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Synthesis and spectroscopic characterization of the first chiral molecular 'hamburger'

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ABSTRACT: The incorporation of the common tetrasubstituted benzene ring **II** between two rigid bisphosphonate spirobiindane units gives rise to two diastereoisomers macrobicyclophanes **VA** and **VB** in high yield. The structures of these two diastereomers were assigned by 1-D and 2-D NMR. Both products shown a structure were the benzene ring is sandwiched between the cyclic frames to form a chiral molecular 'hamburger'. Copyright © 2004 John Wiley & Sons, Ltd.

KEYWORDS: cyclophanes; chiral hamburger; synthesis; stereochemistry

INTRODUCTION

We were recently involved in the synthesis of cleft-like and small chiral cyclic receptor molecules containing phosphonate groups and fully equipped for multipoint binding of basic amino acids (Lys, Arg, His, Lys) of biological interest.[1,2] Using such chiral macrocyclic receptor molecules, we were able to detected some chemoselectivity and also enantiodiscrimination in the complexation studies with the above substrates. For longer α,ω-dicationic diamines, where the distance between the charged nitrogen atoms is more than five bonds, successful enantiodiscrimination was detected. We concluded that for constructing an effective artficial receptor for amino alcohols and dicationic amino acid guest molecules, the host must possess not only negative charges arising from the phosphonate moieties but also a hydrophobic binding site like electron-rich aromatic residues. Therefore, in continuation of these studies, we wanted to incorporate chiral building blocks in our receptor molecules, in addition to rigid elements for a high degree of preorientation, in order to achieve enantioselective and strong recognition of basic amino acids in water.

Because it would be of great interest for biochemistry and for pharmacological studies to dispose of preorganized rigid hosts for biorelevant molecules, we designed some new chiral bimacrocycles capable of a triple binding mode, i.e. exerting attraction for the guests by electrostatic, hydrogen-bond and π-cation interactions. For the electrostatic interactions we resorted to the use of the phosphonate dialkyl ester moiety, which can bear a negative charge when it is hydrolysed to the monoester functionality; the ionization occurs at almost neutral pH values, a prerequisite for molecular recognition under physiological conditions.[3] In order to induce chirality in our macrocycles, we used the spirobisindanol phosphonate unit (**I**) which possesses a C_2 rigid conformation and a geometric constrained structure in which the two hydroxyl groups are fixed in a favourable position for yielding by a template effect the $[1+1]$ cyclization process.[4]

Our strategy was to react **I** with 1,2,4,5-tetrakisbromethylbenzene (**II**) according to the Williamson condensation in order to produce a new chiral macrobicyclic compound, in which a benzene ring is positioned in the centre of a pair of extended chiral cyclophane frames in a molecular equivalent of a 'hamburger'; the phosphonate groups are in external strategic positions for complexation.

RESULTS AND DISCUSSION

Scheme 1 shows the synthetic strategy employed for the preparation of our cyclophanes. The Williamson ether synthetic procedure proved to be very satisfactory; all reagents were converted almost quantitatively and only $[2+1]$ cyclization products were obtained in very hight yield. No doubt this behaviour is due to the geometrically constrained structure of **I**, which possesses the two hydroxyl groups in a favourable position for the cyclization process, instead of the alternative polymerization route, when linkers or spacers of appropriate length are used.

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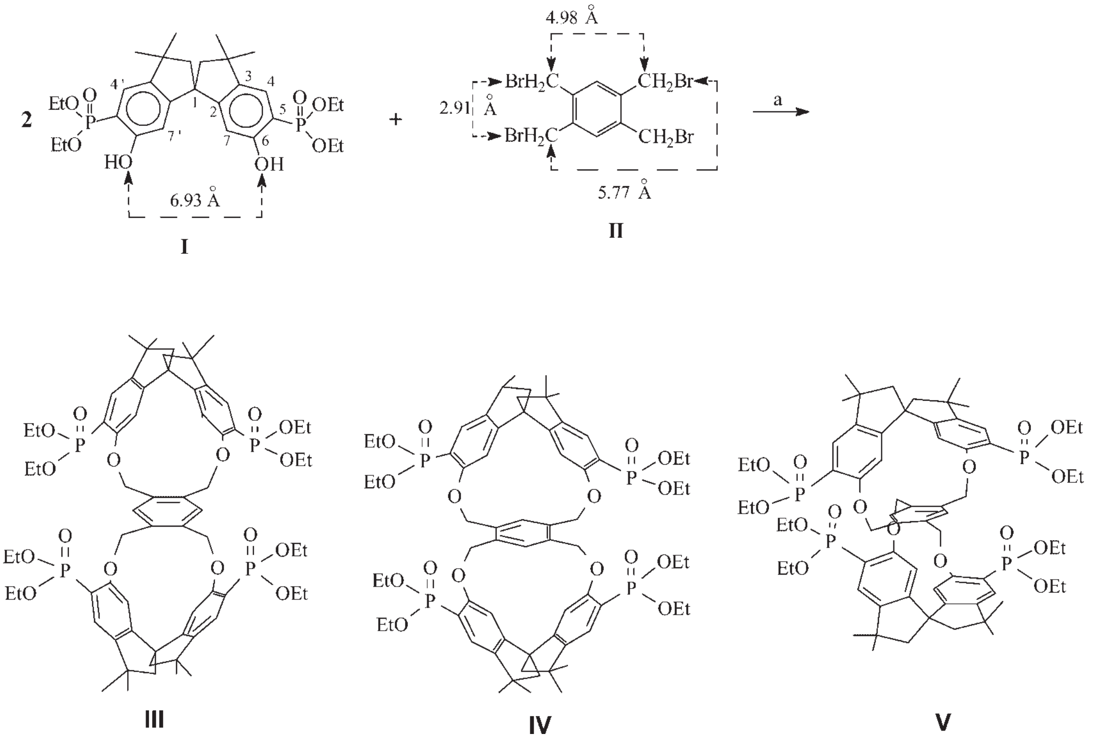


Scheme 1. a, Refluxing acetonitrile, K_2CO_3

Reaction of the racemic monomer phosphonate **I** with 1,2,4,5-tetrakis(bromomethyl)benzene **II** in acetonitrile containing solid potassium carbonate afforded a bromine-free product having $m/z = 1287.5$ (MH^+), thus confirming the 2:1 stoichiometry of the reaction.

The incorporation of the common tetrasubstituted benzene ring between the rigid bisphosphonate spirobiindane units gives rise theoretically to three different isomers i.e. *ortho*–ortho (**III**), *meta*–meta (**IV**) and *para*–para (**V**). Moreover, considering that the spirobiindane phosphonate monomer **I** is a geometrically constrained dissymmetric molecule, which exists as a pair of enantiomers, for each of them a pair of diastereoisomers (i.e. *meso* and *racemic* forms) could be obtainable. Comparison of the OH—OH separation of the phenolic groups in **I** (Hyperchem, 6.93 Å; by x-ray,[4] 6.58 Å) with the bromomethyl C—C distances[5] in **II** (AM1, ranging from 2.91 to 5.77 Å) supports the preferential formation of the dual *para*-substituted product **V**, because less deformation of the molecular frame is required to achieve cyclization.

The 500 MHz ^{1}H NMR spectrum of the isolated crude powder at room temperature in $CDCl_3$ solution, obtained from the reaction outlined in Scheme 1, clearly indicates that a complex mixture of cyclic products is formed. To confirm that our synthesis leads to cyclophanes, we used the ^{31}P NMR technique. Figure 1 shows the ^{31}P NMR spectrum in $CDCl_3$ solution of the crude powder isolated from the reaction in Scheme 1, which is easily interpreted.

Inspection of Fig. 1 reveals the presence of peaks at δ 18.38 ppm (30%), 18.11 ppm (30%), 17.79 ppm (5%) and 17.53 ppm (35%), which are shifted upfield with respect to the corresponding moieties of spirobiindane **I** which resonate at δ 21.24 ppm. This difference is due to the presence of a strong intramolecular hydrogen bond present in **I** involving the phenolic OH and the adjacent P=O group; this interaction is not present after the formation of the macrocycles. If we assume that the two peaks with the same percentage come from the same structure, then the three different sets of signals, which integrate in the ratio 60% (hereafter called major product), 35% (hereafter called minor product) and 5%, suggest that a mixture of three isomers was obtained from the cyclization reaction.

From chemical and steric factors, we can exclude the presence of **III** in the reaction products. In fact, when under the same conditions the spirobiindane compound **I** was reacted with an equimolar amount of the bifunctional α,α'-dibromo-*o*-xylene, no evidence of $[1+1]$ cyclic products was observed and only polymeric compounds were isolated.

Preliminary separation of the crude powder was made on silica gel and after cromatography we recovered 70% of a material, in which the 5% isomer is absent. The other two isomers, possessing the same R_f, were then separated by successive crystallizations; the major isomer had m.p. 145–147 °C and the minor isomer 241–243 °C.

Characterization was performed by FAB-MS, which confirmed that the major and the minor products possess the same molecular weight and they are isomers. In solution the characterization was performed by ^{1}H, ^{13}C and ^{31}P NMR spectroscopy; further, the chemical shifts

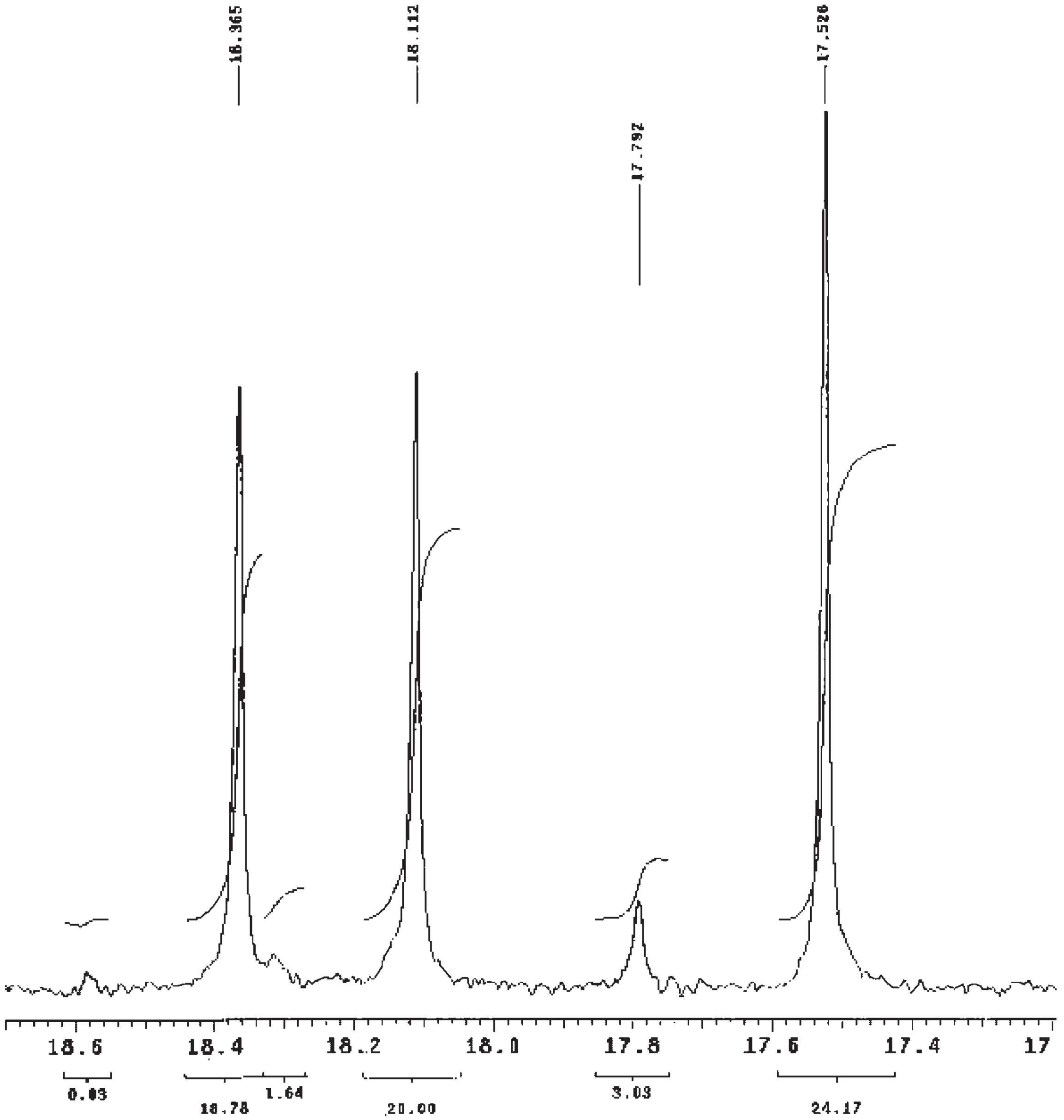


Figure 1. $^{31}P\{H\}$ NMR ($CDCl_3$, 200 MHz) of the crude powder

of the 1-D spectra were assigned to specific atomic positions by COSY and TROESY.

NMR spectroscopy

The 500 MHz ^{1}H NMR spectrum of the minor product at room temperature in $CDCl_3$ solution shows a doublet (δ 7.44, 4,4′-H) and a doublet (δ 5.24, 7,7′-H) for the aromatic hydrogens of the spirobiindane units, a sharp singlet (δ 6.38) for the two aromatic hydrogens of the tetrakismethylbenzene unit, a doublet of doublets centred at (δ 5.40, $\Delta\delta = 0.36$, $^{2}J_{HH} = 12.5$ Hz) for the four bridging benzylic groups and the expected multiplicity for the aliphatic hydrogens. This pattern of ^{1}H NMR resonances, combined with the ^{13}C and ^{31}P NMR spectra, clearly indicates that the minor product possess a high degree of symmetry (e.g. D_2) according to the fact that the hydrogens of the two spirobiindane units and those of the four CH_2 groups are equivalent.

In contrast, the major product shows more complex ^{1}H, ^{13}C and ^{31}P NMR spectra. The two spirobiindane units are no longer homotopic, hence their 4,4′-H_a and 4,4′-H_b hydrogens give rise, in the ^{1}H NMR spectrum, to two different doublets centred at δ 7.52 and 7.49, and the 7,7′-H_a and 7,7′-H_b hydrogens give rise to two different doublets centred at δ 5.39 and 5.13. Moreover, the four bridging benzylic groups are now only pairwise homotopic. In a pair of diastereotopic methylene groups, the hydrogens of each give rise to two doublets of doublets centred at δ 5.26, $\Delta\delta = 0.91$ and δ 5.14, $\Delta\delta = 0.26$, respectively. The expected signals with the appropriate

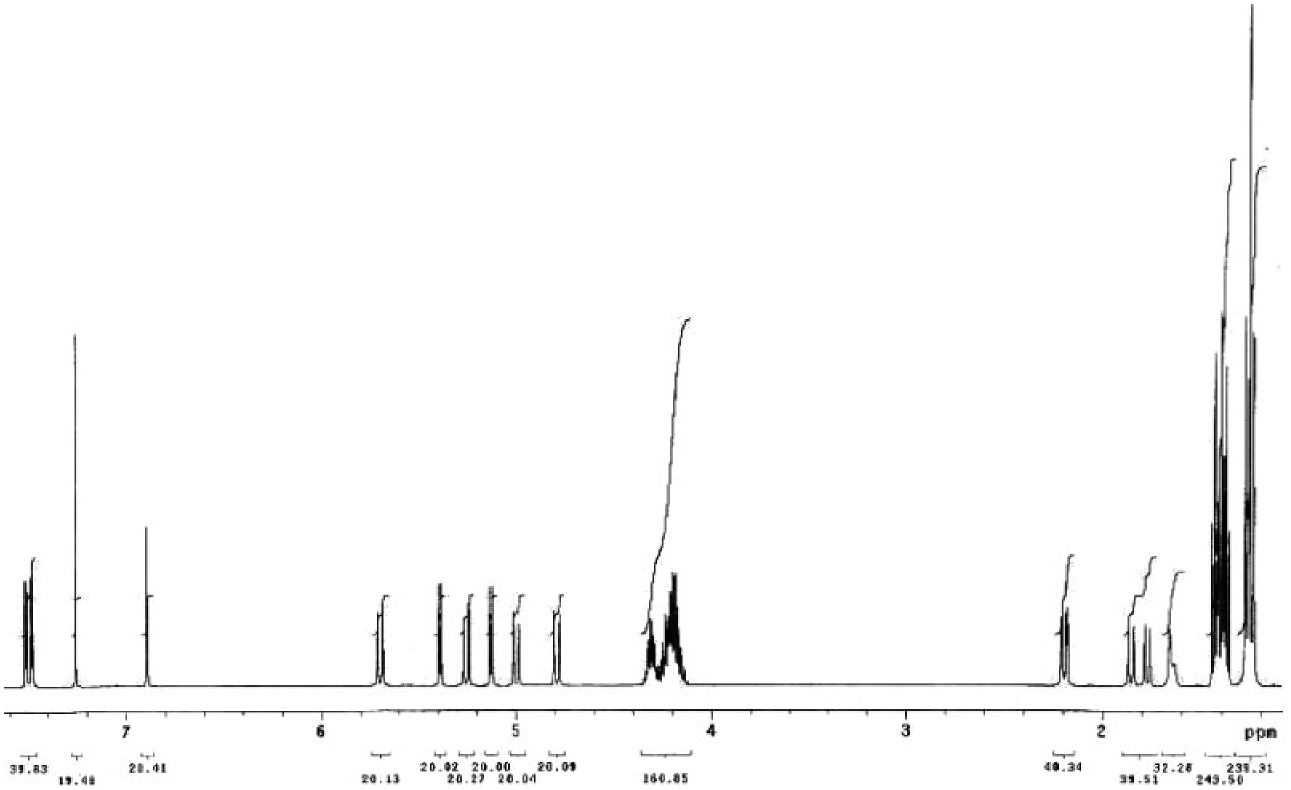


Figure 2. ^{1}H NMR ($CDCl_3$, 500 MHz) of the major product

multiplicity are found for the aliphatic hydrogens (Fig. 2). From the 2-D spectra it was also possible to assign the relative chemical shifts to the methyl groups of the phosphonic groups and to the methylene groups of the spirobiindane fragment.

The major product has a dissymmetric structure (point group symmetry C_2), as evidenced by the presence of two sets of signals, in the ^{1}H, ^{13}C and ^{31}P NMR spectra, for the nuclei of the two spirobiindane units.

ROESY spectra were measured in order to investigate further the conformation of the macrocycles. The ROESY spectrum of the isolated major product is reported in Fig. 3 and shows the expected NOE correlation between the aromatic hydrogens (δ 6.89) of the tetrakismethylbenzene and the two doublets of doublets of the bridging benzylic hydrogens; more interesting the aromatic hydrogens at δ 6.89 shows also NOE with the 7,7′-H$_a$ and 7,7′-H$_b$ hydrogens of the spirobiindane units, which indicates that the macrocycle is congested and stereochemically rigid on the NMR time-scale.

Having gained such information and having already excluded the formation of macrobicycle **III**, the questions that arise now are the following: are the isolated products constitutional or stereoisomers, and if stereoisomers, what is their relative stereochemistry? In order to answer these questions, the following considerations can be of help.

The chemical shifts of the 7,7′-H hydrogens of the spirobiindane units in these macrocycles are very diagnostic for distinguishing between the *para* and *meta* connections within the xylyl unit. In Table 1 are reported same selected signals of the macrocycles (major and minor products) obtained from the reaction in Scheme 1 and a cognate [1 + 1] *para-* or *meta*-cyclophane. Whereas the

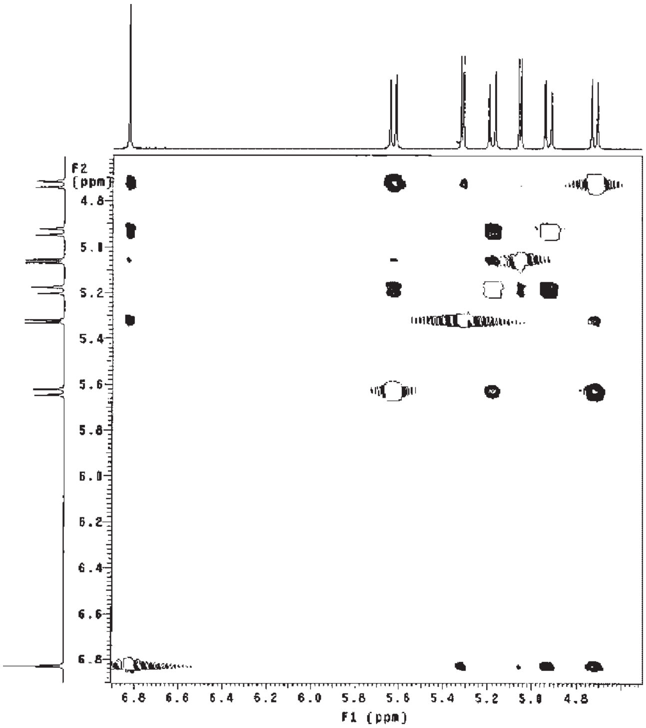
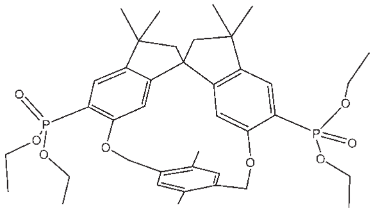
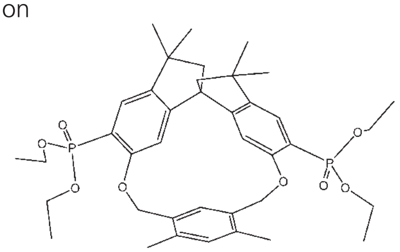


Figure 3. Partial contour plot of TROESY ($CDCl_3$, 500 MHz) of the major product

Table 1. Comparison of selected chemical shifts in $CDCl_3$ solution



Paracyclophane [1 + 1]



Metacyclophane [1 + 1]

Compound	4,4′-H: δ, ppm ($^3J_{HP}$, Hz)	7,7′-H: δ, ppm ($^4J_{HP}$, Hz)	Ph—CH_2—O— ($^2J_{HH}$, Hz)	^{31}P NMR: δ, ppm
Major product	7.52 (15); 7.49 (15)	5.39 (6); 5.13 (6)	5.70, 4.79 (12.5); 5.25, 4.99 (12.5)	18.37, 18.13
Minor product	7.44 (15)	5.24 (6)	5.59, 5.20 (12.5)	17.52
Paracyclophane[4] [1 + 1]	7.52 (15)	5.32 (6)	5.26 (12.5)	18.58
Metacyclophane[4] [1 + 1]	7.57 (15)	6.12 (6)	5.15, 5.01 (13.5)	18.48

4,4′-H chemical shifts are not affected by the connection, the 7,7′-H chemical shifts are strongly dependent on the connection with the xylyl unit. In the *para* connection they are shifted strongly upfield by *ca.* 0.8 ppm compared with the *meta* connection (see Table 1), indicating that they are pointing inside the cage experiencing the deshielding effect of the aromatic nuclei.

From chemical shift considerations and NOE experiments, which reveal that the aryl methyl protons are spatially close to the spirobiindane hydrogens, we could tentatively conclude, invoking Occam's razor, that the two isolated macrocycles are the two possible diastereoisomers of structure **V** in Scheme 1.

Stereochemistry

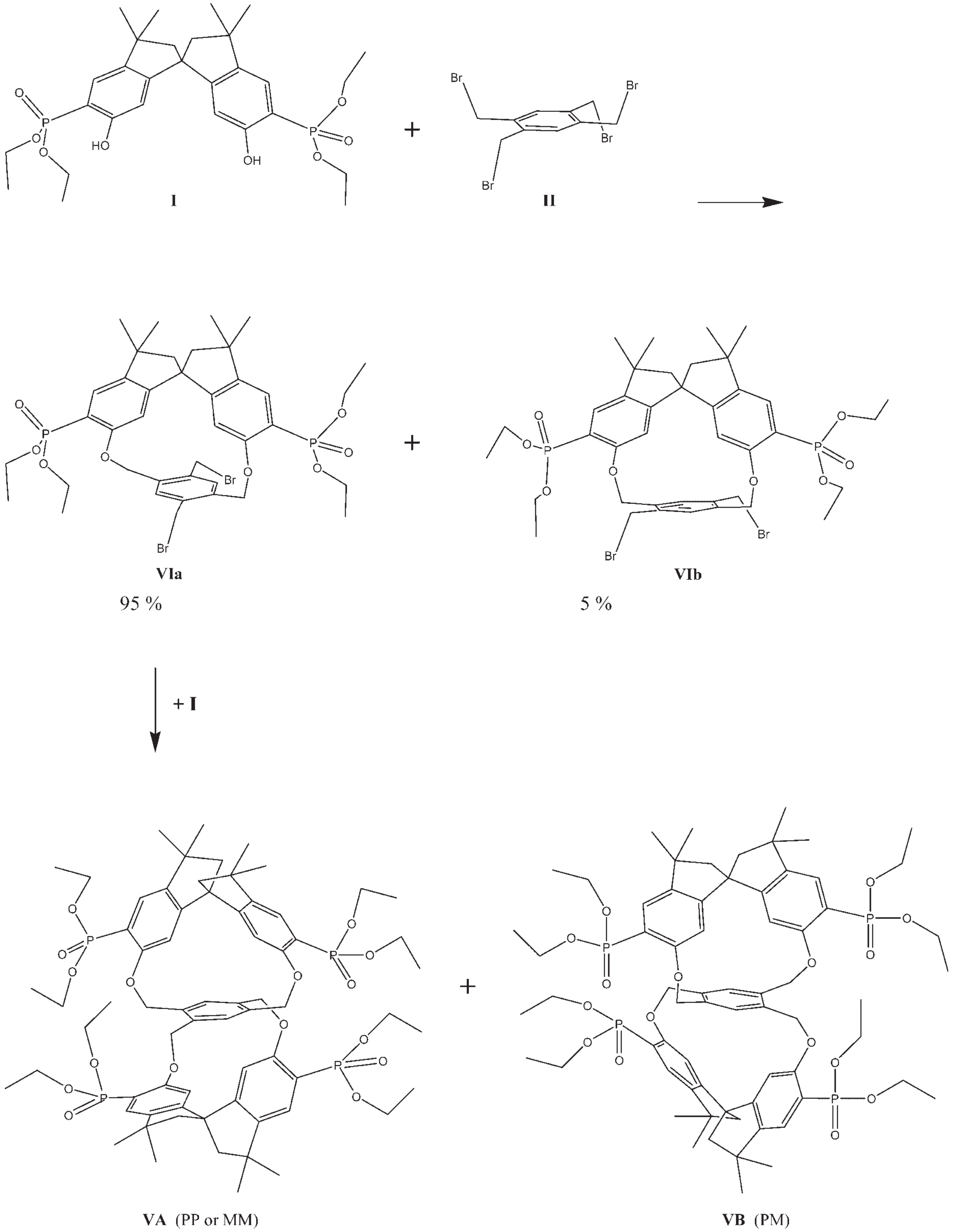
The stereochemical pattern in the macrocycles is intriguing owing to the presence, in the same molecule, of a C_2-symmetrical spirobiindane unit (which is itself chiral) and of a tetrakismethylbenzene bridging moiety which adopts a chiral conformation. (*Ortho*–ortho and *meta*–meta connections give rise to macrobicycles which are conformational mobile and possess symmetry elements of second order, then they are achiral. In particular, in such cases the structures adopted by the macrobicycles come from a match of objects that leads to a 'reverse *coupe du roi*'.[6–8]) It follows that under conditions of restricted rotation of this unit, only two different diastereoisomers are possible in the *first* step of the macrocyclization reaction (Scheme 2). In **VIa** the two homotopic methylene groups of the 1,4-substituted tetrakismethylbenzene ring are pointing out of the molecular cavity and are far from the ring shielding cone of the spirobiindane moiety; the opposite situation arises for **VIb**. Evidence of the formation of structures **VIa** and **VIb** comes from the model reaction of 2,5-dibromomethyl-1,4-xylylene and the spirobiindane phosphonates **I**. From this reaction two diastereoisomers were formed in a ratio of 95:5 as judged by ^{31}P NMR and the predominant product of such [1 + 1] cyclization process is the one diastereomers in which the two xylyl methyl groups are pointing out the molecular cavity of the cycle, as was previously isolated and characterized by x-ray analyses in previous work.[4]

Therefore, reasoning along these lines the *racemic* compound **VIa** (the only one present in our reaction in considerable amount) in the second step reacts again with **I**, which is also a *racemic* mixture, giving rise to a pair of enantiomers (PP, MM, **VA**) and the *meso* form (PM, **VB**), in a ratio of 35:60, respectively.

Examination of structure **VA** (PP or MM, i.e. *racemic* form) reveals that this molecule is chiral, having a dissymmetric structure (point group symmetry D_2), then all constitutionally equivalent atoms of the spirobiindane units and those of the central tetrakismethylbenzene unit are related by symmetry. It follows that the ^{1}H, ^{13}C and ^{31}P NMR spectra of this diastereoisomer should feature one set of signals, with the expected spin–spin coupling, for the 4,4′-H, for the 7,7′-H, for the four diastereotopic CH_2 bridged hydrogens, etc.

In contrast, examination of structure **VB** (PM, i.e. *meso* form) reveals that this molecule has point group symmetry C_2, then also this structure is dissymmetric and chiral (for chiral *meso* compounds, see Ref. 9) but the constitutional equivalent atoms of the spirobiindane units and those of the central tetrakismethylbenzene unit are therefore related pairwise by symmetry. It follows that the ^{1}H, ^{13}C and ^{31}P NMR spectra of the structure **VB** should feature, in the absence of accidental isochronies, two sets of signals, with the expected spin–spin coupling, for the 4,4′-H, for the 7,7′-H, for the four diastereotopic CH_2 bridged hydrogens, etc.

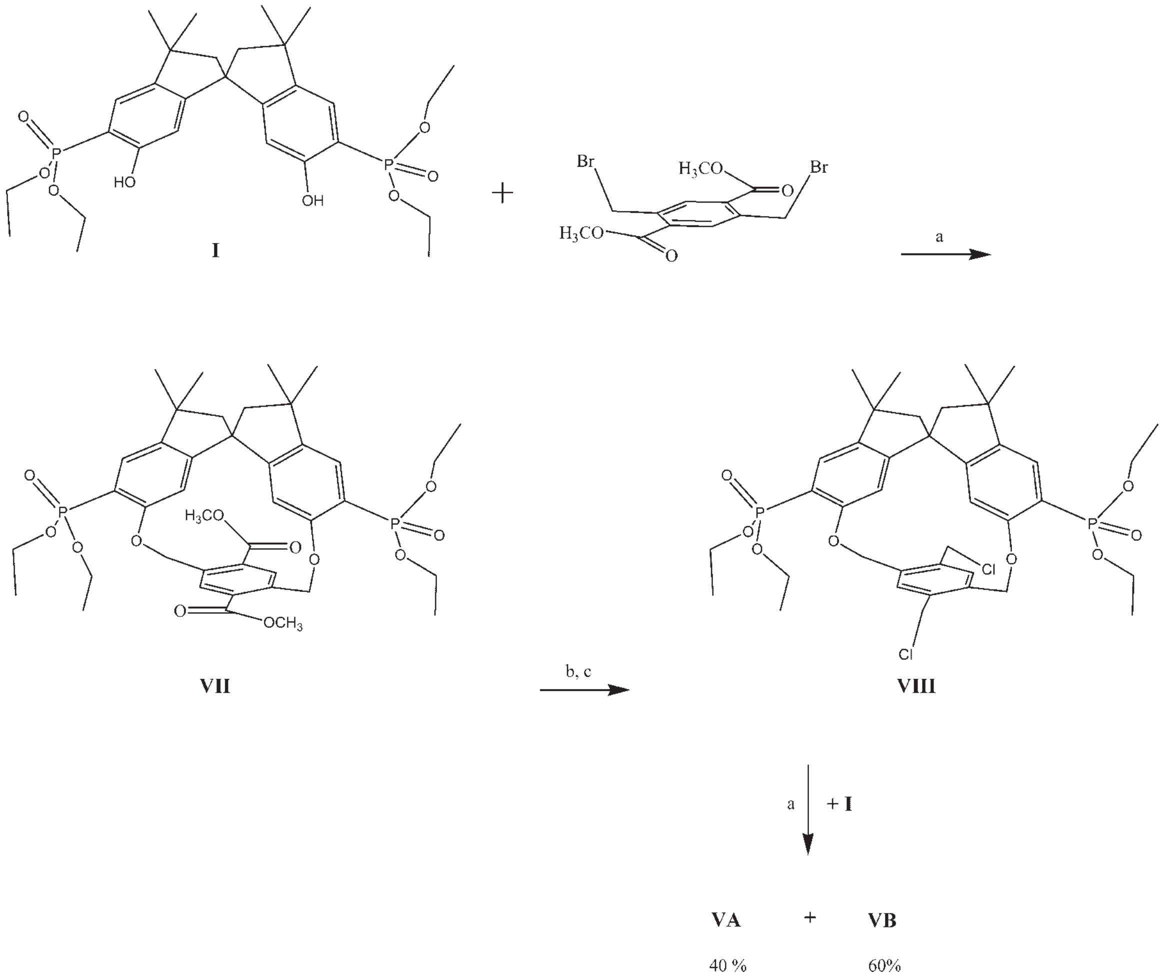
The ^{1}H NMR spectrum of the major product at room temperature in $CDCl_3$ solution (Fig. 2) reveals two



Scheme 2. Possible stepwise pathway for compounds **VA** and **VB**

doublets for the 4,4′-H, two doublets for the 7,7′-H of the aromatic spirobiindane units, two doublets of doublets for the CH_2 bridging hydrogens and also in the aliphatic region two sets of signals are present. Moreover, two sets of peaks are present in the ^{13}C NMR spectra and two sharp peaks with equal intensity are present in the $^{31}P\{^1H\}$ NMR spectra. These results strongly suggest that the major product isolated from our macrocyclization reaction has structure **VB** and the minor product has structure **VA**.

In order to demonstrate that in our cyclization reaction only a step-by-step *para–para* condensation is occuring,



Scheme 3. a, Refluxing acetonitrile, K_2CO_3; b, room temperature, THF, $LiBH_4$; c, 0 °C, DCM, K_2CO_3, $SOCl_2$

we resorted to a stepwise synthesis of macrobicycles **VA** and **VB** as outlined in Scheme 3, using an alternative chemical route. Thus, condensing **I** with 2,5-dibromomethyl-1,4-carbomethoxybenzene the major diastereomer **VII** (formed in $\geqslant 90\%$ yield) was isolated. Following the synthetic routes **b** and **c**, it was converted to the corresponding bischloromethyl derivative **VIII**, which was then allowed to react with an equivalent amount of **I**. Two diastereomers in a ratio of 40:60 were obtained, which possess the same melting-point and the same spectroscopic data for the major and minor products obtained from the one-pot reaction (structures in Scheme 2).

CONCLUSIONS

We synthesized a new class of rigid chiral receptor molecules which can bear negative charges when the phosphonic groups are hydrolys to the monoester functionality. The products obtained, **VA** and **VB**, represent the first example of a chiral molecular 'hambuger' and thus open up new frontiers in the stereochemical use of such molecules.

The highly selective construction of 'hamburger' products **VA** and **VB** in a *para*–para manner, rather than in either a *meta*–meta or an *ortho*–ortho manner, is a direct consequence of the geometry and of the spatial position of the phenolic OH of the spirobiindane unit. The geometry of monomer **I**, although it favours the formation of cyclic products over polymers, is not sufficient for distinguishing in reactivity between *meta*- or *para*-xylylene dibromides because it was shown that it is able to give both the $[1+1]$ intramolecular cyclization products.[4] An important role must be played also by the 1,2,4,5-tetrakis(bromomethyl)benzene in order to yield only a *para*–para connection. Some previous studies[5,10] revealed that the use of this benzylic monomer reacts with spacers of appropriate length in a *para*–para manner only.

The structures of the two diastereoisomers **VA** and **VB** were unambiguously assigned from the presence of a highly diagnostic $7,7'$-H chemical shifts and from the AB systems for the diastereotopic benzylic methylene protons. An independent chemical route to **VA** and **VB** proved without doubt that our bicyclization reaction is occuring in a *para*–para fashion and more important, that the 'hamburgers' obtained possess the structure and stereochemistry discussed above.

In the future, we intend to use these chiral receptor molecules as hosts for dicationic guests and to develop new sensors for basic amino acids.

EXPERIMENTAL

General. All reactions were performed under an inert atmosphere of nitrogen and the solvents were refluxed and freshly distilled before use. ^{1}H, ^{13}C, ^{31}P NMR spectra were recorded on a Varian-Inova 500 MHz instrument operating at 500, 125 and 200 MHz, respectively, using $SiMe_4$ as internal reference and 85% H_3PO_4 as external reference. 2-D experiments were carried out using 1K data points, 256 increments and a relaxation delay of 2.0 s. TROESY spectra were obtained using a 300 ms spin-lock time. Mass spectra were obtained using a double-focusing Kratos MS 50S instrument equipped with a standard FAB source and DS 90 data system using 3-nitrobenzyl alcohol as matrix. Melting-points were determined on a Büchi 530 melting point apparatus and are uncorrected. Yields of the isolated compounds **VA** and **VB** were calculated on the basis of the crude NMR spectra.

Materials. Acetonitrile was dried by distillation from calcium hydride under nitrogen. Spirobiindane phosphonate[11] **I** and 2,5-dibromomethyl-1,4-carbomethoxy-benzene[12] were prepared according to published procedures. Unless stated otherwise, commercial chemicals were used as supplied.

Synthetic Procedure for the 1,1′-Spirobiindan macrobicycles. Solutions of **I** (0.58 g, 1.0 mmol) and 1,2,4,5-tetrakis(bromomethyl)benzene (0.225 g, 0.5 mmol) in freshly distilled CH_3CN (250 ml in total) were added dropwise at equal rates over a period of 3 h, from two different dropping funnels, to a stirred suspension of anhydrous K_2CO_3 (2.8 g, 2 mmol) in anhydrous CH_3CN (150 ml) at refluxing temperature. After the addition was completed, the reaction mixture was refluxed and stirred for 1 day, filtered and the solvent was evaporated to give 0.64 g of white powder, which was purified by column chromatography [SiO_2; EtOAc–MeOH (95:5)] followed by crystallization from cyclohexane–ethyl acetate to give **VA** and **VB** as white crystals.

Structure **VA**. Recrystallization from cyclohexane–ethyl acetate gave the pure product as white crystals: yield 0.22 g (35%), m.p. 241–243 °C; SiO_2, EtOAc–MeOH (95:5), $R_f = 0.18$. FAB-MS (%): *m/z* 1287.5 (100%) $[M + H]^+$, 1309.4 (12%) $[M + Na]^+$. ^{1}H NMR ($CDCl_3$, ppm), δ 7.44 (d, 4H, spiro-4,4′-ArH, $^3J_{HP} = 15$ Hz), 6.38 (s, 2H, ArH), 5.24 (d, 4H, spiro-7,7′-ArH, $^4J_{HP} = 6.0$ Hz), 5.59 (d, 4H, $ArOCH_2Ar$, $^2J_{HH} = 12.5$ Hz), 5.20 (d, 2H, $ArOCH_2Ar$, $^2J_{HH} = 12.5$ Hz), 4.22 (m, 16H, POCH_2CH$_3$), 2.19 (d, 4H, spiroCH$_2$, $^2J_{HH} = 16$ Hz), 1.82 (d, 4H, spiroCH$_2$, $^2J_{HH} = 16$ Hz), 1.41 (t, 12H, POCH$_2\mathit{CH}_3$, $^3J_{HH} = 7$ Hz), 1.34 (t, 12H, POCH$_2\mathit{CH}_3$, $^3J_{HH} = 7$ Hz), 1.28 (s, 12H, spiroCH$_3$), 1.24 (s, 12H, spiroCH$_3$). ^{13}C NMR ($CDCl_3$, ppm), δ 158.05 (d, 3.8 Hz), 154.86 (d, 1.8 Hz), 147.48 (d, 14.1), 136.52, 133.99, 127.54 (d, 7.1 Hz), 120.9 (d, $^1J_{CP} = 187.4$ Hz), 119.77 (d, 11.3 Hz), 72.63, 62.51 (d, 5.8 Hz), 62.09 (d, 5.4 Hz), 57.97, 57.29, 43.12, 31.31, 29.89, 16.45 (d, 2.9 Hz), 16.40 (d, 3.4 Hz). ^{31}P NMR ($CDCl_3$, ppm), δ 17.52.

Structure **VB**. Recrystallization from cyclohexane–ethyl acetate gave the pure product as white crystals: yield 0.38 g (60%), m.p. 145–147 °C; SiO_2, EtOAc–MeOH (95:5), $R_f = 0.18$. FAB-MS (%): *m/z* 1287.5 (100%) $[M + H]^+$, 1309.4 (12%) $[M + Na]^+$. ^{1}H NMR ($CDCl_3$, ppm), δ 7.52 (d, 2H, spiro-4,4′-ArH, $^3J_{HP} = 15$ Hz), 7.49 (d, 2H, spiro-4,4′-ArH, $^3J_{HP} = 15$ Hz), 6.89 (s, 2H, ArH), 5.70 (d, 2H, $ArOCH_2Ar$, $^2J_{HH} = 12.5$ Hz), 5.39 (d, 2H, spiro-7,7′-ArH, $^4J_{HP} = 6.0$ Hz), 5.25 (d, 2H, $ArOCH_2Ar$, $^2J_{HH} = 12.5$ Hz), 5.13 (d, 2H, spiro-7,7′-ArH, $^4J_{HP} = 6.0$ Hz), 4.99 (d, 2H, $ArOCH_2Ar$, $^2J_{HH} = 12.5$ Hz), 4.79 (d, 2H, $ArOCH_2Ar$, $^2J_{HH} = 12.5$ Hz), 4.32–4.15 (m, 16H, POCH_2CH$_3$), 2.20 (d, 2H, spiroCH$_2$, $^2J_{HH} = 13$ Hz), 2.19 (d, 2H, spiroCH$_2$, $^2J_{HH} = 13$ Hz), 1.85 (d, 2H, spiroCH$_2$, $^2J_{HH} = 13$ Hz), 1.77 (d, 2H, spiroCH$_2$, $^2J_{HH} = 13$ Hz), 1.45–1.36 (m, 24H, POCH$_2\mathit{CH}_3$), 1.28 (s, 6H, spiroCH$_3$), 1.26 (s, 12H, spiroCH$_3$), 1.23 (s, 6H, spiroCH$_3$). ^{13}C NMR ($CDCl_3$, ppm), δ 157.76 (d, 4.0 Hz), 157.25 (d, 4.0 Hz), 155.21 (d, 2.4 Hz), 154.66 (d, 2.4 Hz), 146.78 (d, 14.1 Hz), 145.95 (d, 14.0 Hz), 136.88, 135.31, 131.94, 127.91 (d, 7.9 Hz), 127.84 (d, 9.3 Hz), 119.77 (d, $^1J_{CP} = 187.5$ Hz), 119.01 (d, $^1J_{CP} = 186.8$ Hz), 117.83 (d, 10.6 Hz), 116.65 (d, 11.0 Hz), 70.73, 69.87, 62.55 (d, 6.2 Hz), 62.34 (d, 5.9 Hz), 62.05 (d, 5.9 Hz), 61.93 (d, 5.5 Hz), 58.24, 57.75, 57.41, 43.18, 42.97, 31.30, 31.18, 30.19, 30.08, 16.46 (d, 7.1 Hz), 16.40 (d, 6.6 Hz). ^{31}P NMR ($CDCl_3$, ppm), δ 18.37, 18.13.

Structure **VII**. Yield 93%. FAB-MS (%): *m/z* 799.2 (40%) $[M + H]^+$, 821.2 (10%) $[M + Na]^+$. ^{1}H NMR ($CDCl_3$, ppm) δ 7.61 (s, 2H, ArH), 7.58 (d, 2H, spiro-4,4′-ArH, $^3J_{HP} = 15$ Hz), 5.76 (d, 2H, $ArOCH_2Ar$, $^2J_{HH} = 14.0$ Hz), 5.54 (d, 2H, $ArOCH_2Ar$, $^2J_{HH} = 14.0$ Hz), 5.27 (d, 2H, spiro-7,7′-ArH, $^4J_{HP} = 6.0$ Hz), 4.35–4.18 (m, 8H, POCH_2CH$_3$), 3.81 (s, 6H, COOCH$_3$), 2.20 (d, 2H, spiroCH$_2$, $^2J_{HH} = 13$ Hz), 1.90 (d, 2H, spiroCH$_2$, $^2J_{HH} = 13$ Hz), 1.42 (m, 12H, POCH$_2\mathit{CH}_3$), 1.26 (s, 6H, spiroCH$_3$), 1.25 (s, 6H, spiroCH$_3$). ^{13}C NMR ($CDCl_3$, ppm) δ 166.26, 157.62 (d), 155.47, 146.10 (d), 137.83, 132.92, 132.44, 128.34 (d), 118.81 (d, $^1J_{CP} = 178.7$ Hz), 116.02 (d), 69.84, 62.28 (d), 62.12 (d), 58.29, 57.52, 43.24, 31.28, 30.07, 16.45 (t). ^{31}P NMR ($CDCl_3$, ppm), δ 18.45.

Structure **VIII**. Yield 70%. FAB-MS (%): *m/z* 778.4 (100%) $[M]^+$, 780.3 (70%) $[M + 2]^+$. ^{1}H NMR ($CDCl_3$, ppm), δ 7.52 (d, 2H, spiro-4,4′-ArH, $^3J_{HP} = 15$ Hz), 7.02 s, 2H ArH), 5.51 (d, 2H, $ArOCH_2Ar$,

$^2J_{\mathrm{HH}} = 13.0\,\mathrm{Hz}$), 5.48 (d, 2H, spiro-7,7′-ArH, $^4J_{\mathrm{HP}} = 6.0\,\mathrm{Hz}$), 5.41 (d, 2H, $\mathrm{ArOCH_2Ar}$, $^2J_{\mathrm{HH}} = 13.0\,\mathrm{Hz}$), 4.59 (d, 2H, $\mathrm{ArOCH_2Ar}$, $^2J_{\mathrm{HH}} = 12.0\,\mathrm{Hz}$), 4.43 (d, 2H, $\mathrm{ArCH_2Cl}$, $^2J_{\mathrm{HH}} = 12.0\,\mathrm{Hz}$), 4.32–4.24 (m, 8H, $\mathrm{PO}\mathit{CH_2}\mathrm{CH_3}$), 2.20 (d, 2H, $\mathrm{spiroCH_2}$, $^2J_{\mathrm{HH}} = 13\,\mathrm{Hz}$), 1.93 (d, 2H, $\mathrm{spiroCH_2}$, $^2J_{\mathrm{HH}} = 13\,\mathrm{Hz}$), 1.45 (t, 12H, $\mathrm{POCH_2}\mathit{CH_3}$, $^4J_{\mathrm{HP}} = 6.0\,\mathrm{Hz}$), 1.26 (s, 6H, $\mathrm{spiroCH_3}$), 1.24 (s, 6H, $\mathrm{spiroCH_3}$). ^{13}C NMR ($\mathrm{CDCl_3}$, ppm), δ 157.34 (d), 155.75, 146.47 (d), 136.25, 135.74, 132.53, 127.81 (d), 119.23 (d, $^1J_{\mathrm{CP}} = 179.9\,\mathrm{Hz}$), 117.49 (d), 69.48, 62.44 (d), 62.12 (d), 58.26, 57.46, 43.26, 42.39, 31.44, 29.94, 16.50 (t). ^{31}P NMR ($\mathrm{CDCl_3}$, ppm), δ 18.37.

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