A New One-Step Strategy for the Stereochemical Assignment of Acyclic 2- and 3-Sulfanyl-1-alkanols Using the CD Exciton Chirality Method

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A new one-step strategy is described for the stereochemical assignment of acyclic 2- and 3-sulfanyl-1-alkanols using the CD exciton chirality method. Using the 9-anthroate chromophore for the derivatization of both functional groups, the resulting bisignate CD curves unequivocally allow the determination of the stereochemistry from a single CD measurement. The usefulness of the new method is demonstrated using synthesized optically pure 3-sulfanyl-1-hexanols and 2-sulfanyl-1-hexanols as model compounds. The developed microscale method is also useful for the stereochemical assignment of 1,2- and 1,3-diols. To our knowledge this is the first application of the CD exciton chirality method to acyclic 2- and 3-sulfanyl-1-alkanols.

The circular dichroism (CD) exciton chirality method is a versatile and sensitive procedure for determining the absolute configuration and conformation of organic molecules containing two or more chromophores and has been widely used in the field of natural products.[1] Hydroxyl groups are converted into various *p*-substituted benzoates or other chromophores, which may or may not be identical. Exciton coupling is based on the through space coupling of two or more chromophores in chiral substrates, giving rise to bisignate or split CD curves, the signs and shapes of which are defined nonempirically by the spatial arrangement of the interacting chromophores. If the orientation of the electric transition moments is clockwise (looking from the chromophore in front to the chromophore in back), defined as positive chirality, the CD shows a positive first and a negative second Cotton effect (CE) and vice versa.[1] The amplitude[2] of the CD curve is (i) inversely proportional to the square of the interchromophoric distance, (ii) proportional to the chromophoric absorption coefficient, and (iii) depending on the chromophoric projection angle with a maximum at approximately 70°. The exciton chirality method can be extended to nondegenerate systems consisting of different chromophores, as well as chromophores which already preexist in the molecule, e.g., monoene[3] and diene[4] moieties. Chromophores with UV maxima as far apart as 100 nm still can couple. Since the exciton chirality method depends on the conformation of the molecules, the stereochemical assignment is most straightforward and unambiguous in rigid molecules with fixed conformation. Nevertheless, the exciton chirality method has been successfully applied to acyclic 1,2-/1,3-polyols[5,6] and aminopolyols[7] as well as acyclic α-hydroxy carboxylic acids.[8] However, to our knowledge the CD exciton chirality method has not been applied to acyclic 2- and 3-sulfanyl-1-alkanols to date.[9] In the following we describe a simple one-step method for the configurational assignment of 2- and 3-sulfanyl-1-alkanols and diols using 3-sulfanyl-1-hexanol **6**, 2-sulfanyl-1-hexanol **7**, 1,3-butandiol **8**, and 1,2-propandiol **9** as model compounds.

Results and Discussion

Sulfur compounds play an important role as flavor compounds because many of them have very low odor thresholds and contribute considerably to the overall odor impression even at low concentrations.[10] Among this class of compounds there are many optical active sulfur compounds, e.g., 3-sulfanyl-1-hexanol[11] and 3-sulfanyl-2-methylpentanol.[12] The odor properties of diastereomers and enantiomers can differ tremendously and therefore the determination of the absolute configuration is crucial.

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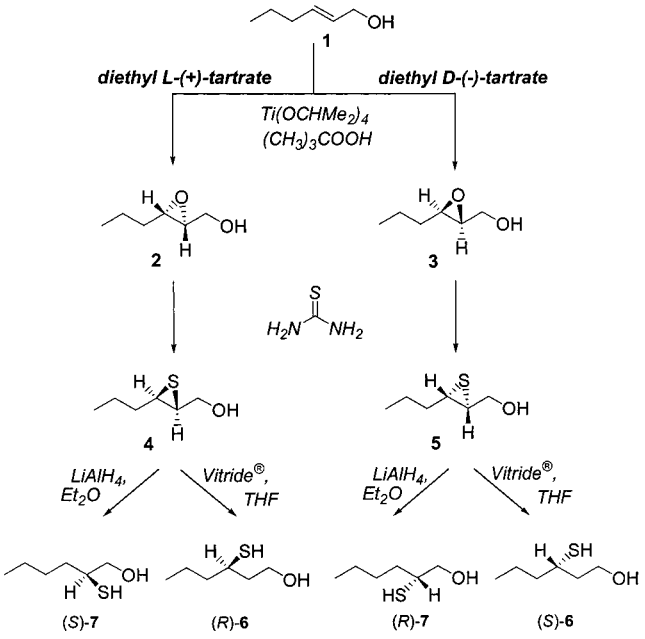
Scheme 1. Synthesis of the Optically Pure 3-/2-Sulfanyl-1-hexanols 6 and 7

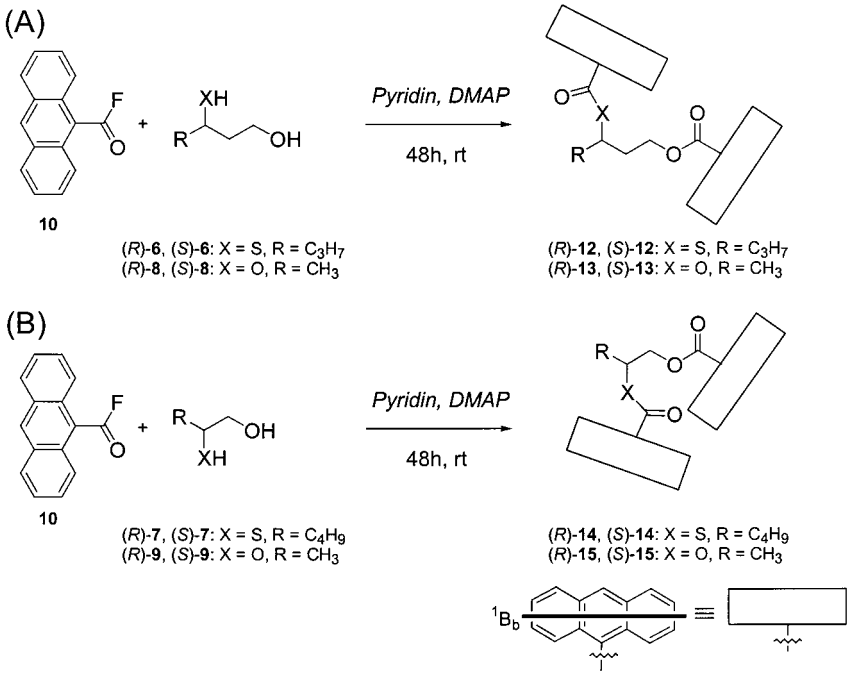


Since the stereochemical assignment of sulfur compounds still remains a difficult task, we developed a new method based on circular dichroism for the stereochemical assignment of 2- and 3-sulfanyl-1-alkanols and extended the applicability of the exciton chirality method for the first time to acyclic thiol groups.

The application of the exciton chirality method to 2- and 3-sulfanyl-1-alkanols requires two chromophores suitable for exciton coupling. For 1,2- and 1,3-diols the bichromophoric exciton chirality method utilizes two different chromophors which are selectively introduced at the two different types of hydroxyls. For example, the primary hydroxyl of a polyol with a 1,2-diol terminus was selectively derivatized with 9-anthroate (λ_{max} 251 nm, ϵ = 142 000[5a,b]) and the other hydroxyl group with *p*-methoxycinnamate[5a,b] or with 2-anthroate[5c] (λ_{max} 258 nm, ϵ = 93 000). This method provides typical fingerprint CD curves and was sucessfully used for the stereochemical assignment of acyclic 1,2- and 1,3-polyols.[5] However, for the bichromophoric method a two-step derivatization/cleanup is necessary and our goal was to develop a simple one-step procedure for the stereochemical assignment of 2- and 3-sulfanyl-1-alkanols using only one chromophoric group. Simple one-step methods for the stereochemical assignment of terminal and internal 1,2- and 1,3-diols using benzoate or *p*-substituted benzoates as chromophores have been described.[6a,b] Another approach, using the 2-anthroate chromophore for the derivatization of both hydroxyls, resulted in intense CD curves for 1,2-diols, but 1,3-diols gave only very weak Cotton effects which were not interpretable.[5c] For this reason we decided to use the 9-anthroate chromophore for the stereochemical assignment of 2- and 3-sulfanylalkanols.

Optically pure 3-sulfanyl-1-hexanols (*S*)-**6** and (*R*)-**6** and 2-sulfanyl-1-hexanols (*S*)-**7** and (*R*)-**7** were synthesized by following the procedure by Pickenhagen and Brönner-Schindler (Scheme 1). Asymmetric epoxidation of (*E*)-2-hexen-1-ol **1** under Sharpless conditions[13] using diethyl L-(+)- and diethyl D-(−)-tartrate led to (2*S*,3*S*)-2,3-epoxy-1-hexanol **2** and its enantiomer **3**, respectively. Treatment of the epoxides **2** and **3** with thiourea gave the corresponding thiiranes **4** and **5** with inverse absolute configuration.[14] Reduction of **4** and **5** with Vitride (sodium bis(2-methoxyethoxy)aluminum hydride) in THF gave the (*R*)-3-sulfanyl-1-hexanol (*R*)-**6** and its enantiomer (*S*)-**6**. Using $LiAlH_4$ in Et_2O for the reduction of **4** and **5** led to the 2-sulfanyl-1-hexanols (*S*)-**7** and (*R*)-**7** together with the corresponding 3-sulfanyl-1-hexanols.[14] Under these conditions the ratio of the formed 2-/3-sulfanyl-1-hexanols was determined to be approximately 2:1 by high-resolution gas chromatography−mass spectrometry (HRGC-

Scheme 2. Functionalization of 3-/2-Sulfanyl-1-hexanol (6, 7), 1,3-Butandiol 8, and 1,2-Propandiol 9 to the Corresponding Bichromophoric Derivatives 12−15 for Configurational Analysis (Bold Line Indicates Transition Dipole)



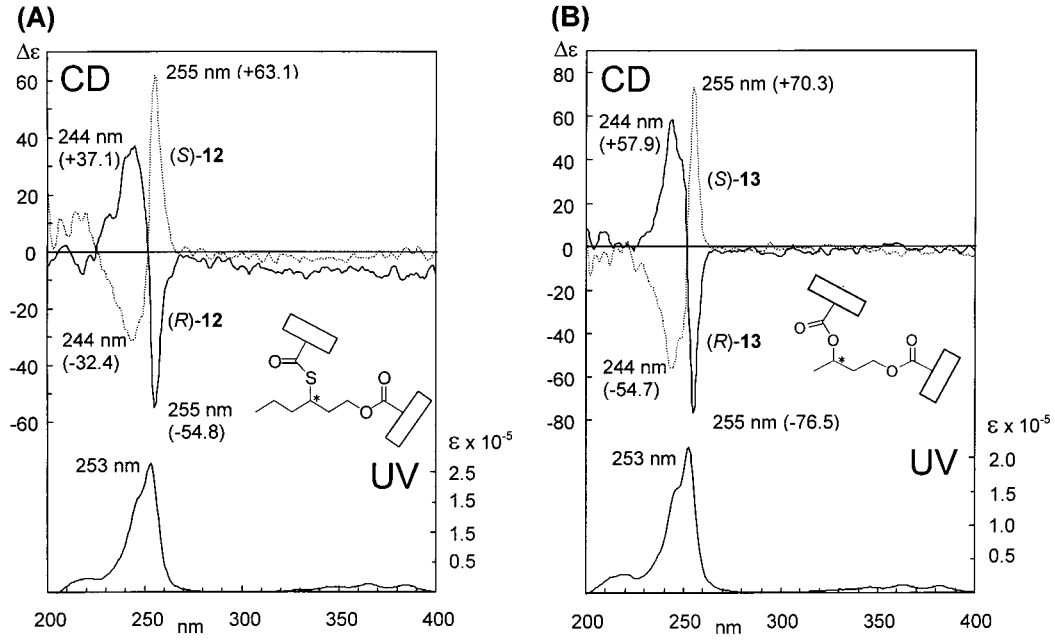
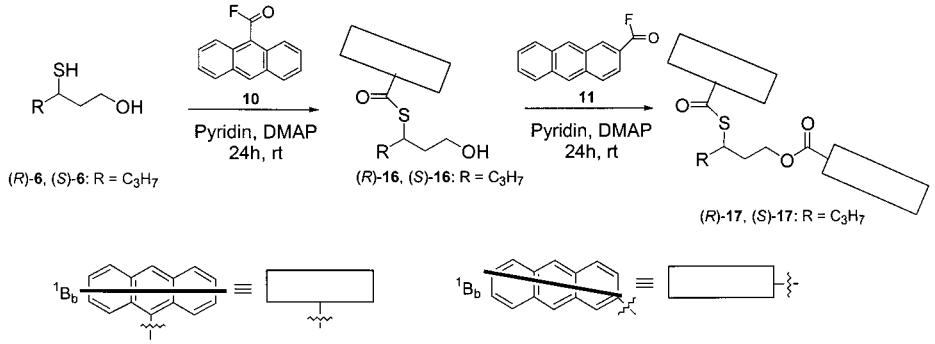


Figure 1. UV and CD spectra of (A) 1-*O*-(9-anthroyl)-3-*S*-(9-anthroyl)-3-sulfanyl-1-hexanol **12** and (B) 1,3-bis-*O*-(9-anthroyl)-1,3-butanediol **13** in acetonitrile.

Scheme 3. Two-Step Derivatization of 3-Sulfanyl-1-hexanols 6 to 1-*O*-(2-Anthroyl)-3-*S*-(9-anthroyl)-3-sulfanyl-1-hexanol 17 (Bold Lines Indicate Transition Dipoles)



MS). The final products (*S*)-**6**, (*R*)-**6**, (*S*)-**7**, and (*R*)-**7** were purified by column chromatography. The optical purity was checked by multidimensional gas chromatography−mass spectrometry (MDGC-MS) using a chiral modified cyclodextrin column and by comparison of the specific rotations with literature data.[14]

The optically pure 3- and 2-sulfanyl-1-hexanols **6** and **7** as well as 1,3-butanediol **8** and 1,2-propanediol **9** were derivatized with 9-anthroyl fluoride **10**[15] to yield the chromophoric derivatives **12**−**15** (Scheme 2), which were subsequently purified by preparative TLC.

The UV and CD data of the bichromophoric esters of 3-sulfanyl-1-hexanols (*R*)-**12** and (*S*)-**12** and 1,3-butandiols (*R*)-**13** and (*S*)-**13** are shown in Figure 1 and Table 1. In the derivatized 3-sulfanyl-1-hexanol (*R*)-**12** the exciton coupling between the two 9-anthroate chromophores give rise to a negative split CD curve with a negative first Cotton effect at 255 nm ($\Delta\epsilon = -54.8$) and a positive second CE at 244 nm ($\Delta\epsilon = +37.1$), amplitude $A = -91.9$. This negative CD shows that the two long axis electric transition dipoles (^1B_b-band, Scheme 2) of the two chromophores constitute a negative chirality and a counterclockwise orientation of the chromophores. The corresponding enantiomer (*S*)-**12** shows a mirror image positive split CD curve with extrema at 255 nm ($\Delta\epsilon = +63.1$) and 244 nm ($\Delta\epsilon = -32.4$), $A = +95.5$. Similar results were obtained for the 1,3-butandiol derivatives. The (*R*)-configured derivative (*R*)-**13** shows also a negative split CD curve with Cotton effects at 255 ($\Delta\epsilon = -76.5$) and 244 nm ($\Delta\epsilon = +57.9$), amplitude $A = -134.4$.

Table 1. CD Data, Cotton Effect,s and Configuration of the Bichromophoric Diesters 12−15 and 17

		Cotton effects[a]				
entry	diester	λ_{max} [nm]	1st $\Delta\epsilon$	λ_{max} [nm]	2nd $\Delta\epsilon$	amplitude[2] A
1	(*R*)-**12**[b]	255	−54.8	244	+37.1	−91.9
2	(*S*)-**12**[b]	255	+63.1	244	−32.4	+95.5
3	(*R*)-**13**[b]	255	−76.5	244	+57.9	−134.4
4	(*S*)-**13**[b]	255	+70.3	244	−54.7	+125.0
5	(*R*)-**14**[b]	256	+151.3	244	−77.2	+228.5
6	(*S*)-**14**[b]	256	−136.0	244	+73.8	−209.8
7	(*R*)-**15**[b]	256	+135.5	243	−71.0	+206.5
8	(*S*)-**15**[b]	256	−145.0	243	+56.9	−201.9
9	(*R*)-**17**[c]	259	+98.3	248	−109.1	+207.4
10	(*S*)-**17**[c]	258	−104.0	249	+98.8	−202.8

[a] The CD effects of enantiomers are not comparable, since the starting material was not enantiomerically pure (see Experimental Section in the Supporting Information, ee values of **6** and **7**). [b] Concentrations were determined from the UV extinction coefficient: $\epsilon_{253} = 215\,000\ M^{-1}\ cm^{-1}$. [c] Concentrations were determined from the UV extinction coefficient: $\epsilon_{255} = 186\,000\ M^{-1}\ cm^{-1}$.

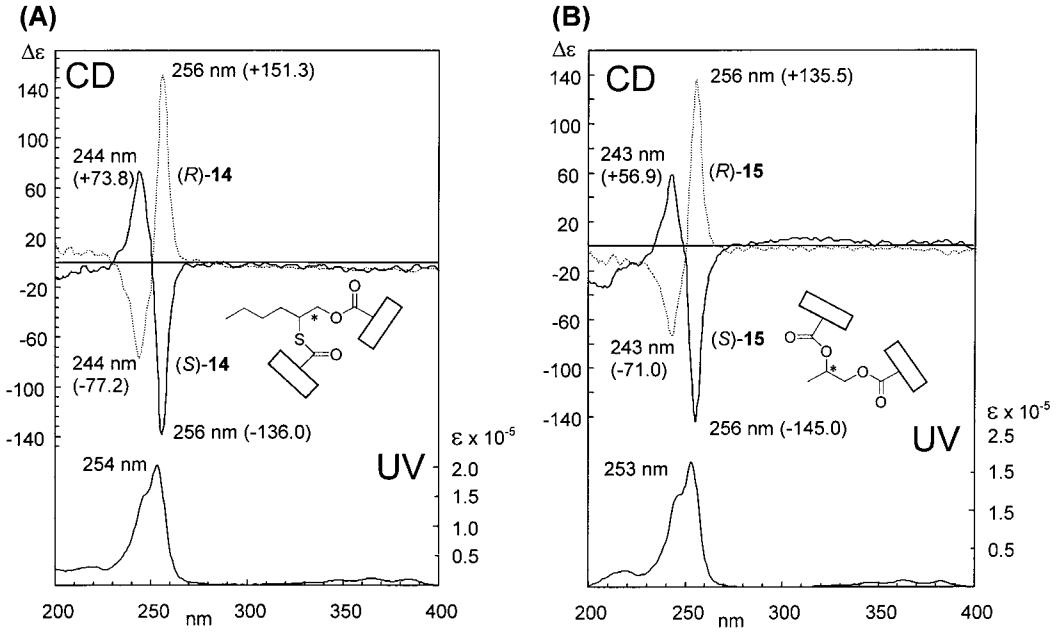


Figure 2. UV and CD spectra of (A) 1-*O*-(9-anthroyl)-2-*S*-(9-anthroyl)-2-sulfanyl-1-hexanol **14** and (B) 1,2-bis-*O*-(9-anthroyl)-1,2-propanediol **15** in acetonitrile.

The (*S*)-**13** enantiomer exhibits a similar CD spectrum with the same shape but opposite signs of the Cotton effects at 255 ($\Delta\epsilon = +70.3$) and 244 nm ($\Delta\epsilon = -54.7$), $A = +125.0$. Comparing the CD spectra of the 3-sulfanyl-1-hexanols **12** (Figure 1A) with the corresponding 1,3-butandiol derivative **13** (Figure 1B) revealed that in both cases the (*R*) configured compounds gave a negative split CD curve and the (*S*)-enantiomers a positive mirror image split CD spectra.

The CD and UV spectra of the derivatized 2-sulfanyl-1-hexanols (*R*)-**14** and (*S*)-**14** as well as the bichromophoric 1,2-propandiol esters (*R*)-**15**, (*S*)-**15** are shown in Figure 2 (see Table 1). In 1-*O*-(9-anthroyl)-2-*S*-(9-anthroyl)-2(*R*)-sulfanyl-1-hexanol (*R*)-**14** the coupling between the two transition dipoles of the chromophores results in a positive split CD curve with a first Cotton effect at 256 nm ($\Delta\epsilon = +151.3$) and a negative CE at 244 nm ($\Delta\epsilon = -77.2$), $A = +228.5$. The enantiomer (*S*)-**14** shows opposite CEs at 256 nm ($\Delta\epsilon = -136.0$) and 244 nm ($\Delta\epsilon = +73.8$), $A = -209.8$. The corresponding 1,2-propanediol derivatives **15** exhibit very similar CD spectra and also a negative split CD curve for the (*S*)-configured compound (*S*)-**15** ($A = -201.9$) and a positive split CD for the (*R*)-enantiomer (*R*)-**15** ($A = +206.5$) (Figure 2A). The absolute values of the amplitudes[2] *A* of chromophoric derivatives **14** and **15** vary from 201.9 to 228.5 and are much larger than the *A*-values for **12** and **13** ($A = 91.9$ to 134.4, Table 1). This can be explained by the closer distance between the chromophores in the case of the derivatized 2-sulfanyl-1-hexanols **14** and the bichromophoric 1,2-propandiol esters **15** compared to 3-sulfanyl-1-hexanols **12** and 1,3-butandiols **13**. In addition to distance effects, the CD amplitude is also affected by the interchromophoric angle of the two interacting chromophores. However, as can be seen from the preferred conformation of (*S*)-**12** and (*S*)-**14** (Figure 4A and 4B), the interchromophoric angles are almost the same (approximately 30 to 50°, see also discussion of Figure 4 below).

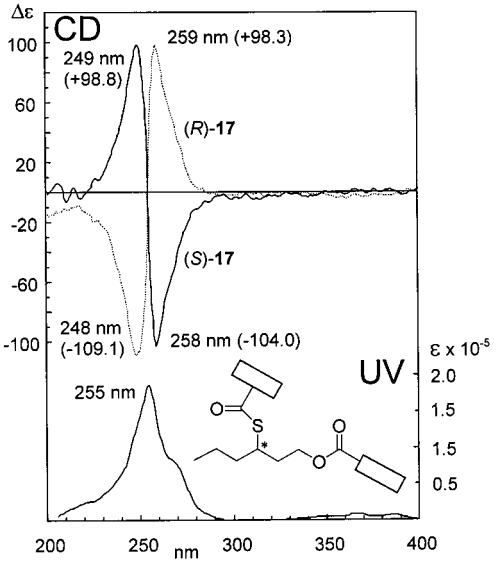


Figure 3. UV and CD spectra of 1-*O*-(2-anthroyl)-3-*S*-(9-anthroyl)-3-sulfanyl-1-hexanol **17** in acetonitrile.

These data clearly demonstrate that the simple one-step derivatization using the 9-anthroate chromophore provides a general microscale method for the absolute configurational assignment of 2- and 3-sulfanyl-1-alkanols and 1,2- and 1,3-diols. Exciton coupling between the two 9-anthroate chromophores leads to strong opposite Cotton effects with absolute *A*-values ranging from 91.9 to 228.5. The preferred sense of twist between the 9-anthroate chromophores follows the same CD pattern for both series of compounds: (i) in the case of 3-sulfanyl-1-hexanols **12** and 1,3-diols **13** counterclockwise orientation (negative chirality) of the transition dipoles of the two chromophores leads to (*S*)-configuration and vice versa (Figure 1), (ii) for 2-sulfanyl-1-alkanols and 1,2-diols negative chirality is characteristic for (*R*)- and positive chirality for (*S*)-configured compounds (Figure 2).

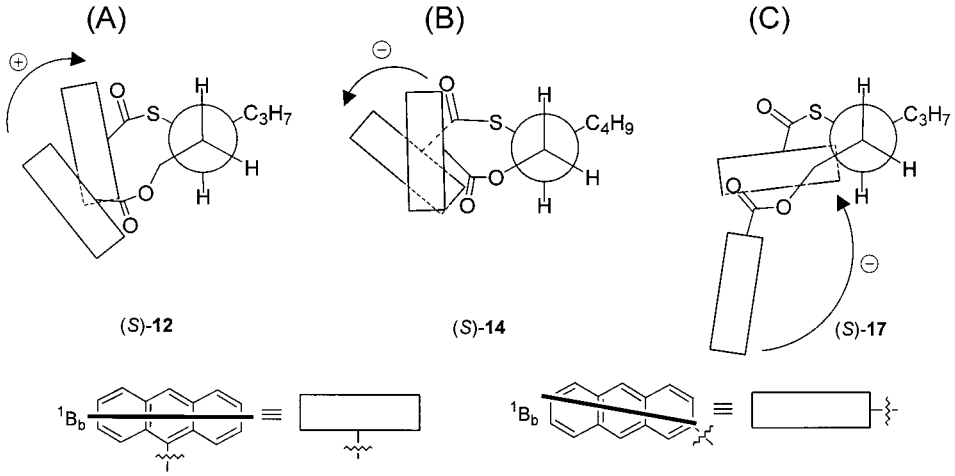


Figure 4. Preferred conformation and the predicted sign of the first Cotton effect of (*S*)-**12**, (*S*)-**14**, and (*S*)-**17**, as determined by computer calculations using MacroModel 5.0[16] (bold lines indicate transition dipoles).

Although the 9-anthroate is sterically hindered and the derivatization of both functional groups proceeds only in low yield (approximately 10%), the described method is very useful for the stereochemical assignment of sulfanyl-1-alkanols and diols for several reasons: (i) only one derivatization/cleanup step is necessary, (ii) the 9-anthroate chromophore is highly fluorescent and the bichromophoric derivatives can be easily separated from the monoesters and the starting material by TLC, (iii) the intense CD spectra with amplitudes ranging from −91.9 to +228.5 allow applications in the μg range.

To have a complete set of data, we also applied the bichromophoric exciton chirality method to optically pure 3-sulfanyl-1-hexanols **6** using two different chromophores. According to Scheme 3 (*R*)-**6** and (*S*)-**6** were first derivatized at the SH group with the 9-anthroate chromophor to give (*R*)-**16** and (*S*)-**16** (these products were formed during the synthesis of **12** as side products). In the second step, the 3-*S*-(9-anthroyl)-3-sulfanyl-1-hexanols **16** were derivatized with 2-anthroyl fluoride **11** to form the bichromophoric derivatives (*R*)-**17** and (*S*)-**17** (Scheme 3). The CD and UV spectra of which are shown in Figure 3. (*R*)-**17** shows a positive split CD curve with a positive first Cotton effect at 259 nm ($\Delta\epsilon = +98.3$) and a negative CE at 248 nm ($\Delta\epsilon = -109.1$), amplitude $A = +207.4$. Enantiomer (*S*)-**17** reveals a mirror image negative split CD spectra with extrema at 258 ($\Delta\epsilon = -104.0$) and 249 nm ($\Delta\epsilon = +98.8$), $A = -202.8$. These results clearly show that the application of the two-step derivatization using the 2- and 9-anthroate chromophore also allows the stereochemical assignment of 3-sulfanyl-1-hexanols **6** and similar compounds. It is interestingly to note that the CD effects for **17** are opposite compared to those for **12** for the same enantiomer. However, this is in agreement with predictions based on molecular modeling calculations using MacroModel 5.0.[16] The low-energy conformation of (*S*)-**12** obtained after local energy minimization and Monte Carlo conformational search showed that the orientation between the two dipole transition moments is clockwise (positive chirality) with an interchromophoric angle of approximately 30° (Figure 4A). This is in agreement with the obtained positive CD couplet for (*S*)-**12** with a positive first CE at 255 nm (see Figure 1, Table 1). In (*S*)-**17** the long axis transition dipoles of the 2- and 9-anthroate constitute a negative chirality (counterclockwise orientation, interchromophoric angle approximately 100°, Figure 4C) leading to a negative experimental CD couplet (Figure 3).

In addition, CD measurements of chromophoric derivatives were performed in hexane as nonpolar solvent (see Supporting Information). In hexane, the CD curves were almost the same; however, the amplitudes were much weaker compared to the those of the CD measured in acetonitrile (e.g., (*S*)-**12** revealed an amplitude *A* of +95.5 in acetonitrile and +40.7 in hexane). This indicates that the preferred conformation which leads to the obtained intense positive or negative split CD curves shown in Figures 1−3 is stabilized by the polarity of the solvent.

In summary, we have demonstrated for the first time that the CD exciton chirality method can be extended to acyclic 2- and 3-sulfanyl-1-alkanols. The simple one-step derivatization using the 9-anthroate chromophore provides a general microscale method for the determination of the absolute configuration. Exciton coupling between the two 9-anthroate chromophores leads to intense positive split CD curves for the (*R*)-configured 2-sulfanyl-1-alkanols and the (*S*)-configured 3-sulfanyl-1-alkanols and vice versa. The developed method is also useful for the stereochemical assignment of 1,2- and 1,3-diols. Furthermore, the application of the two-step derivatization using two different chromophores for both functional groups (2- and 9-anthroate) also results in mirror image split CD curves for both enantiomers and allows the stereochemical assignment of 3-sulfanyl-1-alkanols.

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Supporting Information Available: Experimental section. This material is available free of charge via the Internet at http://pubs.acs.org.

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(15) Zhao, N.; Berova, N.; Nakanishi, K. *Tetrahedron* **1996**, *52*, 2777−2789.
(16) All calculations were performed using MacroModel 5.0 and the MM2 force field in H_2O. At least 100 conformers were searched for each Monte Carlo simulation.