

Article

## Limitations in Determining Enantiomeric Excess of Alcohols by <sup>31</sup>P-NMR of the Phosphonate Derivatives

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O uso de derivados fosfonatos de dialquila diastereoisoméricos na determinação de excessos enantioméricos através da razão entre os sinais de <sup>31</sup>P-NMR anisócronos dos isômeros *meso* e *threo*, foi bem sucedido para álcoois secundários (método de Feringa), porém revelou-se ineficiente para álcoois primários com dois ou mais grupos metilênicos entre as hidroxilas e os centros estereogênicos. Observou-se adicionalmente que era importante obter os espectros acoplados e desacoplados para se certificar dos picos correspondentes aos fosfonatos de dialquila. Entretanto, esta metodologia merece ser aplicada sempre que a quantidade de álcool disponível e sua estrutura não forem fatores limitantes.

The use of diastereomeric alcohol dialkylphosphonate derivatives to determine the enantiomeric excesses via <sup>31</sup>P-NMR signal ratios of anisochronous *meso* and *threo* isomers was successfully applied to secondary alcohols (Feringa's method). Expansion of the methodology to primary alcohols possessing the hydroxyl groups tethered to the stereogenic centers by two or more methylene groups proved the method to be inefficient. The comparison between the coupled and decoupled spectra is important in order to identify the signals corresponding to the dialkylphosphonates. Nevertheless the methodology should be applied whenever the amount of the alcohol and its structure are not the limiting factors.

**Keywords:** <sup>31</sup>P-NMR, enantiomeric excess, chiral alcohols, phosphonate derivatives

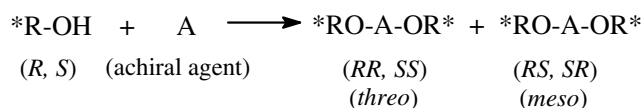
### Introduction

Asymmetric processes and chemical conversion of chiral compounds require chromatographic or NMR methods for the determination of the enantiomeric excesses. The usual approach requires the availability of GC or HPLC chiral columns (chromatography). Chiral derivatizing or complexing agents like chiral lanthanides derivatives (NMR) are alternatively applied. Both NMR and chromatographic methods rely on the formation of diastereomeric derivatives or complexes to achieve the enantiomeric discrimination. The concept of using achiral derivatives to

determine enantiomeric excess by chromatography and NMR was first introduced by Horeau<sup>1</sup>. Horeau's rationale was very simple, by derivatizing racemic alcohols with achiral derivatizing agents, he could detect either by chromatography or by <sup>1</sup>H-NMR the *meso* and *threo* diastereomers. He also observed that the ratio between them was proportional to the enantiomeric excess (Scheme 1).

This concept was adapted by Feringa<sup>2</sup> to <sup>31</sup>P-NMR experiments, using PCl<sub>3</sub> as the achiral derivatizing reagent. Therefore, racemic alcohols were converted into phosphonates in a fast and quantitative reaction, yielding

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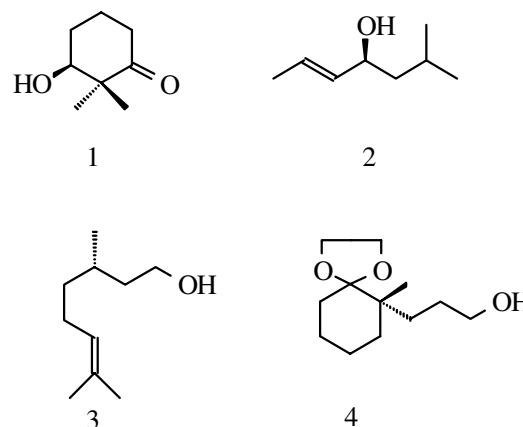
**Scheme 1.** Formation of the *meso* and *threo* alcohols derivatives using achiral reagents.

stereoisomeric mixtures: an enantiomeric pair (*R,R* and *S,S*) and two *meso* compounds (*R,S* and *S,R*), in a 2:1:1 ratio (Scheme 2). These diastereomers were detected by  $^{31}\text{P}$ -NMR, as three signals (0-10 ppm). Application of Horeau's equation<sup>1</sup> ( $p^2 = (K-I)/(K+I)$ , where **K** = (peak area of *threo* / peak areas of *meso* 1 + *meso* 2) and *p* is the optical purity) allowed the calculation of the optical purity of enantiomerically enriched mixtures. This method provided an easy way to determine the enantiomeric excess making use of  $^{31}\text{P}$ -NMR which has a lower detection sensitivity relative to  $^1\text{H}$  ( $6.63 \times 10^{-2}$ ) but fewer signals to observe, thus simplifying the analyses. The method was extended to amines<sup>3</sup> and thiols<sup>4</sup>.

The main purpose of this work was to determine optical purity of alcohols **1-4** (Fig. 1) which were not discriminated with chiral GC and HPLC chiral columns.

## Experimental

$^1\text{H}$ ,  $^{13}\text{C}$  and  $^{31}\text{P}$ -NMR spectra were obtained on a Varian Inova-500 spectrometer with standard pulse sequences operating at 499.885 MHz, 125.695 MHz and 202.135 MHz for  $^1\text{H}$ ,  $^{13}\text{C}$  and  $^{31}\text{P}$ , respectively. The chemical shifts are reported in ppm using TMS (0 ppm) as internal reference for  $^1\text{H}$  and  $^{13}\text{C}$ -NMR spectra and pulses of  $45^\circ$  for  $^1\text{H}$  and  $^{13}\text{C}$  and delay times of 1s and 2s respectively. For  $^{31}\text{P}$ -NMR spectra,  $\text{H}_3\text{PO}_4$  (0 ppm) was used as external reference, 0.03 mol  $\text{L}^{-1}$  of  $\text{PCl}_3$  per samples and 1 mL of  $\text{CDCl}_3$  solution, spectral width 5250 Hz, acquisition time 0.5 s,

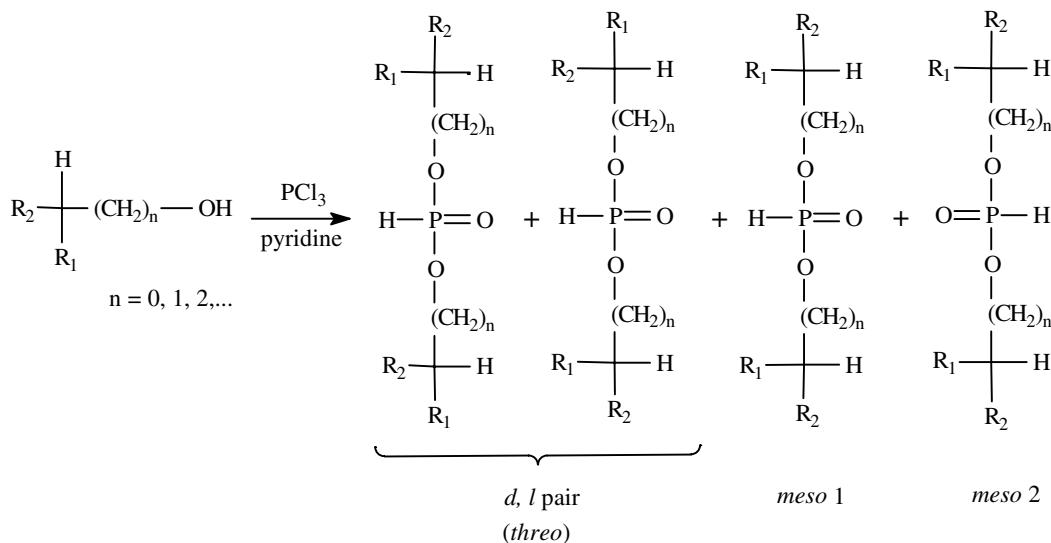


**Figure 1.** Racemic and enantiomerically enriched primary and secondary chiral alcohols used in diastereomeric discrimination experiments applying Feringa's method.

delay of 2 s, 512 scans per spectrum, temperature  $25^\circ\text{C}$ , pulse width  $45^\circ$ , WALTZ decoupling mode, The coupling constants (*J*) are in Hz.

**HPLC** chromatograms were obtained with a Hewlett Packard equipment, model 1090, serie II/M HPLC equipped with a photodiode array detector and a Waters Nova Pack ODS ( $4\ \mu\text{m}$ , 150 mm X 3.9 mm i.d) column eluted with chiral mobile phase ( $\beta$ -cyclodextrin 15 mmol  $\text{L}^{-1}$ ) or a LiChroCART 250-4 ChiraDex GAMMA ( $5\ \mu\text{m}$ , 250 mm X 4 mm i.d) chiral column eluted with  $\text{H}_2\text{O}$ , at a flow rate of  $0.4\ \text{mL min}^{-1}$  and a column temperature of  $30^\circ\text{C}$ .

**GC-MS** analyses were carried out using a HP-5990/5970 system equipped with HP-5 fused silica capillary column (30 m x 0.25 mm x 0.25  $\mu\text{m}$ ); column temperatures were programmed from  $60^\circ\text{C}$  to  $240^\circ\text{C}$  at  $3^\circ\text{C min}^{-1}$ . **GC/MS** Injector and detector temperatures were  $220^\circ\text{C}$  and  $285^\circ\text{C}$  respectively flow rate 1.16 mL



**Scheme 2.** Diastereomers obtained by derivatizing an alcohol enantiomeric mixture with phosphorus trichloride.

min<sup>-1</sup>, split mode. Injection volume, 0.5  $\mu$ L of a solution of about 10 mg mL<sup>-1</sup> of the mixture in ethyl acetate. Helium was used as the carrier gas. The MS were determined at 70 eV. Scanning speed was 0.84 scan sec<sup>-1</sup> from *m/z* 40 to 550. Chiral columns 1) Chrompack CP-Chiralsil-Dex CB (30 m x 0.25 mm x 0.25  $\mu$ m) 2) Heptakis-(2,6-methyl-3-pentyl)- $\beta$ -cyclodextrin (25 m x 0.25 mm x 0.25  $\mu$ m).

*(S)-(+)-3-Hydroxy-2,2-dimethylcyclohexanone, (+)-1*  
(Mori's procedure<sup>5</sup>)

To a round bottom flask (3 L) equipped with a mechanical stirrer, thermometer and containing saccharose (75 g), zinc sulphate (0.2 g) and water (500 mL), fresh baker's yeast (135 g) was added. The mixture was stirred for two hours at room temperature before adding 2,2-dimethyl-1,3-cyclohexanedione (2.4 g, 17.1 mmol). The reaction was further stirred for 3 days at 30 °C. Sodium chloride was added to the reaction mixture and continuously extracted with dichloromethane for 12 h. Solvent evaporation furnished the crude alcohol (4.1 g) and column chromatography eluted with hexane-diethyl acetate 12%, yielded compound **(+)-1** (1.728g, 72%). bp.: 96 - 97 °C / 2.8 mm Hg [lit<sup>5</sup>: 85-87 °C / 3.7 mmHg],  $[\alpha]_D^{20} + 23.7^\circ$  (*c* 2.87, CHCl<sub>3</sub>) [lit<sup>5</sup>: +24,1° (*c* 12, CHCl<sub>3</sub>)]. IR. (film)  $\nu_{\max}$ . (cm<sup>-1</sup>): 3454; 2943-2874; 1705; 1056; <sup>1</sup>H-NMR (500 MHz, CDCl<sub>3</sub>):  $\delta$  1.03 (s, 3H, CH<sub>3</sub>), 1.10 (s, 3H, CH<sub>3</sub>), 1.68 (m, 1H), 1.79 (m; 1H), 1.92 (m, 1H), 2.05 (m, 1H), 2.39 (m, 1H), 2.46 (m, 1H) and 3.75 (dd, 1H, *J* = 7.4 and 3.4). <sup>13</sup>C-NMR (125 MHz CDCl<sub>3</sub>):  $\delta$  19.0 (CH<sub>3</sub>), 20.0 (CH<sub>2</sub>), 22.1 (CH<sub>3</sub>), 27.4 (CH<sub>2</sub>) and 36.8 (CH<sub>2</sub>), 50.9 (C<sub>o</sub>), 77.3 (CH) and 221.8 (C<sub>o</sub>). MS *m/z* (%): 142 (M<sup>+</sup>, 14), 124 (15), 98 (50), 82 (100), 71 (65), 67 (56), 43 (52), 41 (28), 40 (45).

*(R,S)-3-Hydroxy-2,2-dimethylcyclohexanedione, ( $\pm$ )-1*

To a stirred solution of 2,2-dimethyl-1,3-cyclohexanedione (3.5 g; 25 mmol), in methanol (25 mL) at -10 - 0 °C, NaBH<sub>4</sub> (0.236 g; 6.24 mmol) was slowly added. The reaction was monitored by TLC and as soon as the diketone was consumed a solution of HCl (few drops) was added to the reaction. The methanol was evaporated and NaCl<sub>aq</sub> (30 mL) was added before the extraction with dichloromethane was performed (5 x 20 mL). The organic layer was dried over MgSO<sub>4</sub>, filtered and evaporated under reduced pressure. The residue (3.21 g) was purified by column chromatography, eluted with hexane-ethyl acetate 12%, yielding *(R,S)*-3-hydroxy-2,2-dimethylcyclohexanone (2.62 g; 73.8% yield). Spectral data equal to enantiomerically pure **(+)-1**.

*(R,S)-2-methyl-5-hepten-4-ol, ( $\pm$ )-2*

A 100 mL 3-necked flask equipped with reflux condenser was charged with magnesium turnings (2.90 g, 119 mmol) and flame dried under argon atmosphere. A solution of isobutyl bromide (11.0 g, 80 mmol) in diethylether (60.0

mL) was then added dropwise in order to keep the solution under gentle reflux. The reaction mixture was stirred one hour at room temperature after the addition of the isobutyl bromide solution and *trans*-crotonaldehyde (5.6 g, 80 mmol) was added dropwise over 5 min. at 0 °C. The reaction mixture was then stirred at room temperature for an additional hour and quenched at 0 °C with saturated aqueous NH<sub>4</sub>Cl solution (100 mL) and the aqueous layer was extracted with diethylether (2 x 50 mL). The combined organic layers were washed with brine, dried over MgSO<sub>4</sub>, filtered and evaporated under reduced pressure. Distillation (30 mm Hg, 105°C) afforded 7.8 g (61 mmol, 77% yield) of racemic rhynchophorol as a colorless liquid<sup>6</sup>: IR (NaCl, film)  $\nu_{\max}$ . (cm<sup>-1</sup>): 3359 (br), 2954, 2922, 2873, 1670 (w), 1456, 1375, 966 cm<sup>-1</sup>. <sup>1</sup>H-NMR (CDCl<sub>3</sub>, 300 MHz):  $\delta$  0.90 (d; 3H, *J* = 6.6 Hz, CH<sub>3</sub>), 0.91 (d; 3H; *J* = 6.6 Hz, CH<sub>3</sub>), 1.24-1.49 (m; 4H; H-6, H-6 and OH), 1.69 (d; 3H; *J* = 6.9 Hz; CH<sub>3</sub>), 4.10 (q; 1H; *J* = 6.9; H-4); 5.46 (dd; 1H; *J* = 15.4 and 6.9 Hz; H-3), 5.62 (m; 1H; H-2).

*(R)-(+)- $\beta$ -citronellol, (+)-3 and (S)-(-)- $\beta$ -citronellol, (-)-3*

Purchased from Aldrich Chemical Company. ( $\pm$ )-**3** was obtained by a equimolar mixture of both isomers.

*Ketal of the*

*(S)-(-)-1-methyl-1-(3-propanol)-2-cyclohexanone, (-)-4*

Obtained in three steps as follows: **1**) Methyl *(S)*-(-)-1-methyl-2-oxocyclohexanepropionate was readily available by d'Angelo's method<sup>7</sup>. The required ketimine was prepared from 2-methylcyclohexanone (2.61 g, 23 mmol) and 2.8 g (23 mmol) of *(R)*-(+)-1-phenylethylamine (96% ee) in benzene (50 mL) (Dean-Stark trap, 12 h of reflux under dry nitrogen). Most of the benzene was removed from the crude ketimine at atmospheric pressure and after cooling at room temperature, 2.4 g (28 mmol) of dry methyl acrylate were added. The resulting mixture was kept at room temperature for 7 days. The excess of methyl acrylate was removed by distillation under reduced pressure (20 Torr). Acetic acid (1.68 g), water (9.5 mL) and MeOH (4.3 mL) were then added and the mixture was vigorously stirred for 2 h. The solution was saturated with NaCl and extracted with hexane. The organic layers were combined, washed with HCl (1 mol L<sup>-1</sup>), brine, and dried over magnesium sulfate. The solvent was removed under reduced pressure and the residue was distilled (0.1 Torr), leading to 4.2 g (90% yield) of methyl *(S)*-(-)-1-methyl-2-oxocyclohexanepropionate as a clear liquid:  $[\alpha]_D^{20} -33$  (*c* 3, EtOH) [lit.<sup>8</sup>:  $[\alpha]_D^{20} -37$  (*c* 3 EtOH)]. **2**) Ketalization of methyl *(S)*-(-)-1-methyl-2-oxocyclohexanepropionate: a mixture of methyl *(S)*-(-)-1-methyl-2-oxocyclohexanepropionate (1 g, 5 mmol), ethylene glycol (1.58 g, 25 mmol) and PTSA (catalytic amount) in benzene (30 mL), was refluxed for 12

h in a Dean-Stark apparatus. The reaction mixture was thoroughly washed with saturated aqueous NaHCO<sub>3</sub> (2 x 30 mL), brine (30 mL), dried over anhydrous Na<sub>2</sub>SO<sub>4</sub> and concentrated *in vacuo*. Flash chromatography (hexane-ethyl acetate, 4:1) of the resulting residue furnished 1.2 g (99% yield) of the protected ketone as a clear liquid: [ $\alpha$ ]<sub>D</sub><sup>20</sup> -5.3 (c 3.2, CHCl<sub>3</sub>); <sup>1</sup>H-NMR (500 MHz, CDCl<sub>3</sub>):  $\delta$  0.92 (s, 3H, CH<sub>3</sub>), 1.42 (m, 4H), 1.55 (m, 2H), 1.60 (m, 2H), 1.79 (m, 2H), 2.30 (m, 2H), 3.66 (s, 3H, OCH<sub>3</sub>) and 3.94 (m, 4H). MS *m/z* (%): 242 (M<sup>+</sup>, 8), 227 (2), 169 (22), 155 (6), 113 (19), 99 (100), 86 (25), 55 (28), 41 (18). **3** The desired alcohol (-)-**4** was then obtained by reacting the ketal derivative of the methyl (*S*)-(-)-1-methyl-2-oxocyclohexanepropionate (266 mg, 1 mmol) with LiAlH<sub>4</sub> (excess) in anhydrous diethyl ether (25 mL). After 30 min, drops of NaOH solution (1 mol L<sup>-1</sup>) were added to the reaction mixture. Filtration over a celite pad and solvent evaporation under reduced pressure produced 242 mg of crude product. Flash chromatography (hexane-ethyl acetate, 1:1) afforded 235 mg (100% yield) of pure alcohol (-)-**4** as a clear oil: [ $\alpha$ ]<sub>D</sub><sup>20</sup> -2.3 (c 3.6, CHCl<sub>3</sub>); <sup>1</sup>H-NMR (500 MHz, CDCl<sub>3</sub>):  $\delta$  0.92 (s, 3H, CH<sub>3</sub>), 1.42 (m, 2H), 1.44 (m, 2H), 1.48 (m, 2H), 1.50 (m, 2H), 1.54 (m, 2H), 1.62 (m, 2H), 3.61 (m, 2H), and 3.93 (m, 4H). <sup>13</sup>C-NMR (125 MHz, CDCl<sub>3</sub>):  $\delta$  19.4 (CH<sub>3</sub>), 20.8 (CH<sub>2</sub>), 23.6 (CH<sub>2</sub>), 26.9 (CH<sub>2</sub>), 30.3 (CH<sub>2</sub>), 30.5 (CH<sub>2</sub>), 34.2 (CH<sub>2</sub>), 41.0 (C<sub>0</sub>), 63.9 (CH<sub>2</sub>-O), 64.7 and 64.9 (OCH<sub>2</sub>CH<sub>2</sub>O), 113.1(C<sub>0</sub>). MS *m/z* (%): 214 (M<sup>+</sup>, 4), 155 (9), 113 (12), 99 (100), 86 (26), 55 (17), 41 (13). Racemic **4** was obtained by a equimolar mixture of the (-)-**4** and its enantiomer.

#### General procedure for the preparation phosphonate derivatives of alcohols **1-4**

To a stirred solution of alcohol (0.18 mmol) and pyridine (0.5 mmol) in 0.5 mL CDCl<sub>3</sub> was added 0.06 mmol of

freshly distilled PCl<sub>3</sub> dissolved in 0.5 mL of CDCl<sub>3</sub>. After stirring for 10 min, the reaction mixture was transferred into a 5 mm NMR tube and then the spectra were recorded. <sup>31</sup>P-NMR of the phosphonates are depicted in Table 1.

## Results and Discussion

Following the global trend of working with enantiomerically enriched mixtures or pure enantiomers has brought a new problem to our research group, namely, enantiomeric discrimination. Chiral GC and HPLC columns and chiral eluents are not always efficient thus other methods of analysis to assess enantiomeric excess had to be investigated. We were particularly attracted by Feringa's method<sup>2</sup>, mainly due to its low cost.

Thus compounds **1-4**, which were not resolved using standard chiral GC columns (Chrompack CP-Chiralsil-Dex-CB, heptakis-(2,6-dimethyl-3-pentyl)- $\beta$ -cyclodextrin) and/or chiral HPLC column ( $\gamma$ -cyclodextrin) or HPLC eluted with a chiral phase (Waters C-18 eluted with an aqueous solution of  $\alpha$ -cyclodextrin (CD) or  $\beta$ -CD or  $\gamma$ -CD, 15 mmol L<sup>-1</sup>)<sup>8</sup> were submitted to Feringa's method to determine the enantiomeric excess. As the label term "optical purity" obtained by Horeau's formula<sup>1</sup> is becoming obsolete<sup>9</sup> the enantiomeric excess can be assessed by converting the equation into  $ee = [(K-I)/(K+I)]^{1/2} \times 100$ .

Compound (+)-**1** was obtained via enantioselective reduction using *Saccharomyces cerevisiae* but the enantiomeric excess could only be inferred by specific optical rotation compared to the literature<sup>5</sup>. The dialkylphosphonate derivatives of the racemate showed three <sup>31</sup>P signals (Figs. 2b and 2c) in the proton decoupled NMR spectrum with **K** close to 1 (Table 1) indicating that chiral recognition was negligible during the coupling reaction, therefore the enantiomeric excess could be obtained via the ratio of the *threo* and *meso* diastereomers (deconvolution was applied to the

**Table 1.** <sup>31</sup>P-NMR<sup>a</sup> data of phosphonates derivatives obtained from the reaction between the alcohols and PCl<sub>3</sub>.

Alcohol	$\delta_{d,l \text{ pair}}^b$	$\delta_{meso \ 1}^b$	$\delta_{meso \ 2}^b$	ratio <sup>c</sup>
(±)-1	6.75 (dt, 703.5 and 9.0; 805.5)	7.74 (dt, 703.0 and 9.0; 553.2)	4.80 (dt, 704.0 and 9.0; 262.2)	50.3:49.7
(+)-1	6.75 (dt, 703.5 and 9.0; 8004.3)	7.74 (dt, 704.0 and 9.0; 165.0)	4.80 (dt, 703.0 and 9.0; 78.2)	ee = 97.0% <sup>d</sup>
(±)-2	5.89 (dt, 692, 8.0 and 2.2; 370.9)	6.27 (dt, 692, 8.0 and 2.2; 180.6)	5.46 (dt, 692, 8.0 and 2.2; 166.8)	49.4:50.6
(±)-3	8.37 (dq, 691.0 and 9.0)	8.37 (dq, 691.0 and 9.0)	8.37 (dq, 691.0 and 9.0)	e
(-)-3	8.37 (dq, 690.0 and 9.0)	8.37 (dq, 690.0 and 9.0)	8.37 (dq, 690.0 and 9.0)	e
(±)-4	8.40 (dq, 689.0 and 8.7)	8.40 (dq, 689.0 and 8.7)	8.40 (dq, 689.0 and 8.7)	e
(-)-4	8.40 (dq, 690.0 and 8.7)	8.40 (dq, 690.0 and 8.7)	8.40 (dq, 690.0 and 8.7)	e

<sup>a</sup>all the spectra were obtained in CDCl<sub>3</sub>, at 202.135 MHz on a Varian INOVA-500 spectrometer; H<sub>3</sub>PO<sub>4</sub> ( $\delta$  0.0) as an external standard;

<sup>b</sup> $\delta$  (multiplicity, <sup>n</sup>J<sub>PH</sub> in Hz; peak area);

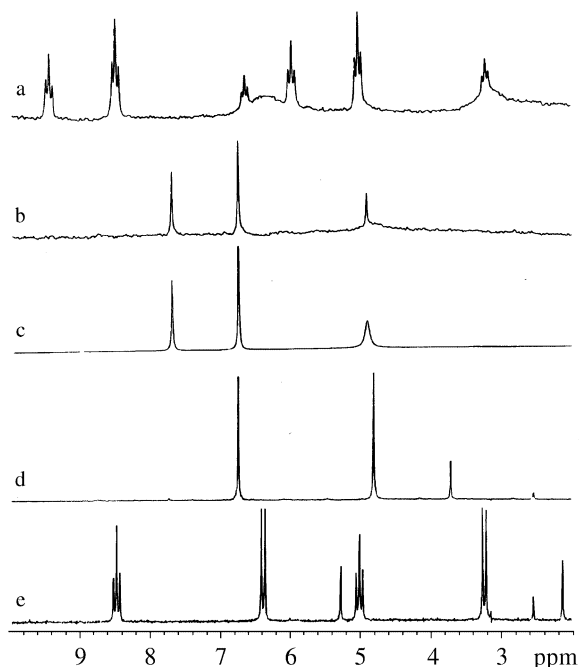
<sup>c</sup>ratio *meso* (1 + 2) : *threo*;

<sup>d</sup>the enantiomeric excess (ee) was calculated from the integrated peak area of *threo* isomer (*d,l* pair) and *meso* isomers, respectively using the modified Horeau's formula<sup>1</sup>  $ee = [(K-I)/(K+I)]^{1/2} \times 100$  where **K** = (peak area of *threo* / peak areas of *meso* 1 + *meso* 2);

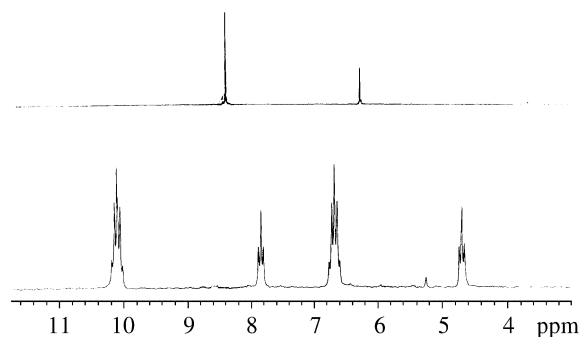
<sup>e</sup>not available due to isochronous <sup>31</sup>P chemical shifts in the diastereomers.

spectrum depicted in 2c for integrating purposes). The dialkylphosphonate derivative signals were further confirmed by proton coupled spectrum (Fig. 2a). The enantiomeric excess obtained by Feringa's method was 97.0%, assuming that *meso* 1/*meso* 2 ratio follows the same value observed for the racemic mixture (Table 1). This strategy was necessary because the *meso* 2 signal, in this particular example, is overlapped by the monoalkyl phosphonated derivative (Table 1, Figs. 2d and 2e). This result was compatible with the ee obtained by optical rotation comparison<sup>5</sup>. Therefore though less precise than a HPLC/UV or GC/FID method the ee was estimated without chiral reagents or columns. In an attempt to improve the precision of the ee determination and inspired in Horeau's pioneer work<sup>1</sup>, the crude phosphonate derivatives of ( $\pm$ )-**1** were analyzed by GC/FID and GC/MS. The analysis revealed that the mixture was too complex and the ee difficult to determine.

Application of the same methodology to alcohol ( $\pm$ )-**2** furnished several <sup>31</sup>P signals in the NMR spectrum due to the presence of monoalkylphosphonate and dialkylphosphonate derivatives in the reaction mixture. The use of the expected phosphorus multiplicity for the dialkylphosphonate derivatives in a <sup>1</sup>H coupled spectrum allowed the recognition of the correct three anisochronous <sup>31</sup>P signals, which were integrated in the decoupled spectrum furnish-



**Figure 2.** <sup>31</sup>P-NMR spectra, 202.135 MHz, CDCl<sub>3</sub> solution and H<sub>3</sub>PO<sub>4</sub> ( $\delta = 0$ ) as external reference. 2a) Proton coupled <sup>31</sup>P-NMR of ( $\pm$ )-**1**. 2b) Proton decoupled <sup>31</sup>P-NMR of ( $\pm$ )-**1**. 2c) Application of deconvolution to Proton decoupled <sup>31</sup>P-NMR of ( $\pm$ )-**1**. 2d) Proton decoupled <sup>31</sup>P-NMR of enantiomerically enriched (+)-(*S*)-**1** 2e) Proton coupled <sup>31</sup>P-NMR of enantiomerically enriched (+)-(*S*)-**1**.



**Figure 3.** <sup>31</sup>P-NMR spectra, 202.135 MHz, CDCl<sub>3</sub> solution and H<sub>3</sub>PO<sub>4</sub> ( $\delta = 0$ ) as external reference. 3a) Proton decoupled <sup>31</sup>P-NMR of ( $\pm$ )-**4**. 3b) Proton coupled <sup>31</sup>P-NMR of ( $\pm$ )-**4**.

ing **K** close to 1 (Table 1). And we concluded that the method was valid for general application of the ee determination of ( $\pm$ )-**2**.

The versatility of the method had no apparent limit but primary alcohols have always been recognized as difficult substrates to be discriminated by chiral chromatography, but Feringa reported the successful application of his method to 2-phenyl-1-butanol<sup>2</sup>. Thus, primary alcohols ( $\pm$ )-**3** and ( $\pm$ )-**4** (Figs. 3a and 3b), showing no separation in the available chiral columns, and possessing two and three methylene groups tethering the hydroxyl group and the stereogenic center, respectively, were selected for the final test. In both cases the phosphorus signals of the diastereomeric dialkylphosphonate derivatives were isochronous (Figs. 3a and 3b). This ineffective discrimination pointed out that Feringa's method is mostly limited to compounds possessing hydroxyl groups at the chiral center.

## Conclusions

The use of Feringa's method is recommended when: chiral chromatography fails; the alcohol is available in amounts ranging from 20 to 30 mg (otherwise more spectrometer time will be used) and finally the hydroxyl groups are close to the stereogenic center. Other stereogenic elements were not tested by Feringa neither by other group.

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