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THE ASYMMETRIC SYNTHESIS OF α-CHLORO α-ALKYL AND α-METHYL α-ALKYL PHOSPHONIC ACIDS OF HIGH ENANTIOMERIC PURITY.

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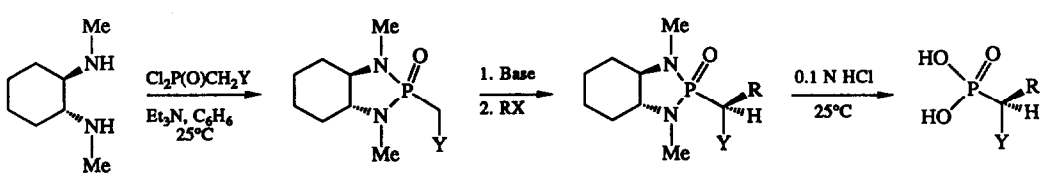
Abstract: A method is described for the synthesis of α-chloro-α-alkyl- and α-methyl-α-alkylphosphonic acids in either enantiomeric form and in high optical purity, based on the asymmetric alkylation of α-substituted bicyclic phosphonamides derived from a C_2 symmetrical diamine.

The phosphonic acids are an important class of compounds that exhibit a variety of unique biological properties.[1] In addition to their inherent activities in a number of areas, they are the molecules of choice when a carboxyl surrogate is sought.[2] In many instances these involve α-substitution by alkyl, amino, and halo groups, were a host of applications in medicinal chemistry can be found.[3] For example, α-chlorophosphonic acids are potent antiviral agents.[4]

To the best of our knowledge, methods for the synthesis of enantiomerically pure (or enriched) compounds in these series have not been reported.[5] We now describe a general protocol for the asymmetric synthesis of α-chloro-α-alkyl and α–methyl-α-alkylphosphonic acids which provides either enantiomer in high optical purity in each series. The process shown in Scheme 1, consists in the treatment of the readily available chloromethyl and ethyl phosphonamides (**1** and **2**), prepared from *(R,R)*-1,2-bis-N-methylamino-cyclohexane[6] with a base such as n-BuLi or LDA in THF followed by addition of an appropriate alkyl halide at -100°C. The resulting products of general structures **3** and **4** are obtained in high yields, and they are of excellent optical purities. These alkylated phosphonamides can be hydrolyzed under mild conditions to give the corresponding α–substituted phosphonic acids in excellent yields. The phosphonic acids in the other enantiomeric series can be similarly obtained starting from the corresponding phosphonamide prepared from the *(S,S)*-diamine.[6]

Scheme 1.



(R,R)

1, Y= Cl, 85%

2, Y= Me, 80%

3, Y= Cl

4, Y= Me

5, Y=Cl

6, Y=Me

Table 1 lists the results of the alkylation of the *(R,R)*-chloromethylphosphonamide **1** (mp. 84°C, hexane, $[\alpha]^{25}_D$ –109.8° c 1.0, $CHCl_3$) with a variety of alkyl halides (entries 1-7) at -100°C.[7] Diastereomeric ratios ranging from 90:10 (entries 1,6,7) to >99:1 (entries 2-4) were observed, and in a number of cases the products were crystalline and amenable to single crystal structure analysis[8] (**3**, R=Et). In the case of the ω-alkoxy halides (entries 6,7), the diastereomeric products could be separated by column chromatography. Treatment of the α-chloro-α-alkylated products with dilute hydrochloric acid gave the corresponding free phosphonic acids **5** in excellent yields. That no racemization had taken place during the hydrolysis was ascertained by treatment of optically pure *(R)*-α–chloro-α-propyl phosphonic acid (R=Et) with thionyl chloride (2 eq.) in dichloromethane (30 min.) then *(R,R)*-1,2-bis-N-methylamino-cyclohexane in the presence of Et_3N in benzene to afford *(R)*-1-chloro-1-propyl phosphonamide **3** ,(R=Et) (Table 1, entry 2) in 67% isolated yield (2 steps), and a >99:1 ratio as evidenced by ^{31}P NMR.

Table 1 α–CHLORO α–ALKYL PHOSPHONIC ACIDS

ENTRY	RX	ALKYLATION(–100°C)				HYDROLYSIS			
		Yield%[a]	Ratio[b]	mp.(°C)	$[\alpha]^{25}_D$[d]	Yield%[e]	mp.(°C)	$[\alpha]^{25}_D$[f]	Config.[g]
***(R,R)* Series**									
1.	CH_3I	87	90:10	75-76°	–99.6°(c 0.5)	95	35-38°	+5.5° (c 1.0)	*R*
2.	CH_3CH_2I	79	>99:1[c]	123-125°	–69.0°(c 0.5)	98	109°	+36.6°(c 1.2)	*R*
3.	$CH_3(CH_2)_2I$	83	>99:1[c]	131-133°	–62.0°(c 1.0)	97	87-88°	+51.2°(c 1.0)	*R*
4.	CH_2=$CHCH_2Br$	80	>99:1[c]	136-137°	–71.5°(c 0.6)	quant.	oil	+32.0°(c 1.0)	*R*
5.	$PhCH_2Br$	86	91:9	103-105°	–15.4°(c 1.0)	quant.	104°	+32.9°(c 0.9)	*R*
6.	TBDPSiO-$(CH_2)_2I$	79	90:10[h]	oil	–21.0°(c 1.3)[i]	95	35°	+55.8°(c 0.55)[j]	*R*
7.	TBDPSiO-$(CH_2)_3I$	76	90:10[h]	56-58°	–34.0°(c 1.4)[i]	88	oil	+21.9°(c 1.65)[j]	*R*
***(S,S)* Series**									
8.	CH_3CH_2I	84	>1:99[c]	124-125°	+68.0°(c 1.0)	97	111°	–36.5°(c 1.25)	*S*
9.	$PhCH_2Br$	85	7:93	103-104°	+17.2°(c 1.3)	98	105°	–35.8°(c 1.32)	*S*

a. Yields of isolated crystalline materials except entry 6 (5~10% of the starting phosphonamide can be recovered); **b.** Diastereomeric ratios (*R*:*S*) evaluated by ^{31}P NMR recorded at 121.42 MHz on a Varian VXR–300 using 85% H_3PO_4 solution as an external reference; **c.** Only one diastereomer was detected by ^1H and ^{31}P NMR **d.** Optical rotations measured on a Perkin–Elmer–281 polarimeter in $CHCl_3$. **e.** Isolated yields after Dowex® 50W–X8, H^+ chromatography. **f.** Optical rotations measured in MeOH. **g.** Configuration established based on the absolute configuration of the precursor alkylated phosphonamide as determined by X–ray crystallography in the case of entry (2); (ref 8). **h.** The mixture of diastereomers was separated on silica gel (EtOAc-MeOH 99:1), TBDPSi = tert-butyldiphenylsilyl. **i.** Value for the major isomer. **j.** Value for the desilylated major isomer.

Alkylation of the *(R,R)*-ethylphosphonamide **2** (mp. 56°C, hexane, $[\alpha]^{25}_D$ –93.5°; c 1.0, $CHCl_3$) by treatment with LDA at -100°C, followed by the desired alkyl halide afforded the corresponding α-alkylated phosphonamide of general structure **4** (Table 2). Excellent diastereoselection ratios were obtained and the products were once again crystalline and suitable for X-ray analysis.[9] In a preliminary report,[10] we had shown that high diastereoselectivity (~90:10) was obtained with ethyl iodide and allyl bromide at -78°C.

We have now extended the reaction to other alkyl halides and it is clear that at -100°C, even better selectivity is observed. Surprisingly, alkylation of the carbanion derived from **2** with benzyl bromide at 0°C gave a 80:20 mixture of α-benzylated compounds in 87% yield (compare, Table 2, entry 3). Hydrolysis under acidic conditions afforded the corresponding α-methyl-α-alkyl phosphonic acids **6** in excellent yields and optical purities.

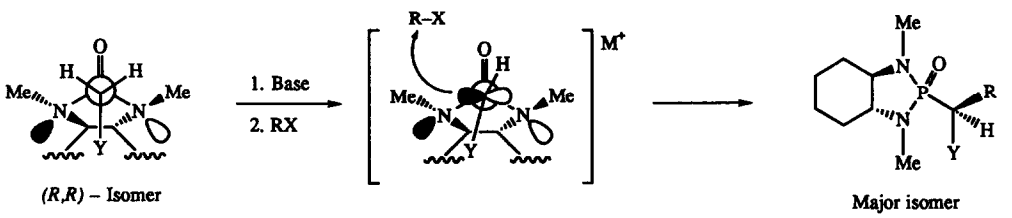
Table 2 α-METHYL α-ALKYL PHOSPHONIC ACIDS

ENTRY	RX	ALKYLATION(-100°C)				HYDROLYSIS			
		Yield%[a]	Ratio[b]	mp.(°C)	$[\alpha]^{25}_D$[d]	Yield%[e]	mp.(°C)	$[\alpha]^{25}_D$[f]	Config.[g]
***(R,R)* Series**									
1.	CH_3CH_2I	76	95:5	95-96°	-81.5°(c 1.0)	90	54-57°	+6.2° (c 1.0)	*R*
2.	CH_2=$CHCH_2Br$	82	94:6[h]	87-88°	-91.5°(c 1.0)	88	oil	-1.1°(c 1.75)	*R*
3.	$PhCH_2Br$	83	97:3	95-97°	-35.2°(c 1.2)	86	122-125°	+23.6°(c 2.2)	*R*
4.	TBDPSiO-$(CH_2)_2I$	68	94:6	oil	-32.5°(c 1.03)	94	35°	+7.0°(c 1.25)[i]	*R*
5.	TBDPSiO-$(CH_2)_3I$	71	>99:1[c]	oil	-35.5°(c 1.1)	92	oil	+23.8°(c 1.1)[i]	*R*
***(S,S)* Series**									
6.	CH_3CH_2I	78	5:95	92-95°	+79.2°(c 1.0)	91	54-56°	-6.1° (c 0.9)	*S*
7.	CH_2=$CHCH_2Br$	83	4:96	86-88°	+91.0°(c 1.0)	88	oil	+1.4°(c 1.4)	*S*
8.	$PhCH_2Br$	84	4:96	96-97°	+33.6°(c 1.0)	82	122-124°	-22.8°(c 1.0)	*S*

a. Isolated crystalline materials except entries 4 and 5 (oils); b–g (same as Table 1); h. Deprotonation (nBuLi, THF, -78°C) of the α-allylated phosphonamide (Table 2, entry 2, ratio 94:6) and deuteration (CD_3OD) gave a product in a diastereomeric ratio of 72:28 (^{31}P NMR). i. Value for the desilylated compound.

The preferential formation of the observed diastereomer in the alkylation of the chloromethyl and ethylphosphonamides **1** and **2** can be anticipated to some extent by examination of molecular models. Thus one can make the reasonable assumption that the attack of the initially formed anion on the electrophile will take place preferentially from the side facing the lone pair of one of the nitrogen atoms rather than the side facing the N-methyl group (Scheme 2). This corresponds to an approach of the more exposed face of a planar anion, which is supported by the recent elegant studies by Denmark and Dorow,[5] on the X-ray crystal structure of a $[Li^+.2THF]_2$ salt of the carbanion derived from 2-benzyl-2-oxo-1,3,2-diazaphosphorinane.

Scheme 2.



(R,R) – Isomer

In addition to their preparative utility in the asymmetric synthesis of the title compounds, these topologically interesting bicyclic phosphonamide reagents are diastereomerically pure in each series by virtue of the utilization of a C_2 symmetrical ligand.[11]

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7. In a typical procedure, a solution of LDA (1.55 mmoles) in dry THF is cooled at -100°C and treated with **1** (0.333 g, 1.41 mmoles) in 4.5 mL of dry THF at -100°C. After 15 min., propyl iodide (0.360 g, 2.11 mmoles) is added. After 10 min., the mixture is quenched at -100°C with excess MeOH then warmed to room temp.. Usual work up and chromatography affords 0.326 g (83%yield) of the α-alkylated product (Table 1, Entry 3).
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11. The chiral diamine could be recovered after Dowex®-H^+ chromatography. All compounds showed satisfactory spectroscopic and analytical results by ^1H, ^{13}C, ^{31}P, NMR, IR and HRMS.

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