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Chiral bicyclic keto lactones: determination of the absolute configuration by the study of chiroptical properties and chemical correlation

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Abstract—Chiral bifunctional oxabicyclodecanediones (keto lactones) were synthesized from the corresponding bicyclo[3.3.1]nonane diones **1**–**5** by employing a regioselective Baeyer–Villiger oxidation. Enantiomers with high enantiomeric excess were obtained by chiral HPLC enantiomer separation on microcrystalline triacetylcellulose column. Circular dichroism spectra of molecules containing two chromophores, namely a carbonyl and lactone in one molecule, were studied. The conformational analysis was performed with the aim to apply the octant and lactone sector rules for the determination of the absolute configuration. Ab initio and molecular mechanics calculations revealed that for all compounds investigated a single conformer, that is *c-tb* for **1a**–**3a** and **1b**–**2b**, and *c-tc* for **4a**, *tc-tc* for **5a** is prevalent in the gas phase at room temperature. The applicability and limitations of the semiempirical rules was demonstrated. The enantiospecific synthesis of enantiomerically enriched keto lactones **1**–**2a** and **1b**–**2b** from the corresponding enantiomeric ketones unambiguously led to the final proof of the absolute configurations.

1. Introduction

The lactone function is widely distributed as a structural fragment in many natural products of bicyclic structure, each and all of them being chiral compounds.[1] The setting of the absolute configuration of chiral lactones is relevant to the systematic study of the relationship between the Cotton effect (CE) in circular dichroism (CD) spectra with the absolute configuration of chiral structures. The chiroptical methods and, in particular, CD spectroscopy have proved indispensable tools for studying the absolute configuration of organic compounds.[2] The advantages of CD spectroscopy compared to other methods used to determine the absolute configuration of enantiomers, that is X-ray anomalous scattering, various other spectroscopic methods, etc., are the relative simplicity of collection and interpretation of the CD data.[3] Moreover, the application of other methods is excluded when minor quantities of chiral compound are available, and when crystals could not be obtained.

The enormous number of applications of CD measurements led to the formulation of semiempirical rules for the correlation of the sign and magnitudes of observed Cotton effects (CE) with the absolute configurations of chiral structures.[4] The use of the rules in the determination of the absolute configuration of molecules has a number of limitations, for example, some of the rules appear to have a weak theoretical basis, and for some chromophores, namely the lactone chromophore, no general rule of analysis of their CEs exists. Several empirical sector rules[5] for the lactone chromophore have been formulated on the ground of the octant rule for carbonyl chromophore. However, no single rule has yet achieved universal applicability though several attempts were made recently.[6] Furthermore, an application of sector rules may be more confusing when two alike or different chromophores are present in the molecule. Firstly, interchromophoric interaction may change the intensity of the CD spectra[7] and the sign of the CE effect as well. Secondly, a particular interest is associated with the applicability of a particular rule for the

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correlation of the absolute configuration with the sign of the CE effect.

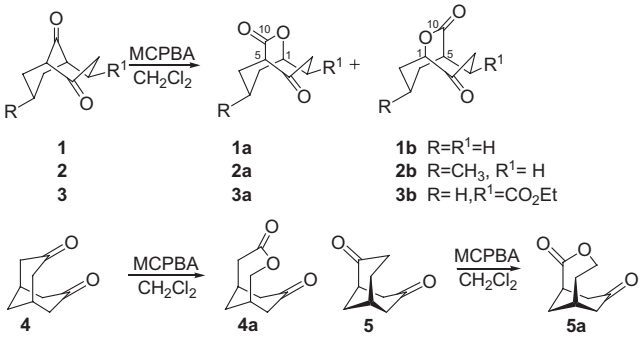
Thus further insight into understanding the rules relating the signs of the Cotton effect to the absolute configurations could be obtained by a study of relevant bicyclic molecules containing the lactone together with carbonyl chromophores in a well-defined three-dimensional relationship. It should be noted that the prevailing conformation of a bicyclic framework should be identified since different conformations of a respectively substituted molecule may prejudice probing of sectors by substituents. Nevertheless, an independent method should be used to prove the absolute configuration determined from the CD spectra. Chemical correlation is one of the appropriate methods. It is also possible for a given molecular geometry to calculate CD data employing two different groups of methods: the independent system approach[8] and the molecular orbital approach.[8,9] The application of CD spectroscopy in conjunction with chemical correlation or calculations is very reliable for proving the absolute configuration.

The aim herein is the synthesis of a series of oxabicyclo[3.3.2]- and [4.3.1]decanediones (keto lactones) and a study of their chiroptical properties. A regioselective Baeyer–Villiger oxidation of the corresponding bicyclo[3.3.1]nonane diketones afforded desired keto lactones, enantiomers of which were resolved by chiral HPLC. Ab initio and molecular mechanics calculations were performed to establish predominant conformer of compounds investigated. Chiroptical properties were studied by CD spectroscopy with the aim to establish a correlation between the signs of the CD bands and the absolute configuration. The final proof of the absolute configurations was obtained by the enantiospecific synthesis of keto lactones **1a**–**2a** and **1b**–**2b** from the corresponding enantiomerically enriched ketones. In addition, keto lactones of the bicyclic structure may be used as chirons for the synthesis of various natural compounds[10] and for the construction of chiral cyclooctane derivatives.[11]

2. Results and discussion

2.1. Synthesis and enantiomer separation of oxabicyclo[3.3.2]- and [4.3.1]decanediones

Chiral oxabicyclo[3.3.2]- and [4.3.1]decanediones (keto lactones) investigated herein are presented in Scheme 1. Racemic keto lactones **1a**–**3a** were synthesized from the corresponding bicyclo[3.3.1]nonane ketones **1**–**3** employing regioselective Baeyer–Villiger oxidation with *m*-CPBA as described previously.[12] The reaction mixture consisted of major keto lactones **1a**–**3a** and minor compounds **1b**–**3b** (ratio 92–85/8–15). Keto lactone **4a** was obtained by oxidation of prochiral bicyclo[3.3.1]nonane-3,7-dione **4** with *m*-CPBA (Scheme 1) following the reported procedure.[13] Enantiomerically pure keto lactone (+)-(1*R*,6*R*)-**5a** was obtained from (+)-(1*R*,5*S*)-bicyclo[3.3.1]nonane-2,7-dione **5**. The latter diketone was synthesized from the corresponding (+)-(1*S*,5*S*)-bicyclo[3.3.1]nonane-2,6-dione enantiomer applying the reaction sequence developed earlier by us, which leads to a carbonyl group shift.[14]



Scheme 1. Synthesis of bicyclic keto lactones.

In recent years enantiomers of various compounds have been available thanks to the development of chromatographic enantioseparation methods.[15] HPLC was used to obtain the enantiomers of various structures on a semipreparative scale and with a series of bicyclic structures successfully resolved on a swollen microcrystalline triacetylcellulose column.[16] However, only a few data are available on lactone resolution by HPLC.[17] We performed chromatographic enantiomer separation of keto lactones **1a**–**4a** with the equipment described earlier[18] using 95% aqueous ethanol as the mobile phase. The chromatogram showed moderately separated peaks in the polarimeter trace. However the UV trace was rather weak or did not revert to the baseline between the peaks. The efficiency of enantiomer resolution is expressed by selectivity factor $\alpha = k'_2/k'_1$, where k'_1 and k'_2 are capacity factors for the first and second eluted enantiomers, respectively (Table 1). The efficiency of separation of the discussed compounds was rather moderate. The first eluted enantiomer of **1a**, **3a**, and **4a** showed negative rotation while the first eluted enantiomer of **2a** showed positive rotation. Fractions taken in the early and late parts of the eluate gave enantiomerically enriched keto lactones. Parameters of chromatographic separation and rotation angles of the first eluted enantiomer are presented in Table 1. Notably the retention time of keto lactones **1a**–**3a** is longer compared to the appropriate ketones **1**–**3** under the same conditions.[19]

Table 1. Chromatographic enantioseparation parameters, capacity k' and selectivity factors α for compounds **1a**–**4a** in 95% aqueous ethanol

Compound	k'_1[a]	k'_2	α[b]	[α], deg cm^2 g^{-1}[c]
(−)-**1a**	4.93	5.91	1.20	−85
(+)-**2a**	2.32	2.75	1.19	145
(−)-**3a**	2.21	2.86	1.29	−54
(−)-**4a**	2.42	3.07	1.27	−12

[a] $k'_i = (t_i - t_o)/t_o$, where t_i is the retention time of enantiomer i, and t_o is the retention time of non-retained compound tri-*tert*-butylbenzene.

[b] $\alpha = k'_2/k'_1$, where k'_1, k'_2 are capacity factors of the first and second eluted enantiomers.

[c] $[\alpha]_D$ values for **1a** and **4a** and $[\alpha]_{546}$ for **2a** and **3a** in EtOH after enantioseparation.

2.2. Conformational analysis of bridged keto lactones

The octant rule could be applied for the determination of the absolute configuration of a carbonyl group containing molecule with a known conformation. The six-membered ring can exist in either a chair or boat conformation, the latter being the less favorable. A more complicated picture is observed in seven-membered rings. The conformers of the cycloheptane ring can be placed into either the chair or boat family, consequently adopting chair, twist-chair boat or twist-boat conformation. The paths between these sets of conformations have proven to be difficult to define and visualize.[20] Introduction of the carbonyl group and oxygen atom onto the ring may decrease conformational uncertainty. However, unless the pattern of substitution and fusion with an additional ring enforces exceptional rigidity, the stability of the minimum energy conformations of boat and chair types seems to be sufficiently close. We performed lowest energy conformational searches for **1a**–**5a** and **1b**–**3b** with a Spartan Pro package using the Monte-Carlo method and an MMFF94 force field.[21] Three or four lowest energy conformers were located in each case and further optimized using the RHF/6-31G* ab initio method. The notation of conformers of the studied compounds is presented in Figure 1.

Calculations of the conformations for two types of keto lactones, that is, containing lactone function in the bridge of the bicyclic framework **1a**–**3a** and **1b**–**3b**, and in more flexible part of the molecule **4a**, **5a** are summarized in Table 2. The *c-tb* conformation was found to be the most stable for compounds **1a**–**3a** and **1b**–**3b**, in which a seven-membered ring containing lactone and ketone functions adopt the boat conformation. For **1a**, **3a** and **1b**, **3b** the *tb-tb* conformation was estimated to be the second lowest energy conformation by the RHF/6-31G* method. In the case of compounds bearing 7-*exo*-methyl substituent, namely **2a** and **2b**, both *tb-tb* and *b-c* conformations are to a great extent disfavored due to the repulsive interaction of the *exo*-methyl group and the lactone bridge. For **2a** and **2b** the double twist chair conformation was calculated to be the second lowest energy conformation.

For **4a**, the chair-twist chair *c-tc* conformer was calculated to be 1.23 kcal/mol (RHF/6-31G*) more stable when compared to the chair-boat *c-b* conformer

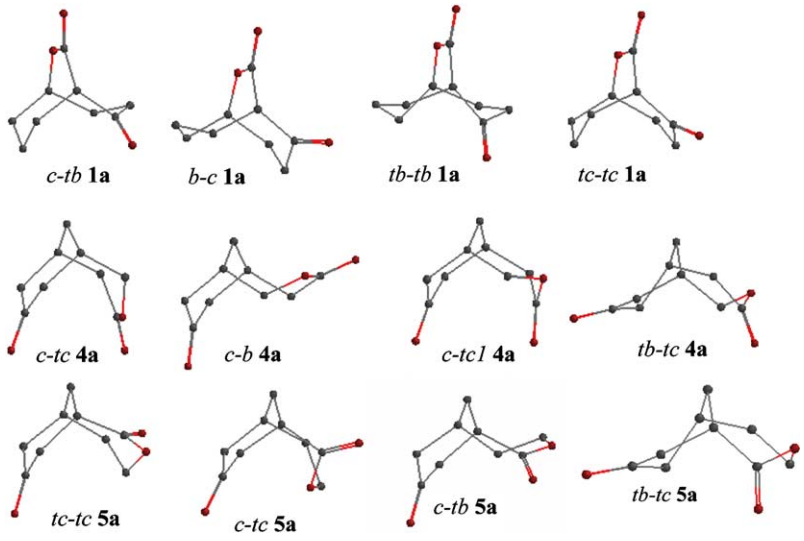


Figure 1. Graphical representation and notation of conformations of keto lactones **1a**, **4a**, and **5a**.

Table 2. Relative energies (RHF/6-31G*) of the conformers of compounds **1a**–**5a** and **1b**–**3b**

Compound	ΔE, kcal/mol					
	b-c	*tc-tc*	*c-tb*	*tb-tb*	*c-tc*	*c-tc1*
1a	4.48 (4.47)[a]	3.54 (4.8)	0	2.73 (3.75)	—	—
2a	8.41 (8.33)	3.62 (5.13)	0	6.08 (6.97)	—	—
3a	3.83 (6.70)	2.58 (5.81)	0	2.22 (4.42)	—	—
1b	6.74 (3.29)	4.85 (3.46)	0	2.46 (3.56)	—	—
2b	10.61 (7.14)	4.90 (3.78)	0	—	—	—
3b	7.0 (4.56)	5.57 (3.66)	0	2.03 (3.71)	—	—
4a	—	—	1.23[b] (1.46)	8.59[c] (9.93)	0	5.64 (6.37)
5a	—	0	3.56 (4.92)	3.80[c] (5.57)	1.82 (4.98)	—

[a] MMFF94 results in parentheses.
[b] *c-b* conformation.
[c] *tb-tc* conformation.

(Fig. 1). The other chair-twist chair conformation, namely *c-tc1* **4a** (Fig. 1), was also obtained and found to be less stable by 5.64 kcal/mol than the *c-tc* conformation. Using the RHF/6-31G* method, double twist chair *tc-tc* conformation of **5a** was found to be more stable than chair-twist chair *c-tc* (1.82 kcal/mol) and chair-twist boat *c-tb* (3.56 kcal/mol) conformations.

The conformational analysis using RHF/6-31G* predicts that for compounds **1a**–**2a** and **1b**–**2b**, *c-tb* conformation is >97% of the equilibrium mixture of the *b-c*, *tc-tc*, *c-tb*, and *tb-tb* conformers, while other conformers having insignificant Boltzmann populations at 298 K. Analogously for **5a**, the *tc-tc* conformer was predominant (>95%). Consequently only the above-mentioned conformers were taken for further consideration. For **4a**, *c-tc* together with *c-b* conformer constitutes >99% of the equilibrium mixture of the *c-b*, *tb-tc*, *c-tc* and *c-tc1* conformers. Percentage populations at 298 K obtained from the ΔE values using Boltzmann statistics are 11% and >88% for *c-b* and *c-tc* conformer, respectively.

2.3. CD spectra and application of the octant rule

The circular dichroism spectra of the first eluted enantiomer of **1a**–**4a** were recorded and analyzed in order to determine the absolute configurations of the enantiomers. A moderate Cotton effect was observed at 293 nm, negative for (−)-**1a** and (−)-**3a**, and positive for (+)-**2a**, while less intense CE of the opposite sign at lower wavelength around 220 nm (Fig. 2) was also seen. Two CEs of the same sign in the CD spectrum were observed for compound (−)-**4a**, that is, more intense at 290 nm and less intense at 220 nm. It is interesting to note that the CEs of **4a** are of the opposite sign to the rotation angle.

The bands around 290 nm and in the region of 210–230 nm in the CD spectra of keto lactones **1a**–**4a** can be assigned to the $n \rightarrow \pi^*$ transitions of the carbonyl and the lactone chromophores, respectively. As the two CEs are well separated in the CD spectra, the application of the octant rule for carbonyl chromophore, which relates the sign of the CE to the chirality of the extrachromophoric environment of the carbonyl group when the conformation of a molecule is known, seemed conceivable. The carbonyl group is one of the most explored chromophores for determining the absolute configuration of chiral structures using the octant rule.[22,23] However, the validity of the octant rule may be equivocal when a carbonyl and another chromophore are present in the molecule. A prediction of the CE sign should be made with precautions with respect to the orientation of chromophores,[24] while the location of the latter into octants may lead to an open question mark on the configuration of the molecule under investigation.[25]

The location of minimized structures (1*S*,5*R*)-**1a** and (1*S*,2*R*,5*R*)-**3a** onto octants by placing the carbonyl chromophore into the origin of the octants is presented in Figure 3. Consideration of the input of the atoms to the CE of (1*S*,5*R*)-**1a** gives a rather distinct result. The lactone carbonyl group and the carbon atom C2 are located in negative octants while oxygen and three carbon atoms C6–C8 are located in positive octants. It seems reasonable to expect that the twisted cycloheptane ring, more specifically the C3–C2 bond and the lactone carbonyl group in the vicinity of the chromophore, should contribute significantly to the CE. A contribution of the α-substituents to the Cotton effect is expected to be

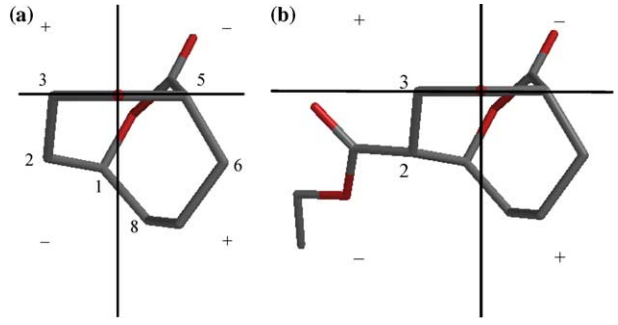


Figure 3. Projections of (−)-(1*S*,5*R*)-**1a** (a) and (−)-(1*S*,2*R*,5*R*)-**3a** (b) into octants placing the carbonyl group in the origin of octants.

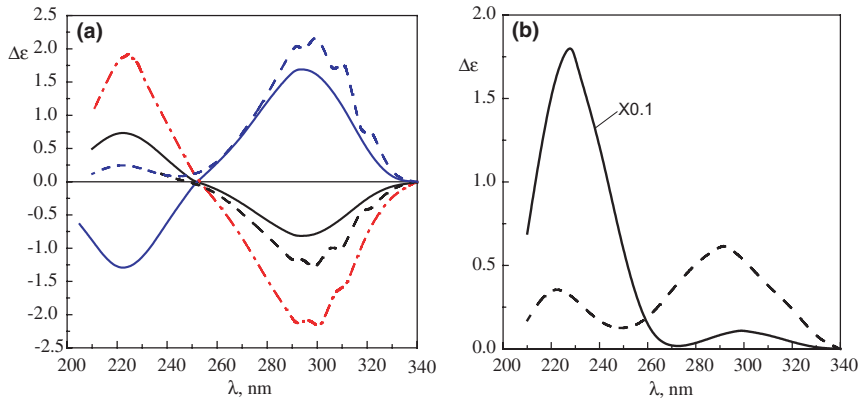


Figure 2. CD spectra of (a) keto lactones (−)-**1a** (—), (+)-**2a** (—), (−)-**3a** (-·-); minor compounds (+)-**1b** (---), (−)-**2b** (---); (b) (−)-**4a** (---) and (+)-**5a** (—) (intensity reduced 10 times).

strongly dependant on the R–C_α–C=O dihedral angle. For the RHF/6-31G* optimized geometry of the (1*S*,5*R*)-**1a** chair-twist boat conformer, the dihedral angle O=C–C_3–C_2 was calculated to be −117.4°, which is close to the values for the axial α-methyl groups in cyclohexanones.[26] Thus, the C3–C2 bond in the so-called primary zigzag arrangement should exert a strong contribution to the observed CE.[27] The C_5–C_6 bond adopts a quasi-axial (bisected) configuration with the O=C–C_5–C_6 dihedral angle calculated to be 65°. Antioctant behavior of the α-methyl groups in bisected configuration was observed for α- and β-pinanones and 2,8,8-trimethylbicyclo[3.2.1]octan-3-ones, with the methyl group playing only a minor role and the framework contribution being significant.[26] Some of the atoms (C1, C8, and the ring oxygen, Fig. 3a) are close to the nodal surfaces and their input into the resulting sign of the CE effect could be inconsiderable. Therefore the major input of the C3–C2 bond in the left bottom and the carbonyl group in the top right negative octants, respectively, should be envisaged.

Consequently a negative sign for the CE effect at 293 nm for the (−)-**1a** enantiomer could be expected and the (1*S*,5*R*) absolute configuration assigned on the basis of the consequential contribution of substituents. Consideration of a (1*S*,5*S*,7*R*)-**2a** projection in the octants leads to analogous conclusions, that is, the most significant input into the sign of the CE will have the C3–C2 bond in the lower right and the carbonyl group in upper left positive octants, respectively. Consequently a positive CE at 293 nm could be predicted and the preliminary (1*S*,5*S*,7*R*) absolute configuration for the (+)-**2a** enantiomer assigned on the basis of the presented considerations.

The projection of *exo*-carbethoxy derivative (1*S*,2*R*,5*R*)-**3a** in octants (Fig. 3b) gives analogous conclusions as for **1a** and **2a**. The primary zigzag contribution of the C3–C3 bond and the ester group in the lower left and the carbonyl group in upper right negative octants, respectively, will have major input into the sign of the CE. Thus a negative CE at 300 nm could be predicted and a preliminary (1*S*,2*R*,5*R*) absolute configuration for the (−)-**3a** enantiomer assigned.

The most stable conformation for compound **4a** was calculated to be a chair-twist chair (Table 2). The projection of minimized (1*R*,6*S*)-**4a** into octants is presented in Figure 4a. Contribution from axial C1–C2 and C6–C5 bonds eliminates each other leaving the O3 atom in the lower left and the carbonyl group in the lower right octants as sole perturbers. Considering the groups probing the octants, it could be expected that there is major input from the lactone carbonyl group to the sign of the CE compared to the oxygen atom of the same group. The octant projection of the considerably less populated *c-b* conformer of **4a** is alike, that is, the sole perturbers are O3 atom in the lower left and the carbonyl group in the lower right octants though more distal from the carbonyl chromophore. Hence a positive CE for both *c-tc* and *c-b* conformers of **4a** is predicted at 290 nm while a (1*R*,6*S*) absolute configuration for (−)-**4a** enantiomer can be assigned on a basis of this ratiocination.

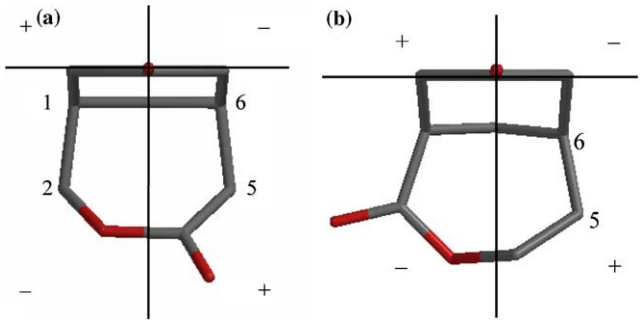


Figure 4. Projection of (−)-(1*R*,6*S*)-**4a** (a) and (+)-(1*R*,6*R*)-**5a** (b) into octants placing the carbonyl group in the origin of octants.

A very intensive CE effect at 220 nm and a significantly less intense CE at 290 nm were observed in the CD spectrum of keto lactone (+)-**5a**. The absolute configuration of this keto lactone is known from the results of enantiospecific synthesis and is unequivocally defined as (1*R*,6*R*). The projection of this keto lactone in octants (Fig. 4b) suggests that the β-axial C6–C5 bond overwhelms the input of the lactone carbonyl group and consequently defines the sign of the CE.

The CD spectra of minor oxidation compounds **1b** and **2b** were also studied. The preparation of (+)-(1*S*,5*R*)-**1b** and (−)-(1*R*,5*R*,7*R*)-**2b** is described in the section on enantiospecific synthesis. In the CD spectra of (+)-**1b** and (−)-**2b** (Fig. 2b), a CE of moderate intensity was observed at 297 nm [positive for (+)-**1b** and negative for (−)-**2b**], which corresponded to the $n\rightarrow\pi^*$ transition of the carbonyl chromophore, while a low intensity band at around 220 nm was assigned to the $n\rightarrow\pi^*$ transition of the lactone chromophore. The relative stability of **1b** and **2b** conformers was calculated by molecular mechanics and ab initio RHF/6-31G* methods (Table 2). The prevailing chair-twist boat conformers of (+)-(1*S*,5*R*)-**1b** and (−)-(1*R*,5*R*,7*R*)-**2b** were located into octants to evaluate the input of the groups into the sign of the CE (Fig. 5.). Analogously to the major isomers **1a**–**3a**, the dihedral angles O=C–C_3–C_4 and O=C–C_1–C_8 for (+)-(1*S*,5*R*)-**1b** were calculated to be 117.06° and −65.35°, respectively. Consequently the major input to

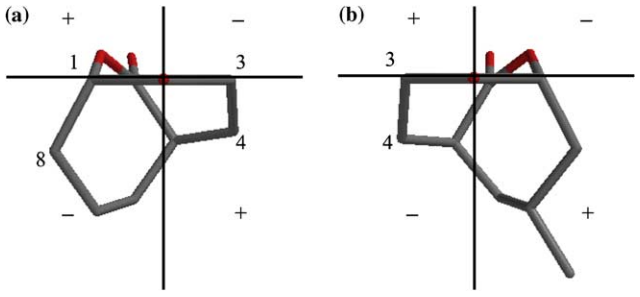


Figure 5. Projections of (+)-(1*S*,5*R*)-**1b** (a) and (−)-(1*R*,5*R*,7*R*)-**2b** (b) into octants placing the carbonyl group in the origin of octants.

the sign of the CE has the C3–C4 bond and the oxygen atoms of the lactone group in the case of (+)-**1b** probing the lower right and upper left positive octants, respectively (Fig. 5a). Analogously for compound (−)-**2b** the C3–C4 bond in the lower left and the oxygen atoms of the lactone group in the upper right negative octants, respectively, determine the sign of the CE (Fig. 5b). The CD spectra of (+)-**1a**, (−)-**2a**, (+)-**3a**, and (+)-**4** enantiomers were mirror images of the spectra presented in Figure 2 and consequently opposite configurations were assigned.

2.4. Consideration of the lactone chromophore

The Cotton effect in the CD spectra of lactones in the region of 210–230 nm was ascribed to the $n \rightarrow \pi^*$ transition of the lactone chromophore. Several empirical sector rules[5] for the lactone and related lactam chromophore have been formulated on the grounds of the octant rule for carbonyl chromophore. Nevertheless, each rule appears to have only a limited range of application and is therefore not of much use for lactones of complex polycyclic structure.[28] Sector rules are applicable for lactones with a planar lactone ring, that is, containing no chiral second sphere according to the Snatzke's definition of spheres.[29] As the lactone ring is not planar, the chirality or helicity of the lactone ring (chiral second sphere contribution) should be regarded as determining the sign of the CE. Beecham[30] stated that the sign of the CE depends on the conformation of the lactone ring, it being negative when the C_β atom is below the plane of lactone group. Legrand and Bucourt[31] proposed a general rule for 5-, 6-, and seven-membered lactones based on the sign of the O–C(=O)–C_α–C_β torsional angle. A negative CE can be expected for a positive torsional angle and vice versa. However, the contribution of the substituents adjacent to lactone chromophore may be not inconsiderable, as demonstrated for γ-lactones.[32] Moreover, ring chirality rules are hardly applicable when a lactone chromophore is simultaneously incorporated into two chiral second spheres, which have different ring size, conformation, and substitution pattern.

All the above-mentioned sector and ring chirality rules are valid only if the lactone chromophore itself is coplanar and, therefore, inherently achiral. Studies of tricyclic lactams have demonstrated a correlation between the sign and magnitude of the twisting C–CO–NH–C chromophore (X-ray) and the sign of $n \rightarrow \pi^*$ CE.[33] For a negative C–CO–NH–C dihedral angle, a negative CE is observed. The same correlation has also been reported for 2-aza-A-homo-5α-cholestan-1-one, a compound that lacks the great rigidity of aza-tricyclo lactams.[34] Recent studies of the chiroptical properties of the 5-dethia-5-oxacepams demonstrated that this rule is also obeyed by a variety of β-lactam derivatives.[35] An interesting example of the relationship between the nonplanarity of the lactone chromophore and the sign of the CE of the rigid oxatricyclodecanone has been reported.[36] For a positive dihedral angle C–CO–O–C, a positive CE was observed with the absolute configuration proven by chemical correlation.

In the CD spectra of keto lactones **1a**–**5a**, a CE at around 220 nm was assigned to the $n \rightarrow \pi^*$ transition of the lactone chromophore. Taking into consideration what was said about the applicability of the rules for the lactone chromophore, chirality or helicity of the lactone ring (chiral second sphere contribution), and/or nonplanarity of the lactone chromophore should be regarded as important for determining the sign of the CE. Nevertheless, the Legrand–Bucourt rule could not be applied to the studied keto lactones **1a**–**3a**, **1b**–**2b** and **5a**, since there are two respective β-C atoms for which dihedral angles O–C(=O)–C_α–C_β of opposite sign (though comparable magnitudes) were found.

The distortion from planarity of the lactone chromophore in structures **1a**–**5a** and **1b**–**2b** was estimated using ab initio calculations. The respective dihedral angles for the most stable conformers of the absolute configuration preliminarily determined using the octant rule are presented in Table 3.

The lactone chromophore is somewhat twisted in the most stable chair-twist boat conformation of keto lactones **1a**–**3a** and **1b**–**2b** as manifested by the COC(=O)C dihedral angle calculated to be approx. 5–7°. However, the deviation from planarity could be exaggerated since no correlation between the positive dihedral angle and the positive CE, as reported in the literature,[36] was observed. It is likely that for keto lactones **1a**–**3a** and **1b**–**2b** the ring chirality contribution to the CE of the lactone chromophore is prevalent.

For the chair-twist chair conformer of (1*R*,6*S*)-**4a**, the deviation from the planarity for lactone chromophore was estimated to be +17°. The nonplanar lactone chromophore in **4a** should be considered as an inherently chiral chromophore, with a positive COC(=O)C dihedral angle leading to the positive CE. However, the moderate intensity of the CE was not completely evident. On the other hand, **4a** is the exclusive structure for which the Legrand–Bucourt rule can be applied. The corresponding dihedral angle O–C(=O)–C_α–C_β was calculated to be +51° for (1*R*,6*S*)-enantiomer and thus a negative CE sign to be expected. These two contradictory effects may lead to the prevalence of the former giving a positive CE effect of moderate intensity.

The absolute configuration of keto lactone **5a** follows from the enantiospecific synthesis and can be unequivo-

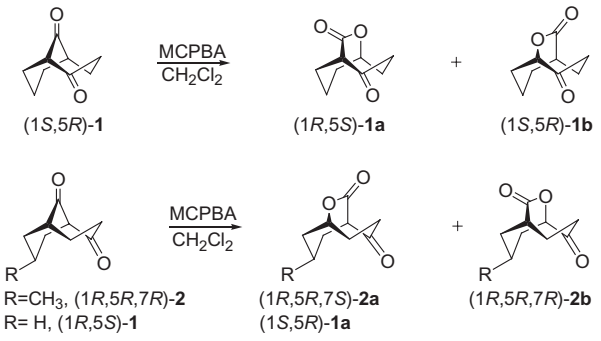
Table 3. Calculated (RHF/6-31G*) dihedral angles for lactones **1a**–**5a** and **1b**–**2b**

Compound	Dihedral angles, deg	
	COC(=O)C	COC(=O)
(−)-(1*S*,5*R*)-**1a**	−5.29	174.51
(+)-(1*S*,5*S*,7*R*)-**2a**	5.17	−174.64
(−)-(1*S*,2*R*,5*R*)-**3a**	−7.91	172.0
(+)-(1*S*,5*R*)-**1b**	−5.29	175.42
(−)-(1*R*,5*R*,7*R*)-**2b**	5.2	−175.55
(−)-(1*R*,6*S*)-**4a**	17.63	−163.8
(+)-(1*R*,6*R*)-**5a**	30.25	−153.58

cally defined as (1*R*,6*R*). An unusually intense CE effect for keto lactone **5a** was observed and can be accounted for by the significant twisting of the lactone chromophore in this structure. The $\Delta\varepsilon$ values for the lactone chromophore typically stand at around 1 unit.[34] The magnitude of the CE of inherently dissymmetric chromophores is typically larger by one or two orders of magnitudes compared to those from inherently symmetric but dissymmetrically perturbed chromophores. The distortion from planarity of the lactone chromophore was calculated to be ca. 30° (Table 3) for the most stable double twist chair conformer of (1*R*,6*R*)-**5a**. The nonplanar and thus inherently chiral lactone chromophore in **5a** with the positive COC(=O)C dihedral angle exerts a strong contribution to the positive CE. As a result the sign and magnitude of the experimental CE for **5a** corresponds to the absolute configuration, which was established from the chemical correlation.

2.5. Proof of the absolute configuration by the chemical correlation

Although the application of the semiempirical rules in many cases correlates well with the absolute configuration for certain compounds, the final conclusion is not secure. We performed enantiospecific synthesis of keto lactones **1a**–**2a** to validate the preliminary conclusions made on the basis of the octant rule. The synthesis is outlined in Scheme 2.



Scheme 2. Synthesis of enantiomerically enriched keto lactones.

The enantiomerically enriched ketones (−)-**1**, (+)-**1**, and (−)-**2** were obtained as described previously.[37] The enantiomeric lactones (−)- and (+)-**1a** and (−)-**2a** were obtained by employing Baeyer–Villiger oxidation according to the procedures developed for these compounds.[12] The configuration of the stereogenic centers of **1a** and **2a** does not change. However the priority of the substituents changes and thus the notation of the respective atoms did change to the opposite. The results of the enantiospecific synthesis are summarized in the Table 4.

The enantiomerically enriched minor oxidation products **1b**–**2b** were also isolated. The configuration of the stereogenic centers in these compounds was predetermined by the configuration of the bridgehead atoms in the starting ketones and does not change during the oxidation. Thus a (1*S*,5*R*) and (1*R*,5*R*,7*R*) configuration can be assigned to (+)-**1b** and (−)-**2b** enantiomers, respectively.

Table 4. The absolute configuration and the rotation angles of the compounds obtained by enantiospecific synthesis

Diketone	Ee[a]	Keto lactones	$[\alpha]_{546}$, deg cm^2 g^{-1}[b]
(−)-(1*R*,5*S*)-**1**	70	(−)-(1*S*,5*R*)-**1a**	−135
(+)-(1*S*,5*R*)-**1**	81	(+)-(1*R*,5*S*)-**1a**	146
		(+)-(1*S*,5*R*)-**1b**	183
(−)-(1*R*,5*R*,7*R*)-**2**	83	(−)-(1*R*,5*R*,7*S*)-**2a**	−142
		(−)-(1*R*,5*R*,7*R*)-**2b**	−71

[a] Ee values of the starting ketones, determined as in Ref. 37.
[b] Values in EtOH.

The obtained results unequivocally prove the absolute configuration of (−)-**1a** to be (1*S*,5*R*), while for the (−)-**2a** enantiomer (1*R*,5*R*,7*S*). These results are in accordance with the preliminary assigned configuration (−)-(1*S*,5*R*)-**1a** and (+)-(1*S*,5*S*,7*R*)-**2a** based on the application of the octant rule.

3. Conclusions

Several chiral bifunctional oxabicyclodecanediones related to naturally occurring compounds were synthesized from the corresponding bicyclo[3.3.1]nonane diones **1**–**5** by employing the regioselective Baeyer–Villiger oxidation. Chiral HPLC enantiomer separation afforded enantiomeric keto lactones with high enantiomeric excess. The conformational analysis by ab initio and molecular mechanics calculations revealed that for all compounds investigated, a single conformer, that is *c*-*tb* for **1a**–**3a** and **1b**–**2b**, and *c*-*tc* for **4a**, *tc*-*tc* for **5a** was prevalent in the gas phase at room temperature. Circular dichroism spectra of molecules containing two chromophores, namely the carbonyl and lactone in one molecule, were studied. A correlation between the sign of the CE effect and the absolute configuration in studied keto lactones was also found. The applicability and limitations of the semiempirical rules have been demonstrated. The enantiospecific synthesis of enantiomerically enriched keto lactones **1a**–**2a** and **1b**–**2b** from the corresponding enantiomeric ketones unambiguously led to the final proof of the absolute configurations.

4. Experimental section

4.1. Materials and general procedures

The enantiomeric bicyclic diketones **1**, **2**, and **5** used herein were synthesized according to procedures previously described by us.[14,37] Racemic keto lactones **1a**–**3a** and **4a** were obtained as described in Refs. 12,13, respectively. Melting points were recorded with a Koefler melting apparatus and are not corrected. ^{1}H and ^{13}C NMR spectra were recorded on a Bruker DRX400 at 400 MHz for protons and 100.6 MHz for carbon in $CDCl_3$. Mass spectra were run by GC–MS on Varian SATURN 5 and a Hewlett–Packard 6980 instrument with mass selective detector HP 5973 using Supelcowax

capillary column (30 m×0.25 mm), and HRMS obtained on a Jeol JMS-SX 102 spectrometer. GLC analysis was carried out on a Varian 3700 instrument (FID) by using DB 23 (J & W) (carrier gas nitrogen) and SPB-5 column (carrier gas He). IR spectra obtained in KBr on Perkin Elmer Spectrum BX spectrometer. The CD spectra were recorded on a Jasco Model J-500 A spectropolarimeter using 95% aqueous ethanol while UV spectra were recorded using spectral grade ethanol. Optical rotations were measured on a Perkin–Elmer 141 and on a Polamat-A polarimeters at 20 °C. Enantiomer separation of lactones was performed on a swollen microcrystalline triacetylcellulose (TAC) column using the equipment described earlier with 95% aqueous ethanol as the mobile phase.[18] Chromatography was performed using silica gel Kieselgel 60 (0.040–0.063 mm) for flash chromatography and Kieselgel 60 F_{254} plates for TLC. Ab initio and molecular mechanics calculations were performed using a SPARTAN Pro program package.[21]

4.2. Indices of enantiomers after the HPLC resolution

4.2.1. (−)-(1*S*,5*R*)-9-Oxabicyclo[3.3.2]decane-4,10-dione 1a. $[\alpha]_D^{20} = -85$ (*c* 0.013, EtOH); UV: λ_{max} (log ε) 290 (1.49), 230 (2.18); CD: λ_{max} ($\Delta\varepsilon$/dm^3 mol^{-1} cm^{-1}) 293 (−0.82), 252 (0), 220 (0.79).

4.2.2. (+)-(1*S*,5*S*,7*R*)-7-Methyl-9-oxabicyclo[3.3.2]decane-4,10-dione 2a. $[\alpha]_{546}^{20} = +145$ (*c* 0.069, EtOH); UV: λ_{max} (log ε) 290 (1.51), 230 (2.07); CD: λ_{max} ($\Delta\varepsilon$/dm^3 mol^{-1} cm^{-1}) 293 (1.70), 252 (0), 220 (−1.39).

4.2.3. (−)-(1*S*,2*R*,5*R*)-Ethyl 4,10-dioxo-9-oxabicyclo-[3.3.2]decane-2-carboxylate 3a. $[\alpha]_{546}^{20} = -54$ (*c* 0.11, EtOH); UV:λ_{max} (log ε) 291 (1.65), 218 (2.53); CD: λ_{max} ($\Delta\varepsilon$/dm^3 mol^{-1} cm^{-1}) 300 (−2.16), 253 (0), 225 (1.93).

4.2.4. (−)-(1*R*,6*S*)-3-Oxabicyclo[4.3.1]decane-4,8-dione 4a. $[\alpha]_D^{20} = -12$ (*c* 0.06, EtOH); UV: λ_{max} (log ε) 276 (1.55), 218 (1.97); CD: λ_{max} ($\Delta\varepsilon$/dm^3 mol^{-1} cm^{-1}) 290 (0.62), 220 (0.40).

4.3. General procedure for oxidation of *1*, *2*, and *5* with *m*-CPBA

To a stirred solution of bicyclic diketones (0.3 mmol) in dichloromethane (5.0 mL), a 1.5 M excess of *m*-CPBA (75%) and $NaHCO_3$ (~4 molar excess to *m*-CPBA) were added. The reaction mixture was stirred at room temperature for 1.5 h. Solid sodium sulfite (0.1 g) and water (0.1 mL) were then added and stirred for 0.5 h. The mixture was filtered over Na_2SO_4 layer, dried over Na_2SO_4, and evaporated. The solid residue was purified by flash chromatography to give the keto lactones.

4.3.1. (+)-(1*R*,5*S*)-9-Oxabicyclo[3.3.2]decane-4,10-dione 1a (50 mg, 90%) and (+)-(1*S*,5*R*)-9-oxabicyclo-[3.3.2]decane-2,10-dione 1b (4 mg, 7%). Compound **1a**: mp 99–101 °C; $[\alpha]_{546}^{20} = +146$ (*c* 1, EtOH); $C_9H_{12}O_3$: calcd C, 64.27; H, 7.19; found C, 64.50; H, 7.16. Compound **1b**: $[\alpha]_{546}^{20} = +183$ (*c* 0.1, EtOH). CD: λ_{max} ($\Delta\varepsilon$/dm^3 mol^{-1} cm^{-1}) 297 (2.07), 220 (0.28).[38] HRMS (EI) 168.0789. $C_9H_{12}O_3$ requires 168.0786. IR, ^{1}H and ^{13}C NMR, and MS are identical with the reported for racemate.[12]

4.3.2. (−)-(1*S*,5*R*)-9-Oxabicyclo[3.3.2]decane-4,10-dione 1a (49 mg, 89%). $[\alpha]_{546}^{20} = -135$ (*c* 1, EtOH).

4.3.3. (−)-(1*R*,5*R*,7*S*)-7-Methyl-9-oxabicyclo[3.3.2]decane-4,10-dione *2a* (48 mg, 88%) and (−)-(1*R*,5*R*,7*R*)-7-methyl-9-oxabicyclo[3.3.2]decane-2,10-dione *2b* (3 mg, 6.0%). Compound **2a**: mp 78–80 °C; $[\alpha]_{546}^{20} = -142$ (*c* 1, EtOH); $C_{10}H_{14}O_3$ calcd C, 65.90; H, 7.75; found C, 65.67; H, 7.54. Compound **2b**: $[\alpha]_{546}^{20} = -71$ (*c* 0.16, EtOH); CD: λ_{max} ($\Delta\varepsilon$/dm^3 mol^{-1} cm^{-1}) 297 (−1.26), 248 (0), <220 (positive).[38] HRMS (EI) 182.0947; $C_{10}H_{14}O_3$ requires 182.0943. IR, ^{1}H and ^{13}C NMR, and MS are identical with the reported for racemate.[12]

4.3.4. (+)-(1*R*,6*R*)-3-Oxabicyclo[4.3.1]decane-2,8-dione *5a* (6 mg, 17%). Mp 110–111 °C; $[\alpha]_{546}^{20} = +15$ (*c* 0.86, $CHCl_3$); UV λ_{max} (log ε) 275 (2.11), 228 (2.66 sh); CD: λ_{max} ($\Delta\varepsilon$/dm^3 mol^{-1} cm^{-1}) 298 (1.10), 228 (18.6); HRMS (EI) 168.0785; $C_9H_{12}O_3$ requires 168.0786. IR, ^{1}H and ^{13}C NMR, and MS are identical with the reported for racemate.[12]

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