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# Synthesis of 1,4-Phenylene-*bis*-aminomethanephosphonates: The Stereochemical Aspect

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ABSTRACT: *The synthesis of new 1,4-phenylene-bis-(N-alkylaminomethane)-bis-phosphonates* **3Aa–3Da** *by the addition of dialkyl or diaryl phosphites to the azomethine bond of 1,4-phenylene Schiff bases is reported. Some NMR studies on the stereochemistry of dialkyl phosphite addition to terephthalic bis-imines showing the exclusive formation of the meso-form are presented. The mechanism and the origin of such a high stereoselectivity are discussed.* © 2000 John Wiley & Sons, Inc. Heteroatom Chem 11:144–151, 2000

## *INTRODUCTION*

Aminophosphonic acids as isosteres of natural aminoacids have been well known since the late 1940s, when Chavane [1] published for the first time the synthesis of aminomethanephosphonic acid—the phosphonic analog of glycine. Since then, over 1000 articles covering different aspects of their synthesis have been published [2]. We also contributed to this topic [3–5] by publishing the synthesis of the furanic series of these compounds.

The biologic activity of these aminophosphonic acids was also largely studied and discussed. It was discovered that the phosphonic analog of $\beta$-alanine is a component of the bacterial cell wall [6] and protects the cell against destruction. Their herbicidal and antibacterial properties were also largely examined [7,8], confirming their high activity (e.g., alaphosphalines).

In search of new starting materials for polymers having various interesting properties, we dealt with *bis*-aminophosphonic acids and esters. Because this topic seemed very interesting to us from the synthesis point of view, we studied it further and would like to report the synthesis of some new 1,4-phenylene-*bis*-(*N*-alkylaminomethane)-*bis*-phosphonates, which are perspective starting compounds for polymer synthesis.

To our knowledge, only several articles have covered this topic. Pudovik *et al.* [9] presented the synthesis of four phenylene-phosphonates using the Kabachnik-Fields method. But they neglected completely the spectral characterization of products. Issleib et al. [10] Barycki et al. [11] and Garncarz [12] reported the hydrolysis of tetraethyl 1,4-phenylene-*bis*-(*N*-benzyl-aminomethane)-*bis*-phosphonate and tetraethyl 1,4-phenylene-*bis*-(*N*-benzhydrylaminomethane)-*bis*-phosphonate as a key step in the synthesis of the corresponding acids. The synthesis of the esters was carried out without any solvent, and they neither isolated nor characterized these esters. Failla and Finocchiaro [13] reported the synthesis and monohydrolysis of some phenylene-*bis*-(*N*-alkylaminomethane)-*bis*-phosphonates and Failla et al. [14] presented some of their NMR data. Finally Zimmer and Thomas [15] synthesized 1,4-phenylene-*bis*-(*N*-*p*-nitroanilinomethane)-*bis*-phosphonates, which were subsequently utilized in further reactions.

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Barycki et al. [11] have observed an intriguing phenomenon. They noticed that the final diacid gave one set of signals in the $^{1}H$ NMR spectrum and a single signal in the $^{31}P$ NMR spectrum, concluding that the attack on the second azomethine bond is stereocontrolled; thus the reaction is stereoselective. The product should be either a pair of enantiomers or a meso-form. But they did not study the case to state the stereochemistry of the reaction.

Caccamese et al. [16] reported chiral HPLC studies on the addition of diethyl phosphite to dibenzylideneethylenediamine, detecting that it led to the *meso*-form. Moreover, Failla et al. [17] confirmed the formation of the *meso*-form by X-ray analyses. We were interested to check whether the addition of phosphites to phenylene-*bis*-imines behaved in the same or some other way.

We report here NMR studies on the stereochemistry of dialkyl phosphite addition to phenylene *bis*-imines and an easy-to-use synthesis of new tetraalkyl 1,4-phenylene-*bis*-(*N*-alkyl-aminomethane)-*bis*-phosphonates providing products in fair yields.

## *RESULTS AND DISCUSSION*

The first step was the preparation of Schiff bases derived from terephthalic aldehyde. They were obtained by the condensation of the aldehyde with the corresponding amine in nearly quantitative yield [7].

Then the addition of dialkyl- or diaryl phosphites to their azomethine bonds was carried out (Scheme 1).

Barycki et al. [11] performed this reaction without solvent, but this method turned out to be ineffective, as the separation and purification of the products were rather troublesome. The authors did not isolate the esters but hydrolyzed the products to the acids. We were obliged to search for a proper solvent, and, after having tested several of them, we have chosen toluene. Its convenience comes not only from providing products in higher yields but also from easier work-up and from shortening the reaction time.

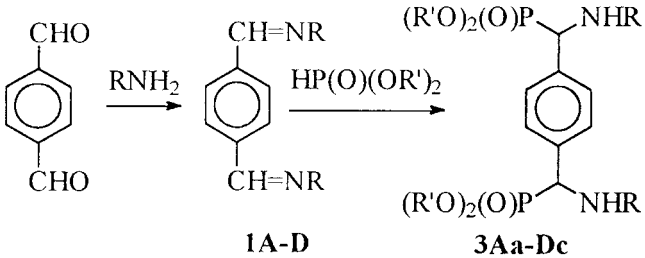
Indeed, the reaction lasted around 5 hours when the mixture was refluxed in toluene. To compare, when the reaction was carried out in acetonitrile, it demanded over 30 hours of refluxing.

Products were obtained in 46–58% yield, which is satisfactory and relatively high, considering that the addition of phosphite to bis-Schiff bases is much more difficult than the mono-addition [11]. All results are collected in Table 1.

Our observation concerning the stereochemistry of addition of phosphites to the azomethine bond of bis-imines was similar to Barycki's [11] observation; we determined the formation of the exclusive diastereoisomer. It was confirmed, by the analysis of the post-reaction mixture, that no other product part from unreacted substrates was formed. In order to establish whether two enantiomers or the meso-form occurs, we prepared 1,4-phenylene-*bis*-(*N*-benzyl-aminomethane)-*bis*-phosphonic acid (**4**) following the previously reported procedure [11] and transformed it into its chiral salt with (*R*)-α-methylbenzylamine (**5**) (Scheme 2).

An NMR study showed the formation of a salt-$^{31}P$ chemical shift occurred at 17.04 ppm, about 1 ppm upfield from the starting aminophosphonic acid **4.** Slight deshielding was also observed in the $^{1}H$ NMR spectra.

To confirm this observation, we performed another experiment. Starting *bis*-phosphonate **3Aa** was converted into its chiral salt (**6**) with (*S*)-mandelic acid. NMR studies showed the clear formation of a salt - $^{31}P$ chemical shift occurred at 24.73 ppm, at about 0.1 ppm downfield from the starting *bis*-ami-

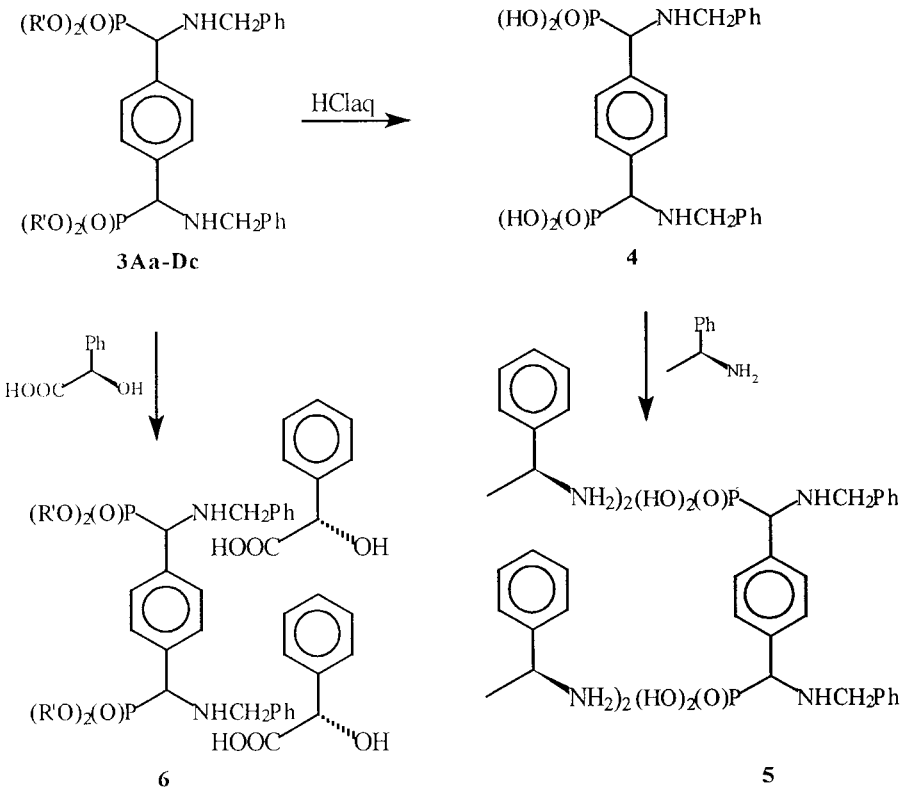



R=**A**: $CH_2Ph$; **B**: $CH_2Fur$; **C**: $CMe_3$; **D**: CHMePh
R'=**a**: $CH_2CH_3$; **b**: Ph; **c**: $CH_2Ph$

**SCHEME 1**

**TABLE 1**

| *Starting Schiff Base* | *Starting Phosphite* | *Resulting Ester* | *Method* | *Time (h)* | *Yield (%)* |
|---|---|---|---|---|---|
| **1A** | **2a** | **3Aa** | A | 24 | 43 |
| **1A** | **2a** | **3Aa** | B | 5 | 49 |
| **1A** | **2b** | **3Ab** | B | 5 | 48 |
| **1A** | **2c** | **3Ac** | B | 6 | 48 |
| **1B** | **2b** | **3Bb** | B | 7 | 49 |
| **1B** | **2c** | **3Bc** | B | 5 | 52 |
| **1C** | **2b** | **3Cb** | B | 5 | 54 |
| **1C** | **2c** | **3Cc** | B | 5 | 52 |
| **1D** | **2a** | **3Da** | B | 6 | 44 |
| **1D** | **2c** | **3Dc** | B | 6 | 48 |




**SCHEME 2**

nophosphonate. $^{1}H$ and $^{13}C$ NMR signals were shifted downfield about 0.5 and 0.3 ppm, respectively. But the most significant change was the shift of the $^{1}H$ NMR signal corresponding to the NH group—a broad singlet occurred at 5.59 ppm about 2.7 ppm downfield from the NH signal in the starting ester **3Aa** ($\delta_H$ = 2.88 ppm).

In both cases only one set of NMR signals was observed.

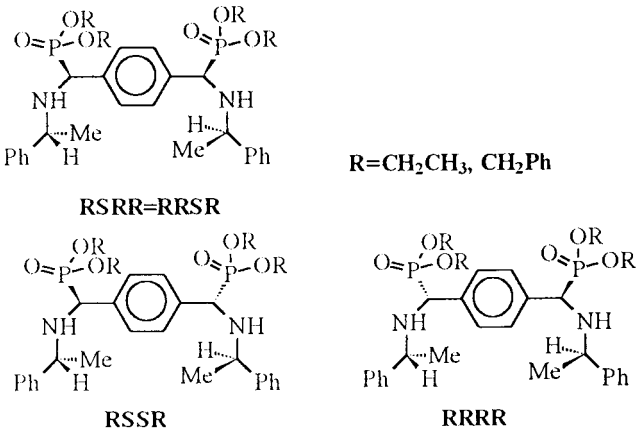
We reason that if the product were the pair of enantiomers, this conversion would result in two diastereoisomers. Thus, the salt should give two sets of $^{1}H$ and $^{13}C$ NMR signals and two separate $^{31}P$ NMR signals. But, if the acid (**4**) existed as a meso-form, the salt would be a single isomer, giving one set of NMR signals (Scheme 2).

Our NMR study on the salt showed only one set of signals in the $^{31}P$, $^{1}H$, and $^{13}C$ NMR spectra. This demonstrates clearly that the addition of dialkyl phosphites to *bis*-imines of terephthalic aldehyde results in the formation of the meso-form.

We studied also the stereochemical behavior of the addition of dialkyl phosphites to chiral *bis*-imines. The addition of diethyl and dibenzyl phosphites (**2a** and **2c** respectively) to *N,N*-terephthalidene-*bis*-(*R*)-$\alpha$-methylbenzylamine **1D** was carried out in refluxing toluene. $^{1}H$ and $^{31}P$ NMR studies showed clearly the formation of three diastereoisomers in a 1:1:8 ratio for both (**3Da** and **3Dc**) cases. Although we failed to separate the isomers, the analysis of NMR spectra showed that the two minor products correspond to the RRRR and RSSR diastereoisomers (Scheme 3). Each of them gave two $^{31}P$ NMR signals of equal intensity ($\delta$ = 22.65 and 22.64; 22.59 and 22.58 for **3Da** as well as $\delta$ = 24.41 and 24.34; 23.84 and 23.79 for **3Dc**) demonstrating magnetic nonequivalence of the two phosphorus atoms in the molecule. And indeed, two phosphorus atoms in RRRR and RSSR diastereoisomers should be magnetically nonequivalent, as their molecules show no symmetry.

The $^{31}P$ NMR signals of the major product ($\delta$ = 22.63 for **3Da** and $\delta$ = 24.28 for **3Dc**) should thus correspond to a meso-like form RRSR≡RSRR as they occurred as single peaks. It demonstrates the equivalence of both phosphorus atoms and indeed the RRSR≡RSRR diastereoisomers should have equivalent phosphorus atoms due to their higher degree of symmetry.

It is of importance to state that introducing the




**SCHEME 3**

chiral group to the molecule of *bis*-imine diminished the stereoselectivity of the phosphite addition; the reaction with an achiral imine led to an exclusive isomer, while, as it was shown, the reaction with chiral (*R*-α-methylbenzylimine **1D** led to three isomers.

Why are diastereoisomers formed in a 1:1:8 ratio? According to Yuan's work [18] and our previous observation [6], the addition of a dialkyl phosphite to chiral mono-Schiff bases is stereoselective and Cram rules can be utilized. Although Cram rules apply to 1,2-related centers, Yamamoto [21] applied them to the addition to Schiff bases, this reaction being 1,3-related.

We would like to suggest that the discussed system is subjected to the influence of two counteracting factors controlling the stereochemistry: first is the action of the chiral centers at the nitrogen atoms; the second entails the same factor, which controls the stereochemistry of phosphite addition to achiral imines.

As for the first factor, which follows the rules of the Cram-Cram addition, it would force the formation of the RRRR isomer as a major product (Scheme 4), the imine adopting three conformational states **Ca, Cb,** and **Cc** (Scheme 4).

In the case of the conformation **Ca,** Cram–Cram (RSSR), *anti*-Cram–*anti*-Cram (RRRR), Cram–*anti*-Cram (RRSR), and *anti*-Cram–Cram (RSRR) products would be formed. So, the major product would be the RSSR diastereoisomer. For both **Cb** and **Cc** conformations the RRRR diastereoisomer should be a major product. So, if the influence of chiral centers in the Schiff bases was the only factor determining the stereochemistry, then based on Cram rules, the RRSR≡RSRR isomer should be formed in minor amount.

But the influence of the second factor is much stronger, forcing the formation of RRSR≡RSRR diastereoisomer; that is why it formed in a 4-fold excess. The same factor, controlling the stereochemistry in the case of the achiral imine caused the formation of a meso-form as the exclusive diastereoisomer.

The mechanism of the reaction is still unknown; thus, it is difficult to explain the origin of the stereoselectivity. If we consider a two-step mechanism postulated by Barycki et al. [11], the newly created stereogenic center probably controls the formation of the second center.

It is to say that 1,6-stereocontrol is not very probable due to the distance. So, there must be a different phenomenon controlling the stereochemistry. Our hypothesis concentrates on hydrogen bonding between the P=O bond and the hydrogen atom from the molecule of the phosphite (Scheme 5).

Simultaneously, two molecules of the mono-aminophosphonate would form the dimer, which would force the conformation of the mono-aminophosphonate, as presented in Scheme 5. In this way, the addition of the phosphite molecule to the azomethine bond would be forced to proceed from the side of the phosphonic group causing the formation of the RS≡SR meso-form. However, as of now, it is nothing more than a hypothesis; we have no proof for such a hydrogen bonding as we failed in the attempted isolation the mono-aminophosphonic intermediate. However, this reasoning seems to us to be the most convincing explanation of such a high and remarkable degree of stereocontrol.

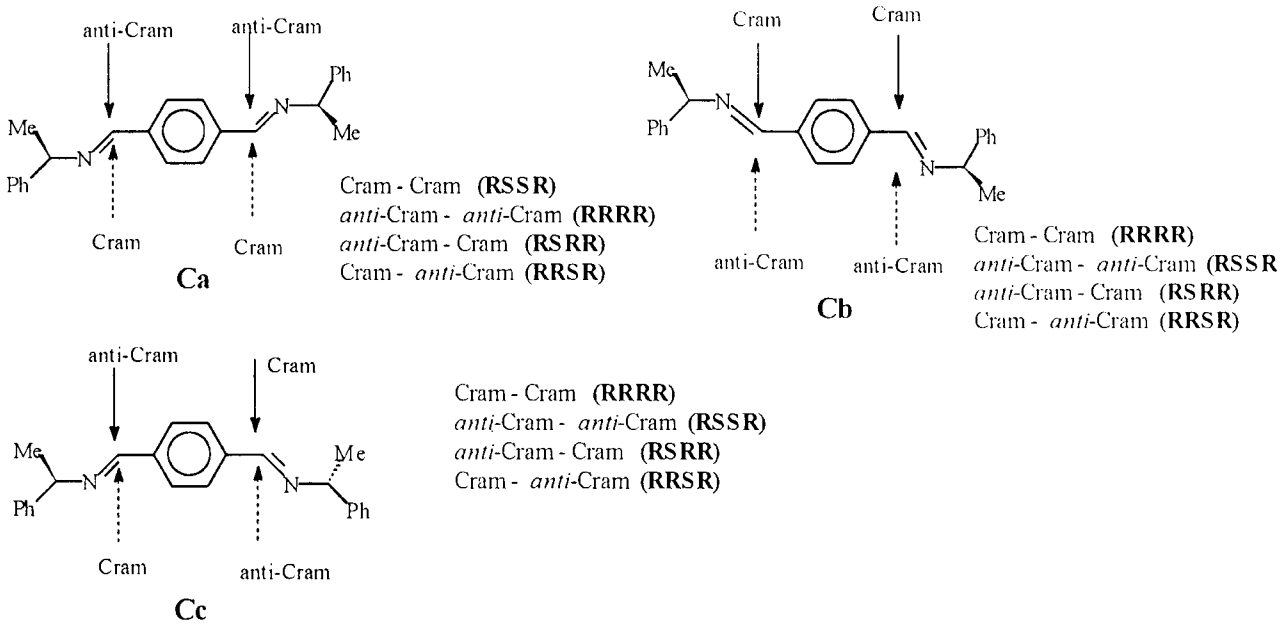
The study on establishing the mechanism is in progress.

## *EXPERIMENTAL*

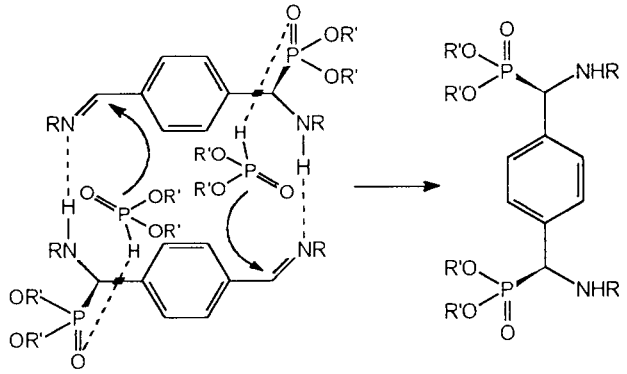
All solvents were routinely distilled and dried prior to use. Terephthalic aldehyde (Lancaster), benzylamine, furfurylamine, diethyl and dibenzyl phosphites (Aldrich) diphenyl phosphite and *tert*-butylamine (Fluka) were used as received. All NMR spectra were recorded on a Varian 200 Gemini BB or a Brucker 300AC spectrometer. Elemental analyses were provided by the Center of Microanalysis of the Center for Molecular and Macromolecular Studies in Łódź. Melting points were measured on a Meltemp II apparatus and are not corrected.

### *Preparation of N,N′-terephthalylidenoalkylamines* (**1A–D**)

Terephthalic aldehyde (1.34 g, 10 mmol) was dissolved in methanol (40 mL) and then the corresponding amine (20 mmol) was added. The mixture was stirred overnight, and the precipitated solid was




**SCHEME 4**




**SCHEME 5**

then collected by filtration, dried, and recrystallized to obtain the desired Schiff bases.

### *N,N'-Terephthalylidenebenzylamine* (**1A**)

Y = 84%, m.p. 103–105°C, lit[17]: 104–105°C. $^1$H NMR ($CDCl_3$, 200 MHz): $\delta$ 8.38 (s, CH=N, 2H); 7.82 (s, $C_6H_4$, 4H); 7.33 (m, ArH, 10H); 4.81 (s, $CH_2Ph$, 4H). Elem. Anal. Calcd. for $C_{22}H_{20}N_2$: C, 84.58; H, 6.45; N, 8.97. Found: C, 84.66; H, 6.51; N, 8.91

### *N,N,'-Terphthalylidenefurfurylamine* (**1B**)

Y = 80%, mp: (water-methanol 1:1) 106–108°C. $^1$H NMR ($CDCl_3$, 200 MHz): $\delta$ 8.35 (s, CH=N, 2H); 7.80 (s, $C_6H_4$, 4H); 7.39 (m, $H_5$fur, 2H); 6.35 (m, $H_3$fur, 2H); 6.29 (m, $H_4$fur, 2H); 4.79 (s, $CH_2$Fur, 4H). Elem. Anal. calcd. for $C_{18}H_{16}N_2$: C 73.95; H 5.52; N 9.58. Found: C 73.66; H 5.51; N 9.61

### *N,N'-Terephthalylidene tert-butylylamine* (**1C**)

Y = 81%, m.p. 88–90°C, lit[18]: 91°C. $^1$H NMR ($CDCl_3$, 200 MHz): $\delta$ 8.29 (s, CH=N, 2H); 7.78 (s, $C_6H_4$, 4H); 1.31 (s, $CH_3$, 18H). Elem. Anal. Calcd. for $C_{16}H_{24}N_2$: C, 78.64; H, 9.90; N, 11.46. Found: C, 78.46; H, 9.81; N, 11.41.

### *N,N'-Terephthalylidene* (*R*)-*α-methyl benzylamine* (**1D**)

Y = 84%, m.p. 91–93°C. $^1$H NMR ($CDCl_3$, 200 MHz): $\delta$ 8.38 (s, CH=N, 2H); 7.81 (s, $C_6H_4$, 4H); 7.47–7.20 (m, ArH, 10H); 4.55 ($q_D$, $J$ = 6.5 Hz, CH-N, 2H); 1.59 (d, $J$ = 6.5 Hz, $CH_3$, 6H). Elem. Anal. Calcd. for $C_{24}H_{24}N_2$: C, 84.67; H, 7.11; N, 8.23. Found: C, 84.20; H, 7.39; N, 8.44.

### *Preparation of Tetraalkyl 1,4-Phenylene-bis-*(*N-alkylaminomethane*)*-bis-phosphonates* (**3Aa–3Dc**)

*Method A.* The Schiff base (**1A–C**) (5 mmol) was dissolved in acetonitrile (20 mL), and then the dialkyl phosphite (2a–c) (10 mmol) was added, which was followed by the addition of several drops of trifluoroacetic acid. The mixture was refluxed for

24 hours, acetonitrile was evaporated in vacuo, and the residue was dissolved in 10% $HCl_{aq}$-ethanol (4:1) and washed with ether. Ethereal solutions were discarded, and the aqueous layer was then made alkaline and was extracted with dichloromethane (3 × 40 mL). Organic layers were dried and evaporated, and the residue was recrystallized.

*Method B.* The Schiff base (**1A–C**) (5 mmol) was dissolved in toluene (30 mL), and then the dialkyl phosphite (**2a–c**) (10 mmol) was added. The mixture was refluxed for 5 to 7 hours. After cooling to room temperature, the solid precipitate was collected by filtration, washed, and dried. Products were purified by recrystallization or column chromatography (eluted with AcOEt-hexane (2:1)).

### *Tetraethyl 1,4-Phenylene-bis-*(*N-benzylaminomethane*)*-bis-phosphonate* (**3Aa**)

m.p. 89–91°C. $^1$H NMR ($CDCl_3$, 200 MHz): $\delta$ 7.44 (s, ArH, 4H); 7.35–7.20 (m, ArH, 10H); 4.20–3.78 (m, $\underline{CH_2}CH_3$, 8H); 4.04 (d, $^2J_{PH}$ = 19.2 Hz, CHP, 2H); 3.82 (d, $^2J_{HH}$ = 13.7 Hz, $CH_2$Ph, 2H); 3.55 (d, $^2J_{HH}$ = 13.7 Hz, $CH_2$Ph, 2H); 1.28 and 1.12 (2t, $J$ = 7.1 Hz, $CH_2\underline{CH_3}$, 6H). $^{13}$C NMR ($CDCl_3$, 50 MHz): $\delta$ 139.27 ($C_{ipso}$); 135.54 ($C_{ipso}$); 128.81 ($C_{meta}$); 128.40 ($C_{ortho}$); 128.31 ($C_{para}$); 127.17 ($C_{o+m}$); 62.80 and 62.84 (2d, $^2J_{PC}$ = 18.9 Hz, Et); 59.35 (d, $^1J_{PC}$ = 152.8 Hz); 51.29 (d, $^3J_{PC}$ = 18.1 Hz, Bz); 16.39 and 16.35 (2d, $^2J_{PC}$ = 14.3 Hz, Et). $^{31}$P NMR ($CDCl_3$, 81 MHz): $\delta$ 24.05. Elem. Anal. Calcd. for $C_{30}H_{42}N_2O_6P_2$: C, 61.22; H, 7.19; N, 4.76; P, 10.56. Found: C, 61.30; H, 7.19; N, 4.81; P, 10.28.

$^1$H NMR ($CD_3C(O)CD_3$, 300 MHz): $\delta$ 7.51 and 7.50 (2s, ArH, 4H); 7.38–7.20 (m, ArH, 10H); 4.20–3.78 (m, $\underline{CH_2}CH_3$, 8H); 4.04 (d, $^2J_{PH}$ = 24.2 Hz, CHP, 2H); 3.84 (d, $^2J_{HH}$ = 13.7 Hz, $CH_2$Ph, 2H); 3.57 (d, $^2J_{HH}$ = 13.7 Hz, $CH_2$Ph, 2H); 2.88 (broad s, NH, 2H); 1.25 and 1.07 (2t, $J$ = 7.1 Hz, $CH_2\underline{CH_3}$, 6H). $^{13}$C NMR ($CD_3C(O)CD_3$, 75 MHz): $\delta$ 140.93 ($C_{ipso}$); 137.00 ($C_{ipso}$); 129.63 ($C_{meta}$); 129.60 ($C_{ortho}$); 129.15 ($C_{para}$); 127.78 ($C_{o+m}$); 63.12 and 62.08 (2d, $^2J_{PC}$ = 18.9 Hz, Et); 60.22 (d, $^1J_{PC}$ = 152.8 Hz); 51.85 (d, $^3J_{PC}$ = 18.1 Hz, Bz); 16.73 and 16.69 (2d, $^2J_{PC}$ = 14.3 Hz, Et). $^{31}$P NMR ($CD_3C(O)CD_3$, 121 MHz): $\delta$ 24.67.

### *Tetrabenzyl 1,4-Phenylene-bis-*(*N-benzylaminomethane*)*-bis-phosphonate* (**3Ac**)

m.p. 168–170°C. $^1$H NMR ($CDCl_3$, 200 MHz): $\delta$ 7.41 (s, ArH, 4H); 7.31–7.09 (m, ArH, 30H); 5.12–4.90 (AM part of AMX system, $^2J_{HH}$ = 12.6 Hz, $^3J_{PH}$ = 8.4 Hz and $^3J_{PH}$ = 7.5 Hz, $OCH_2$Ph, 4H); 4.92–4.62 (AM part of AMX system, $^2J_{HH}$ = 12.8 Hz, $^3J_{PH}$ = 8.2 Hz and $^3J_{PH}$ = 6.6 Hz, $OCH_2$Ph, 4H); 4.19 (d, $^2J_{PH}$ = 18.3 Hz, CHP, 2H); 3.79 (d, $^2J_{HH}$ = 13.1 Hz, $CH_2$Ph, 2H); 3.51 (d, $^2J_{HH}$ = 13.1 Hz, $CH_2$Ph, 2H). $^{31}$P NMR ($CDCl_3$, 81 MHz): $\delta$ 23.47. Elem. Anal. Calcd. for $C_{50}H_{50}N_2O_6P_2$: C, 71.76; H, 6.02; N, 3.35; P, 7.40. Found: C, 71.75; H, 5.96; N, 3.42; P, 7.56.

### *Tetraphenyl 1,4-Phenylene-bis-*(*N-benzylaminomethane*)*-bis-phosphonate* (**3Ab**)

m.p. 154–156°C. $^1$H NMR ($CDCl_3$, 200 MHz): $\delta$ 7.57 (s, $C_6H_4$, 4H); 7.40–6.88 (m, ArH, 30H); 4.41 (d, $^2J_{PH}$ = 19.3 Hz, CHP, 2H); 3.91 (d, $^2J_{HH}$ = 13.9 Hz, $CH_2$Ph, 2H); 3.64 (d, $^2J_{HH}$ = 13.1 Hz, $CH_2$Ph, 2H); 2.35 (broad s, NH, 2H). $^{31}$P NMR ($CDCl_3$, 81 MHz): $\delta$ 15.47. Elem. Anal. Calcd. for $C_{46}H_{42}N_2O_6P_2$: C, 70.76; H, 5.42; N, 3.59; P, 7.93. Found: C, 70.53; H, 5.42; N, 3.60; P, 7.68.

### *Tetraphenyl 1,4-Phenylene-bis-*(*N-furfurylaminomethane*)*-bis-phosphonate* (**3Bb**)

m.p. 157–160°C. $^1$H NMR ($CDCl_3$, 200 MHz): $\delta$ 7.56 (s, $C_6H_4$, 4H); 7.37 (m, $H_5$fur, 2H); 7.26–6.86 (m, ArH, 20H); 6.30 (m, $H_3$fur, 2H); 6.11 (dd, $J$ = 3.5 and 2.0 Hz, $H_4$fur, 2H); 4.44 (d, $^2J_{PH}$ = 18.0 Hz, PCH, 2H); 3.91 (d, $^2J_{HH}$ = 14.6 Hz, $CH_2$Fur, 2H); 3.64 (d, $^2J_{HH}$ = 14.6 Hz, $CH_2$Fur, 2H); 2.36 (s, NH, 2H). $^{31}$P NMR ($CDCl_3$, 81 MHz): $\delta$ 15.48. Elem. Anal. Calcd. for $C_{42}H_{38}N_2O_6P_2$: C, 66.31; H, 5.03; N, 3.68; P, 8.14. Found: C, 66.48; H, 4.96; N, 3.83; P, 8.22.

### *Tetrabenzyl 1,4-Phenylene-bis-*(*N-furfurylaminomethane*)*-bis-phosphonate* (**3Bc**).

m.p. 139–142°C. $^1$H NMR ($CDCl_3$, 200 MHz): $\delta$ 7.39 (s, $C_6H_4$, 4H); 7.31–7.16 (m, ArH, 20H); 7.12 (m, $H_5$fur, 2H); 6.27 (dd, $J$ = 3.1 and 2.0 Hz, $H_4$fur, 2H); 6.03 (d, $J$ = 3.1 Hz, $H_3$fur, 2H); 5.05–4.85 (AM part of AMX system, $^2J_{HH}$ = 11.8 Hz, $^3J_{PH}$ = 8.4 Hz and $^3J_{PH}$ = 7.3 Hz, $OCH_2$Ph, 4H); 4.91–4.67 (AM part of AMX system, $^2J_{HH}$ = 11.9 Hz, $^3J_{PH}$ = 7.8 Hz and $^3J_{PH}$ = 6.8 Hz, $OCH_2$Ph, 4H); 4.13 (d, $^2J_{PH}$ = 18.3 Hz, CHP, 2H); 3.78 and 3.53 (2d, $^2J_{HH}$ = 14.6 Hz, $CH_2$Fur, 4H), 2.15 (s, NH, 2H). $^{31}$P NMR ($CDCl_3$, 81 MHz): $\delta$ 22.69. Elem. Anal. Calcd. for $C_{46}H_{46}N_2O_6P_2$: C, 67.64; H, 5.68; N, 3.43; P, 7.57. Found: C, 67.82; H, 5.72; N, 3.64; P, 7.68.

### *Tetrabenzyl 1,4-Phenylene-bis-*(*N-tert-butylaminomethane*)*-bis-phosphonate* (**3Cc**).

m.p. 156–158°C. $^1$H NMR ($CDCl_3$, 200 MHz): $\delta$ 7.43 (s, $C_6H_4$, 4H); 7.31 (m, ArH, 8H); 7.24 (m, ArH, 8H); 7.09 (m, ArH, 4H); 5.17–5.04 (AB part of AMB sys-

tem, $^2J_{HH}$ = 10.8 Hz, $^3J_{PH}$ = 7.6 Hz and $^3J_{PH}$ = 7.0 Hz, $OCH_2Ph$, 4H); 4.85–4.45 (AM part of AMX system, $^2J_{HH}$ = 11.9 Hz, $^3J_{PH}$ = 7.8 Hz and $^3J_{PH}$ = 6.8 Hz, $OCH_2Ph$, 4H); 4.24 (d, $^2J_{PH}$ = 24.4 Hz, CHP, 2H); 0.92 (s, $CH_3$, 18H). $^{31}$P NMR ($CDCl_3$, 81 MHz): $\delta$ 19.89. Elem. Anal. Calcd. for $C_{44}H_{54}N_2O_6P_2$: C, 68.68; H, 7.07; N, 3.64; P, 8.03. Found: C, 68.79; H, 6.98; N, 3.58; P, 7.97.

*Tetraphenyl 1,4-Phenylene-bis-*(*N-tert-butylaminomethane*)*-bis-phosphonate* (**3Cb**).

m.p. 170–172°C. $^1$H NMR ($CDCl_3$, 200 MHz): $\delta$ 7.43 (s, $C_6H_4$, 4H); 7.30–7.02 (m, ArH, 16H); 6.81 (m, ArH, 4H); 4.54 (d, $^2J_{PH}$ = 25.8 Hz, CHP, 2H); 1.90 (broad s, NH, 2H); 1.01 (s, $CH_3$, 18H). $^{31}$P NMR ($CDCl_3$, 81 MHz): $\delta$ 15.41. Elem. Anal. Calcd. for $C_{40}H_{46}N_2O_6P_2$: C, 67.41; H, 6.51; N, 3.93; P, 8.69. Found: C, 67.58; H, 6.53; N, 3.98; P, 8.62.

*Tetraethyl 1,4-Phenylene-bis-[N-*(*R*)*-α-methyl-benzylaminomethane]-bis-phosphonate* (**3Da**).

$^1$H NMR ($CDCl_3$, 200 MHz): $\delta$ 7.29 (s, ArH, 4H); 7.24 (m, ArH, 10H); 4.15 (q, $J$ = 6.5 Hz, CH-N, 2H); 4.10–3.60 (m, $\underline{CH_2}CH_3$, 8H); 4.04 and 3.82 (d, $^2J_{PH}$ = 19.2 Hz, CHP, 2H); 1.34 and 1.09 (2t, $J$ = 7.1 Hz, $CH_2\underline{CH_3}$, 6H); 1.32 (d, $J$ = 6.5 Hz, $CHCH_3$, 6H). $^{31}$P NMR ($CDCl_3$, 81 MHz): $\delta$ 22.65 (5%); 22.64 (5%); 22.63 (80%); 22.59 (5%); 22.58 (5%). Elem. Anal. Calcd. for $C_{32}H_{46}N_2O_6P_2$: C, 62.33; H, 7.52; N, 4.54; P, 10.02. Found: C, 62.67; H, 7.39; N, 4.69; P, 10.28.

*Tetrabenzyl 1,4-Phenylene-bis-[N-*(*R*)*-α-methyl-benzylaminomethane]-bis-phosphonate* (**3Dc**)

$^1$H NMR ($CDCl_3$, 200 MHz): $\delta$ 7.34 (s, ArH, 4H); 7.32 (m, ArH, 30 H); 5.19–4.96 (ABX system, $^3J_{PH}$ = 8.3 Hz, $^2J_{HH}$ = 11.7 Hz, $^3J_{PH}$ = 6.8 Hz, Bz, 4H); 4.89–4.53 (AMX system, $^3J_{PH}$ = 7.9 Hz, $^2J_{HH}$ = 11.7 Hz, $^3J_{PH}$ = 6.6 Hz, Bz, 4H); 4.16 and 4.14 (d, $^2J_{PH}$ = 19.6 Hz, CHP, 2H); 3.85–3.77 (m, CHN); 2.21 (s, NH, 2H). $^{31}$P NMR ($CDCl_3$, 81 MHz): $\delta$ 24.41 (5%); 24.34 (5%); 24.28 (80%); 23.84 (5%); 23.76 (5%). Elem. Anal. Calcd. for $C_{52}H_{54}N_2O_6P_2$: C, 72.21; H, 6.29; N, 3.24; P, 7.16. Found: C, 72.60; H, 6.39; N, 3.35; P, 7.39.

*1,4-Phenylene-bis-*(*N-benzylaminomethane*)*-bis-phosphonic Acid Hydrochloride* (**4**)

The acid was prepared following the published procedure [11] and obtained as its hydrochloride in quantitative yield, m.p. 257–260°C, lit. [11] 258–261°C. $^1$H NMR ($CD_3OD$, 200 MHz): $\delta$ 7.49 (s, ArH, 4H); 7.39–7.24 (m, ArH, 10H); 4.13 (d, $^2J_{PH}$ = 16.2 Hz, CHP, 2H); 3.79 (d, $^2J_{HH}$ = 13.7 Hz, $CH_2Ph$, 2H); 3.51 (d, $^2J_{HH}$ = 13.7 Hz, $CH_2Ph$, 2H). $^{31}$P NMR ($CD_3OD$, 81 MHz): $\delta$ 18.15.

*Preparation of Chiral Salts* **5** *and* **6**

Aminophosphonic ester **3Aa** or acid **4** was packed into a NMR tube and was dissolved in 0.5 mL of the appropriate deuterated solvent (acetone D6 and methanol D4, respectively); spectra were recorded and then solutions of appropriate chiral agents (*S*-mandelic acid and *R*-*α*-methylbenzylamine, respectively) in the same deuterated solvents were added. Spectra were immediately recorded, showing the formation of salts.

*Chiral Salt* **5.** $^1$H NMR ($CD_3OD$, 200 MHz): $\delta$ 7.61 (s, ArH, 4H); 7.53–7.21 (m, ArH, 30H); 4.26 (d, $^2J_{PH}$ = 15.9 Hz, CHP, 2H); 4.19 (q, $J$ = 6.5 Hz, CH-N, 4H); 3.79 (d, $^2J_{HH}$ = 13.7 Hz, $CH_2Ph$, 2H); 3.51 (d, $^2J_{HH}$ = 13.7 Hz, $CH_2Ph$, 2H); 1.38 (d, $J$ = 6.5 Hz, $CHCH_3$, 12H). $^{31}$P NMR ($CD_3OD$, 81 MHz): $\delta$ 17.04.

*Chiral Salt* **6.** $^1$H NMR ($CD_3C(O)CD_3$, 300 MHz): $\delta$ 7.54–7.49 (m, ArH, 14H); 7.37–7.20 (m, ArH, 10H); 5.59 (broad s, $NH_2^+$, OH, 6H); 5.21 (s, CH, 2H); 4.20–3.78 (m, $\underline{CH_2}CH_3$, 8H); 4.04 (d, $^2J_{PH}$ = 24.2 Hz, CHP, 2H); 3.84 (d, $^2J_{HH}$ = 13.5 Hz, $CH_2Ph$, 2H); 3.57 (d, $^2J_{HH}$ = 13.5 Hz, $CH_2Ph$, 2H); 1.28 and 1.11 (2t, $J$ = 7.1 Hz, $CH_2\underline{CH_3}$, 6H). $^{13}$C NMR ($CD_3C(O)CD_3$, 75 MHz): $\delta$ 174.65 (C=O); 140.85 ($C_{ipso}$); 140.78 ($C_{ipso}$); 136.80 ($C_{ipso}$); 129.63($C_{meta}$); 129.18 ($C_{ortho}$); 129.15 ($C_{para}$); 129.11 ($C_{meta}$); 128.74 ($C_{ortho}$); 127.81 ($C_{para}$); 127.58 ($C_{o+m}$); 73.50 (CH); 63.12 and 62.08 (2d, $^2J_{PC}$ = 18.9 Hz, Et); 60.02 (d, $^1J_{PC}$ = 152.8 Hz); 51.78 (d, $^3J_{PC}$ = 18.1 Hz, Bz); 16.73 and 16.69 (2d, $^2J_{PC}$ = 14.3 Hz, Et). $^{31}$P NMR ($CD_3C(O)CD_3$, 121 MHz): $\delta$ 24.72.

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