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Chiral isothiocyanates – An approach to determination of the absolute configuration using circular dichroism measurement

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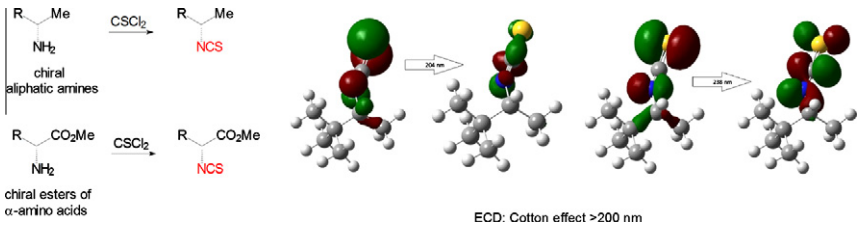
HIGHLIGHTS

- Several chiral 2-isothiocyanates were synthesized and their ECD spectra were measured.
- TD DFT calculations (B3LYP/6-311+G(2d,p), PCM) reproduced all observed Cotton effects.
- Cotton effect in the range of 210–230 nm depends on the configuration of C-2.
- Correlation between CE at 210–230 nm and configuration of C-2 was observed also in presence of other stereogenic centers.

GRAPHICAL ABSTRACT



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ABSTRACT

Chiral alkyl 2-isothiocyanates have been obtained from enantiopure, aliphatic amines. ECD measurements allowed us to correlate an absolute configuration at C-2 with a sign of the Cotton effect (CE) observed for n–π^* transition at the longer-wavelength range of the spectrum. Chirooptical data calculated for all enantiomers were consistent with the measured CE values and indicated that the weak absorption band at 240 nm could give an important information concerning the stereochemistry of simple, chiral isothiocyanates. Optically active esters of 2-isothiocyanatocarboxylic acids, prepared from α-amino acids, showed two absorption bands located over 195 nm. The more intensive band near 200 nm and the weak absorption located at 250 nm were related to n–π^* transitions in NCS group. TD DFT calculations carried out for methyl esters of 2-isothiocyanatocarboxylic acids showed the correlation between signs of CE determined for both absorption bands, and the absolute configuration on C-2.

1. Introduction

For many years isothiocyanates have attracted considerable attention because of their wide application in the organic synthesis, easy of preparation, and stability. Simple aryl and alkyl isothiocyanates have been used for synthesis of thioureas and thioamides [1], as well as precursors for various sulfur containing heterocycles [2–5]. A particular interest was directed to 2-isothiocyanatocarboxylates that have found applications not only as convenient reactants for preparation of heterocyclic carboxylic acids [6–8] but also as precursors of 2,3-diaminoacids [9,10]. Our research on the oxidative coupling of 2-isothiocyanatocarboxylic esters [9] prompted us to look for a simple and easy method for determination of an absolute configuration of the investigated 2-isothiocyanatoesters. The prepared 2-isothiocyanate derivatives were usually amorphous solids or oils (and their conversion into crystalline form needed additional chemical transformations). Thus we assumed that chirooptical methods would be an efficient alternative for an X-ray structure determination. However, published data concerning applications of CD technique in the field of chiral isothiocyanates were rather limited.

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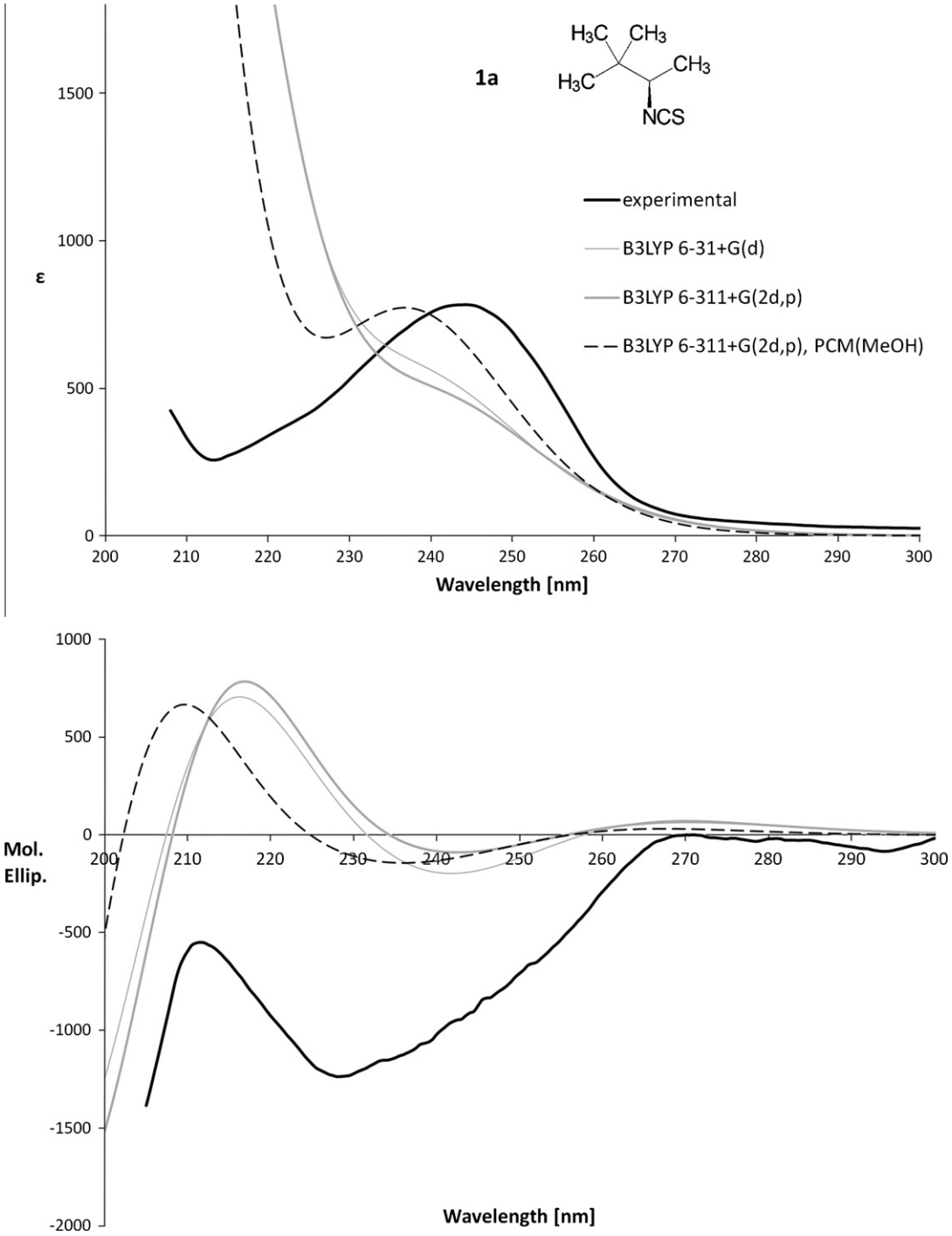


Fig. 1. Comparison of the measured and calculated UV–VIS and CD spectra of (*3R*)-3-isothiocyanato-2,2-dimethylbutane **1a**.

The first attempt to investigate optical properties of chromophoric (cottonogenic) —NCS substituents in 2-isothiocyanatocarboxylates was made by Crabbé et al. [11] but precise measurements and analysis of a weak CE were impossible because of the technical reasons. After that report further investigations of chirooptical properties of isothiocyanates have been virtually neglected. Fifty years after Crabbe's work Gawroński et al. [12] published very important article devoted to the circular dichroism of chiral thioureas and isothiocyanates but focused mainly on exciton-coupled CD spectra. The authors have compared experimental and calculated UV and ECD spectra of some chiral 1,2-diaminocyclohexane derivatives and revealed that —NCS chromophoric group can be very useful for stereochemical investigations of chiral amine derivatives.

Analysis of CD spectra including signs of Cotton effects and shape of absorption bands is nowadays the standard procedure widely applied for determination of absolute configuration. Configuration of some chiral compounds can be however inferred only from signs of Cotton effects according to two types of semiempirical rules – sector rules and helicity (chirality) rules. The sector rules have been assigned to inherently achiral chromophores and based on three principal theories: the one-electron theory [13], the coupled oscillator theory [14], and the electromagnetic (coupling) theory [15]. The one-electron theory has been dedicated

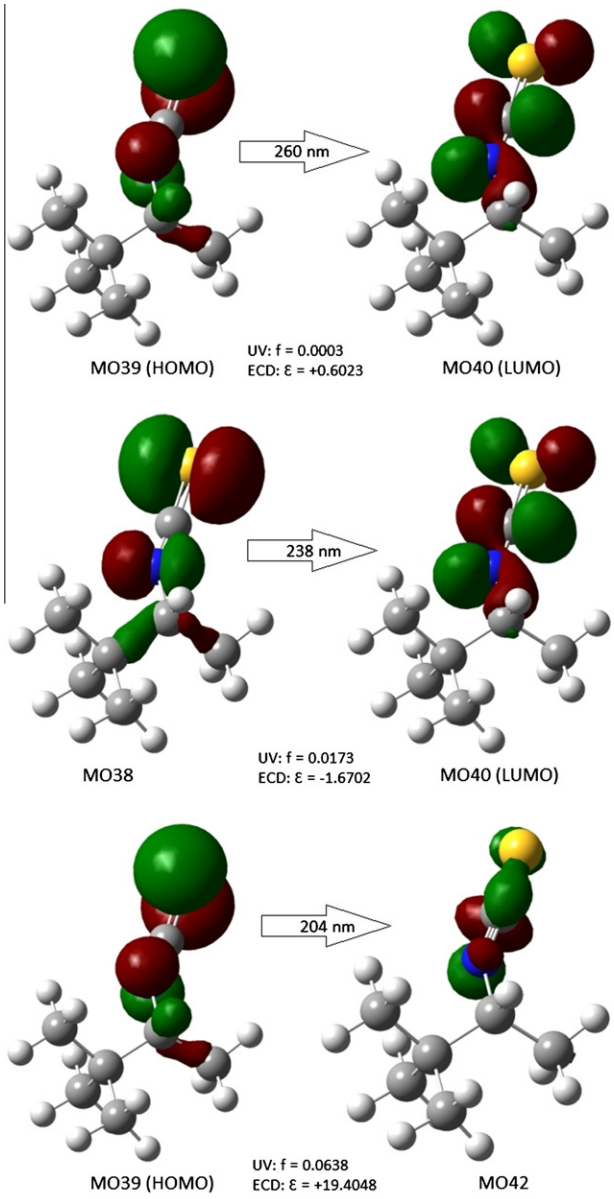


Fig. 2. Key molecular orbitals involved in transitions calculated for ECD spectrum of **1a**.

mainly to n–π^* transitions and stated the theoretical grounds for the *octant rule* that allows to correlate the absolute configuration of chiral ketones (including steroidal ketones) with measured CE signs [16]. Development of the sector rules led to *sector rule for alkenes* [17], *bifurcated sector rule for chiral allenes* [18], *quadrant rule* proposed for chiral benzylic alcohols [19], chiral benzylic derivatives (known as *Brewster-Buta/Smith-Fontana sector rule*) [20] and mandelic acid derivatives [21], *salicylideneamino chirality rule* designed for investigation of the absolute configuration of chiral, primary amines [22] and *benzoate sector rule* designated for determination of absolute configuration of chiral, cyclic secondary alcohols [23]. The coupled oscillator theory described the optical activity of chiral compounds bearing two or more achiral chromophores characterized by strong electric transition moments. The development of this theory in the case of two interacting chromophores furnished the *exciton splitting method* that allowed to easily deduce absolute configuration of a stereogenic center based on analysis of bisignate CE couplets [24].

Helicity rules have been established for inherently chiral chromophores that could be observed in unsaturated ketones, dienes, twisted alkenes, disulfides and helicenes. The most important semiempirical methods used for determination of absolute configuration are *β,γ-unsaturated ketone helicity rule* [25a] (that can be also applied for homoconjugated aldehydes and acid derivatives) and *diene helicity rule* [25].

In this paper we report results of our research on application of circular dichroism (CD) measurements to establishing absolute configuration of chiral isothiocyanates. The measurements were supported by TD DFT calculations of CD spectra.

2. Results and discussion

Our research has been divided into three parts – at the beginning we studied chirooptical properties of simple alkyl 2-isothiocyanates. Measurements of UV and ECD spectra were followed by conformational analysis of alkyl 2-isothiocyanates and calculation of their electronic spectra. The second step consisted of analysis of methyl 2-isothiocyanatocarboxylic esters bearing an additional chromophore attached to the stereogenic center. Simulated ECD spectra were compared with those obtained in the experimental way. Finally, our earlier observations and conclusions were verified using chiral esters of 2-isothiocyanatocarboxylic acids with enantiopure alcohols and diols. These compounds served as test samples.

Structure optimization of (3*R*)-3-isothiocyanato-2,2-dimethylbutane **1a** was performed using the density functional theory

Table 1
TD DFT conformational analysis of alkyl 2-isothiocyanates (**1a** and **2a**) and 2-isothiocyanatocarboxylates (**3a**–**5a**).

Compound	Conformer	Dihedral angles (°)					C—N—C angle (°)	ΔG (kJ/mol)	Population (%)
		dh1[a]	dh2[b]	dh3[c]	dh4[d]	dh5[e]			
1a	cf1	172	–	–	–	–	151		100
2a	cf1	−169	−171	–	–	–	150	0	61.2
	cf2	161	−61	–	–	–	149	2.696	20.6
	cf3	−167	−61	–	–	–	150	3.019	18.1
3a	cf1	−36	−158	−177	–	–	144	0	52.7
	cf2	−53	26	178	–	–	147	0.270	47.3
4a	cf1	−33	−157	−177	58	−56	145	0	73.3
	cf2	−34	−156	−177	75	53	144	2.505	26.7
5a	cf1	−23	−160	−177	60	178	144	0	67.3
	cf2	−33	30	178	61	−179	148	1.788	32.7

[a] C—N—C2—C3 (**1a** and **2a**), C—N—C2—C1 (**3a**, **4a**, and **5a**).
[b] N—C2—C3—C4 (**2a**), N—C2—C1—OMe (**3a**, **4a**, and **5a**).
[c] C2—C1—O—C.
[d] N—C2—C3—C4.
[e] C2—C3—C4—H (**4a**), C2—C3—C4—C5 (**5a**).

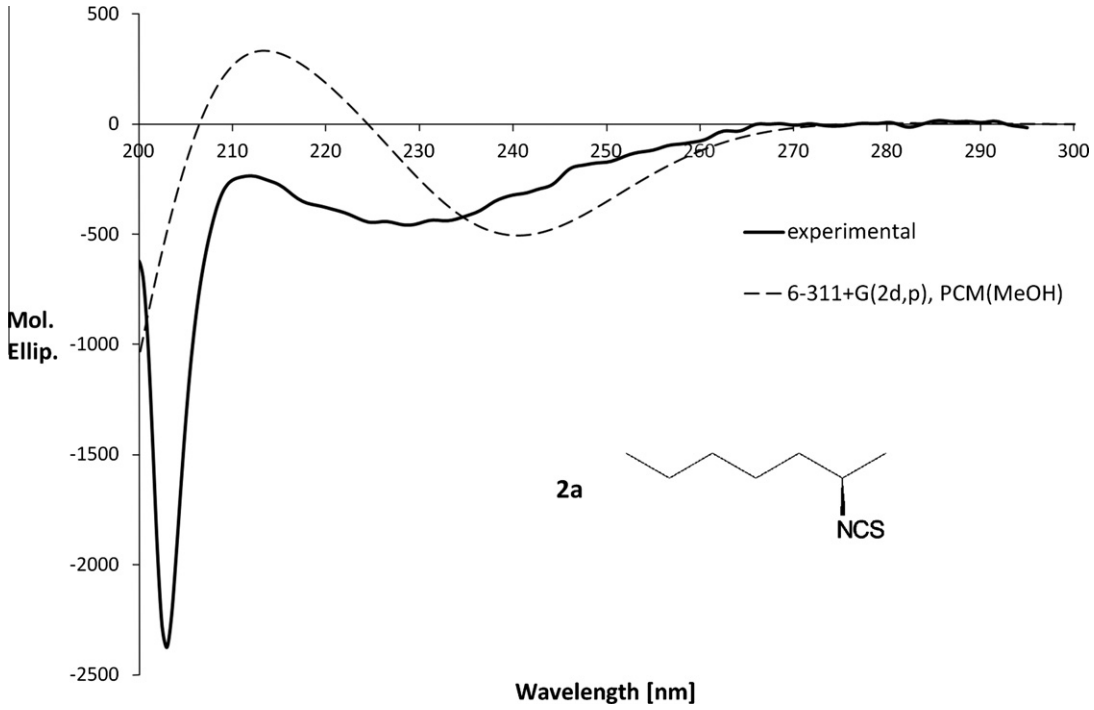


Fig. 3. Calculated and measured ECD spectra of (*2R*)-2-isothiocyanatoheptane **2a**.

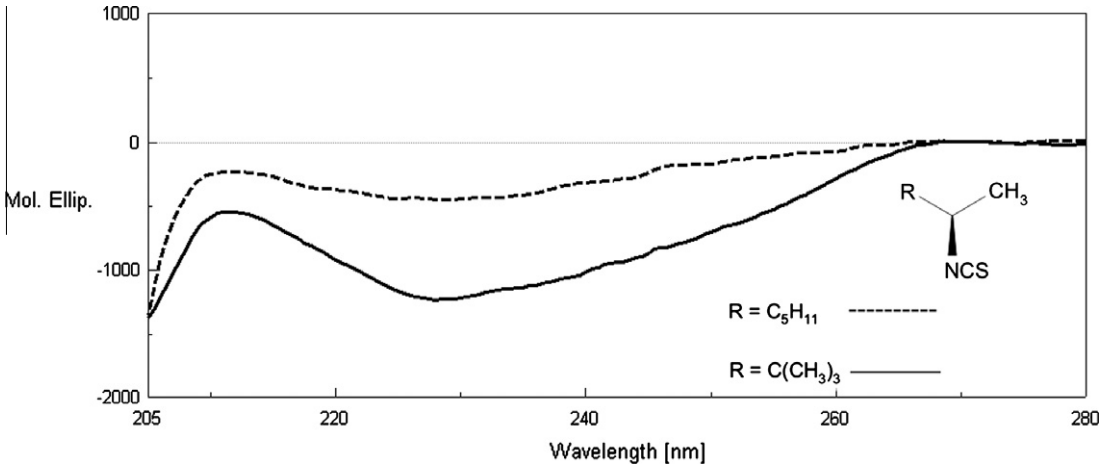


Fig. 4. Relationships between absolute configuration and signs of the Cotton effects observed for enantiopure alkyl 2-isothiocyanates.

(DFT) method at the B3LYP/6-311+G(2d,p) level. Calculations showed that there was only one conformer responsible for absorption in the UV range. Isothiocyanate group was bent and the calculated angle C2—N═C was 150°. Measured UV–VIS spectrum of **1a** showed an absorption band at λ_{max} = 244 nm assigned to the formally forbidden transition n–π* in the —NCS fragment of the alkyl isothiocyanate. The second absorption band correlated with a π–π* transition in the —NCS chromophore appeared below 195 nm, out of the range of recording (Fig. 1). Both calculated and measured absorption bands assigned to the n–π* transitions appeared in the range of 210–250 nm. Thus, we restrained the recording region and selected methanol as the most convenient solvent.

Calculated UV and ECD spectra using B3LYP/6-31+G(d), and B3LYP/6-311+G(2d,p) basis sets were in reasonable agreement with the experimental spectra of **1a** in terms of sign, range, and relative intensity (Fig. 1). However modeling a molecule in solution provided significantly improved results. We decided to use the polarized continuum (PCM) model. In this relatively simple method the solvent is considered as a continuum of uniform dielectric constant and the molecule is located in a cavity defined as the union of a series of interlocking atomic spheres. All further ECD simulations were done in the same method (B3LYP/6-311+G(2d,p), PCM/MeOH).

The first transition (HOMO → LUMO, n–π*) was forbidden and with oscillator strength *f* = 0.0003 was not visible in UV spectrum. However, this transition was detected in the ECD spectrum as a very weak, positive band located around 270 nm. Weak, negative CE observed at 228 nm was assigned to formally forbidden n–π* transition. This transition had much higher oscillator strength *f* = 0.0173 due to the same orientation in space and therefore better overlap of the both involved molecular orbitals (Fig. 2). In calculated spectrum this absorption band is centered at 238 nm. According to calculations a positive band assigned to higher transition

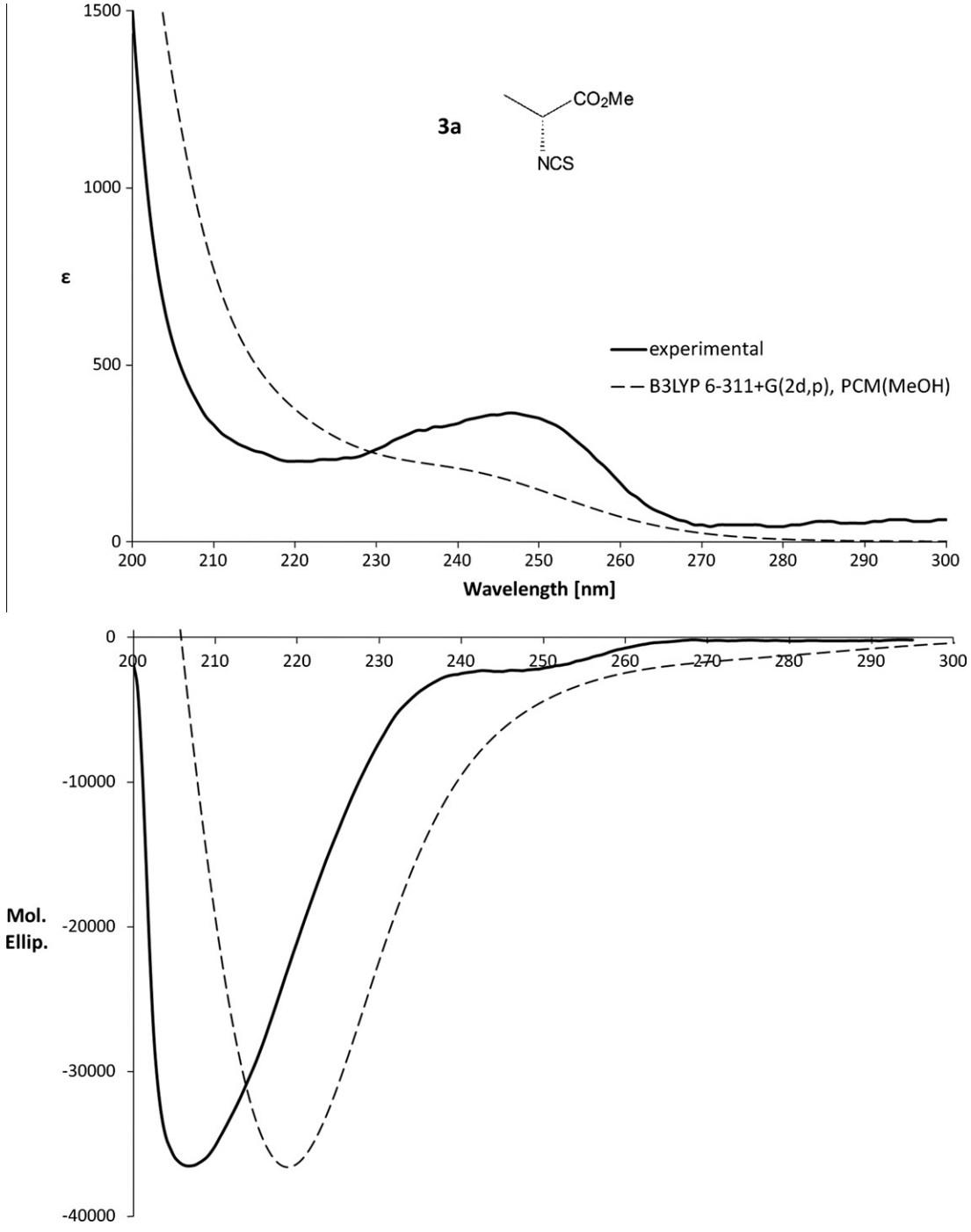


Fig. 5. Calculated and measured UV and ECD spectra of methyl (*2R*)-2-isothiocyanatopropanoate **3a**.

from the HOMO should be observed at 210 nm. In the experimental ECD spectrum this band is partially covered by strong negative signals at shorter wavelengths.

The bands correlated with π–π^* transitions of the —NCS group have not been observed in the experimental spectrum because they appeared out of a measuring range – calculations showed their position below 160 nm.

Conformational analysis of (*2R*)-2-isothiocyanatoheptane **2a** indicated a presence of three major conformers and their relative populations were summarized in Table 1. Similarly to **1a** the isothiocyanate moiety was bent giving the angle C2—N═C near 150°. The simulated spectrum was obtained as a weighted mean of all spectra calculated for examined conformers. Comparison of the recorded and calculated ECD spectra of the isothiocyanate **2a** showed a striking similarity. A weak, negative CE for n–π^* transition was observed at 229 nm whereas the simulated spectrum showed this absorption band at 239 nm. The most intensive negative Cotton effect assigned to the π–π^* transition of the —NCS group was calculated to appear at 185 nm, which is below the range of recording (Fig. 3).

These two examples have pointed out that a sign of the CE assigned to formally forbidden transition n–π^* in —NCS group at the stereogenic center C-2 can be correlated with the absolute configuration at this center. This is of importance in the case when the main absorption band of π–π^* transition in the —NCS substituent exceeds a lower limit of the recording. The experiment carried

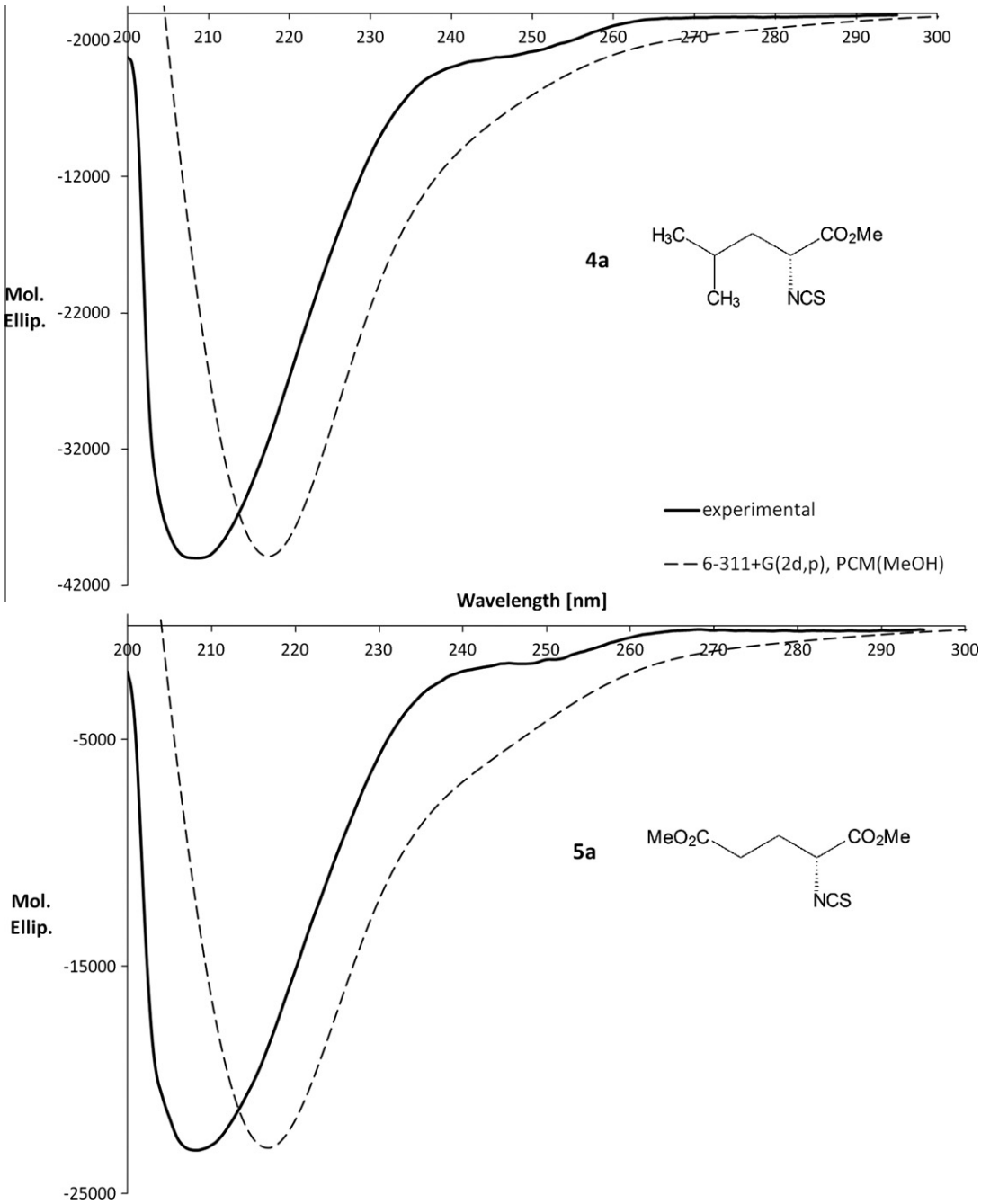


Fig. 6. Calculated and measured ECD spectra of chiral (*2R*)-2-isothiocyanatocarboxylates **4a** and **5a**.

out for simple alkyl isothiocyanates showed that the positive CE can be assigned to *S* enantiomers, whereas *R* enantiomers of alkyl isothiocyanates give the negative CE (Fig. 4). Our observations were consistent with those previously reported for chiral 1,2-diisothiocyanatocyclohexane [12]. The determined correlation remained unchangeable for measured samples in methanol and acetonitrile.

The next phase of our research included analysis of chirooptical behavior of methyl and ethyl 2-isothiocyanatocarboxylates. In comparison with 2-alkylisothiocyanates investigated earlier 2-isothiocyanatocarboxylates were more complex case for analysis. They have two chromophores bonded to the same stereogenic center and hence exhibit higher conformational diversity. Moreover interactions between both cottonogenic moieties are possible.

Methyl (*2R*)-2-isothiocyanatopropanoate **3a** obtained in two steps from unnatural D-alanine has been chosen as the simplest model of chiral 2-isothiocyanatoester. Conformational analysis of **3a** showed two major conformers with an equilibrium ratio 52.7:42.3 (Table 1). Calculation of UV–VIS spectrum of **3a** led us to results similar to the experimental data. ECD spectrum recorded for the methanolic solution of **3a** exhibited a strong negative CE at 206.5 nm and very weak negative CE at 245 nm. It corresponds to absorption bands – at 196 nm and at 250 nm – observed in UV–VIS spectrum of **3a**. The very weak, long-wave absorption is more likely assigned to n–π^* transitions in —NCS group. Simulations reproduced sign and shape of the both observed bands significantly shifted to shorter wavelengths (Fig. 5).

Methyl (*2R*)-2-isothiocyanato-4-methylpentanoate **4a** showed a strong negative CE at 208.5 nm and very weak negative CE at 244 nm (Fig. 6). Geometry optimization showed three conformers of **4a** with an equilibrium ratio 89.8:7.7:2.5 (Table 1). Simulated

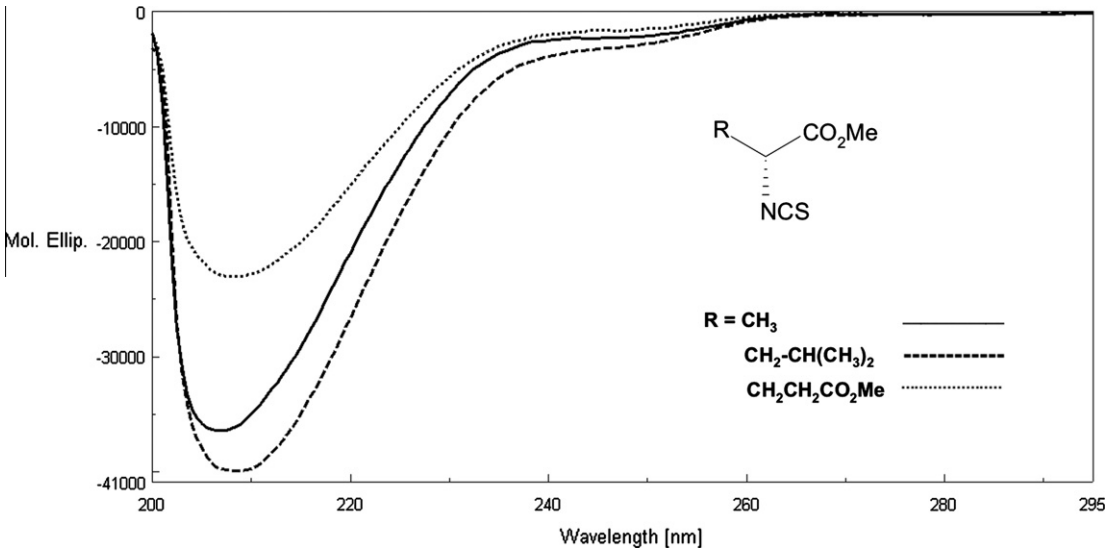


Fig. 7. Correlations of signs of the Cotton effects and absolute configurations observed for enantiopure methyl 2-isothiocyanatocarboxylates.

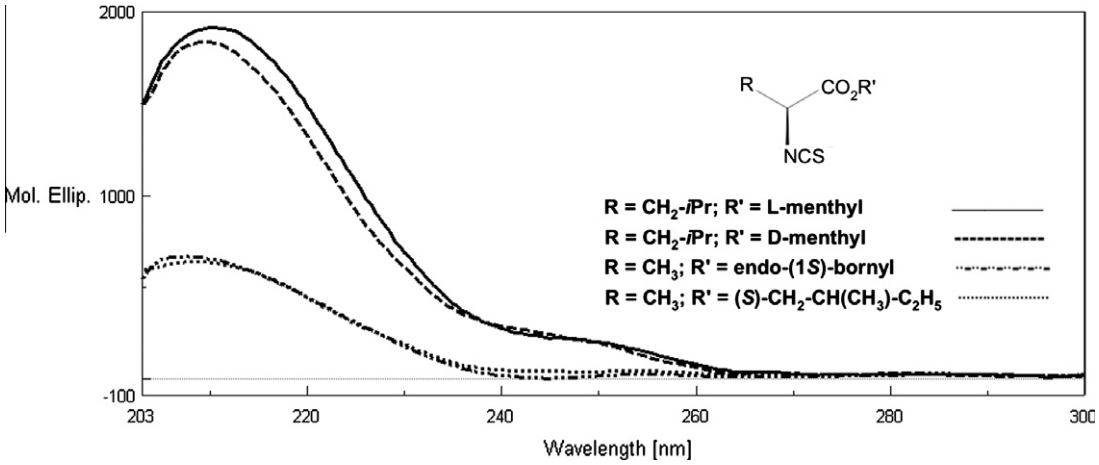


Fig. 8. CD spectra of chiral esters derived from (*2S*)-2-isothiocyanatocarboxylates. The configuration of an ester group does not have any effect on a sign of the CE.

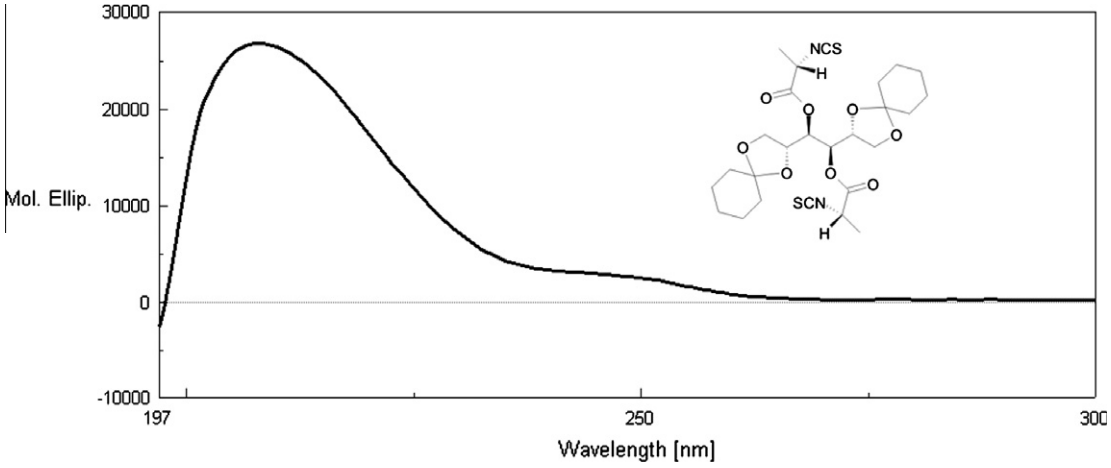


Fig. 9. CD spectrum measured for the chiral ester **10c** shows the correlation between sign of the CE and absolute configuration on C-2 of 2-isothiocyanatocarboxylic acid. The positive CE indicates *S* configuration at the C-2 stereogenic centers.

ECD spectrum of **4a** was very similar to the recorded one. Measurement of ECD spectra of dimethyl (*2R*)-2-isothiocyanatopentanedioate **5a** provided very similar results showing two negative Cotton effects at 208.5 and 244 nm. The calculated ECD spectrum of **5a** was nearly identical with the recorded spectrum (Fig. 6).

In general, the absolute configuration of chiral alkyl 2-isothiocyanatocarboxylic esters can be easily established based on a sign of the CE in the range of 205–210 nm. Similarly to the alkyl isothiocyanates investigated earlier, 2-isothiocyanatocarboxylates show strong negative CE for enantiomers *R* and the positive CE for their optical antipodes (Fig. 7).

The third step of our investigations consisted of the synthesis of some esters of enantiopure 2-isothiocyanatocarboxylic acids with chiral alcohols and diols. We intended to clarify if any chiral ester group could have an effect on a sign of the CE. Experiment that we have carried out allowed us to verify applicability and find limitations of the above-mentioned method. ECD spectra recorded for *endo*-(1*S*)-bornyl (*S*)-2-isothiocyanatopropanoate **6**, L-menthyl (*S*)-2-isothiocyanato-4-methylpentanoate **7**, D-mentyl (*S*)-2-isothiocyanato-4-methylpentanoate **8** and (2*S*)-2-methylbutyl (*2S*)-2-isothiocyanatopropanoate **9b** showed in the region 205–210 nm strong, positive CE (Fig. 8) indicating absolute configuration *S* at the stereogenic center C-2.

Chiral diester, 1,2,5,6-di-O-cyclohexylideno-D-mannitol-3,4-di-O-[(*2S*)-2-isothiocyanatopropanoate] **10c** gave the ECD spectrum with the positive CE at 207.6 nm confirming an absolute configuration *S* at the both stereogenic centers C-2 of 2-isothiocyanatopropanoate (Fig. 9).

3. Conclusion

Absolute configuration of chiral alkil isothiocyanates can be established by means of circular dichroism (CD) measurements. Analysis of the chirooptical properties of simple *R* and *S* alkyl isothiocyanates bearing –NCS group at the stereogenic center showed that a sign of the Cotton effect observed in the range of 220–230 nm depends on the absolute configuration at this center. Although this longer-wavelength absorption related to a forbidden n–π^* transition in the —NCS group is weak it could play an important role when other, stronger absorption bands cannot be observed. In particular, calculated ECD spectra with the TD DFT method show that the strong π–π^* absorption of the —NCS moiety can be usually observed below 190 nm – this short-wavelength range imposes essential limitations for solvents and measurement conditions. On the other hand chiral 2-isothiocyanatocarboxylic esters derived from α-amino acids show a strong absorption band over 200 nm assigned to n–π^* transition in the NCS chromophore. The sign of a Cotton effect observed near 210 nm is correlated with absolute configuration at C-2 and it is independent on the configuration of any chiral ester group. Circular dichroism spectra of methyl 2-isothiocyanatocarboxylic esters can be easily reproduced using TD DFT method at the B3LYP/6-311+G(2d,p) level with the PCM/methanol solvent model with very high accuracy.

4. Experimental

4.1. General methods

NMR spectra were recorded on a Bruker Avance II 300 MHz spectrometer (using TMS as an internal standard). IR spectra were measured using a FT-IR spectrometer Nicolet IR200 with a single-reflection ATR head. Microanalyses were carried out using CHNS Vario Micro-Cube analyzer and their results were in good agreement with the calculated values. Gas chromatography was performed using PerkinElmer Clarus 500 apparatus equipped with Elite-5MS capillary column. GC/MS analyses were carried out using Thermo Scientific ISQ Single Quadrupole GC–MS, equipped with Elite-5MS capillary column. Column chromatography was performed using commercial Merck silica gel 60 (230–400 mesh ASTM) and TLC analysis was carried out using Merck TLC silica gel 60 plates. Optical rotation measurements were performed using Jasco P-2000 polarimeter. Melting points were measured on an Electrothermal 9100 apparatus. CD and UV spectra were recorded using Jasco J-815 spectrometer with 10 mm (UV) and 2 mm (CD) path lengths. The sample concentrations (mmol/L) for CD measurements were as follows: 5.305 (**1a**), 3.319 (**2a**), 3.935 (**3a**), 4.866 (**4a**), 5.058 (**5a**), 4.112 (**6**), 12.20 (**7**), 5.650 (**8**), 4.570 (**9b**), 1.040 (**10c**).

4.2. Computations

All calculations were carried out with the GAUSSIAN 03W rev. E.01 program [26]. Conformational analysis of all studied compounds was performed with the use of B3LYP functional and 6-31+G(d) basis set. The final optimization of the conformers found was accomplished with B3LYP/6-311+G(2d,p) basis set for molecules in vacuo. Then Gibbs energies of the conformers were calculated using the same DFT level and polarized continuum (PCM) model for modeling of the solvent (methanol).

In order to eliminate known systematic errors in Gibbs energies a scaling factor (0.9877) was used for zero-point energies calculations [27]. ECD calculations were performed with the TD DFT method at B3LYP/6-311+G(2d,p) level with the PCM/methanol solvent model. The ECD spectra of all significant conformers were constructed from Gauss curves with the bandwidth 0.25 eV at 1/e peak height. The final simulated spectra were composed of appropriate spectra of conformers weighted according to their relative population.

4.3. Syntheses of enantiopure alkyl isothiocyanates and 2-isothiocyanatocarboxylic esters

(Tables 2 and 3).

4.3.1. (3R)-3-Isothiocyanato-2,2-dimethylbutane ***1a*** and (3S)-3-isothiocyanato-2,2-dimethylbutane ***1b***

(*3R*)-3-isothiocyanato-2,2-dimethylbutane **1a** and (*3S*)-3-isothiocyanato-2,2-dimethylbutane **1b** have been prepared according to the literature data [28,29].

4.3.2. Representative synthesis of (2R)-(-)-2-isothiocyanatoheptane ***2a***

A mixture of commercial (*2R*)-(-)-2-aminoheptane (0.431 g; 3.74 mmol), chloroform (40 mL), and water (30 mL) was treated with thiophosgene (0.31 mL; 0.467 g; 4.06 mmol) and sodium bicarbonate (0.691 g; 8.22 mmol). The resulting mixture was stirred for 2 h. Then the lower organic layer was separated and dried over Na_2SO_4. Next, the mixture was concentrated and crude oily product was purified using column chromatography (silica gel, cyclohexane – ethyl acetate 5:1) to give pure (*2R*)-(-)-2-isothiocyanatoheptane **2a** as a yellow oil possessing mushroom-like odor (0.505 g, 86%); $[\alpha]_D^{24} - 79.8^\circ$ (c 0.012 M in $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$): δ_H 0.91 (t, *J* 6.9 Hz, 3H), 1.30 (m, 4H), 1.34 (d, *J* 6.5 Hz, 3H), 1.57 (m, 4H,), 3.75 (ddq, *J* 6.4, 6.4 and 6.5 Hz, 1H) ppm; ^{13}C NMR (75 MHz, $CDCl_3$): δ_C 13.9, 21.8, 22.4, 25.7, 31.2, 37.5, 54.0, 129.7 ppm; Anal. Calcd. for $C_8H_{15}NS$: C, 61.09; H, 9.61; N, 8.91. Found: C, 61.00; H, 9.68; N, 8.83.

4.3.3. (2S)-(+)-2-isothiocyanatoheptane ***2b***

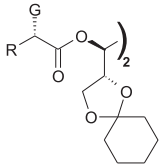
(*2S*)-(+)-2-isothiocyanatoheptane **2b** has been prepared analogously to the above-mentioned procedure. Column chromatography afforded pure **2b** as a yellow oil having disagreeable smell;

Table 2
Chiral alkyl isothiocyanates and 2-isothiocyanatocarboxylates – optical rotations and synthetic methods.

NCS R R'	R	R′	C-2 configuration	$[\alpha]_D$	Literature
1a	CH_3	^{tert}Bu	R	−36.6	[15]
1b	^{tert}Bu	CH_3	S	+36.9	[16]
2a	CH_3	$^{n}C_5H_{11}$	R	−79.8	–
2b	$^{n}C_5H_{11}$	CH_3	S	+80.9	–
3a	CH_3	CO_2Me	R	−23.9	[18]
3b	CO_2Me	CH_3	S	+23.4	[19]
4a	CH_2—^{i}Pr	CO_2Me	R	+17.9	–
4b	CO_2Me	CH_2—^{i}Pr	S	−18.0	[20]
5a	$CH_2CH_2CO_2Me$	CO_2Me	R	+18.7	–
5b	CO_2Me	$CH_2CH_2CO_2Me$	S	−18.8	[21]
6	CO_2-endo-(*1S*)-bornyl	CH_3	S	+168.0	–
7	CO_2-L-menthyl	CH_2—^{i}Pr	S	+92.1	–
8	CO_2-D-menthyl	CH_2—^{i}Pr	S	+204.0	–
9b	CO_2-(*2S*)-2-methylbutyl	CH_3	S	+17.8	–

Table 3
Chiral 1,2,5,6-di-O-cyclohexylideno-D-mannitol-3,4-O-diesters – configurations and optical rotations.

	R	G	C-2 configuration	$[\alpha]_D$
10a	CH_3	$NHCO_2{}^{tert}$Bu	S	+42.9
10b	CH_3	NH_3^+ Cl^-	S	+41.2
10c	CH_3	NCS	S	+41.2



(0.481 g, 82%); $[\alpha]_D{}^{24}$ + 80.9° (c 0.011 M in $CHCl_3$); Anal. Calcd. for $C_8H_{15}NS$: C, 61.09; H, 9.61; N, 8.91. Found: C, 61.15; H, 9.72; N, 8.92.

4.3.4. Methyl 2-isothiocyanatocarboxylic esters 3–5

Methyl 2-isothiocyanatocarboxylic esters 3–5 have been obtained from appropriate α-amino acid methyl esters in accordance with procedure described for **2a** [30].

*4.3.4.1. Methyl (2R)-(-)-2-isothiocyanatopropanoate **3a**.* [31], $[\alpha]_D$ − 23.9° (c 0.020 M in $CHCl_3$).

*4.3.4.2. Methyl (2S)-(+)-2-isothiocyanatopropanoate **3b**.* [32], $[\alpha]_D$ + 23.4° (c 0.022 M in $CHCl_3$).

*4.3.4.3. Methyl (2R)-(+)-2-isothiocyanato-4-methylpentanoate **4a**.* Methyl (*2R*)-(+)-2-isothiocyanato-4-methylpentanoate **4a** and dimethyl (*2R*)-(+)-2-isothiocyanato-pentanedioate **5a** have not been yet described in the literature. Both esters have been synthesized in accordance with the Floch method [30] and purified by vacuum distillation.

*4.3.4.4. Methyl (2S)-(-)-2-isothiocyanato-4-methylpentanoate **4b**.* [33], $[\alpha]_D$ − 18.0° (c 0.016 M in $CHCl_3$).

*4.3.4.5. Dimethyl (2S)-(-)-2-isothiocyanato pentanedioate **5b**.* [34]. $[\alpha]_D$ − 18.8° (c 0.010 M in $CHCl_3$).

*4.3.5. Representative synthesis of endo-(1S)-bornyl (2S)-2-isothiocyanatopropanoate **6***

A mixture of L-alanine *endo*-(1*S*)-bornyl ester hydrochloride (7.09 g; 27.1 mmol) [10], chloroform (60 mL), and water (40 mL) was treated with thiophosgene (2.10 mL; 3.17 g; 27.7 mmol) and sodium bicarbonate (6.83 g; 81.3 mmol). The resulting mixture was stirred vigorously until the orange solution turns pale yellow (40–70 min.). After the thiophosgene was consumed, the lower organic layer was separated and dried over $MgSO_4$. Next, the mixture was concentrated and crude oily product was purified using column chromatography (silica gel, cyclohexane – ethyl acetate 5:1) to give pure *endo*-(*1S*)-bornyl (*2S*)-2-isothiocyanatopropanoate **6**. Yellowish oil (1.050 g, 79%); $[\alpha]_D$ + 168.0° (c 0.12 M in acetone). IR (ATR): 2981, 2954, 2048, 1736, 1218 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$): δ_H 0.86 (s, 3H), 0.89 (s, 3H), 0.91 (s, 3H), 1.01 (m, 1H), 1.30 (m, 2H), 1.59 (d, *J* 7.1 Hz, 3H), 1.72 (m, 1H), 1.77 (m, 1H), 1.91 (m, 1H), 2.40 (m, 1H), 4.31 (q, *J* 7.1 Hz, 1H), 4.97 (m, 1H) ppm; ^{13}C NMR (75 MHz, $CDCl_3$): δ_C 13.5, 18.8, 19.5, 19.6, 27.1, 28.0, 36.7, 44.8, 48.0, 48.9, 55.0, 82.5, 137.5, 169.2 ppm; GC–MS (EI): *m/z* 267 (M^+), 181, 137, 136, 121, 95, 81; Anal. Calcd. for $C_{14}H_{21}NO_2S$: C, 62.88; H, 7.92; N, 5.24. Found: C, 62.95; H, 7.79; N, 5.30.

*4.3.6. (+) L-menthyl (2S)-2-isothiocyanato-4-methylpentanoate **7***

Ester has been prepared from L-leucine-L-menthyl ester hydrochloride [31] based on the described above protocol. Yellowish oil (0.972 g, 74%); $[\alpha]_D{}^{24}$ + 92.1° (c 0.12 M in acetone). IR (ATR): 2956, 2928, 2058, 1740, 1269 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$): δ_H 0.76 (d, *J* 7.0 Hz, 3H), 0.87 (m, 1H), 0.91 (d, *J* 7.0 Hz, 3H), 0.91 (d, *J* 6.5 Hz, 3H), 0.95 (d, *J* 6.5 Hz, 3H), 0.98 (d, *J* 6.4 Hz, 3H), 1.04 (m, 1H), 1.44 (m, 3H), 1.67 (m, 3H), 1.82 (m, 3H), 4.22 (q, 1H), 1.98 (m, 1H), 4.75 (dt, *J* 4.4 and 10.9 Hz, 1H) ppm; ^{13}C NMR (75 MHz, $CDCl_3$): δ_C 16.2, 20.7, 21.1, 21.9, 22.7, 23.3, 25.1, 26.2, 31.4, 34.1, 40.6, 42.0, 46.8, 58.2, 76.8, 136.9, 168.4 ppm; GC–MS (EI): *m/z* 311 (M^+), 183, 174, 139, 138, 97, 83; Anal. Calcd. for $C_{17}H_{29}NO_2S$: C, 65.56; H, 9.38; N, 4.50. Found: C, 65.65; H, 9.45; N, 4.61.

*4.3.7. (+) D-menthyl (2S)-2-isothiocyanato-4-methylpentanoate **8***

Ester has been prepared from L-leucine-D-menthyl ester hydrochloride [31].

Yellow oil (0.856 g, 81%); $[\alpha]_D{}^{24}$ + 204° (c 0.10 M in acetone); IR (ATR): 2959, 2931, 2118, 1736, 1276 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$): δ_H 0.75 (d, *J* 7.0 Hz, 3H), 0.87 (m, 1H), 0.91 (d, *J* 7.1 Hz, 3H), 0.91 (d, *J* 6.5 Hz, 3H), 0.94 (d, *J* 4.1 Hz, 3H), 0.95 (d, *J* 6.4 Hz, 3H), 1.08 (m, 1H), 1.46 (m, 3H), 1.68 (m, 3H), 1.86 (m, 3H), 2.04 (m, 1H), 4.22 (m, 1H), 4.74 (dt, *J* 4.4 and 10.9 Hz, 1H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ_C 16.1, 20.9, 21.3, 22.1, 22.9, 23.3, 25.3, 26.3, 31.6, 34.2, 40.7, 42.1, 47.0, 58.5, 76.7, 136.9, 168.6 ppm; Anal. Calcd. for $C_{17}H_{29}NO_2S$: C, 65.56; H, 9.38; N, 4.50. Found: C, 65.61; H, 9.26; N, 4.57.

4.3.8. Representative two-step synthesis of (2S)-2-methylbutyl (2S)-2-isothiocyanatopropanoate ***9b***

Representative two-step synthesis of (2*S*)-2-methylbutyl (2*S*)-2-isothiocyanatopropanoate **9b** via protected (2*S*)-2-methylbutyl (2*S*)-[(2-tert-butoxycarbonyl)amino] propanoate **9a**.

4.3.8.1. Synthesis of intermediate (2S)-2-methylbutyl (2S)-[(2-tert-butoxycarbonyl)amino] propanoate ***9a***. A 100 mL Erlenmeyer flask was charged with DCM (50 mL), N-Boc-L-AlaOH (2.00 g; 10.6 mmol) and DCC (2.18 g; 10.6 mmol). Reactants were stirred at room temperature for 30 min and (*2S*)-(-)-2-methyl-1-butanol (1.20 mL; 0.983 g; 11.1 mmol) and DMAP (0.123 g; 1.01 mmol) were added. The reaction mixture was stirred overnight and next evaporated under reduced pressure. The remainder was dissolved in ethyl acetate (80 mL), DCU was filtered off and the organic solution was washed with 5% HCl aq (36 mL) and brine (30 mL). Organic layer was dried using anhydrous $MgSO_4$. Evaporation of the solvent gave a crude product which was purified on column chromatography (SiO_2; eluent $CHCl_3$ – MeOH 30:1) to give pure **9a** as a colorless oil (1.96 g, 72%); $[\alpha]_D^{23} - 4.1°$ (c 0.011 M in $CHCl_3$). IR (ATR): 3361, 2967, 2935, 1712, 1248 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ_H 0.89 (t, *J* 7.4 Hz, 3H), 0.91 (d, *J* 6.8 Hz, 3H), 1.18 (m, 1H), 1.37 (d, *J* 7.2 Hz, 3H), 1.41 (m, 1H), 1.43 (s, 9H), 1.70 (m, 1H), 3.94 (dd, *J* 6.6 and 10.8 Hz, 1H), 3.98 (dd, *J* 6.1 and 10.8 Hz, 1H), 4.30 (m, 1H), 5.05 (br s, 1H) ppm; ^{13}C NMR (75 MHz, $CDCl_3$): δ_C 11.2, 16.3, 18.8, 25.9, 28.3, 34.1, 49.3, 69.8, 79.7, 155.1, 173.4 ppm; Anal. Calcd. for $C_{13}H_{25}NO_4$: C, 60.21; H, 9.72; N, 5.40. Found: C, 60.15; H, 9.75; N, 5.51.

4.3.8.2. Transformation of intermediate ***9a*** *to (2S)-2-methylbutyl (2S)-2-isothiocyanatopropanoate* ***9b***. Three-necked 100 mL flask equipped with argon inlet and protected from the moisture was placed on a magnetic stirrer and (2*S*)-2-methylbutyl (2*S*)-[(2-tert-butoxycarbonyl)amino] propanoate **9a** (1.76 g; 6.80 mmol) dissolved in DCM (55 mL) was added. Next TFA (12.4 mL; 19.03 g; 167 mmol) was added and the reaction mixture was stirred under argon at room temperature for 2.5 h. After the deprotection was completed, DCM and TFA were evaporated at 45 °C under reduced pressure and the residue was transferred into Erlenmeyer 250 mL flask and dissolved in $CHCl_3$ (40 mL). Next thiophosgene (0.52 mL; 0.786 g; 6.80 mmol) was added dropwise to the flask, sodium hydrogen carbonate (1.71 g; 20.4 mmol) and water (60 mL) were added and reactants were intensively stirred for 1 h. Lower organic layer was separated, dried with anhydrous $MgSO_4$ and solvent was evaporated giving a crude oily product. Purification was carried out by distillation under reduced pressure (124–126 °C at 9 mmHg) to furnish pure **9b** as the yellowish oil (0.750 g, 55%); $[\alpha]_D^{24} = +17.8°$ (c 0.003 M; $CHCl_3$); IR (ATR): 2964, 2935, 2878, 2059, 1743, 1458, 1379, 1289, 1198, 1149, 1054 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ_H 0.91 (t, *J* 7.4 Hz, 3H), 0.95 (d, *J* 6.8 Hz, 3H), 1.22 (m, 1H), 1.44 (m, 1H), 1.59 (d, *J* 7.1 Hz, 3H), 1.77 (m, 1H), 4.01 (dd, *J* 6.6 and 10.5 Hz, 1H), 4.08 (dd, *J* 5.94 and 10.5 Hz, 1H), 4.33 (q, *J* 7.1 Hz, 1H) ppm; ^{13}C NMR (75 MHz, $CDCl_3$): δ_C 11.1, 16.3, 19.5, 25.9, 34.0, 54.9, 70.9, 137.3, 169.0 ppm; GC–MS (EI): *m*/*z* 201 (M^+), 132, 86, 71; Anal. Calcd. for $C_9H_{15}NO_2S$: C, 53.70; H, 7.51; N, 6.96. Found: C, 53.78; H, 7.65; N, 7.05.

4.3.9. Three step synthesis of 1,2,5,6-di-O-cyclohexylideno-D-mannitol-3,4-di-O-[(2S)-2-isothiocyanatopropanoate] ***10c***

4.3.9.1. Preparation of 1,2,5,6-di-O-cyclohexylideno-D-mannitol-3,4-di-O-[(2S)-2-(N-tert-butyloxycarbonyl)aminopropanoate] ***10a***. Protected N-Boc L-alanine (2.270 g, 12 mmol) and DCC (2.47 g; 12 mmol) were dissolved in DCM (75 mL) at 0 °C. The reaction mixture was stirred at 0 °C for 30 min. and next 1,2;5,6-di-O-cyclohexylidene-D-mannitol [35] (1.71 g; 5.00 mmol) and DMAP (0.14 g) were added to the flask. An ice-bath was removed and reactants were stirred for 30 h at room temperature. Next the solvent was evaporated, ethyl acetate (75 mL) was added to the flask and precipitate DCU was separated by filtration. The filtrate containing diester was washed with 5% HCl (25 mL) and brine (20 mL), dried over Na_2SO_4 and evaporated. The crude product – 1,2,5,6-di-O-cyclohexylideno-D-mannitol-3,4-di-O-[(*2S*)-2-(N-*tert*-butyloxycarbonyl)aminopropanoate] – was purified on column chromatography (SiO_2; eluent: $CHCl_3$ – MeOH 10:1; R_f on TLC 0.88) to give pure diester **10a** (1.965 g, 57%); $[\alpha]_D^{23} + 42.9°$ (c 0.003 M in $CHCl_3$); ^1H NMR (300 MHz, $CDCl_3$): δ_H 1.38 (t, *J* 7.25 Hz, 6H), 1.43 (s, 18H), 4.19 (m, 2H), 4.32 (m, 2H), 5.30 (m, 2H) ppm; ^{13}C NMR (75 MHz, $CDCl_3$) δ_C 18.2, 23.7, 23.9, 25.1, 28.3, 34.6, 36.1, 49.3, 65.6, 72.5, 73.5, 79.9, 110.1, 155.2, 172.2 ppm; Anal. Calcd. for $C_{34}H_{56}N_2O_{12}$: C, 59.63; H, 8.24; N, 4.09. Found: C, 59.78; H, 8.45; N, 3.92.

4.3.9.2. Deprotection of diester ***10a*** *to (+) 1,2,5,6-di-O-cyclohexylideno-D-mannitol-3,4-di-O-[(2S)-2-aminopropanoate] dihydrochloride* ***10b***. Round-bottomed 100 mL flask placed on a magnetic stirrer and equipped with argon inlet was charged with 1,2,5,6-di-O-cyclohexylideno-D-mannitol-3,4-di-O-[(*2S*)-2-(N-*tert*-butyloxycarbonyl)aminopropanoate] **10a** (0.606 g; 0.885 mmol) and 4 N HCl in dioxane (20 mL). The reactants were stirred under argon at room temperature for 2 h and after the deprotection was completed, dioxane was evaporated under reduced pressure (temperature should not exceed 55 °C) and remainder was dried for 3 h over $CaCl_2$ at room temperature. Next anhydrous diethyl ether (5 mL) was added and the obtained suspension was cooled to −20 °C, filtered off and the solid product was dried under vacuum. The obtained 1,2,5,6-di-O-cyclohexylideno-D-mannitol-3,4-di-O-[(*2S*)-2-aminopropanoate] dihydrochloride **10b** (0.303 g, 61%) was pure enough to be transformed into 2-isothiocyanate ester **10c**; $[\alpha]_D^{23} + 41.2°$ (c 0.002 M in $CHCl_3$); ^1H NMR (300 MHz, $CDCl_3$): δ_H 1.44 (d, *J* 6.31 Hz, 6H), 1.74 (m, 4H), 1.51 (m, 16H), 3.73 (m, 2H), 3.97 (m, 2H), 4.10 (m, 2H), 4.27 (m, 2H), 5.36 (m, 2H) ppm; ^{13}C NMR (75 MHz, $CDCl_3$): δ_C 15.6, 23.5, 24.4, 26.3, 41.2, 47.9, 66.3, 69.2, 72.5, 109.1, 170.4 ppm; Anal. Calcd. for $C_{24}H_{42}Cl_2N_2O_8$: C, 51.71; H, 7.59; N, 5.02. Found: C, 51.48; H, 7.89; N, 4.88.

4.3.9.3. Synthesis of (+) 1,2,5,6-di-O-cyclohexylideno-D-mannitol-3,4-di-O-[(2S)-2-isothiocyanatopropanoate] ***10c***. A suspension of 1,2,5,6-di-O-cyclohexylideno-D-mannitol-3,4-di-O-[(*2S*)-2-aminopropanoate] dihydrochloride **10b** (0.226 g; 0.405 mmol) in chloroform (50 mL) was placed on a magnetic stirrer and cooled to −78 °C. Next thiophosgene (0.062 mL; 0.093 g; 0.81 mmol) was added in one batch and DIEA (0.42 mL; 0.314 g; 2.43 mmol) in chloroform (3 mL) was dropped to the solution. The reaction mixture was stirred for 5 min. at −78 °C and 60 min. at room temperature. Next the solvent was evaporated under reduced pressure (temperature should not exceed 40 °C) and oily product 8 was purified using column chromatography (SiO_2; eluent: $CHCl_3$ – MeOH 30:1; R_f on TLC: 0.48) to give 1,2,5,6-di-O-cyclohexylideno-D-mannitol-3,4-di-O-[(*2S*)-2-isothiocyanatopropanoate] **10c** as yellow oil (0.122 g, 54%); $[\alpha]_D^{25} + 41.2°$ (c 0.012 M in $CHCl_3$); ^1H NMR (300 MHz, $CDCl_3$): δ_H 1.58 (m, 20H), 1.62 (d, *J* 7.08 Hz, 6H), 3.84 (dd, *J* 5.6 and 8.4 Hz, 2H), 3.98 (dd, *J* 6.1 and 8.4 Hz, 2H), 4.16 (m, 2H), 4.38 (q, *J* 7.1 Hz, 2H), 5.37 (d, *J* 7.1 Hz, 2H) ppm; ^{13}C NMR (75 MHz, $CDCl_3$): δ_C 19.5, 23.7, 23.8, 25.0, 26.3, 34.6, 36.2, 54.8, 66.0, 73.3, 73.9, 110.4, 138.1, 167.8 ppm; Anal. Calcd. for $C_{26}H_{36}N_2O_8S_2$: C, 54.91; H, 6.38; N, 4.93. Found: C, 54.97; H, 6.30; N, 4.86.

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