Development of an Axial Chirality Switch

Stefan Reichert and Bernhard Breit*

Institut für Organische Chemie und Biochemie, Albert-Ludwigs-Universität Freiburg i. Brsg., Albertstr. 21, 79104 Freiburg i. Brsg., Germany

bernhard.breit@chemie.uni-freiburg.de

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ABSTRACT



Switching axial chirality: The development and synthesis of a new axial chiral system, which shows solvent-dependent atropisomerism, is described. Control of axial chirality by the choice of solvent was studied by NMR and CD spectroscopy.

In the past few years, there has been an increased interest in the development and synthesis of systems capable of performing a defined function on a molecular scale.¹ This includes molecular switches, characterized as systems which due to the action of an external stimulus can change reversibly between two distinct states. Known examples are switchable rotaxanes and catechanes,² conformational switches,³ redox switches,⁴ as well as photo and chiroptical switches.⁵ In many cases, processes known from nature have served as role models for the design of artificial systems. In this context, we became interested in the natural product FD-594 which, dependent on the polarity of the solvent, can exist in two conformations having opposite helicity (solvent-dependent atropisomerism, Figure 1).⁶

A detailed conformational analysis of the aglycon of FD-594 (1) revealed that the helicity of the biaryl axis is connected to the preferred conformation in the central sixmembered ring C.⁶ Thus, the two hydroxy substituents at carbon atoms 6 and 7 can occupy either a pseudobisequatorial (biseq-1) or a pseudobisaxial position (bisax-1) (Figure 1) which is a function of the solvent polarity. According to proton NMR experiments in chloroform ($\mu = 1.14$ D, $\epsilon =$ 4.89, $E_{\rm T}^{\rm N} = 0.259$),⁷ FD-594 (1) prefers the biseq-1 conformation (${}^{3}J_{6,7} = 9.2$ Hz)⁸ to allow the formation of a stabilizing intramolecular hydrogen bond between the hydroxyl groups on C6 and C7.

However, when switching to methanol ($\mu = 2.88$ D, $\epsilon = 32.66$, $E_{\rm T}^{\rm N} = 0.762$)⁷ as the solvent, the intramolecular hydrogen bond is broken, and minimization of gauche

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Figure 1. Solvent-dependent atropisomerism of FD-594 (1, R = H). Left: pseudobisequatorial hydroxyl substituents on C6 and C7 (biseq-1). Right: pseudobisaxial hydroxyl substituents on C6 and C7 (bisax-1).

interaction of the hydroxy substituents at C6/C7 now favors the bisax-1 conformation (${}^{3}J_{6,7} = 3.6$ Hz) and induces a switch in helicity of the biaryl axis.

Intrigued by this interesting conformational behavior of FD-594 (1), we became interested in the development of a simplified artificial model system which could mimic the solvent-dependent atropisomerism. As a minimal central core, we identified the 9,10-dihydrophenanthren skeleton⁹ which corresponds to the BCD-ring system of FD-594 (1, Scheme 1). The identification of the role of the methoxy substituent



at the D-ring in FD-594 (1) was an important aspect. We speculated that the gauche orientation of the hydroxy substituents at C6 and C7 is disfavored by $A^{1,3}$ -strain¹⁰ exerted by the *ortho*-methoxy substituent at ring D. Therefore, the influence of substituents R at carbon 1 of the model system (2–6) should be explored. Furthermore, the hydroxyl groups at positions 4 and 5 were incorporated into the model system (protected as methyl ethers) because, if this concept was successful, the system could behave and be used as a switch-

able BINOL derivative with potentially manifold applications in supramolecular chemistry and asymmetric catalysis.¹¹

To get an idea about the influence of the ortho substituent R on relative energies of biseq and bisax conformations, we performed density functional gas-phase calculations for the model systems 2-6 on the B3LYP/6-311+G(3df,2p)// B3LYP/6-31G* level with Gaussian03.¹² Thus, for all model systems, geometry optimization for both distinguished conformers was performed and the corresponding relative energies were compared. For molecules 2 ($E_{rel(zpe)} = 1.5$ kcal/ mol), 3 ($E_{\text{rel(zpe)}} = 1.4$ kcal/mol), and 6 ($E_{\text{rel(zpe)}} = 1.8$ kcal/ mol), the biseq conformation was energetically favored. Conversely, for molecules 4 ($E_{rel(zpe)} = 2.2$ kcal/mol) and 5 $(E_{\rm rel(zpe)} = 2.4 \text{ kcal/mol})$, the corresponding bisax conformation is preferred. Thus, with increasing steric demand of the substituent R in the 1 position, the biseq conformation becomes disfavored, which goes along with an increase of A^{1,3}-strain in the biseq conformation between the hydroxy substituent at C10 and the R substituent at C1 (Scheme 1). However, the situation for the methoxy-substituted system 6 is different.

Here, the calculation suggests the possibility for an additional stabilizing intramolecular hydrogen bond between the hydroxy substituent at C10 and the methoxy substituent at C1 (Figure 2). According to the gas-phase calculations,



Figure 2. Optimized geometries $(B3LYP/6-31G^*)$ of (R,R)-6. Left: biseq conformer with 2 hydrogen bonds. Right: bisax conformer.

the stabilizing effect of this additional hydrogen bond overcompensates the $A^{1,3}$ -strain.

To determine the preferred conformations of model systems 2-6 in solution, compounds 2-6 were prepared following a divergent strategy which allows the synthesis of all compounds from a common precursor.

Thus, 3-methoxybenzaldehyde **7** was converted into the corresponding cyclohexyl imine (Scheme 2). Position-selective ortho metalation with LTMP¹³ and trapping of the intermediate aryllithium species with iodine furnished iodide **8** in an almost quantitative yield. To effect a biaryl coupling toward the sterically crowded tetra-ortho-substituted biaryl

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system **9**, a mild variant of the Ullmann coupling with copper(I) thiophenecarboxylate (CuTC) was chosen.¹⁴ After acidic workup, the bisaldehyde **9** was obtained in good yield (86%). Monobromination of **9** gave regioselectively biphenyl system **10** (Scheme 2).



CuTC = copper(I) thiophenecarboxylate; b.o.r.s.m. = based on recovered starting material.

The unsubstituted model system 2 was obtained by samarium diiodide mediated anti diastereoselective pinacol coupling of bisaldehyde 9 (Table 1).¹⁵ After protection of

Table 1.	Synthesis of Model Compounds $2-6$	
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entry	conditions	substrate	product (yield)
1	(1) SmI ₂ , THF, 0 °C	9	2 (88%)
2	(1) CyNH ₂ , MgSO ₄ , CH ₂ Cl ₂ , rt	10	3(19%)
	 (2) <i>n</i>-BuLi, THF, - 78 °C, then (PhSO₂)₂NF, HCl (3) SmI₂, THF, 0 °C 		
3	 (1) CyNH₂, MgSO₄, CH₂Cl₂, rt (2) <i>n</i>-BuLi, THF, - 78 °C then C₂Cl₆, HCl (3) SmI₂, THF, 0 °C 	10	4 (36%)
4	(1) SmI ₂ , THF, 0 °C	10	5(72%)
5	 (1) CyNH₂, MgSO₄, CH₂Cl₂, rt (2) <i>n</i>-BuLi, THF, - 78 °C then Davis oxaziridine, HCl (3) dimethyl sulfate, DME (4) SmI₂, THF, 0 °C 	10	6 (44%)

the bisaldehyde function in **10** as the corresponding bisimine, bromine lithium exchange and subsequent trapping with an

appropriate electrophile allowed us to install the desired substituents at carbon 1. Final pinacol coupling furnished the model compounds 3-6 in moderate to good yields (Table 1).

With the thus-obtained model systems 2-6, NMR studies were performed in methanol and in chloroform to determine the preferred conformation in solution. It is known that the barrier of rotation of biaryl systems is lowered, if they are bridged by a six-membered ring.¹⁶ At room temperature, molecules **2**, **3**, and **6** showed broadened signals due to an exchange process. Therefore, the conformer population for all diols **2**–**6** was determined by integration of the signals for H9 and H10 in the proton NMR measured at T = 240 K (Table 2).¹⁷

Table 2.	Conformer	Equilibria	for Diols	2-6	Determined	by
NMR at 2	240 K ^a					

entry	compound	solvent	biseq (%)	bisax (%)
1^{b}	2	CD_3OD	94	6
2^b		$CDCl_3$	98	2
3	3	CD_3OD	nd	>99
4		$CDCl_3$	32	68
5	4	CD_3OD	nd	>99
6		$CDCl_3$	nd	>99
7	5	CD_3OD	nd	>99
8		$CDCl_3$	nd	>99
9	6	CD_3OD	nd	>99
10		$CDCl_3$	58	42
11		toluene- d_8	82	18

^{*a*} nd = not detected. Assignment of the corresponding conformations has been made on the basis of the size of the ${}^{3}J_{9,10}$ coupling constant. ^{*b*} For symmetrical compound **2**, the ${}^{3}J_{9,10}$ coupling constant was determined employing a nondecoupled HSQC experiment.

In the case of the unsubstituted diol 2, the biseq conformation was preferred in chloroform as well as in methanol. For the chlorine- and bromine-substituted derivatives 4 and 5, only the bisax conformation was detectable in both methanol and chloroform, which is in agreement with the calculations. However, in the case of the fluorine- and methoxy-substituted systems 3 and 6, respectively, a significant influence of the nature of the solvent on the conformational equilibrium could be observed. Thus, for **6** in methanol, the bisax conformation is populated to more than 99% (Table 2, entry 9). However, when going to $CDCl_3$ as the solvent, a 58:42 equilibrium in favor of the biseq conformer was detected (entry 10). Interestingly, when using the even less polar solvent toluene $(\mu = 0.30 \text{ D}, \epsilon = 2.38, E_{\text{T}}^{\text{N}} = 0.099)$, the equilibrium could be shifted far toward the biseq conformer (Table 2, entry 11). Thus, in agreement with theory, the methoxy-substituted biaryl system 6 seemed an appropriate candidate to imitate

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the helicity switch of the natural product FD-594 (1). Hence, rac-6 was separated into its enantiomers employing preparative HPLC (Chiracel AD-H).

For enantiomerically pure **6**, CD spectra were recorded in *n*-hexane ($\mu = 0.0$ D, $\epsilon = 1.88$, $E_T^N = 0.009$) and in methanol ($\mu = 2.88$ D, $\epsilon = 32.66$, $E_T^N = 0.762$), respectively (Figure 3). As expected, the CD spectra behave like mirror



Figure 3. Experimental and calculated CD spectra for the (*R*,*R*)enantiomer of **6**. Blue: exptl CD curve of P-(*R*,*R*)-**6** in *n*-hexane ($c = 1.3 \times 10^{-5}$ M, rt). Magenta: calcd CD curve of P-(*R*,*R*)-**6**. Red: exptl CD curve of M-(*R*,*R*)-**6** in methanol ($c = 1.3 \times 10^{-5}$ M, rt). Yellow: calcd CD curve of M-(*R*,*R*)-**6**.

images and thus confirm a complete helicity switch of the biaryl chromophore as a consequence of change in solvent environment. From comparison with known 9,10-dihydrophenanthene derivatives, the helicity of the biaryl chromophore was assigned as P-**6** in *n*-hexane and as M-**6** in methanol.^{9,18} With the known relative configuration at C9 and C10 from NMR experiments, the absolute configuration

can be assigned as P-(R,R)-**6** in *n*-hexane and as M-(R,R)-**6** in methanol.¹⁸ Additionally, CD spectra of **6** were calculated employing quantum chemical methods (TD-B3LYP/TZ-VP).¹⁹ Comparison between calculated and experimental CD curves confirmed the configurational assignment for **6** (Figure 3).^{12,19}

These experiments illustrate that the axial chirality of 6 can be controlled by choice of the solvent environment. Hence, the solvent-dependent atropisomerism of the complex natural product FD-594 (1) could be transferred to the much simpler model system 6. Modification of 6 and its application as a molecular switch as well as a switchable ligand for asymmetric catalysis are the subjects of current research in these laboratories.

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Supporting Information Available: Experimental procedures and full spectroscopic data for all new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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