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# Enhanced chromatographic resolution of alcohol enantiomers as phosphate or phosphonate derivatives

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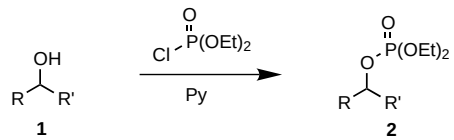
**Abstract**—Phosphate and phosphonate derivatives of chiral alcohols show enhanced resolution by HPLC using a chiral support. Labile derivatives were also prepared that allow separation and recovery of the corresponding alcohol after basic hydrolysis.


## 1. Introduction

HPLC using a chiral support is a powerful analytical method for measuring enantioenrichment.[1] In cases where sufficient resolution is obtained, chiral HPLC may also be used for the isolation of useful quantities of enantiopure materials.[2] For poorly resolved mixtures of enantiomers, conversion to more readily resolved derivatives is often possible.[3] While this approach has lost some favor in recent years as the ability to separate underivatized enantiomers has grown, derivatization can still be a valuable tool for solving difficult or challenging problems. Herein, we report the generally improved resolution of some alcohol enantiomers as their phosphate or phosphonate derivatives.

## 2. Results and discussion

During the course of one of our projects it was observed that chiral molecules containing a phosphonate moiety are well separated by HPLC on the Chiralpak® AD column. This observation suggested that phosphate derivatives **2** (Scheme 1) of alcohols could potentially be useful for evaluating the enantiopurity of alcohols. Therefore, a series of phosphate analogs **2a**–**2i** of alcohols **1a**–**1i** was prepared and then analyzed on a Chiralpak AD analytical column using *iso*-propyl alcohol in hexane as the mobile phase (Table 1). In most of the cases studied, superior resolution was observed with the phosphate derivative compared to the alcohol itself. Benzylic phosphates showed remarkable baseline separation as exemplified in Fig. 1 for compound **2a**. Separation was also observed in difficult cases such as 2-octanol **1h**. The phosphate derivative **2h** of 2-octanol provided a resolution of 0.6. In the case of compounds **2f** and **2g** no resolution was achieved. For comparison the pivaloyl derivatives[4] were also prepared and subjected to the same HPLC conditions. In all cases resolution was found to be lower than the corresponding phosphates except in the cases of pivalates **10c** and **10i**.




**Scheme 1.**

To verify whether this unique separation was specific to phosphate analogs or could also be extended to molecules containing a phosphonate group, the benzylphosphonate analogs of alcohols **1a**, **1d** and **1e** were also prepared. The (4-bromomethylbenzenephosphonate alkylating agent **5** was synthesized as described in Scheme 2 from 4-iodotoluene **3**.[5] The derivatized alcohols **6a**, **6d** and **6e** were then injected onto HPLC under the previously described conditions. Very good resolution was obtained in the cases of **6d** and **6e**. Therefore, even though the phosphonate group is remote from the stereogenic center, it can still provide good separation.

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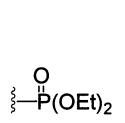
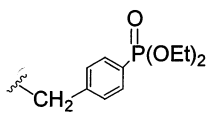
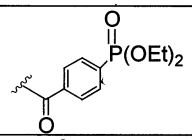
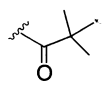
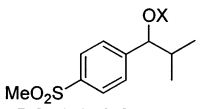
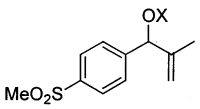
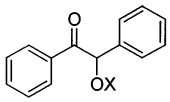
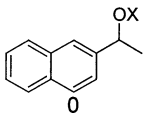
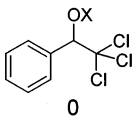
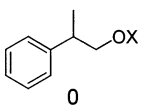
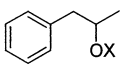
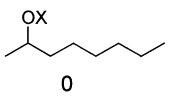
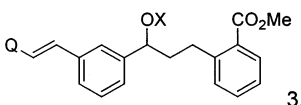
**Table 1.** Resolution parameters for racemic compounds on AD column with 10% *iso*-propanol/hexane[12,13]

| X = | H |  |  |  |  |
|---|---|---|---|---|---|
| | **1** | **2**[7] | **6**[8] | **9**[9] | **10** |
| | | | $K'_1$, α, Rs | | |
| **a** |  5.8, 1.1, 0.6 | 5.2, 1.6, 2.4 | 0 | 5.0, 1.2, 1.7 | 1.7, 1.5, 2.1 |
| **b** |  5.4, 1.1, 0.9 | 7.3, 1.3, 2.8 | nd | 8.7, 1.3, 2.3 | 1.7, 1.3, 1.6 |
| **c** |  4.8, 1.3, 1.6 | 3.1, 1.4, 2.8 | nd | 7.4, 1.5, 3.2 | 1.0, 2.3, 4.6 |
| **d** |  0 | 1.7, 1.7, 1.6 | 4.5, 2.2, 8.1 | 6.5, 0.5, 0.8 | 0.3, 1.6, 0.9 |
| **e** |  0 | 1.2, 1.4, 1.6 | 1.4, 1.5, 1.5 | 1.5, 1.1, 0.6 | 0.1, 2.8, 1.3 |
| **f** |  0 | 0 | nd | 2.0, 1.1, 0.7 | 0 |
| **g** |  0 | 0 | nd | 2.6, 1.1, 0.6 | 0 |
| **h** |  0 | 0.8, 1.2, 0.6 | nd | 1.3, 1.1, 0.6 | 0 |
| **i** |  8.0, 1.1, 0.6 | 3.9, 1.3, 1.5 | nd | 5.9, 1.6, 2.3 | 5.3, 1.6, 3.5 |

Q = 6-chloroquinoline

These results led us to prepare labile derivatives of alcohols containing a phosphonate group. The 4-phosphonate benzoic acid **8** was prepared as described in Scheme 3.[6] The alcohol was then treated with the acid chloride in $CH_2Cl_2$ with pyridine in the presence of DMAP. In all cases the observed resolution was superior than for the corresponding alcohols even with the alcohols **1f** and **1g** where no separation was observed with phosphate analogs.

Improved resolution of the enantiomers of phosphate and phosphonate derivatives is not exclusive to the AD column or to the technique of HPLC. We observed improved resolution of the enantiomers of phosphate and phosphonate derivatives using both HPLC and supercritical fluid chromatography (SFC) on several additional chiral supports including Chiralpak AS, Chiralcel OJ and Whelko columns.

To be useful for preparative chromatography, a derivatizing agent must be easily removed. Since the labile phosphonate derivatives gave good resolution, we decided to apply this method to the resolution of the enantiomers of chiral alcohol, **1b**, a precursor used in

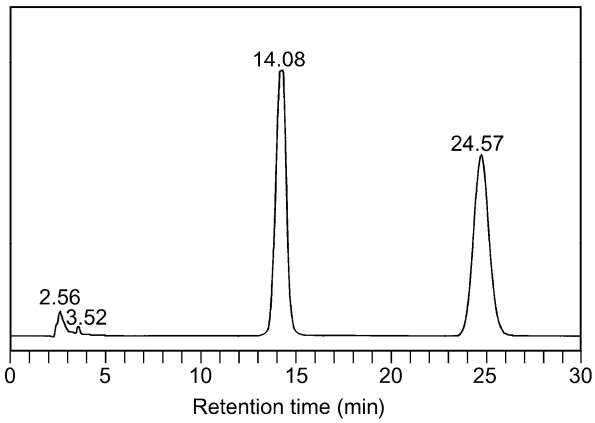
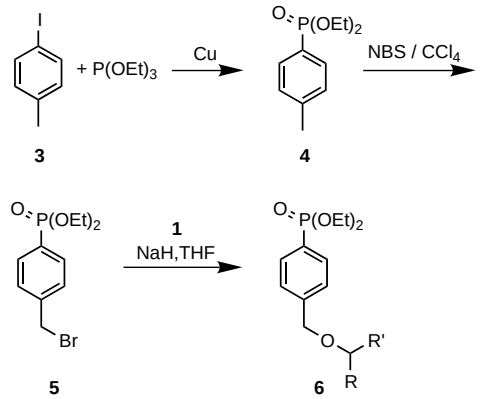
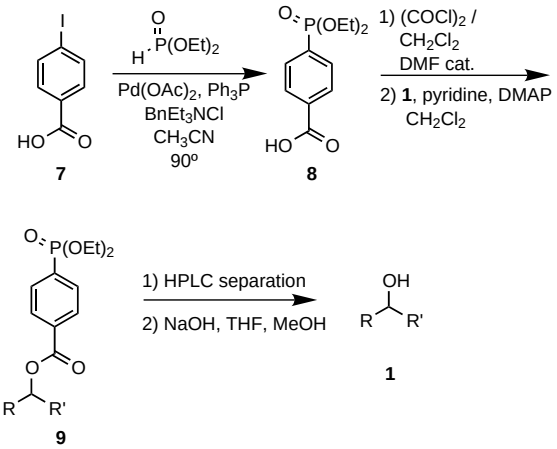



**Figure 1.** HPLC Chromatogram of compound **2a** on Chiralpak® AD column 10% *iso*-propanol/hexane.




**Scheme 2.**




**Scheme 3.**

the synthesis of one of our cyclooxygenase-2 inhibitors. The benzoylphosphonate derivative **9b** was prepared on 2 g scale in 60% yield. Preparative chromatography on 0.5 g scale afforded the individual enantiomers of **9b** in greater than 98% e.e. with excellent recovery.[10] The corresponding alcohols were regenerated in 83% yield without loss of enantioenrichment by basic hydrolysis with aqueous NaOH.[11]

## 3. Conclusion

In summary, improved chromatographic resolution of phosphate and phosphonate derivatives of chiral alcohols was demonstrated. The development of a labile phosphonate derivatizing reagent allowed us to separate appreciable quantities of enantiopure material and to regenerate the corresponding alcohols after basic hydrolysis. For now, the nature of the enhanced resolution of the enantiomers of phosphate and phosphonate derivatives remains unclear.

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7. The phosphate derivatives **2** were prepared as follows: to a 4 M solution of the alcohol in pyridine, cooled at 0°C was added diethyl phosphochloridate (1.3 equiv.). The reaction mixture was allowed to warm to room temperature and stirred for 2 h. The reaction mixture was partitioned between water and ether. The organic phase was washed with 2N aqueous HCl and saturated aqueous $NaHCO_3$. The organic phase was dried over $Na_2SO_4$ and evaporated to dryness. The residue was purified by flash chromatography using as eluent hexane/ethyl acetate 1:1 to afford the desired phosphate derivative.
8. The methylphenyl phosphonate derivatives **6** were prepared as follows: to a solution of diethyl 4-methylphenylphosphonate **4**[5] (4.00 g, 17.4 mmol) in $CCl_4$ (40 mL) was added NBS (3.10 g, 17.4 mmol) and a catalytic amount of benzoyl peroxide. After photolysis for a period of 2 h, the reaction mixture was diluted with hexane (40 mL) and filtered over celite. Purification after evaporation of the residue using flash chromatography

with hexane/ethyl acetate 1:1 afforded 3.93 g (73%) of compound **5**. $^1$H NMR (500 MHz, acetone-$d_6$) $\delta$ 7.81 (m, 2H), 7.78 (m, 2H), 4.73 (s, 3H), 4.10 (m, 4H), 1.29 (t, 6H). $^{13}$C NMR (125.6 MHz, acetone-$d_6$) $\delta$ 143.05, 132.39, 129.72, 129.72, 62.06, 32.70, 16.15 HRMS calcd for $C_{11}H_{17}BrO_3P$ $(M+H)^+$: 307.0099, found: 307.0097.
To a solution of the alcohol in THF and cooled at 0°C was added NaH. The mixture was stirred for 15 minutes. Then diethyl [4-(bromomethyl)phenyl]phosphonate **5** (1.5 equiv.) was added and the solution was allowed to warm to room temperature and stirred for 1 h. The reaction was poured in water and extracted with ethyl acetate. The organic phase was dried and evaporated to dryness. The residue was purified by flash chromatography using hexane/ethyl acetate (30:70) to afford desired methyl phenyl phosphonate **6**.

9. The ester analogs **9** were prepared as follows: to a solution of 4-(diethoxyphosphoryl)benzoic acid **8**[6] in $CH_2Cl_2$ cooled at 0°C was added a catalytic amount of DMF followed by oxalyl chloride 1.2 equiv. The reaction mixture was allowed to warm to room temperature and stirred for 0.5 h. The reaction was then cooled to 0°C and pyridine (2 equiv.) followed by the alcohol were added. The reaction mixture was allowed to warm to room temperature and stirred overnight. The reaction was quenched with water and extracted with ethyl acetate. The organic phase was washed with 2N aqueous HCl solution twice and then with saturated aqueous $NaHCO_3$. The organic extracts were dried and evaporated to dryness. The residue was purified by flash chromatography with hexane/ethyl acetate (20:80) to afford the desired benzoate derivative **9**.
10. The **9b** enantiomers were separated on a Chiralpak® column (5×50 cm) using 40% EtOH in hexane to 80% EtOH in hexane with a flow rate of 60 mL/min; $\lambda$ 270 nM; more mobile enantiomer $[\alpha]_D$ +45.0 (*c* 0.86, acetone); less mobile enantiomer $[\alpha]_D$ −44.2 (*c* 0.6, acetone). $^1$H NMR (500 MHz, acetone-$d_6$) $\delta$ 8.29 (m, 2H), 8.01 (d, 2H), 7.96 (m, 2H), 7.81 (d, 2H), 6.59 (s, 1H), 5.34 (s, 1H), 5.14 (s, 1H), 4.14 (m, 4H), 3.15 (s, 3H), 1.79 (s, 3H), 1.31 (t, 6H). $^{13}$C NMR (125.6 MHz, acetone-$d_6$) $\delta$ 164.40, 144.83, 143.01, 141.58, 135.90, 134.47, 133.49, 132.33, 129.85, 128.00, 114.17, 78.98, 62.34, 43.78, 18.17, 16.18. HRMS calcd for $C_{22}H_{28}O_7PS$ $(M+H)^+$: 467.1293, found: 467.1295.
11. The resolved benzoate derivatives **9b** (0.10 g,) were dissolved in THF/$CH_3OH$ (2:1, 2 mL) and treated with 2 equiv. of NaOH at room temperature for 1 h. The mixtures were acidified with HCl 1N and extracted with ethyl acetate. The extracts were dried over $Na_2SO_4$ and evaporated to dryness. The residue was purified by flash chromatography using as eluent hexane/ethyl acetate 30% to afford both of the desired alcohols 0.040 g or 83%. The optical rotation for alcohols **1b** are −39.6 (*c* 0.5 acetone) and +41.9 (*c* 0.5, acetone) from more mobile and less mobile esters, respectively. Data for alcohol from more mobile esters: $^1$H NMR (500 MHz, acetone-$d_6$) $\delta$ 7.92 (2H, d), 7.68 (2H, d), 5.31 (1H, d), 5.22 (1H, s), 4.92 (1H, s), 4.81 (1H, d), 3.12 (3H, s), 1.59 (s, 3H). $^{13}$C NMR (125.6 MHz, acetone-$d_6$) $\delta$ 149.87, 147.62, 140.43, 127.45, 127.42, 111.72, 76.79, 43.89, 17.17. HRMS calcd for $C_{11}H_{15}BrO_3S$ $(M+H)^+$: 227.0741, found: 227.0741.
12. (a) Column: 0.46×25 cm; (b) $K'_1$: (Capacity factor of more mobile enantiomer)=(retention time of more mobile enantiomer−dead time/dead time; (c) $\alpha$ (separation factor)=(capacity factor of less mobile enantiomer/$K'_1$; (d) $R_s$ (resolution factor)=2×(difference of retention times of less and more mobile enantiomers/sum of the band width of the two enantiomer peaks).
13. All new compounds have been fully characterized spectroscopically and elemental composition established by high-resolution mass spectroscopy or combustion analysis.