Pergamon

SCIENCE DIRECT®

Tetrahedron 59 (2003) 7791–7801

TETRAHEDRON

Bridged bioxepines and bi[10]paracyclophanes—synthesis and absolute configuration of a bi[10]paracyclophane with two chiral planes and one chiral axis

Werner Tochtermann,[a,*] Dirk Kuckling,[a] Christine Meints,[a] Jürgen Kraus[b] and Gerhard Bringmann[b,*]

[a]*Institut für Organische Chemie, Universität Kiel, Olshausenstraβe 40, D-24098 Kiel, Germany*
[b]*Institut für Organische Chemie, Universität Würzburg, Am Hubland, D-97074 Würzburg, Germany*

Received 11 April 2003; revised 17 July 2003; accepted 24 July 2003

Abstract—A preparative synthesis of novel bioxepines and bi[10]paracyclophanes with *meso*- and *rac*-configuration is described. The bi[10]paracyclophane (−)-**6b** with two elements of planar chirality and one chiral axis has been obtained in enantiomerically pure form. Its absolute configuration was determined by quantum chemical calculation of the circular dichroism and comparison with the experimental CD spectrum.

1. Introduction

Chiral molecules devoid of stereogenic centers are of particular interest.[1–6] Bioxepines and bi[10]paracyclophanes would be rewarding target molecules because these compounds contain even three stereogenic elements: two chiral planes and one chiral axis. This structural feature should lead to different stereoisomers. Bi[10]paracyclophanes with identical substitution patterns in the two aryl rings are especially interesting from a stereochemical point of view. There should be enantiomers with p*M*,p*M*- and with p*P*,p*P*-configuration and isomers with p*M*,p*P*-configuration. At first sight the latter could be called *meso*-compounds. If, however, the rotation around the central biaryl single bond is rotationally hindered in these dimeric cyclophanes, the compounds are expected to adopt axially chiral conformations. It has been known for a long time that the most famous *meso*-compound, *meso*-tartaric acid, prefers chiral conformations in solution and in the crystalline state as well.[7] The compound is, however, optically inactive because the preferred conformations equilibrate rapidly at ambient temperature because of low energy barriers. Therefore, it was an aim of our project to characterize a p*M*,p*P*-configured compound that is still optically active because of hindered rotation around the central biaryl axis.[8]

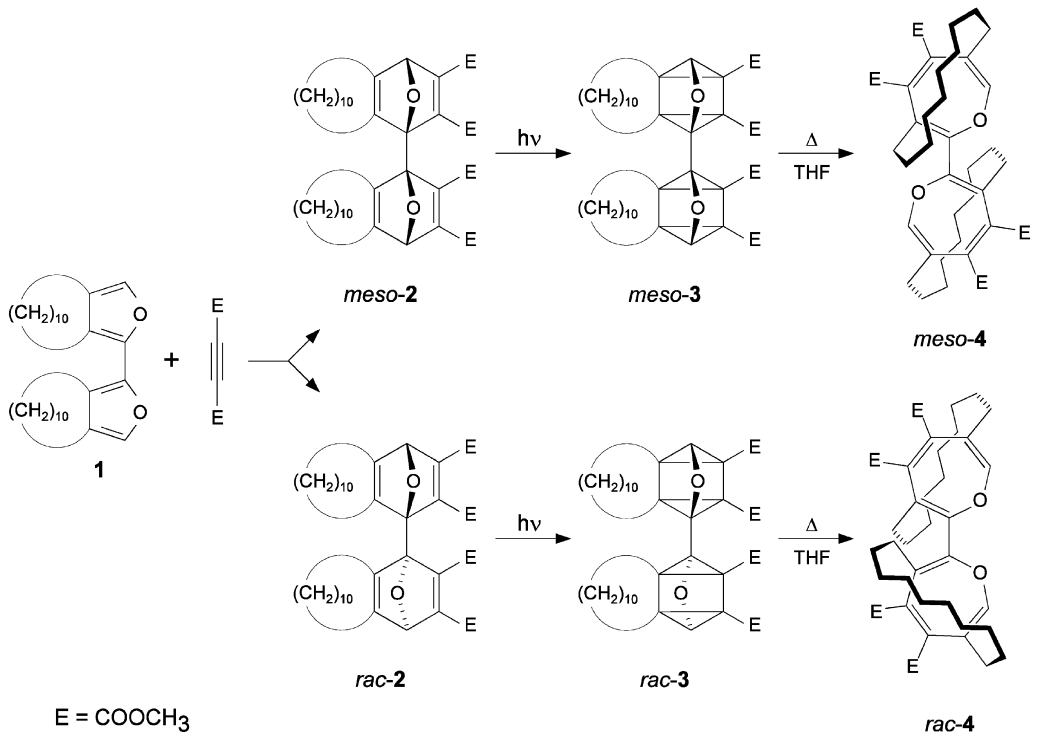
Keywords: oxepines; cyclophanes; circular dichroism; quantum chemical CD calculations; planar chirality; axial chirality.
* Corresponding authors. Fax: +49-6398-993172 (W.T.); Tel.: +49-931-888-53-23 (G.B.); fax: +49-931-888-4755 (G.B.);
e-mail: bringman@chemie.uni-wuerzburg.de

0040–4020/$ - see front matter © 2003 Elsevier Ltd. All rights reserved.
doi:10.1016/j.tet.2003.07.009

2. Results and discussion

For this purpose, our previous synthesis of [10]paracyclophanes[9] was transferred to the bifuran **1**, which was obtained from 3,4-decamethylenefuran[9] 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 (yield 77%) of the bioxanorbornadienes *meso*-**2** and *rac*-**2**, which were separated by column chromatography. Irradiation in diethyl ether/dichloromethane (5:1) or in diethyl ether yielded the corresponding bioxaquadricyclanes *meso*-**3** and *rac*-**3**, which were thermolyzed to the bioxepines *meso*-**4** and *rac*-**4**,[10,11] respectively. As expected the conversions *meso*-**2**→*meso*-**3**→*meso*-**4** and *rac*-**2**→*rac*-**3**→*rac*-**4** proceeded stereospecifically within the *meso*- and *rac*-series. For preparative purposes it was more convenient to irradiate and thermolyze the *meso*-**2**/*rac*-**2** mixture directly and to separate the diastereomers at the level of the bioxepines **4**, which was achieved by column chromatography (see Section 4).

The assignments to the *meso*- and *rac*-series were achieved as follows: We also synthesized homologs with penta-, hexa-, and heptamethylene chains in a related project and established their configurations by an X-ray structural analysis[12,13] of the respective *meso*-configured hexamethylene bioxanorbornadiene [i.e. *meso*-**2**, but with $(CH_2)_6$ instead of $(CH_2)_{10}$] and by comparison of selected ^{13}C NMR data. The differences of the chemical shifts of the singlets of the two carbon atoms bearing the methylene chain were significantly larger in the *rac*-series than for the



Scheme 1. Synthesis of the diastereomeric bioxepines *meso*- and *rac*-**4**.

corresponding *meso*-diastereomers. In addition all *meso*-compounds showed higher melting points than the *rac*-isomers (Table 1).

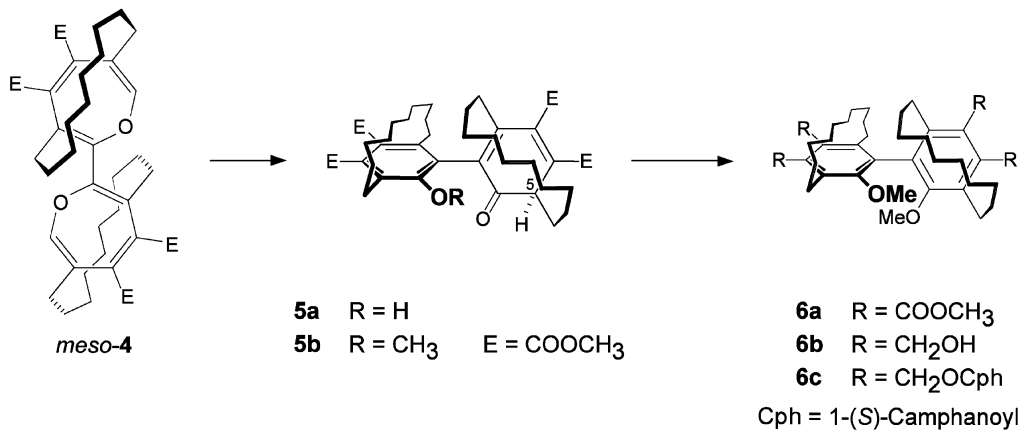
Finally, we succeeded in likewise obtaining an X-ray structural analysis of the authentic bioxepine *rac*-**4**,[14] i.e. with the decamethylene bridges. Since the conversions **2→3→4** occur stereospecifically, without any interconversion between the *meso*- and the *rac*-series, all of the other assignments were thus established as well.

Table 1. Comparison of selected ^{13}C NMR data (singlets [ppm] of the olefinic carbons in the cycloalkene ring) and melting points of *meso*- and *rac*-bioxanorbornadienes **2** with various lenthgs of the methylene chains

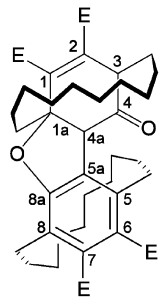
	$(CH_2)_5$	$(CH_2)_6$	$(CH_2)_7$	$(CH_2)_{10}$
meso-**2**	150.17 150.38	149.20 149.50	148.52 148.95	149.32 150.91
Mp (°C)	192	211	209	202
rac-**2**	148.66 151.56	147.67 150.19	147.02 149.67	147.93 151.86
Mp (°C)	178	151	177	171

Aromatization[10] of the bioxepine *meso*-**4** with trifluoroacetic acid yielded the ketophenol **5a** (Scheme 2), in which one of the six-membered rings exists as a cyclohexadienone, i.e. in the tautomeric keto form, thus minimizing the steric strain as resulting from the decamethylene bridges. This structural assignment was deduced from the NMR spectra, which showed signals for 5-H at δ=4.25 (dd, ^3J=7.5, 3.8 Hz), for C-5 at δ=51.72 (d) and for the keto group on C-6 at δ=200.62 (s) ppm.

Two-fold *O*-methylation of **5a** to give **6** proved to be difficult and was achieved, after numerous efforts, only in two



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



7 E = $COOCH_3$

Figure 1. By-product **7** of the monomethylation of **5a** to **5b**.

steps, initiated by its monomethylation with sodium methoxide/dimethyl sulfate to give **5b**. Like **5a**, this product was found to exist in the tautomeric keto form according to signals for 5-H at 4.02–4.12 (m), for C-5 at δ=51.89 (d) and for C-6 at δ=198.21 (s) ppm. An interesting by-product (yield 9%) of this reaction was the dibenzofuran derivative **7** arising from the intramolecular Michael-type 1,6-addition of the phenoxide to the cyclohexadienone part of **5a**. In **7** the two decamethylene bridges can adopt sterically favorable arrangements above and below the two six-membered rings. The formation of an ether bridge to give **7** is reminiscent of the heterocyclic ring closure in the biosynthesis of morphine after the phenol-oxidative coupling step (Fig. 1).[15]

Treatment of **5b** with potassium *tert*-butoxide/methyl triflate finally gave the desired dimethyl ether **6a** (yield 63%). The ^{1}H NMR spectra with two singlets at δ=3.42 and 3.63 for the methoxy groups in the *ortho* positions and the ^{13}C NMR spectra with the (nearly) full set for all 42 carbon atoms provided evidence of a configurationally stable structure **6a** with two diastereomorphous halves.

6a is racemic because the biaryl axis was not introduced in an enantioselective way. In previous studies we had managed to resolve racemic oxepines and paracyclophanes via diastereomeric camphanoates and had been able determine their absolute configurations.[5] A resolution of the biparacyclophane **6a** succeeded here after its reduction to **6b** with lithium aluminum hydride and HPLC of the diastereomeric tetracamphanoates **6c**. The chromatographically faster diastereomer (+)-**6c**, which was obtained diastereomerically pure (de>95%) showed signals for the methoxy protons at δ=3.28 (s) and 3.60 (s) ppm. The fractions containing the other diastereomer (−)-**6c′** as the major component (de=50%) had methoxy groups at δ=3.30 and 3.58 (s) ppm. Treatment of (+)-**6c** with sodium methoxide/methanol yielded the enantiomerically pure target compound (−)-**6b**.

The heterochiral character of the chiral planes in **6b** was evident from its synthesis from *meso* precursors and from its (nearly) full set of signals in ^{13}C NMR, so that only two possible—enantiomeric—structures should remain to be distinguished, viz p*P*,a*P*,p*M*-**6b** (which is identical to p*M*,a*P*,p*P*-**6b**) and p*P*,a*M*,p*M* (=p*M*,a*M*,p*P*-**6b**). Thus, as a consequence of the symmetric constitution and the presence of two differently configured elements of planar chirality, the determination of the configuration of the rotationally hindered biaryl axis would permit to distinguish between the two enantiomeric structures.

A powerful method for the assignment of the absolute configurations of most different of compounds with stereogenic centers, axes, or with planar chirality, even in the case of entirely novel-type structures like **6b**, is the quantum chemical calculation of the predicted circular dichroism (CD) spectrum of the compound and comparison with the experimental CD spectrum.[16–19]

In the present case, the conformational space of **6b** was analyzed arbitrarily starting with the p*P*,a*P*,p*M*-enantiomer. The rotation of the two phenyl rings around the biaryl axis was found to be significantly restricted, but the substituents ($-CH_2OH$ and $-OMe$) and, in particular, the two bridging alkane chains showed a high conformational flexibility. Therefore, we performed a preliminary study using a Random-Search algorithm, which scans the conformational space randomly. Starting with ten arbitrarily generated and semiempirically preoptimized conformers, a total of 65 different structures were found; an alignment of all these structures is shown in Figure 2(b). The conformations thus

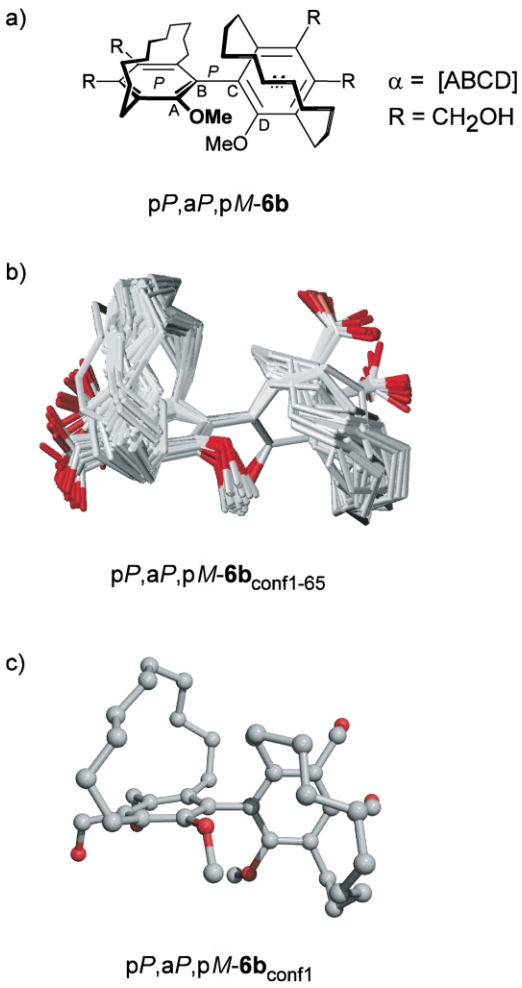


Figure 2. (a) Definition of the dihedral angle α of p*P*,a*P*,p*M*-**6b**; (b) superposition of all conformers found by the Random-Search algorithm; (c) conformation representing the global energetic minimum.

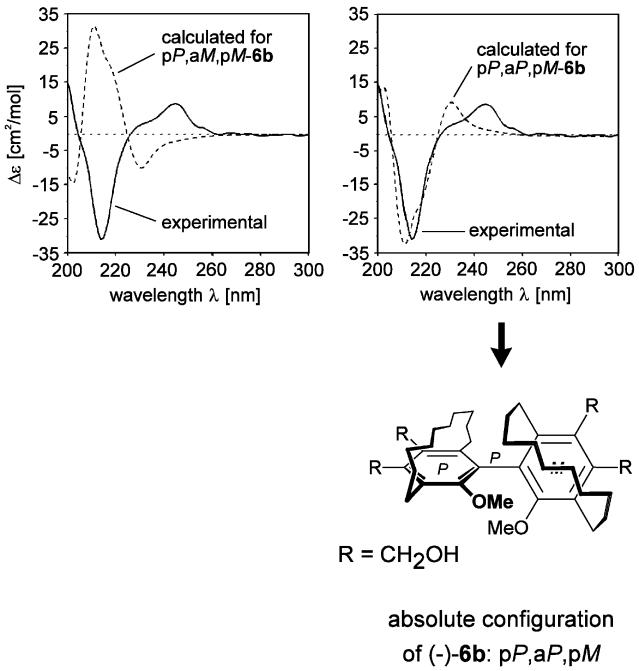


Figure 3. Determination of the absolute configuration of (−)-**6b**.

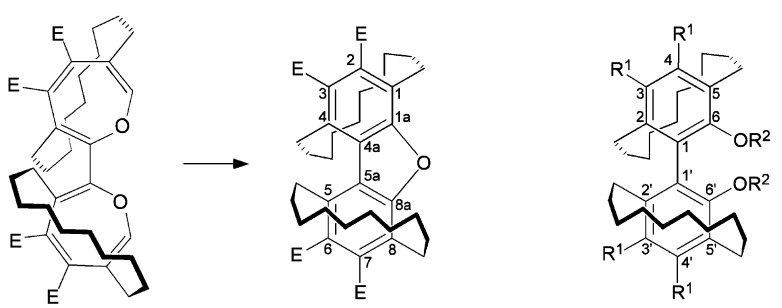
identified were further optimized using the semiempirical AM1 method.

The dihedral angle α that describes the position of the two phenyl rings relative to each other (Fig. 2(a)), adopted values mainly in a range of 88–94°, in some cases even reaching 107°, but these conformers did not have any energetic relevance ($\Delta\Delta H_f$>13 kcal/mol). The $-CH_2OH$ substituents in *meta*- and *ortho*-positions showed weak H bonds (d_{H-O} ca. 220 pm) to each other, whereas, the oxygen atom was either located within the plane of the corresponding phenyl ring or—energetically more favored—above or below this plane. The two diastereotopic methoxy groups *ortho* to the biaryl axis were found to differ in their conformational behavior, since one of them (viz the OMe group that is located on the 'left' phenyl ring) was subject to a high steric pressure due to the neighborhood of two alkane bridges. (Fig. 2(c)). Only one stable conformation was identified for this methoxy substituent, whereas the other one showed orientations below and above the corresponding phenyl ring with nearly similar ΔH_f values.

The structures obtained displayed energies that varied in a range of 16 kcal/mol; besides the global minimum (Fig. 2(c)), only four conformations were found within an energetic cut-off of 3 kcal/mol, located 0.89, 1.08, 1.92, and 2.37 kcal/mol higher than the global minimum. For the calculation of the overall CD spectrum, only these five conformers lowest in energy were thus expected to deliver significant contributions to the theoretical overall CD spectrum. For these five conformers, the CD spectra were calculated and then added up Boltzmann weighted, i.e. according to the enthalpies of formation of the corresponding conformers, to give the theoretical overall CD spectrum of the p*P*,a*P*,p*M*-enantiomer, which was subsequently submitted to a UV correction[16] (see also Section 5). Reflection of this spectrum at the zero line generated the theoretical spectrum predicted for the p*P*,a*M*,p*M*-enantiomer. The experimental CD spectrum was found to be in very good agreement with the one calculated for p*P*,a*P*,p*M*-**6b** (Fig. 3), whereas, it was approximately the mirror image of the spectrum computed for p*P*,a*M*,p*M*-**6b**. Consequently, the bi[10]paracyclophane (−)-**6b**, as obtained from (+)-**6c**, was assigned the absolute stereostructure as shown in Figure 3, i.e. with p*P*,a*P*,p*M*-configuration.

Equipped with a four-fold *ortho*-substituted biaryl axis, the bi[10]paracyclophanes synthesized here are configurationally stable at this central C,C-single bond. Heating (+)-**6b** for 8 h in diglyme up to 140°C only led to a slight decrease of the specific rotation, which might be attributed to side reactions of the four benzylic hydroxyl groups. From this a racemization barrier $\Delta G^{\neq}_{413}$ of higher than 149 kJ mol^{-1} was estimated.

Reactions analogous to the synthesis of **6b** from *meso*-**4** were also carried out with the bioxepine *rac*-**4** in order to get insight into the properties of the respective compounds of the *rac*-series (Scheme 3). The main product of the aromatization of *rac*-**4** with trifluoroacetic acid, however, was the dibenzofuran **8** (yield 61%). Its formation can be explained as follows: The X-ray structural analysis[14] shows that in the solid state *rac*-**4** prefers a conformation in which the two decamethylene bridges have a large



Scheme 3. Synthesis of *rac*-bi[10]paracyclophanes.

distance being located above and below the seven-membered rings, whereas the two oxepine oxygens lie relatively close to one another. Their non-bonding distance is only 279.8 ppm.

The reaction of *rac*-**4** with acid probably leads to a stereoisomer of the ketophenol **5a** as the key intermediate. In the *rac*-case, the intramolecular attack of the phenolic hydroxyl group to the keto group giving a hemiacetal and subsequent elimination of water is the preferred pathway, because here the two bridges lie on opposite sides of the six-membered rings. Such an arrangement of the methylene bridges can be achieved in the *meso*-series only by the intramolecular Michael-type 1,6-addition to give **7**. Besides the dibenzofuran **8**, the bis-phenol *rac*-**9a** was formed in 14% yield. Its *O*,*O*-dimethylation with sodium hydride/dimethyl sulfate gave the dimethyl ether *rac*-**9b**, which was reduced with $LiAlH_4$ to give *rac*-**9c** (yield 73%). Compounds *rac*-**9b** and *rac*-**9c** are stereoisomers of **6a** and **6b**, respectively. In contrast to **6a** and **6b**, *rac*-**9a**–*rac*-**9c** show only the half set of ^{13}C NMR signals because of the presence of homomorphous molecular halves, which makes these compounds possess C_2 symmetry.

As the rotation around the biaryl axis of **9a**–**9c** should also be hindered, two diastereomers (plus the respective enantiomers), should exist: the p*M*,a*M*,p*M* isomer (plus its p*P*,a*P*,p*P*-enantiomer) and the p*P*,a*M*,p*P*-isomer (plus its p*M*,a*P*,p*M*-enantiomer). However, for each of the compounds **9a**–**9c**, we isolated only one of these two possible diastereomers.

This observation may be explained as follows: the aromatization of oxepines with acid should always proceed via the valence tautomeric arene oxides.[10] This will also be the case for *rac*-**4**, where the equilibrium lies far on the side of the oxepine according to its ^1H NMR spectrum, with a chemical shift of δ=6.34 ppm for the oxepine protons. It is reasonable to assume that for sterical reasons the reaction proceeds only via an intermediate biarene oxide, in which the two decamethylene chains and the two oxirane oxygens as well lie on opposite sides of the six-membered rings, thus leading to only one (racemic) diastereomer of **9**. If the above considerations are correct, this racemic mixture should have the (pM^*,aP^*,pM^*)-configuration.

3. Conclusion

This paper describes a preparative approach to novel bridged bioxepine and bi[10]paracyclophane systems. Special attention was devoted to their reactivity and to their stereostructures. Representatives of the *meso*- and *rac*-series were characterized.

The bi[10]paracyclophanes have three stereogenic elements, two chiral planes and one chiral axis. An interesting example is (−)-**6b**, which consists of two planar chiral units of identical constitution but of opposite configuration. Its absolute (p*P*,a*P*,p*M*)-configuration was determined by quantum chemical CD calculations and comparison of the predicted CD spectrum with the experimental one.

According to textbook definitions, *meso*-stereoisomers are 'achiral members of a set of diastereomers'[3] and are 'optically inactive'.[20] Therefore, (−)-**6b** is not a *meso*-compound. The molecule is chiral and configuratively stable because of hindered rotation around the biaryl axis and therefore, shows optical activity.[21]

4. Experimental

4.1. General aspects

IR: Perkin–Elmer FTIR 1600, 1625; Paragon 1000 FTIR. UV: Zeiss DMR 10. $^1H/^{13}C$ NMR: Bruker AC 200 P, AM 300, DRX 500; TMS int. standard. Assignments marked with *, ** etc. may be exchanged. MS: Finnigan MAT 8200 and MAT 8230; direct inlet (El: 70 eV; Cl isobutane). Column Chromatography (CC): Baker Silica gel 40–60 μm. TLC: Macherey–Nagel SIL G/UV_{254}. HPLC: Pump C-6000 Merck, Darmstadt, column Li Chrosorb Si 60-7 (250×25 mm), flow 10 mL/min; ethyl acetate/cyclohexane (3:7), detector RI 8110, Bischoff. CD: Dichrograph CD6 Jobin Yvon (ethanol). Irradiations: High-pressure mercury lamp TQ 718 in diethyl ether/dichloromethane 5:1–5:4. Melting Points (uncorrected): Büchi 510. Optical rotations: Perkin–Elmer 241. Elemental Analyses: Mikroanalytisches Laboratorium Ilse Beetz; D-96301 Kronach. All solvents and reagents were purified and dried according to common procedures. Reactions with organometallic compounds and hydrides were performed under an argon or nitrogen atmosphere.

4.2. Synthesis of bioxanorbornadienes

4.2.1. 2,2′-Bi-(3,4-decamethylenefuran) (1). 53.0 mL (85.0 mmol) of a 1.6 M solution of *n*-butyllithium in hexane were added dropwise to a stirred solution of 3,4-decamethylenefuran[9] (17.1 g, 83.0 mmol) in 300 mL anhydrous THF at −78°C. The solution was allowed to warm up to −10°C and stirred for 4 h. Then anhydrous nickel(II)-chloride (5.40 g, 41.7 mmol) was added and stirring was continued for 17 h at room temperature. The reaction was quenched with 240 mL of 1N HCl and dichloromethane (1.6 L) was added. The organic layer was washed with 2N HCl (200 mL), the aqueous layer was extracted with dichloromethane (100 mL). The combined organic layers were washed with sat. aqueous $NaHCO_3$ and water and finally dried with magnesium sulfate. The solvent was removed in vacuo. Recrystallization of the residue from cyclohexane provided 6.29 g (37%) **1** as a pale yellow compound, mp 139°C. IR (KBr): ν=2920, 2855, 1073, 900 cm^{-1}. UV (CH_3CN): λ_{max} (log ε)=291 (sh, 4.11), 294 (4.12), 309 (sh, 3.87) nm. ^1H NMR ($CDCl_3$): δ=1.10–1.95 (m, 32H, 16CH_2), 2.15–2.72 (m, 8H), 7.16 (s, 2H) ppm. ^{13}C NMR ($CDCl_3$): δ=20.35 (t, 2CH_2), 20.87 (t, 2CH_2), 23.15 (t, 2CH_2), 23.72 (t, 2CH_2), 25.12 (t, 2CH_2), 26.10 (t, 2CH_2), 26.30 (t, 4CH_2), 28.64 (t, 2CH_2), 29.41 (t, 2CH_2), 122.12 (s, C-3/C-3′), 127.40 (s, C-4/C-4′), 137.75 (d, C-5/C-5′), 143.21 (s, C-2/C-2′). MS (El): *m*/*z* (%)=410 (M^+, 100). Calcd for

$C_{28}H_{42}O_2$ (410.64): C, 81.90; H, 10.31. Found: C, 81.85; H, 10.22.

4.2.2. Tetramethyl (1*R*,1′*S*)-1,1′-bi-(1,4,6,7,8,9,10,11,12,13,14,15-dodecahydro-1,4-epoxy-benzocyclododecene-2,3-dicarboxylate) (*meso*-2) and tetramethyl (1*R,1′*R**)-(±)-1,1′-bi-1,4,6,7,8,9,10,11,12,13,14,15-dodecahydro-1,4-epoxy-benzocyclododecene-2,3-dicarboxylate (*rac*-2).** A solution of **1** (793 mg, 1.93 mmol) and dimethyl acetylene–dicarboxylate (2.3 mL, 18.8 mmol) in 70 mL dry toluene was heated under reflux for 4 h. The reaction mixture was cooled and concentrated in vacuo. Diethyl ether was added to the residue. Cooling to 5°C provided 1.04 g (77%) of a 4:1 mixture of *meso*-**2**/*rac*-**2** as a colorless solid. Column chromatography (Et_2O) on aluminum oxide (neutral, act. II–III) afforded at first some pure *meso*-**2** (R_f=0.78), followed by an unresolved *meso*-**2**/*rac*-**2** mixture, and finally some pure *rac*-**2** (R_f=0.58) was obtained. Because of this difficult separation procedure it proved to be much more convenient to irradiate and thermolyze the *meso*-**2**/*rac*-**2** mixture directly and to resolve the bioxepines **4** by column chromatography (see Section 4.5). For preparative purposes, **1** (17.2 g, 42.0 mmol) and dimethyl acetylenedicarboxylate (59.0 g, 480 mmol) in 1.5 L toluene were converted to **2** as described above. Yield 22.6 g (77%) of a 4:1-mixture of *meso*-**2**/*rac*-**2** as a colorless solid.

Compound meso-**2**: colorless crystals, mp 202°C (CH_2Cl_2/pentane). IR (KBr): ν=1739, 1717 (C=O), 1657 (C=C) cm^{-1}. UV (CH_3CN): λ_{max} (log ε)=203 nm (4.22). ^1H NMR ($CDCl_3$, 200 MHz): δ=1.00–1.65 (m, 32H, CH_2), 2.05–2.50 (m, 8H, CH_2), 3.71 (s, 6H, OCH_3), 3.75 (s, 6H, OCH_3), 5.46 (s, 2H) ppm. ^{13}C NMR ($CDCl_3$, 50 MHz): δ=21.90 (t, $2CH_2$), 23.14 (t, $2CH_2$), 23.46 (t, $2CH_2$), 23.81 (t, $2CH_2$), 23.90 (t, $2CH_2$), 24.34 (t, $2CH_2$), 25.10 (t, $2CH_2$), 25.19 (t, $2CH_2$), 25.51 (t, $2CH_2$), 25.64 (t, $2CH_2$), 52.00 (q, $2OCH_3$), 52.12 (q, $2OCH_3$), 85.57 (d, C-4/C-4′), 96.19 (s, C-1/C-1′), 146.66 (s, C-3/C-3′), 149.32* (s, C-5/C-5′), 150.91* (s, C-16/C-16′), 159.12 (s, C-2/C-2′), 162.22 (s, $2COOCH_3$), 165.36 (s, $2COOCH_3$) ppm. MS (Cl) *m*/*z* (%)=695 ($[M+H]^+$, 9), 143 (100). Calcd for $C_{40}H_{54}O_{10}$ (694.9): C, 69.14; H, 7.83. Found: C, 68.87; H, 7.91.

Compound rac-**2**: colorless crystals, mp 171°C (CH_2Cl_2/pentane). IR (KBr): ν=1734, 1711 (C=O), 1655 (C=C) cm^{-1}. UV (CH_3CN): λ_{max} (log ε)=206 (4.39), 228 (sh, 3.92) nm. ^1H NMR ($CDCl_3$, 300 MHz): δ=1.02–1.62 (m, 32H, CH_2), 2.08–2.53 (m, 8H, Allyl-H), 3.71 (s, 6H, OCH_3), 3.74 (s, 6H, OCH_3), 5.45 (s, 2H) ppm. ^{13}C NMR ($CDCl_3$, 75 MHz): δ=21.95 (t, $2CH_2$), 23.05 (t, $2CH_2$), 23.30 (t, $2CH_2$), 23.83 (t, $2CH_2$), 24.12 (t, $2CH_2$), 24.29 (t, $2CH_2$), 25.25 (t, $4CH_2$), 25.53 (t, $2CH_2$), 25.57 (t, $2CH_2$), 51.87 (q, $2OCH_3$), 52.05 (q, $2OCH_3$), 85.71 (d, C-4/C-4′), 96.25 (s, C-1/C-1′), 145.75 (s, C-3/C-3′), 147.93* (s, C-5/C-5′), 151.86* (s, C-16/C-16′), 159.49 (s, C-2/C-2′), 162.42 (s, $2COOCH_3$), 165.29 (s, $2COOCH_3$) ppm. MS (Cl) *m*/*z* (%)=695 ($[M+H]^+$, 56), 143 (100). Calcd for $C_{40}H_{54}O_{10}$ (694.9): C, 69.14; H, 7.83. Found: C, 69.23; H, 7.75.

4.3. Procedure for the synthesis of the bioxaquadricyclanes *meso*-3 and *rac*-3

Solutions of 0.2–0.8 mmol of pure *meso*-**2** or *rac*-**2** in 150 mL diethyl ether were irradiated in separate runs for 2 h at room temperature under nitrogen. The solution was concentrated in vacuo and the residue recrystallized.

4.3.1. Tetramethyl (14*R*,14′*S*)-14,14′-bi-(15-oxapentacyclo[10.5.0.0.^{1,16}0.^{12,14}0.^{13,17}]heptadecane-14,17-dicarboxylate) (*meso*-3). Yield (78%), colorless crystals, mp 113°C (CH_2Cl_2/pentane). IR (KBr): ν 3080 (C–H), 1718 (C=O), 1079 (C–O) cm^{-1}. ^1H NMR ($CDCl_3$, 90 MHz): δ=1.10–1.71 (m, 34H, CH_2) 1.80–2.25 (m, 6H, CH_2), 3.64 (s, 6H, OCH_3), 3.68 (s, 6H, OCH_3), 4.69 (s, 2H) ppm. ^{13}C NMR ($CDCl_3$, 50 MHz): δ=20.22 (t, $2CH_2$), 20.87 (t, $2CH_2$), 23.40 (t, $2CH_2$), 23.95 (t, $2CH_2$), 24.45 (t, $2CH_2$), 24.99 (t, $2CH_2$), 26.76 (t, $2CH_2$), 27.02 (t, $2CH_2$), 27.35 (t, $2CH_2$), 27.67 (t, $2CH_2$), 34.45* (s, C-13/C-13′), 38.05* (s, C-17/C-17′), 41.90** (s, C-12/C-12′), 46.75** (s, C-1/C-1′), 51.64 (q, $2OCH_3$), 51.73 (q, $2OCH_3$), 74.54 (d, C-16/C-16′), 76.59 (s, C-14/C-14′), 166.60 (s, $2COOCH_3$), 168.25 (s, $2COOCH_3$) ppm. MS (El): *m*/*z* (%)=694 (M^+, 52), 662 (M^+, 100).

4.3.2. Tetramethyl (14*R,14′*R**)-(±)-14,14′-bi-(15-oxapentacyclo [10.5.0.0.^{1,16}0.^{12,14}0.^{13,17}]heptadecane-14,17-dicarboxylate) (*rac*-3).** Yield (81%), colorless crystals, mp 95–96°C (CH_2Cl_2/pentane). IR (KBr): ν=3095 (C–H), 1734, 1721 (C=O), 1084 (C–O) cm^{-1}. ^1H NMR ($CDCl_3$, 90 MHz): δ=1.10–1.75 (m, 34H, CH_2) 1.87–2.27 (m, 6H, CH_2), 3.65 (s, 12H, OCH_3), 4.69 (s, 2H) ppm. ^{13}C NMR ($CDCl_3$, 75 MHz): δ=20.79 (t, $2CH_2$), 21.10 (t, $2CH_2$), 23.77 (t, $2CH_2$), 24.34 (t, $2CH_2$), 24.95 (t, $2CH_2$), 25.08 (t, $2CH_2$), 26.75 (t, $4CH_2$), 27.32 (t, $2CH_2$), 27.71 (t, $2CH_2$), 35.03* (s, C-13/C-13′), 37.45* (s, C-17/C-17′), 42.84** (s, C-12/C-12′), 46.14** (s, C-1/C-1′), 51.58 (q, $4OCH_3$), 74.02 (d, C-16/C-16′), 77.58 (s, C-14/C-14′), 166.43 (s, $2COOCH_3$), 167.95 (s, $2COOCH_3$) ppm. MS (El): *m*/*z* (%)=694 (M^+, 100).

4.4. Procedure for the synthesis of the bioxepines *meso*-4 and *rac*-4

Solutions of 0.25–0.7 mmol *meso*-**3** or *rac*-**3** in 20–40 mL THF were heated under reflux for 2 h. The residue obtained after removal of the solvent in vacuo was chromatographed on aluminum oxide (neutral, act. II–III) with diethyl ether.

4.4.1. Tetramethyl (*M*,*P*)-2,2′-bi-(3,6-decanooxepine-4,5-dicarboxylate) (*meso*-4). Yield (81%), yellow foam. IR (KBr): ν=1735, 1724 (C=O), 1618 (C=C), 1258 (=C–O), 1075 (C–O) cm^{-1}. UV (C_2H_5OH): λ_{max} (log ε)=217 (sh, 4.52) nm. ^1H NMR ($CDCl_3$, 200 MHz): δ=1.04–1.72 (m, 32H, CH_2), 1.97–2.15 (m, 2H, CH_2) 2.33–2.51 (m, 6H, CH_2), 3.78 (s, 6H, OCH_3), 3.79 (s, 6H, OCH_3), 6.31 (d, ^4J=1.1 Hz, 2H, oxepine-H) ppm. ^{13}C NMR ($CDCl_3$, 50 MHz): δ=25.72 (t, $2CH_2$), 26.53 (t, $2CH_2$), 26.85 (t, $2CH_2$), 27.29 (t, $2CH_2$), 27.54 (t, $2CH_2$), 27.66 (t, $2CH_2$), 28.31 (t, $2CH_2$), 28.55 (t, $2CH_2$), 28.61 (t, $2CH_2$), 29.79 (t, $2CH_2$), 52.37 (q, $2OCH_3$), 52.41 (q, $2OCH_3$), 127.18* (s, C-3/C-3′), 127.82* (s, C-6/C-6′), 137.82** (s, C-5/C-5′), 139.83** (s, C-4/C-4′), 147.01 (d, C-7/C-7′), 150.41 (s, C-2/C-2′), 166.73 (s, $2COOCH_3$), 166.87 (s, $2COOCH_3$) ppm. MS (El): *m*/*z* (%)=694 (M^+, 66), 315 (100).

4.4.2. Tetramethyl (±)-(*M,*M**)-2,2′-bi-(3,6-decanooxepine-4,5-dicarboxylate) (*rac*-4).** Yield (84%), yellow crystals, mp 137–138°C (ether/pentane). IR (KBr): ν= 1733, 1722 (C=O), 1615 (C=C), 1260 (=C–O), 1075 (C–O) cm^{-1}. UV (CH_3CN): λ_{max} (log ε)=200 (4.26), 232 (4.17), 318 (3.67) nm. ^1H NMR ($CDCl_3$, 200 MHz): δ= 1.01–1.72 (m, 32H, CH_2), 1.97–2.48 (m, 8H, CH_2), 3.79 (s, 6H, OCH_3), 3.80 (s, 6H, OCH_3), 6.34 (d, ^4J=1.1 Hz, 2H, oxepine-H) ppm. ^{13}C NMR ($CDCl_3$, 50 MHz): δ=25.64 (t, $2CH_2$), 26.20 (t, $2CH_2$), 26.59 (t, $2CH_2$), 26.89 (t, $2CH_2$), 27.18 (t, $4CH_2$), 27.98 (t, $2CH_2$), 28.26 (t, $2CH_2$), 28.40 (t, $2CH_2$), 29.02 (t, $2CH_2$), 52.33 (q, $2OCH_3$), 52.38 (q, $2OCH_3$), 126.55* (s, C-3/C-3′), 127.86* (s, C-6/C-6′), 137.28** (s, C-5/C-5′), 140.18** (s, C-4/C-4′), 147.42 (d, C-7/C-7′), 151.17 (s, C-2/C-2′), 166.75 (s, 2*C*$OOCH_3$), 166.98 (s, 2*C*$OOCH_3$) ppm. MS (El): *m*/*z* (%)=694 (M^+, 94), 315 (100). Calcd for: $C_{40}H_{54}O_{10}$ (694.9) C, 69.14; H, 7.83. Found: C, 69.08; H, 7.83.

4.5. Preparative synthesis of the bioxepines *meso*-4 and *rac*-4

11.3 g (16 mmol) of the 4:1 mixture (see Section 4.2.2) *meso*-**2**/*rac*-**2** were dissolved in 500 mL diethyl ether and 400 mL dichloromethane and irradiated for 1 h under nitrogen at room temperature. Two identical runs were combined and the solvents were evaporated in vacuo. The yellow residue was dissolved in 500 mL THF and heated under reflux for 2 h. After evaporation of the solvent the residue was at first filtered over aluminum oxide (neutral, act. II–III) with diethyl ether and finally subjected to column chromatography with diethyl ether/pentane (1:2) on aluminum oxide. The first fraction (R_f=0.15) provided 2.55 g (11%) yellow *rac*-**4** after recrystallization from dichloromethane/diethyl ether/pentane, mp 137°C. The second fraction afforded 13.4 g (59%) *meso*-**4** as a non-crystalline yellow foam.

4.6. Synthesis of bi[10]paracyclophane derivatives

4.6.1. Tetramethyl (±)-2,5;2′,5′-didecano-5,6-dihydro-6′-hydroxy-6-oxo-biphenyl-3,4;3′,4′-tetracarboxylate (5a). A solution of *meso*-**4** (13.4 g, 19.2 mmol) and trifluoroacetic acid (58 mL) in dichloromethane (500 mL) was stirred at room temperature for 24 h. The solution was neutralized with 2N Na_2CO_3. The brown residue of the organic layer obtained after usual work-up was filtered over aluminum oxide (neutral, act. II–III) with diethyl ether. Yield 4.96 g (37%) **5a** as colorless crystals, mp 170°C. IR (KBr): ν= 3430 (OH), 1722 (C=O), 1612 (C=C), 1550 (C=C) cm^{-1}. UV (CH_3CN): λ_{max} (log ε)=224 (4.46), 259 (sh, 3.84), 286 (sh, 3.50) nm. ^1H NMR ($CDCl_3$, 300 MHz): δ=0.22–0.40 (m, 1H, CH_2), 0.48–1.83 (m, 32H, CH_2), 1.38–2.25 (m, 2H, CH_2), 2.42–2.68 (m, 3H, CH_2), 2.90–3.01 (m, 1H, CH_2), 3.39–3.49 (m, 1H, CH_2), 3.81 (s, 3H, OCH_3), 3.85 (s, 3H, OCH_3), 3.87 (s, 3H, OCH_3), 3.88 (s, 3H, OCH_3), 4.25 (dd, ^3J=7.5 Hz, ^3J=3.8 Hz, 1H, H-5), 5.44 (s, exchangeable, 1H, OH) ppm. ^{13}C NMR ($CDCl_3$, 50 MHz): δ=21.05 (t, $2CH_2$), 23.17 (t, CH_2), 25.70 (t, $2CH_2$), 26.12 (t, CH_2), 26.45 (t, $2CH_2$), 26.61 (t, CH_2), 26.81 (t, CH_2), 26.87 (t, CH_2), 26.96 (t, CH_2), 27.03 (t, CH_2), 27.23 (t, CH_2), 28.23 (t, CH_2), 28.38 (t, $2CH_2$), 28.49 (t, CH_2), 30.93 (t, CH_2), 33.22 (t, CH_2), 51.72 (d, C-5), 52.12 (q, OCH_3), 52.15 (q, OCH_3), 52.44 (q, OCH_3), 52.55 (q, OCH_3), 124.04* (s, C-1′), 124.09* (s, C-5′), 126.08′ (s, C-2′), 131.32** (s, C-1), 134.60** (s, C-3′), 135.81** (s,C-3), 140.55 (s,C-4′), 143.68 (s, C-4), 153.35*** (s, C-2), 153.93*** (s, C-6′), 164.83 (s, *C*$OOCH_3$), 165.98 (s, *C*$OOCH_3$), 168.12 (s, *C*$OOCH_3$), 168.59 (s, *C*$OOCH_3$), 200.62 (s, C-6) ppm. MS (El): *m*/*z* (%)=694 (M^+, 38), 662 (M^+, 100). Calcd for: $C_{40}H_{54}O_{10}$ (694.9): C, 69.14; H, 7.83. Found: C, 69.18; H, 7.75.

4.6.2. Tetramethyl (±)-2,5;2′,5′-didecano-5,6-dihydro-6′-methoxy-6-oxo-biphenyl-3,3′,4,4′-tetracarboxylate (5b) and tetramethyl (±)-1a,3;5,8-didecano-1a,3,4,4a-tetrahydro-4-oxo-dibenzofuran-1,2,6,7-tetracarboxylate (7). Sodium methoxide (664 mg, 12.30 mmol) and dimethyl sulfate (1.20 mL, 11.80 mmol) were added to a stirred solution of **5a** (2.65 g, 3.80 mmol) in dry methanol (150 mL). The mixture was stirred at room temperature for 17 h. After the addition of dichloromethane (300 mL) the reaction was quenched with water and 2N HCl. Usual work-up and column chromatography of the residue of the organic layer on aluminum oxide (basic, II–III) with diethyl ether/pentane (1:1) provided 240 mg (9%) colorless **7** (R_f=0.35) and 1.08 g (40%) yellow **5b** (R_f=0.23). **5b**: mp 178°C (CH_2Cl_2/diethyl ether/pentane). IR (KBr): ν=1734, 1617, 1550, 1254 cm^{-1}. UV (C_2H_5OH): λ_{max} (log ε)=221 (4.53), 289 (sh, 3.63) nm. ^1H NMR ($CDCl_3$, 200 MHz): δ=0.18–0.41 (m, 1H, CH_2), 0.45–1.95 (m, 32H, CH_2), 1.98–2.40 (m, 2H, CH_2), 2.46–2.95 (m, 4H, CH_2), 3.22–3.40 (m, 1H, CH_2), 3.55 (s, 3H, OCH_3), 3.79 (s, 3H, OCH_3), 3.84 (s, 3H, OCH_3), 3.86 (s, 3H, OCH_3), 3.88 (s, 3H, OCH_3), 4.02–4.12 (m, 1H, H-5) ppm. ^{13}C NMR ($CDCl_3$, 50 MHz): δ=21.11 (t, CH_2), 23.37 (t, CH_2), 25.20 (t, CH_2), 25.89 (t, CH_2), 26.41 (t, CH_2), 26.82 (t, CH_2), 26.88 (t,CH_2), 26.96 (t, $2CH_2$), 27.07 (t, $2CH_2$), 27.12 (t, $2CH_2$), 27.16 (t, CH_2), 27.38 (t, CH_2), 28.17 (t, CH_2), 28.26 (t, CH_2), 28.43 (t, CH_2), 28.59 (t, CH_2), 31.70 (t, CH_2), 32.76 (t, CH_2), 51.89 (d, C-5), 52.41 (q, 2 ester–OCH_3), 52.55 (q, 2 ester–OCH_3), 61.29 (q, ether–OCH_3), 128.10* (s, C-1′), 130.96* (s, C-5′), 131.71* (s, C-2′), 132.56** (s, C-1), 135.49** (s, C-3′), 137.51** (s, C-3), 140.69 (s, C-4′), 143.40 (s, C-4), 149.83 (s, C-2), 159.72 (s, C-6′), 165.30 (s, *C*$OOCH_3$), 166.24 (s, *C*$OOCH_3$), 168.42 (s, *C*$OOCH_3$), 198.21 (s, C-6) ppm. MS (El): *m*/*z* (%)=708 (M^+, 100). Calcd for: $C_{41}H_{56}O_{10}$ (708.9): C, 69.47; H, 7.96. Found: C, 69.43; H, 7.92.

Compound **7**: mp 193–194°C (CH_2Cl_2/diethyl ether/pentane). IR (KBr): ν=1738 (C=O), 1638, 1571 (C=C) cm^{-1}. UV (CH_3CN): λ_{max} (log ε)=226 (3.55), 336 (sh, 2.01), 430 (2.09) nm. ^1H NMR ($CDCl_3$, 200 MHz): δ=0.61–1.78 (m, 32H, CH_2), 1.90–2.03 (m, 3H, CH_2), 2.53 (ddd, ^2J= 13.6 Hz, ^3J=8.6, 5.0 Hz, 1H, C=C–CH_2), 2.68–2.97 (m, 3H, CH_2), 3.12 (dt, ^2J=13.6 Hz, ^3J=5.6 Hz, 1H, C=C–CH_2), 3.38–3.44 (m, 1H, 3-H), 3.79 (s, 6H, $COOCH_3$), 3.82 (s, 3H, $COOCH_3$), 3.83 (s, 3H, $COOCH_3$), 4.36 (s, 1H, 4a-H) ppm. ^{13}C NMR ($CDCl_3$, 50 MHz): δ=23.32 (t, CH_2), 23.87 (t, 2C, CH_2), 24.47 (t, CH_2), 24.70 (t, CH_2), 24.91 (t, CH_2), 25.25 (t, CH_2), 25.82 (t, CH_2), 25.89 (t, CH_2), 26.02 (t, CH_2), 26.35 (t, CH_2), 27.26 (t, CH_2), 27.32 (t, CH_2), 27.49 (t, CH_2), 28.16 (t, CH_2), 28.25 (t, $2CH_2$), 28.48 (t, CH_2), 28.60 (t, CH_2), 39.53 (t, CH_2), 47.01 (d, C-3), 52.28 (q, 2COO*C*H_3), 52.36 (q, COO*C*H_3), 52.50 (q, COO*C*H_3), 59.22 (d, C-4a), 92.51 (s, C-1a), 121.69 (s,

C-6), 123.41 (s, C-8), 126.07 (s, C-5a), 135.06 (s, C-1)*, 135.22 (s, C-2)*, 137.99 (s, C-7)*, 140.01 (s, C-5), 157.94 (s, C-8a), 164.77 (s, *C*OOCH$_3$), 166.09 (s, *C*OOCH$_3$), 168.41 (s, *C*OOCH$_3$), 168.56 (s, *C*OOCH$_3$), 207.73 (s, C-4) ppm. MS (El): *m/z* (%)=694 (M^+, 100). MS (Cl): *m/z* (%)=695 (M^++1, 11), 663 (M^+−CH_3O, 100). Calcd for: $C_{40}H_{54}O_{10}$ (694.9): C, 69.14; H, 7.83. Found: C, 69.00; H, 7.95.

4.6.3. Tetramethyl (±)-(p*M*,a*M* *,p*P*)-2,5;2′,5′-didecano-6,6′-dimethoxybiphenyl-3,3′,4,4′-tetracarboxylate (6a). Monomethyl ether **5b** (75 mg, 0.11 mmol) in dichloromethane (5 mL) was added dropwise to potassium *tert*-butoxide (17 mg, 0.15 mmol) in THF (3 mL) at 0°C. After stirring for 2 h the mixture was cooled to −15°C and methyl triflate (0.05 mL, 0.46 mmol) was added. The reaction was quenched after 30 min by addition of 2N KOH. The organic compounds were taken up in dichloromethane. The usual work-up and column chromatography on silica gel with diethyl ether/pentane provided 48 mg (63%) **6a** (R_f=0.30). **6a**: colorless crystals, mp 199–200°C (CH_2Cl_2/diethyl ether/pentane). IR (KBr): ν=1733, 1550, 1266, 1036 cm^{-1}. UV (CH_3CN): λ_{max} (log ε)=222 (3.61), 290 (2.35) nm. ^{1}H NMR ($CDCl_3$, 200 MHz): δ=0.36–2.19 (m, 32H, CH_2), 2.44 (ddd, ^2J=13.9 Hz, ^3J=9.2, 4.7 Hz, 1H, C═C−CH*H*), 2.58–3.29 (m, 6H, C═C−CH_2), 3.42 (s, 3H, C═C−O−CH_3), 3.48 (ddd, ^2J=14.5 Hz, ^3J=7.5, 2.5 Hz, 1H, C═C−CH*H*), 3.63 (s, 3H, C═C−O*C*H_3), 3.82 (s, 3H, COO*C*H_3) 3.86 (s, 3H, COO*C*H_3), 3.89 (s, 6H, 2COO*C*H_3) ppm. ^{13}C NMR ($CDCl_3$, 50 MHz): δ=25.44 (t, CH_2), 25.74 (t, CH_2), 26.32 (t, CH_2), 26.65 (t, CH_2), 27.36 (t, 2C, CH_2), 27.48 (t, 2C, CH_2), 27.59 (t, CH_2), 27.78 (t, 2C, CH_2), 28.19 (t, 2C, CH_2), 28.30 (t, CH_2), 28.90 (t, 2C, CH_2), 29.17 (t, CH_2), 29.27 (t, CH_2), 30.96 (t, CH_2), 32.52 (t, CH_2), 52.38 (q, 2COO*C*H_3), 52.42 (q, 2COO*C*H_3), 61.09 (q, C−O−CH_3), 61.31 (q, ═C−O−CH_3), 128.18 (s, C-3′)*, 128.32 (s, C-3)*, 132.20 (s, 2C, C-5, C-5′)** , 133.32 (s, C-1′)** , 134.52 (s, C-1)** , 134.95 (s, C-4′)** , 135.13 (s, C-4)** , 141.85 (s, C-2)*** , 142.45 (s, C-2)*** , 158.37 (s, C-6′)**** , 158.96 (s, C-6)**** , 168.51 (s, *C*OOCH$_3$), 168.62 (s, *C*OOCH$_3$), 168.68 (s, 2*C*OOCH$_3$) ppm. MS (El): *m/z* (%)=722 (M^+, 100). Calcd for: $C_{42}H_{58}O_{10}$ (722.9): C, 69.78; H, 8.09. Found: C, 69.76; H, 8.04.

4.6.4. (±)-(p*M*,a*M* *,p*P*)-2,5;2′,5′-Didecano-3,3′,4,4′-tetrahydroxymethyl-6,6′-dimethoxybiphenyl (6b). A solution of **6a** (330 mg, 0.46 mmol) in 10 mL diethyl ether was added dropwise to lithium aluminum hydride (140 mg, 3.70 mmol) in diethyl ether (10 mL). After heating under reflux for 1 h the reaction was quenched with 2N HCl. Usual work-up and concentration in vacuo provided crystalline **6b** (221 mg, 79%). **6b**: colorless crystals of mp 221–222°C (ethyl acetate). IR (KBr): ν=3386 (O−H) cm^{-1}. UV (CH_3CN): λ_{max} (log ε)=215 (3.68) nm. ^{1}H NMR (DMSO-d_6, 200 MHz): δ=0.37–1.93 (m, 35H, CH_2), 2.55–3.02 (m, 5H, CH_2), 3.25 (s, 3H, ═C−O−CH_3), 3.46 (s, 3H, ═C−O−CH_3), 4.49–4.80 (m, 8H, ═C−CH_2OH), 4.86–4.93 (m, exchangeable, 1H, ═C−CH_2OH), 4.98–5.14 (m, exchangeable, 3H, ═C−CH_2OH) ppm. ^{13}C NMR (DMSO-d_6, 50 MHz): δ=24.75 (t, CH_2), 24.97 (t, CH_2), 25.23 (t, CH_2), 25.33 (t, CH_2), 25.73 (t, 2C, CH_2), 26.56 (t, 2C, CH_2), 26.88 (t, CH_2), 27.51 (t, 2C, CH_2), 27.98 (t, CH_2), 28.38 (t, 2C, CH_2), 28.61 (t, CH_2), 28.77 (t, 2C, CH_2), 28.92 (t, CH_2), 29.58 (t, CH_2), 31.69 (t, CH_2), 58.09 (t, ═C−*C*H_2OH), 58.40 (t, ═C−*C*H_2OH), 58.64 (t, ═C−*C*H_2OH), 59.82 (t, ═C−*C*H_2OH), 60.43 (q, ═C−O−*C*H_3), 60.76 (q, C−O−*C*H_3), 130.90 (s, C-1)*, 131.29 (s, C-1)*, 131.34 s, C-5′)*, 131.87 (s, C-5)*, 135.63 (s, C-3′)** , 135.80 (s, C-3)** , 139.44 (s, 2C, C-4, C-4′)*** , 140.19 (s, C-2′)*** , 140.27 (s, C-2)*** , 155.91 (s, C-6′)**** , 156.18 (s, C-6)**** ppm. MS (El): *m/z* (%)=610 (M^+, 90). MS (Cl): *m/z* (%)=611 (M^*+1, 24); 593 (M^*+1−H_2O, 100); 575 (M^*+1−2H_2O, 32); exact mass calcd for $C_{38}H_{58}O_6$: 610.4233. Found: 610.4234.

4.6.5. (7*S*,7′*S*,7″*S*,7‴*S*,p*M*,a*M* */a*P* *p*P*)-3,3′,4,4′-Tetracamphanoyloxymethyl-2,5;2′,5′-didecano-6,6′-dimethoxybiphenyl (6c/6c′). (−)-(1*S*)-Camphanoyl chloride (62 mg, 0.29 mmol) was added to a solution of **6b** (35 mg, 0.06 mmol) in 2 mL pyridine at 0°C. After 4 days at room temperature, dichloromethane and water were added to quench the reaction. Usual work-up and column chromatography of the residue of the organic layer on silica gel with diethyl ether provided 64 mg (84%) of the diastereomeric mixture **6c/6c′** as a colorless oil. ^{1}H NMR ($CDCl_3$, 300 MHz): δ=0.41–3.09 (m, 184H, CH_2, C−CH_3), 3.28 (s, 3H, O−CH_3), 3.30 (s, 3H, O−CH_3), 3.58 (s, 3H, O−CH_3), 3.60 (s, 3H, O−CH_3), 5.28–5.71 (m, 16H, CH_2−OCph) ppm. ^{13}C NMR ($CDCl_3$, 50 MHz): δ=9.68 (q, 4C, C−*C*H_3), 9.70 (q, 4C, C−*C*H_3), 16.65–16.91 (q, 16C, C−*C*H_3), 25.15–32.38 (t, 56C, CH_2), 54.15–54.82 (s, 16C, C-10−C-10‴, C-13−C-13‴), 60.94 (q, ═C−O−*C*H_3), 61.00 (q, ═C−O−*C*H_3), 61.14 (q, 2C, ═C−O−*C*H_3), 62.39 (t, 4C, CH_2−OCph), 62.67 (t, CH_2−OCph), 62.74 (t, CH_2−OCph), 62.81 (t, CH_2−OCph), 62.91 (t, CH_2−OCph), 90.96 (s, 2C, C-7‴)*, 91.00 (s, 4C, C-7″, C-7′)*, 91.07 (s, 2C, C-7‴)*, 129.45/129.58 (s, C-1′)** , 129.80/129.83 (s, C-1)** , 132.77/132.82 (s, C-5′)*** , 133.94/134.01 (s, C-5)*** , 134.04/134.12 (s, C-3′)*** , 134.37 (s, 2C, C-3)*** , 134.67/134.75 (s, C-4′)*** , 134.87/134.99 (s, C-4)*** , 142.08 (s, 2C, C-2′)**** , 142.18 (s, 2C, C-2)**** , 157.73 (s, ═C−O−CH_3), 157.79 (s, ═*C*−O−CH_3), 158.82 (s, ═*C*−O−CH_3), 158.85 (s, ═*C*−O−CH_3), 167.55 (s, 2C, C═O, ester), 167.61 (s, 4C, C═O, ester), 167.66 (s, 2C, C═O, ester), 177.88 (s, 4C, C═O, γ-lactone), 177.96 (s, 4C, C═O, γ-lactone) ppm. MS (El): *m/z* (%)=1331 (M^+, 4) 1133 [M^+−$C_{10}H_{13}O_4$ (OCph), 41]; 935 (M^+−2OCph, 49); 736 (M^+−3OCph).

4.6.6. HPLC separation of the diastereomeric camphanoates 6c/6c′. Preliminary thin layer chromatography experiments on silica gel with ethyl acetate/cyclohexane (3:7) showed that a separation into two fractions with R_f=0.41 and 0.38 was possible. 222 mg of **6c/6c′** were subjected to eleven separate HPLC resolutions with the above solvent. The collected first fractions containing 100 mg (+)-**6c** were once more subjected to the same procedure once again, finally affording 80 mg (36%) of diastereomerically pure (+)-**6c** (de>95%) as a colorless oil (^{1}H NMR). The collected second fractions were treated in the same way, giving 83 mg (37%) (−)-**6c′** with a de of 50% (^{1}H NMR of the OCH_3 signals). (+)-**6c**: $[\alpha]_D^{18}$=3.46, $[\alpha]_{578}^{18}$=3.56, $[\alpha]_{546}^{18}$=4.01, $[\alpha]_{436}^{18}$=7.82 (*c* 2.02, $CHCl_3$). ^{1}H NMR ($CDCl_3$, 300 MHz): δ=0.49–3.08 (m, 92H, CH_2, C−CH_3), 3.28 (s, 3H, −O−CH_3), 3.60 (s, 3H, −O−CH_3), 5.29–5.64 (m, 8H, CH_2−OCph) ppm. ^{13}C NMR ($CDCl_3$, 125 MHz): δ=9.70 (q, 4C, C−*C*H_3), 16.82 (q, 8C, C−*C*H_3),

25.16–32.01 (t, 28C, CH_2), 54.20–54.78 (s, 8C, C-10–C-10‴, C-13–C-13‴), 60.95 (q, =C–O–CH_3), 61.13 (q, =C–O–CH_3), 62.43 (t, 2C, CH_2–OCph), 62.73 (t, 2C, CH_2–OCph), 90.92 (s, C-7)*, 90.97 (s, C-7)*, 91.02 (s, 2C, C-7″, C-7‴)*, 129.40 (s, C-1′)**, 129.69 (s, C-1)**, 132.67 (s, C-5′)***, 133.79 (s, C-5)***, 134.09 (s, C-3′)***, 134.31 (s, C-3)***, 134.48 (s, C-4′)***, 134.70 (s, C-H)***, 141.91 (s, C-2′)****, 142.05 (s, C-2)****, 157.67 (s, =*C*–O–CH_3), 158.63 (s, =*C*–O–CH_3), 167.54 s, C=O, ester), 167.58 (s, C=O, ester), 167.67 (s, 2C, C=O, ester), 177.96 (s, C=O, γ-lactone), 178.01 (s, 2C, C=O, γ-lactone), 178.06 (s, C=O, γ-lactone) ppm.

Compound (−)-**6c′** (de 50%): $[\alpha]_D^{18}=-0.85°$, $[\alpha]_{578}^{18}=-1.05°$, $[\alpha]_{546}^{18}=-1.35°$, $[\alpha]_{436}^{18}=-4.91°$ (*c* 2.00, $CHCl_3$). ^{1}H NMR ($CDCl_3$, 300 MHz): δ=0.42–3.10 (m, 92H, CH_2, CH_3), 3.30 (s, 3H, O–CH_3), 3.58 (s, 3H, O–CH_3), 5.31–5.70 (m, 8H, CH_2–OCph) ppm.

4.6.7. (−)-(p*P*,a*P*,p*M*)-2,5;2′,5′-Didecano-3,3′,4,4′-tetrahydroxymethyl-6,6′-dimethoxybiphenyl [(−)-6b]. To a solution of (+)-**6c** (80 mg, 0.06 mmol) in methanol (30 mL) sodium methoxide (259 mg, 4.80 mmol) was added. After heating under reflux for 4 h the solvent was evaporated in vacuo. Water, 5N HCl and diethyl ether were added with ice cooling. Column chromatography of the residue of the organic layer after usual work-up on silica gel with ethyl acetate/diethyl ether (1:5) provided 23 mg (63%) of (−)-**6b**: mp 225–226°C (ethyl acetate/diethyl ether/pentane). $[\alpha]_D^{17}=-16.69$, $[\alpha]_{578}^{17}=-17.42$, $[\alpha]_{546}^{17}=-19.75$, $[\alpha]_{436}^{17}=-34.60$ (*c* 0.82; C_2H_5OH). ^{1}H NMR (DMSO-d_6, 300 MHz): δ=0.35–1.95 (m, 35H, CH_2), 2.59–2.97 (m, 5H, CH_2), 3.25 (s, 3H, O–CH_3), 3.45 (s, 3H, O–CH_3), 4.61–4.82 (m, 8H, CH_2OH), 4.84–4.95 (m, 1H, CH_2OH), 4.97–5.14 (m, 3H, CH_2–O*H*) ppm. MS (El): *m*/*z* (%)=610 (M^+, 100), 574 (M^+-2H_2O, 22). MS (Cl): *m*/*z* (%)=611 (M^++1, 11), 593 (M^++1−H_2O, 100); exact mass calcd for $C_{38}H_{58}O_6$: 610.4233. Found: 610.4233.

By the same procedure (+)-**6b** was obtained from (−)-**6c′**. $[\alpha]_D^{17}=7.60$, $[\alpha]_{578}^{17}=7.80$, $[\alpha]_{546}^{17}=9.12$, $[\alpha]_{436}^{17}=17.08$ (*c* 0.86, C_2H_5OH).

Heating of (+)-**6b** for 8 h in diglyme solution up to 140°C led only to a slight decrease of the optical rotation ($[\alpha]_{365}^{17}=24.42\rightarrow23.42$, *c* 0.9, diglyme).

4.6.8. Tetramethyl (±)-(p*M,p*M**)-1,4;5,8-didecanodibenzofuran-2,3,6,7-tetracarboxylate (8) and tetramethyl (±)-(p*M**,a*P**,p*M**)-2,5;2′,5′-didecano-6,6′-dihydroxybiphenyl-3,3′,4,4′-tetracarboxylate (9a) (in Scheme 3, only the p*P*-stereoisomers are shown).** Compound *rac*-**4** (1.39 g, 2.00 mmol) was treated with trifluoroacetic acid in the same way as *meso*-**4** (see Section 4.6.1). The crude product was subjected to column chromatography on silica gel. Elution with dichloromethane afforded at first 825 mg (61%) **8**. Further elution with dichloromethane/diethyl ether (2:1) provided 191 mg (14%) **9**. Compound **8**: mp 278°C (diethyl ether/pentane). IR (KBr): ν=1733, 1723, 1600 cm^{-1}. UV (CH_3CN) λ_{max} (log ε)=257 (3.54), 290 (sh, 3.16) nm. ^{1}H NMR ($CDCl_3$, 200 MHz): δ=0.03–1.71 (m, 28H, CH_2), 1.75–2.10 (m, 4H, CH_2), 3.07 (ddd, ^2J=13.3 Hz, ^3J=7.5, 5.6 Hz, 2H, C=C–CH_2), 3.22–3.49 (m, 6H, C=C–CH_2), 3.93 (s, 12H, $COOCH_3$) ppm. ^{13}C NMR ($CDCl_3$, 50 MHz): δ=25.56 (t, 2C, CH_2), 25.83 (t, 2C, CH_2), 26.48 (t, 2C, CH_2), 26.64 (t, 2C, CH_2), 26.71 (t, 2C, CH_2), 27.06 (t, 2C, CH_2), 27.35 (t, 2C, CH_2), 27.75 (t, 2C, CH_2), 27.83 (t, 2C, CH_2), 32.96 (t, 2C, CH_2), 52.59 (q, 2C, $COOCH_3$), 52.62 (q, 2C, $COOCH_3$), 124.63 (s, 2C, C-3, C-6), 126.05 (s, 2C, C-2, C-7), 129.85 (s, 2C, C-1, C-8), 131.87 (s, 2C, C-4a, C-5a), 136.86 (s, 2C, C-4, C-5), 156.67 (s, 2C, C-1a, C-8a), 168.03 (s, 2C, $COOCH_3$), 169.06 (s, 2C, $COOCH_3$) ppm. MS (El): *m*/*z* (%)=676 (M^+, 28) 644 (M^+-CH_3OH, 33); 629 ($M^+-CH_3OH-CH_3$, 100). Calcd for: $C_{40}H_{52}O_{10}$ (676.8): C, 70.98; H, 7.74. Found: C, 71.35; H, 7.71.

Compound **9a**: mp 265°C (dichloromethane/diethyl ether/pentane). IR (KBr): ν=3534, 3428 (O–H), 1740, 1723, 1702, 1557 cm^{-1}. UV (CH_3CN): λ_{max} (log ε)=221 (4.42), 296 (sh, 3.77) nm. ^{1}H NMR ($CDCl_3$, 300 MHz): δ=0.34–0.69 (m, 6H, CH_2), 0.73–1.45 (m, 22H, CH_2), 1.61–1.45 (m, 4H, CH_2), 2.35 (ddd, ^2J=13.8 Hz, $^3J_{7\text{-Hb},8\text{-Ha}}=^3J_{7'\text{-Hb},8'\text{-Ha}}$=7.4 Hz, $^3J_{7\text{-Hb},8\text{-Hb}}=^3J_{7'\text{-Hb},8'\text{-Ha}}$=4.3 Hz, 2H, 7-$H_b$, 7′-$H_b$), 2.75 (ddd, ^2J=13.6 Hz, $^3J_{16\text{-Hb},15\text{-Ha}}=^3J_{16'\text{-Hb},15'\text{-Ha}}$=10.3 Hz, $^3J_{16\text{-Hb},15\text{-Hb}}=^3J_{16'\text{-Hb},15'\text{-Hb}}$=5.3 Hz, 2H, 16-$H_b$, 16′-$H_b$), 2.98 (ddd, ^2J=13.6 Hz, $^3J_{16\text{-Ha},15\text{-Ha}}=^3J_{16'\text{-Ha},15'\text{-Ha}}$=8.4 Hz, $^3J_{15\text{-Ha},15\text{-Hb}}=^3J_{16'\text{-Ha},15\text{-Hb}}$=4.8 Hz, 2H, 16-$H_a$, 16′-$H_a$), 3.06 (dt, ^2J=13.8 Hz, $^3J_{7\text{-Ha},8\text{-Ha}}=^3J_{7'\text{-Ha},8'\text{-Ha}}=^3J_{7\text{-Ha},8\text{-Hb}}=^3J_{7'\text{-Ha},8'\text{-Hb}}$=4.9 Hz, 2H, 7-$H_a$, 7′-$H_a$), 3.85 (s, 6H, $COOCH_3$), 3.89 (s, 6H, $COOCH_3$), 5.40 (s, exchangeable, 2H, OH) ppm. ^{13}C NMR ($CDCl_3$, 75 MHz): δ=25.29 (t, 2C, CH_2), 25.68 (t, 2C, CH_2), 26.70 (t, 2C, CH_2), 26.90 (t, 2C, CH_2), 26.94 (t, 2C, CH_2), 27.21 (t, 2C, CH_2), 27.79 (t, 2C, CH_2), 28.87 (t, 2C, CH_2), 29.54 (t, 2C, CH_2), 30.49 (t, 2C, CH_2), 52.35 (q, 2C, $COOCH_3$), 52.47 (q, 2C, $COOCH_3$), 122.89 (s, 2C, C-3, C-3′), 126.58 (s, 2C, C-5, C-5′)*, 126.82 (s, 2C, C-4, C-4′)*, 135.68 (s, 2C, C-1, C-1′), 142.85 (s, 2C, C-2, C-2′), 153.36 (s, 2C, C-6, C-6′), 168.31 (s, 2C, $COOCH_3$), 168.41 (s, 2C, $COOCH_3$) ppm. MS (El): *m*/*z* (%)=694 (M^+, 39), 662 (M^+-CH_3OH, 100), 630 (M^+-2CH_3OH, 15), 603 ($M^+-CH_3COOH-CH_3O$, 19).

4.6.9. Tetramethyl (±)-(p*M,a*P**,p*M**)-2,5;2′,5′-didecano-6,6′-dimethoxybiphenyl-3,3′,4,4′-tetracarboxylate (9b) (in Scheme 3, only the p*P*-stereoisomers are shown).** A 60% suspension of sodium hydride (36 mg, 0.90 mmol) in mineral oil was washed twice with pentane. After addition of 20 mL THF, **9a** (223 mg, 0.32 mmol) in 5 mL THF was added dropwise. After 1 h dimethyl sulfate (0.10 mL, 1.05 mmol) was added dropwise. The mixture was stirred overnight at room temperature and quenched with 2N KOH. The organic products were dissolved in diethyl ether. Usual work-up and column chromatography on silica gel with diethyl ether/pentane (1:1) provided 121 mg (52%).

Compound **9b**: mp 236–238°C (dichloromethane/diethyl ether/pentane). IR (KBr): ν=1732 (C=O), 1545, 1209 cm^{-1}. UV (CH_3CN): λ_{max} (log ε)=233 (4.57) nm. ^{1}H NMR ($CDCl_3$, 200 MHz): δ=0.55–1.83 (m, 32H, CH_2), 2.41 (ddd, ^2J=14.0 Hz, ^3J=8.4 Hz, ^3J=3.6 Hz, 2H, =C–HC*H*), 2.84–3.06 (m, 6H, =C–CH_2), 3.76 (s, 6H, =C–O–CH_3), 3.83 (s, 6H, $COOCH_3$), 3.89 (s, 6H, $COOCH_3$) ppm. ^{13}C NMR ($CDCl_3$, 50 MHz): δ=25.54 (t, 2C, CH_2), 26.23 (t, 2C, CH_2), 27.09 (t, 2C, CH_2), 27.20 (t,

2C, CH_2), 27.33 (t, 2C, CH_2), 27.61 (t, 2C, CH_2), 27.79 (t, 2C, CH_2), 27.97 (t, 2C, CH_2), 28.24 (t, 2C, CH_2), 30.44 (t, 2C, CH_2), 52.30 (q, 2C, $COOCH_3$), 52.40 (q, 2C, $COOCH_3$), 61.57 (q, 2C, $=C-C-OCH_3$), 127.23 (s, 2C, C-3, C-3′), 130.10 (s, 2C, C-5, C-5′)*, 131.39 (s, 2C, C-1, C-1′)*, 135.31 (s, 2C, C-4, C-4′), 142.20 (s, 2C, C-2, C-2′), 160.68 (s, 2C, C-6, C-6′), 168.59 (s, 2C, $COOCH_3$), 168.82 (s, 2C, $COOCH_3$) ppm. MS (El): *m/z* (%)=722 (M^+, 75) 661 (M^+-CH_3OH, 100). Calcd for: $C_{42}H_{58}O_{10}$ (722.9): C, 69.78; H, 8.09. Found: C, 69.72; H, 8.13.

4.6.10. (±)-(p*M,a*P**,p*M**)-2,5;2′,5′-Didecano-3,3′,4,4′-tetrahydroxymethyl-6,6′-dimethoxybiphenyl (9c) (in Scheme 3, only the p*P*-stereoisomers are shown).** *Compound* **9c** was prepared by reduction of **9b** (167 mg, 0.23 mmol) in THF with lithium aluminum hydride by the same procedure as described for **6a** (see Section 4.6.4). Yield 103 mg (73%), mp 250 251°C (ethyl acetate). IR (KBr): ν=3382, 1549, 1261 cm^{-1}. UV (CH_3CN): λ_{max} (log ε)=203 (4.50), 230 (4.62), 294 (3.34) nm. ^1H NMR (DMSO-d_6, 200 MHz): δ=0.49–1.83 (m, 34H, CH_2), 2.67–3.12 (m, 6H, CH_2), 3.56 (s, 6H, O–CH_3), 4.52–4.82 (m, 8H, $=C-CH_2OH$), 4.94–4.98 (m, exchangeable, 2H, OH), 5.06–5.11 (m, exchangeable, 2H, OH) ppm. ^{13}C NMR (DMSO-d_6, 75 MHz): δ=24.78 (t, 2C, CH_2), 25.54 (t, 2C, CH_2), 26.28 (t, 2C, CH_2), 26.57 (t, 4C, CH_2), 27.51 (t, 4C, CH_2), 27.61 (t, 2C, CH_2), 28.07 (t, 2C, CH_2), 29.14 (t, 2C, CH_2), 58.34 (t, 2C, $=C-CH_2OH$), 58.52 (t, 2C, $=C-CH_2OH$), 60.86 (q, 2C, OCH_3), 129.40 (s, 2C, C-1, C-1′)*, 129.85 (s, 2C, C-5, C-5′)*, 134.59 (s, 2C, C-3, C-3′), 139.91 (s, 2C, C-4, C-4′)**, 140.04 (s, 2C, C-2, C-2′)**, 157.97 (s, 2C, C-6, C-6′) ppm. MS (El): *m/z* (%)=610 (M^+, 25), 574 (M^+-2H_2O, 100).

5. Computational

5.1. Conformational analysis

The conformational analysis of p*P*,a*P*,p*M*-**6b** was performed on Silicon Graphics OCTANE workstations R10000 by means of the AM1[22] parameterization as implemented in the program package VAMP7.0,[23] starting from preotimized geometries generated by the Random-Search algorithm of SYBYL6.4[24] using the TRIPOS[24] force field.

5.2. CD calculations

The main chromophores of bi[10]cyclophane (−)-**6b** that are responsible for the CD behavior, are the two phenyl groups connected by a biaryl axis, making (−)-**6b** a perfect molecule for the application of our CD program package using the semiempirical CNDO/S[25] method, which, as shown in the successful application to similar problems, is well suited for the calculation of $\pi\rightarrow\pi^*$ transitions of compounds with systems of conjugated double bonds.[18,25]

The calculations of the chiroptical properties were performed on LinuX PentiumII workstations by means of the BDZDO/MCDSPD[26] program package, which allows the calculation of excitation energies and rotational strengths for a given molecular geometry. The wave functions required for the calculations for the electronic transitions from the ground state to excited states were obtained by CNDO/S-CI[27] calculations with a CI expansion including 576 singly occupied configurations and the ground state determinant. Mainly due to the neglect of doubly excited configurations by the BDZDO/MCDSPD program, the calculated transition energies showed a systematic shift,[28] whose sign and magnitude can be obtained by comparison of the theoretical UV spectrum (to be calculated by the same program) with the experimental one. By taking into account this systematic UV shift, the virtually identical shift of the computed overall CD spectrum can be compensated and thus corrected.

For a better visualization, the rotational strengths were transformed into $\delta\varepsilon$ values and superimposed with a Gaussian band shape function.

Acknowledgements

We thank the Fonds der Chemischen Industrie and the Deutsche Forschungsgemeinschaft (Graduiertenkolleg ‘Elektronendichte’) for financial support and M. Lehrmann, A. Geiβ, S. Neumann, and A. Reule for technical assistance.

References

1. Prelog, V.; Helmchen, G. *Angew. Chem. Int. Ed. Engl.* **1982**, *21*, 567–583.
2. Schlögl, K. *Top. Curr. Chem.* **1984**, *125*, 27–62.
3. Eliel, E. L.; Wilen, S. H.; Mander, L. N. *Stereochemistry of Organic Compounds*; Wiley: New York, 1994; pp 1119–1190, 1202.
4. Bringmann, G.; Harmsen, S.; Schupp, O.; Walter, R. In *Stereoselective Reactions of Metal-Activated Molecules*; Werner, H., Sundermeyer, J., Eds.; Vieweg: Braunschweig, 1995; pp 137–142.
5. Tochtermann, W.; Olsson, G.; Vogt, C.; Peters, E.-M.; Peters, K.; von Schnering, H. G. *Chem. Ber.* **1987**, *120*, 1523–1532.
6. Tochtermann, W.; Olsson, G.; Mannschreck, A.; Stühler, G.; Snatzke, G. *Chem. Ber.* **1990**, *123*, 1437–1439.
7. Ascenso, J.; Gil, V. M. S. *Can. J. Chem.* **1980**, *58*, 1376–1379, and literature cited therein.
8. Part of this work was published as a preliminary communication: Tochtermann, W.; Kuckling, D.; Meints, Ch.; Kraus, J.; Bringmann, G. *Tetrahedron: Asymmetry* **1999**, *10*, 21–24, For the present full paper, the conformational studies have now been extended using an inital Random-Search algorithm providing improved data on the conformational behavior (like more minimum structures and better energies), leading to the same overall result, in particular to the same attribution of the absolute configuration, showing that the computational effort of the initial investigation had been entirely sufficient.
9. Tochtermann, W.; Haase, M. *Chem. Ber.* **1984**, *117*, 2293–2299.
10. Review: von Angerer, S.; Tochtermann, W.; 4th ed. *Methods in Organic Chemistry (Houben-Weyl)*; 1998; Vol. E9d. pp 1–64.
11. Recently the synthesis of a tetrahydrobioxepine was reported: Baylon, C.; Heck, M.-P.; Mioskowski, C. *J. Org. Chem.* **1999**, *64*, 3354–3360.

12. Peters, K.; Peters, E.-M.; Vanselow, B.; Tochtermann, W. *Z. Kristallogr., NCS* **1998**, *213*, 93–94, see also 95–96.
13. X-Ray structural analyses of related compounds have also been published: (a) Peters, K.; Peters, E.-M.; Karl, B.; Tochtermann, W. *Z. Kristallogr., NCS* **1997**, *212*, 369–370. (b) Peters, K.; Peters, E.-M.; Kuckling, D.; Tochtermann, W. *Z. Kristallogr., NCS* **1998**, *213*, 97–98.
14. Peters, K.; Peters, E.-M.; Meints, Ch.; Tochtermann, W. *Z. Kristallogr., NCS* **2001**, *216*, 305–306.
15. Dewick, P. M. *Medicinal Natural Products, A Biosynthetic Approach*; 2nd ed. Wiley: Chichester, 2002; p 328.
16. Review:Bringmann, G.; Busemann, S. In *Natural Product Analysis*; Schreier, P., Herderich, M., Humpf, H. U., Schwab, W., Eds.; Vieweg: Braunschweig, 1998; pp 195–212.
17. Bringmann, G.; Tasler, S.; Endress, H.; Kraus, J.; Messer, K.; Wohlfarth, M.; Lobin, W. *J. Am. Chem. Soc.* **2001**, *123*, 2703–2711.
18. Bringmann, G.; Menche, D.; Kraus, J.; Mühlbacher, J.; Peters, K.; Peters, E.-M.; Brun, R.; Bezabih, M.; Abegaz, B. M. *J. Org. Chem.* **2002**, *67*, 5595–5610.
19. Bringmann, G.; Mühlbacher, J.; Messer, K.; Dreyer, M.; Ebel, R.; Nugroho, B. W.; Wray, V.; Proksch, P. *J. Nat. Prod.* **2003**, *66*, 80–85.
20. Mislow, K. *Introduction to Stereochemistry*; W.A. Benjamin: New York, 1966; p 89.
21. Recently, optically active and inactive rotamers of a bitriptycyl derivative were isolated that were configurationally stable because of hindered internal rotation around the central single bond: Toyota, S.; Nakagawa, T.; Kotani, M.; Oki, M.; Uekusa, H.; Ohashi, Y. *Tetrahedron* **2002**, *58*, 10345–10351.
22. Dewar, M. J. S.; Zoebisch, E. G.; Healy, E.; Steward, J. J. P. *J. Am. Chem. Soc.* **1985**, *107*, 3902–3909.
23. Rauhut, G.; Chandrasekhar, J.; Alex, A.; Beck, B.; Sauer, W.; Clark, T. VAMP 7.0; Accelrys Inc., Munich, Inselkammerstrasse 1, 82008 Unterhaching-Munich, Germany.
24. SYBYL; Tripos Associates, 1699 St. Hanley Road, Suite 303, St. Louis, MO 63144, USA.
25. Bringmann, G.; Kraus, J.; Schmitt, U.; Puder, C.; Zeeck, A. *Eur. J. Org. Chem.* **2000**, 2729–2734.
26. Downing, J.W., Program Package DBZDO/MCDSPD, Department of Chemistry and Biochemistry, University of Colorado, Boulder, USA, modified by Fleischhauer, J.; Schleker, W.; Kramer, B. Ported to LinuX by Gulden, K.-P.
27. Del Bene, J.; Jaffé, H. *J. Chem. Phys.* **1968**, *58*, 1807–1813.
28. Kutzelnigg, W. *Einführung in die theoretische Chemie (Chemie)*; Weinheim: New York, 1978; Vol. 2. pp 535–540.