

Structural Investigation of a Configurationally Stable Seven-Membered Bridged Biaryl of Relevance for Atroposelective Biaryl Syntheses*

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The atroposelective ring opening of lactone-bridged biaryl systems is the key step in the total synthesis of a series of axially chiral biaryl natural products and useful reagents or catalysts for asymmetric synthesis. For a more in-depth understanding of the mechanism and stereochemical course of this remarkable cleavage reaction, a seven-membered ether analog of such useful biaryl lactones has been investigated structurally, both experimentally, by X-ray diffraction analysis, and by *ab initio* calculations (B3LYP/6-31G*). In a nearly perfect agreement, both methods show that these seven-membered bridged biaryls do not constitute helicene-like distorted molecules, but ‘true’ biaryls, whose sufficiently long lactone or ether bridge allows the two aromatic systems to adopt a large dihedral angle to each other, without any noticeable deviation from planarity for the two aromatic systems – in contrast to related six-membered analogs, which can rather be considered as helicene-like twisted polycyclic systems.

Key words: Bridged Biaryls, Crystal Structure, Density Functional Theory Calculations

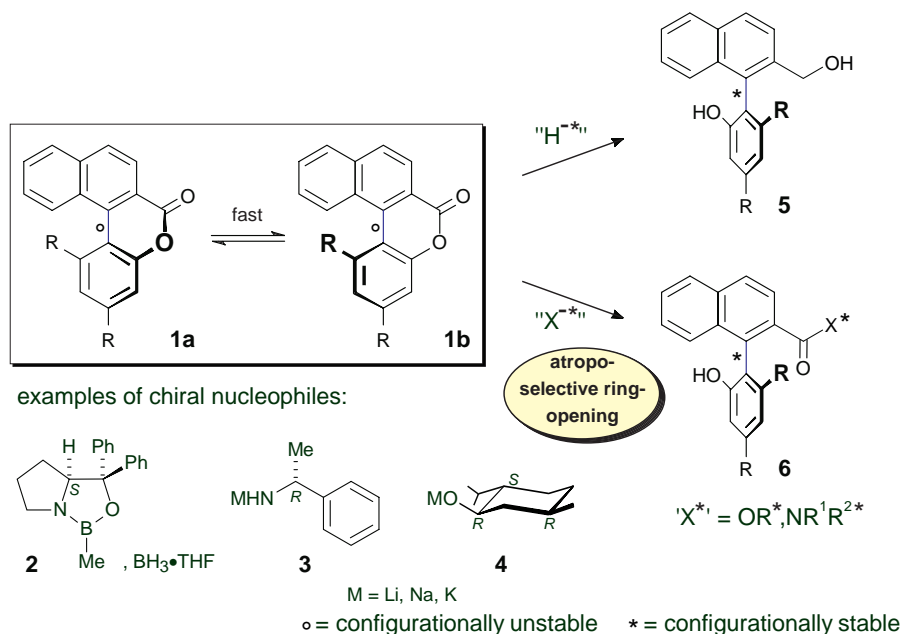
Introduction

Six-membered lactone-bridged biaryls of type **1** (Scheme 1) have proven to be useful intermediates in the atropo-enantio- or -diastereoselective synthesis of axially chiral biaryls [2]: by using *e.g.* chiral H-, O-, or N-nucleophiles like **2**, **3**, or **4**, they can be opened with high stereoselectivities to give the corresponding ring cleavage products **5** or **6** – or, if desired, the respective atropisomers [1, 3]. Substantial information on the nature of this remarkable ring opening process and the origin of the stereoselectivity was obtained from experimental (*i.a.* NMR and X-ray diffraction) work and, in parallel, from computational investigations of the structures and dynamics of such lactones, both by semiempirical (AM1, PM3, MNDO) [4–6] and *ab initio* (HF and DFT) calculations [7], ultimately leading to the calculations of

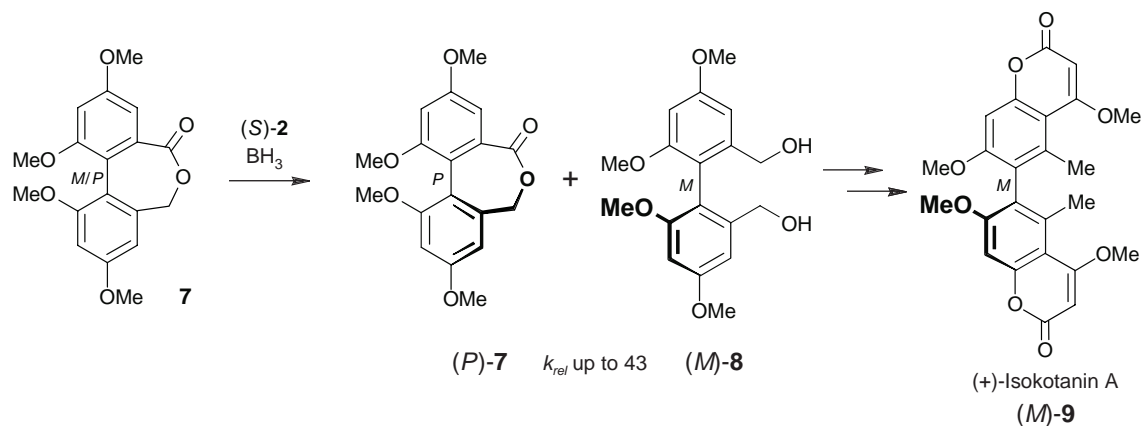
the entire mechanistic course of the ring-cleavage reaction [8, 9]. Accordingly, the lactones **1** do not constitute typical biaryls, but are, due to the short lactone bridge, rather to be addressed as helicene-like distorted – and thus chiral – tetracyclic ring systems. Another consequence of the short bridge is the drastically lowered atropisomerization barrier, so that (in contrast to the configurationally stable open-chain products **5** or **6**) the two enantiomeric forms of the lactones, **1a** and **1b**, rapidly interconvert at room temperature, showing that the stereochemical principle of the atroposelective ring cleavage of **1** must be that of a dynamic kinetic resolution (Scheme 1). The method has proven its efficiency and broad applicability in the atroposelective synthesis of numerous pharmacologically active natural products and useful reagents and ligands for asymmetric organic synthesis [10, 11].

We have recently extended this efficient principle, the ‘lactone method’, to the use of structurally related, but seven-membered biaryl lactones like **7** as

* “Novel concepts in directed biaryl synthesis”, part 104. For part 102, see: Lit. [1].



Scheme 1. Six-membered ring lactones in the atroposelective synthesis of axially chiral compounds: helical, but configurationally unstable, and hence substrates for dynamic kinetic resolutions.



Scheme 2. Atroposelective ring cleavage of seven-membered ring lactones in the total synthesis of (+)-isokotanin A [(*M*)-**9**] [14].

likewise stereochemically interesting and preparatively useful ring cleavage substrates (Scheme 2) [12–14]. In contrast to the above-mentioned lactones of type **1**, the seven-membered analogs are configurationally stable. Their ring cleavage *e.g.* with (*S*)-**2**· BH_3 thus has to proceed by non-dynamic kinetic resolution, leading to the enantioselective formation of (*M*)-**8**, an intermediate in the atropo-enantioselective total synthesis of (+)-isokotanin A [(*M*)-**9**], and unreacted (*P*)-**7** with remarkably high relative rate constants (here $k_{\text{rel}} = 43$ analytically, and $k_{\text{rel}} = 26$ for preparative batch sizes) [14].

To learn more about the structures of such seven-membered bridged biaryls and thus of lactol-type ring cleavage intermediates [15, 16], we have, as also previously in the field of six-membered analogs [17], started synthesizing and analyzing the corresponding cyclic ethers [18, 19] (here compound **10**) as more stable (and thus more easily investigated) models for the rapidly opening lactol intermediate in the reductive cleavage of **7**. The ether-bridged biaryl **10** had already been prepared in an optically active form [20], and it had also been obtained as a minor by-product (< 20%) in the attempted reductive deoxygenation of **8** [14].

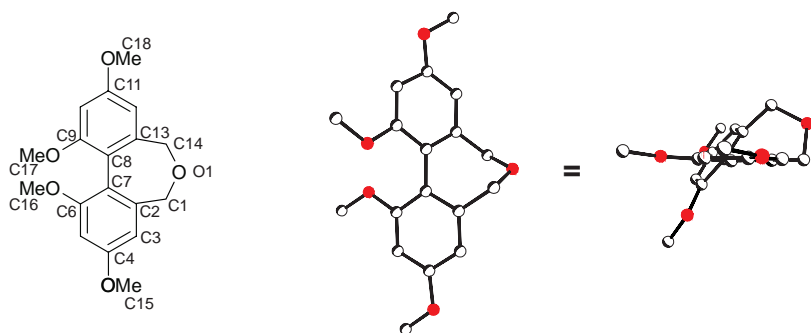
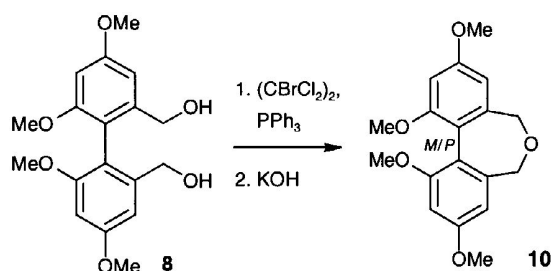


Fig. 1. Atom numbering and crystal structure of **10**; of the two atropo-enantiomeric forms present in the unit cell, only the *P*-isomer is shown, arbitrarily; hydrogen atoms are omitted for reason of clarity. In the middle, a topview of **10** is shown and on the right side a view along the series C-4, C-7, C-8, C-11 (*i.e.* including the biaryl axis).



Scheme 3. Preparation of the cyclic ether **10** in a racemic form.

Results and Discussion

Synthesis

For X-ray crystallographic investigations, it turned out to be useful to take racemic material of **10**, because of its better crystallization properties as compared to those of enantiopure material as obtained earlier [14,20]. For this purpose, a directed synthesis to **10** was developed, by treatment of the diol **8** with the reagent combination 1,2-dibromotetrachloroethane/ PPh_3 [21] and further *in situ* transformation of the intermediate bromo alcohol to give **10**, by using KOH under phase transfer conditions. This permitted to prepare **10** on a sufficiently large scale for crystallization attempts (Scheme 3).

Crystal structure analysis

Crystals of racemic **10** of sufficient quality for X-ray structure analysis were obtained by careful recrystallization from Et_2O /petroleum ether. Compound **10** crystallized in the triclinic space group $P\bar{1}$, with two formula units (*viz.* the two enantiomeric forms of **10**) in the unit cell. Crystal data are presented in Table 1 and selected bond lengths are reported in Table 2 according to the atom labels in Fig. 1.

Table 1. Crystal data and structure refinement for **10**.

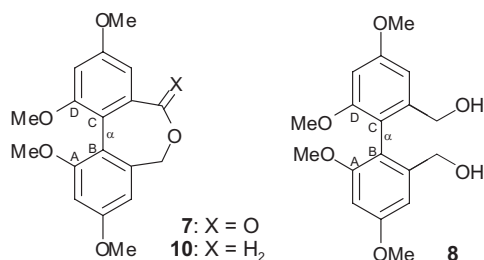
Empirical formula	$\text{C}_{18}\text{H}_{20}\text{O}_5$
Molecular mass	316.34
Crystal system	triclinic
Space group	$P\bar{1}$
Unit cell dimensions	$a = 871.30 (5) \text{ pm}$ $b = 901.81 (5) \text{ pm}$ $c = 1032.60 (6) \text{ pm}$ $\alpha = 100.147 (4)^\circ$ $\beta = 96.175 (4)^\circ$ $\gamma = 100.015 (4)^\circ$
Formula units per cell	$Z = 2$
Unit cell volume (V)	$778.47 (8) \times 10^6 \text{ pm}^3$
Calculated density	1.350 Mg/m^3
Crystal size	$500 \times 300 \times 200 \mu\text{m}^3$
Radiation, wavelength	Mo-K α , 71.073 pm
Temperature of measurement	293 (1) K
θ Range	2.02° to 25.38°
Range in hkl	$-10 \leq h \leq +10$ $-10 \leq k \leq +10$ $0 \leq l \leq +12$
Total no. reflections	11420
Independent reflections	2856
Reflections with $I > 2\sigma(I)$	2001
Data / parameters	2856 / 212
Goodness-of-fit on F^2	0.951
Final R indices ^{a,b} [$I > 2\sigma(I)$]	$R1 = 0.0366$ $wR2 = 0.0927$
R Indices (all data)	$R1 = 0.0495$ $wR2 = 0.0963$
$g1, g2^c$	0.055800, 0
Largest diff. peak and hole	$0.127/-0.189 \text{ e } 10^{-6} \text{ pm}^{-3}$

$$^a R1 = \frac{\sum \|F_o\| - \|F_c\|}{\sum \|F_o\|}; \quad ^b wR2 = \frac{[\sum w(F_o^2 - F_c^2)^2]^{1/2}}{[\sum w(F_o^2)^2]^{1/2}}; \quad ^c w = [\sigma^2(F_o^2) + (g_1P)^2 + g_2P]^{-1}; \quad P = [\max(F_o^2, 0) + 2F_c^2]/3.$$

As expected from the structure of the related seven-membered lactone **7** investigated previously [14], the two substituted benzene ring systems in **10** are, each of them, virtually flat, with only very small deviations from planarity (RMS (root-mean-square deviation) to benzene: 0.017 Å for both rings). As a measure for the molecular distortion at the biaryl axis we have previ-

Table 2. Selected bond lengths (pm) of **10** in the solid state.

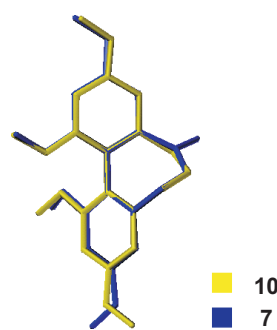
C1-O1	143.56 (16)	C9-O9	136.67 (16)
C1-C2	150.13 (17)	C9-C10	137.82 (19)
C2-C3	139.00 (17)	C10-C11	138.8 (2)
C2-C7	139.86 (18)	C11-O11	136.90 (11)
C3-C4	138.03 (18)	C11-C12	138.00 (19)
C4-C5	138.29 (19)	C12-C13	139.94 (18)
C4-O4	137.00 (16)	C13-C14	150.60 (18)
C5-C6	138.92 (18)	C14-O1	143.53 (16)
C6-O6	136.22 (15)	C15-O4	142.48 (17)
C6-C7	139.96 (18)	C16-O6	141.86 (15)
C7-C8	148.54 (18)	C17-O9	141.84 (17)
C8-C13	139.07 (19)	C18-O11	141.3 (2)
C8-C9	140.93 (18)		

Fig. 2. Definition of the dihedral angles at the biaryl axes of **7**, **8**, and **10**.

ously used the dihedral angle α (ABCD) [17,18]. For a definition of this angle, see Fig. 2.

The two aromatic rings of **10**, although not orthogonal to each other, adopt a relatively large dihedral angle to each other (57.7° , see Table 3 and Fig. 1 right), nearly identical to that of the lactone **7** (57.5° [17]) and in agreement with a major shift difference ($\delta = 4.13$ vs. 4.39 ppm) and thus diastereotopically highly differentiated character of the geminal benzylic protons in the ^1H NMR spectrum (see Experimental Section).

These dihedral angles in **7** and **10** are distinctly larger than for related six-membered lactones like **1** ($R = \text{OMe}$), in which the respective value is 32.2° [17]. In that case, the six-membered cyclic ether corresponding to **1** (again $R = \text{OMe}$) has a significantly larger value (40.3°) than the lactone [18], while for the seven-membered ring systems investigated here, the structures of **7** and **10** match nearly perfectly with each other (see Figure 3). Both for **7** and **10**, the bridge is long enough to permit the system to behave nearly like an open-chain biaryl – except for the dihedral angle, which is usually in the region of orthogonality for true open-chain biaryls (e.g. 93.1° for **8** [14]). Thus, the bridge – be it an ether or an ester linkage – does not significantly influence the geometry of the two par-

Fig. 3. Matchplot demonstrating the close similarity of the structures of lactone **7** and ether **10** (again exemplarily for the *P*-atropoisomers).Table 3. Dihedral angles (deg) of **7**, **8**, and **10**, as determined by X-ray diffraction and calculation of the structures.

	7	10	8
α (ABCD)			
exp.	57.5 ^a	57.7	93.1 ^a
calcd.	52.6	55.7	93.9

^a Determined here from the data published in lit. [14].

tial system of the biaryl moieties as long as it generates a large, seven-membered ring system, while in related six-membered heterocycles the cyclic ethers differ structurally more significantly from the far more strain-distorted lactones because here even slight differences in hybridization and bond lengths will increase or decrease ring strain substantially [17, 18].

Comparison of experimental and calculated structures

In parallel, all of the structures of the compounds **7**, **8**, and **10** treated here were also investigated by *ab initio* calculations according to the density functional theory (DFT), using the B3LYP/6-31G* basis set, and the minimum structures obtained were compared to the experimental ones. The theoretical results match the experimental data nearly perfectly, not only for the cyclic ether **10**, but also for the lactone **7** and likewise for the open-chain diol **8** (Figure 4), thus demonstrating the predictive value of these methods in giving information on the structures of such biaryl compounds – and thus also of, e.g., reactive and thus unstable intermediates like lactols, which normally escape any experimental structural analysis by their rapid ring cleavage.

Experimental and Computational Section

Synthesis of racemic **10**

The cyclic ether **10** had already been synthesized in enantiopure form for an investigation of the isomerization process

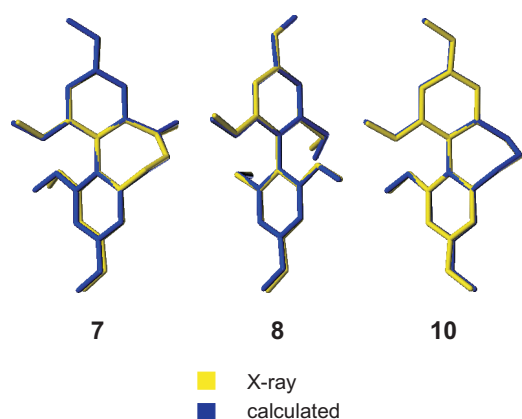


Fig. 4. Superimposed experimental (bright) and calculated (B3LYP/6-31G*, dark) structures of **7**, **8**, **10** (again only the *P*-enantiomers are shown for reason of comparability).

at the biaryl axis [20], and had, in more recent work, been obtained as a by-product, likewise in an optically active form, in the conversion of diol **8** into the corresponding dibromide [14]. For the synthesis of racemic material, the following procedure was applied.

To a solution of **8** (11.8 mg, 3.5 μ mol) in CH_2Cl_2 (0.5 ml), triphenylphosphine (18.6 mg, 7.1 μ mol) and 1,2-dibromotetrachloroethane (11.6 mg, 3.6 μ mol) were added at r.t., and stirring was continued for 20 min. Then 1.0 ml of 2 N potassium hydroxide and a catalytic amount of NBu_4I were added, and the mixture was stirred vigorously for further 2 h. The organic layer was separated and the aqueous phase was extracted twice with ether. The solvent was removed from the combined extracts and the residue was purified by filtration over silica gel and recrystallization from Et_2O /petroleum ether (b. p. 40–60 $^\circ\text{C}$), to give 7.1 mg (2.2 μ mol) of **10**, in 63% yield as colorless blocks. M. p. 128 $^\circ\text{C}$. – IR (KBr): $\nu = 2958$ (m), 2857 (m), 1640 (s), 1602 (s), 1157 (s), 1009 (s) cm^{-1} . – ^1H NMR (CDCl_3 , 400 MHz): $\delta = 3.82$ (s, 6 H, OMe), 3.86 (s, 6 H, OMe), 4.13 (d, $^2J = 11.2$ Hz, 2 H, CH_2O), 4.39 (d, $^2J = 11.2$ Hz, 2 H, CH_2O), 6.57 (d $^3J = 2.2$ Hz, aryl-H), 6.60 (d $^3J = 2.2$ Hz, aryl-H). – $^{13}\text{C}\{^1\text{H}$ decou-

pled} NMR (CDCl_3 , 100 MHz): $\delta = 55.4$ (s, OMe), 55.83 (s, OMe), 67.7 (CH_2O), 99.2, 105.5, 118.3, 137.0, 157.6, 160.4 (aryl-C). – MS: m/z (%) = 316 (100) [M^+], 301 (8) [$\text{M}^+ - \text{CH}_3$], 273 (45) [$\text{M}^+ - \text{C}_3\text{H}_7$].

Crystal structure determination

The crystal of **10** was glued on the tip of a glass fibre and used for intensity data collection on a BRUKER Smart-APEX with a D8 goniometer, employing $\text{Mo-K}\alpha$ radiation in an ω -scan mode. The data were integrated with SAINT [22]. The structure was solved by direct methods (SHELXS-97) [23] and refined by full matrix least square calculations on F^2 (SHELXL-97) [24]. All non-hydrogen atoms in **10** were located by difference Fourier syntheses and refined anisotropically. All hydrogen atoms were placed in idealized calculated positions and allowed to ride on their corresponding carbon atoms with fixed isotropic contributions. Further information on crystal data and data collection are summarized in Table 1. Interatomic distances are shown in Table 2. For details on the labelling of the atoms see Figure 1. All other information on the crystal structure analysis has been deposited with the Cambridge Crystallographic Data Centre. The data are available free of charge as a CIF file upon request on quoting CCDC No. 194396, the author names, the journal name and page numbers. For details on the structures of **7** and **8**, see Lit. [14].

Computational Methods

Quantum chemical calculations were performed on i686-Linux workstations using the Gaussian 98 [25] program package. Input geometries were obtained using the TRIPOS force field as implemented within SYBYL 6.7.1 [26] on a Silicon Graphics OCTANE (R10000).

Acknowledgements

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