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A Highly Convenient Route to Optically Pure α-Aminophosphonic Acids

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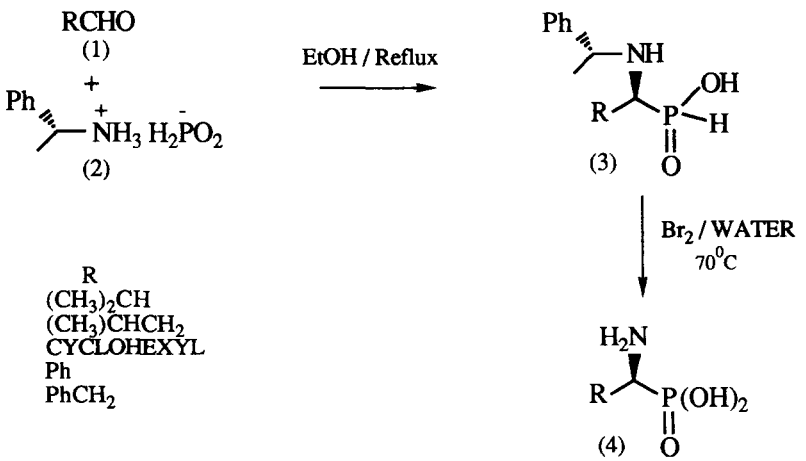
Abstract: *Pure diasteriomers, obtained simply and directly by reaction of hypophosphorous acid salts of (R)(+) or (S)(-) - N-α-methylbenzylamine with aldehydes, can be simultaneously deprotected and oxidised in one step to provide a highly convenient synthesis of α - aminophosphonic acids in high optical purity.*

α - Aminophosphonic acids, the phosphonic acid analogues of α-amino carboxylic acids, are an important class of compounds that exhibit a variety of interesting and useful properties. Extensive investigations over the last twenty years have shown they are of particular importance in biological and medicinal research[1]. A number are now known to be potent antibiotics[2], enzyme inhibitors[3] and pharmocological agents[4]. They also show remarkable activity as pesticides[5], insecticides and herbicides[6].

Such an impressive array of applications has stimulated considerable interest in their synthesis and there are now a wide variety of synthetic routes to racemic α-aminophosphonic acids[7]. However new routes to individual



Scheme 1

enantiomers are still urgently required since those currently available often involve difficult separations or the use of enzymes and frequently lack generality, give variable optical yields or require multi-step synthetically demanding sequences[8]. We now report a highly convenient, general, two-step route which provides α-aminophosphonic acids in high optical purity in either enantiomeric form.

TABLE 1.

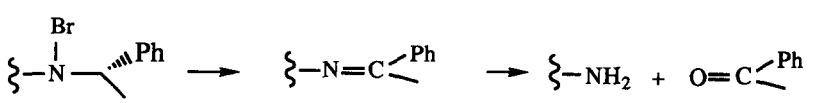
DIASTERIOMERIC PHOSPHONOUS ACID CONDENSATION PRODUCTS (3)

R	Reaction Time (hr)	M.P. ^0C	Yield[b] %	$[\alpha]_D^0$c=1 2M NaOH
S(-) Amine Series				
CH_3[a]				
$(CH_3)_2CH$	4	220-3	45	-82.0
$(CH_3)_2CHCH_2$	4	215-7	29	-88.0
CYCLOHEXYL	6	221-4	50	-48.0
Ph	2	242-3	33	-37.0
$PhCH_2$	2 days	193-6	19	-68.0
R(+) Amine Series				
CH_3[a]				
$(CH_3)_2CH$	4	223-5	49	+81.0
$(CH_3)_2CHCH_2$	4	218-20	33	+89.0
CYCLOHEXYL	6	228-30	32	+48.7
Ph	2	241.5-2.5	35	+40.0
$PhCH_2$	2 days	190-5	20	+67.0

(a) Gave a dark coloured solution from which no product could be isolated
(b) Based on hypophosphorous acid salt

Our approach is based on a convenient and general method of synthesis of racemic α-aminophosphonous acids reported by Baylis et al[9] which involves as a key step the addition of the hypophosphorous acid salt of diphenylmethylamine to aldehydes.

Chiral hypophosphorous acid salts (2) were prepared by the dropwise addition of (R)(+)- or (S)(-)-N-α-methylbenzylamine to the anhydrous hypophosphorus acid[10] in dry ethanol with cooling to prevent the temperature rising above 25^0C. The precipitated salts were filtered off and washed with dry ethanol and then with dry ether. The salts (2) reacted with a small excess of the appropriate aldehyde in refluxing ethanol to give a precipitate. Filtration and washing with ethanol gave the corresponding N-protected α-aminophosphonous acid (3) (Table 1). ^1H NMR spectra of these products indicated that each was obtained as a single diastereomer[11] Compounds (3) were then stirred with bromine-water[12] at 70^0C and the reaction monitored by ^1H NMR for the disappearance of signals due to the α-methylbenzyl group. On completion of reaction the aqueous solution was decanted and evaporated to dryness under vacuum. The resulting oil was dissolved in ethanol and treated with propylene oxide to give a precipitate of the α–aminophosphonic acid (4)[13] (Table 2.).



Scheme 2

In addition to the expected conversion of (3) to the corresponding phosphonic acid, treatment with bromine -water also removes the α-methylbenzyl group thus providing a simultaneous oxidation-deprotection sequence. This offers a substantial advantage over previously published procedures[14] since the removal of the N-protecting group in organophosphorus compounds by hydrogenolysis can cause difficulty. Cleavage of the N-α-methylbenzyl group by bromine-water under these conditions was unexpected and to our knowledge has not previously been reported. A possible explanation involves a bromination-dehydrobromination sequence (Scheme 2). The imine thus formed would hydrolyse under the reaction conditions forming the amine group. Evidence in support of such a mechanism is provided by the isolation of bromoacetophenone as the main reaction side-product which could result from initially released acetophenone undergoing acid-catalysed bromination.

TABLE 2

α - AMINOPHOSPHONIC ACIDS (4)

R	Reaction Time hr	Reaction Temp.^{0}C	Yield[b] %	$[\alpha]_D^0$c=1 2M NaOH	$[\alpha]_{D,litt.}^0$	Conf.
(S)(-) Amine Series						
$(CH_3)_2CH$	6	70	88	+1.0	+1.0 [15]	R
$(CH_3)_2CHCH_2$	6	70	67	-27.4	-28.0 [c, 16]	R
CYCLOHEXYL	8	70	65	-5.0	- [d]	-
Ph	2wks.[a]	RT	77	+13.5	+18.0 [15]	R
$PhCH_2$	8	70	87	-37.0	-38.9 [17]	R
(R)(+) Amine Series						
$(CH_3)_2CH$	6	70	87	-1.0	-1.0 [15]	S
$(CH_3)_2CHCH_2$	6	70	82	+26.8	+27.0 [c, 16]	S
CYCLOHEXYL	8	70	73	+5.4	- [d]	-
Ph	2wks[a]	RT	82	-16.0	-18.0 [15]	S
$PhCH_2$	8	70	92	+35.0	+37.0 [17]	S

(a) Shorter times and higher reaction temperature resulted in increased racemization (b) Based on (3), (c) Value is for $[\alpha]_{578}$, (d) Not available

A comparison of the $[\alpha]_D$ values obtained for compounds (4) with literature values (Table 2), where available, indicates high levels of optical purity. This, together with its convenience and generality suggests that this is now the method of choice for the synthesis of single enantiomers of α-aminophosphonic acids and their esters[18].

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11 ^{1}H NMR data for (3) [D_2O/NaOD, 300MHz];
(S)(-) Amine Series: R = $(CH_3)_2CH$, δ 0.72 & 0.8 (dd, 6H, *J* = 7.1Hz $(CH_3)_2CH$), 1.31 (d, 3H, *J* = 6.6Hz, CH_3), 1.9 m,1H, $(CH_3)_2CH$), 2.16 (dd, 1H, *J* = 3.3Hz, *J* = 9.7Hz, N-CH-P), 4.08 (q, 1H, *J* = 6.6Hz, $CHCH_3$), 6.13 & 7.8 (d, 1H, *J* = 500Hz, PH), 7.315 (m, 5H, Ar-H); R=$(CH_3)_2CHCH_2$, δ 0.31 & 0.69 (dd, 6H, *J* = 6.3Hz, $(CH_3)_2CH$), 1.15 (m, 2H, CH_2), 1.26 (d, 3H, *J* = 6.5Hz, CH_3), 1.42 (m, 1H, $(CH_3)_2CH$), 2.30 (m, 1H, N-CH-P), 4.05 (q, 1H, *J* = 6.5Hz, $CHCH_3$), 5.94 & 7.60 (d, 1H, *J* = 500Hz, PH), 7.30 (m, 5H, Ar-H) R = Cyclohexyl, δ 0.95 - 1.45 (m,11H, Cyclohexyl), 1.95 (m, 1H, N-CH-P), 3.75 (q, 1H, $CHCH_3$), 5.95 & 7.6(d, 1H, *J* = 500Hz, PH), 7.10 (m, 5H, Ar-H) R = Ph, δ 1.24 (d, 3H, *J* = 6.5Hz, $CHCH_3$), 3.75 (m, 2H, $CHCH_3$ & N-CH-P), 5.92 & 7.65 (d, 1H, *J* = 500Hz, PH), 7.20 (m, 5H, Ar-H)
R = $PhCH_2$, δ 1.05 (d, 3H, $CHCH_3$), 2.2 (m, 1H, N-CH-P), 2.40 &2.90 (2xm, 2H, CH_2), 3.95 (q, 1H, $CHCH_3$), 5.9 & 7.55 (d, 1H, *J* = 500Hz, PH), 6.60 - 7.20 (m, 10H, Ar-H)
(R)(+) Amine Series: R = $(CH_3)_2CH$, δ 0.70 & 0.78 (dd, 6H, *J* = 7Hz, $CH_3)_2CH$), 1.30 (d, 3H, *J* = 6.6Hz, CH_3), 1.85 (m, 1H, $(CH_3)_2CH$), 2.14 (dd, 1H, *J* = 3.55, *J* = 9.7Hz, N-CH-P), 4.05 (q, 1H, *J* = 6.6Hz, $CHCH_3$), 6.10 & 7.77 (d, 1H, *J* = 500Hz, PH), 7.30 (m, 5H, Ar-H); R = $(CH_3)_2CHCH_2$, δ 0.31 & 0.70 (dd, 6H, *J* = 6.35, $(CH_3)_2CH$), 1.16 (m, 2H, CH_2), 1.30 (d, 3H, *J* = 6.5Hz, CH_3),1.40 (m, 1H, $(CH_3)_2CH$), 2.30 (m, 1H, N-CH-P), 4.04 (q, 1H, *J* = 6.5Hz, $CHCH_3$), 5.95 & 7.61 (d, 1H, *J* = 500Hz,PH),7.30 (m, 5H, Ar-H); R = Cyclohexyl, δ 0.95 - 1.65 (m, 11H, Cyclohexyl), 2.1 (m, 1H, N-CH-P), 4.05 (q, 1H, *J* = 6.5Hz, $CHCH_3$), 6.1 & 7.78 (d, 1H, *J* = 500Hz, PH), 7.30 (m, 5H, Ar-H); R = Ph, δ 1.24 (d, 3H, *J* = 6.5Hz, $CHCH_3$), 3.76 (m, 2H, $CHCH_3$ & N-CH-P), 5.94 & 7.67 (d, 1H, *J* = 500Hz, PH), 7.23 (m, 5H, Ar-H); R = $PhCH_2$, δ 1.05 (d, 3H, *J* = 6.5Hz, $CHCH_3$), 2.35 (m, 2H, H-C-H & N-CH-P), 2.85 (m, 1H, H-C-H), 3.95 (q, 1H, *J* = 6.5Hz, $CHCH_3$), 5.9 & 7.59 (d, 1H, *J* = 500Hz, PH), 6.60 - 7.20 (m, 10H, Ar-H)

12 Aliquots of bromine-water were added at intervals to the reaction mixture.

13 ^{1}H NMR data for (4) [D_2O, 300MHz];
R = $(CH_3)_2CH$, δ 1.1 (dd, 6H, *J* = 6.9Hz, $(CH_3)_2CH$), 2.21 (m, 1H, $(CH_3)_2CH$), 3.10 (dd, 1H, *J* = 6.4Hz, *J* = 14.3Hz, N-CH-P), R = $(CH_3)_2CHCH_2$, δ 0.90 (dd, 6H, *J* = 5.8Hz, $(CH_3)_2CH$), 1.63 (m, 3H, $CHCH_2$), 3.29 (m, 1H, N-CH-P), R = Cyclohexyl, δ 0.65 – 1.75 (m, 11H, Cyclohexyl), 2.20 (m, 1H, N-CH-P), R = Ph, δ 4.22 (d, 1H, *J* = 17.6, N-CH-P), 7.40 (s, 5H, Ar-H), R = $PhCH_2$, δ [2.40 (m, 1H) & 2.80 (m, 1H) $PhCH_2$], 3.23 (m, 1H, N-CH-P), 7.30 (m, 5H, Ar-H)

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18 We have now prepared single enantiomers of a number of alkyl and aryl esters from (4)

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