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A Simple and General Method for the Asymmetric Synthesis of α-Aminophosphonic Acids

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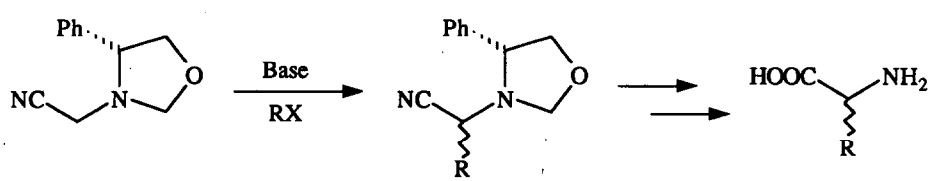
Abstract : A simple and general method for the asymmetric synthesis of α-aminophosphonic acids is described. A chiral phosphonate prepared in one step from R-(-)-phenylglycinol was alkylated with good diastereoselectivity using different electrophiles.

The α-aminophosphonic acids are important compounds possessing interesting biological activities by themselves or when incorporated into peptides[1]. During the two last decades the interest has grown for methods of obtaining α-aminophosphonic acids in non-racemic form[2]. From the different available methods, the asymmetric synthesis recently described by Hanessian[2n] appears to be very efficient giving both high chemical yields and enantiomeric excesses.

We wish to report herein our own results in this area: in spite of less impressive stereoselectivity our method is distinguished by its great simplicity and the rapid access to the starting material.

The method is an extension of that which we used some years ago to prepare substituted α-aminonitriles **2** and then α-aminoacids **3** using compound **1** as the chiral starting material (Scheme 1)[3].



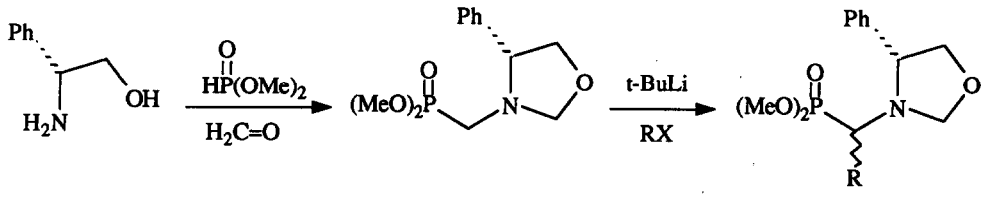
1 **2** **3**

Scheme 1

We planned the preparation of the phosphonate derivative **4** as an analog of aminonitrile **1**. Condensation of R-(-)-phenylglycinol, formaldehyde and dimethyl phosphite in refluxing methanol gave **4**[4] (Scheme 2) as a

stable crystalline compound { $[\alpha]_D^{20}$ -119 (c=1, $CHCl_3$), mp 78-79°C, 65% yield after recrystallization from ether }. Large amounts of phosphonate **4** can be easily obtained in this one-step procedure.

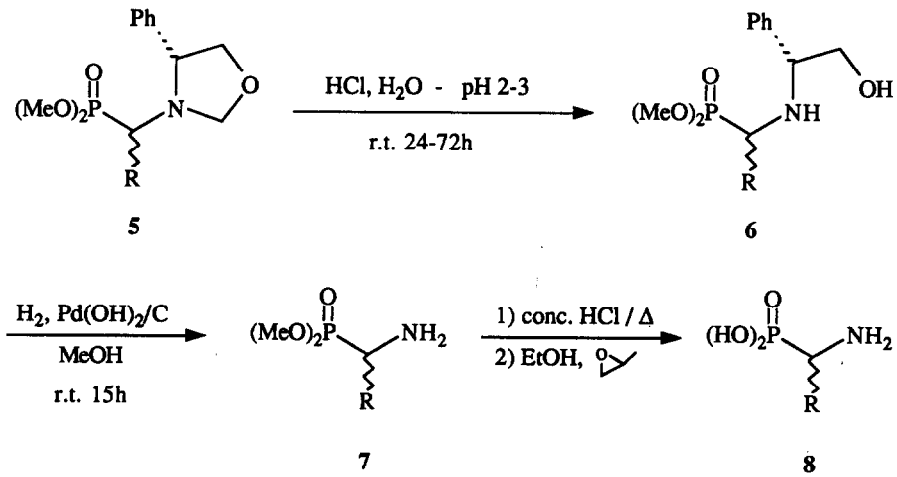
Treatment of **4** with 2 eq. of t-BuLi[5] at -78°C in THF, followed by quenching of the carbanion with the appropriate alkyl halide gave alkylated derivatives **5**[6] (Scheme 2, Table). The crude reaction mixture was monitored by HPLC and ^1H and ^{31}P NMR to determine the diastereomeric ratio of **5**. The results are summarized in the Table. Stereoselectivity varied from a modest 26% d.e., obtained for the methyl derivative, to 76% d.e. observed for the ethyl and benzyl derivatives. The reason for such a large variation between results for methyl and ethyl is not understood. In the case of alkylation with methyl iodide, a slight improvement was observed when the reaction was conducted at -100°C; furthermore neither the diastereoselectivity nor the yield were effected when TMEDA (3eq.) was used as cosolvent.



4 **5**

Scheme 2

Alkylated derivatives **5** were transformed to α-alkylated α-aminophosphonic acids **8** by stepwise transformations (Scheme 3). The oxazolidine ring of **5** was first hydrolyzed (dilute HCl, pH 2) to give aminoalcohol **6** (70% yield).



5 **6** **7** **8**

Scheme 3

Table : Diastereoselective alkylation of phosphonate **4** and hydrolysis to the aminophosphonic acids **8**

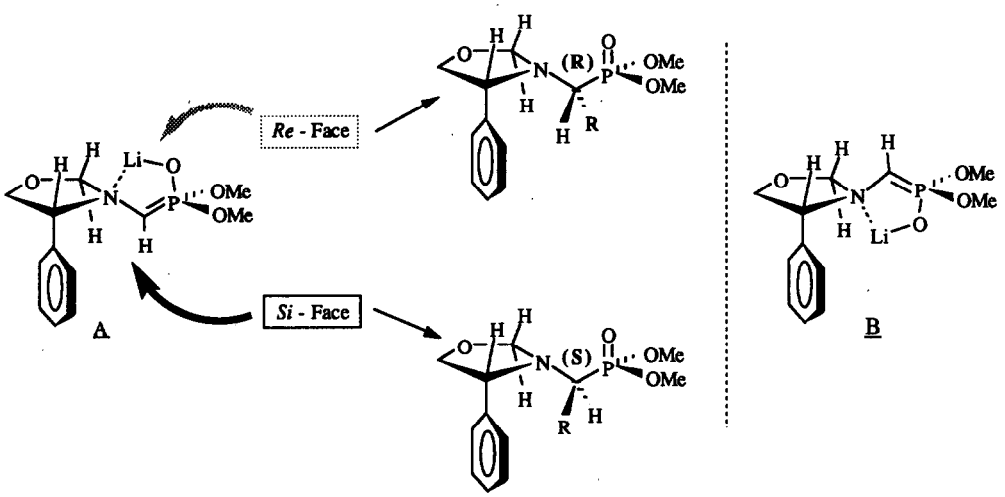
		5			8			
	RX	Yield (%)	Ratio	d.e. (%)	$[\alpha]_{578}$ c=1, 1*N* NaOH	$[\alpha]_{578}$ lit. c=1, 1*N* NaOH	e.e. (%)	Config.
a	CH_3I	75	63:37	26	-4	-16 [7]	25	R
	CH_3I *	86 *	68:32 *	36 *	-	-	-	-
b	C_2H_5I	50	88:12	76	-16	-21 [8]	76	R
c	CH_2=CH-CH_2Br	60	76:24	52	-	-	-	-
d	$PhCH_2Br$	60	88:12	76	-37	-49 [7]	75.5	R

* experiment conducted at -100°C

Hydrogenolysis of **6** (H_2, $Pd(OH)_2/C$) gave aminophosphonate **7** (80% yield) which was hydrolyzed (concentrated HCl, Δ) to give aminophosphonic acid **8** (80-90% yield). The e.e. of α-aminophosphonic acids **8**, determined from the optical rotations, are in good agreement with the d.e. of phosphonic ester **5** (determined by HPLC and NMR).

Separation of diastereomeric mixtures of **5** can be envisionned to prepare pure aminophosphonic acids. This has been achevied in the case of **5d** giving an enriched compound of 96% d.e. which was transformed to **8d** ($[\alpha]_{578}$ -46 (c=1, 1*N* NaOH); 94% e.e.).

The optical rotation permitted the attribution of absolute configuration and thus allowed us to propose a working model A (Figure) in which deprotonated aminophosphonate **4** - in a stable conformation owing to minimal non-bonding interactions and possible chelating control - reacts with electrophiles from the less hindered *Re* -face. An alternative model B in which the phosphonomethyl group and the phenyl group would be *trans* relative to the oxazolidine ring, was not taken into account since in this case no diastereofacial selectivity could be expected.



Figure

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4- Preparation of **4** : Formalin (37%; 35 mL) was added at room temperature to a stirred solution of R-(-)-phenylglycinol (13.72 g; 0.1 mol) and dimethylphosphite (11 mL; 0.12 mol) in 40 mL of methanol. The mixture was refluxed for 2h, cooled, poured into water, then extracted with Et_2O. The organic layers were dried ($MgSO_4$) and evaporated under vacuum to give a white crystalline compound which was recrystallized from ether (17.6 g; 65% yield).

5- Attempts to deprotonate phosphonate **4** using LDA (1-4 eq.), KHMDS or NaHMDS (2 eq.), n-BuLi (1-3 eq.) or 1 eq. t-BuLi proved unsuccessful.

6- In a typical experiment t-BuLi (1.5 M in pentane, 1.6 mmol) was added to a solution of phosphonate **4** (0.75 mmol) in dry THF (10 mL) cooled at -78°C. After 20 min alkyl halide (8 mmol) was added to the yellow solution. The reaction was quenched with water after disappearance of starting material (ca 30 min) and then allowed to warm to room temperature. Flash-chromatography of the crude mixture afforded the α-alkylated compound (yield 60-85% see Table).

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8- The optical rotation value of enantiomerically pure **8b** is not reported in the literature; the value noted here was calculated from the rotation and e.e. reported by Hanessian[2n].

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