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Convenient Synthesis of Optically Active α-Hydroxyphosphinic Acids

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ABSTRACT: *The reaction of O-menthyl phenylphosphonite* **1** *with aromatic aldehydes in the presence of Me_3SiCl provided the O-menthyl α-hydroxyphosphinates* **2**. *Acidic hydrolysis of* **2** *gave the corresponding α-hydroxyphosphinic acids* **3**. *The (+)-enantiomer of* **3a** *and* **3b**, *adduct of benzaldehyde and 4-methylbenzaldehyde respectively, were obtained via multiple recrystallization. The absolute configuration of (+)-***3a** *was determined as S by X-ray crystallography.* © 2003 Wiley Periodicals, Inc. Heteroatom Chem 14:312–315, 2003; Published online in Wiley InterScience (www.interscience.wiley.com). DOI 10.1002/hc.10150

INTRODUCTION

α-Hydroxyphosphonic acids are compounds with wide ranging biological activities. The addition of compounds containing a P—H bond (such as dialkyl phosphites) to aldehydes or ketones, the Pudovik reaction, is the most versatile pathway to these compounds [1]. This reaction mainly proceedes in the presence of a basic catalyst [2] or a metal fluoride [3]. Only a few examples of the acid-catalyzed or noncatalytic Pudovik reaction have been reported. The reaction is very sluggish without a catalyst. The absolute configuration of the α-carbon of α-hydroxyphosphonic acid derivatives has an important influence on their biological activities. Hence, the enantioselective synthesis of these compounds has attracted much attention of organic chemists [4]. Three methods were involved in the synthesis of optically active α-hydroxyphosphonic acids via the enantioselective Pudovik reaction. Firstly, the chiral catalysts, such as quinine [5], chiral lewis acid containing titanium [6], and chiral metal alkoxides [7], etc. were used. Secondly, chiral aldehydes reacted with dialkyl phosphite [8]. Additionally, chiral dialkyl phosphite or chiral phosphorous diamide reacted with aldehydes [9]. α-Hydroxyphosphinic acids are also an important class of biologically active substance. However, to the best of our knowledge, few reports dealt with the synthesis of α-hydroxyphosphinic acids.

Recently, we discovered that optically active α-hydroxyphosphinic acids could be obtained via the reaction of *O*-menthyl phenylphosphonite with aromatic aldehydes in presence of Me_3SiCl. This investigation provided a new convenient method for the synthesis of optically active α-hydroxyphosphinic acids.

RESULTS AND DISCUSSION

The reaction of *O*-menthyl phenylphosphonite **1** with aromatic aldehydes in the presence of Me_3SiCl afforded the *O*-menthyl α-hydroxyphosphinates **2**. There exist two chiral centers (α-C and P) in **2**. Therefore, four diastereomers are possible. They could be clearly observed in the ^{31}P NMR spectra. Attempts

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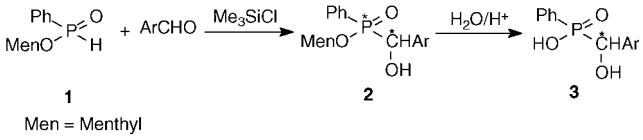
TABLE 1 Data of **2**

					Elemental Analysis (Calc./Found)		
2	*Ar*	*m.p. (°C)*	*$[\alpha]_D^{20}$ (c 1, $CHCl_3$)*	*Yield (%)*	*C*	*H*	*N*
a	C_6H_5	149–182	−31.1	73.1	71.48/71.30	8.08/8.07	
b	4-MeC_6H_4	164–174	−23.0	74.8	71.98/72.09	8.24/7.95	
c	3-$O_2NC_6H_4$	105–184	−42.2	83.9	64.02/63.90	7.71/7.45	3.20/3.06
d	2,4-$Cl_2C_6H_3$	143–190	−35.5	88.8	60.67/60.54	6.43/6.20	
e	4-ClC_6H_4	148–195	−18.0	75.4	65.63/65.56	7.18/6.97	
f	2-Naphthyl	177–188	−29.0	88.0	74.29/74.04	7.62/7.35	

to separate the four isomers via crystallization or column chromatography on silica gel failed. Acidic hydrolysis of **2** provided the corresponding α-hydroxyphosphinic acids **3**, which retain only the asymmetric α-carbon. Experimental data of **2** and **3** are summarized in Tables 1–4.



The ^{31}P NMR spectra (δ value and ratio of peak area) of the crude products **2** were similar to those of the products after recrystallization or column chromatography. The ee values of **3** could not be determined by ^{31}P NMR spectroscopy as the addition of a chiral amine, such as (−)-α-phenylethylamine, cinchonine, to transform the acid into a pair of diastereomeric salts did not cause a splitting of the signals. The use of chiral HPLC or GC to separate of the two enantiomers of acid **3** was unsuccessful. Finally, the classic method was used to determine the enantioselectivity of this reaction: Multiple recrystallization of the acids **3a** and **3b** till their melting points and specific rotation values were no more changed. Then the multiply recrystallized products **3a** and **3b** could be considered as a single enantiomer. From their specific rotation compared to those of the crude products **3a** and **3b**, the enantioselectivity (ee value) of **3a** and **3b** could be determined as 10.3% and 18.2%, respectively. Thus only a low enantioselectivity was realized in the reaction of **1** with aromatic aldehydes.

X-Ray crystallography was used to confirm the configuration of the recrystallized enantiomerically pure (+)-**3a**. Its molecular structure is shown in Fig. 1. The dihedral angle between the two benzene rings is 4.6°. The distance of atom P to the benzene ring plane (C(1)–C(2)–C(3)–C(3)–C(4)–C(5)–C(6)) is −0.0191 Å. The packing diagram of (+)-**3a** in a unit cell is shown in Fig. 2. The interatomic distance for O(3)–H(1)···O(1) (0.5-x, 1-y, 1-z) is 2.748 Å, which shows that there is a hydrogen bond between O(3) and O(1) and it is also the important force for the packing. The flack x parameter is −0.0001 and the four groups (or atoms) connected to C(7) are shown in Fig. 1, so the absolute configuration of the α-carbon (C(7)) can be determined as *S* [10]. CCDC 198717 contains the supplementary crystallographic data for this paper. These data can be obtained free of charge via www.ccdc.cam.ac.uk/conts/retrieving.html (or from

TABLE 2 NMR Data of **2**

2	*δ ^{31}P*	*δ ^{1}H NMR (J in Hz)*
a	36.94, 36.66, 35.74, 34.80	0.40–2.37 (m, 18H), 3.96–4.50 (m, 2H), 4.96–5.22 (m, 1H, $^2J_{PH} = 7.89$), 7.04–7.83 (m, 10H)
b	36.94, 36.69, 35.97, 34.89	0.42–1.92 (m, 18H), 2.30 (d, 3H), 3.20 (br, 1H), 4.00–4.48 (m, 1H), 4.92–5.10 (m, 1H, $^2J_{PH} = 6.26$), 6.92–7.88 (m, 9H)
c	35.97, 35.50, 34.79, 34.05	0.40–2.05 (m, 18H), 3.64 (br, 1H), 4.00–4.36 (m, 1H), 5.06–5.27 (m, 1H, $^2J_{PH} = 7.20$), 7.18–8.26 (m, 9H)
d	37.50, 37.03, 35.29, 34.24	0.44–2.03 (m, 18H), 3.39 (br, 1H), 4.05–4.52 (m, 1H), 5.49–5.68 (m, 1H, $^2J_{PH} = 5.22$), 7.08–7.94 (m, 8H)
e	37.84, 37.22, 35.74, 34.70	0.40–2.37 (m, 18H), 3.20 (br, 1H), 4.00–4.46 (m, 1H), 4.95–5.14 (m, 1H, $^2J_{PH} = 6.26$), 7.15–7.80 (m, 9H)
f	36.50, 36.13, 35.60, 34.71	0.42–2.15 (m, 18H), 3.93 (br, 1H), 3.96–4.43 (m, 1H), 5.14–5.25 (m, 1H, $^2J_{PH} = 6.26$), 7.04–7.83 (m, 12H)

TABLE 3 Data of **3**

					Elemental Analysis (Calc./Found)		
3	*m.p. (°C)*	*$[\alpha]_D^{20}$ (c 1, MeOH)*	*Yield (%)*	*ee[a] (%)*	*C*	*H*	*N*
a	195–199	+6.3	79.7	10.3	62.90/63.03	5.28/5.38	
b	184–188	+11.6	58.9	18.2	64.12/64.10	5.76/5.83	
c	181–185	+2.7	87.7		53.25/53.14	4.12/3.90	4.77/4.75
d	177–180	+2.6	46.4		49.24/49.04	3.50/3.73	
e	200–204	+7.7	84.2		55.24/55.18	4.28/4.11	
f	187–190	+4.8	36.7		68.46/68.25	5.07/5.17	

[a]From the specific rotation value compared with those of multiply recrystalled enantiomeric pure (+)-**3a** and (+)-**3b**, respectively. For (+)-**3a**: m.p. 210–213°C; $[\alpha]_D^{20}$ + 61.3 (*c* 1, MeOH). For (+)-**3b**: m.p. 197–199°C; $[\alpha]_D^{20}$ + 66.8 (*c* 1, MeOH).

the Cambridge Crystallographic Data Centre, 12, Union Road, Cambridge CB2 1EZ, UK: fax: +44 1223 336033: or deposit@ccdc.cam.ac.uk).

In contrast to the Pudovik reaction (see Introduction Section), in the reaction of *O*-menthyl phenylphosphonite **1** with aromatic aldehydes, basic catalysts, such as Et_3N, pyridine, DCM (*N*,*N*′-dicyclohexyl-4-morpholinecaboxamidine), EtONa, and BF_3Et_2O could not accelerate the reaction. It was found that the addition of Me_3SiCl did markedly accelerate this reaction. While the addition product could be detected only after stirring for 24 h without Me_3SiCl, large amounts of product was formed after 0.5 h in the presence of Me_3SiCl.

An acceleration effect of Me_3SiCl on the Pudovik reaction is not reported in the literature. The reaction mechanism is still unclear. At first we thought this reaction may proceed in two steps. The first step is the formation of *O*-menthyl *O*-trimethylsilyl phenylphosphonite (**4**) via the reaction of **1** with Me_3SiCl. Then, the reaction of in situ formed phosphonite **4** with the aldehydes via a Abramov reaction [11] provided the products **2**. Nevertheless, no new signal of the phosphonite **4** was observed in the ^{31}P NMR spectroscopy even after stirring the mixture of phosphonite **1** and Me_3SiCl for 24 h. Therefore, this reaction seems unlikely to take place via the phosphonite **4**. Further investigations are necessary to interpret the mechanism of this reaction.

TABLE 4 NMR Data of **3**

3	*δ ^{31}P*	*δ ^{1}H NMR (J in Hz)*
a	36.47	4.74 (br, 2H), 4.87 (d, 1H, $^2J_{PH}$ = 10.82), 7.23–7.76 (m, 10H)
b	39.44	2.26 (s, 3H), 4.97 (br, 2H), 4.97 (d, 1H, $^2J_{PH}$ = 8.10), 7.25–7.77 (m, 9H)
c	38.18	4.90 (br, 2H), 5.17 (d, 1H, $^2J_{PH}$ = 11.34), 7.36–8.24 (m, 9H)
d	37.81	4.90 (br, 2H), 5.48 (d, 1H, $^2J_{PH}$ = 9.73), 7.26–7.78 (m, 8H)
e	38.77	4.90 (br, 2H), 5.02 (d, 1H, $^2J_{PH}$ = 10.71), 7.23–7.67 (m, 9H)
f	39.29	3.30 (br, 2H), 5.19 (d, 1H, $^2J_{PH}$ = 11.48), 7.30–7.89 (m, 12H)

EXPERIMENTAL

^1H and ^{31}P NMR were recorded in $CDCl_3$ or CD_3OD on a Bruker AC-P200 instrument, using TMS as an internal standard for ^1H NMR and 85% H_3PO_4 as an external standard for ^{31}P NMR. Specific rotations were measured on a Perkin-Elmer 241MC polarimeter. Elemental analyses were conducted on a Yanaco CHN Corder MT-3 automatic analyzer. Melting points were determined on a MP-500 melting point apparatus. All temperatures are uncorrected. PCl_3 was used after redistillation.

Preparation of Compound **1**

To a solution of (−)-menthol (46.9 g, 0.30 mol) in 20 ml CH_2Cl_2 was added dropwise phenylphosphorous dichloride (26.9 g, 0.15 mol) at 0–5°C under nitrogen atmosphere. The resulting mixture was stirred for 12 h at room temperature. After the removal of the solvent, the crude product was distilled in vacuo to remove menthyl chloride (62–68°C/93 Pa). The remaining oil was the *O*-menthyl phenylphosphonite **1** (41.9 g), 99.6% yield. n_D^{20} 1.5154, $[\alpha]_D^{16}$ −56.0 (*c* 1, THF). ^{31}P NMR (δ, $CDCl_3$):

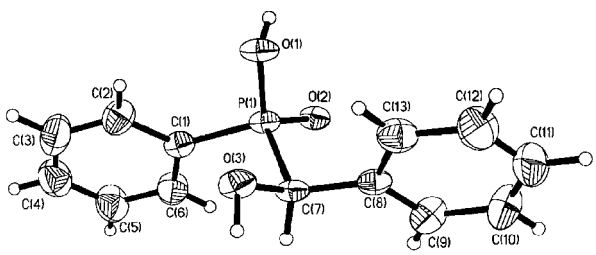


FIGURE 1 Molecular structure of (+)-**3a**.

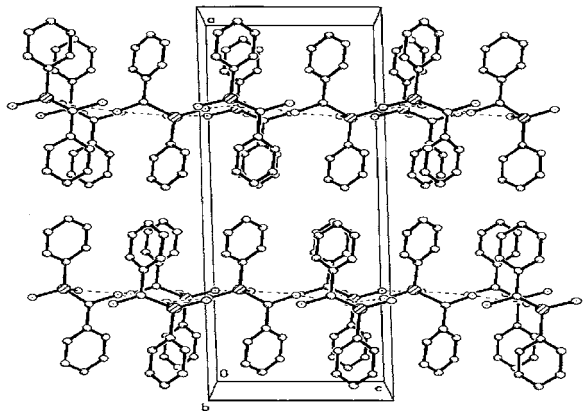


FIGURE 2 Packing diagram of (+)-**3a** in a unit cell.

21.36 (s, 51.8%), 24.56 (s, 48.2%). ^{1}H NMR (δ, $CDCl_3$): 0.63–2.43 (m, 18H), 4.16–4.43 (m, 1H), 7.66 (d, 1H, $^1J_{PH} = 552$ Hz), 7.36–7.93 (m, 5H). HRMS: [M^+] 280.15944 (Calc. 280.15922).

Reaction of **1** *with Aromatic Aldehydes (General Procedure)*

To a mixture of **1** (2.80 g, 10 mmol) and 3.5 ml Me_3SiCl was added dropwise aldehyde (10 mmol) at 0°C. The resulting mixture was stirred at room temperature. After 1 h white floccule appeared; 2 ml anhydrous CH_2Cl_2 was added and the mixture was stirred till the aldehyde disappeared (monitored by TLC). After the removal of the solvent, the crude product was purified by column chromatography (silica gel 200–300 mesh, 1:1 petroleum ether/ethyl acetate as the eluent) to afford an oily product. Recrystallization from petroleum ether/ethyl acetate (1:1) gave **2** as a white solid.

Hydrolysis of ***2*** *(General Procedure)*

A mixture of **2** (10 mmol), 30 ml 6 N HCl, and 80 ml 1,4-dioxane was stirred at 80°C until **2** disappeared (monitored by TLC or ^{31}P NMR). After the removal of the solvent, the crude product was washed with chloroform (3 × 10 ml) to provide α-hydroxyphosphinic acids **3** as white solid.

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