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An efficient synthesis of α- and β-aminophosphonic esters from α-amino acids

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Abstract—Catalytic hydrogenation of *N*-Boc aziridine 2-phosphonates derived from 3-amino-2-hydroxyphosphonates affords *N*-Boc α-aminophosphonic esters in high enantiomeric purities. Alternatively, the α-hydroxy β-aminophosphonic esters can be reduced into β-aminophosphonic esters by radical deoxygenation.

Aminophosphonic acids are attractive substitutes for aminocarboxylic acids in the design of enzyme inhibitors. These phosphonic acids have found applications as potent active compounds with a large range of biological activities: antibacterial agents,[1] enzyme inhibitors,[2] haptens for catalytic antibodies,[3] or anti HIV agents.[4] Presently, a number of methods are available for the synthesis of optically pure and enriched α-aminophosphonic acids, via resolution, enzymatic techniques, or asymmetric synthesis.[5] An attractive alternative route would be to control the reductive opening of 2,3-aziridinophosphonates. Indeed, these heterocycles may be prepared in an optically active form by various methods such as Darzens-type condensation of carbanions derived from chiral phosphonamides,[6] addition to chiral sulfinimides,[7] cyclisation of α-hydroxy β-aminophosphonates obtained by asymmetric aminohydroxylation of unsaturated phosphonates[8] or reduction of chiral 2*H*-azirinephosphonates.[9] However, little is known concerning the regioselectivity of the hydrogenolytic cleavage of these aziridines and non-convergent results were reported for *N*-tosyl aziridines.[10]

We report here that the *N*-Boc-protected *cis* aziridines derived from *syn* α-hydroxy β-aminophosphonates are regioselectively hydrogenated to give optically enriched α-aminophosphonates (Scheme 1).

Nucleophilic addition of phosphites to aldehydes constitutes one of the simplest entries to α-hydroxyphosphonic acid derivatives. Applied to α-aminoaldehydes, this reaction allows easy access to α-hydroxy β-aminophosphonates. However, the diastereoselectivity of this reaction is highly dependent on the nature of the protecting group.[11] We decided to study the *N*-Boc derivatives because this protective group is one of the most interesting in peptide synthesis. In a first experiment, the aldehyde **1a** derived from phenylalanine[12] was reacted at room temperature with trimethylsilylphosphite.[13] After acid hydrolysis the corresponding phosphonates **2a** and **3a** were obtained in a 63:37 ratio (Table 1, entry 1).[14] In an effort to obtain better diastereoselectivity, the same reaction was conducted at low temperature in the presence of a Lewis acid. With titanium tetrachloride, the reaction was slow enough and the phosphonates were isolated in essentially the same diastereomeric ratio (entry 2). The use of tin tetrachloride allowed us to increase this ratio up to 80:20; however, we were unable to achieve total conversion of the aldehyde. We then turned our attention towards the activation of the nucleophile. Such an activation by fluorides was previously reported[15] and using potassium fluoride in DMF at room temperature, we obtained the phosphonates **2a** and **3a** in good yield and satisfactory diastereomeric excess (entry 5). Similar results were obtained with other aminoaldehydes.

These 2-hydroxy 3-aminophosphonates were then converted into *N*-Boc aziridines. In a first experiment **2d** was submitted after separation to a Mitsunobu reaction (triphenylphosphine–diisopropylazodicarboxylate in THF). However, a 2-*t*-butoxy-1,3-oxazoline resulting from the intramolecular substitution of the activated hydroxyl by the Boc carbonyl oxygen was isolated as the main product. Mixtures of phosphonates **2** and **3**

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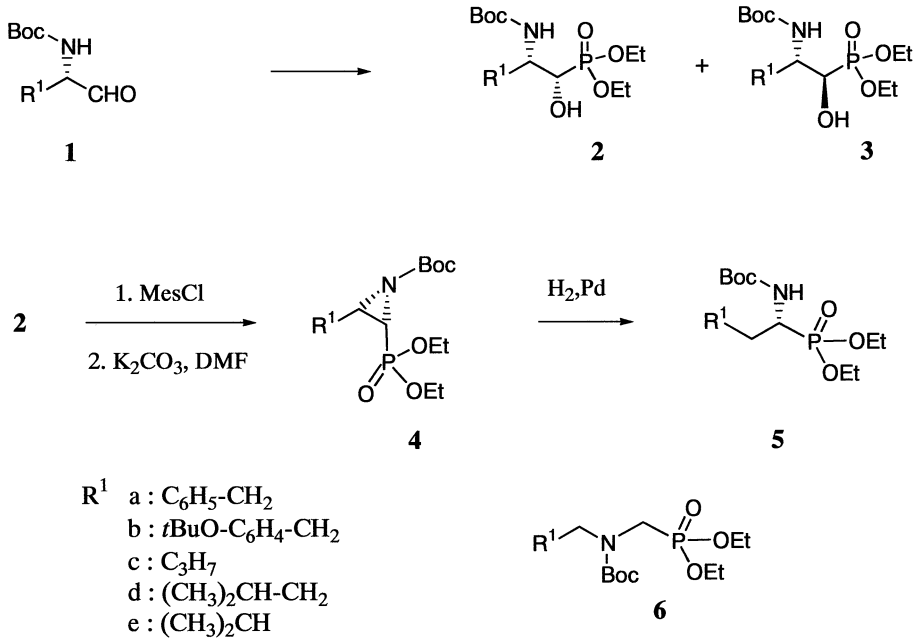


Scheme 1.

Table 1. Stereoselective hydrophosphonylation of aldehydes **1**

Entry	Aldehyde	Method	Temp. (time)	**2**:**3**	Yield (%)
1	**1a**	A	20°C (24 h)	63:37	85
2	**1a**	B	−78°C (10 h)	60:40	63
3	**1a**	C	−78°C (6 h)	74:26	53
4	**1a**	D	0°C (20 h)	73:27	92
5	**1a**	E	0°C (24 h)	82:18	75
6	**1b**	E	20°C (24 h)	80:20	82
7	**1c**	E	20°C (18 h)	87:13	76
8	**1d**	E	20°C (15 h)	81:19	74
9	**1e**	E	20°C (18 h)	78:22	68

A: $(EtO)_2P$-$OSiMe_3$, CH_2Cl_2; B: $(EtO)_2P$-$OSiMe_3$, $TiCl_4$ (1.4 equiv.), CH_2Cl_2; C: $(EtO)_2P$-$OSiMe_3$, $SnCl_4$ (1.4 equiv.), CH_2Cl_2; D: $(EtO)_2P(O)H$, CsF, neat; E: $(EtO)_2P(O)H$, KF, DMF.

were then mesylated[16] and, after separation of the minor components, cyclised in the presence of potassium carbonate in DMF to give pure *cis* aziridines exclusively in excellent yields.[17]

These aziridines were then submitted to catalytic hydrogenation. First, the reactions were carried out in ethanol in the presence of Pearlman catalyst. Phosphonates resulting from a highly regiocontrolled β ring-opening reaction were obtained in nearly quantitative yields. However, unexpectedly, they were isolated as a 1:1 mixture of compounds **5** and **6**, resulting from the cleavage of the aziridine C–C bond. This result was probably due to the presence of the Boc protecting group which was not a powerful enough activating group to transform the nitrogen atom into a good leaving group.

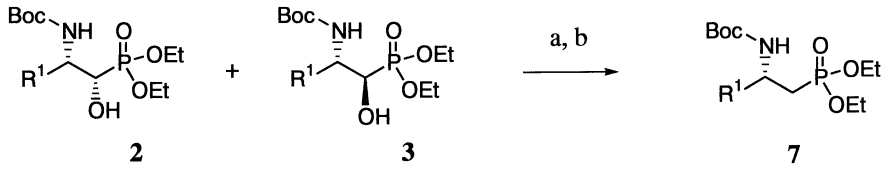
We then decided to modify the catalyst and were pleased to observe that when the reaction was conducted in the presence of a catalytic amount of 10% Pd-on-carbon, the formation of compound **6** was almost entirely suppressed. The (*R*) α-aminophosphonic esters **5** were then isolated in good yields and high enantiomeric purities except for compound **4e** which showed a low reactivity (Table 2).[18]

However, in contrast with the Pearlman catalyst, the use of Pd-on-carbon always led to the formation of a small amount (1–3%) of the *N*-Boc-protected β-aminophosphonic esters, a result which was established

Table 2. Hydrogenolysis of aziridines **4**

Aziridine	**5** (yield %)[a]	$[\alpha]_D^{20}$ (*c*, solvent)	Conf.
4a	77	−14.1 (2.68, $CHCl_3$)	*R*
4b	65	−14.2 (3.45, CH_2Cl_2)	*R*
4c	64	−27.0 (4.20, $CHCl_3$)	*R*
ent-**4d**	68	+24.0 (3.45, $CHCl_3$)	*S*
4e	5	–	–

[a] Isolated yield.



2 3 7

Scheme 2. *Reagents and conditions*: (a) thiocarbonyldiimidazole (2 equiv.), $(CH_2Cl)_2$, 20°C, 20 h, 95%; (b) Et_3SiH (10 equiv.), $(BzO)_2$ (2 equiv.), refluxing 1 h, 80–85%.

by comparing GLC and HPLC results of the crude reaction mixture with authentic samples of racemic β-aminophosphonic esters prepared by reductive amination of β-ketophosphonates.[19] These compounds resulting from the attack in the α-position of the phosphonate group were easily removed by flash chromatography.

Hydrogenolysis of the *trans* aziridine obtained by cyclisation of the mesylate derived from the *anti* phosphonate **3a** was also regioselective and, as expected, gave the (*S*) α-aminophosphonic ester *ent*-**5a** of opposite configuration. However, probably due to steric hindrance and to a more difficult approach of the *trans* aziridine moiety near the catalyst surface, hydrogenolysis was more difficult to achieve and only resulted in 63% yield.

The easy access to 3-amino-2-hydroxyphosphonates allowed us to elaborate a simple method for synthesising optically active β-aminophosphonic esters, the preparation of which are rare enough.[20] Our approach was based on the reductive deoxygenation of the hydroxyphosphonates **2** and **3**. In a first approach, the mesylates derived from these phosphonates were reacted with lithium triethylborohydride, a reagent known to easily cleave the C–O bond of sulfonates.[21] However, due to its basic properties, this reducing agent afforded the aziridines **4** only. We turned then our attention towards the radical cleavage of imidazolylthiocarbonates.[22] These compounds were prepared in nearly quantitative yields by reaction of aminohydroxyphosphonates with thiocarbonyldiimidazole. Further reduction of these intermediates with triethylsilane in the presence of benzoylperoxide afforded *N*-Boc-protected β-aminophosphonic esters **7** in good yields and high optical purities (Scheme 2).[23]

Thus, by using the stereoselective condensation of α-aminoaldehydes with diethylphosphonates, we succeeded to synthesise α- or β-aminophosphonates at will in high enantiomeric purities.

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14. ^{31}P NMR was found to be the most convenient method for determining the diastereomeric ratio of phosphonates **2** and **3**. In all cases, the *syn* isomer appears downfield compared to the *anti* isomer[11] (**2a**: 24.11 ppm, **3a**: 23.68 ppm in $CDCl_3$).
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16. It is noteworthy that the mesylates were considerably more crystalline and easier to purify by flash chromatography than the starting hydroxyphosphonates.
17. The cyclisations were conducted by heating the mesylates derived from **2** at 80°C in pure DMF for 4 hours: yields:

4a: 82%; **4b**: 92%; **4c**: 83%; **4d**: 77%; **4e**: 79%. The stereochemical assignment of the aziridines was based on the large ring proton coupling constants observed for the *cis* isomers ($^3J_{HH}$: 6–7 Hz for the *cis* isomers and 2–3 Hz for the *trans* isomers); cf. Refs. 8 and 9.

18. The enantiomeric purities were measured by chiral GLC (25 m Chirasil D-Val from Chrompack) for **5a** (92%), **5c** (92%) and **5d** (94%). In order to confirm the *R* absolute configuration, the phosphonate **5c** was deprotected with trifluoroacetic acid and the optical rotation of the resulting free aminophosphonate {$[\alpha]_D^{20}=-13$ (*c* 1.9, $CHCl_3$)} compared with those of the literature: $[\alpha]_D^{20}=-11$ (*c* 1.9, $CHCl_3$), 82% e.e. See: Gajda, T. *Tetrahedron: Asymmetry* **1994**, *5*, 1965–1972.
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23. The reaction was conducted on the mixture of **2** and **3**: Total yields from **2**+**3**: (*S*)-**7a** (76%): $[\alpha]_D^{20}=-8$ (*c* 1.40, CH_2Cl_2); (*S*)-**7b** (70%): $[\alpha]_D^{20}=-7$ (*c* 1.0, CH_2Cl_2); (*S*)-**7e** (74%): $[\alpha]_D^{20}=-9$ (*c* 2.05, CH_2Cl_2). Optical purities were measured by HPLC (Chiracel-OD from Daicel; hexane:2-propanol 9:1) for **7a** (e.e.: 98%) and **7b** (e.e.: 98%) or by GLC (50 m XE60-*S*-Valine-*S*-α-PEA from Chrompack) for **7e** (e.e.: 95%).