The Phosphonate-Phosphate and Phosphate-Phosphonate Rearrangement and Their Applications, 3[◇]

Enantioselective Deprotonation of Benzyl Phosphates by Homochiral Lithium Amide Bases – Configurational Stability of Benzyl Carbanions with a Dialkoxyphosphoryloxy Substituent and Their Rearrangement to Optically Active α-Hydroxy Phosphonates

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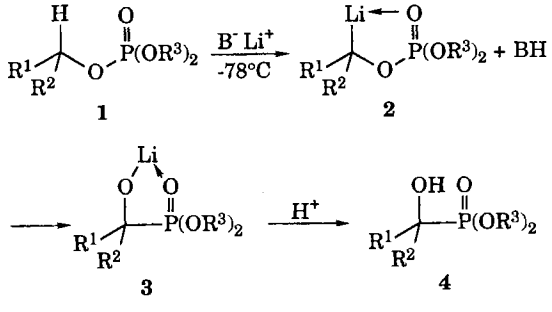
Received March 3, 1995

Key Words: Phosphate-phosphonate rearrangement / Carbanions, benzylic, configurational stability of / Phosphonates / Lithium amides, homochiral

Benzyl dialkyl phosphates are deprotonated enantioselectively by homochiral lithium amides of isopropyl(1-phenylethyl)amine or bis(1-phenylethyl)amine. The short-lived benzylic carbanions formed are virtually configurationally stable relative to the rearrangement to optically active phenylhydroxymethylphosphonates. The enantiomeric excesses are up to 50%. The pro-(*S*) hydrogen is removed by amides having (*S*) configuration. Homochiral diethyl (*S*)-phenyl[D_1]methyl phosphate [(*S*)-**16c**] is deprotonated by both LDA and *n*-BuLi with a high primary kinetic isotope effect ($k_{H/D} \approx 50$) and isomerizes to the corresponding α-hydroxy phosphonate with an enantiomeric excess of up to 85%.

The phosphate-phosphonate rearrangement is an isomerization reaction of carbanions carrying a dialkoxyphosphoryloxy substituent. Phosphates **1** can only be deprotonated by BuLi or LDA, if at least one of the substituents R^1 and R^2 is an aryl[2,3] or alkenyl[4] group (Scheme 1).

Scheme 1



The intermediate carbanion **2** is a short-lived species with the lithium being part of a five-membered chelate ring. It is a dipole-stabilized carbanion[5] comparable in its structure to compounds where the $(R^3O)_2P(O)$ group is replaced by 2,4,6-*i*Pr_3PhC(O)[6] or $R_2NC(O)$[7]. The latter residue was introduced by Hoppe et al. and has proven exceptionally useful for the preparation of configurationally stable carbanions[8]. The intermediate carbanion **2** rearranges at −78 °C as soon as it is formed to the lithiated α-hydroxy phosphonate **3**, which turns into phosphonate **4** during workup of the reaction mixture. The driving force for this process is the stronger O–Li versus C–Li bond, overcompensating the loss in stability by going from a P–O to a P–C bond. The stereochemistry of the reaction was elucidated by using R^1 = Ph and R^2 = Me as substituents. The rearrangement proceeds with retention of configuration at the carbon atom[3]. This result implies that carbanion **2** is configurationally stable for the short period of its existence relative to the migration of the $(R^3O)_2P(O)$ group (microscopic stability). The corresponding carbanion with a diisopropylcarbamoyloxy substituent is configurationally stable in hexane and diethyl ether at −78 °C (macroscopic stability) and can react with a variety of electrophiles[9]. The reverse process, **4** → **1**, is the phosphonate-phosphate rearrangement[1,10]. These isomerizations are related to the Brook- and anti-Brook rearrangement in silicon organic chemistry with configurationally stable silyloxy-substituted carbanions as intermediates[11].

This work was initiated for three reasons. First, we wanted to study the feasibility to generate carbanions of type **2** (R^2 = H) enantioselectively. Second, we intended to unravel the configurational stability of carbanions **2** (R^2 = H). At last, we hoped that these carbanions would give optically active α-hydroxyphenylmethylphosphonates on rearrangement. Some *para*-substituted α-hydroxyphenylmethylphosphonic acids are of pharmacological interest as inhibitors of inositol monophosphatase[12]. Three different phosphoric esters, benzyl dimethyl, benzyl diethyl, and benzyl diisopropyl phosphate, were studied in greater detail.

[◇] Part 2: Ref.[1].

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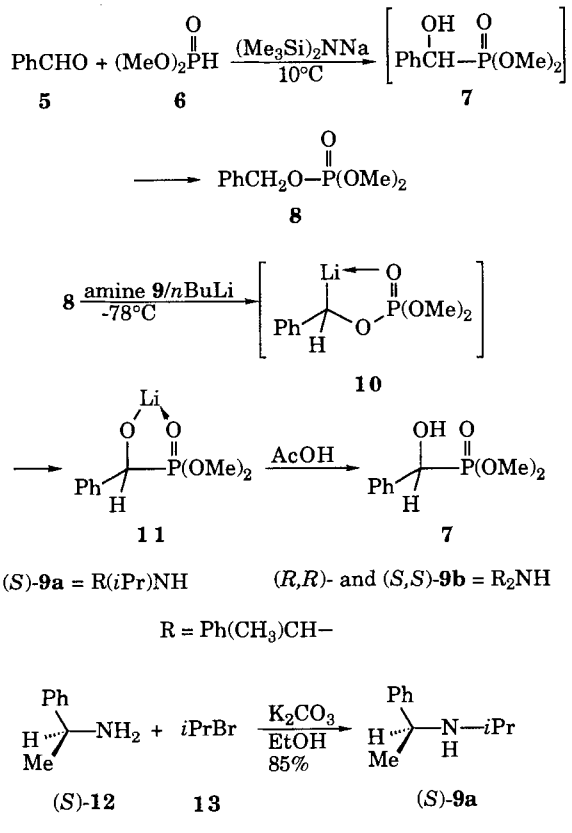
Homochiral Base-Induced Phosphate-Phosphonate Rearrangement

The first substrate used was benzyl dimethyl phosphate (**8**) which was prepared by addition of hydrogen dimethyl phosphite (**6**) to benzaldehyde followed by a phosphonate-phosphate rearrangement (Scheme 2). Phosphate **8** was allowed to react at −78 °C with homochiral lithium amide bases[13] generated from the corresponding amine and *n*-butyllithium. Three readily available homochiral amines, (*S*)-isopropyl(1-phenylethyl)amine [(*S*)-**9a**] and (*R*,*R*)- and (*S*,*S*)-bis(1-phenylethyl)amine [(*R*,*R*)- and (*S*,*S*)-**9b**] were explored for their applicability to deprotonate benzyl phosphates enantioselectively. The synthesis of the known secondary amine (*S*)-**9a** was improved (Scheme 2)[14].

Scheme 2



A mixture of (*S*)-1-phenylethylamine, isopropyl bromide, and potassium carbonate was refluxed in ethanol for one week. The isolated product contained up to 5% of the starting amine which was removed by formation of the hydrochloride.

When phosphate **8** was treated with 1.5 equiv. of the lithium salt of (*S*)-**9a** in diethyl ether for one hour and the reaction quenched with acetic acid, the hydroxy phosphonate **7** was isolated in 26% yield and had $[\alpha]_D^{20} = -5.9$ (entry 1, Table 1). Comparison with literature data revealed that this specific rotation corresponds to an ee of 13%[15,16]. Furthermore, the hydroxy phosphonate is enriched in the (*S*) enantiomer. When the reaction was conducted in THF under otherwise identical conditions, the yield increased to 35% and the ee to 28% (entry 2). When the C_2-symmetric amine (*R*,*R*)-**9b** was used, the yield remained low (30%), but the ee of the product having a positive sign of optical rotation could be raised to 52% (entry 3). The low yields obtained in the three experiments might result from dealkylation at the phosphorus atom. These results demonstrate that homochiral lithium amides are useful bases for the enantioselective formation of optically active α-hydroxyphenylmethylphosphonates. The yield can be improved by changing substituents at the phosphorus atom.

Table 1. Phosphate-phosphonate rearrangement of dialkyl benzyl phosphates **16**

Entry	Start.mat.	Solvent	Base / mmol[a]	Product	Yield (%)	$[\alpha]_D^{20}$(c)[b]	ee (%)[c]
1	**8**	Et_2O	**9a** / 1.5	**7**	26	-5.9 (1.4)	13
2	**8**	THF	**9a** / 1.5	**7**	35	-13.0 (1.5)	28
3	**8**	THF	(*R*,*R*)-**9b** / 1.5	**7**	30	+23.6 (1.3)	52
4	**16a**	Et_2O	**9a** / 1.5	**19a**	47	-10.5 (1.1)	27
5	**16a**	THF	**9a** / 1.5	**19a**	63	-8.9 (1.5)	23
6[d]	**16a**	THF	(*R*,*R*)-**9b** / 1.5	**19a**	60	+14.2 (1.4)	37
7	**16a**	Et_2O	**9a** / 4.0	**19a**	58	-13.9 (5.9)	36
8[e]	**16a**	Et_2O	**9a** / 4.0	**19a**	46	-9.9 (4.7)	25
9	**16a**	Toluene	**9a** / 2.0	**19a**	10	-3.9 (1.1)	10
10	**16a**	THF	(*R*,*R*)-**9b**/ 4.0	**19a**	22	+18.1 (2.7)	47
11[d]	**16a**	THF	(*R*,*R*)-**9b** / 1.5	**19a**	64	+15.8 (1.5)	41
12	**16b**	THF	(*S*,*S*)-**9b** / 1.5	**19b**	68	-17.1 (1.6)	44
13	**16b**	Et_2O	**9a** / 1.5	**19b**	43	-5.2 (0.9)	13
14	**16a**	Et_2O	Sparteine / 2.0	**19a**	65	+3.0 (7.6)	8
15	**16a**	Toluene	Sparteine / 2.0	**19a**	63	+3.5 (7.6)	9
16	**16d**	Et_2O	**9a** / 4.0	**19c**	76	-13.9 (9.4)	49
17[e]	**16d**	Et_2O	**9a** / 4.0	**19c**	80	-13.8 (2.4)	49
18	**16d**	Et_2O	**9a** / 1.5	**19c**	67	-8.7 (2.6)	31
19	**16d**	THF	(*R*,*R*)-**9b** / 1.5	**19c**	63	+6.7 (1.5)	24
20	**16d**	Et_2O	(*S*,*S*)-**9b** / 1.5	**19c**	52	-7.9 (1.3)	28
21	(*S*)-**16c**	Et_2O	iPr_2NH / 2.0	**19b**:**19a** (24:1)	81	+32.9 (1.7)	85[f]
22	(*S*)-**16c**	THF	TMEDA / 1.5	**19b**:**19a** (7:3)	47	+17.1 (1.2)	44[f]
23	(*S*)-**16c**	THF	*n*BuLi / 1.5	**19b**:**19a** (3:2)	67	+20.9 (1.5)	54[f]
24	(*S*)-**16c**	Et_2O	*n*BuLi / 1.0	**19b**:**19a** (49:1)	62	+25.6 (1.3)	66
25	(*S*)-**16c**	THF	*n*BuLi / 1.0	**19b**:**19a** (49:1)	47	+22.3 (1.2)	66[f]
26	(*S*)-**16c**	Toluene	*n*BuLi / 1.0	**19b**:**19a** (49:1)	46	+27.5 (1.1)	71
27	**16e**	THF	(*S*,*S*)-**9b** / 1.5	**19d**	57	-13.5 (2.2)	24[f]
28	**16f**	THF	(*S*,*S*)-**9b** / 1.5	**19e**	48	-28.7 (2.6)	63[f]

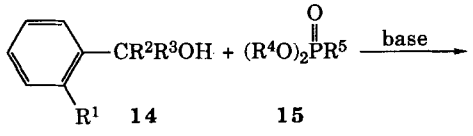
[a] If amines were used a stoichiometric amount of *n*BuLi was added as well. *s*BuLi was used for entries 14 and 15. All reactions were carried out at −78 °C for 1 h unless stated otherwise. – [b] Diethyl phosphonates were measured in $CHCl_3$, all other phosphonates in acetone. Concentrations are rounded to the nearest tenth. The $[\alpha]_D^{20}$ values of the optically pure hydroxy phosphonates are: for **7**: −45.8 (*c* = 1.32, acetone)[16]; for **19a**: +38.6 (*c* = 2.4, $CHCl_3$) and for **19c**: −28.2 (*c* = 1.7, acetone)[16]. – [c] All ee values except for those indicated were determined from optical rotation data. – [d] Reaction time 5 min. – [e] Reaction temperature −100 °C. – [f] Determined by ^{1}H-NMR spectroscopy of Mosher's esters.

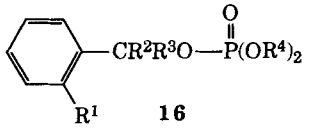
It is not possible yet to determine the step where the enantioselectivity is introduced. There are two distinct steps on the way from the phosphate to the α-hydroxy phosphonate, deprotonation and rearrangement. It is likely that the homochiral amides remove one of the two enantiotopic benzylic hydrogen atoms preferentially to form an enantiomerically enriched carbanion. If it is at least partially configurationally stable for the short period of its existence prior to rearrangement, an optically active α-hydroxy phosphonate will result. The second step where the homochiral base could influence the enantiomeric ratio is the rearrangement itself. Lithium tends to be tetracoordinated in organic compounds. If the carbanion is racemic and configurationally labile at the microscopic level and one of the ligands at lithium is the amine, diastereomeric complexes of carbanions **10** will result. Their difference in the rate of rearrangement will produce an optically active α-hydroxy

phosphonate **11** (kinetic control). Which of the two explanations is the correct one will be discussed later.

Benzyl diethyl and benzyl diisopropyl phosphates were investigated as well to study the influence of substituents at the phosphorus atom on the enantioselectivity of the phosphate-phosphonate rearrangement. These phosphates were prepared according to Scheme 3. In the case of benzyl diethyl phosphates **16a–c, e, f** the benzyl alcohols were transformed with BuLi into lithium alkoxides which were treated with diethyl chlorophosphate. Benzyl diisopropyl phosphate (**16d**) was prepared from benzyl alcohol and phosphoryl bromide **15b** generated from hydrogen diisopropyl phosphite and NBS at −20 °C and used directly.

Scheme 3





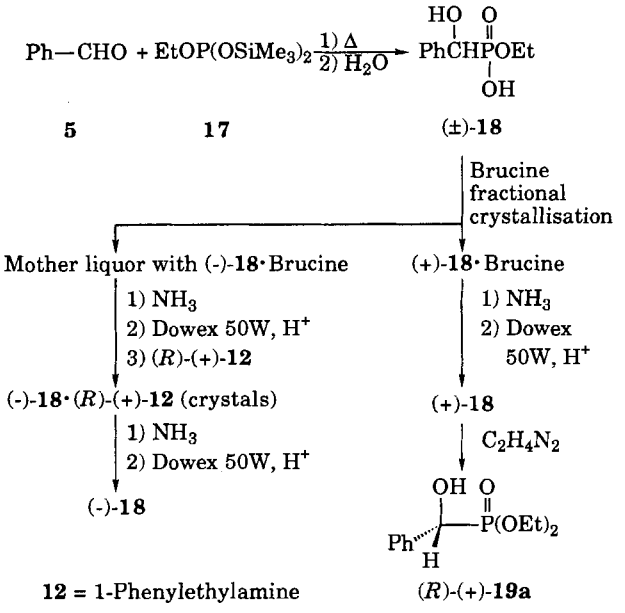
	R¹	R²	R³	R⁴
14a	H	H	H	
b	H	D	D	
(*S*)-**14c**	H	H	D	
d	Me	H	H	
e	OMe	H	H	
16a	H	H	H	Et
b	H	D	D	Et
(*S*)-**16c**	H	H	D	Et
d	H	H	H	*i*Pr
e	Me	H	H	Et
f	OMe	H	H	Et

15a R^4 = Et, R^5 = Cl
b R^4 = *i*Pr, R^5 = Br

The specific rotation of optically pure diethyl 1-hydroxyphenylmethylphosphonate was needed to determine rapidly the enantiomeric excess of products obtained by enantioselective phosphate-phosphonate rearrangement. As it is not known, we prepared it by chemical resolution (Scheme 4).

The hydroxy phosphonate monoethyl ester (±)-**18** was prepared by addition of ethyl bis(trimethylsilyl) phosphite (**17**) to benzaldehyde and successive hydrolysis[3]. The oily acid was resolved by using brucine as auxiliary. The salt of the dextrorotatory acid crystallized by allowing a solution in ethanol/diethyl ether to cool very slowly. It was recrystallized twice to constant specific rotation, transformed into the ammonium salt and passed through a column with Dowex 50W × 8, H^+. The free acid (+)-**18** was esterified with diazoethane to afford (+)-**19a**. The optical purity of acid (+)-**18** was determined by means of ^{1}H-NMR spectroscopy. The spectrum does not show a splitting of the CHP proton signal after addition of excess (+)-1-phenyl-

Scheme 4

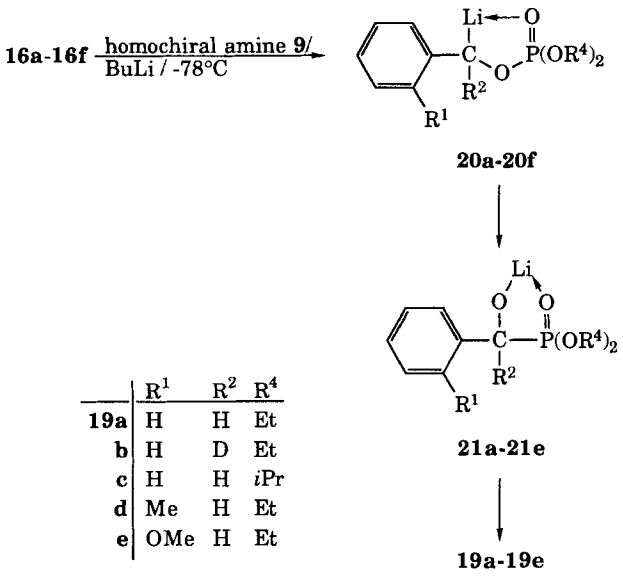


ethylamine[3]. Racemic phosphonate **18** shows two doublets with J = 13 Hz, $\Delta\delta$ = 18 Hz at 250 MHz. The ee of phosphonic acid monoethyl ester is therefore at least 98%. The dimethyl and diisopropyl ester of α-hydroxyphenylmethylphosphonic acid have a negative sign of rotation for the enantiomers with (*S*) configuration[15,16]. As we assume this holds also for the diethyl ester, the dextrorotatory ester **19a** should have (*R*) configuration. The free acid (−)-**18** recovered from the mother liquor of the brucine salt was crystallized to constant specific rotation as its (+)-1-phenylethylammonium salt, from which it can be obtained in the same way as free acid (+)-**18** from the brucine salt.

Benzyl diethyl phosphate (**16a**) was subject to the phosphate-phosphonate rearrangement under a variety of conditions (change of solvent, chiral amine, equivalents of lithium amide, and temperature: see Scheme 5; entries 4–11, Table 1). The yields of phosphonate **19a** increased up to 64%, which is definitely higher than with the corresponding dimethyl phosphate. With homochiral amine (*S*)-**9a**/*n*BuLi the ee values of phosphonates (−)-**19** obtained in both diethyl ether and THF are similar (entries 4 and 5). The C_2-symmetric amide of (*R*,*R*)-**9b** improves the ee significantly to 37% (entry 6). When the amount of base was increased from 1.5 to 4 equiv., the ee increases too, but decreases again, if the reaction temperature was −100 instead of −78 °C (entries 7 and 8). The worst results in terms of yield (10%) and ee (10%) are obtained in toluene as solvent (entry 9). Use of 4 equiv. of lithium amide in THF yields from phosphate **16a** a phosphonate with the highest ee observed (50%), but the yield drops to 22% (entry 10). When the reaction time was just 5 min instead of the most frequently used 60 min, yield and ee of the product were not affected (entries 6 and 11). Enantiomerically enriched deuterated phosphonates can be prepared similarly from dideuterated benzyl phosphate **16b** (entries 12 and 13). When (−)-spar-

teine/*s*BuLi was used to induce a phosphate-phosphonate rearrangement, yields and ee values of the phosphonate formed were very low in both diethyl ether and toluene as solvents (entries 14 and 15). In contrast, (−)-sparteine in combination with *n*BuLi or *s*BuLi turned out to be an excellent base for highly enantioselective deprotonations of carbamates with a shielded carbonyl group as found by Hoppe et al.[8].

Scheme 5



	R^1	R^2	R^4
19a	H	H	Et
b	H	D	Et
c	H	H	*i*Pr
d	Me	H	Et
e	OMe	H	Et

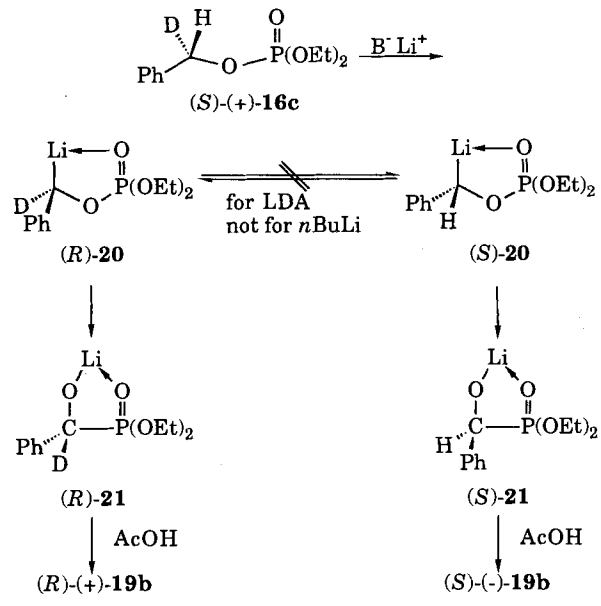
The more bulky benzyl diisopropyl phosphate (**16d**) afforded α-hydroxy phosphonates **19c** with ee values ranging from 24 to 49% and yields between 52 and 80% (entries 16–20). Here the enantiomeric purity and the yield are significantly higher with 4 equiv. of lithium amides than with 1.5 equiv. The enantioselectivities of the rearrangement are similar, irrespective of the amide used.

In all cases studied (*S*)- or (*R*)-1-hydroxyphenylmethylphosphonates were formed preferentially, if the amides were generated from amines (*S*)-**9a** and (*S,S*)-**9b** or (*R,R*)-**9b**, respectively.

The homochiral, deuterated (*S*)-benzyl phosphate **16c**, prepared by horse liver alcohol dihydrogenase-catalyzed reduction of deuterated benzaldehyde to (*S*)-[α-D_1]benzyl alcohol[17] and phosphorylation, was isomerized to phosphonate **19b** with LDA, *n*BuLi, or *n*BuLi/TMEDA (Scheme 6).

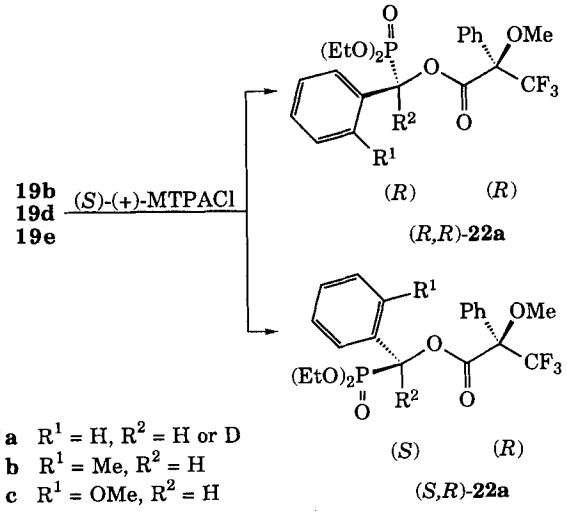
With two equiv. of LDA as base and diethyl ether as solvent deuterated hydroxy phosphonate (*R*)-**19b** was formed in 81% yield with an ee of 86% and a deuterium content of 96% as determined by ^{1}H-NMR spectroscopy (400 MHz). This corresponds to a primary kinetic isotope effect of 24 at −78°C (entry 21)[18]. Abstraction of hydrogen gives the (*R*)-configurated benzylic carbanion (*R*)-**20** which isomerizes to phosphonate (*R*)-**21** with retention of configuration at the carbon atom during the migration of the diethylphosphoryl group. Loss of deuterium affords (*S*)-(−)-**19c** (not drawn in Scheme 6). A deuterium content of 96% would thus translate into an ee of 92% assuming that by

Scheme 6



loss of hydrogen from phosphate (*S*)-(+)-**16c** only (*R*)-(+)-**19b** and by loss of deuterium only (*S*)-(−)-**19c** is formed. This value was also calculated on the assumption that the deuterated hydroxy phosphonate has the same specific optical rotation as the nondeuterated one. Hydroxy phosphonate **19b** was also derivatized with (*S*)-(+)-Mosher acid chloride [(*S*)-(+)-MTPACl] to determine the ee by another method (Scheme 7). The ^{1}H-NMR spectrum shows that the hydroxy phosphonate of the major diastereomer has (*R*) configuration. The methoxy group of the MTPA group of the major diastereomer resonates at higher field than that of the minor diastereomer. This is in agreement with conformation models as given in Scheme 7, where the phenyl ring in (*R,R*)-**22a** shields the methoxy group, which is not possible in (*S,R*)-**22a**[16,19]. The ee was calculated from the relative intensities of the methoxy signals as 85%.

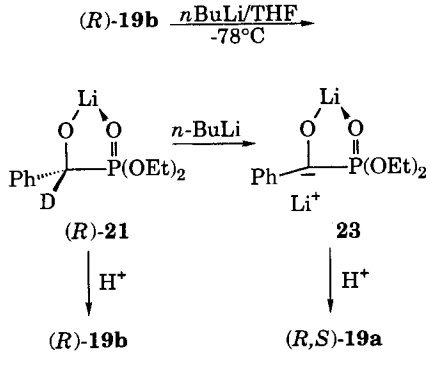
Scheme 7



22a R^1 = H, R^2 = H or D
b R^1 = Me, R^2 = H
c R^1 = OMe, R^2 = H

An ee of 85% clearly indicates that benzylic carbanion (*R*)-**20** is virtually configurationally stable and that only 3.5% of the molecules change their configuration to (*S*)-**20**. When *n*BuLi alone or in combination with TMEDA was used as base, yields, deuterium contents, and ee values decreased (entries 22 and 23). The ee values as determined by use of Mosher's esters and ^{1}H-NMR spectroscopy are in agreement with the values determined from specific optical rotations. But the spectrum also revealed that the non-deuterated hydroxy phosphonate was completely racemic. When stoichiometric amounts of *n*BuLi were allowed to react with chiral phosphate **16c**, the deuterium content increased to 98% giving a kinetic isotope effect of about 50 (entries 24–26)[18]. The solvent (Et_2O, THF, toluene) does not seem to exert a strong influence on the rearrangement (entries 24–26). The lower ee values in comparison with LDA as base are diagnostic of a more labile carbanion (*R*)-**20** of which about 20% racemize. The low deuterium content in reactions with excess *n*BuLi is caused by an additional deprotonation of carbanion **20** to dianion **23**, which is configurationally labile and racemizes completely (Scheme 8). By treatment with acetic acid the dianion is protonated to give racemic hydroxy phosphonate **19a**. This explanation was independently tested by treating deuterated hydroxy phosphonate (*R*)-**19b** with *n*BuLi at −78 °C in THF. A portion of the deuterium, 20 and 25%, respectively, was replaced by protium. The isolated α-hydroxy phosphonate (*R*)-**19b** contained 80% (75%) of deuterium and had an ee of 75% (76%) relative to the starting material.

Scheme 8



To study the steric influence of substituents on the phenyl ring on the phosphate-phosphonate rearrangement, phosphates **16e** and **16f** with an *ortho*-methyl or *ortho*-methoxy group, respectively, were prepared (Scheme 3). The corresponding hydroxy phosphonates **19d** and **19e** had ee values of 24 and 63% and were formed in yields of 57 and 48% (entries 27 and 28). The *ortho*-methoxy group as an additional ligand to bind lithium increases the enantioselectivity of the deprotonation.

The experiments with the chiral, deuterated benzyl phosphate (*S*)-**16c** demonstrate that the configurational stability of benzylic carbanions with a dialkoxyphosphoryloxy substituent depends on the base with which they are generated. They are less labile when they are generated with LDA as base than with *n*BuLi. This difference possibly results from the diisopropylamine. It could become a ligand of lithium tending to be tetracoordinated as soon as it is formed. The weak Li–N bond could cause a stronger interaction of lithium with the oxygen of the P=O bond, and the phosphorus atom becomes more electrophilic. The attack of the carbanion on the phosphorus atom will be speeded up, and the lifetime of the carbanion is shortened relative to a complex with a solvent molecule (THF, diethyl ether) as ligand, if *n*BuLi is used as base. The configurational stability of these benzylic carbanion is virtually independent of the solvent.

In summary, it was demonstrated that homochiral lithium amides deprotonate benzyl dialkyl phosphates enantioselectively to benzylic carbanions which are nearly completely configurationally stable. The pro-(*S*) hydrogen is removed by the lithium amides of (*S*)-**9a** and (*S,S*)-**9b**. The pro-(*R*) hydrogen is lost preferentially when amides of opposite configuration are used. The carbanions rearrange with retention of configuration to enantiomerically enriched phosphonates as soon as they are formed. The corresponding carbamoyloxy-substituted carbanion is partly configurationally stable relative to the addition to an aldehyde[20]. The dialkoxyphosphoryloxy group acts as an intramolecular electrophile, which can be used to probe the configurational stability of short-lived carbanions.

We thank the *Fonds zur Förderung der wissenschaftlichen Forschung* (projects no. P8671-MOB and 6537C) for support.

Experimental

TLC: Merck precoated TLC plates, silica gel 60, F_{254}, detection: UV and/or spraying with a 2% solution of $Ce(IV)SO_4 \cdot 4\ H_2O$ in 2 N H_2SO_4 and heating. – Flash chromatography: Merck silica gel 60, 0.040–0.063 mm. – Eluents: Petroleum ether (PE, boiling point 60–95 °C), ethyl acetate (EA). – IR: Perkin-Elmer FT 1600 IR spectrometer (NaCl: film; Si[21]: a solution of the sample in Uvasol $CHCl_3$ was applied to a Si plate, and the solvent was allowed to evaporate). – ^{1}H NMR: Bruker spectrometers AC 250 or AM 400 WB; TMS as internal standard. – Optical rotation: Perkin-Elmer polarimeter 141 (1-dm cell). – Melting points: Reichert Thermovar, not corrected. – Reactions were carried out in dry solvents. THF was distilled from potassium, diethyl ether from $LiAlH_4$. – The secondary amines (*S,S*)- and (*R,R*)-**9b** were prepared and purified according to refs.[14,22] via the hydrochloride salts which were crystallized twice. The regenerated amines were purified by bulb-to-bulb distillation (92 °C/0.04 Torr; ref.[23] 86–96 °C/0.05 Torr); for (*S,S*)-**9b**: $[\alpha]_D^{20} = -157.3$ (c = 1.085, EtOH) {ref.[24] $[\alpha]_D = -157.0$ (c = 2.4, EtOH)}; $[\alpha]_D^{20} = -162.2$ (c = 0.85, $CHCl_3$) {ref.[23] $[\alpha]_D^{20} = -171.6$ (c = 6.71, $CHCl_3$)}.

(*S*)-(+)-α-Methoxy-α-(trifluoromethyl)phenylacetyl chloride [JPS Chimie; $[\alpha]_D^{20} = +136.5$ (c = 5.2, CCl_4), ee > 99.5%] was used for derivatization of α-hydroxy phosphonates.

Benzyl Dimethyl Phosphate (**8**): To a stirred solution of freshly distilled benzaldehyde (3.18 g, 30 mmol) and hydrogen dimethyl phosphite (**6**, 3.85 g, 35 mmol) in DMSO (dry, 30 ml) containing water (0.9 ml) was added sodium bis(trimethylsilyl)amide (0.90 g, 5 mmol) at 10 °C. This solution was stirred for 24 h at room temp. 2 N HCl was added, and the mixture was extracted with diethyl ether. The organic layer was washed with 2 N HCl, a saturated aq. solution of $NaHCO_3$, and water and dried ($MgSO_4$). The solvent was evaporated and the residue subjected to bulb-to-bulb distil-

lation (115°C/4 Torr), purified by flash chromatography (PE/EA, 1:5; R_f = 0.45) and again subjected to bulb-to-bulb distillation (115°C/4 Torr; ref.[25] 100°C/0.05 Torr) to yield phosphate **8** (4.46 g, 35%) as an oil. – ^{1}H NMR (250 MHz, $CDCl_3$): δ = 3.70 (d, J = 11.0 Hz, 6H, 2 OCH_3), 5.10 (d, J = 8.3 Hz, 2H, $PhCH_2$), 7.40 (m, 5H, Ph).

(S)-(−)-Isopropyl(1-phenylethyl)amine [(*S*)-**9a**]: A mixture of (*S*)-(−)-1-phenylethylamine (24.2 g, 25 ml, 0.2 mol), 2-bromopropane (36.9 g, 28.2 ml, 0.3 mol), potassium carbonate (41.5 g, 0.3 mol), potassium iodide (16.6 g, 0.1 mol), and ethanol (60 ml) was refluxed for 8 d. Water (200 ml) and NaOH (10 g) were added to the cold mixture. The product was extracted with diethyl ether (3 × 100 ml). The combined organic layers were washed with water, dried ($MgSO_4$), and concentrated in vacuo. Fractional distillation of the residue through a short Vigreux column yielded amine (*S*)-(−)-**9a** (27 g, 83%) as a colorless liquid containing up to 5% of starting amine; b.p. 76–78°C/20 Torr, $[\alpha]_D^{20}$ = −57.0 (c = 0.93, $CHCl_3$) [ref.[14] $[\alpha]_D^{20}$ = +61.4 (c = 2.23, $CHCl_3$) for (*R*)-(+)-amine purified as HCl salt]. It is further purified as its HCl salt as reported in the literature. The free amine was regenerated and distilled to afford a product with b.p. 81–82°C, n_D^{23} = 1.4947, $[\alpha]_D^{20}$ = −61.8 (c = 0.94, $CHCl_3$).

Ethyl Hydrogen Hydroxyphenylmethylphosphonate [(±)-**18**]: Phosphite **17** (50.8 g, 200 mmol) was added dropwise with stirring and cooling with water to benzaldehyde (21.2 g, 200 mmol, freshly distilled)[3]. When the exothermic reaction had ceased, the reaction mixture was heated at 100°C for 1 h, cooled, and water (100 ml) was added. After stirring for 18 h at room temp., a solution of NaOH (10 g of NaOH in 100 ml of water) was added until the solution was neutral (thymolphthalein). The organic phase was separated and the aqueous phase continuously extracted with diethyl ether for 3 h. The extracts were discarded. The aqueous phase was acidified with dilute H_2SO_4 (12 ml of conc. H_2SO_4 in 50 ml of water). The phosphonic acid (±)-**18** was continuously extracted with diethyl ether for 2 h. Then more dilute H_2SO_4 (5 ml of conc. H_2SO_4 in 30 ml of water) was added, and extraction was continued for 4 h. The combined extracts were concentrated in vacuo and dried (0.01 Torr/2 hr) to give 33.0 g (76%) of (±)-**18** as an oil containing a small amount of impurities (^{1}H NMR) and which could not be induced to crystallize. – ^{1}H NMR (250 MHz, $CDCl_3$): δ = 1.16 (t, J = 7.4 Hz, 3H, CH_3), 3.90 (m, 2H, CH_2O), 4.03 (d, J = 6.4 Hz, 1H, PCH), 7.40 (m, 7H, Ph, 2 OH). On addition of excess (*R*)-(+)-1-phenylethylamine to the sample the ^{1}H-NMR spectrum shows two doublets [δ = 4.63 (J = 13 Hz) and 4.56 (J = 13 Hz)] for the PCH groups of the two diastereomeric salts[3].

Resolution of the Phosphonic Acid (±)-**18**. The acid (24.07 g, 111.4 mmol) and brucine (43.93 g, 111.4 mmol, dried at 100°C/1 Torr) were dissolved in warm ethanol (about 100 ml). Diethyl ether (about 300 ml) was added, and the warm solution (37°C) was allowed to cool down to +5°C overnight in a Dewar vessel containing warm water (38°C). The solution was seeded with crystals obtained from ethanol/acetone/diethyl ether. The crystals of the brucine salt were collected and dried; $[\alpha]_D^{20}$ = +5.2 (c = 1.72, ethanol). This salt was recrystallized twice from ethanol/diethyl ether in the same way as before to afford 23.5 g (69%) of the brucine salt of (+)-**18**; m.p. 114–116°C; $[\alpha]_D^{20}$ = +9.2 (c = 2.24, ethanol). The free acid obtained from the salt had 98% ee [see preparation of (+)-**19a**]. – From the mother liquors of the brucine salt the free acid was regenerated (see preparation of (+)-**19a**). It was dissolved in dichloromethane and an equivalent amount of (+)-1-phenylethylamine was added. The salt of (−)-**18** obtained was crystallized from dichloromethane/diethyl ether by allowing the solution to cool to 1°C very slowly (flask in Dewar vessel). The crystals {$[\alpha]_D^{20}$ = −13.8 (c = 2.17, ethanol)} were recrystallized twice to yield a salt with m.p. 133–136°C (phase transition at 117–125°C); $[\alpha]_D^{20}$ = +14.2 (c = 2.5, EtOH); ee 98%.

Diethyl Hydroxyphenylmethylphosphonate [(+)-**19a**]: A mixture of the brucine salt of (+)-**18** (10.0 g, 16.4 mmol), aqueous ammonia (10%, 100 ml), and dichloromethane (40 ml) was stirred until the salt had dissolved. The organic phase containing the brucine was separated. The aqueous phase was extracted with dichloromethane (40 ml) and concentrated in vacuo. The residue was dissolved in water and the solution passed through a column with Dowex 50W × 8, H^+ (50 ml). The eluate was concentrated in vacuo and the residue dried (0.1 mm/6 h; room temp.) to yield 3.2 g (90%) of free phosphonic acid (+)-**18** as a colorless viscous oil; $[\alpha]_D^{20}$ = +42.9 (c = 2.0, ethanol). The ^{1}H-NMR spectrum is identical with the spectrum of the racemic acid. The ^{1}H-NMR spectrum of the same sample after the addition of excess (+)-1-phenylethylamine shows only one doublet (δ = 4.63) for the benzylic hydrogen (ee 98%).

Phosphonic acid (+)-**18** (2.7 g, 12.5 mmol) was dissolved in diethyl ether and esterified with diazoethane. The crude product was purified by flash chromatography using dichloromethane/acetone (9:1) to elute a yellow impurity, followed by dichloromethane/acetone (7:3) to elute diethyl phosphonate (+)-**19a**, (dichloromethane/acetone, 9:1; R_f = 0.22). (+)-**19a** was isolated as colorless crystals (2.4 g, 79%), $[\alpha]_D^{20}$ = +38.2 (c = 2.71, $CHCl_3$); m.p. 75°C (diisopropyl ether), $[\alpha]_D^{20}$ = +38.6 (c = 2.40, $CHCl_3$). – IR (CH_2Cl_2; Perkin-Elmer 377); $\tilde{\nu}$ = 3590 cm^{-1}, 3290, 3025, 2950, 1425, 1252, 1025. – ^{1}H NMR ($CDCl_3$; 80 MHz, Bruker WP 80 CW): δ = 1.23 and 1.28 (2 t, J = 7.3 Hz, 2 CH_3), 3.45 (br. s, 1H, OH), 4.05 (m, 4H, 2 OCH_2), 5.04 (d, J = 13.0 Hz, 1H, PhCH), 7.60 (m, 5H, Ph). – $C_{11}H_{17}O_4P$ (244.2): calcd. C 54.10, H 7.02; found C 53.90, H 6.84.

Benzyl Diisopropyl Phosphate (**16d**): A solution of hydrogen diisopropyl phosphite (8.31 g, 50 mmol) in CH_2Cl_2 (20 ml) was added dropwise to a mixture of NBS (8.90 g, 50 mmol) in CH_2Cl_2 (20 ml) under argon at −20°C. After stirring for 1 h a solution of benzyl alcohol (4.33 g, 40 mmol) and 4-(dimethylamino)pyridine (0.1 g) in pyridine (6.5 ml, 80 mmol) was added, and the mixture was allowed to warm to room temp. Volatile components were removed in vacuo, and the residue was taken up in CH_2Cl_2. The solution was washed with 2 N HCl and water, then stirred vigorously with concentrated ammonia for 2 h. The organic phase was separated and washed with 2 N HCl, a saturated aq. solution of $NaHCO_3$, water and dried ($MgSO_4$). The solvent was evaporated and the residue purified by flash chromatography (PE/EA, 3:1; R_f = 0.29) and bulb-to-bulb distillation (b.p. 135°C/4 Torr) to afford phosphate **16d** (3.85 g, 31%) as an oil. – IR (NaCl): $\tilde{\nu}$ = 2980 cm^{-1}, 2936, 1455, 1386, 1275, 1214, 1179, 1143, 1109. – ^{1}H NMR (250 MHz, $CDCl_3$): δ = 1.31 (2 d overlapping to a t, J = 6.0 Hz, 12H, 2 $OCHMe_2$), 4.63 (m, 2H, 2 $OCHMe_2$), 5.03 (dd, J = 7.7, 1.1 Hz, 2H, $PhCH_2$), 7.37 (m, 5H, Ph). – $C_{13}H_{21}O_4P$ (245.3): calcd. C 57.33, H 7.78; found C 57.17, H 7.96.

General Procedure for the Preparation of Diethyl Phosphates **16a–c**, **16e**, *and* **16f**: To a stirred solution of benzyl alcohols **14a–e** (18.7 mmol) in freshly distilled THF (10 ml) at −78°C under argon were added dropwise dry 1,3-dimethyl-2-imidazolidinone (2.40 g, 2.30 ml, 21 mmol) and a solution of *s*BuLi in cyclohexane (12%, 15.8 ml, 21 mmol). After 5 min diethyl chlorophosphate (3.62 g, 3.03 ml, 21 mmol) was added by means of a syringe. The mixture was allowed to warm up slowly to room temp. overnight. The solvent was evaporated, the residue was taken up in CH_2Cl_2, and the obtained solution was stirred with a concentrated aq. solution of

NH_3 for 1 h. The organic phase was separated and washed with 2 N HCl, a saturated aq. solution of $NaHCO_3$ and water, dried ($MgSO_4$), then concentrated in vacuo. The residue was purified by flash chromatography (PE/EA, 1:5) and bulb-to-bulb distillation (except **16e** and **16f**) to give phosphates **16a–c**, **16e**, and **16f** as oils.

Benzyl Diethyl Phosphate (**16a**): Yield 3.20 g (70%); R_f = 0.56; b.p. 130°C/4 Torr ref.[26].

Diethyl Phenyl[D_2]methyl Phosphate (**16b**): Yield 3.45 g (75%); R_f = 0.58; b.p. 130°C/4 Torr. – IR (NaCl): $\tilde{\nu}$ = 3063 cm^{-1}, 3032, 2984, 2933, 2909, 1498, 1479, 1450, 1394, 1370, 1274, 1166, 1032. – ^{1}H-NMR (250 MHz, $CDCl_3$): δ = 1.25 (dt, J = 7.2, 0.6 Hz, 6H, 2 OCH_2Me), 4.10 (m, 4H, 2 OCH_2Me), 7.37 (m, 5H, Ph).

(S)-(+)-Diethyl Phenyl[D_1]methyl Phosphate (**16c**): Yield 2.71 g (59%); R_f = 0.56; b.p. 130°C/4 Torr. – IR (NaCl): $\tilde{\nu}$ = 2983 cm^{-1}, 1270, 1034, 975. – ^{1}H NMR (250 MHz, $CDCl_3$): δ = 1.30 (td, J = 6.9, 1.0 Hz, 6H, 2 OCH_2Me), 4.10 (m, 4H, 2 OCH_2Me), 5.05 (dt, J = 7.9, 1.5 Hz, 1H, PhCHD), 7.35 (m, 5H, Ph). – $[\alpha]_D^{20}$ = +0.63 (c = 16.2, CH_2Cl_2).

Diethyl (2-Methylphenyl)methyl Phosphate (**16e**): Yield 3.49 g (72%), R_f = 0.63. – IR (NaCl): $\tilde{\nu}$ = 2983 cm^{-1}, 2909, 1608, 1464, 1393, 1370, 1273, 1223, 1191, 1166, 1032. – ^{1}H NMR (250 MHz, $CDCl_3$): δ = 1.26 (dt, J = 7.2, 0.8 Hz, 6H, 2 OCH_2Me), 2.33 (s, 3H, PhMe), 4.04 (m, 4H, 2 OCH_2Me), 5.04 (d, J = 7.5 Hz, 2H, $PhCH_2$), 7.20 (m, 4H, Ph). – $C_{12}H_{19}O_4P$ (258.3): calcd. C 55.81, H 7.42; found C 55.60, H 7.41.

Diethyl (2-Methoxyphenyl)methyl Phosphate (**16f**): Yield 3.28 g (64%), R_f = 0.49. – IR (NaCl): $\tilde{\nu}$ = 2983 cm^{-1}, 2909, 1605, 1591, 1496, 1465, 1441, 1393, 1251, 1202, 1165, 1123, 1032. – ^{1}H NMR (250 MHz, $CDCl_3$): δ = 1.34 (dt, J = 7.2, 0.8 Hz, 6H, 2 OCH_2Me), 3.83 (s, 3H, PhOMe), 4.10 (quint, J = 7.2 Hz, 4H, 2 OCH_2Me), 5.10 (d, J = 7.2 Hz, 2H, $PhCH_2$), 6.90 (m, 2H, Ph), 7.30 (m, 2H, Ph). – $C_{12}H_{19}O_5P$ (274.3): calcd. C 52.55, H 6.98; found C 52.27, H 6.96.

General Procedure for the Phosphate-Phosphonate Rearrangement: To a solution of amine **9** (1.5 mmol) (Table 1) in freshly distilled dry THF at −20°C under argon was added a solution of *n*BuLi in *n*-hexane (15%, 0.9 ml, 1.5 mmol) by means of a syringe. The mixture was stirred for 5 min, cooled to −78°C, and the phosphate **16a–f** was added dropwise. After stirring for 1 h acetic acid (1 ml) was added, the mixture was warmed to room temp., and the solvent was removed in vacuo. The residue was taken up in methanol, the obtained solution passed through a column filled with Amberlyst 15 H^+ (10 ml) and the eluate concentrated. The residue was taken up in CH_2Cl_2, the solution washed with 2 N HCl, a saturated aq. solution of $NaHCO_3$ and water and then dried with $MgSO_4$. The filtrate was concentrated and the residue purified by flash chromatography (PE/EA, 1:1) to give the hydroxyphosphonates **7**, **19a–e** (Table 1). The ^{1}H-NMR spectra of **7**, **16a**, and **16d** are identical with those of authentic samples.

Diethyl Hydroxy(2-methylphenyl)methyl Phosphonate (**19d**): R_f = 0.39 (PE/EA, 1:5), $[\alpha]_D^{20}$ = −13.5 (c = 2.15, $CHCl_3$). – IR (Si): $\tilde{\nu}$ = 3282 cm^{-1}, 2982, 2930, 1489, 1443, 1392, 1234, 1043, 970. – ^{1}H NMR (250 MHz, $CDCl_3$): δ = 1.16 (t, J = 7.2 Hz, 3H, OCH_2CH_3), 1.23 (t, J = 7.2 Hz, 3H, OCH_2CH_3), 2.34 (s, 3H, PhMe), 4.01 (m, 4H, 2 OCH_2CH_3), (br. s, 1H, OH), 5.23 (d, J = 11 Hz, 1H, PhC*H*OH), 7.10–7.70 (m, 5H, Ph). – $C_{12}H_{19}O_4P$ (258.3): calcd. C 55.81, H 7.42; found C 56.06, H 7.19.

Diethyl Hydroxy(2-methoxyphenyl)methyl Phosphonate (**19e**): R_f = 0.28 (PE/EA, 1:5), $[\alpha]_D^{20}$ = −28.7 (c = 2.60, $CHCl_3$). – IR (Si): $\tilde{\nu}$ = 3286 cm^{-1}, 2982, 2930, 1601, 1493, 1464, 1440, 1392, 1288, 1247, 1163, 1050, 970. – ^{1}H NMR (250 MHz, $CDCl_3$): δ = 1.17 (t, J = 7.2 Hz, 3H, OCH_2CH_3), 1.29 (t, J = 7.2 Hz, 3H, OCH_2CH_3), 3.84 (s, 3H, PhOMe), 4.03 (m, 4H, 2 OCH_2CH_3), 4.39 (br. t, J = 7.0 Hz, 1H, OH), 5.45 (br. dd, J = 7.0, 12.0 Hz, 1H, PhC*H*OH), 6.85–7.50 (m, 4H, Ph). – $C_{12}H_{19}O_5P$ (274.3): calcd. C 52.55, H 6.98; found C 53.01, H 7.12.

Treatment of Hydroxy Phosphonate **19b** *with an Excess of nBuLi:* To a solution of **19c** {0.06 g, 0.25 mmol, $[\alpha]_D^{20}$ = +25.6 (c = 1.3, $CHCl_3$)} in freshly distilled dry THF (5 ml) under argon at −78°C was added by means of a syringe a solution of *n*-BuLi in *n*-hexane (15%, 0.4 ml, 0.6 mmol). After stirring at −78°C for 1 h acetic acid (0.4 ml) was added, and the mixture was warmed to room temp. The solvent was evaporated and the residue taken up in CH_2Cl_2. The obtained solution was washed with 2 N HCl, a saturated aq. solution of $NaHCO_3$ and water, then dried with $MgSO_4$. The solvent was evaporated and the residue purified by flash chromatography (PE/EA, 1:5) to yield 0.04 g [66%, $[\alpha]_D^{20}$ = +19.3 (c = 1.0, $CHCl_3$), ee 75% of starting material] of a mixture of the hydroxy phosphonates **19a** and **19b** (4:1).

A second experiment with **19b** {$[\alpha]_D^{20}$ = +22.3 (c = 1.2, $CHCl_3$)} gave a mixture of the hydroxy phosphonates **19a** and **19b** {3:1, $[\alpha]_D^{20}$ = +16.9 (c = 0.8, $CHCl_3$), ee 76% of starting material}.

General Procedure for the Synthesis of Mosher Derivatives of Hydroxy Phosphonates **19b, d, e**: To a solution of hydroxy phosphonate (0.1 mmol) in dry CH_2Cl_2 (1 ml) and dry pyridine (1 ml) was added a solution of (*S*)-(+)-MTPACl in dry CH_2Cl_2 (86 mg, 0.34 mmol). After stirring of this solution overnight at room temp., water (0.5 ml) was added, and the stirring was continued for 30 min. Volatile components were removed in vacuo, the residue was taken up in CH_2Cl_2 and the solution washed with 2 N HCl, a saturated solution of $NaHCO_3$, and water, then dried ($MgSO_4$). The solvent was evaporated and the residue purified by flash chromatography to give the corresponding Mosher derivatives in yields up to 80%.

[1] F. Hammerschmidt, *Monatsh. Chem.* **1993**, *124*, 1063–1069.
[2] G. Sturz, B. Corbel, *C. R. Acad. Sci., Ser. C*, **1973**, *276* (26), 1807–1810, 277 (10), 395–398; G. Sturz, B. Corbel, J.-P. Paugam, *Tetrahedron Lett.* **1976**, *1*, 47–50.
[3] F. Hammerschmidt, H. Völlenkle, *Liebigs Ann. Chem.* **1986**, 2053–2064.
[4] G. Sturz, J.-J. Yaouanc, F. Krausz, B. Labeeuw, *Synthesis* **1980**, 289–291.
[5] P. Beak, D. B. Reitz, *J. Am. Chem. Soc.* **1978**, *100*, 275–316; N. G. Rondan, K. N. Houk, P. Beak, W. J. Zajdl, J. Chandrashekhar, P. v. R. Schleyer, *J. Org. Chem.* **1981**, *46*, 4108–4110.
[6] P. Beak, L. C. Carter, *J. Am. Chem. Soc.* **1981**, *103*, 2363–2373; methyl 2,4,6-tri-*tert*-butylbenzoate was also deprotonated: R. Schlecker, D. Seebach, W. Lubosch, *Helv. Chim. Acta* **1978**, *61*, 512–526.
[7] P. Knochel, *Angew. Chem.* **1992**, *104*, 1486–1488; *Angew. Chem. Int. Ed. Engl.* **1992**, *31*, 1459.
[8] D. Hoppe, F. Hintze, P. Tebben, M. Paetow, H. Ahrens, J. Schwerdtfeger, P. Sommerfeld, J. Haller, W. Guarnieri, S. Kolczewski, T. Hense, I. Hoppe, *Pure Appl. Chem.* **1994**, *66*, 1479–1486.
[9] A. Carstens, D. Hoppe, *Tetrahedron* **1994**, *50*, 6097–6108.
[10] A. N. Pudovik, M. G. Zimin, *Pure Appl. Chem.* **1980**, *52*, 989–1011.
[11] A. G. Brook, *Acc. Chem. Res.* **1974**, *7*, 77–84; R. Hoffmann, R. Brückner, *Chem. Ber.* **1992**, *125*, 2731–2739.
[12] A. M. Macleod, R. Baker, M. Hudson, K. James, M. B. Roe, M. Knowles, G. MacAllister, *Med. Chem. Res.* **1992**, *2*, 96–101.
[13] P. J. Cox, N. S. Simpkins, *Tetrahedron: Asymmetry* **1991**, *2*, 1–26.
[14] C. M. Cain, R. P. C. Cousins, G. Coumbarides, N. S. Simpkins, *Tetrahedron* **1990**, *46*, 523–544.
[15] Ab. A. Smaardijk, S. Noorda, F. van Bolhuis, H. Wynberg, *Tetrahedron Lett.* **1985**, *26*, 493–496.

[16] Y.-F. Li, F. Hammerschmidt, *Tetrahedron: Asymmetry* **1993**, *4*, 109–120.
[17] R. H. Wightman, J. Staunton, A. R. Battersby, K. R. Hanson, *J. Chem. Soc., Perkin Trans. 1*, **1972**, 2355–2364.
[18] D. Hoppe, M. Paetow, F. Hintze, *Angew. Chem.* **1993**, *105*, 430–432; *Angew. Chem. Int. Ed. Engl.* **1993**, *32*, 394.
[19] F. Hammerschmidt, Y.-F. Li, *Tetrahedron* **1994**, *50*, 10253–10263.
[20] R. W. Hoffmann, T. Rühl, J. Harbach, *Liebigs Ann. Chem.* **1992**, 725–730.
[21] W. Mikenda, *Vibrational Spectroscopy* **1992**, *3*, 327–330.
[22] C. G. Overberger, N. P. Marullo, R. G. Hiskey, *J. Am. Chem. Soc.* **1960**, *83*, 1374–1378.
[23] J. A. Marshall, J. Lebreton, *J. Am. Chem. Soc.* **1988**, *110*, 2925–2931.
[24] M. B. Eleveld, H. Hogeveen, E. P. Schudde, *J. Org. Chem.* **1986**, *51*, 3635–3642.
[25] J. Cheymol, P. Chabrier, M. Selim, P. Leduc, *C. R. Acad. Sci.* **1958**, *247*, 1014–1015.
[26] H.-G. Henning, G. Hilgetag, G. Busse, *J. Prakt. Chem.* **1966**, *33*, 188–198.

[95031]