Chromatographic enantiomer separation and absolute configuration of spiro[benzo-1,3-dioxole-2,9′-bicyclo[3.3.1]nonan]-2′-one and the corresponding diastereomeric hydroxy acetals

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Eugenius Butkus,[*a] **Ulf Berg,**[b] **Arvydas Stončius**[a] **and Audrius Rimkus**[a]

[a] *Department of Organic Chemistry, Vilnius University, Naugarduko 24, 2006 Vilnius, Lithuania*

[b] *Organic Chemistry 1, Department of Chemistry, University of Lund, PO Box 124, S-22100 Lund, Sweden*

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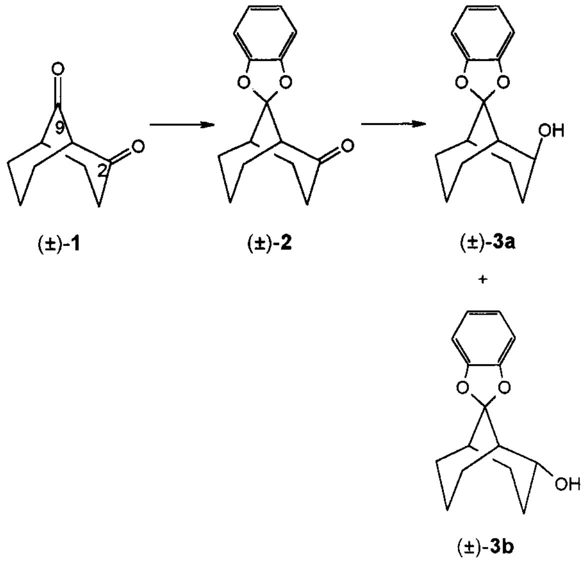
The enantiomers of spiro[benzo-1,3-dioxole-2,9′-bicyclo[3.3.1]nonan]-2′-one **2** and the corresponding diastereomeric *exo*-2′- and *endo*-2′-hydroxy acetals **3a**,**b** obtained from this monoacetal were resolved by HPLC on a swollen microcrystalline triacetylcellulose column. The absolute configuration of the enantiomers of **2** and **3a**,**b** was assigned based on the signs of the Cotton effect and employing the octant rules for the carbonyl and the aromatic chromophores. The low intensity of the band at 290 nm in the CD spectrum of monoacetal **2** was accounted for by the interaction of the carbonyl and aromatic chromophores.

Semiempirical rules correlating absolute configuration with the sign of the Cotton effect (CE) in circular dichroism (CD) spectra are applicable to inherently achiral chromophores.[1] Two types of these rules, *i.e.* sector rules and helicity rules, depending on the chromophores present in molecules, have been successfully explored to explain CD behavior of chiral structures. The rules are based on theoretical studies of transitions, however the simplicity of generalization is very useful when applied to stereochemical studies. Some model structures with more than a single inherently achiral chromophore could add to the validity of the above mentioned rules. The carbocyclic ring systems seem to be a suitable model to study the application of the rules and to relate the sign of the CE to the absolute configuration. Recently we have reported on the enantiomer separation and circular dichroism spectra of bicyclo[3.3.1]nonane-2,9-dione **1** and its pyrocatechol derivative **2**.[2,3] The absolute configuration of the molecules studied has been established by applying the octant rule, as the carbonyl group is one of the most explored chromophores in determination of the absolute configuration of chiral structures using the octant rule.[4] However, the theoretical computation of the CD spectra using a method developed by Schellman *et al.*[5,6] diverged from the experimental data for the diketone **1**, and the assignment of the absolute configuration of the (−)-enantiomer has been reversed.[7] The failure of the octant rule for **1** could be explained by the interaction of the two carbonyl chromophores since they are placed close to the nodal planes where the Cotton effects change sign.[8] A further insight into understanding the rules relating the signs of the Cotton effect to the absolute configurations could be obtained by a study of chiral bicyclononanes of a suitable molecular structure. Molecules containing the carbonyl and other chromophores in a comparatively well defined spatial relationship are very interesting from this point of view. The aim of this work was to study the relationship of the octant rule to the configuration of the bicyclononane structures containing two chromophores, which might be of interest considering the possible interaction between non-conjugated chromophores in this framework.

Results and discussion

Synthesis of model structures

The structures studied here include the monoacetal derivative **2** and hydroxy acetals **3a**,**b**. The synthesis of monoacetal **2** which contains two different chromophores was accomplished by a regioselective protection of the carbonyl group at position C9 in diketone **1** by a reaction with pyrocatechol.[9] The corresponding protected alcohols, *i.e.* hydroxy acetals **3a**,**b** were obtained by reduction of the carbonyl group in monoacetal **2** (Scheme 1).



Scheme 1

The stereoselectivity of the reduction of 2,9-diketone **1** has been studied earlier.[9] In this work the reduction of the carbonyl group at C2 was expected to proceed with analogous stereoselectivity with common complex hydrides. However, the reduction of the carbonyl group in **2** with $NaBH_4$ and $LiAlH_4$ was not diastereoselective or showed a low diastereoselectivity, respectively (Table 1). Treatment of monoacetal **2** with two highly hindered hydrides, *i.e.* lithium tri-*tert*-butoxyaluminohydride (LTBA) and lithium tri-*sec*-butylborohydride (L-Selectride®, Aldrich), showed different selectivity on reductions. The selectivity exhibited by LTBA was nearly the same as with $LiAlH_4$. The reduction of **2** with LTBA is controlled by the same factors as $LiAlH_4$ although the difference in transition states should give the larger excess of thermodynamically more

Table 1 Reduction of **2** with selected complex hydrides at 20 °C

Entry	Hydride reagent	Solvent	Reaction time/h	**3a**/**3b** ratio
1	$NaBH_4$	CH_3OH	4	51:49
2	$LiAlH_4$	THF	1	35:65
3	LTBA	THF	24	41:59
4	L-Selectride	THF	30	97:3

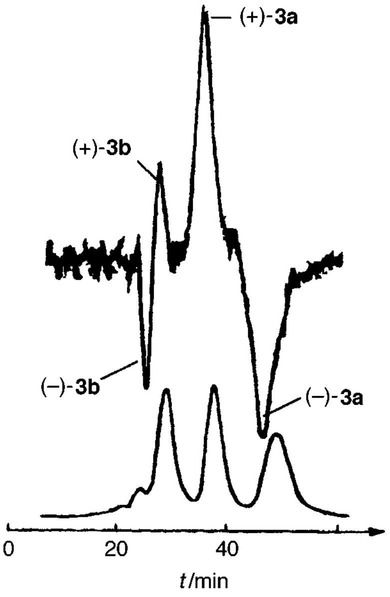


Fig. 1 Chromatogram and polarimetric detection (λ 365 nm) of hydroxy acetals **3a**,**b** (5 mg in 1 cm^3 of ethanol injected). Ethanol flow rate 1 cm^3 min^{-1}.

stable *endo*-alcohol **3b**.[10] When the reduction of **2** was carried out with L-Selectride the reaction proceeded with significant stereoselectivity (≥97%). The highly selective *endo*-attack of L-Selectride at position C2 and lack of stereoselectivity with $NaBH_4$ makes it impossible to explain the stereoselectivity in terms of only stereoelectronic or thermodynamic factors. The Felkin term as well as the Ahn and Cieplak terms favor *exo*-attack despite steric hindrance though it leaves the question of which of the effects is more important[11] (a detailed investigation on the reduction stereoselectivity of this and related structures is to be published).

Chromatographic enantiomer separation

Enantiomer separation of the monoacetal **2** and the diastereomeric bicyclic hydroxy acetals **3a**,**b** on a swollen microcrystalline triacetylcellulose (TAC) column was performed using the equipment described earlier with 95% aqueous ethanol as the mobile phase.[12] Compound **2** was successfully resolved on a TAC column, however a mixture consisting of both diastereomeric hydroxy acetals **3a** and **3b** in a comparable ratio (*ca.* 1:1) could not be resolved. The separation of all four diastereomers was achieved by injecting the mixture with predominating *exo*-hydroxy acetal **3a**. The chromatogram showed well separated peaks in the polarimeter trace and the UV trace almost reverted to the baseline between the peaks (Fig. 1) although the selectivity factors were rather low (Table 2). The first eluted enantiomer of diastereomeric hydroxy acetals **3a**,**b** showed negative rotation while two subsequently eluted enantiomers showed positive rotation. The elution order of the diastereomers was established by examination of fractions by GLC and ^1H NMR and was as follows: (−)-**3b**, (+)-**3b**, (+)-**3a**, and (−)-**3a**. Fractions taken in the first and last parts of the eluate gave enantiomerically enriched (−)- and (+)-hydroxy acetals **3a**,**b** (e.e. ≥50%) and reinjection of the concentrated eluates gave the enantiomerically pure material. Parameters of chromatographic enantioseparation are presented in Table 2.

Table 2 Capacity k' and selectivity factors α for compounds **2** and **3a**,**b** in 95% aqueous ethanol

Compound	k'_1[a]	k'_2	α
2	1.29	1.70	1.31
3b	0.35	0.50	1.42[b]
3a	1.25	2.07	1.65

[a] The capacity factors for the first and second eluted enantiomers k'_1 and k'_2, respectively, and the selectivity factors α were calculated according to the equations given in ref. 13. [b] Calculated using polarimetric detection.

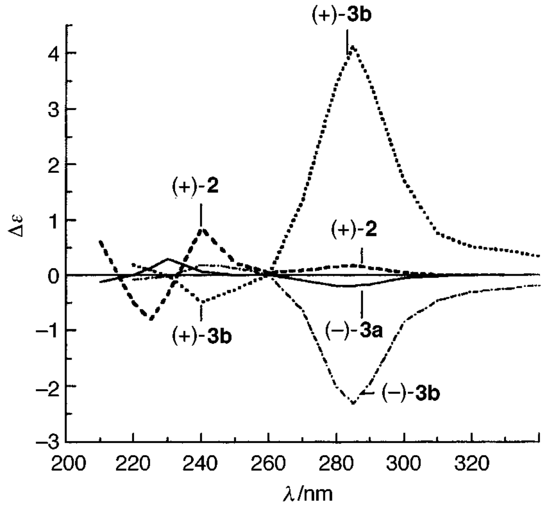


Fig. 2 CD spectra of (+)-(1*S*,5*R*)-**2** (– – –), (−)-(1*R*,2*R*,5*S*)-**3b** (····), (+)-(1*R*,2*R*,5*R*)-**3b** (–·–·), and (−)-(1*R*,2*S*,5*S*)-**3a** (——).

Analysis of the CD spectrum of 2

The CD spectra of **2** and **3a**,**b** were recorded and analyzed in order to determine the absolute configuration of the enantiomers.

The first eluted (+)-monoacetal **2** showed a complex CD spectrum with a negative band centered at 225 nm, a positive band at 240 nm and the last weaker positive band at 286 nm (Fig. 2). The sign of the Cotton effect in the molecule **2** is determined by the carbonyl and the aromatic chromophores in the chiral structure. Two possible projections of (+)-**2** in the octants should be considered, placing the carbonyl or aromatic chromophores at the origin of the coordinates. The contributions from different chromophores are assumed to be additive, however the way in which different parts of a molecule interact to generate the resulting sign and magnitude of the CE is still being debated.

In order to assign the absolute configuration of (+)-**2** we started with the consideration of the carbonyl group which is the first and one of the most explored chromophores in determination of the absolute configuration using the octant rule.[14] The rule is derived from the local symmetry of the carbonyl group, dividing all space surrounding the carbonyl chromophore into eight octants formed by the intersection of the three orthogonal planes. The two carbonyl symmetry planes divide all space about the C=O group into quadrants and the third non-symmetric surface perpendicular to and bisecting the C=O bond divides all space into front and back octants. The sign of the CE of the n→π* transition of this group is predicted considering the octant occupied by a particular atom or group. More recently, it has been suggested that the third nodal plane bisecting the C=O bond forms a concave third surface to explain the CE of bridged bicyclic and tricyclic ketones, in accordance with CNDO/S calculations.[15] Consequently if β-axial substituents to the carbonyl group fall into front octants this corresponds to anti-octant (dissignate) behavior of substituents while β-equatorial substituents follow the octant

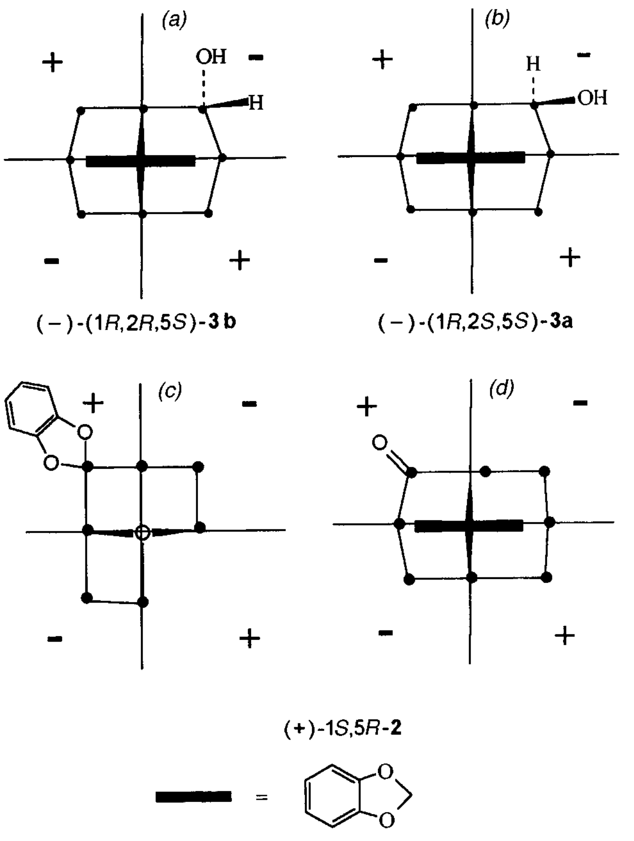


Fig. 3 The projections of (−)-(1*R*,2*S*,5*S*)-hydroxyacetal **3b** (*a*), (−)-(1*R*,2*R*,5*S*)-hydroxyacetal **3a** (*b*), and of (+)-(1*S*,5*R*)-monoacetal **2** into octants with the carbonyl (*c*), and the aromatic (*d*) chromophores at the origin of coordinates (bold line indicates the 1,2-dioxophenylene chromophore).

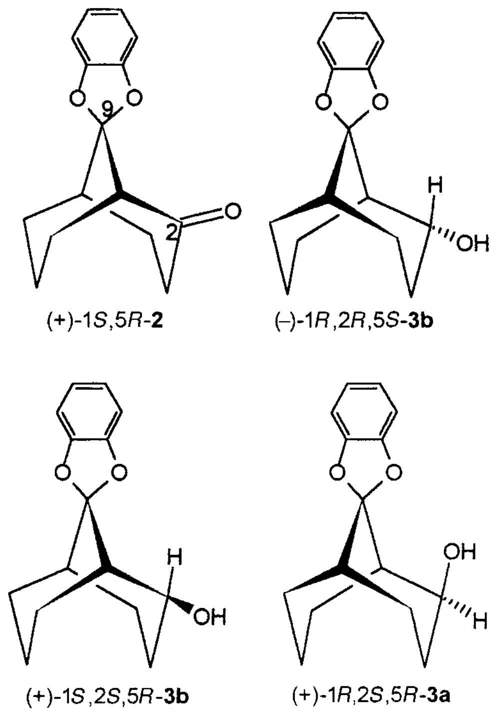
rule.[16] We considered monoacetal **2** as containing a 1,2-dioxophenylene substituent in a β-position to the carbonyl group. The location of the (1*S*,5*R*)-**2** structure, placing the carbonyl chromophore at the origin of the coordinates, makes a major contribution of the 1,2-dioxophenylene group into the upper left (or lower right) back octant (Fig. 3*c*). The preferred conformation of **2** has to be known to predict the configuration. Molecular mechanics (MM2) calculations gave the relative energy of the double-chair conformation to be the most stable by 1.8 kJ mol^{-1}. This should give a positive sign of the Cotton effect (+CE) which is what was observed in the CD spectrum of (+)-**2** (Fig. 2).

The 1,2-dioxophenylene chromophore and the CD spectra of 3a,b and 2

The 1,2-dioxophenylene chromophore which has C_{2v} symmetry has been studied less extensively. The ^1L_b transition is the interference of the π→π* aromatic transitions and the n→π* transitions of the oxygen atoms. The electric transition moment μ_e of the ^1L_b band is oriented along the C_2 axis and the direction of the magnetic transition moment m_m is directed into the plane of the aromatic ring. The transitions are either electrically or magnetically forbidden for planar chromophores, however the scalar term $\mu_e m_m$ is not zero and the rotational strength is still generated by a chiral environment.[17]

To interpret the CD spectra of the hydroxy acetals we pursued the investigation by the application of the sector rule developed for the 1,2-dioxophenylene chromophore.[18] In the CD spectrum of the first eluted (−)-hydroxy acetal **3b** (Fig. 2) there are three well-defined high intensity maxima, *i.e.* a negative band at 285 nm is the so-called α-band, at 242 nm is a positive p-band and at 220 nm is a negative band. The first Cotton effect near 290 nm is related to the ^1L_b transitions of the 1,2-dioxophenylene chromophore. A reversed CD spectrum was observed for (+)-**3b**. A difference in intensity of the CD spectra of (+)-**3b** and (−)-**3b** was due to the lower enantiomeric purity of (−)-**3b**.

A significant difference in intensity of the CD band at 285 nm in the diastereomeric optically active 2-*exo*-hydroxy acetal **3a** and 2-*endo*-derivative **3b** was observed (Fig. 2). In the CD spectrum of (+)-**3b** the ^1L_b band is much more intense ($\Delta\varepsilon >$ 4.0) than in the corresponding (+)-**3a** ($\Delta\varepsilon < 0.4$). Examination of the molecular models shows that in the latter case the weakly perturbing hydroxy group is parallel to one nodal plane of the aromatic chromophore and makes a small angle with the second one, and also is close to the third symmetry non-derived nodal plane. A third nodal surface considering the aromatic chromophore is definitely not planar although the detailed form of it is not known. Therefore only a weak CE should be expected for this structure. Thus the *exo*-hydroxy group has an insignificant contribution to the intensity of the CE. In contrast, the *endo*-hydroxy group is further from the nodal planes and its contribution is considerably greater to the CE. The projections of the (−)-**3a** and (−)-**3b** structures into octants are shown in Fig. 3*a* and 3*b*, respectively and it follows that the magnitude of the CE is strongly dependent on the orientation of the hydroxy group in this bicyclic structure. This indicates that the third nodal plane in the aromatic chromophore, which corresponds to the *xy* plane in ketones, presumably lies close to the oxygen atoms and does not intersect the center of the benzene ring. These results conform with the observation that β-axial hydroxy groups do not make "anti-octant" contributions, unlike alkyl groups, and this also confirms that the shape and location of the third nodal surface differ from substituent to substituent.[8] Thus an analysis of the CD spectra of hydroxyacetals **3a,b** has permitted us to assign the absolute configuration of the compounds presented in Scheme 2.



Scheme 2

The information on the intensity of the ^1L_b band of the 1,2-dioxophenylene chromophore obtained from the CD spectra of the enantiomeric hydroxyacetals **3a,b** was used to determine the absolute configuration of monoacetal (+)-**2**. The asymmetry of this molecule and consequently the sign and magnitude of the CE are determined by the contribution of the carbonyl group into octants when regarding the aromatic chromophore, since the rest of the monoacetal **2** molecular structure probes front octants. A rather strong positive CE was predicted for the (+)-(1*S*,5*R*)-**2** structure by placing the aromatic chromophore at the origin of the octants (Fig. 3*d*). Consequently, the configuration of (+)-**2** is (1*S*,5*R*) and is in an agreement with the previous conclusion about the carbonyl chromophore. The stereochemical relationship between the structures was demonstrated by the oxidation of (+)-*exo*-hydroxyacetal **3a** to (+)-monoacetal **2**, the identity of (+)-**2** proved by the rotation angle and spectroscopic methods.

Interpretation of the CD spectra intensities

The comparatively low intensity ($\Delta\varepsilon \leqslant 0.3$) of the band at 290 nm for (+)-**2** may be accounted for by the mode of interaction of the non-conjugated chromophores in this structure. Higher intensity of the CD bands has usually been observed in the CD spectra of chiral molecules with two interacting non-conjugated chromophores in comparison with structures having one chromophore.[19] Analogous observations for β,γ-unsaturated ketones have been rationalized in terms of homoconjugation.[20] The CE depends on the interchromophoric geometry and the generalized octant rule has been proposed to account for this effect.[21] The rotational strength is dependent on the distance between the chromophores and in particular on the appropriate orientation of chromophores, *e.g.* a significant increase in the CE has been observed in some δ,ε-unsaturated ketones.[22] It has been recognized that the strongest interactions occur when the angle between planes containing the aromatic and the C=O chromophores is in the range 90–120°.[23]

The intensity of the band at 290 nm in the CD spectrum of (+)-**2** was lower than in some saturated ketones of a related structure.[24] The low intensity of the band at 290 nm for (+)-**2** was accounted for by the geometric orientation of the chromophores in this structure. We attributed the low intensity of the ^1L_b transition in the CD spectrum to the interaction of the carbonyl and aromatic chromophores in monoacetal (+)-**2** due to the orientation of the $\pi\rightarrow\pi^*$ transition with respect to the carbonyl group. The angle between the planes of these chromophores in the minimized structure of **2** was found to be *ca.* 70°, thus the rotational strength should be rather weak. The interaction gives a weakly dissignate CE which leads to the similar or lower intensity of the band of the same sign compared to that of the isolated chromophores, due to withdrawal of electrons from the carbonyl group by the aromatic chromophore.[25]

The interchromophoric interaction in **2** was further supported by the NMR spectral data. Electronic interaction between chromophores in difunctional systems, *e.g.* diketones, unsaturated ketones, *etc.*, may be detected by the carbonyl carbon ^{13}C NMR shifts compared to those of their respective monocarbonyl congeners[26] (*cf.*, however ref. 27). The shielding of the C=O carbon atom would appear to indicate an electronic interaction between groups in the molecule. A larger shielding of the carbonyl carbon ($\Delta\delta_{C=O} > -2$ ppm) relative to a monofunctional analog should be considered as evidence of a strong transorbital interaction, while much reduced $\Delta\delta$ values are expected for decreased interaction between the carbonyl and the other chromophore.[28] In the case of monoacetal **2**, the chemical shift of the carbonyl carbon $\delta_{C=O}$ of parent bicyclo[3.3.1]nonan-2-one varies between 216.9 and 217.3 ppm.[29,30] The increase in shielding ($\Delta\delta$) of the carbonyl carbon relative to this ketone and monoacetal **2** ($\delta_{C=O} = 212.01$ ppm) was in the range −4.89 to −5.29 ppm and was in support of the proposed interchromophoric interaction.

In conclusion, the enantiomeric separation of some bicyclic compounds was accomplished and their absolute configuration was assigned employing the octant rules for the carbonyl and the aromatic chromophores. The low intensity of the band at 290 nm in the CD spectrum of monoacetal **2** was accounted for by the interaction of the carbonyl and aromatic chromophores in this molecule. The CD and ^{13}C NMR data indicated the dissignate interchromophoric interaction in the (+)-**2** structure.

Experimental

The solvents were distilled and dried before reduction by conventional methods. IR spectra were measured on a Specord M80 instrument. Proton and carbon nuclear magnetic resonance spectra were recorded in deuteriochloroform on a Varian XL 300 spectrometer and chemical shifts are reported in parts per million (δ) relative to tetramethylsilane as an internal standard. The CD spectra were recorded with a Jasco Model J-500 A spectropolarimeter and the UV spectra were recorded on a Cary 2290 spectrophotometer using spectral grade ethanol. Optical rotations at the sodium D line were measured in a 10 cm cell on a Perkin-Elmer 141 polarimeter. GLC analysis was performed on a Varian 3700 instrument, 25 m × 0.25 mm DB-23 (J&W) capillary column, carrier gas nitrogen. Thin layer chromatography was performed using Silufol aluminium sheets precoated with silica gel and column chromatography using silica gel L40/100 (Czech Republic). Melting points were determined on a Kofler block and are uncorrected.

Bicyclo[3.3.1]nonane-2,9-dione 1 and s*piro*[benzo-1,3-dioxole-2,9′-bicyclo[3.3.1]nonan]-2′-one 2

1 and **2** were prepared as described previously.[2,9] (+)-**2**: UV λ_{max} (log ε) 228 (3.52) and 283 (3.70); $[\alpha]_D^{25}$ +39.7 (*c* 0.07, EtOH); CD, λ_{max} ($\Delta\varepsilon$/mol^{-1} cm^{-1}) 225 (−0.80), 240 (+0.88), 286 (+0.20).

Reductions of monoacetal 2

(*a*) Sodium borohydride (26 mg, 0.67 mmol) was added to a stirred solution of ketone **2** (0.15 g, 0.61 mmol) in methanol (5 ml) at room temperature. Reaction was controlled by TLC and GLC. After 4 h, the mixture was hydrolyzed with 1 M HCl solution, evaporated and continuously extracted with diethyl ether. Evaporation of solvent left a solid mixture of **3a** and **3b**, yield 0.13 g (87%).

(*b*) Lithium aluminium hydride (0.02 g, 0.53 mmol) solution in THF (5 ml) was added dropwise to a solution of ketone **2** (0.1 g, 0.41 mmol) in THF (3 ml) and was stirred for 1 h at room temperature. The reaction mixture was hydrolyzed with 1 M HCl solution, evaporated and continuously extracted with diethyl ether. Evaporation of the solvent gave a solid mixture of **3a** and **3b**, yield 0.08 g (79.5%).

(*c*) Lithium tri-*tert*-butoxyaluminohydride (0.22 g, 0.87 mmol) solution in THF (5 ml) was added to a stirred solution of ketone **2** (0.15 g, 0.61 mmol) in THF (5 ml) at room temperature. The reaction mixture was stirred for 30 h, then poured into acidified water and extracted with diethyl ether. Evaporation of the solvent left a solid mixture, yield 0.11 g (72.7%).

(*d*) A solution of lithium tri-*sec*-butylborohydride (0.13 ml, 0.61 mmol) in THF (5 ml) was added to 0.1 g (0.41 mmol) ketone **2** in tetrahydrofuran (5 ml) and was stirred at room temperature overnight. The reaction mixture was hydrolyzed with 1 M HCl solution, evaporated and continuously extracted with diethyl ether. Evaporation of the solvent and recrystallization of the solid residue gave 0.08 g (79.5%) of **3a**; δ_H 6.81 (4H, m), 4.03 (1H, $w_{1/2}$ 10 Hz, m), 2.4–1.4 (13 H, m).

Spectral data for hydroxy acetals 3a,b

(−)-**3a**, mp 120–122 °C, $[\alpha]_D^{25}$ −46.4 (*c* 0.11, CHCl$_3$), ν_{max} (KBr)/cm^{-1} 735, 1080, 1235, 3425 and 3550; λ_{max}/nm (log ε) 199 (4.66), 233 (3.50) and 285 (3.67); CD, λ_{max} ($\Delta\varepsilon$/mol^{-1} cm^{-1}) 235 (−0.07), 285 (+0.19).

(−)-**3b**, mp 186–188 °C, $[\alpha]_D^{25}$ −67.7 (*c* 0.05, CHCl$_3$); CD, λ_{max} ($\Delta\varepsilon$/mol^{-1} cm^{-1}) 220 (−0.08), 240 (+0.19), 286 (−2.32).

(+)-**3b**, mp 139–140 °C, $[\alpha]_D^{25}$ +76.0 (*c* 0.12, CHCl$_3$); CD, λ_{max} ($\Delta\varepsilon$/mol^{-1} cm^{-1}) 220 (+0.19), 240 (−0.49), 260 (0), 285 (+4.12).

Oxidation of (+)-*exo*-spiro[benzo-1,3-dioxole-2,9′-bicyclo-[3.3.1]nonan]-2′-ol (3a)

To a cooled solution of 7 mg (0.03 mmol) of (+)-**3a** in 0.5 ml of acetone a 1/7 volume of solution prepared from 30 mg of $Na_2Cr_2O_7\cdot 2H_2O$, 0.3 ml of water and 0.025 ml of conc. H_2SO_4 was added dropwise. The reaction mixture was stirred for 2 h at room temperature. The reaction product was extracted into diethyl ether (3 × 1 ml), the combined extracts were dried over K_2CO_3 and concentrated. The residue was chromatographed on a microcolumn with silica gel (eluent, chloroform). Evaporation of the solvent gave 4 mg of (+)-**2** (>98% purity by GLC), $[\alpha]_D^{20}$ +0.7 (*c* 0.02, EtOH), identical with the sample obtained by HPLC separation.

Acknowledgements

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