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TETRAHEDRON: *ASYMMETRY*

# Synthesis and absolute configuration of a bi[10]paracyclophane with two chiral planes and one chiral axis

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**Abstract**

The bi[10]paracyclophane (−)-**6b** with two chiral planes and one chiral axis has been synthesized in enantiomerically pure form. Its absolute configuration was determined by quantum chemical calculation of the circular dichroism and comparison with the experimental CD spectrum. © 1999 Elsevier Science Ltd. All rights reserved.

Chiral molecules devoid of stereogenic centers are of particular interest.[1–7] Here we report on the synthesis and the elucidation of the absolute configuration of (−)-**6b**, the first bi[10]paracyclophane with two chiral planes and one chiral axis.

For that purpose our previous synthesis of [10]paracyclophanes[8] was transferred to the bifuran **1**, which was obtained from 3,4-decamethylenefuran[8] after lithiation with *n*-butyllithium and coupling with nickel(II) chloride (Scheme 1). Diels–Alder reaction of **1** with dimethyl acetylene dicarboxylate afforded a 4:1 mixture (77%) of the bioxanorbornadienes *meso*-**2** and *rac*-**2**, which were separated by column chromatography. Irradiation† yielded the corresponding bioxaquadricyclanes, which were thermolyzed to the bioxepines *meso*-**4** and *rac*-**4**.[8,9] For preparative purposes it is more convenient to irradiate and thermolyze the *meso*-**2**/*rac*-**2** mixture directly and to separate the bioxepines **4** by column chromatography.‡

The assignments of the *meso*- or *rac*-series were derived from crystal structure analyses[10–12] of other homologs and by comparison of the $^{13}$C NMR spectra of **2**. Aromatization of the bioxepine *meso*-**4** with trifluoroacetic acid yielded the ketophenol **5a** (Scheme 2), in which one of the six-membered rings exists in the tautomeric keto form because of steric hindrance.§ Twofold *O*-methylation of **5a** was achieved after numerous efforts only in two steps by monomethylation with sodium methoxide/dimethyl sulfate

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† High-pressure mercury lamp TQ 718, ether:dichloromethane (5:1) or ether, respectively, 2 h.

‡ Aluminum oxide (II–III), ether:pentane (1:2), yield 12% *rac*-**4** and 50% *meso*-**4**.

§ Selected data: $^{13}$C NMR (50 MHz, $CDCl_3$): δ 51.89 (d, C–H), 198.21 (s, C=O).


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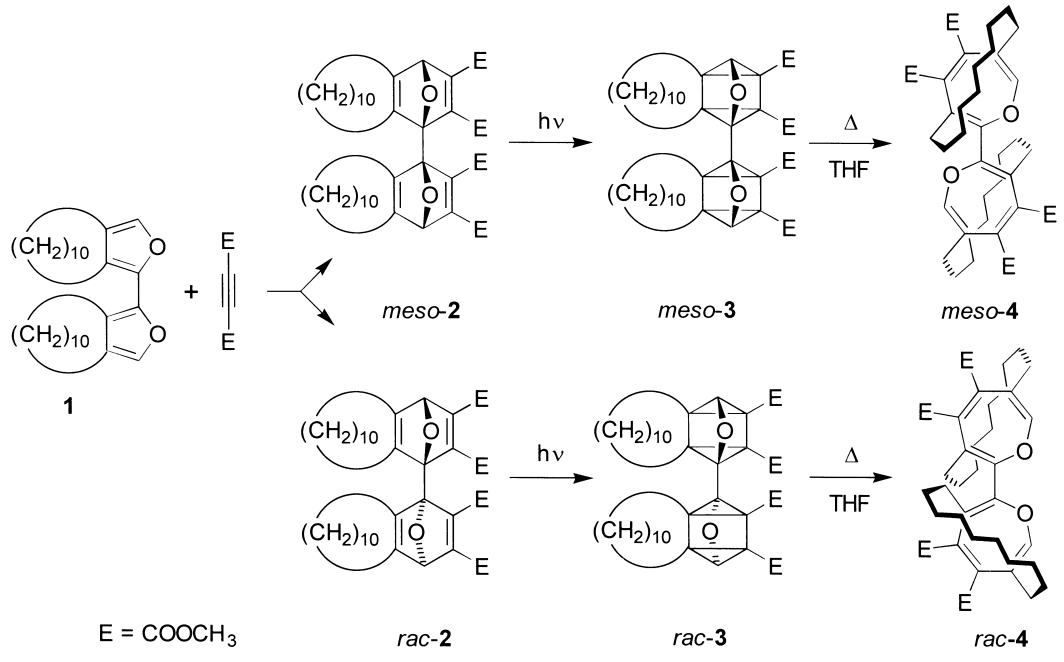
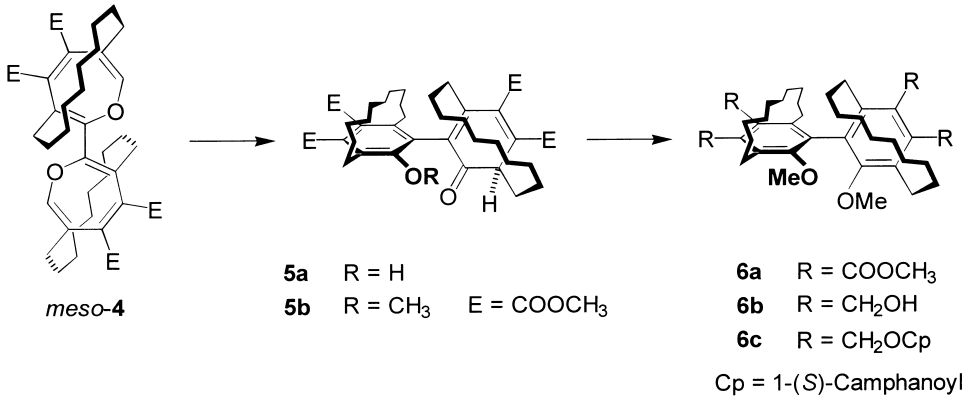



Scheme 1. Synthesis of the diastereomeric bioxepines *meso*- and *rac*-**4**[8,9]

to give **5b** and subsequent treatment of **5b** with potassium *tert*-butoxide/trifluoromethanesulfonic acid methyl ester to give **6a** (yield 40%). The $^{1}$H NMR spectrum with two singlets for the methoxy groups[¶] in the *ortho* positions and the $^{13}$C NMR spectrum provide evidence for a configurationally stable structure **6a** with two diastereomorphous halves.




Scheme 2. Synthesis of the target molecule (−)-**6b**

Treatment of *rac*-**4** with trifluoroacetic acid yielded a bis-phenol which was dimethylated to give a stereoisomer of **6a**. According to its NMR spectrum, which shows only the half set of signals, this compound has $C_2$ symmetry.

[¶] Selected data: $^{1}$H NMR (200 MHz, $CDCl_3$): δ 3.42 (s, 3H, Ar–$OCH_3$), 3.63 (s, 3H, Ar–$OCH_3$); $^{13}$C NMR (50 MHz, $CDCl_3$): δ 158.37 (s, C–$OCH_3$), 158.96 (s, C–$OCH_3$).

**6a** is racemic because the biaryl axis was not introduced via an enantioselective synthesis. A resolution was possible after reduction to **6b** with $LiAlH_4$ and by HPLC[||] of the diastereomeric tetracamphanoates **6c**. Compound (+)-**6c** was obtained diastereomerically pure.[††] Treatment of (+)-**6c** with sodium methoxide/methanol yielded the enantiomerically pure target molecule (−)-**6b**.

The heterochiral character of the chiral planes in (−)-**6b** was evident from its synthesis from *meso* precursors, so that only two possible — enantiomeric — structures should remain to be distinguished, p*P*,a*P*,p*M*- and p*P*,a*M*,p*M*-**6b** (=p*M*,a*M*,p*P*-**6b**). As a consequence, the determination of the configuration of the rotationally hindered biaryl axis allowed both of the enantiomeric structures to be distinguished. Quantum chemical calculation of the circular dichroism (CD) spectrum and comparison with the experimental CD spectrum is a successful method to determine the absolute configurations of centro, axial, and planar chiral compounds of various structures.[13] In the present case, the conformational space of (−)-**6b** was analyzed by the semiempirical AM1 method, choosing arbitrarily the p*P*,a*P*,p*M*-enantiomer. Besides the global minimum (Fig. 1) seven further minimum structures were found within an energetic cut-off of approximately 4 kcal/mol, located 0.343, 0.606, 0.940, 2.075, 2.381, 2.760, and 3.6062 kcal/mol higher than the global minimum.

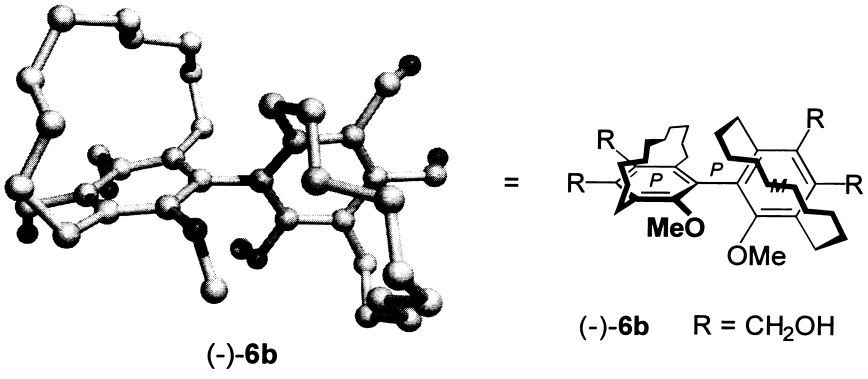



Figure 1. Conformation of (−)-**6b** representing the global energetic minimum

For each of the eight conformers detected, the individual CD spectrum was calculated separately. The resulting single CD spectra were Boltzmann weighted according to the enthalpies of formation of the corresponding conformers and added up to give the theoretical overall CD spectrum of the p*P*,a*P*,p*M*-enantiomer. Reflection of this spectrum at the zero line generated the theoretical spectrum of the p*P*,a*M*,p*M*-enantiomer. The calculated and subsequently UV-corrected[13] CD spectrum of p*P*,a*P*,p*M*-**6b** is in very good agreement with the experimental one (Fig. 2), whereas the theoretical spectrum of p*P*,a*M*,p*M*-**6b** is approximately the mirror image of it. Consequently, the bi[10]paracyclophane (−)-**6b**, which was obtained from (+)-**6c**, can be assigned the absolute p*P*,a*P*,p*M*-configuration.

(−)-**6b** represents a novel biaryl system which consists of two planar chiral units of identical constitution but of opposite configuration. Nevertheless, (−)-**6b** is not a *meso* compound.[1–3] The molecule is chiral and configuratively stable because of hindered rotation around the biaryl axis and therefore shows optical activity.[14]

[||] Pump C-6000, Merck Darmstadt; column LiChrosorb Si 60-7 (250×25 mm), Merck Darmstadt; flow 10 ml/min; ethyl acetate:cyclohexane (3:7); detector RI 8110, Bischoff.

[††] Chromatographically faster diastereomer, selected data: $^1$H NMR (300 MHz, $CDCl_3$): δ 3.28 (s, 3H, Ar–$OCH_3$), 3.60 (s, 3H, Ar–$OCH_3$); de >95%.

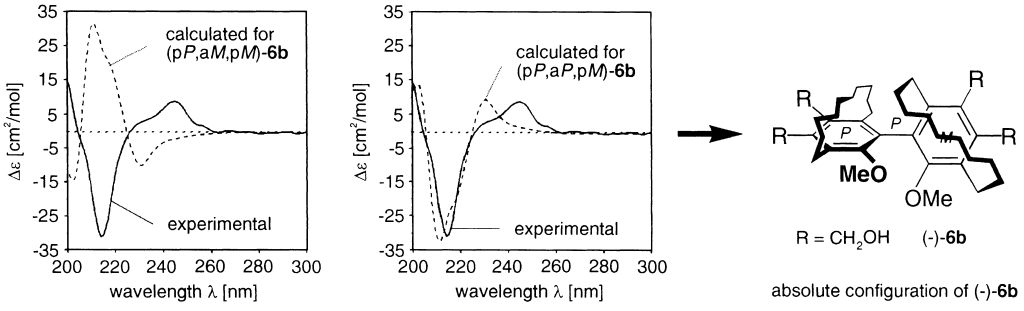



Figure 2. Determination of the absolute configuration of (−)-**6b**

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