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Enantiomer separation and absolute configuration of densely functionalized 2-oxatricyclo[4.3.1.$0^{3,8}$]decanes by CD spectroscopy and chemical correlation

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Abstract

Enantiomer separation by HPLC on a swollen microcrystalline triacetylcellulose column of highly substituted 2-oxatricyclo[4.3.1.$0^{3,8}$]decane (2-oxaprotoadamantane) structures afforded enantiomers of this molecule. Application of the octant rule to the carbonyl chromophore to establish the absolute configuration of the enantiomers did not lead to an unequivocal conclusion. The enantioselective synthesis of 4-bromo-3-methoxy-oxaprotoadamantanone was performed from homochiral (+)-(1*S*,5*S*)-bicyclo[3.3.1]nonane-2,6-dione thus permitting the assignment of the (1*R*,3*S*,4*S*,6*R*,8*R*)-configuration to the title structures. © 2000 Elsevier Science Ltd. All rights reserved.

Recently, we reported on a rather unexpected ring closure in the reaction of 3,7-dibromobicyclo-[3.3.1]nonane-2,6-dione under Favorskii-like reaction conditions.[1] A characteristic feature of this reaction is the formation of a new stereogenic center in a densely substituted 2-oxa-tricyclo[4.3.1.$0^{3,8}$]decane (2-oxaprotoadamantane) structure, within a total of five carbon atoms being stereogenic in the final tricyclic structure containing the carbonyl chromophore. Chiral polycyclic structures have been the subject of much interest in studying chiroptical properties in the past; however, only a limited number of examples is reported on the application of circular dichroism (CD) spectroscopy for the determination of the absolute configuration of functionalized carbocyclic structures.[2] Optically active compounds of highly substituted 2-oxaprotoadamantane are suitable models to demonstrate the effects of through-bond and through-space electronic interactions in the generation of rotational strength in the electronic transitions. Therefore, the aim of this work was the enantiomer separation of 2-oxaprotoadamantanes **1**–**4**, a study of the CD spectra and the determination of the absolute configuration of enantiomers.

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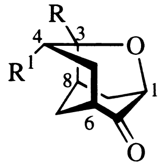
In recent years optically active compounds have been available thanks to the development of chromatographic methods for the resolution of enantiomers.[3] HPLC is used to obtain the enantiomers of various structures on a semipreparative scale, and a series of bicyclic structures have been successfully resolved.[4] We performed enantiomer separation of substituted 2-oxaprotoadamantane derivatives **1**–**4** by chromatography on a swollen microcrystalline triacetylcellulose column with the equipment described earlier[5] using 95% aqueous ethanol as the mobile phase. The chromatogram showed rather well 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 low. The first eluted enantiomer of 2-oxaprotoadamantanones **1** and **2** showed negative rotation while the first eluted enantiomer of **3** and **4** showed positive rotation. The subsequent eluted enantiomers showed the reverse rotation angle.

Fractions taken in the early and late parts of the eluate gave enantiomerically enriched 2-oxaprotoadamantanes with enantiomeric excesses ~40%,[6] and reinjection of the concentrated eluates afforded materials of higher ees.



1 R=OCH$_3$, R^1=Br
2 R=OCH$_3$, R^1=Cl
3 R=CN, R^1=Br
4 R=CN, R^1=Cl

Table 1
Capacity k' and selectivity factors α for compounds **1**–**4**

Compound	k'_1 [a]	k'_2	α	$[\alpha]_D^{25}$, deg· cm^2· g^{-1} [b]
1	0.82	1.02	1.24	−16.0 (*c* 0.02, CHCl$_3$)
2	1.00	1.18	1.18	−6.0 (*c* 0.07,CHCl$_3$)
3	1.53	1.78	1.17	+18.3 (*c* 0.12, CHCl$_3$)
4	1.35	1.64	1.21	+48.0 (*c* 0.05, CHCl$_3$)

[a] $k'_1=(t_1-t_0)/t_0$, where t_1 and t_0 are the retention times of enantiomer and non-retained reference compound tri-*tert*-butylbenzene; [b] $[\alpha]_D$ values measured in ethanol directly after HPLC separation

The circular dichroism (CD) spectra were recorded and analyzed in order to determine the absolute configuration of the enantiomers **1**–**4**. CD spectroscopy has proven to be a powerful method for studying the absolute configuration of chiral structures.[7] The enormous number of applications of CD measurements led to the formulation of the octant rule for the correlation of the sign and magnitude of the observed Cotton effect (CE) with the absolute configuration of chiral molecules containing the carbonyl chromophore.[8]

The CD spectra of the studied compounds exhibited a positive Cotton effect around 290 nm (Fig. 1). This band is ascribed to an n→π* transition of the carbonyl chromophore. The band of the CE of (–)-**2** is shifted to a lower wavelength probably due to a stronger electronic effect of the chlorine atom. The intensity of the CD spectra of this and compound **4** was also lower though the origin of it requires further studies.

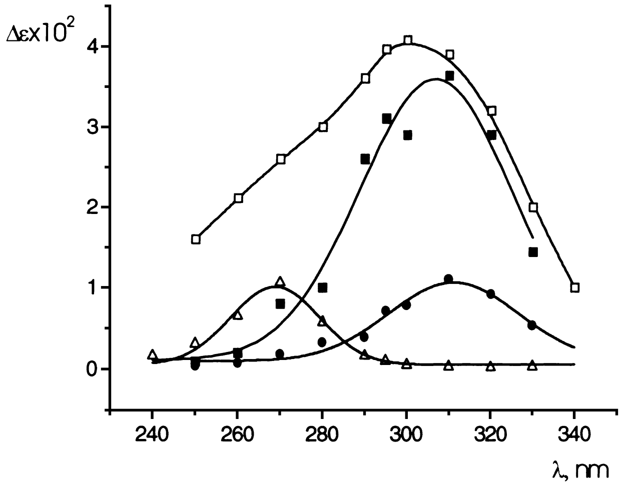


Figure 1. CD spectra of first eluted enantiomers of (–)-**1** (□), (–)-**2** (△), (+)-**3** (■), and (+)-**4** (●) in ethanol

The octant rule was applied to establish the absolute configuration of 2-oxaprotoadamantanones locating the molecule into octants. A six-membered ring with the carbonyl group is in a rigid conformation in this structure, and placing the latter into octants is straightforward. Fig. 2 shows the location of the 4-bromo-3-methoxy (–)-**1** structure minimized by molecular mechanics MMFF94[9] into octants.

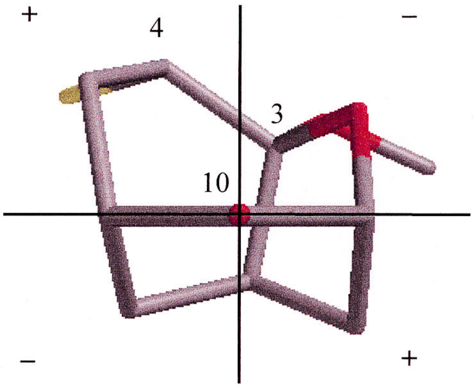
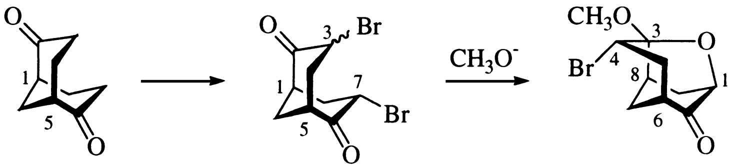


Figure 2. Projection of minimized (–)-**1** into octants

However, the sign of the CE could not be predicted directly by applying the octant rule. The contribution to the sign of CE of a ring oxygen atom and two substituents, i.e. of a methoxy group and bromine atom could not be evaluated even qualitatively. The two oxygen atoms, namely the ring oxygen and the methoxy group, are located in the upper right back octant and should give a negative Cotton effect, though the opposite effect of the bromine in the upper left back octant should be considered. The effect of a ring oxygen on the $n \rightarrow \pi^*$ carbonyl transition in saturated six-membered heterocyclic systems has been investigated, and it was shown that introduction of a ring oxygen results in an anti-octant effect and smaller rotational strength.[10] In addition to this observation, an analogous anti-octant effect was observed in some adamantanone derivatives, and this should also be taken into account.[11] The modified octant rule where the third nodal plane bisecting the C=O bond forms a concave third surface was proposed to account for some substituent effects[12] in polycyclic ketones though again this did not give any definite conclusion on the sign of the CE in our case. Thus, an attempt to evaluate the contribution of the substituents into the CE and establish the absolute configuration of 2-oxaprotoadamantanones using the octant rule did not give the unequivocal answer.

The absolute configuration of analogous carbocyclic protoadamantanone molecule and related cage-shaped structures has been determined by CD spectroscopy and chemical configuration correlations.[13] Therefore, it was a challenge to synthesize the 2-oxaprotoadamantane system in enantiomerically pure form to prove the absolute configuration of enantiomers obtained by HPLC separation. Thanks to an easy access to the enantiomerically pure starting (+)-(*1S,5S*)-bicyclo-[3.3.1]nonane-2,6-dione **5**[14] we performed this synthesis according to the reaction shown in Scheme 1.



(+)-(1*S*,5*S*)-**5** (+)-(1*R*,3*S*,5*R*,7*S*)-**6** (–)-(1*R*,3*S*,4*S*,6*R*,8*R*)-**1**

Scheme 1.

The starting (+)-(1*S*,5*S*)-diketone **5** was obtained in *ee* 95% from the racemic dione by the enzymatic reaction with baker's yeast in 6 days.[15] The ring closure of a dibromo derivative **6** was accomplished in the presence of sodium methoxide. The absolute configuration of the 2-oxaprotoadamantane structure **1** is predetermined by the configuration of starting (+)-(1*S*,5*S*)-diketone **5** since the configuration of bridgehead atoms does not change during the intramolecular cyclization reaction outlined in Scheme 1. The configuration of the rest of the chiral atoms in this tricyclic structure is mutually dependent on the configuration of the first two and therefore we assign the (1*R*,3*S*,4*S*,6*R*,8*R*) configuration to (–)-4-bromo-3-methoxy-2-oxaprotoadamantanone **1**. The analysis of the projection of (–)-**1** into octants (Fig. 2) reveals that the anti-octant effect of the O-2 atom together with the contribution of the bromine atom gives rise to the positive CE for the $n \rightarrow \pi^*$ carbonyl transition in this structure. Examination of molecular models shows that the methoxy group is somewhat closer to the nodal plane and its input into the sign of the CE is considerably smaller. The absolute configuration of compounds **2**–**4** is analogous on the basis of similar CD spectra (Fig. 1) to mention only that the configuration of stereogenic atom at C-3 in carbonitriles **3** and **4**[16] is *R* due to the change in priority of substituents.

In conclusion, the enantiomers of oxaprotoadamantanones were resolved by HPLC and the absolute configuration was established from the analysis of CD spectra and proven by the chemical correlation performing enantioselective synthesis of (–)-(1*R*,3*S*,4*S*,6*R*,8*R*)-4-bromo-3-methoxy-2-oxaprotoadamantanone from starting (+)-(1*S*,5*S*)-diketone **1**. The optically active 2-oxaprotoadamantanones obtained in this work are to our knowledge the first enantiomers of this molecular system.

Acknowledgements

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