Convenient Procedure for the Preparation of Optically Active Phosphonates Using the Chirality of (*S*)-(−)-α-Methylbenzylamine

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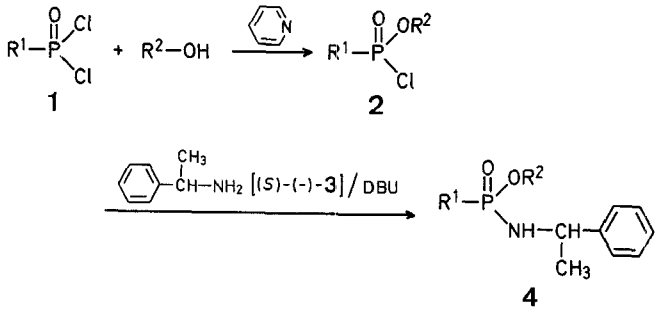
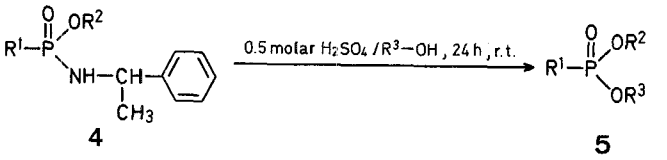
The search for a practical method for the preparation of optically active phosphonates has been a subject of considerable recent interest[1]. To our knowledge, three types of methods have been reported for the preparation of optically active phosphonates. One method involves separation of the diastereomeric complex of methyl 1-naphthylmethanephosphonate and (−)-α-(2,4,5,7-tetranitro-9-fluorenylideneamino-oxy)-propanoic acid[2], which is limited to a special case. The other methods consist of the separation of diastereomeric acyclic or cyclic phosphonamidates, followed by acid- and/or base-catalyzed alcoholysis. Although L-proline ethyl ester was used as the chiral moiety of an acyclic phosphonamidate[3], it is too labile to handle at room temperature. On the other hand, diastereomeric cyclic phosphonamidates were prepared with suitably substituted bifunctional carbohydrates[4] or with (−)-ephedrine[5]. In these cases, after the fractionation of the diastereomeric isomers, stereoselective and stereospecific cleavage of P—O and P—N bonds is necessary to obtain the chiral phosphonates. The stereospecificity of the P—O and P—N bond cleavage varies with both the substrate and the reactant. Especially, many difficulties arise in the alcoholysis of the P—O bonds of these compounds depending on the kind of alcohol.

Now, we report a new and convenient method for the preparation of optically active phosphonates using (*S*)-(−)-α-methylbenzylamine **3**, which is an easily available and stable chiral starting material[5]. Phosphonochloridate **2**, prepared from the phosphonic dichloride **1** and an alcohol, was reacted with **3** in tetrahydrofuran (THF) at room temperature in the presence of diazabicycloundecene (DBU), followed by purification by chromatography to afford a diastereomeric mixture of the corresponding phosphonamidate **4** in 64–77% yield.



The isomers of **4** can be easily separated by fractional crystallization with a mixture of benzene/hexane (1:5) at room temperature. The physical data and yields of each isomer **4a–c** are given in Table 1. Acid-catalyzed alcoholysis of **4a–c** at room temperature for 24 h afforded stereoselectively the corresponding phosphonates **5** in 46–62% yields.



The physical data of products **5a–i** are shown in Table 2. The enantiomeric purities and the absolute configurations were determined according to Refs.[4,7] using Eu(hfc)$_3$.

Phosphonamidates 4; General Procedure:

(*S*)-(−)-α-Methylbenzylamine (**3**; 60 mmol) and DBU (60 mmol) in tetrahydrofuran (20 ml) is added slowly dropwise to a stirred solution of phosphonochloridate **2** (60 mmol) in tetrahydrofuran (20 ml) at 0 °C. The mixture is stirred for an additional 2 h, filtered, and the solvent is evaporated under reduced pressure to give the crude product **4** which is purified by silica gel column chromatography, eluting with chloroform.

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Table 1. *N*-(α-Methylbenzyl)-phosphonamidates **4a–c**

Product No.	R^1	R^2	Yield [%][a]	m.p. [°C]	$[\alpha]_D^{20}$ (*c*, $CHCl_3$)	Molecular formula[b]	^{1}H-N.M.R. ($CDCl_3$) δ [ppm]
4a	C_6H_5	C_6H_5	31	151–152°	−39.5° (1.79)	$C_{20}H_{20}NO_2P$ (337.4)	1.40 (d, 3H, J=7.0 Hz); 4.3 (m, 1H); 6.9–7.9 (m, 15H)
4a′	C_6H_5	C_6H_5	20	124–126°	−51.6° (2.02)	$C_{20}H_{20}NO_2P$ (337.4)	1.40 (d, 3H, J=7.0 Hz); 4.3 (m, 1H); 6.8–7.9 (m, 15H)
4b	C_6H_5	$C_6H_5CH_2$	24	159–160°	−55.8° (2.06)	$C_{21}H_{22}NO_2P$ (351.4)	1.42 (d, 3H, J=6.6 Hz); 4.4 (m, 1H); 5.02 (d, 2H, J=7.1 Hz); 7.2–7.9 (m, 15H)
4b′	C_6H_5	$C_6H_5CH_2$	21	105–106°	−65.6° (2.02)	$C_{21}H_{22}NO_2P$ (351.4)	1.37 (d, 3H, J=6.6 Hz); 3.9–4.3 (m, 2H); 4.62 (dd, 1H, J=6.3 Hz, 12.2 Hz); 4.99 (dd, 1H, J=6.8 Hz); 7.1–7.9 (m, 15H)
4c	CH_3	C_6H_5	35	127–128°	+4.05 (2.02)	$C_{15}H_{18}NO_2P$ (275.3)	1.41 (d, 3H, J=16.1 Hz); 1.55 (d, 3H, J=6.8 Hz); 4.5 (m, 1H); 7.0–7.3 (m, 10H)
4c′	CH_3	C_6H_5	29	91–93°	−112.5 (2.32)	$C_{15}H_{18}NO_2P$ (275.3)	1.31 (d, 3H, J=16.8 Hz); 1.34 (d, 3H, J=6.6 Hz); 4.4 (m, 1H); 7.1–7.3 (m, 10H)

[a] Yield of isolated product based on **3**.
[b] Satisfactory microanalyses obtained: (C ±0.27; H ±0.23; N ±0.26; P ±0.27).

Table 2. Optically Active Phosphonates **5a–i**

Product No.	R^1	R^2	R^3	Yield [%][a]	$[\alpha]_D^{20}$ (*c*, $CHCl_3$)	b.p. [°C]/ torr	Molecular formula[b]	^{1}H-N.M.R. (CCl_4) δ [ppm]
5a	C_6H_5	C_6H_5	CH_3	60	(*R*): +38.1° (1.45)[c]	105–108°/ 0.02	$C_{13}H_{13}O_3P$ (248.2)	3.78 (d, 3H, J=11.0 Hz); 7.0–7.9 (m, 10H)
				58	(*S*): −38.8° (1.24)[c]			
5b	C_6H_5	C_6H_5	C_2H_5	62	(*R*): +34.4° (2.16)[c]	110–115°/ 0.02	$C_{14}H_{15}O_3P$ (262.2)	1.30 (t, 3H, J=7.1 Hz); 4.05 (dt, 2H, J=7.2 Hz); 7.0–7.8 (m, 10H)
				60	(*S*): −33.6° (1.26)[c]			
5c	C_6H_5	C_6H_5	n-C_3H_7	58	(*R*): +29.5° (2.36)[c]	113–117°/ 0.02	$C_{15}H_{17}O_3P$ (276.3)	0.87 (t, 3H, J=7.0 Hz); 1.6 (m, 2H); 3.95 (dt, 2H, J=7.5 Hz, 6.0 Hz); 6.9–7.8 (m, 10H)
				61	(*S*): −29.1° (1.08)[c]			
5d	C_6H_5	$C_6H_5CH_2$	CH_2	55	(*R*): +15.5° (2.15)	110–111°/ 0.02	$C_{14}H_{15}O_3P$ (262.2)	3.71 (d, 3H, J=11.2 Hz); 5.09 (dd, 1H, J=7.8 Hz, 11.7 Hz); 5.17 (dd, 1H, J=7.7 Hz); 7.3–7.9 (m, 10H)
				57	(*S*): −17.3° (0.52)			
5e	C_6H_5	$C_6H_5CH_2$	C_2H_5	52	(*R*): +17.5° (1.45)	112–115°/ 0.02	$C_{15}H_{17}O_3P$ (276.3)	1.25 (t, 3H, J=7.3 Hz); 3.95 (dt, 2H, J=7.5 Hz); 4.80 (dd, 1H, J=8.0 Hz, 12.2 Hz); 5.10 (dd, 1H, J=7.9 Hz); 7.2–7.8 (m, 10H)
				50	(*S*): −18.1° (1.66)			
5f	C_6H_5	$C_6H_5CH_2$	n-C_3H_7	57	(*R*): +11.4° (1.14)	130–133°/ 0.02	$C_{16}H_{19}O_3P$ (290.3)	0.87 (t, 3H, J=7.0 Hz); 1.6 (m, 2H); 3.8 (m, 2H); 4.80 (dd, 1H, J=8.0 Hz, 12.1 Hz); 5.00 (dd, 1H, J=8.0 Hz); 7.2–7.8 (m, 10H)
				53	(*S*): −13.2° (1.12)			
5g	CH_3	C_6H_5	CH_3	51	(*R*): +22.5° (1.30)	73–78°/ 0.02	$C_8H_{11}O_3P$ (186.1)	1.57 (d, 3H, J=17.0 Hz); 3.70 (d, 3H, J=11.0 Hz); 7.07 (s, 5H)
				53	(*S*): −21.8° (1.07)			
5h	CH_3	C_6H_5	C_2H_5	49	(*R*): +11.7° (0.80)	77–78°/ 0.02	$C_9H_{13}O_3P$ (200.2)	1.25 (t, 3H, J=7.5 Hz); 1.48 (d, 3H, J=18.1 Hz); 4.05 (dt, 2H, J=7.8 Hz); 7.05 (s, 5H)
				46	(*S*): −10.9° (1.36)			
5i	CH_3	C_6H_5	n-C_3H_7	48	(*R*): +8.17 (1.15)	82–85°/ 0.02	$C_{10}H_{15}O_3P$ (214.2)	0.85 (t, 3H, J=6.0 Hz); 1.5 (m, 2H); 1.45 (d, 3H, J=18.0 Hz); 3.8–4.2 (m, 2H); 7.05 (s, 5H)
				53	(*S*): −8.65 (1.48)			

[a] Yield of isolated product of ~100% optical purity and ≥95% chemical purity (by G.L.C. and ^{1}H-N.M.R.).
[b] Satisfactory microanalyses obtained: (C ±0.19; H ±0.17; P ±0.19).
[c] These values are smaller than those reported[2], but these phosphonates are in a high state of optical purity by N.M.R.

Separation of Isomers of Phosphonamidates 4 by Fractional Crystallization; General Procedure:
Phosphonamidate **4** (10 g) is dissolved in a boiling solution of benzene/hexane (1:5; 70–100 ml), and the resulting solution is allowed to cool and stored at room temperature. The crystals are collected on a filter and washed with a small volume of the same solvent. These crystals are recrystallized three times from the same solvent to afford an optically pure, high-melting diastereomer. The first mother liquor is concentrated to give a solid, which is recrystallized three times from benzene/hexane (1:7; 50–80 ml). The other optically pure, low-melting diastereomer is thus obtained.

Phosphonates 5; General Procedure:
A solution of phosphonamidate **4** (3 mmol) in 0.5 molar ethanolic sulfuric acid (20 ml) is stirred at room temperature for 24 h. The reaction mixture is diluted with water (40 ml) and extracted with ether (3 × 40 ml). The extract is washed with 5% aqueous sodium hydrogen carbonate solution (2 × 30 ml) and water (2 × 30 ml), dried with sodium sulfate, and concentrated. The residue is distilled under reduced pressure. The purity (≥95%) of the products is checked by G.L.C. (OV-17, 3 mm × 3 m) and N.M.R. spectroscopy.

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