Journal of the Mexican Chemical Society
ISSN: 1870-249X
editor.jmcs@gmail.com
Sociedad Química de México
México

González Morales, Angelina; Fernández Zertuche, Mario; Ordóñez, Mario
Simultaneous separation and assignment of absolute configuration of γ-amino-β-hydroxyphosphonates by NMR using (S)-methoxyphenylacetic acid (MPA)
Journal of the Mexican Chemical Society, vol. 48, núm. 4, 2004, pp. 239-245
Sociedad Química de México
Distrito Federal, México

Rev. Soc. Quím. Méx. **2004**, *48*, *239-245*

Investigación

Simultaneous Separation and Assignment of Absolute Configuration of γ-Amino-β-Hydroxyphosphonates by NMR Using (*S*)-Methoxyphenylacetic Acid (MPA)

Angelina González-Morales, Mario Fernández-Zertuche, and Mario Ordóñez*

Centro de Investigaciones Químicas. Universidad Autónoma del Estado de Morelos, Av. Universidad No. 1001. 62210 Cuernavaca, Morelos, México. E-mail: palacios@ciq.uaem.mx

Recibido el 28 de agosto del 2004; aceptado el 20 de octubre de 2004

Dedicated to the memory of Dr. Raymundo Cruz Almanza

Abstract. γ-(*N*,*N*-disubstituted)amino-β-hydroxypropylphosphonates are important intermediates in the preparation of enantiomerically pure γ-amino-β-hydroxypropylphosphonic acid (GABOB^{P}), an analogue of γ-amino-β-hydroxybutyric acid (GABOB), which acts in a variety of clinical conditions including schizophrenia, epilepsy, and other character-based disorders including severe convulsions. The synthesis of γ-amino-β-hydroxypropylphosphonic acid (GABOB^{P}) enantiomerically pure is now an area of great interest, and for this reason, a variety of synthetic routes have been developed.
Key words: γ-amino-β-hydroxypropylphosphonic acid (GABOB^{P}), assignment of absolute configuration, (*S*)-methoxyphenylacetic acid (MPA)

Resumen. Los γ-amino-β-hidroxipropilfosfonatos *N*,*N*-disubstituidos son importantes intermediarios en la preparación de ácidos γ-amino-β-hidroxipropilfosfónicos enantioméricamente puros (GABOB^{P}), análogos del ácido γ-amino-β-hidroxibutírico (GABOB), el cual se utiliza en una gran variedad de tratamientos clínicos incluyendo esquizofrenia, epilepsia, y en otras enfermedades incluyendo convulsiones severas. La síntesis de ácidos γ-amino-β-hidroxipropilfosfónicos enantioméricamente puros es ahora una de las áreas de gran interés, motivo por el cual varias rutas de síntesis han sido desarrolladas en los dos últimos años.
Palabras clave: ácido γ-amino-β-hidroxipropilfosfónico (GABOB^{P}), asignación de la configuración absoluta, ácido (*S*)-metoxifenilacético (MPA)

Introduction

The synthesis of both enantiomers of a chiral compound is a very important task in asymmetry synthesis. To attain this goal, traditional methods require the use of either antipode of chiral material to obtain stereoisomers with opposite configurations, where the determination of the optical purity and absolute configuration is a must.

Several analytical instrumental methods exist for the determination of absolute configuration. The most known are X-ray crystallography, followed by chiroptical methods (e.g. circular dichroism (CD) [1], optical rotatory dispersion (ORD), or specific optical rotation) [2]; however, their use is not devoid of some inconveniences and limitations related sometimes to the instrument, such as the specificity of the method used which requires a special training for its use, and in other cases the sample, which in the case of X-ray diffraction requires a monocrystal of good quality. Other methods include specific rotation [3], infrared vibrational [4], and vibrational Raman optical activity [5].

Recently, different approaches to the problem of determining absolute configuration have emerged, based on NMR spectroscopy. These techniques are very appealing, because of the undoubted advantages, which include: (1) the instrument is available in most laboratories; (2) an in-depth understanding of the fundamentals of the method is not necessary to apply this method; (3) a small amount of sample is needed, and this can be recovered; and (4) because the analysis is conducted in solution, it is applicable to both solid and liquid samples. Consequently, in recent years there has been a marked increase in the number of papers describing the use of NMR for the assignment of the absolute configuration of organic compounds [6]. Thus, the determination of the absolute configuration by NMR involves the transformation of the chiral substrate to two different species (e.g. diastereomers). In the classical approach developed by Dale and Mosher [7], this transformation can be carried out; (a) by reaction of the compound of unknown configuration with the two enantiomeric forms of a chiral derivatizing agent (CDA), generally an arylmethoxyacetic acid derivative, such as methoxytrifluoromethylphenylacetic acid (Mosher's reagent) or methoxyphenylacetic acid (MPA), (Figure 1); and (b) by reaction of the substrate in both configurations (racemic mixture) with only one enantiomer of the chiral derivatizing agent (CDA), producing two diastereomeric derivatives. The different orientation of the aromatic shielding cone effect in the diastereomeric derivatives leads to a selective shielding or deshielding of the R_1 or R_2 substituents at the asymmetric center [8]. Thus, the spatial relationship between R_1/R_2 and the aryl ring is correlated to the observed chemical shift change. In the Figure 1, the R_1 substituent of the (*R*,*R*) diastereomer is at higher field than the R_2 substituent. Inversely, R_2 in the

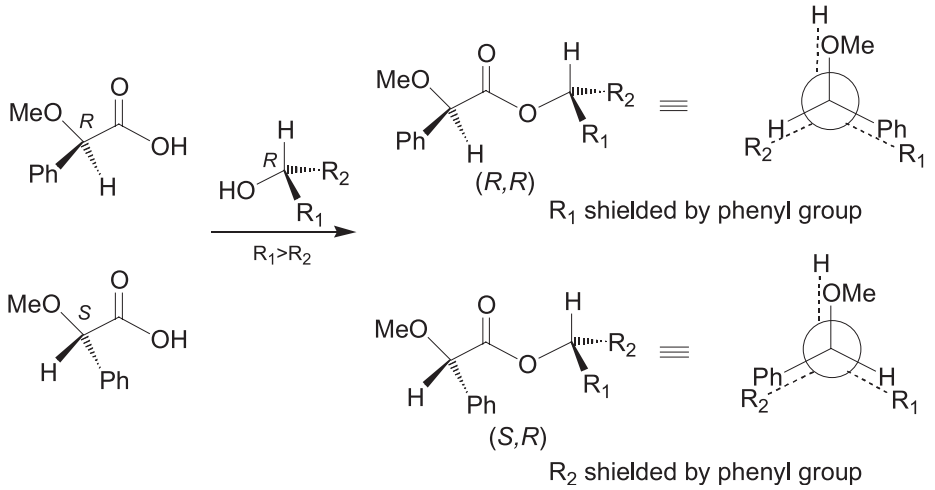
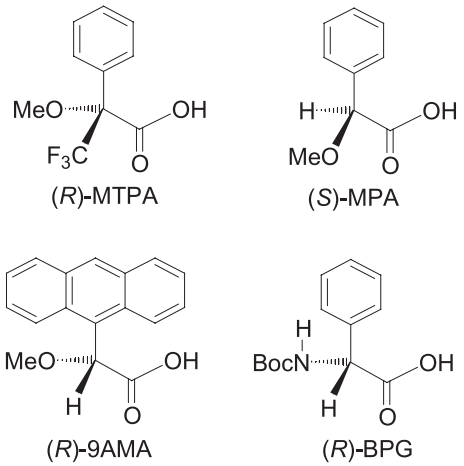


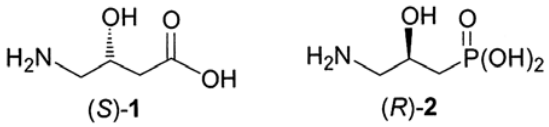
Fig. 1. Derivatization of secondary alcohol with methoxyphenylacetic acid. R_1 is defined arbitrarily as the higher priority group compared with R_2.

(*S*,*R*) derivative shifts more upfield relative to R_1. Consequently the absolute configuration of the alcohol would be established. Although the nuclei used in NMR experiments include ^{2}H, ^{13}C, ^{31}P, ^{29}Si, ^{1}H NMR remains to be the most popular method.

Between the most important chiral derivatizing compounds used for the resolution and assignment of the absolute configuration of secondary alcohols and amines found in the literature include the methoxytrifluoromethylphenylacetic acid (MTPA), methoxyphenylacetic acid (MPA), 9-anthrylmethoxyacetic acid (9-AMA), and Boc-phenylglycine (BPG).



In this paper we show that (*S*)-methoxyphenylacetic acid [(*S*)-MPA] is a reliable reagent for the simultaneous separation and determination of the absolute configuration of γ-(*N*,*N*-disubtituted)amino-β-hydroxypropylphosphonates, which are important intermediaries for the synthesis of enantiomerically pure γ-amino-β-hydroxypropylphosphonic acid GABOB^{P} **2** [9], an analogue of (*R*)-γ-amino-β-hydroxybutyric acid (*L*-GABOB) **1** [10].



Results and Discussion

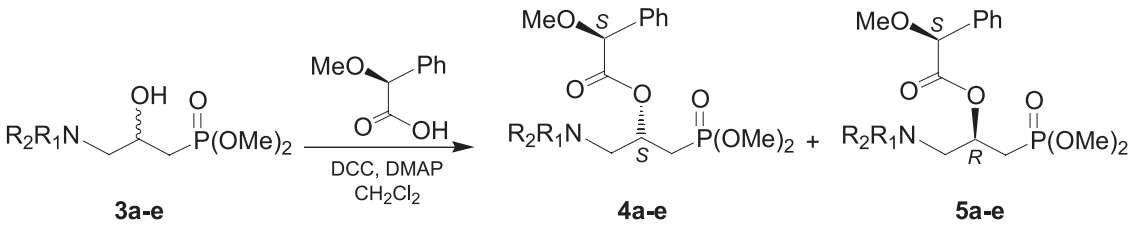
The mixtures of γ-(*N*,*N*-disubstituted)amino-β-hydroxypropylphosphonates **3a-e** [11] were treated with (*S*)-methoxyphenylacetic acid [(*S*)-MPA] in the presence of DCC and DMAP in dichloromethane as solvent at room temperature, to obtain the corresponding mandelates **4** and **5**. The mixtures of diastereomers **4a-e** and **5a-e** were cleanly separated on column chromatography affording in all cases the diastereomer **4a-e** as the less polar compound, and the diastereomer **5a-e** as the more polar compound. Table 1 summarizes the results obtained.

According to the model developed by Trost [12], it is assumed that the representative conformer in terms of NMR is the one in which the methoxy, carbonyl, and C(1')H groups are situated in the same plane, as observed in the extended Newman projection (Figure 2). In this manner, we expected that in the diastereomers **4a-e**, the phenyl group shields the methylene and methyl protons of the $CH_2P(O)(OMe)_2$ moiety, whereas in the diastereomers **5a-e**, the shielding goes over the methylene protons and the protons of the R_1 and R_2 substituents on the $CH_2NR_1R_2$ fragment.

The comparison of selected chemical shifts in ^{1}H and ^{31}P NMR revealed some significant differences between diastereomers **4a-e** and **5a-e**. (Figures 3 and 4).

In the analysis of some selected chemical shifts in the ^{1}H and ^{31}P NMR spectra for mandelates **4a-e** and **5a-e**, we found

Table 1. Preparation of the mandelate derivatives **4a-e** and **5a-e**.



3a-e **4a-e** **5a-e**

entry	**3a-e** (ratio)[a]	R_1	R_2	Yield (%)[b]	Yield (%)[c]
1	**3a** (50:50)	Bn	Bn	43	45
2	**3b** (d)	(*S*)-CH(CH$_3$)Ph	Bn	35	61
3	**3c** (d)	(*R*)-CH(CH$_3$)Ph	Bn	50	33
4	**3d** (d)	(*S*)-CH(CH$_3$)Ph	(*S*)-CH(CH$_3$)Ph	13	65
5	**3e** (d)	(*R*)-CH(CH$_3$)Ph	(*R*)-CH(CH$_3$)Ph	67	21

[a]Initial ratio. [b]Less polar diastereomer. [c]More polar diastereomer. [d]The ratio was different to 50:50.

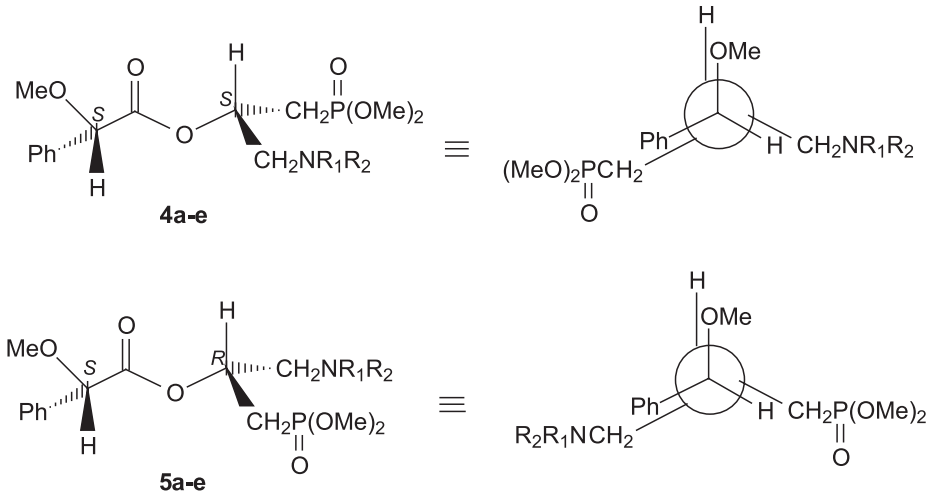


Fig. 2. Extended Newman projections for the diastereomers **4a-e** and **5a-e**.

that in effect, the protons of the $CH_2P(O)(OMe)_2$ fragment in diastereomers **4a-e** are at higher field than those in diastereomers **5a-e** (Figures 3 and 4). On the other hand, the protons in the $CH_2NR_1R_2$ fragments in diastereomers **5a-e** are at higher field than those in diasteromers **5a-e**. Additionally, the ^{31}P NMR chemical shifts for the **4a-e** diastereomer appear at a higher field than the **5a-e** methylmandelates. This can be explained by the spatial relationship between $CH_2P(O)(OMe)_2/CH_2NR_1R_2$ fragments and the phenyl group of (*S*)-methoxyphenylacetic acid (MPA). Further confirmation was given by single crystal X-ray analysis of dimethyl 3-[(*S*,*S*)-*N*-*N*-bis(α-methylbenzylamino)]-(2*R*)-hydroxypropylphosphonate (*R*,*S*,*S*)-**3d** diastereomerically pure[11], obtained after hydrolysis of mandelate (*R*,*S*,*S*,*S*)-5d with lithium hydroxide.

In conclusion, the (*S*)-methoxyphenylacetic acid (MPA) method for determining the absolute configuration of chiral compounds, is applicable to γ-(*N*,*N*-disubstituted)amino-β-hydroxypropylphosphonates. The spatial relationship between $CH_2P(O)(OMe)_2/CH_2NR_1R_2$ fragments and the phenyl group in the acid moiety is reflected in the chemical shift differences Δδ through the anisotropic time-weighted shielding effect of the phenyl ring.

Experimental

Optical rotations were taken at 20 °C on a Perkin-Elmer 241 polarimeter in an 1 dm tube; concentrations are given in g/100

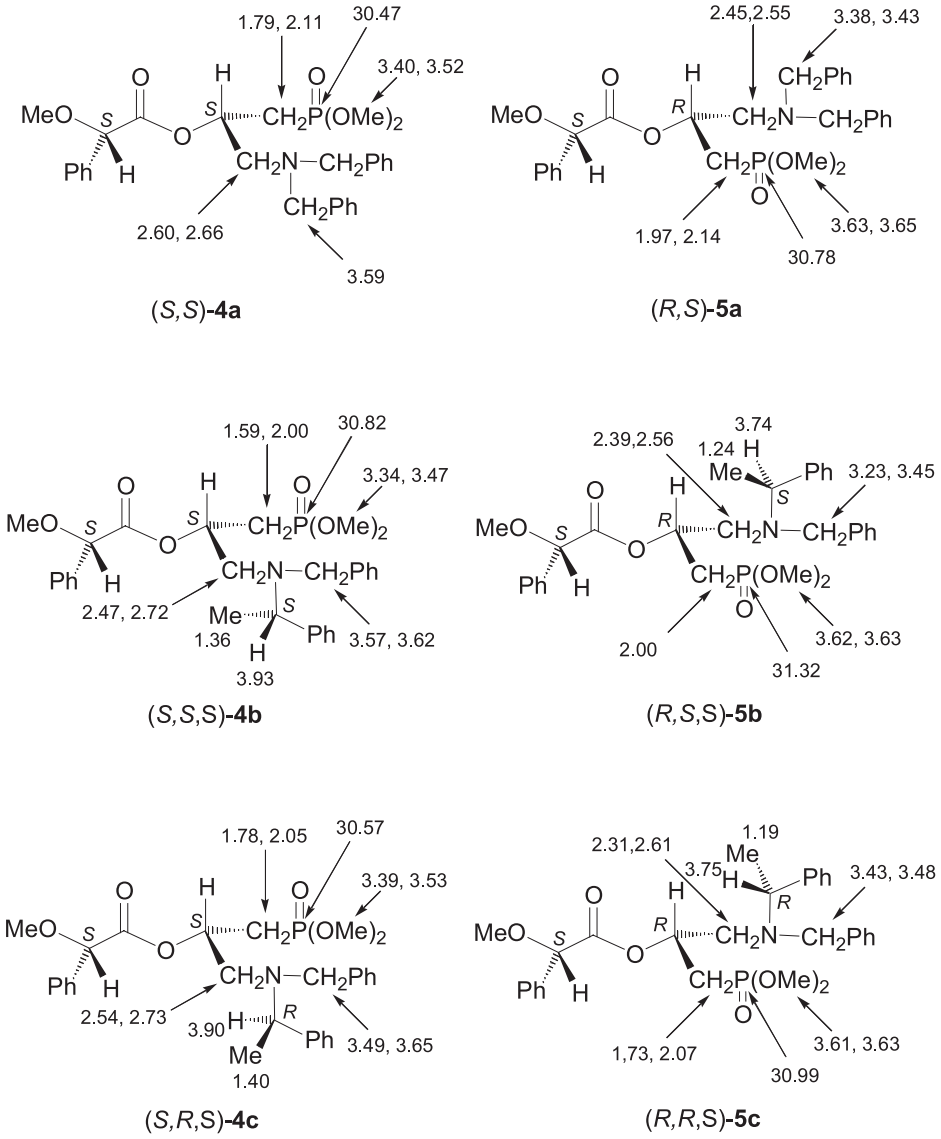


Fig. 3. Selected chemical shifts of mandelates **4a-c** and **5a-c** at 400 MHz in $CDCl_3$.

mL. For flash chromatography, silica gel 60 (230-400 mesh ASTM, Merck) was used. ^1H NMR spectra were recorded on a Varian (400 MHz) and ^{13}C NMR on AMX-500 (100 MHz). The spectra were recorded in D_2O or $CDCl_3$ solution, using TMS as internal reference. Microanalyses were registered on an Elemental VARIO EL III.

Flasks, stirrings bars, and hypodermic needles used for the generation of organometallic compounds were dried for ca. 12 h at 120 °C and allowed to cool to room temperature in a dessicator over anhydrous calcium sulphate. Anhydrous solvents (ethers) were obtained by distillation from benzophenone ketyl.

General procedure for the preparation of mandelates derivatives 4a-e and 5a-e. A solution of 1.0 equiv of β-hydroxypropylphosphonate **3a-e** and 1.6 equiv of (*S*)-*O*-methylmandelic acid [(*S*)-MPA] in dry dichloromethane under nitrogen was treated with 0.15 equiv of dimethylaminopyridine (DMAP) and 1.6 equiv of 1,3-dicyclohexylcarbodiimide (DCC) also in dry dichloromethane. The reaction mixture was stirred at room temperature for 7 h. After this period of time, the 1,3-dicyclohexylurea (DCU) formed during the course of the reaction was filtered off and the liquid layer was evaporated in vacuum and the crude product was purified by column chromatography.

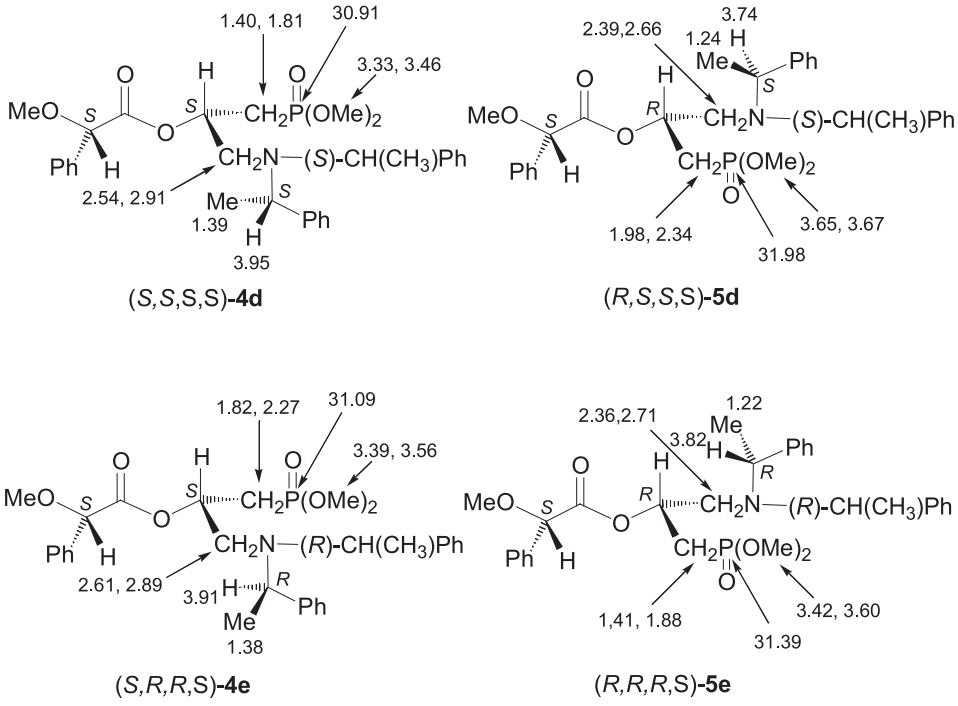


Fig. 4. Selected chemical shifts of mandelates **4d-e** and **5d-e** at 400 MHz in $CDCl_3$

Preparation of the mandelates 4a and 5a. The preparation of (*S,S*)-**4a** and (*R,S*)-**5a** have been described by Ordóñez et al [9a].

Preparation of mandelates 4b and 5b. The reaction was carried out starting from β-hydroxypropylphosphonate **3b** (545 mg, 1.44 mmol), (*S*)-*O*-methylmandelic acid (384 mg, 2.3 mmol), 1,3-dicyclohexylcarbodiimide (477 mg, 2.3 mmol), dimethylaminopyridine (27 mg, 0.2 mmol) in dry dichloromethane (20 mL). The crude product was purified by column chromatography using ethyl acetate:hexane (13:9) to afford 270 mg (35%) of diastereomer (*S,S,S*)-**4b** (less polar) and 460 mg (61%) of diastereomer (*R,S,S*)-**5b** (more polar), both as colorless oils.

Diastereomer (*S,S,S*)-4b. $[\alpha]_D$ = -25.7 (c = 4.5 $CHCl_3$). ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.36 (d, J = 6.8 Hz, 3H, C*H*$_3$CH), 1.59 (ddd, J = 16.8, 16.8, 8 Hz, 1H, C*H*$_2$P), 2.02 (ddd, J = 19.2, 16.0, 4.4 Hz, 1H, C*H*$_2$P), 2.47 (dd, J = 13.2, 6.4 Hz, 1H, C*H*$_2$N), 2.72 (ddd, J = 13.2, 6.0, 3.6 Hz, 1H, C*H*$_2$N), 3.34 (d, J = 11.0 Hz, 3H, (C*H*$_3$O)$_2$P), 3.39 (s, 3H, C*H*OC*H*$_3$), 3.47 (d, J = 11.0 Hz, 3H, (C*H*$_3$O)$_2$P), 3.57 (d, J = 13.6 Hz, 1H, C*H*$_2$Ph), 3.62 (d, J = 13.6 Hz, 1H, C*H*$_2$Ph), 3.93 (q, J = 6.8 Hz, 1H, C*H*CH$_3$), 4.66 (s, 1H, C*H*OCH$_3$), 5.13-5.24 (m, C*H*OCO), 7.20-7.48 (m, 15H, H_{arom}). ^{13}C NMR (100 MHz, $CDCl_3$) δ, 13.5 (*C*H$_3$CH), 27.5 (d, J = 141.2 Hz, *C*H$_2$P(O)), 52.2 (d, J = 6.8 Hz, (*C*H$_3$O)$_2$P), 53.0 (d, J = 11.3 Hz, (*C*HCH$_2$N), 55.3 (*C*H$_2$Ph), 57.3 (*C*H$_3$CH), 57.7 (*C*HOCH$_3$), 68.8 (d, J = 3 Hz, *C*H$_2$N), 82.5 (*C*HOCH$_3$), 126.9 (C_{arom}), 127.3 (C_{arom}), 128.0 (C_{arom}), 128.2 (C_{arom}), 128.5 (C_{arom}), 128.7 (C_{arom}), 128.9 (C_{arom}), 135.9 (C_{arom}), 139.6 (C_{arom}), 142.2 (C_{arom}), 169.8 (C=O). ^{31}P NMR (200 MHz, $CDCl_3$) δ 30.82.

Diastereomer (*R,S,S*)-5b. $[\alpha]_D$ = -11.7 (c = 6.5 $CHCl_3$). ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.24 (d, J = 6.8 Hz, 3H, C*H*$_3$CHPh), 2.00 (ddd, J = 18.8, 9.2, 9.2 Hz, 2H, C*H*$_2$P), 2.39 (ddd, J = 14.0, 5.6, 2.8 Hz, 1H, C*H*$_2$N), 2.56 (dd, J = 13.6, 6.0 Hz, 1H, C*H*$_2$N), 3.23 (d, J = 13.6 Hz, 1H, C*H*$_2$Ph), 3.38 (s, 3H, C*H*OCH$_3$), 3.45 (d, J = 13.6 Hz, 1H, C*H*$_2$Ph), 3.62 (d, J = 11.0 Hz, 3H, (C*H*$_3$O)$_2$P), 3.63 (d, J = 11.0 Hz, 3H, (C*H*$_3$O)$_2$P), 3.74 (q, J = 6.8 Hz, 1H, C*H*CH$_3$), 4.72 (s, 1H, C*H*OCH$_3$), 5.15-5.26 (m, C*H*OCO), 7.18-7.48 (m, 15H, H_{arom}). ^{13}C NMR (100 MHz, $CDCl_3$) δ 15.2 (*C*H$_3$CH), 27.7 (d, J = 141.2 Hz, *C*H$_2$P(O)), 52.3 (d, J = 6.1 Hz, (*C*H$_3$O)$_2$P), 52.5 (d, J = 6.8 Hz, (*C*H$_3$O)$_2$P), 53.0 (d, J = 12.9 Hz, (*C*HCH$_2$N), 55.1 (*C*H$_2$Ph), 57.4 (*C*H$_3$CH), 58.3 (*C*HOCH$_3$), 68.9 (d, J = 4.5 Hz, (*C*H$_2$N), 82.4 (*C*HOCH$_3$), 126.8 (C_{arom}), 126.8 (C_{arom}), 127.3 (C_{arom}), 127.9 (C_{arom}), 128.1 (C_{arom}), 128.5 (C_{arom}), 128.6 (C_{arom}), 128.7 (C_{arom}), 135.9 (C_{arom}), 139.6 (C_{arom}), 141.7 (C_{arom}), 169.7 (C=O). ^{31}P NMR (200 MHz, $CDCl_3$) δ 31.32.

Preparation of mandelates 4c and 5c. The reaction was carried out starting from β-hydroxypropylphosphonate **3c** (1.07 g, 2.84 mmol), (*S*)-*O*-methylmandelic acid (753 mg, 4.5 mmol), 1,3-dicyclohexylcarbodiimide (935 mg, 4.54 mmol),

dimethylaminopyridine (52 mg, 0.43 mmol) in dry dichloromethane (50 mL). The crude product was purified by column chromatography using ethyl acetate:hexane (13:9) to afford 740 mg (50%) of diastereomer (*S,R,S*)-**4c** (less polar) and 500 mg (33%) of diastereomer (*R,R,S*)-**5c** (more polar), both as colorless oils.

Diastereomer (*S,R,S*)-4c. $[\alpha]_D$ = +57.3 (c = 4.5, $CHCl_3$). ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.40 (d, J = 7.0 Hz, 3H, C*H*$_3$CHPh), 1.78 (ddd, J = 17.6, 16.0, 7.2 Hz, 1H, C*H*$_2$P), 2.05 (ddd, J = 18.4, 15.6, 5.2 Hz, 1H, C*H*$_2$P), 2.54 (ddd, J = 13.2, 6.4, 2.9 Hz, 1H, C*H*$_2$N), 2.73 (dd, J = 13.6, 5.6 Hz, 1H, C*H*$_2$N), 3.39 (d, J = 10.8 Hz, 3H, (C*H*$_3$O)$_2$P), 3.40 (s, 3H, C*H*OCH$_3$), 3.49 (d, J = 13.6 Hz, 1H, C*H*$_2$Ph), 3.53 (d, J = 10.8 Hz, 3H, (C*H*$_3$O)$_2$P), 3.65 (d, J = 13.6 Hz, 1H, C*H*$_2$Ph), 3.90 (q, J = 7.0 Hz, 1H, C*H*CH$_3$), 4.58 (s, 1H, C*H*OCH$_3$), 5.16-5.26 (m, C*H*OCO), 7.24-7.36 (m, 15H, H_{arom}). ^{13}C NMR (100 MHz, $CDCl_3$) δ 15.0 (*C*H$_3$CH), 27.7 (d, J = 141.2 Hz, *C*H$_2$P(O)), 52.2 (d, J = 6.1 Hz, (*C*H$_3$O)$_2$P), 52.3 (d, J = 6.1 Hz, (*C*H$_3$O)$_2$P), 53.3 (d, J = 10.6 Hz, (*C*HCH$_2$N), 55.4 (*C*H$_2$Ph), 57.4 (*C*H$_3$CH), 58.1 (*C*HOCH$_3$), 68.8 (d, J = 3.1 Hz, (*C*H$_2$N), 82.4 (*C*HOCH$_3$), 126.9 (C_{arom}), 127.3 (C_{arom}), 128.0 (C_{arom}), 128.1 (C_{arom}), 128.3 (C_{arom}), 128.5 (C_{arom}), 128.6 (C_{arom}), 128.9 (C_{arom}), 135.9 (C_{arom}), 139.7 (C_{arom}), 142.0 (C_{arom}), 169.8 (C=O). ^{31}P NMR (200 MHz, $CDCl_3$) δ 30.57.

Diastereomer (*R,R,S*)-5c. $[\alpha]_D$ = +21.7 (c = 5.6, $CHCl_3$). ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.19 (d, J = 6.8 Hz, 3H, C*H*$_3$CHPh), 1.73 (ddd, J = 16.4, 16.4, 8.4 Hz, 1H, C*H*$_2$P), 2.07 (ddd, J = 19.6, 16.0, 4.02 Hz, 1H, C*H*$_2$P), 2.31 (dd, J = 13.6, 6.4, Hz, 1H, C*H*$_2$N), 2.61 (ddd, J = 13.6, 6.0, 3.2 Hz, 1H, C*H*$_2$N), 3.41 (s, 3H, C*H*OCH$_3$), 3.43 (d, J = 14.0 Hz, 1H, C*H*$_2$Ph), 3.48 (d, J = 13.6 Hz, 1H, C*H*$_2$Ph), 3.61 (d, J = 11.0 Hz, 3H, (C*H*$_3$O)$_2$P), 3.63 (d, J = 11.0 Hz, 3H, (C*H*$_3$O)$_2$P), 3.75 (q, J = 6.8 Hz, 1H, CHCH$_3$), 4.74 (s, 1H, C*H*OCH$_3$), 5.14-5.26 (m, C*H*OCO), 7.18-7.48 (m, 15H, H_{arom}). ^{13}C NMR (100 MHz, $CDCl_3$) δ 13.8 (*C*H$_3$CH), 27.9 (d, J = 141.9 Hz, *C*H$_2$P(O)), 52.4 (d, J = 6.8 Hz, (*C*H$_3$O)$_2$P), 52.7 (d, J = 6.8 Hz, (*C*H$_3$O)$_2$P), 52.8 (d, J = 12.2 Hz, *C*HCH$_2$N), 55.4 (*C*H$_2$Ph), 57.5 (*C*H$_3$CH), 57.6 (*C*HOCH$_3$), 68.7 (d, J = 4.6 Hz, (*C*H$_2$N), 82.7 (*C*HOCH$_3$), 126.9 (C_{arom}), 127.0 (C_{arom}), 127.5 (C_{arom}), 128.1 (C_{arom}), 128.1 (C_{arom}), 128.3 (C_{arom}), 128.7 (C_{arom}), 128.8 (C_{arom}), 128.9 (C_{arom}), 136.0 (C_{arom}), 139.7 (C_{arom}), 142.2 (C_{arom}), 170.0 (C=O). ^{31}P NMR (200 MHz, $CDCl_3$) δ 30.99.

Preparation of mandelates 4d and 5d. The reaction was carried out starting from β-hydroxypropylphosphonate **3d** (450 mg, 1.15 mmol), (*S*)-*O*-methylmandelic acid (306 mg, 1.84 mmol), 1,3-dicyclohexylcarbodiimide (380 mg, 1.84 mmol), dimethylaminopyridine (21 mg, 0.17 mmol) in dry dichloromethane (20 mL). The crude product was purified by column chromatography using ethyl acetate:hexane (13:9) to afford 83 mg (13%) of diastereomer (*S,S,S,S*)-**4d** (less polar) and 403 mg (65%) of diastereomer (*R,S,S,S*)-**5d** (more polar), both as colorless oils.

Diastereomer (*S,S,S,S*)-4d. $[\alpha]_D$ = -20.9 (c = 3.5, $CHCl_3$). ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.39 (d, J = 7.2 Hz, 6H, C*H*$_3$CHPh), 1.82 (ddd, J = 18.8, 16.0, 4.4 Hz, 2H, C*H*$_2$P), 2.53 (dd, J = 14.4, 6.8 Hz, 1H, C*H*$_2$N), 2.91 (ddd, J = 14.4, 6.8, 3.6 Hz, 1H, C*H*$_2$N), 3.33 (d, J = 10.8 Hz, 3H, (C*H*$_3$O)$_2$P), 3.43 (s, 3H, C*H*$_3$OCH), 3.46 (d, J = 10.8 Hz, 3H, (C*H*$_3$O)$_2$P), 3.95 (q, J = 6.8 Hz, 2H, C*H*CH$_3$), 4.73 (s, 1H, C*H*OCH$_3$), 5.00 (m, 1H, C*H*OCO), 7.20-7.48 (m, 15H, H_{arom}). ^{13}C NMR (100 MHz, $CDCl_3$) δ 18.3 (*C*H$_3$CH), 27.4 (d, J = 141.1 Hz, *C*H$_2$PO), 49.9 (d, J = 12.2 Hz, (*C*HCH$_2$N), 52.3 (d, J = 5.3 Hz, (*C*H$_3$O)$_2$P), 52.3 (d, J = 6.1 Hz, (*C*H$_3$O)$_2$P), 57.6 (*C*HCH$_3$), 58.3 (*C*HCH$_2$P), 70.2 (d, J = 3.1 Hz, (*C*H$_2$N), 82.7 (*C*HOCH$_3$), 126.9 (C_{arom}), 127.0 (C_{arom}), 127.5 (C_{arom}), 127.5 (C_{arom}), 127.9 (C_{arom}), 128.0 (C_{arom}), 128.3 (C_{arom}), 128.6 (C_{arom}), 128.7 (C_{arom}), 128.8 (C_{arom}), 136.1 (C_{arom}), 144.0 (C_{arom}), 170.0 (C=O). ^{31}P NMR (200 MHz, $CDCl_3$) δ 30.91.

Diastereomer (*R,S,S,S*)-5d. $[\alpha]_D$ = -10.7 (c = 2.9, $CHCl_3$). **^{1}H NMR** (400 MHz, $CDCl_3$) δ 1.24 (d, J = 6.8 Hz, 6H, C*H*$_3$CHPh), 1.99 (ddd, J = 15.6, 15.6, 9.6 Hz, 1H, C*H*$_2$P), 2.34 (ddd, J = 19.2, 16.0, 3.2 Hz, 1H, C*H*$_2$P), 3.39 (dd, J = 14.4, 4.8 Hz, 1H, C*H*$_2$N), 2.66 (dd, J = 14.4, 8.0 Hz, 1H, C*H*$_2$N), 3.34 (s, 3H, C*H*$_3$OCH), 3.67 (d, J = 10.8 Hz, 3H, (C*H*$_3$O)$_2$P), 3.65 (d, J = 10.8 Hz, 3H, (C*H*$_3$O)$_2$P), 3.74 (q, J = 7.2 Hz, 2H, C*H*CH$_3$), 4.74 (s, 1H, C*H*OCH$_3$), 5.17 (m, 1H, C*H*OCO), 7.12-7.42 (m, 15H, H_{arom}). ^{13}C NMR (100 MHz, $CDCl_3$) δ 19.6 (*C*H$_3$CH), 27.4 (d, J = 142.7 Hz, *C*H$_2$PO), 49.9 (d, J = 13.6 Hz, (*C*HCH$_2$N), 52.5 (d, J = 7.6 Hz, (*C*H$_3$O)$_2$P), 52.6 (d, J = 7.6 Hz, (*C*H$_3$O)$_2$P), 57.6 (*C*H$_3$CH), 59.0 (*C*HCH$_2$P), 70.7 (d, J = 6.1 Hz, (*C*H$_2$N), 82.5 (*C*HOCH$_3$), 127.0 (C_{arom}), 127.5 (C_{arom}), 127.8 (C_{arom}), 128.3 (C_{arom}), 128.5 (C_{arom}), 128.8 (C_{arom}), 136.3 (C_{arom}), 143.9 (C_{arom}), 170.2 (C=O). ^{31}P NMR (200 MHz, $CDCl_3$) δ 31.98.

Preparation of mandelates 4e and 5e. The reaction was carried out starting from β-hydroxypropylphosphonate **3e** (530 mg, 1.35 mmol), (*S*)-*O*-methylmandelic acid (360 mg, 2.17 mmol), 1,3-dicyclohexylcarbodiimide (447 mg, 2.17 mmol), dimethylaminopyridine (25 mg, 0.20 mmol) in dry dichloromethane (30 mL). The crude product was purified by column chromatography using ethyl acetate:hexane (13:9) to afford 489 mg (67%) of diastereomer (*S,R,R,S*)-**4e** (less polar) and 154 mg (21%) of diastereomer (*R,R,R,S*)-**5e** (more polar), both as colorless oils.

Diastereomer (*S,R,R,S*)-4e. $[\alpha]_D$ = +23.5 (c = 2.9, CH_3Cl). **^{1}H NMR** (400 MHz, $CDCl_3$) δ 1.38 (d, J = 6.8 Hz, 6H, C*H*$_3$CHPh), 1.82 (ddd, J = 23.6, 15.6, 7.6 Hz, 1H, C*H*$_2$P), 2.27 (ddd, J = 19.2, 16.0, 4.8 Hz, 1H, C*H*$_2$P), 2.61 (ddd, J = 14.4, 9.6, 3.2 Hz, 1H, C*H*$_2$N), 2.89 (dd, J = 14.4, 6.4 Hz, 1H, C*H*$_2$N), 3.37 (s, 3H, C*H*$_3$OCH), 3.39 (d, J = 11.6 Hz, 3H, (C*H*$_3$O)$_2$P), 3.56 (d, J = 11.6 Hz, 3H, (C*H*$_3$O)$_2$P), 3.91 (q, J = 6.8 Hz, 2H, C*H*CH$_3$), 4.51 (s, 1H, C*H*OCH$_3$), 5.08-5.17 (m, 1H, C*H*OCO), 7.21-7.36 (m, 15H, H_{arom}). ^{13}C NMR (100 MHz, $CDCl_3$) δ 19.2 (*C*H$_3$CH), 27.5 (d, J = 141.2 Hz, *C*H$_2$PO), 49.3 (d, J = 10.6 Hz, (*C*HCH$_2$N), 52.2 (d, J = 6.1 Hz,

($CH_3O)_2P$), 52.4 (d, J = 6.8 Hz, ($CH_3O)_2P$), 57.3 ($CHCH_3$), 58.5 ($CHCH_2P$), 70.2 (d, J = 3.0 Hz, CH_2N), 82.3 ($CHOCH_3$), 126.8 (C_{arom}), 127.3 (C_{arom}), 127.8 (C_{arom}), 127.9 (C_{arom}), 128.2 (C_{arom}), 128.4 (C_{arom}), 128.5 (C_{arom}), 128.6 (C_{arom}), 135.9 (C_{arom}), 143.9 (C_{arom}), 169.9 (C=O). ^{31}P NMR (200 MHz, $CDCl_3$) δ 31.09.

Diastereomer (*R,R,R,S*)-5e. $[\alpha]_D$ = +18.1 (c = 3.3, CH_3Cl). **^{1}H NMR** (400 MHz, $CDCl_3$) δ 1.22 (d, J = 6.8 Hz, 6H, CH_3CHPh), 1.44 (ddd, J = 25.2, 16.0, 8.8 Hz, 1H, CH_2P), 1.88 (ddd, J = 19.2, 15.6, 3.6 Hz, 1H, CH_2P), 2.36 (dd, J = 14.4, 7.2 Hz, 1H, CH_2N), 2.71 (ddd, J = 14.4, 6.4, 3.6 Hz, 1H, CH_2N), 3.42 (s, 3H, CH_3OCH), 3.60 (d, J = 10.8 Hz, 3H, ($CH_3O)_2P$), 3.61 (d, J = 10.8 Hz, 3H, ($CH_3O)_2P$), 3.82 (q, J = 6.8 Hz, 2H, $CHCH_3$), 4.74 (s, 1H, $CHOCH_3$), 4.92-5.03 (m, 1H, CHOCO), 7.10-7.45 (m, 15H, H_{arom}). ^{13}C NMR (100 MHz, $CDCl_3$) δ 18.0 (CH_3CH), 27.6 (d, J = 141.9 Hz, $CH_2P(O)$), 49.8 (d, J = 12.9 Hz, $CHCH_2N$), 52.4 (d, J = 6.1 Hz, ($CH_3O)_2P$), 52.7 (d, J = 6.1 Hz, ($CH_3O)_2P$), 57.6 (CH_3CH), 58.3 ($CHCH_2P$), 69.8 (d, J = 4.6 Hz, CH_2N), 82.7 ($CHOCH_3$), 126.9 (C_{arom}), 127.4 (C_{arom}), 127.7 (C_{arom}), 1278 (C_{arom}), 128.0 (C_{arom}), 128.2 (C_{arom}), 128.3 (C_{arom}), 128.7 (C_{arom}), 128.9 (C_{arom}), 136.2 (C_{arom}), 144.1 (C_{arom}), 170.1 (C=O). ^{31}P NMR (200 MHz, $CDCl_3$) δ 31.39.

Acknowledgments

We wish to thank CONACYT of Mexico, for financial support via grant 41657-Q for this work. One of us, AGM, also wishes to thank CONACYT for a Graduate Scholarship.

References

1. (a) Berova, N.; Nakanishi, K.; Woody, R. W. *Circular Dichroism: Principles and Applications*; Wiley-VCH Publishers: New York, **2000**. (b) Lightner, D.; Gurst, J. E. *Organic Conformational Analysis and Stereochemistry from Circular Dichroism Spectroscopy;* Wiley-VCH Publishers: New York, **2000**.
2. (a) Charney, E. *Molecular Basis of Optical Activity: Optical Rotatory Dispersion and Circular Dichroism*; Krieger Pub Co. **1985**. (b) Cooley, J. H.; Williams, R. V. *J. Chem. Ed.* **1997**, *7*4, 585-586.
3. Polavarapu, P. L. *Chirality* **2002**, *14*, 768-781.
4. Wang, F.; Wang, Y.; Polavarapu, P. L.; Li, T.; Drabowics, J.; Pietrusiewcs, K. M.; Zygo, K. *J. Org. Chem.* **2002**, *67*, 6539-6541.
5. Constante, J.; Hecht, L.; Polavarapu, P. L.; Collet, A.; Barron, L. D. *Angew. Chem. Int. Ed. Engl.* **1997**, *36*, 885-887.
6. (a) Seco, J. M.; Quiñoá, E.; Riguera, R. *Chem. Rev.* **2004**, *104*, 17-117 and references herein. (b) Seco, J. M.; Tseng, L.-H.; Godejohann, M.; Quiñoá, E.; Riguera, R. *Tetrahedron:Asymmetry* **2002**, *13*, 2149-2153. (c) Seco, J. M.; Quiñoá, E.; Riguera, R. *Tetrahedron: Asymmetry* **2001**, *12*, 2915-2925. (d) Latypov, S. K.; Seco, J. M.; Quiñoá, E.; Riguera, R. *J. Org. Chem.* **1996**, *61*, 8569-8577.
7. Dale, J. A.; Mosher, H. S. *J. Am. Chem. Soc.* **1973**, *95*, 512-519.
8. Lewis, R. A.; Korpium, O.; Mislow, K. *J. Am. Chem. Soc.* **1968**, *90*, 4847-4853.
9. (a) Ordóñez, M.; González-Morales, A.; Ruiz, C.; De la Cruz-Cordero, R.; Fernández-Zertuche, M.*Tetrahedron: Asymmetry* **2003**, *14*, 1775-1779. (b) Yuan, C.; Wang, K.; Li, J.; Li, Z. *Phosphorus, Sulfur Silicon and Relat. Elem.* **2002**, *177*, 2391-2397. (c) Yuan, C.; Wang, K.; Li, J.; Li, Z. *Heteroatom Chem.* **2002**, *13*, 153-156. (d) Wroblewsky, A. E.; Halajewska-Wosik, A. *Tetrahedron: Asymmetry* **2003**, *14*, 3359-3363. (e) Very recently, enzymatic synthesis of (*S*)-phosphogabob was reported: Wang, K.; Zhang, Y.; Yuan, C. *Org. Biomol. Chem.* **2003**, *1*, 3564-3569.
10. Jain, R. P.; Williams, R. M. *Tetrahedron* **2001**, *57*, 6505-6509 and references herein.
11. The γ-(*N*,*N*-disubstituted)amino-β-hydroxyphosphonates 3a-e were prepared by reduction of the corresponding γ-(*N*,*N*-disubstituted)amino-β-ketophosphonates. Ordóñez, M.; González-Morales, A.; Salazar-Fernández, H. *Tetrahedron:Asymmetry* **2004**, *15*, 2719-2725.
12 (a) Trost, B. M.; Belletire, J. L; Godleski, S.; McDougal, P. G.; Balkovec, J. M. *J. Org. Chem.* **1986**, *51*, 2370-2374. (b) Trost, B. M.; Bunt, R. C.; Pulley, S. R. *J. Org. Chem.* **1994**, *59*, 4202-4205.