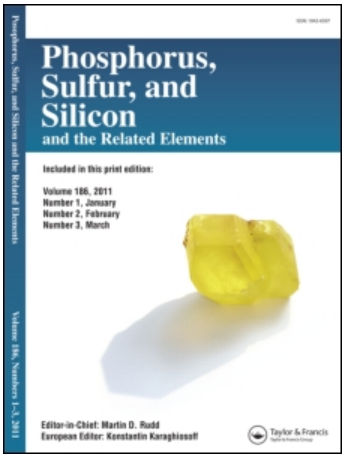

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REACTION OF THE LITHIUM DERIVATIVE OF DIETHYL 2-(OR 3-)METHYLPHENYLMETHANEPHOSPHONATE WITH KETONES. AN EXAMPLE OF HIGH SYN-STEREOSELECTIVITY

Nikolay G. Vassilev[a]; Jordanka Petrova[b]; Marko Kirilov[b]
[a] Institute of Organic Chemistry, Bulgarian Academy of Sciences, Sofia, Bulgaria [b] Faculty of Chemistry, University of Sofia, Sofia, Bulgaria

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REACTION OF THE LITHIUM DERIVATIVE OF DIETHYL 2-(OR 3-)METHYLPHENYLMETHANEPHOSPHONATE WITH KETONES. AN EXAMPLE OF HIGH SYN-STEREOSELECTIVITY

NIKOLAY G. VASSILEV
Institute of Organic Chemistry, Bulgarian Academy of Sciences, Sofia 1113, Bulgaria

and

JORDANKA PETROVA and MARKO KIRILOV
Faculty of Chemistry, University of Sofia, 1 James Bourchier Av., 1126 Sofia, Bulgaria

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The reaction of the lithium derivative of diethyl ester of 2-(or 3-)methylphenylmethanephosphonic acid (**1-Li**) with a large number of symmetric and unsymmetric ketones **2a–r** is studied at −70°C in THF, the corresponding adducts—diethyl esters of 1-(2- or 3-methylphenyl)-2,2-dialkyl(phenyl)-2-hydroxyethanephosphonic acid **3a–r** being isolated. The results of stereospecific olefination of the β-hydroxyphosphonates **3j**, **3k**, **3o** and **3p** indicate the influence of combined steric effects in ketones **2** and ortho- and metha-methyl substituted benzylphosphonates **1**. Spectral investigations and PM3-calculations prove high synstereoselectivity of the reaction of ortho-methyl substituted benzylphosphonates **1a** with studied ketones.

Key words: Stereoselectivity; arylmethanephosphonate carbanion; reaction with ketones; 2-hydroxyethanephosphonates; atropisomers; PM3-calculations.

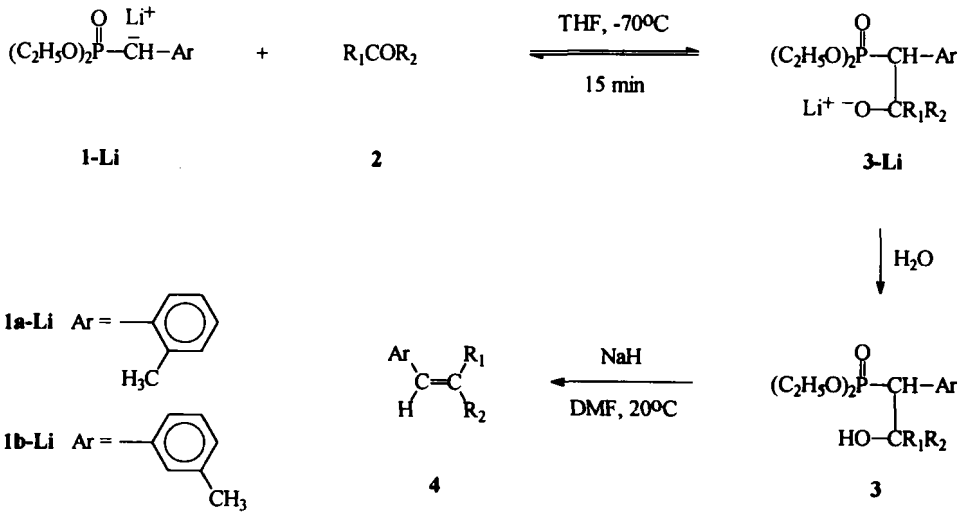
INTRODUCTION

Recently we have studied the Wittig-Horner reaction of Li-diethylbenzylphosphonate with aldehydes[1] and ketones.[2] It was found that in this case the aldol stage of the reaction is not stereoselective or threo isomers predominate, while the same reaction of N,N,N′,N′-tetramethyldiamides of benzylphosphonic acid with aldehydes is erythro stereoselective.[3–6] We have studied also restricted rotation of the phenyl group in the above mentioned β-hydroxyphosphonates.[7] It was found that the restricted rotation takes place only in adducts of benzylphosphonic esters or diamides with ketones and not in adducts with aldehydes.

In the present paper we report the synthesis of ortho- and metha-methyl substituted β-hydroxyphosphonates used as dynamic NMR-spectroscopy model compounds, an observed atropisomerism of the ortho-substituted isomers, as well as data about the olefination stage of the reaction.

RESULTS AND DISCUSSION

We have studied the reaction of the lithium derivative of diethyl ester of 2-methylphenylmethanephosphonic acid **1a-Li** as well as of diethyl ester of 3-methylphenylmethanephosphonic acid **1b-Li** with a large number of symmetric or unsymmetric ketones **2**. The reaction was carried out at −70°C in THF for 15 min (see Scheme I) in accordance with our previous investigation of the influence of the reaction conditions on the equilibrium.[2] After hydrolysis the diethyl esters of 1-(2- or 3-methylphenyl)-2,2-dialkyl(phenyl)-2-hydroxyethanephosphonic acid **3** were obtained (Scheme I, Table I).



SCHEME I

It was established by ^1H NMR studies that the crude reaction products **3c–3e** and **3m–3r** represented diastereomeric mixtures, the RR,SS("threo")-isomer being the prevailing one (see Table I). The reaction with 2-methylcyclohexanone **2m**, and 2-chlorocyclohexanone **2o** was highly threo-stereoselective, only "threo" diastereoisomers being isolated. The relative configurations of the adducts **3c–3e** and **3m–3r** were determined on the basis of our previous NMR spectral investigation on the stereochemistry of 1-phenyl-2,2-dialkyl(phenyl)-2-hydroxyethanephosphonates.[2] The observed relationships

$$\Delta\delta_{CH_3}^{threo} < \Delta\delta_{CH_3}^{erythro*}$$

and

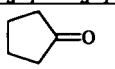
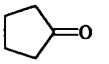
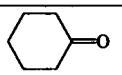
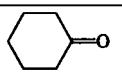
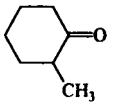
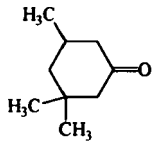
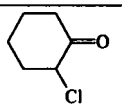
$$\delta_{OH}^{threo} > \delta_{OH}^{erythro2,8}$$

were used for assignment of the relative configuration of the diastereomers.

*The CH_3 groups in the two CH_3CH_2O fragments are non-equivalent.

TABLE I

Yields and constants of the phosphonates 3

Adducts 3	Ar	Ketone 2	Yields % *(**) of 3	"Erythro"/ "Threo" 3#	M.p.## °C
3a	C_6H_4-CH_3-(2)	CH_3COCH_3	(83)	-	oil
3b	C_6H_4-CH_3-(3)	CH_3COCH_3	(88)	-	oil
3c	C_6H_4-CH_3-(3)	$CH_3COC_3H_7$	50(76)	28/72	oil
3d	C_6H_4-CH_3-(3)	$CH_3COCH(CH_3)_2$	17(20)	33/67	oil
3e	C_6H_4-CH_3-(2)	$C_2H_5COC_2H_5$	60	-	64-65
3f	C_6H_4-CH_3-(3)	$C_2H_5COC_2H_5$	76	-	49-50
3g	C_6H_4-CH_3-(3)	$C_3H_7COC_3H_7$	16(33)	-	oil
3h[10]	C_6H_4-CH_3-(2)		40	-	53-54
3i	C_6H_4-CH_3-(3)		84(84)	-	oil
3j	C_6H_4-CH_3-(2)		66(80)	-	34-35
3k	C_6H_4-CH_3-(3)		60(82)	-	62-63
3l	C_6H_4-CH_3-(3)		56	0/100	98-99
3m	C_6H_4-CH_3-(3)		(76)	40/60	83-84
3n	C_6H_4-CH_3-(3)		72	0/100	72-73
3o	C_6H_4-CH_3-(2)	$CH_3COC_6H_5$	44(43)	11/89	103-104
3p	C_6H_4-CH_3-(3)	$CH_3COC_6H_5$	38(44)	24/76	105-107
3r	C_6H_4-CH_3-(3)	$C_6H_5COC_6H_5$	7	-	168-169

The elemental analyses for **3** are in good agreement with the theoretical values. IR(nujol): 1020-1040 and 1050-1070 cm^{-1} ($\upsilon_{P\text{-}O\text{-}C}$); 1210-1230 cm^{-1} ($\upsilon_{P=O}$); 3400-3500 cm^{-1}(υ_{OH}-bonded).

* Yield of product washed with hexane.

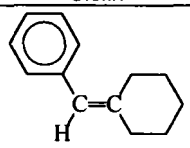
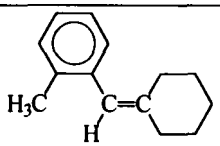
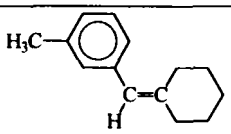
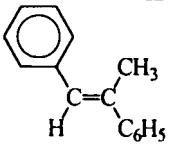
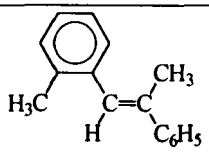
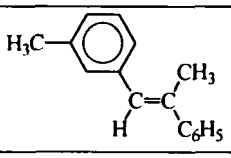
and (**) determined by ^1H NMR (250 MHz). For erythro/threo ratio the signals were used as follows: **3c** (δ): 3.12 and 3.20; **3d**: 3.26 and 3.37; **3m**: 2.96 and 3.00; **3o**: 5.10 and 5.66; **3p**: 5.04 and 5.62. For the determination of the yields of **3** the integral intensity of the signals for CH_2 (for **1**) and CH (for **3**) protons are used.

M.p. of recrystallized compounds **3**.

The elimination process of the sodium derivatives of **3j**, **3k**, **3o** and **3p** was studied in conditions of stereospecific olefination,[9] i.e., with NaH in DMF at room temperature. The yields of the corresponding alkenes **4**, compared with these from diethyl benzylphosphonate adducts (see Table II) indicate that the steric hindrance in the ketone combined with ortho and metha methyl groups in the phosphonate phenyl are of great importance for the stage of elimination. In the cases of **3o** and **3p** at the above mentioned conditions the equilibrium is shifted completely to the starting **1** (after hydrolysis of **1-Na**) and **2** (proved as 2,4-dinitrophenylhydrazons), the yields of alkenes **4o** and **4p** being negligible. As seen in Table II, when the starting ketone is cyclohexanone, the yields of the corresponding alkenes (**4j** and

TABLE II

Yields of the olefins **4**

No	Olefin	Yields %
*		50
4j		54
4k		49
*		40
4o		5.8[a]
4p		6.2[a]

* Data from ref. No 2

[a] The yields of the isolated 2, 4-dinitrophenylhydrazons of the corresponding ketones **2o** and **2p** are 67% and 91% respectively.

4k) are always higher in comparison with the adducts with acetophenone (**4o** and **4p**). This can be explained with possible steric acceleration of the elimination of the intermediate adducts **3j-Na** and **3k-Na**. Indeed, it was found that the rotational barrier of the phenyl group in these adducts calculated by dynamic NMR investigations[7] show a higher value of the barrier in **3k** (ΔG^{*} = 61.36 ± 0.29 kJmol^{-1}) in comparison to **3p** (ΔG^{*} = 49.19 ± 0.22 kJmol^{-1}). This is indication for higher steric strain in **3k**, leading to a favoured transition state of carbonylolefination.

The present study confirms our previous conclusion on the different reactivity of Li-salts of tetramethyldiamides and esters of phenylmethanephosphonic acids towards aldehydes and ketones.[1-4,6] While in the aldol stage of the reaction with

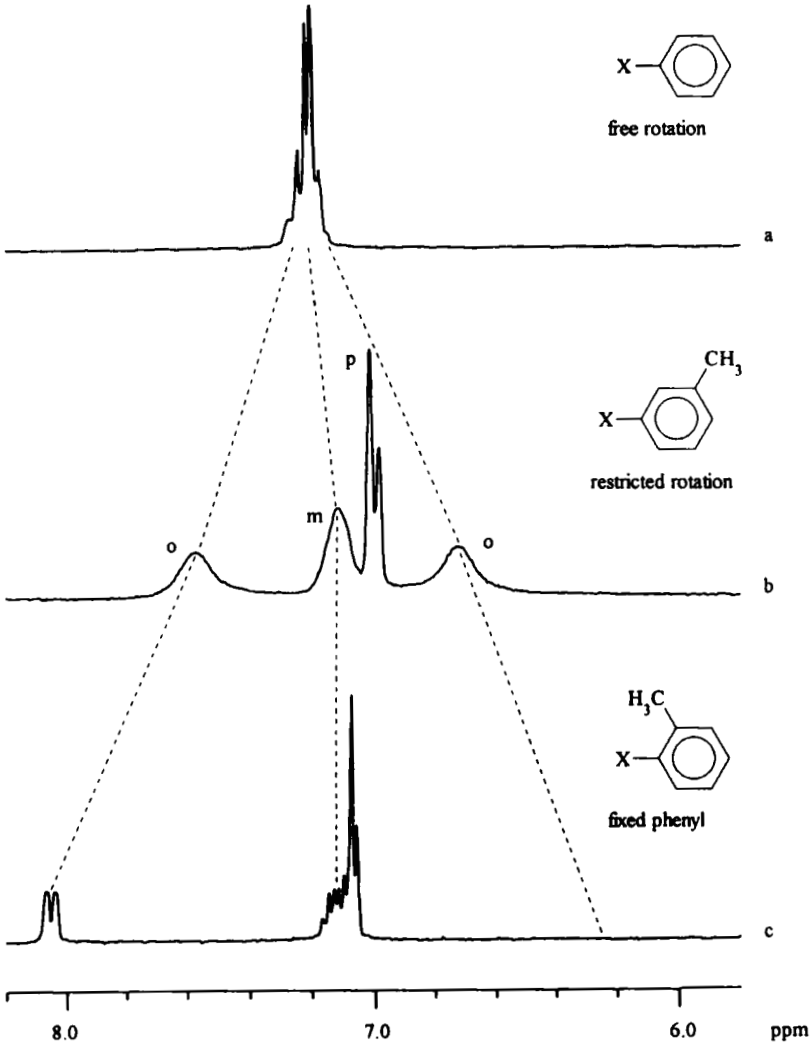


FIGURE 1 Representative ^{1}H NMR spectra (CCl_4, room temperature) for free rotating, restricted and fixed phenyl ring: (a) spectrum of diethyl ester of 2-hydroxy-4-methyl-1-phenylpentanephosphonic acid,[1] (b) spectrum of **3m** and (c) spectrum of **3e**.

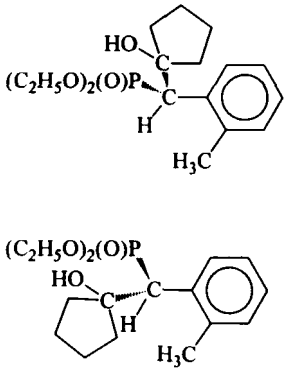


FIGURE 2 (RS,SR) Syn atropisomer of the compound **3h**.

aldehydes the rise of the temperature from $-70°$ to 20°C leads to increase of the erythro/threo ratio, in the same conditions the reaction with ketones is entirely shifted to the starting reactants, obviously due to the steric effect in the intermediates. The restricted rotation of the phenyl group, observed in the ^1H NMR spectra only of the adducts with ketones,[7] proves the above explanation.

The ^1H NMR investigations of the adducts, obtained from ortho substituted benzylphosphonic acid and ketones (**3a**, **3e**, **3h**, **3j** and **3o**) show, that the rotational barrier of the phenyl group is so high that only one rotamer is present (see Figure 1). In this case the obtained isomers **3a**, **3e**, **3h** and **3j** can be assumed as diastereomers based on the presence of one asymmetric C-atom and chiral axis, due to the fixed position of the phenyl group. We consider that these diastereomers have syn configuration (syn position of the H-atom at C-1 toward the CH_3-group in the phenyl group of the phosphonate). As was shown by X-ray analysis of **3h**[10] in solid state it is built up as centrosymmetric dimers (corresponding enantiomers) of hydrogen bonded molecules in which the above mentioned H-atom and CH_3-group are in syn position (Figure 2). Analogous atropisomers are isolated in the case of 1-(1'naphthyl)-2,4-dioxo(or 2-thio-4-oxo)-hexahydropyrimidines[11] and their stereochemistry is discussed.[12]

Because atropisomers are usually defined as isolable conformers,[13] we tried to detect anti isomer, by measuring ^1H NMR spectra of **3h** in DMSO at high temperature. Unfortunately compound **3h** breaks down at about 140°C. With the aim to compare the heat of formation of syn and anti isomers and to estimate the height of the rotational barrier of the phenyl group, the PM3 calculations† of the adducts **3a** (Table III) were performed. The heats of formation were calculated for conformers k1, k2 and k3 (Figure 3), although the IR spectra of **3a** in diluted (10^{-3} M) tetrachloromethane solution showed the almost exclusive presence of conformers with intramolecular hydrogen bond (υ_{OH} = 3453 cm^{-1}). As seen in Table III, the heat of formation (H_f) indicates that the syn isomer is much more stable than the anti isomer and the values of calculated populations for anti isomer are zero.

†PM3 calculations of the similar compounds[7] gave the best correlation between the calculated rotational barrier of the phenyl group and experimental dynamic NMR data.

TABLE III

PM3-results for compound **3a**

Conformations	n_i	$(H_f)_i$ (kJmol^{-1})	$(H^{\neq})_i$ (kJmol^{-1})	$(\Delta H^{\neq})_i$ (kJmol^{-1})	$\Delta H^{\neq}_{av}$ (kJmol^{-1})
$k1^{syn}$	0.063	-856.92	-757.97	98.95	
$k2^{syn}$	0.047	-856.21	-748.94	107.27	125.69
$k3^{syn}$	0.889	-864.49	-734.79	128.70	
$k1^{anti}$	0.000	-829.90			
$k2^{anti}$	0.000	-834.88			
$k3^{anti}$	0.000	-840.65			

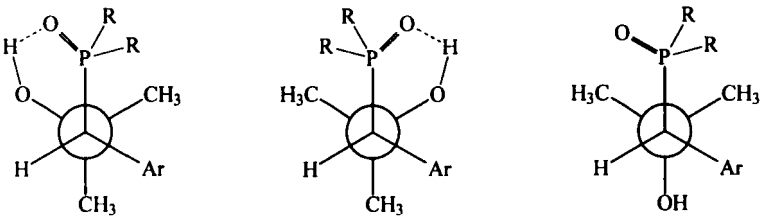
n_i - population of conformers

$(H_f)_i$ - Heat of formation for the ground state

$(H^{\neq})_i$ - Heat of formation for the transition state (due to rotation of the phenyl ring)

$\Delta(H^{\neq})_i = (H^{\neq})_i - (H_f)_i$

$\Delta H^{\neq}_{av} = \sum_i n_i \cdot \Delta(H^{\neq})_i$



k1 k2 k3

R = OCH_3 Ar = C_6H_4-CH_3-(2)

FIGURE 3 Possible conformations of the calculated compound **3a**.

The calculated rotational barrier of the phenyl group is very high (125.69 kJmol^{-1}), which supports the possibility of atropisomerism.

On the basis of NMR investigation, X-ray data and PM3-calculations a conclusion can be made for syn-stereoselective reaction of Li-derivative of the diethyl ester of 2-methylphenylmethanephosphonic acid with studied ketones.

EXPERIMENTAL

The reaction of **1** with **2** was carried out under dry argon in anhydrous THF. ^{1}H NMR-spectra of the adducts **3** were recorded on BRUKER WM-250 with TMS as internal standard and $CDCl_3$ as solvent.

IR-spectra were registered on Specord-71IR. The qualitative tlc investigations were carried out on Silicagel 60F (aluminium sheets "Merck") using ethylacetate-hexane 1:1 as mobile phase (for adducts) or hexane (for olefins).

Synthesis of diethyl esters of 2,2-dialkyl(phenyl)-2-hydroxy-1-(2- or 3-methylphenyl)ethanephosphonic acids

General procedure. To a solution of **1** (10 mmol) in 20 ml anhydrous THF, cooled to −70°C, butyllitium (10 mmol, 1.5 M in hexane), diluted with 6 ml of THF, is added under argon. After 15 min stirring, the ketone **2** is added (10 mmol in 6 ml THF) and the reaction mixture is kept at this temperature for 15 min. The mixture is hydrolysed with 10 ml water, extracted with CH_2Cl_2 and after evaporation of the organic solvents the crude product **3** is studied by ^{1}H NMR and tlc. The adducts **3a–3d**, **3f**, **3g** and **3i–3k** were purified by column chromatography on Silicagel-60 Size 0.063–0.200 nm using hexane-ethylacetate as eluent. The adducts **3e**, **3h** and **3e–3o** were purified by recrystallization from hexane.

(RS,SR)Diethyl ester of 2-hydroxy-2-methyl-1-(2-methylphenyl)propanephosphonic acid **3a**. ^{1}H NMR ($CDCl_3$): δ 0.93 (t, J = 7.0 Hz, 3H) and 1.34 (t, J = 7.0 Hz, 3H, OCH_2CH_3), 1.19 (s, 3H, CH_3), 1.45 (s, 3H, CH_3), 2.33 (s, 3H, 2-CH_3), 3.38–3.50 (m, 1H) and 3.75–3.85 (m, 1H) and 4.00–4.22 (m, 3H, OCH_2 + OH), 3.53 (d, $^2J_{PH}$ = 24.6 Hz, 1H, CH), 7.12–7.88 (m, 4H, Ph).

(±)Diethyl ester of 2-hydroxy-2-methyl-1-(3-methylphenyl)propanephosphonic acid **3b**. ^{1}H NMR ($CDCl_3$): δ 0.93 (t, J = 7.0 Hz, 3H) and 1.34 (t, J = 7.0 Hz, 3H, OCH_2CH_3), 1.19 (s, 3H, CH_3), 1.45 (s, 3H, CH_3), 2.33 (s, 3H, 3-CH_3), 3.38–3.50 (m, 1H) and 3.75–3.85 (m, 1H) and 4.00–4.22 (m, 3H, OCH_2 + OH), 3.53 (d, $^2J_{PH}$ = 24.6 Hz, 1H, CH), 7.12–7.88 (m, 4H, Ph).

(RR,SS)Diethyl ester of 2-hydroxy-2-methyl-1-(3-methylphenyl)pentanephosphonic acid **3c**. ^{1}H NMR ($CDCl_3$): δ 0.90 (t, J = 7.0 Hz, 3H) and 0.96 (t, J = 7.0 Hz, 3H, OCH_2CH_3), 1.12 (d, J = 1.0 Hz, 3H, CH_3), 1.33 (t, J = 7.1 Hz, 3H, CH_3), 1.3–1.7 (m, 4H, CH_2), 2.33 (s, 3H, 3-CH_3), 3.20 (d, $^2J_{PH}$ = 23.3 Hz, 1H, CH), 3.4–3.6 (m, 1H) and 3.7–3.9 (m, 1H) and 4.0–4.2 (m, 2H, OCH_2), 4.4 (s, 1H, OH), 7.0–7.4 (m, 4H, Ph).

(RR,SS)Diethyl ester of 2-hydroxy-2,4-dimethyl-1-(3-methylphenyl)butanephosphonic acid **3d**. ^{1}H NMR ($CDCl_3$): δ 0.90 (t, J = 7.0 Hz, 3H) and 1.33 (t, J = 7.0 Hz, 3H, OCH_2CH_3), 0.91 (s, 3H, CH_3), 0.98 (d, J = 6.7 Hz, 3H, CH_3), 1.03 (d, J = 6.7 Hz, 3H, CH_3), 2.1–2.3 (sp,‡ J = 6.7 Hz, 1H, CH), 2.34 (s, 3H, 3-CH_3), 3.37 (d, $^2J_{PH}$ = 23.4 Hz, 1H, CH), 3.4–3.5 (m, 1H) and 3.7–3.8 (m, 1H) and 4.0–4.2 (m, 2H, OCH_2), 4.67 (s, 1H, OH), 7.1–7.3 (m, 4H, Ph).

(RS,SR)Diethyl ester of 2-ethyl-2-hydroxy-1-(2-methylphenyl)butanephosphonic acid **3e**. ^{1}H NMR ($CDCl_3$): δ 0.68 (t, J = 7.4 Hz, 3H, CH_3), 0.81 (t, J = 7.0 Hz, 3H) and 1.36 (t, J = 7.0 Hz, 3H, OCH_2CH_3), 0.95 (t, J = 7.3 Hz, 3H, CH_3), 1.2–1.5 (m, 2H, CH_2), 1.8–2.1 (m, 2H, CH_2), 2.31 (s, 3H, 2-CH_3), 3.01–3.10 (m, 1H) and 3.65–3.74 (m, 1H) and 4.01–4.24 (m, 2H, OCH_2), 3.54 (d, $^2J_{PH}$ = 25.4 Hz, 1H, CH), 4.43 (s, 1H, OH), 7.16–8.05 (m, 4H, Ph).

(±)Diethyl ester of 2-ethyl-2-hydroxy-1-(3-methylphenyl)butanephosphonic acid **3f**. ^{1}H NMR ($CDCl_3$): δ 0.74 (t, J = 7.5 Hz, 3H, CH_3), 0.86 (t, J = 7.1 Hz, 3H) and 1.35 (t, J = 7.1 Hz, 3H, OCH_2CH_3), 0.94 (t, J = 7.4 Hz, 3H, CH_3), 1.12–1.32 (m, 2H, CH_2), 1.72–1.93 (m, 2H, CH_2), 2.34 (s, 3H, 3-CH_3), 3.20 (d, $^2J_{PH}$ = 24.0 Hz, 1H, CH), 3.20–3.35 (m, 1H) and 3.70–3.85 (m, 1H) and 3.98–4.23 (m, 2H, OCH_2), 4.26 (s, 1H, OH), 7.16–7.30 (m, 4H, Ph).

(±)Diethyl ester of 2-hydroxy-1-(3-methylphenyl)-2-propylpentanephosphonic acid **3g**. ^{1}H NMR ($CDCl_3$): δ 0.72 (t, J = 6.8 Hz, 3H) and 0.94 (t, 7 = 7.2 Hz, 3H, CH_3), 0.86 (t, J = 7.0 Hz, 3H) and 1.35 (t, J = 7.0 Hz, 3H, OCH_2CH_3), 1.09–1.81 (m, 8H, CH_2), 2.34 (s, 3H, 3-CH_3), 3.18 (d, $^2J_{PH}$ = 23.9 Hz, 1H, CH), 3.24–2.33 (m, 1H) and 3.72–3.83 (m, 1H) and 4.00–4.26 (m, 2H, OCH_2), 4.29 (s, 1H, OH), 7.09–7.29 (m, 4H, Ph).

(RS,SR)Diethyl ester of 1-(1-hydroxycyclopentyl)-1-(2-methylphenyl)methanephosphonic acid **3h**.[2]

(±)Diethyl ester of 1-(1-hydroxycyclopentyl)-1-(3-methylphenyl)methanephosphonic acid **3i**. ^{1}H NMR ($CDCl_3$): δ 0.92 (t, J = 7.0 Hz, 3H) and 1.34 (t, 7 = 7.0 Hz, 3H, OCH_2CH_3), 1.26–2.02 (m, 8H, CH_2), 2.34 (s, 3H, 3-CH_3), 3.12 (d, $^2J_{PH}$ = 23.3 Hz, 1H, CH), 3.41–2.51 (m, 1H) and 3.77–3.87 (m, 1H) and 4.03–4.25 (m, 2H, OCH_2), 4.23 (s, 1H, OH), 7.05–7.21 (m, 4H, Ph).

(RS,SR)Diethyl ester of 1-(1-hydroxycyclohexyl)-1-(2-methylphenyl)methanephosphonic acid **3j**. ^{1}H NMR ($CDCl_3$): δ 0.87 (t, J = 6.7 Hz, 3H) and 1.34 (t, J = 6.5 Hz, 3H, OCH_2CH_3), 1.17–2.06 (m, 10H, CH_2), 2.34 (s, 3H, 2-CH_3), 3.22–3.32 (m, 1H) and 3.71–3.80 (m, 1H) and 3.81–4.22 (m, 2H, OCH_2), 3.53 (d, $^2J_{PH}$ = 25.1 Hz, 1H, CH), 4.18 (s, 1H, OH), 7.16–7.96 (m, 4H, Ph).

(±)Diethyl ester of 1-(1-hydroxycyclohexyl)-1-(3-methylphenyl)methanephosphonic acid **3k**. ^{1}H NMR ($CDCl_3$): δ 0.92 (t, J = 7.0 Hz, 3H) and 1.33 (t, J = 7.0 Hz, 3H, OCH_2CH_3), 1.02–1.93 (m, 10H,

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CH_2), 2.34 (s, 3H, 3-CH_3), 3.19 (d, $^2J_{PH}$ = 23.6 Hz, 1H, CH), 3.35–3.51 (m, 1H) and 3.74–3.89 (m, 1H) and 3.98–4.24 (m, 2H, OCH_2), 4.21 (s, 1H, OH), 6.87–7.65 (m, 4H, Ph).

(RR,SS)Diethyl ester of 1-(1-hydroxy-2-methylcyclohexyl)-1-(3-methylphenyl)methanephosphonic acid **3l**. ^{1}H NMR ($CDCl_3$): δ 0.94 (d, J = 6.8 Hz, 3H, CH_3), 1.14 (t, J = 7.0 Hz, 3H) and 1.27 (t, J = 7.0 Hz, 3H, OCH_2CH_3), 1.32–2.09 (m, 9H, CH_2 + CH), 2.34 (s, 3H, 3-CH_3), 3.59 (d, $^2J_{PH}$ = 24.7 Hz, 1H, CH), 3.84–4.12 (m, 4H, OCH_2), 4.14 (s, 1H, OH), 7.08–7.26 (m, 4H, Ph).

(RR,SS)Diethyl ester of 1-(1-hydroxy-3,3,5-trimethylcyclohexyl)-1-(3-methylphenyl)methanephosphonic acid **3m**. ^{1}H NMR ($CDCl_3$): δ 0.75 (d, J = 6.5 Hz, 3H, CH_3), 0.89 (s, 3H, CH_3), 1.15 (s, 3H, CH_3), 0.90 (t, J = 7.0 Hz, 3H) and 1.34 (t, J = 7.0 Hz, 3H, OCH_2CH_3), 0.65–1.96 (m, 7H, CH_2 + CH), 2.34 (s, 3H, 3-CH_3), 2.96 (d, $^2J_{PH}$ = 23.0 Hz, 1H, CH), 3.39–3.52 (m, 1H) and 3.75–3.87 (m, 1H) and 4.00–4.26 (m, 2H, OCH_2), 3.87 (s, 1H, OH), 6.7–8.3 (m, 4H, Ph).

(RR,SS)Diethyl ester of 1-(2-chloro-1-hydroxycyclohexyl)-1-(3-methylphenyl)methanephosphonic acid **3n**. ^{1}H NMR ($CDCl_3$): δ 1.14 (t, J = 7.0 Hz, 3H) and 1.28 (t, J = 7.0 Hz, 3H, OCH_2CH_3), 1.3–2.5 (m, 9H, CH_2), 2.36 (s, 3H, 3-CH_3), 3.54 (s, 1H, CH), 3.8–4.2 (m, 5H, OCH_2 + OH), 7.1–7.4 (m, 4H, Ph).

(RRS,SSR)Diethyl ester of 2-hydroxy-1-(2-methylphenyl)-2-phenylpropanephosphonic acid **3o**. ^{1}H NMR ($CDCl_3$): δ 0.79 (t, J = 7.0 Hz, 3H) and 0.81 (t, J = 7.0 Hz, 3H, OCH_2CH_3), 1.26 (s, 3H, CH_3), 2.38 (s, 3H, 2-CH_3), 3.21–3.38 (m, 2H) and 3.50–3.75 (m, 2H, OCH_2), 3.95 (d, $^2J_{PH}$ = 24.8 Hz, 1H, CH), 5.66 (s, 1H, OH), 7.20–8.06 (m, 9H, Ph).

(RR,SS)Diethyl ester of 2-hydroxy-1-(3-methylphenyl)-2-phenylpropanephosphonic acid **3p**. ^{1}H NMR ($CDCl_3$): δ 0.78 (t, J = 7.1 Hz, 3H) and 0.83 (t, J = 7.2 Hz, 3H, OCH_2CH_3), 1.25 (d, J = 1.7 Hz, 3H, CH_3), 2.37 (s, 3H, 3-CH_3), 3.17–3.79 (m, 4H, OCH_2), 3.55 (d, $^2J_{PH}$ = 23.4 Hz, 1H, CH), 5.62 (s, 1H, OH), 7.11–7.57 (m, 9H, Ph).

(±)Diethyl ester of 2,2-diphenyl-2-hydroxy-1-(3-methylphenyl)ethanephosphonic acid **3r**. ^{1}H NMR ($CDCl_3$): δ 0.83 (t, J = 7.1 Hz, 3H) and 0.87 (t, J = 7.1 Hz, 3H, OCH_2CH_3), 2.23 (s, 1H, 3-CH_3), 3.12–3.77 (m, 4H, OCH_2), 4.33 (d, $^2J_{PH}$ = 24.1 Hz, 1H, CH), 6.23 (s, 1H, OH), 6.89–7.78 (m, 14H, Ph).

Conversion of the sodium salts of the hydroxyphosphonate adducts **3-Na**.[9] The mixture of equimolar quantity **3** and NaH in DMF is stirred 3 hrs at room temperature under argon. After hydrolysis with water, extraction with hexane and ether, the reaction mixture is dried over $MgSO_4$. After evaporation of the solvents the product is purified by column chromatography on alumina using hexane as solvent.

The PM3-calculations[14] of **3a** were carried out using the program package MOPAC 6.0,[15] run on a personal computer. To keep the calculation time to a minimum, compound **3a** was treated as dimethyl ester. All molecular parameters were optimized in order to obtain the heat of formation of the ground state. Then the dihedral angle defining the rotation of the phenyl group was varied, optimising the rest of the parameters, to obtain the transition state energy.

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