# Synthesis of Diastereomeric Bicyclo[3.3.1]nonane Dibenzoyl Esters and Study of Their Chiroptical Properties

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ABSTRACT A synthesis of diastereomeric bicyclic dibenzoyl esters derived from enantiomerically pure (1S,5S)-bicyclo[3.3.1]nonane-2,6-dione was accomplished. Molecules containing two benzoyl chromophores with different configuration in the bicyclic framework were obtained. Chiroptical properties of the synthesized enantiomerically pure molecules were studied. Diastereomeric esters exhibited exciton couplets in the circular dichroism (CD) spectra because of transannular interaction between non-conjugated benzoate chromophores. The conformational effects and solvent impact on the exciton coupling were examined by CD spectroscopy. Theoretical computation of the CD spectra of diastereomers correctly reproduced the sign of the exciton couplets in the studied molecules, however, no major solvent dielectric constant influence and conformational effects *per se* on the exciton coupling was observed. *Chirality 00:000–000, 2012.* © 2012 Wiley Periodicals, Inc.

*KEY WORDS:* absolute configuration; CD spectroscopy; DFT calculations; exciton coupling; enantiospecific synthesis

#### **INTRODUCTION**

Chiral molecules having two chromophores with strong electric-dipole allowed transitions couple to each other through space (exciton coupling).<sup>1,2</sup> This phenomenon was intensively studied over the years by the circular dichroism (CD) spectroscopy, and many examples are available in the literature demonstrating employment of the exciton chirality method for stereochemical studies. It was used to set the absolute configuration<sup>3</sup> and to study solvent influence upon the intensity of the bands in the CD spectra.<sup>4</sup> CD spectroscopy is not only a tool for studying the absolute configuration of organic molecules but also provides means to examine interactions between chromophores. In majority of examples known in the literature, appropriate polychromophoric molecular structures were chosen to study the impact of the spatial orientation of chromophores, as well as the conformational and solvent effects, on the exciton coupling.

Because of a proper molecular geometry, bridged bicyclic compounds are suitable model structures for studying chiroptical properties and interaction between the non-conjugated chromophores.<sup>5–7</sup> Herein, we present the synthesis of chiral diastereomeric bicyclo[3.3.1]nonane dibenzoyl esters 3, 4, 9 and the respective monoesters 7 and 8 (Scheme 1), and a study of their CD spectra. The benzoate chromophores with an intense  $\pi$ - $\pi^*$  absorptions are classical excitons that give rise to a characteristic pair of CD bands with opposite signs originating from the <sup>1</sup>L<sub>a</sub> transitions. In addition, conformationally labile bicyclo [3.3.1] nonane framework that may adopt the chair-chair and chair-boat conformation provides a good model to study the contribution of conformers to the CD spectra<sup>8</sup> and, at the same time, more complicated picture of the exciton coupling. Recent advances on calculation of chiroptical properties have greatly enhanced its value in determining absolute configuration of chiral molecules. In particular, the time-dependent density functional theory (TDDFT)<sup>5</sup> has become an important tool in theoretical CD spectroscopy because of a reasonable balance between accuracy and computational efficiency. As the chiroptical properties of © 2012 Wiley Periodicals, Inc.

conformationally flexible molecules depend on the contribution of all the populated conformers, theoretical methods became indispensable tools for the elucidation of the conformational factors on the overall shape of the CD spectra.<sup>8</sup> Herein, conformational analysis of the diastereomeric dibenzoates **3**, **4**, and **9** was performed, and dependence of the CD spectra on the conformational ambiguity was studied by using TDDFT methodology.

#### MATERIALS AND METHODS Instrumentation

Proton and carbon nuclear magnetic resonance spectra were recorded in deuterated chloroform if not stated otherwise on a Varian Unity INOVA spectrometer (Varian, Palo Alto, CA, USA) at 300 MHz for protons and 75 MHz for carbon, and chemical shifts are reported in parts per million relative to tetramethylsilane as an internal standard. The CD and UV spectra were recorded with a JASCO J-815 spectrometer (Jasco, Tokyo, Japan) at  $20 \,^{\circ}$ C in a 0.1 cm cell. The stock solutions were prepared by weighting compound into volumetric flask and diluting with UV-grade solvents. The CD spectra were measured in millidegrees and normalized into  $\epsilon_{max}$  [lmol<sup>-1</sup> cm<sup>-1</sup>]/ $\lambda$ [nm] units. Optical rotations were measured on a KRÜSS P3001RS automatic digital polarimeter at 589 nm, and  $[\alpha]^{20}$  values are given in  $10^{-1} \deg \operatorname{cm}^{-1} \operatorname{g}^{-1}$ , and concentrations are given in units of g/100 cm<sup>3</sup>. IR spectra were recorded in KBr pellets on a PerkinElmer Spectrum BX spectrometer (PerkinElmer, Waltham, MA, USA). Elemental analysis was performed by the analytical laboratory of the Chemistry Faculty, Vilnius University. Thin-layer chromatography was carried out on Kieselgel 60 F254 (Merck) sheets coated with silica gel, and Kieselgel 60 silica gel (0.040-0.063 mm, Merck, Darmstadt, Germany) was used for column chromatography. Melting points were recorded with a Koefler melting apparatus and are not corrected.

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Scheme 1. Reagents: a) NaBH<sub>4</sub>, MeOH, 0 °C; b) PhCOCl, DIPEA, DMAP, DCM, 0 °C  $\rightarrow \Delta$ ; c) PhCO<sub>2</sub>H, Ph<sub>3</sub>P, DIAD, THF, 0  $\rightarrow 60$  °C; d) TsOH·H<sub>2</sub>O, acetone, 40 °C.

#### Synthesis

The synthesis of starting enantiomerically pure (+)-(1S,5S)-bicyclo [3.3.1]nonane-2,6-dione **1** and 6,6-ethylenedioxybicyclo[3.3.1]nonane-2-one **5** was performed following the procedures described earlier.<sup>9,10</sup> (+)-(1S,2R,5S,6R)-bicyclo[3.3.1]nonane-2,6-diol **2** and *endo*-2-ol **6** were prepared from the diketone **1** and monoprotected ketone **5**, respectively, by a reduction with sodium borohydride.

## Endo, Endo -(+)-(1S,2R,5S,6R)-bicyclo[3.3.1]nonane-2, 6-diol (2)

Sodium borohydride (375 mg, 9.87 mmol) was slowly added to a cooled  $0 \,^{\circ}$ C solution of 1 (500 mg, 3.29 mmol) in 20 ml of dry methanol. The reaction mixture was stirred for 2 h at  $0 \,^{\circ}$ C, then Celite was added and the mixture was evaporated to dryness. The residue was purified by column chromatography (eluent ethyl acetate) to yield 470 mg of 2 (92%).

[α]<sub>D</sub> = +59 (1.0, EtOH) (lit [α]<sub>D</sub> = +55 (1.0, EtOH)<sup>11</sup> and [α]<sub>D</sub> = +59.0 (0.77, EtOH)<sup>12</sup>); <sup>1</sup>H NMR (CD<sub>3</sub>OD): δ 3.81 (ddd, *J* = 12.3, 6.0, 4.8 Hz, 2H), 2.09 (dd, *J* = 12.3, 6.0 Hz, 2H), 1.88–1.73 (m, 4H), 1.72–1.39 (m, 6H). <sup>13</sup>C NMR (CD<sub>3</sub>OD): δ 73.1, 32.9, 32.1, 30.2, 22.5.

# (+)-(1S,2R,5S)-6,6-ethylenedioxybicyclo[3.3.1] nonane-2-ol (6)

The hydroxy monoacetal **6** was synthesized from acetal **5** by reduction with sodium borohydride using the same procedure as for diol **2**. The product was purified by column chromatography (eluent ethyl acetate and petroleum ether 1:2) to yield 89% of **6**.

 $[\alpha]_D$  = +42.1 (1.40, CHCl<sub>3</sub>); mp 75–77 °C; <sup>1</sup>H NMR:  $\delta$  3.97–3.81 (m, 5H), 2.06–1.47 (m, 12H).  $^{13}C$  NMR:  $\delta$  111.1, 72.9, 64.4, 64.3, 36.0, 34.0, 33.0, 31.1, 30.1, 24.7, 22.0. $^{13}$ 

### Endo, Endo (+)-(1S,2R,5S,6R)-bicyclo[3.3.1]nonane-2, 6-diyl dibenzoate (3)

A solution of **2** (100 mg, 0.641 mmol) and DMAP (10 mg, 0.082 mmol) in 5 ml of dry dichloromethane was cooled to 0 °C under an argon atmosphere. DIPEA (0.45 ml, 2.56 mmol) was added to the reaction mixture, followed by a slow addition of PhCOCI (0.30 ml, 2.56 mmol). The reaction mixture was stirred at room temperature for 1 h and then refluxed for 12 h. The reaction mixture was diluted with dichloromethane and washed with sat. NaHCO<sub>3</sub>, brine, dried over Na<sub>2</sub>SO<sub>4</sub> and filtered. Celite was added to the filtrate, and the mixture was evaporated to dryness. The residue was purified by column chromatography (eluent ethyl acetate and petroleum ether 1:20) to yield 128 mg of **3** (55%).

 $[\alpha]_{\rm D}$  = +89.8 (1.28, CHCl<sub>3</sub>); mp 60–61 °C; IR  $\nu_{\rm max}/{\rm cm}^{-1}$  2920, 1711, 1451, 1277, 711; <sup>1</sup>H NMR:  $\delta$  8.01–7.98 (m, 4H), 7.51–7.49 (m, 2H), 7.48–7.34 Chirality DOI 10.1002/chir

(m, 4H), 5.20 (ddd, J=11.2, 6.4, 4.9 Hz, 2 H), 2.20–1.57 (m, 8H), 1.77 (s, 2H), 1.62–1.57 (m, 2H). <sup>13</sup>C NMR:  $\delta$  166.0, 133.0, 130.9, 129.7, 128.5, 75.7, 32.3, 31.0, 27.9, 23.8; *Anal.* Calcd for C<sub>23</sub>H<sub>24</sub>O<sub>4</sub>: C 75.80; H 6.64. Found: C 75.67; H 6.73.

## Exo, Exo-(+)-(1S,2S,5S,6S)-bicyclo[3.3.1]nonane-2,6-diyl dibenzoate (4)

A solution of **2** (100 mg, 0.641 mmol), PhCO<sub>2</sub>H (626 mg, 5.13 mmol), and Ph<sub>3</sub>P (1.34 g, 5.13 mmol) in 10 ml of dry THF was cooled to 0 °C, and DIAD (1.0 ml, 5.13 mmol) was added under an argon atmosphere. The reaction mixture was stirred at room temperature for 1 h and then stirred in a closed vessel for 48 h at 60 °C under an argon atmosphere. Celite was added to the cooled reaction mixture and evaporated to dryness. The residue was purified by column chromatography (eluent ethyl acetate and petroleum ether 1:20) to yield 105 mg of **4** (45%).

$$\label{eq:alpha} \begin{split} & [\alpha]_D = +70.2 \ (0.57, CHCl_3); mp \ 114-115 \ ^\circ C; IR \ \nu_{max}/cm^{-1} \ 2927, 1708, 1450, \\ & 1277, \ 714; \ ^1H \ NMR; \ \delta \ 8.06-7.98 \ (m, \ 4H), \ 7.52-7.49 \ (m, \ 2H), \ 7.47-7.19 \\ & (m, \ 4H), \ 5.22-5.16 \ (m, \ 2H), \ 2.17-1.75 \ (m, \ 10H), \ 1.74-1.45 \ (m, \ 2H), \ ^{13}C \\ & NMR; \ \delta \ 165.9, \ 132.9, \ 131.1, \ 129.7, \ 128.5, \ 74.3, \ 35.5, \ 31.8, \ 26.4, \ 23.8; \ \textit{Anal.} \\ & Calcd \ for \ C_{23}H_{24}O_4; \ C \ 75.80; \ H \ 6.64. \ Found: \ C \ 75.79; \ H \ 6.69. \end{split}$$

## Exo-(+)-(1S,2S,5S)-6,6-ethylenedioxybicyclo[3.3.1] nonane-2-yl benzoate (7) and Endo-(+)-(1S,2R,5S)-6, 6-ethylenedioxybicyclo[3.3.1]nonane-2-yl benzoate (8)

The monoesters **7** and **8** were synthesized from monoacetal **6** following the same procedures described for diesters **3** and **4** earlier. The crude products were purified by column chromatography (eluent ethyl acetate and petroleum ether 1:10) to yield 78 and 74% of **7** and **8**, respectively.

**7**: [α]<sub>D</sub> = +34.6 (1.3, CHCl<sub>3</sub>); mp 81–83 °C; IR v<sub>max</sub>/cm<sup>-1</sup>2942, 1710, 1451, 1280, 1103, 721; UV (EtOH),  $\lambda_{max}$ , nm (ε·10<sup>-4</sup>, dm<sup>3</sup> mol<sup>-1</sup> cm<sup>-1</sup>): 230 (1.1), 273 (0.099), 280 (0.082). <sup>1</sup>H NMR: δ 8.08–8.05 (m, 2H), 7.59–7.53 (m, 1H), 7.47–7.42 (m, 2H), 5.16 (m, 1H), 4.02–3.87 (m, 4H), 2.11–1.78 (m, 13H). <sup>13</sup>C NMR: δ 165.9, 132.9, 129.7, 128.5, 110.9, 74.2, 64.5, 64.4, 36.5, 31.8, 31.5, 26.4, 26.2, 25.6, 22.1; *Anal.* Calcd for C<sub>18</sub>H<sub>22</sub>O<sub>4</sub>: C 71.50; H 7.33. Found: C 71.57; H 7.29.

**8**:[α]<sub>D</sub> = +32.5 (2.0, CHCl<sub>3</sub>); mp 62–64 °C; IR ν<sub>max</sub>/cm<sup>-1</sup> 2938, 1716, 1452, 1279, 1114, 713; UV (EtOH),  $\lambda_{max}$ , nm (ε·10<sup>-4</sup>, dm<sup>3</sup> mol<sup>-1</sup> cm<sup>-1</sup>): 229 (1.1), 273 (0.096), 280 (0.079). <sup>1</sup>H NMR: δ 8.07–8.04 (m, 2H), 7.58–7.52 (m, 1H), 7.46–7.41 (m, 2H), 5.20 (ddd, *J*=10.5, 6.5, 4.8 Hz, 1H), 4.02–3.87 (m, 4H), 2.12–1.61 (m, 13H). <sup>13</sup>C NMR: δ 166.0, 132.9, 130.9, 129.7, 128.4, 110.9, 75.8, 64.5, 64.4, 35.9, 33.0, 31.1, 30.9, 26.5, 24.5, 23.2; *Anal.* Calcd for C<sub>18</sub>H<sub>22</sub>O<sub>4</sub>: C 71.50; H 7.33. Found: C 71.54; H 7.45.

## Exo, Endo-(+)-(1S,2S,5S,6R)-bicyclo[3.3.1]nonane-2, 6-diyl dibenzoate (9)

A solution of **8** (53 mg, 0.175 mmol) and *p*-toluenesulfonic acid monohydrate (10 mg, 0.053 mmol) in 5 ml of acetone was stirred at 40 °C for 1 h. The reaction mixture was evaporated to dryness, dissolved in dichloromethane, washed with sat. NaHCO<sub>3</sub>, brine, dried over Na<sub>2</sub>SO<sub>4</sub>, filtered, and evaporated. The obtained residue was used without further purification and converted to the corresponding monobenzoate of **2** via reduction with sodium borohydride as described earlier for **2**. Purification by column chromatography (eluent ethyl acetate and petroleum ether 1:2) afforded 39 mg (86%) of the intermediate monobenzoate of bicyclo[3.3.1]nonane-2,6diol **2**. <sup>1</sup>H NMR:  $\delta$  8.07–8.04 (m, 2H), 7.58–7.53 (m, 1H), 7.45–7.41 (m, 2H), 5.22 (ddd, *J*=11.7, 6.8, 5.0 Hz, 1H), 3.93 (ddd, *J*=16.0, 6.0, 5.0 Hz, 1H), 2.18–1.53 (m, 12H). <sup>13</sup>C NMR:  $\delta$  166.1, 132.9, 130.9, 129.7, 128.4, 76.0, 72.9, 33.8, 32.5, 31.4, 31.0, 27.9, 23.9, 22.6.

The diester **9** was synthesized from bicyclo[3.3.1]nonane-2,6-diol monobenzoate following the same procedure as described earlier for diester **4**. The crude product was purified by column chromatography (eluent ethyl acetate and petroleum ether 1:20) to yield 30 mg (47%) of **9**.

 $[\alpha]_D$  = +3.7 (1.35, CHCl<sub>3</sub>); mp 118–119 °C; IR  $\nu_{max}/cm^{-1}$  2934, 1712, 1452, 1276, 1110, 718;  $^{1}H$  NMR:  $\delta$  8.14–8.09 (m, 4H), 7.63–7.57 (m, 2H), 7.52–7.45 (m, 4H), 5.33–5.28 (m, 2H), 2.32–1.45 (m, 12H).  $^{13}C$  NMR:  $\delta$  165.99, 165.85, 133.0, 132.9, 131.0, 130.8, 129.7, 129.0, 128.5, 75.7, 74.3, 31.3, 31.3, 27.8, 27.4, 26.7, 26.3, 21.3; Anal. Calcd for  $C_{23}H_{24}O_4$ : C 75.80; H 6.64. Found: C 75.89; H 6.76.

#### **Computational Details**

Conformational search of **3–4** and **9** was performed with SPARTAN'10<sup>14</sup> using Monte Carlo method and MMFF94 force field. The minimum energy conformers found by molecular mechanics have been further optimized using Gaussian software<sup>15</sup> at DFT/B3LYP/6-31G\* level, followed by calculations of their harmonic vibrational frequencies to verify their stability and to calculate conformational free energies; population percentages were calculated using  $\Delta G$  and applying Boltzmann statistics at T=298.15 K.

The electronic CD calculations of the conformers have been carried out by means of the Gaussian software<sup>15</sup> employing the TDDFT approach, the B3LYP functional and the 6-31G\* basis set. The rotational strength calculations have been carried out both in velocity  $(R_{vel})$  and length formalism  $(R_{len})$ ; the results in the two formalisms were almost identical. The CD spectra of the individual conformers were simulated by overlapping Gaussian functions for each transition<sup>16</sup> using SpecDis.<sup>17</sup> The half-width at 1/e of the peak maximum ( $\sigma$ ) value of 0.26 eV and  $R_{vel}$  was used in this work. The calculated spectra of 3-4 and 9 were Boltzmann averaged according to the population percentages of individual conformers and were red-shifted by 5 nm in relation to the experimental ones to match the experimental  $\lambda_{max}$ value of the long wavelength Cotton effect (CE). Additionally, for compound 3, the geometry of the conformers in ethanol solution was optimized using PCM model at B3LYP/6-31G\* level and electronic circular dichroism (ECD) spectra were calculated at the same level of theory. Boltzmann averaged ECD spectrum of 3 calculated at PCM/DFT/6-31G\* level was simulated using  $\sigma 0.26 \,\mathrm{eV}$ , and  $R_{\mathrm{vel}}$  and was not wavelength corrected.

## RESULTS AND DISCUSSION Synthesis

The (+)-(1S,5S)-bicyclo[3.3.1]nonane-2,6-dione **1** was obtained in an enantiomerically pure form by kinetic resolution of the corresponding racemic diketone by using Baker's yeast.<sup>9</sup> Synthesis of the respective monoprotected acetal 6,6-ethylenedioxybicyclo[3.3.1]nonane-2-one **5** was performed following the procedure described earlier.<sup>10</sup> The reduction of carbonyl groups in **1** as well as in **5** with sodium borohydride afforded exclusively *endo*-isomer as was proved for the racemic compound,<sup>18</sup> leading to *endo*, *endo*-(+)-(1S,2R,5S,6R)-2,6-diol **2** and *endo*-2-ol **6**, respectively.

Endo, endo-(+)-(1S,2R,5S,6R)-bicyclo[3.3.1]nonane-2,6-diyl dibenzoate 3 was obtained by a standard benzoylation procedure (Scheme 1). The inversion of the *endo* configuration of substituents in the bicyclo[3.3.1]nonane molecule has not been described previously to our knowledge. The exo, exodibenzoate 4 was synthesized from diol 2 by a Mitsunobu reaction with diisopropyl azodicarboxylate via adducts with triphenylphosphine and inversion of the configuration. The <sup>1</sup>H NMR spectrum of dibenzoate **3** is in correspondence with the  $C_2$  symmetry and resonance signal of the  $C_{2,6}$  exo-protons appears as doublet of doublet of doublets at 5.20 ppm with large spin-spin coupling constants to protons at  $C_{3,7}$  and  $C_{1,5}$ (11.2, 6.4 and 4.9 Hz, respectively). For a comparison, in the <sup>1</sup>H NMR spectrum of 4, the resonance signal of protons adjacent to the benzoyl group appears as a broad unresolved multiplet, and small coupling constants of the endo-proton are characteristic to this configuration.

Synthesis of the *endo*, *exo*-diester **9** involved the reduction of monoacetal **5** with NaBH<sub>4</sub>, followed by selective benzoylation of the intermediate *endo*-alcohol **6** under Mitsunobu or standard conditions to give the corresponding *exo*-monobenzoates and *endo*-monobenzoates **7** and **8**, respectively. Subsequent deprotection of the *endo*-monobenzoate **8** with p-TsOH in acetone afforded the corresponding carbonyl derivative, the reduction of which followed by Mitsunobu reaction yielded *endo*, *exo*-dibenzoate **9** (Scheme 1).

This molecule is not of  $C_2$  symmetry what is well seen from the signals of protons adjacent to the benzoyl group in the <sup>1</sup>H NMR spectrum. Two sets of signals correspond to the *exo*protons and *endo*-protons at the C<sub>2</sub> and C<sub>6</sub> bearing benzoyl groups.

# Conformational Analysis, CD Spectra and Theoretical Computations

The benzoate chromophores with intense  $\pi$ - $\pi^*$  absorptions are well-studied excitons that give rise to a characteristic pair of CD bands with opposite signs originating from the  ${}^{1}L_{a}$ transitions. In the synthesized diastereomeric esters, these chromophores have different stereochemical orientation in a conformationally labile bicyclo[3.3.1]nonane molecule. The bicyclic framework may adopt the chair-chair and chair-boat conformations, thus giving a good model of the contribution of all conformers to the CD spectra and, at the same time, more complicated picture of the exciton coupling.

We performed lowest energy conformational search of **3**, **4**, and **9** with SPARTAN'10 using Monte Carlo method and MMFF94 force field. Three or four low-energy conformers within 1 kcal/mol energy window were located in each case and were further optimized using Gaussian and the DFT/B3LYP/6-31G\* method. The relative free energies and populations of conformers are listed in Table 1.

In general, for all diastereomeric dibenzoates MMFF94 calculations predict three (four in the case of 9) stable chair-chair conformations, whereas corresponding chair-boat conformers are much higher in energy (5.97, 3.89 and 4.14 kcal/mol for 3, 4, and 9, respectively) and thus insignificantly populated. The benzoate moieties adopt conformation typical for alkyl benzoates,8 that is, s-trans conformation around the benzoate (O)C-O bond with the ester carbonyl group syn with respect to bicyclic methine  $H-C_{2.6}$  hydrogens. At the B3LYP/6-31G\* level, low-energy chair-chair conformers of 3, 4, and 9 are comparably populated and differ principally with regard to the conformation around HC<sub>2,6</sub>-O bond, as expressed by a torsion angle (O)C–O–C–H (Table 1). For 3,  $C_1$  symmetric conformer (a) with the negative and positive torsion angles (O)C-O-C-H was found to be the most stable, whereas the two less stable  $C_2$  symmetric conformers (b) and (c) were found to be almost equally populated. In the case of **4**, the  $C_2$  and  $C_1$  symmetric conformers (**a**) and (b) were found to be quite close in energy and both significantly populated. Conformer (a) with both positive torsion angles (O)C-O-C-H was found to be the most stable in the case of endo, exo-diastereomer 9, whereas the least stable conformers (c) and (d) were characterized by the negative/ positive and positive/negative torsion angles (O)C-O-C-H of the benzoate moieties, respectively. The notation of conformers of the diesters **3–4** and **9** is presented in Figure 1.

In the experimental CD spectra of the dibenzoates 3, 4, and 9, the exciton couplet located at the chromophore  ${}^{1}L_{a}$ transition wavelength near 230 nm was observed. In concordance with the exciton-type coupling, the strong absorption maxima at the same wavelength are observed in the UV spectra. For diendo and diexo benzoates 3 and 4, the positive intense exciton couplet due to coupling between the two  ${}^{1}L_{a}$ transitions was observed, whereas the endo, exo-benzoate 9 exhibited couplet of the opposite sign and virtually the same intensity. Unequivocally, the exciton through-space coupling was confirmed by a comparison with the respective mono

Ester	Conformer (symmetry)	ΔG, kcal/mol	Population, %	Torsion angle (O)C–O–C–H, (°)	Angle between transition moments, (°)
Diendo- <b>3</b>	a (C <sub>1</sub> )	0.00	52.8	-31.3, 32.3	73.3
	b (C <sub>2</sub> )	0.43	25.7	-32.7	46.6
	c (C <sub>2</sub> )	0.53	21.5	30.9	86.2
Diexo- <b>4</b>	a (C <sub>2</sub> )	0.00	46.1	-36.4	37.7
	b (C <sub>1</sub> )	0.18	33.9	32.2, -35.2	63.8
	c (C <sub>2</sub> )	0.49	20.0	34.6	79.3
Endo,exo-9	a (C <sub>1</sub> )	0.00	39.3	34.2, 34.3	-68.6
	b (C <sub>1</sub> )	0.32	22.8	-32.3, -34.6	-107.5
	c (C <sub>1</sub> )	0.41	19.7	-32.7, 33.9	-91.5
	d (C <sub>1</sub> )	0.45	18.2	34.9, -33.9	-93.7

TABLE 1. Relative free energies, populations, symmetries, and torsion angles for low-energy conformers of 3, 4, and 9, calculated at the B3LYP/6-31G\* level



Fig. 1. Geometry of low-energy conformers of 3-4 and 9 calculated at the B3LYP/6-31G\* level (H atoms omitted for clarity).

congeners **7** and **8**, the CD spectra of which were of a very low intensity (Fig. 2).

The sign of the exciton coupling observed in the CD spectra is in accordance with the orientation of the chromophores (Fig. 1), that is, all conformers of **3** (or **4**) are characterized by a positive helicity of the interacting transition electric dipole moments, which are polarized along the axis of the benzoate chromophore, almost parallel to the C–O bond of the respective hydroxyl compound. Analogously, for all the conformers of *endo, exo*-benzoate **9** negative twist defined by interacting transition moments is in agreement with the observed negative couplet in the CD spectrum.

The solvent effect (solvatochromism) on the CD spectra of the dibenzoates **3**, **4**, and **9** was also studied. The CD spectra were recorded in solvents of different polarity—ethanol, dichloromethane, cyclohexane, 2,2,2-trifluoroethanol, however, no significant effect on the intensity and position of the respective CEs was observed (Table 2). This indicates that the dielectric constant of media has no major effect on the conformational distribution (Table 1) or conformers exhibit very similar CD spectra in terms of intensity and position.

The experimental spectrum is the weighted-average spectrum of the respective conformers, thus the theoretical computation of the CD spectra of the individual conformers was performed.

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The electronic excitation energies and rotational strengths in the gas phase have been calculated for the conformers of diesters **3**, **4**, and **9** using TDDFT with the 6-31G\* basis set and the B3LYP model. The calculated rotatory strengths ( $R_{vel}$ ) were simulated into the CD curves assuming a Gaussian band shape with a half-width at 1/e of the peak maximum ( $\sigma$ ) value of 0.26 eV, approximately matching the broadening of the CD bands in the experimental spectra. For a comparison with the experimental CD data, the spectra of individual conformers calculated at B3LYP/6-31G\*//B3LYP/6-31G\* level were redshifted to match the experimental  $\lambda_{max}$  value of the long wavelength CE and are presented in Figures 3–5.

The predicted spectra for the individual conformers of diesters **3** and **4** were very similar regarding the pattern, absolute and relative intensity of the Cotton effects. In each case, a strong positive couplet due to exciton coupling between  ${}^{1}L_{a}$ transitions was predicted (Figs. 3 and 4). Theoretical calculations<sup>19</sup> have shown that the intensity of the split Cotton effect for the vicinal dibenzoates is maximal at a dihedral angle of ca. 70° and is inversely proportional to the square of the interchromophoric distance. As the difference of the latter for conformers of the same diasteromeric ester **3** (or **4**) is negligible,



Fig. 2. CD spectra of 3 (—), 4 (– –), 7 (–…–.), 8 (–…–.), and 9 (…) and representative UV spectra of 3 (—) and 8 (–…–.).

TABLE 2. The CD and UV spectral data for compounds 3, 4, and 7-9

Compound	Solvent	UV, $\lambda_{max}$ , nm ( $\epsilon$ ·10 <sup>-4</sup> , dm <sup>3</sup> mol <sup>-1</sup> cm <sup>-1</sup> )	CD, $\lambda_{\text{max}}$ , nm ( $\Delta \varepsilon$ , dm <sup>3</sup> mol <sup>-1</sup> cm <sup>-1</sup> )
Diendo- <b>3</b>	CH <sub>3</sub> CH <sub>2</sub> OH	230 (2.2), 273 (0.16), 280 (0.13)	222 (-6.0), 237 (+14.2)
Diendo- <b>3</b>	$CH_2Cl_2$	230 (2.6), 273 (0.21), 280 (0.17)	222 (-5.3), 236 (+16.6)
Diendo- <b>3</b>	Cyclo-C <sub>6</sub> H <sub>12</sub>	228 (2.2), 272 (0.17), 280 (0.14)	222 (-3.6), 233 (+14.6), 236 (+13.9)
Diendo- <b>3</b>	CF <sub>3</sub> CH <sub>2</sub> OH	230 (2.7), 270 (0.029)	221 (-7.5), 238 (+20.0)
Diexo-4	CH <sub>3</sub> CH <sub>2</sub> OH	230 (2.1), 273 (0.15), 280 (0.12)	221 (-4.5), 235 (+12.7),
Diexo-4	CH <sub>2</sub> Cl <sub>2</sub>	230 (2.4), 273 (0.20), 280 (0.17)	221 (-2.2), 236 (+14.5)
Diexo-4	Cyclo-C <sub>6</sub> H <sub>12</sub>	228 (2.5), 272 (0.19), 280 (0.15)	221 (-2.6), 233 (+15.7), 235 (+15.6)
Diexo-4	CF <sub>3</sub> CH <sub>2</sub> OH	231 (2.6), 271 (0.050), 281 (0.0072)	221 (-6.7), 238 (+18.2)
Exo,endo-9	CH <sub>3</sub> CH <sub>2</sub> OH	230 (2.2), 273 (0.19), 280 (0.16)	221 (+5.7), 236 (-11.0), 238 (-11.3)
Exo,endo-9	$CH_2Cl_2$	230 (2.4), 273 (0.20), 280 (0.16)	220 (+5.8), 222 (+5.7), 235 (-11.9), 237 (-11.9)
Exo,endo-9	Cyclo-C <sub>6</sub> H <sub>12</sub>	229 (2.7), 273 (0.24), 280 (0.21)	220 (+6.9), 233 (-12.3), 237 (-12.7)
Exo,endo-9	CF <sub>3</sub> CH <sub>2</sub> OH	231 (2.4), 270 (0.011)	221 (+6.1), 237 (-14.3)



**Fig. 3.** Top panel: CD spectra for individual conformers of **3** (**a**, - -; **b**, --; **c**, ----), calculated at B3LYP/6-31G\* level; bottom panel: Boltzmann averaged CD spectrum of **3** calculated at B3LYP/6-31G\* (----) and PCM/B3LYP/6-31G\* (---) levels; experimental CD spectrum of **3** (---) in ethanol. All spectra calculated at B3LYP/6-31G\* level were wavelength corrected.



Fig. 4. Top panel: CD spectra for individual conformers of 4 (a, ---; b -; c, --; b, calculated at B3LYP/631G\* level; bottom panel: Boltzmann averaged CD spectrum of 4 calculated at B3LYP/631G\* level and experimental CD spectrum of 4 (--) in ethanol. All calculated spectra were wavelength corrected.



**Fig. 5.** Top panel: CD spectra for individual conformers of **9** (a, —; b, …; c – –; d, –··-;), calculated at B3LYP/631G\* level; bottom panel: Boltzmann averaged CD spectrum of **9**, calculated at B3LYP/631G\* level and experimental CD spectrum of **9** (—) in ethanol. All calculated spectra were wavelength corrected.

the calculated amplitude of the exciton couplets correlates with the calculated angle between the corresponding transition moments (Table 1) in the dichromophoric molecules. Thus, in the case of **3**, the most intense exciton couplets (A = +50.5and 43.8) are predicted for the conformers (**c**) and (**a**), for which the calculated distances and angles between transition moments are  $0.979 \text{ nm}/86.2^{\circ}$  and  $0.983 \text{ nm}/73.3^{\circ}$ , respectively. In comparison, for conformer (**b**), where the angle and distance between transition moments are  $46.6^{\circ}$  and 0.998 nm, respectively, substantially smaller exciton coupling amplitude (+35.7) is predicted. The calculated intensity of the exciton couplets A = +26.4, 38.5, and 48.5, respectively for the conformers **a**-**c** of dibenzoate **4** follows the same trend (calculated distances between transition moments are 1.015, 0.989, and 0.963 nm, respectively; for angles between transitions, see Table 1).

Analogously, strong negative exciton couplets were predicted for all conformers of *endo*, *exo*-diasteromer **9** (Fig. 5).

Qualitatively, CD spectra of **3–4** and **9**, averaged on the basis of the Boltzmann population of the respective conformers, are in a good agreement with the experimental data, that is, the sign of the exciton couplet and relative intensity of the corresponding CEs are correctly reproduced. B3LYP/ 6-31G\* calculations predict small rotational strengths at *Chirality* DOI 10.1002/chir

250–260 nm corresponding to  ${}^{1}L_{b}$  transition of the benzoate chromophore, resulting in a net weak long-wavelength region CE in the Boltzmann-averaged CD of **3–4** and **9**. This is in accordance with the experimentally observed small CEs for benzoate  ${}^{1}L_{b}$  transition in these esters. The CD spectra of **3–4** and **9**, calculated using semi-empirical ZINDO/S method, were in much worse agreement with the experimental data.<sup>20</sup> Although the sign of the exciton couplets was correctly reproduced, the respective CEs were substantially (ca. 20 nm) blue-shifted; in addition, long-wavelength region CEs of comparable intensity corresponding to the benzoate chromophore  ${}^{1}L_{b}$  transition were also predicted.

Molecular orbital analysis of investigated diastereomeric esters allows us to confirm that the coupling mechanism between two benzoate chromophores is mainly excitonic. The exciton couplet in the calculated CD spectra of diastereomeric benzoates 3-4 and 9 originates from the two intense, close-lying transitions with opposite signs of the rotational strengths. Analysis of Kohn-Sham molecular orbitals (MO) revealed that single-electron excitations from highest occupied molecular orbital (HOMO) and occupied MOs HOMO-3, HOMO-2, HOMO-1 to lowest unoccupied molecular orbital (LUMO) and LUMO +1 contribute to the two absorption bands of the exciton couplet. For instance, for the most stable conformer of endo, endo-diastereomer 3, the electronic excitations MO 95  $\rightarrow$  MO 98 and MO 94  $\rightarrow$  MO 99, polarized parallel to the long axis of the benzoate chromophore, play a dominant role (contribution 42.4 and 19.9%) in the positive rotatory strength located at 225.5 nm ( $R_{\rm vel}$  = 346·10<sup>-40</sup> cgs). Contribution of the other single-electron excitations MO 96  $\rightarrow$  MO 99 and MO 97  $\rightarrow$  MO 98 to the positive rotatory strength at 225.5 nm is 7 and 6.2%, respectively. The negative transition of the exciton couplet is located at 223.9 nm ( $R_{vel} = -308 \cdot 10^{-40} \text{ cgs}$ ), and the contributions in terms of one-electron excitations are MO 94  $\rightarrow$  MO 99 (41.3%), MO 95  $\rightarrow$  MO 98 (22.6%), MO 96  $\rightarrow$  MO 99 (13.8%), and MO 97  $\rightarrow$  MO 98 (7.1%). The molecular orbitals involved in the key transitions in the calculated CD for the conformer (a) of dibenzoate 3 are shown in Figure 6.

In general, the excitation energies calculated at B3LYP/ 6-31G\* level were consistently underestimated in comparison with the experimental spectra. The blue shift of the calculated CD spectra relative to the experimental ones is not uncommon<sup>21,22</sup> and can be as a result of the errors in the density functional and the neglect of solvent and vibrational effects. Conformers of 3 were reoptimized with the use of the Polarizable Continuum Model (PCM) of solvent (ethanol) in conjunction with B3LYP/6-31G\*, followed by calculations of CD spectra at the PCM/B3LYP/6-31G\* level of theory. The respective structures reoptimized at the PCM/DFT/6-31G\* level were similar to those obtained with the use of B3LYP/ 6-31G\* method, except for small changes in the bond lengths and values of (O)C-O-C-H torsion angles; the computed relative populations of the conformers (79.1, 10.7, and 10.2% for conformers a, b, and c, respectively; cf. Table 1) were affected to a small extent. Analogously to the calculations in vacuum, PCM/B3LYP/6-31G\* predicts intensive positive exciton couplets for all the conformers of 3. The position of the CEs in the Boltzmann-averaged CD spectrum of 3 is in excellent agreement with the experimentally observed ones (Fig. 3). The use of the PCM model, however, required substantially larger computational costs; thus, gas-phase calculations at B3LYP/6-31G\* level, which provide acceptable compromise Chirality DOI 10.1002/chir



**Fig. 6.** Molecular orbitals involved in key transitions in the calculated CD for the conformer **(a)** of dibenzoate **3** at B3LYP/6-31G\* level.

between the accuracy and the computational costs, were used for qualitative analysis of the CD spectra.

#### CONCLUSIONS

Synthesis of diastereomeric bicyclo[3.3.1]nonane dibenzoyl esters derived from enantiomerically pure (1S,5S)-2,6-dione was accomplished, and molecules containing two identical chromophores with different spatial arrangement in the bicyclic ring system were obtained. CD spectra of the synthesized chiral structures were studied. The exciton coupling was observed in the CD spectra regardless of the orientation of the chromophores in dichromophoric molecules. The conformational effects and solvent impact on the interaction of the chromophores were examined by CD spectroscopy. TDDFT calculated CD spectra of diastereomers were in a good agreement with the experimental data, though showing no major conformational effect on the exciton coupling. In addition, the solvent did not affect the conformational distribution significantly and had negligible effect on the CD spectra.

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