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Diastereoselective synthesis of β-amino-α-hydroxy phosphonates via oxazaborolidine catalyzed reduction of β-phthalimido-α-keto phosphonates

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Abstract

Reduction of β-phthalimido-α-keto phosphonates, obtained through an Arbuzov reaction between the appropriate acid chloride and triethyl phosphite, with boranes and oxazaborolidine as catalyst, afforded β-phthalimido-α-hydroxy phosphonates in good yields and high diastereoselectivity. Deprotection of the amino group gave the title compounds.

Keywords: amino acids; amino acid derivatives; Arbuzov reaction; phosphonic acids; phosphonic acid derivatives.

Since the discovery of (2-aminoethyl)phosphonic acid in 1959,[1] and the isolation of 2-amino-1-hydroxyethylphosphonic acid from *Acanthamoeba castellanii*,[2] there has been a growing interest in the synthesis of phosphorus derivatives of amino acids because of their wide range of activities. In particular, 2-amino-1-hydroxyalkylphosphonic acids and congeners are inhibitors of proteolytic enzymes such as renin and HIV-protease.

To the best of our knowledge, only a few examples of synthetic approaches to optically active β-amino-α-hydroxy phosphonic acids and derivatives are reported in the literature. In most of the cases, addition of dialkyl phosphites to selected *N*-blocked α-aminoaldehydes derived from natural amino acids produced variable mixtures of β-amino-α-hydroxy phosphonates.[3]

As a part of our continuous interest in the synthesis of non-proteinogenic amino acids,[4] we wish to report here a simple entry to chiral 2-amino-1-hydroxy phosphonates which takes advantage of the diastereoselective reduction of the keto group of β-phthalimido-α-keto phosphonates by means of catalytic amounts of oxazaborolidine with catecholborane or borane–dimethylsulfide complex as the reducing agents.

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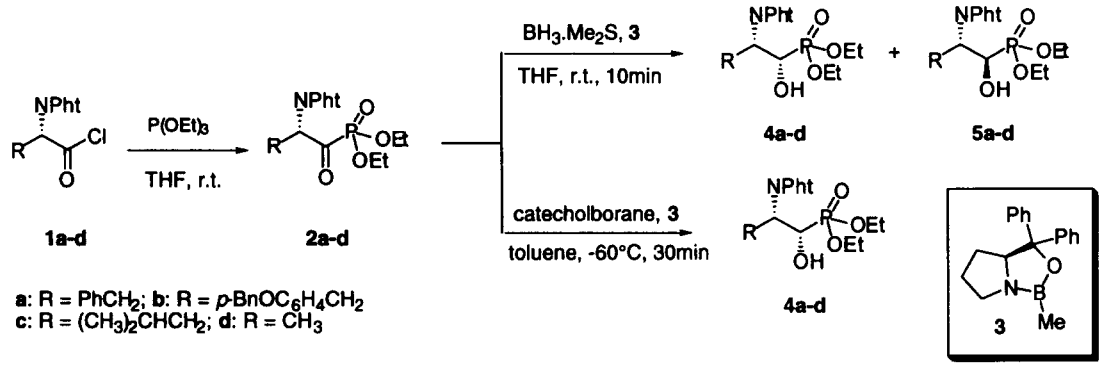
All starting compounds were synthesized by the Arbuzov reaction between the appropriate acyl chloride **1a–d**[5] and triethyl phosphite. According to Scheme 1, the crude diethyl acyloxyphosphonates **2a–d** were reacted with a borane–dimethylsulfide complex in tetrahydrofuran at room temperature or catecholborane in toluene at –60°C,[6] in the presence of a catalytic amount (12 mol%) of freshly prepared oxazaborolidine **3**.[7]



Scheme 1.

Reductions with the borane–dimethylsulfide complex afforded the mixtures of diastereoisomers **4a–d** and **5a–d** (Table 1).

On the other hand, highest diastereoselectivity was achieved when we used catecholborane as the reductant, with only **4a–d** being obtained (Table 2).

A significant exception to this trend of reactivity was offered by compound **2e** (R=Me_2CH), which was converted to the hydroxy phosphonate **4e** by reduction with both the borane–dimethylsulfide complex and catecholborane (Scheme 2).[8]

To assign the stereochemistry of the major isomers **4a–e**, compound **4a** was converted to the corresponding oxazolidinone **7**, by removal of the phthalimido protecting group with hydrazine and subsequent

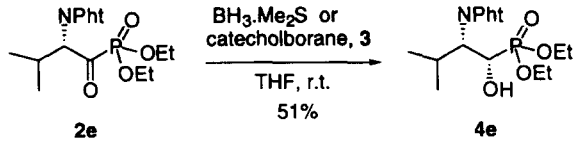
Table 1
Reductions of keto phosphonates **2a–d** with the borane–dimethylsulfide complex

Compounds 4 and 5	Yield (%)[a]	Ratio 4/5[b]	^{31}P NMR (ppm)[c]
a	66	8:1	**4a**: 21.29, **5a**: 23.15
b	60	8:1	**4b**: 21.35, **5b**: 23.21
c	66	9:1	**4c**: 21.25, **5c**: 23.13
d	62	10:1	**4d**: 21.29, **5d**: 22.83

Table 2
Reductions of keto phosphonates **2a–d** with catecholborane

Compounds 4	Yield (%)[a]	$[\alpha]_D^{25}$	^{31}P NMR (ppm)[c]
a	66	-46[d]	21.29
b	63	-50.64[d]	21.35
c	70	+16[e]	21.25
d	77	+26.45[e]	21.29

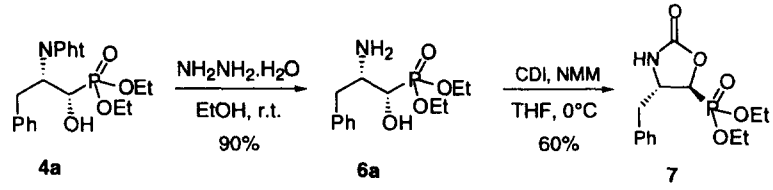
In **Table 1** and **Table 2**: [a] yield of isolated products (flash cromatography) based on **1**; [b] determined by ^{31}P NMR and HPLC; [c] recorded at 81 MHz in $CDCl_3$, using H_3PO_4 as the external standard; [d] c 1, $CHCl_3$; [e] c 1, MeOH



2e 4e

Scheme 2.

cyclization of the intermediate amine **6a** with carbonyldiimidazole (CDI) and *N*-methylmorpholine (NMM) (Scheme 3).



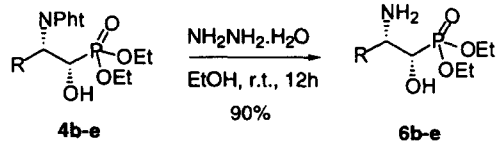
4a 6a 7

Scheme 3.

NMR spectra (^{1}H and ^{31}P) and $[\alpha]_D$ of **7** agreed with those of the reported one,[9] thus excluding any appreciable racemization of **1a** or **2a** and establishing a *syn* relationship between the hydroxyl and the phthalimido groups in **4a**. The relative stereochemistry of all derivatives **4** was assigned by analogy to **4a**.

The stereochemical outcomes of the reductions fit with Corey's model, which involves a transition state where the phosphonate moiety represents the large group. The hydride attack occurring preferentially from the *re* face produces the *S* configuration at the newly created stereogenic centre.[10]

The phosphonates **4b–e** were eventually reacted with hydrazine (Scheme 4) to furnish diethyl 2-amino-1-hydroxy phosphonates **6b–e** in quantitative yields.[11]



4b-e 6b-e

Scheme 4.

In conclusion, the oxazaborolidine catalyzed reduction of β-phthalimido-α-keto phosphonates with catecholborane opens the way to a simple and diastereoselective transformation of natural α-amino acids into β-amino-α-hydroxy phosphonates.

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6. Experimental procedure for the borane–dimethylsulfide complex reductions: A solution of **2** (1 mmol) in THF (2 ml) was slowly added to a solution of borane–dimethylsulfide complex (0.66 mmol) and **3** (0.12 mmol) in THF (2 ml). The mixture was stirred at room temperature for 10 min, then cooled (0°C) and treated with a solution of HCl in MeOH (1.2 mmol). After stirring for 30 min, the solvent was evaporated and the hydrochloride of the amino alcohol was filtered. Evaporation of the filtrate and flash chromatographic purification of the residue afforded the mixture of the alcohols **4** and **5**. Experimental procedure for the catecholborane reductions: To a cooled (–60°C) solution of **2** (1 mmol) and **3** (0.12 mmol) in toluene (2 ml), was slowly added a solution of catecholborane (1.5 mmol) in toluene (2 ml). The mixture was stirred at the same temperature for 30 min, then diluted with ether and washed with $NaHCO_3$ solution. The phases were separated, the organic extracts dried (Na_2SO_4) and concentrated. The residue was dissolved in EtOAc and the HCl salt of the aminoalcohol precipitated as previously described. The filtrate was concentrated and the residue purified by flash chromatography.
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8. Compound **4e**: $[\alpha]_D^{25}$ +13.7 (c 1, $CHCl_3$); ^{31}P NMR: 21.71.
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11. All new compounds gave satisfactory spectroscopic and analytical data. ^1H NMR were recorded at 200 MHz in $CDCl_3$. Selected data for **6a–e** as follows. Compound **6a**: $[\alpha]_D^{25}$ +4.17 (c 1.27, MeOH). ^1H NMR: δ 1.31 (t, J=7 Hz, 6H, $P(OCH_2\mathit{CH_3})_2$), 2.6–3.0 (m, 2H, $\mathit{CH_2}Ph$), 3.13 (br, 3H, NH_2 and OH), 3.4–3.6 (m, 1H, $\mathit{CH}NH_2$), 3.71 (d, $^2J_{HP}$=6.7 Hz, $^3J_{HH}$=2 Hz, 1H, *CH*OH), 4.13 (m, 4H, $P(O\mathit{CH_2}CH_3)_2$), 7.2–7.3 (m, 5H, arom.); ^{31}P NMR: 24.61. Compound **6b**: oil, $[\alpha]_D^{25}$ –4.3 (c 1.86, $CHCl_3$); ^1H NMR: δ 1.32 (t, J=7Hz, 3H, $P\text{-}OCH_2\mathit{CH_3}$), 1.33 (t, J=7 Hz, 3H, $P\text{-}OCH_2\mathit{CH_3}$), 2.6–3.0 (m, 5H, $\mathit{CH_2}Ph$ and NH_2 and OH), 3.55 (m, 1H, $\mathit{CH}NH_2$), 3.71 (d, $^2J_{HP}$=6.3 Hz, $^3J_{HH}$=1.7 Hz, 1H, *CH*OH), 4.0–4.3 (m, 4H, $P(O\mathit{CH_2}CH_3)_2$), 5.05 (s, 2H, $O\mathit{CH_2}Ph$), 6.93 (d, J=8.6 Hz, 2H, arom.), 7.14 (d, J=8.6 Hz, 2H, arom.), 7.3–7.5 (m, 5H, arom.); ^{31}P NMR: δ 24.6. Compound **6c**: oil, $[\alpha]_D^{25}$ –2.7 (c 0.41, $CHCl_3$); ^1H NMR: δ 0.9 (d, J=6.5 Hz, 6H, $(\mathit{CH_3})_2CH$), 1.35 (m, 8H, $P(OCH_2\mathit{CH_3})_2$ and $(CH_3)_2CH\mathit{CH_2}$), 1.5–1.7 (m, 1H, $(CH_3)_2\mathit{CH}$), 2.56 (br, 3H, NH_2 and OH), 3.3–3.5 (m, 1H, $\mathit{CH}NH_2$), 3.64 (dd, $^2J_{HP}$=6 Hz, $^3J_{HH}$=2 Hz, 1H, *CH*OH), 4.1–4.3 (m, 4H, $P(O\mathit{CH_2}CH_3)_2$); ^{31}P NMR: δ 24.86. Compound **6d**: oil, $[\alpha]_D^{25}$ +7.8 (c 0.73, MeOH); ^1H NMR: δ 1.22 (dd, $^3J_{HH}$=6.6 Hz and $^4J_{HP}$=1.05 Hz, 3H, $\mathit{CH_3}CH$), 1.34 (t, J=7 Hz, 6H, $P(OCH_2\mathit{CH_3})_2$), 3.04 (br, 3H, NH_2 and OH), 3.41 (m, 1H, $\mathit{CH}NH_2$), 3.60 (dd, $^2J_{HP}$=6 Hz, $^3J_{HH}$=3.6 Hz, 1H, *CH*OH), 4.18 (m, 4H, $P(O\mathit{CH_2}CH_3)_2$); ^{31}P NMR: δ 24.59. Compound **6e**: oil, $[\alpha]_D^{25}$ –2.3 (c 0.26, $CHCl_3$); ^1H NMR: δ 0.95 (d, J=6.7Hz, 6H, $(\mathit{CH_3})_2CH$), 1.2–1.4 (m, 6H, $P(OCH_2\mathit{CH_3})_2$), 1.87 (m, 1H, $(CH_3)_2\mathit{CH}$), 2.9–3.1 (m, 1H, $\mathit{CH}NH_2$), 3.6 (br, 3H, NH_2 and OH), 3.8–3.9 (dd, $^2J_{HP}$=6.6 Hz, $^3J_{HH}$=2 Hz, 1H, *CH*OH), 4.0–4.3 (m, 4H, $P(O\mathit{CH_2}CH_3)_2$); ^{31}P NMR: δ 25.