were recorded in aqueous solution while those for the open-chain sulfides[14] were in heptane solution. Since sulfur transitions are n → σ* in nature, a polar solvent would stabilize the nonbonding orbitals and cause a blue shift of the spectrum. The shift observed here is approximately 6–10 nm toward shorter wavelengths, the positive 229–230-nm band being shifted to 223 nm and the negative 201–210 nm band to 197 nm. The greater magnitude of the 223-nm band relative to that at 197 nm[21] explains the absence of the very small oppositely signed CD band at long wavelengths and of the shoulder observed at shorter wavelength and leaves only the 197-nm band observable.

Having thus demonstrated that the "difference curve" method could be useful in providing the general feature of a CD spectrum for open chain sulfides, the method was next applied to L-selenolanthionine (**4b**). The difference curve (Figure 2) between the CD spectra of **4b** and **4c** suggests that there are at least three optically active transitions for the C–Se–C selenide chromophore in the range 190–250 nm. Optically active open-chain selenides which do not have any other chromophore in the molecule have not yet been reported. On the basis of symmetry considerations and semiempirical calculations, Rosenfield and Moscowitz[15] proposed an assignment for the three lowest lying optically active C–S–C transitions. The first two lowest lying transitions are from a nonbonding 3p sulfur orbital to antibonding orbitals between sulfur and carbon atoms. These are the n → σ* transitions. The third band is assigned as an atomic-like transition which involves electron excitation from a nonbonding orbital to a 3d atomic orbital of sulfur only. Since Se and S have similar atomic character, the three Cotton effects observed for the Se contribution (Figure 2) could probably also be accounted for by an analogous rationale except that the molecular orbitals involved here consist of different atomic orbitals, namely, the nonbonding 4p and 4d atomic Se orbitals.

D-Selenocystathionine (**2**) and D-alloselenocystathionine (**3**) are diastereomers that differ in the absolute configuration of one of the two asymmetric carbons. The CD spectra of these two acids are shown in Figure 3. Both spectra have only one CD maximum. However, because of the difference at one asymmetric center, not only are the Cotton effects of opposite sign, but the positions of their maxima also differ by 15 nm. If one takes the difference of the two structures **3** and **2**, the contributions of the two identical asymmetric centers would cancel out, and one would be left with two L-selenomethionine-like molecules. The CD difference curve is therefore expected to be twice that of L-selenomethionine (**5b**) (vide infra). The "difference curve" is shown in Figure 4 together with the CD spectrum of L-selenomethionine, multiplied by 2. The excellent agreement on position and magnitude of the two CD curves in Figure 4 thus illustrates the additive nature of the Cotton effects related to the selenide and carboxyl chromophores and shows that two asymmetric centers separated by four atoms are far enough apart to have little or no interactions electronically. Similar conclusions drawn from CD measurements on sulfur-containing amino acids have been arrived at by Jung et al.[16] Therefore it is possible to assign the absolute configuration of both of the two asymmetric centers of a pair of selenium-containing amino acid diastereomers such as **2** and **3** by a CD study as follows: (a) The CD difference curve (**3** minus **2**) is equal to twice that of L-selenomethionine (**5b**). At the two asymmetric centers which are different in **3** and **2**, **3** therefore has the L and **2** must have the D configuration. (b) Since the Cotton effects are additive in nature, and the contribution due to the n → π* transition is larger than that due to the selenide chromophore (vide infra), that compound

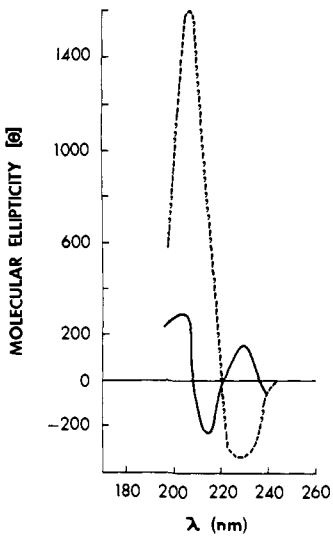
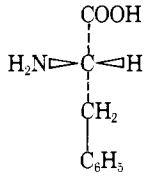


Figure 5. CD difference curves for L-(+)-methionine·HCl (**5a**) and L-(+)-2-aminocaproic acid·HCl (**5c**) (—) and L-(+)-selenomethionine·HCl (**5b**) and L-(+)-2-aminocaproic acid·HCl (**5c**) (- - -).

in which both asymmetric centers have the same configuration will have the larger Cotton effect. In this case, compound **2** (Table I) will therefore have the D configuration also at the other asymmetric center.

The CD spectra of the closely analogous L-selenomethionine (**5b**) and L-methionine (**5a**) show apparently simple positive CD maxima corresponding to the L configuration as does their methylene analogue L-2-aminocaproic acid (**5c**) (Table I). In order to reveal the chiroptical contribution of the heteroatom (S or Se) in **5b** and **5a**, a "difference curve" method is again employed for comparison, and the results are shown in Figure 5. Whereas in the L-selenolanthionine series (**4a** and **4b**) the heteroatom (S or Se) is separated by one carbon from the asymmetric center, in the two acids **5a** and **5b** the heteroatom (S or Se) is two carbons away from the center of asymmetry. This difference in structure not only decreases the magnitude of the ellipticity due to S or Se, but it also reverses the sign of each Cotton effect due to S or Se, compared to those shown in Figure 2. The decrease in ellipticity can be understood on the basis of first-order perturbation theory. The reversal of the sign of the Cotton effects, although unexpected, finds an analogy in the L-amino acid derivatives **8** and **9** which also show a reversal of sign[18] when an additional methylene group is inserted between the asymmetric center and the observed chromophore, in this case the 260-nm band of benzene. Similar inversion of the Cotton effect for the carbonyl chromophore[19] has been analyzed in terms of a conformational equilibrium change.[20]



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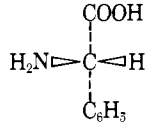

8

Natural (+)-selenocystathionine, isolated from the seeds of Lecythis Ollaria,[9-11] is not attacked by D-amino acid oxidase and on the basis of this negative enzymatic reaction has been assigned the L,L-configuration.[11] Although such a negative result does not unambiguously prove the absolute configuration, the CD is seen (Table I) to be the mirror image of that of synthetic D-selenocystathionine, and the stereochemistry of the natural product can thus be confirmed as L,L.

Experimental Section

CD measurements were made on a Roussel-Jouan Dichrograph II CD spectrometer at pH 1 in aqueous solution at room temperature. CD curves were recorded in terms of molecular ellipticity units [θ]. CD data are given below for the zero line intersections, lowest wavelengths measured, and the maxima and shoulders observed.

L-(+)-Selenomethionine·HCl: $[\alpha]^{23.5}D$ +13.0° (*c* 0.038, 0.2 N HCl); CD (*c* 0.038, 0.2 N HCl), $[\theta]_{235}$ 0, $[\theta]_{206}$ +5480, $[\theta]_{198}$ +3490.

L-(+)-Selenolanthionine·2HCl: $[\alpha]^{23.5}D$ +29.2° (*c* 0.0257, 0.2 N HCl); CD (*c* 0.0257, 0.2 N HCl), $[\theta]_{250}$ 0, $[\theta]_{220}$ +3580, $[\theta]_{210}$ +2320, $[\theta]_{200}$ +8420, $[\theta]_{197}$ +7580.

D-(−)-Selenocystathionine·2HCl: $[\alpha]D$ −37.7° (*c* 0.0305, 0.2 N HCl); CD (*c* 0.0305, 0.2 N HCl); CD (*c* 0.0305, 0.2 N HCl), $[\theta]_{225}$ 0, $[\theta]_{201}$ −9990, $[\theta]_{195}$ −4440.

D-(−)-Alloselenocystathionine·2HCl: $[\alpha]^{26}D$ −9.8° (*c* 0.0254, 0.2 N HCl); CD (*c* 0.0254, 0.2 N HCl), $[\theta]_{240}$ 0, $[\theta]_{216}$ +4440, $[\theta]_{200}$ 0.

L-(+)-Cysteine·HCl: $[\alpha]^{25}D$ +5.1° (*c* 2, 5 N HCl); CD (*c* 0.436, 0.2 N HCl), $[\theta]_{250}$ 0, $[\theta]_{208}$ +5130, $[\theta]_{195}$ +3340.

L-(−)-*S*-Methylcysteine·HCl: $[\alpha]^{20}D$ −9.5° (*c* 0.058, 0.2 N HCl); CD (*c* 0.058, 0.2 N HCl), $[\theta]_{250}$ 0, $[\theta]_{223}$ +5130, $[\theta]_{205}$ +2320, $[\theta]_{197.5}$ 0, $[\theta]_{195}$ −1550.

L-(+)-Methionine·HCl: $[\alpha]^{19}D$ +19.2° (*c* 0.0573, 0.2 N HCl); CD (*c* 0.0537, 0.2 N HCl), $[\theta]_{240}$ 0, $[\theta]_{205}$ +4060, $[\theta]_{195}$ +2560.

L-(+)-Lanthionine·2HCl: $[\alpha]D$ +3° (*c* 5, 2.4 N NaOH); CD (*c* 0.0648, 0.2 N HCl), $[\theta]_{250}$ 0, $[\theta]_{217.5}$ +9220, $[\theta]_{197.5}$ 0.

L-(+)-Cystathionine·2HCl: $[\alpha]^{23}D$ + 23.1° (*c* 1, 1 N HCl); CD (*c* 0.0298, 0.2 N HCl), $[\theta]_{245}$ 0, $[\theta]_{217.5}$ +6050, $[\theta]_{212}$ +5400, $[\theta]_{200}$ +9160, $[\theta]_{191.5}$ 0, $[\theta]_{190}$ −1960.

L-(+)-2-Aminobutyric acid·HCl: $[\alpha]^{21}D$ +13.3° (*c* 0.548, 0.2 N HCl); CD (*c* 0.548, 0.2 N HCl), $[\theta]_{245}$ 0, $[\theta]_{207.5}$ +3150, $[\theta]_{193}$ +1560.

L-(+)-2-Aminovaleric acid·HCl: $[\alpha]D$ +16.01° (*c* 0.3, 0.2 N HCl); CD(*c* 0.3, 0.2 N HCl), $[\theta]_{245}$ 0, $[\theta]_{207.5}$ +3910, $[\theta]_{195}$ +2450.

L-(+)-2-Aminocaproic acid·HCl: $[\alpha]D$ +15.20° (*c* 0.296, 0.2 N HCl); CD (*c* 0.296, 0.2 N HCl), $[\theta]_{245}$ 0, $[\theta]_{207.5}$ +3885, $[\theta]_{195}$ +2340.

L,L-(+)-α,ε-Diaminopimelic acid·2HCl: $[\alpha]D$ +38.5° (*c* 2.6, 5 N HCl); CD (*c* 0.184, 0.1 N HCl), $[\theta]_{235}$ 0, $[\theta]_{204}$ +6850, $[\theta]_{189}$ 0.

(+)-Selenocystathionine·2HCl (natural product): $[\alpha]D$ +38.6° (*c* 0.029, 0.1 N HCl); CD (*c* 0.029, 0.1 N HCl), $[\theta]_{225}$ 0, $[\theta]_{200}$ +11290, $[\theta]_{190}$ 0.

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References and Notes

(1) This paper forms part 18 of the series "Optical Rotatory Dispersion and Absolute Configuration".
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