Stereoselective Synthesis of β-Amino-α-hydroxy(allyl)phosphinates and an Application to the Synthesis of a Building Block for Phosphinyl Peptides

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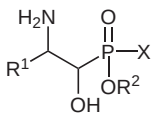
Abstract: Hydrophosphinylation of *N*,*N*-dibenzyl-α-amino aldehydes with ethyl allylphosphinate in the presence of (*S*)-ALB afforded *anti*-β-amino-α-hydroxy(allyl)phosphinates in high diastereoselectivity. The hydrophosphinylation product was transformed to a potentially useful transition state mimic for hydrolysis of dipeptides.

Key words: phosphorus, amino aldehyde, β-amino-α-hydroxy(allyl)phosphinates, hydrophosphinylation, diastereoselectivity

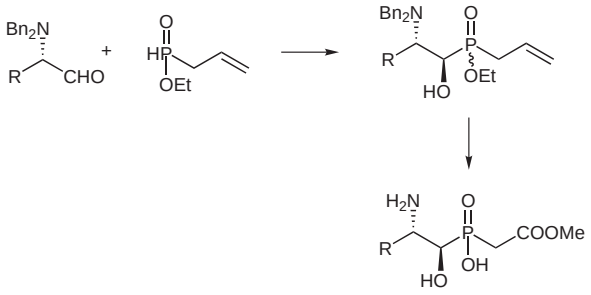
Compounds containing phosphinic acid functional group are currently an area of considerable importance due to their interesting biological properties.[1] The β-amino-α-hydroxyphosphinic acids **1** serve as the key intermediates for the synthesis of potent inhibitor of human renin and HIV protease (Figure 1).[2,3] The protease inhibitory activity is reported to be dependent upon the stereochemistry of the asymmetric centers of the β-amino alcohol moiety. We recently found that the AlLibis(binaphthoxide) (ALB)[4]-catalyzed hydrophosphinylation of *N*,*N*-dibenzyl-α-amino aldehydes with ethyl phosphinate [$H_2P(O)OEt$] proceeds in a highly diastereoselective manner.[5] Both *syn*- and *anti*-β-amino-α-hydroxy-H-phosphinates (**1**/X = H) were prepared selectively as *N*,*N*-dibenzyl protecting form by tuning the chirality of the catalyst. These hydrophosphinylation products seemed to be useful intermediates for the synthesis of versatile β-amino-α-hydroxyphosphinyl derivatives (**1**/X = alkyl) by elongation from the phosphorus atom. However, the alkylation of the phosphinate functionality with aldehydes, acrylates and allyl halides in the presence of TMSCl and Et_3N[6] resulted in poor yields of the desired products due to the steric congestion around the phosphorus atom arising from the bulky dibenzyl protecting group on the nitrogen atom.[5a,b]



1: X=H or alkyl

Figure 1

In view of obtaining β-amino-α-hydroxyphosphinyl derivatives (**1**/X = alkyl) in searching for potent biologically active compounds, we envisaged the methodology based upon using alkylated ethyl phosphinate as a nucleophile for the hydrophosphinylation. The β-amino-α-hydroxy(allyl)phosphinates would be useful synthetic intermediates toward a variety of their derivatives through conversion of the double bond to the other functional group. Here, we disclose a highly diastereoselective synthesis of *anti*-β-amino-α-hydroxy(allyl)phosphinates through hydrophosphinylation of *N*,*N*-dibenzyl-α-amino aldehydes with ethyl allylphosphinate.[7] In addition, we describe *anti*-β-amino-α-hydroxy(allyl)phosphinate was a useful intermediate for the stereoselective synthesis of β-amino-α-hydroxy(methoxycarbonylmethyl)phosphinic acid, which would be applicable as a building block for peptidic transition state analogue inhibitors of protease (Scheme 1).[8]



Scheme 1

Treatment of *N*,*N*-dibenzyl-α-amino aldehydes **2a**–**c**[9] with ethyl allylphosphinate in the presence of (*R*)-ALB (20 mol%), generated from (*R*)-binaphthol and $LiAlH_4$, at 0 °C for 12 h afforded a mixture of *syn*-**3a**–**c** and *anti*-**3a**–**c** in 48–74% yield (Table 1).[10] While the diastereoselectivity for these reactions were varied slightly depending upon the substituents of **2a**–**c**, poor diastereoselectivity were observed (entries 1, 3 and 5). When reactions were conducted with (*S*)-ALB in place of (*R*)-ALB under the same conditions, preferable formation of *anti*-adducts (*anti*-**3a**–**c**) were observed (entries 2, 4 and 6). The ratios of *syn*-**3a**–**c** and *anti*-**3a**–**c** were generally high and determined to be up to 5:95. The results clearly showed that the pair of **2a**–**c** with (*S*)-ALB was matched for inducing high diastereoselectivity.[11] This trend was consistent with the previous results of ALB-catalyzed hy-

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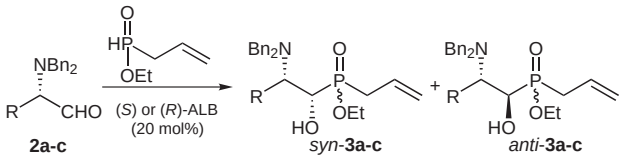
Table 1 Hydrophosphinylation of **2a–c** with Ethyl Allylphosphinate Catalyzed by ALB

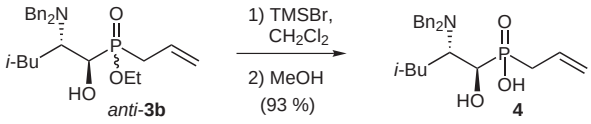


Entry[a]	Substrate	ALB	*syn*:*anti*[b]	Yield (%)[c]
1	**2a**	(*R*)-ALB	50:50	74
2	**2a**	(*S*)-ALB	7:93	63
3	**2b**	(*R*)-ALB	58:42	71
4	**2b**	(*S*)-ALB	5:95	51
5	**2c**	(*R*)-ALB	24:76	48
6	**2c**	(*S*)-ALB	6:94	52

[a] All reactions were carried out in THF at 0 °C for 12 h.
[b] Determined by ^{31}P NMR analysis of crude products.
[c] Combined yields of *syn*- and *anti*-isomers.

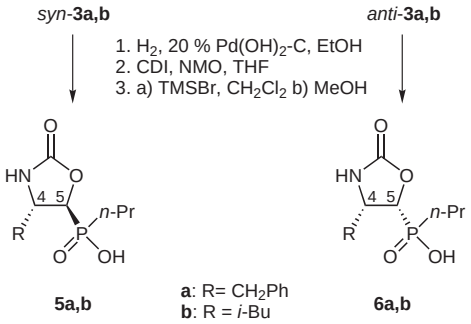
drophosphinylation of *N*,*N*-dibenzyl-α-amino aldehydes with ethyl ethylphosphinate.[5b]

The hydrophosphinylation products *syn*-**3a**,**b** and *anti*-**3a**,**b**, separable by column chromatography on silica gel, were obtained as a mixture of diastereomers arising from the chirality of the phosphorus atom. Treatment of *anti*-**3b** with TMSBr followed by methanolysis afforded phosphinic acid **4** as a single product in 93% yield (Scheme 2).[12] In this compound, the asymmetric character of the phosphorus atom is lost by the rapid exchange of the acidic proton between the phosphoryl (P=O) and the acidic (P–OH) sites.[13]



Scheme 2

The stereochemistry of *syn*-**3a**,**b** and *anti*-**3a**,**b** were confirmed after converting to the corresponding oxazolidin-2-ones **5a**,**b** and **6a**,**b**, respectively (Scheme 3). Hydrogenolysis of *syn*-**3a**,**b** followed by sequential *N*,*O*-carbonylation with *N*,*N*-carbonyldiimidazole (CDI) in the presence of *N*-methylmorpholine (NMO) and deesterification with TMSBr and methanolysis gave the corresponding oxazolidin-2-ones **5a**,**b**. In an analogous manner, **6a**,**b** were obtained starting from *anti*-**3a**,**b**. The vicinal stereochemistry of **5a**,**b** and **6a**,**b** were deduced by comparison of their ^{1}H NMR (400 MHz, CD_3OD) spectra (Table 2). The proton H-5 for **5a** resonated at δ 4.46 ($J_{4,5}$ = 5.2 Hz), but that for **6a** resonated at δ 4.91 ($J_{4,5}$ = 8.8 Hz). The similar trend in the chemical shifts and the vicinal coupling constants were also observed with **5b** and **6b**. The chemical shifts of H-5 and the vicinal coupling constants of oxazolidin-2-ones have been used to assign the relative stereochemistry, normally *trans*-isomers appearing at higher field than those of *cis*-isomers and coupling constants $J_{4,5}$ of *cis*-isomers being bigger than those of *trans*-isomers.[14] On the basis of the empirical rules, **5a**,**b** and **6a**,**b** were assigned to be *trans* and *cis*, respectively.[15]



Scheme 3

Table 2 The ^{1}H NMR (400 MHz, CD_3OD) Data of **5a,b** and **6a,b**.

Compound	H-5 (δ ppm)	$J_{4,5}$ (Hz)
5a	4.46	5.2
5b	4.37	5.6
6a	4.91	8.8
6b	4.79	8.9

The (*S*)-ALB-catalyzed hydrophosphinylation product *anti*-**3c**, inseparable from the minor product *syn*-**3c**, was obtained as a mixture of the diastereomers arising from the chirality of the phosphorus atom (*anti*-**3c**-**A**, *anti*-**3c**-**B**). The diastereomerically pure *anti*-**3c**-**A** (mp: 108–110 °C) was isolated from the mixture upon recrystallization from hexane and ethyl acetate. The relative configuration of *anti*-**3c**-**A** was determined unequivocally by X-ray crystallographic analysis (Figure 2).[16,17]

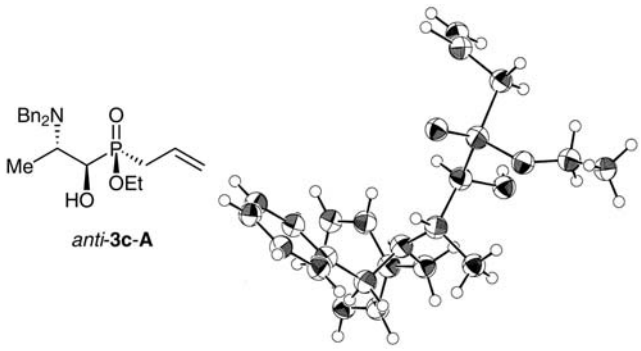
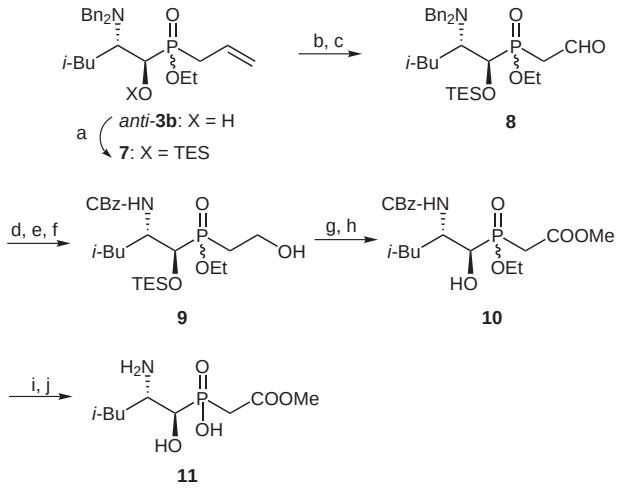


Figure 2 ORTEP drawing of *anti*-**3c**-**A**

With *anti*-**3b** having the defined stereochemistry at the asymmetric center of the amino alcohol moiety in hand, we next examined the oxidative transformation of the vinyl group to the carbomethoxy functional group, which constitute the synthesis of β-amino-α-hydroxy(methoxycarbonylmethyl)phosphinic acid, a building block for peptidic transition state analogue inhibitors of protease (Scheme 4). Treatment of *anti*-**3b** with TESCl and imidazole afforded **7** in 87% yield. Oxidative cleavage of the olefin moiety using with OsO_4 -$NaIO_4$ gave the dihydroxylation product and the aldehyde **8** in 21% yield and 8% yield, respectively. The poor yield of the oxidation product seems likely to be associated with unfavorable coordination of OsO_4 with the tertary amine inhibitting access of the oxidant to the olefin under the conditions. Then, we employed AD-mix-α reagent as an oxidant; the cinchona alkaloid ligand might be expected to prevent the unfavorable interaction between **7** and the OsO_4.[18] Dihydroxylation of **7** with AD-mix-α reagent under the conditions of Sharpless gave the corresponding dihydroxylation product, without purification, which was treated with $NaIO_4$ to give aldehyde **8** in 72% yield (2 steps). Conversion of **8** to the methyl ester **10** was achieved via **9** in a moderate overall yield by the reduction-oxidation sequence which included exchange of the *N*,*N*-dibenzyl protecting group to the Cbz group as shown in Scheme 4.[19] Treatment of **10** with TMSBr followed by methanolysis afforded β-amino-α-hydroxy(methoxycarbonylmethyl)phosphinic acid **11** in 90% yield.[20]



Scheme 4 a) TESCl, imidazole, DMF (87%); b) AD-mix-α, *t*-BuOH-H_2O (1:1); c) $NaIO_4$, H_2O–MeOH–$CHCl_3$ (72%, 2 steps); d) $LiBH_4$, Et_2O (76%); e) H_2, $Pd(OH)_2$–C, EtOH; f) CBz-Cl, $NaHCO_3$, Et_2O–H_2O (72%, 2 steps); g) Jones reagent, acetone; h) HCl, MeOH (31%, 2 steps); i) TMSBr, CH_2Cl_2; j) MeOH (90%, 2 steps)

In conclusion, we have developed ALB-catalyzed hydrophosphinylation of *N*,*N*-dibenzyl-α-amino aldehydes with ethyl allylphosphinate to afford *anti*-β-amino-α-hydroxy(allyl)phosphinates, which were useful intermediates allowing for a conversion into a building block for phosphinyl peptides. Further application of the present hydrophosphinylation methodology to the synthesis of biologically active compounds is under investigation.

Acknowledgement

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(10) **Genaral Procedure for the Hydrophosphinylation of 3a–c in the Presence of (*S*)-ALB**. To a solution of ethyl allylphosphinate (804 mg, 6.0 mmol) in THF (4 mL) was added 0.1 M THF solution of (*S*)-ALB (8 mL, 0.8 mmol), prepared from (*S*)-BINOL (458 mg, 1.6 mmol) and $LiAlH_4$ (30.4 mg, 0.8 mmol) in situ, and a solution of **2a**–**c** (4.0 mmol) in THF (8 mL) at 0 °C under stirring. After being stirred for 12 h at the same temperature, the mixture was diluted with H_2O and extracted with $CHCl_3$. The combined extracts were washed with brine and dried over $MgSO_4$. Removal of solvent gave a residue, which was chromatographed on silica gel (hexane–EtOAc = 2:1) to give *syn*-**3a**–**c** and *anti*-**3a**–**c**.
syn-**3a**. This compound was obtained as a mixture of diastereomers arising from the chirality of the phosphorus atom in a ratio of 1:1.6. Mp 87–89 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.42–7.20 (15 H, m), 5.91–5.79 (0.5 H, m), 5.58–5.46 (0.5 H, m), 5.28–5.21 (1 H, m), 4.93–4.88 (1 H, m), 4.16–4.12 (2 H, m), 3.84–3.59 (3 H, m), 3.53–3.43 (2 H, m), 3.04–2.94 (1 H, m), 2.82-2.60 (1 H, m), 2.44–2.34 (0.5 H, m), 2.25–2.16 (0.5 H, m), 1.34 (3 H, t, *J* = 7.0 Hz); ^{31}P NMR (162 MHz, $CDCl_3$) δ 52.35, 50.21; IR (KBr) 3215, 1046 cm^{-1}; EIMS *m/z* 464 (MH^+). Anal. calcd for $C_{28}H_{34}NO_3P$: C, 72.55; H, 7.39. Found: C, 72.44; H, 7.25.

anti-**3a**. This compound was obtained as a mixture of diastereomers arising from the chirality of the phosphorus atom in a ratio of 1:1.1. Mp 168–170 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.27–7.06 (15 H, m), 5.87–5.71 (1 H, m), 5.29–5.05 (2 H, m), 4.15–3.92 (3 H, m), 3.87 (2 H, d, *J* = 14.1 Hz), 3.59 (2 H, d, *J* = 14.1 Hz), 3.49–3.38 (1 H, m), 3.18–3.07 (2 H, m), 2.78–2.50 (2 H, m), 1.20 (3 H, t, *J* = 7.0 Hz), 1.18 (3 H, t, *J* = 7.0 Hz); ^{31}P NMR (162 MHz, $CDCl_3$) δ 49.18, 49.05; IR (KBr) 3259, 1033 cm^{-1}; EIMS *m/z* 464 (MH^+). Anal. calcd for $C_{28}H_{34}NO_3P$: C, 72.55; H, 7.39. Found: C, 72.30; H, 7.35.

syn-**3b**. This compound was obtained as a mixture of diastereomers arising from the chirality of the phosphorus atom in a ratio of 1:1. Oil; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.33–7.28 (10 H, m), 5.88–5.77 (0.5 H, m), 5.58–5.46 (0.5 H, m), 5.25–4.86 (2 H, m), 4.13–4.05 (2 H, m), 3.88 (2 H, d, *J* = 13.1 Hz), 3.59 (2 H, d, *J* = 13.1 Hz), 3.53–3.46 (1 H, m), 3.28–3.14 (1 H, m), 2.77–2.56 (1 H, m), 2.39–2.11 (1 H, m), 2.11–2.04 (1 H, m), 1.83–1.67 (2 H, m), 1.31 (3 H, t, *J* = 7.0 Hz), 1.04–0.99 (6 H, m); ^{31}P NMR (162 MHz, $CDCl_3$) δ 51.75, 50.22; IR(neat) 3262, 1036 cm^{-1}; EIMS *m/z* 430 (MH^+). High resolution MS calcd for $C_{25}H_{37}NO_3P$ (MH^+): 430.2511. Found: 430.2488.

anti-**3b**. This compound was obtained as a mixture of diastereomers arising from the chirality of the phosphorus atom in a ratio of 1:1.1. Mp 141–143 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.35–7.20 (10 H, m), 5.91–5.76 (1 H, m), 5.30–5.15 (2 H, m), 4.22–3.91 (3 H, m), 3.88 (1 H, d, *J* = 13.6 Hz), 3.85 (1 H, d, *J* = 13.6 Hz), 3.53 (1 H, d, *J* = 13.6 Hz), 3.52 (1 H, d, *J* = 3.6 Hz), 3.22–3.11 (1 H, m), 2.82–2.39 (2 H, m), 1.80–1.70 (1 H, m), 1.40–1.29 (2 H, m), 1.24 (1.5 H, t, *J* = 7.0 Hz), 1.20 (1.5 H, t, *J* = 7.0 Hz), 0.91 (3 H, d, *J* = 6.7 Hz), 0.58 (1.5 H, d, *J* = 6.5 Hz), 0.55 (1.5 H, d, *J* = 6.5 Hz); ^{31}P NMR (162 MHz, $CDCl_3$) δ 50.05, 49.44; IR (KBr) 3278, 1033 cm^{-1}; EIMS *m/z* 430 (MH^+). Anal. calcd for $C_{25}H_{36}NO_3P$: C, 69.91; H, 8.45. Found: C, 69.77; H, 8.28.

(11) For improving the *syn*-diastereoselectivity, we also examined hydrophosphinylation of **2b** using other types of binaphthol-modified heterobimetallic complexes [(*R*)-LPB[21] and (*R*)-GaLB[22]]. However, the *syn*-selectivity was not observed. The (*R*)-LPB catalyzed reaction showed moderate *anti*-selectivity (*syn*-**3b**:*anti*-**3b** = 22:78). A poor *anti*-selectivity (*syn*-**3b**:*anti*-**3b** = 44:51) was observed with (*R*)-GaLB.

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(16) X-Ray crystal data of *anti*-**3c**-**A** were collected by a Mac-Science DIP Image plate diffractometer. The structure was solved by a direct method using SIR-97[23] and refined with a full matrix least-squares method.[24] Molecular formula = $C_{22}H_{30}NO_3P$, M_r = 387.46, orthorhombic, space group = $P2_12_12_1$, *a* = 8.454(5), *b* = 11.111(2), *c* = 23.484(10) Å, *V* = 2205.9(2) Å^3, *T* = 296 K, *Z* = 4, D_x = 1.167 Mg m^{-3}, (Mo-Kα) = 0.71073 Å, μ = 0.145 mm^{-1}, *R* = 0.050 over 2591 independent reflections.

(17) Crystallographic data (excluding structure factors) for the X-ray crystal structure analysis reported in this paper have been deposited with the Cambridge Crystallographic Data Center (CCDC) as supplementary publication No. CCDC 187211. Copies of the data can be obtained, free of charge, on application to CCDC, 12 Union Road, Cambridge CB2 1EZ, UK [fax:+44(1223)336033 or e-mail: deposit@ccdc.cam.ac.uk].

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(20) **11**. Amorphous; $[\alpha]_D^{26}$ = –7.21 (*c* 0.67, MeOH); ^{1}H NMR (400 MHz, CD_3OD) δ 4.17 (1 H, dd, *J* = 5.3, 5.3 Hz), 3.73 (3 H, s), 3.69–3.54 (1 H, m), 3.23–3.00 (2 H, m), 1.87–1.59 (3 H, m), 1.00 (3 H, d, *J* = 5.9 Hz), 0.97 (3 H, d, *J* = 6.2 Hz); ^{31}P NMR (162 MHz, CD_3OD) δ 41.91; ^{13}C NMR (100 MHz, CD_3OD) δ 168.4, 68.9 (d, J_{PC} = 119.5 Hz), 59.1, 53.0, 38.8, 36.0 (d, J_{PC} = 81.7 Hz), 25.9, 23.5, 21.8; IR(neat) 3314, 2956, 1729, 1115 cm^{-1}; FABMS *m/z* 254 (MH^+). High resolution MS calcd for $C_9H_{21}NO_5P$ (MH^+): 254.1157. Found: 254.1164.

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