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Stereodivergent Synthesis of β-Amino-α-hydroxyphosphonic Acid Derivatives by Lewis Acid Mediated Stereoselective Hydrophosphonylation of α-Amino Aldehydes

Tsutomu Yokomatsu, Takehiro Yamagishi, and Shiroshi Shibuya*

Tokyo College of Pharmacy, 1432-1 Horinouchi, Hachioji, Tokyo 192-03, Japan

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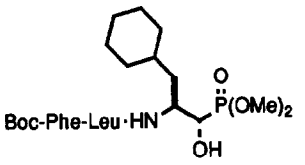
Abstract: The highly diastereoselective synthesis of β-amino-α-hydroxyphosphonic acid derivatives was achieved by Lewis acid mediated hydrophosphonylation of α-dibenzylamino aldehyde. Diastereofacial differentiation could be controlled in either a chelation or a non-chelation manner by simple tuning of the nature of phosphoric nucleophiles.

The chiral β-amino alcohol moiety frequently serves as an isosteric functional group for asparatic protease inhibitors and functions as a transition-state mimetic of hydrolysis of dipeptides.[1] Hydroxyethylene dipeptide isosteres, statine and its analogs have been proved to function as peptidemimetic inhibitors in peptidic framework.[1] Stereoselective introduction of additional bioisosteres such as phosphonic and phosphinic functional groups to the α-position in the β-amino alcohol moiety would be useful to improve inhibitory activities to protease.[2,3] Recently, the β-amino-α-hydroxyphosphonic acid derivative (**1**)[2] and the phosphinic anlogues (**2**)[3] with peripheric C_2-symmetry were synthesized as new hybrid transition-state inhibitors of proteolytic enzymes such as renin and human immunodeficiency virus (HIV) protease and exhibit potent and selective inhibitory activities.[3] In order to obtain a range of inhibitors containing phosphorus and to elucidate their biological activities and mechanisms, the stereocontrolled synthesis of β-amino-α-hydroxyphophonic acid derivatives is required.



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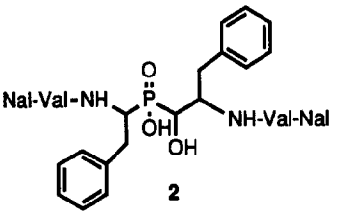

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Hydrophosphonylation of α-amino aldehydes with phosphoric nuleophiles should constitute one of the simplest entries to chiral β-amino-α-hydroxyphosphonic acid derivatives. However few reports on reactivity and stereoselectivity of α-amino aldehydes toward heteroatomic nucleophiles such as phosphorus are available.[2,3] In this paper we report that *N*,*N*-dibenzyl α-amino aldehydes[4] react with various phosphoric nucleophiles in the presence of titanium(IV) chloride ($TiCl_4$) to give the adducts in high diastereoselectivity. The stereoselectivity could be controlled in either a chelation or a non-chelation manner by simple tuning of the nucleophilic nature of phosphorus.

First, hydrophosphonylation of an α-amino aldehyde using diethyl *t*-butyldimethylsilylphosphite (**3**) as nucleophile was carried out according to the method of Evans.[5] Treatment of α-dibenzylamino aldehyde (**4**),[6] derived from L-phenylalanine, with diethyl silylphosphite (**3**) in CH_2Cl_2 at 0 °C for 40 h, followed by

desilylation [*n*-Bu_4NF, THF, room temparature] of the siloxy adducts (**5a** and **6a**) gave the *erythro* β-amino-α-hydroxyphosphate (**5b**),[7] mp 127-129 °C, $[\alpha]_D^{19}$+28.6 (c 0.9, $CHCl_3$), and the *threo* diastereoisomer (**6b**),[7] mp 87-88 °C, $[\alpha]_D^{19}$+39.0 (c 1.1, $CHCl_3$), in a ratio of 2.8 : 1 in 76% yield. These were readily separated by column chromatography on silica gel. The diastereoselectivity was not improved even at low temperature (-20 °C). The stereostructures of **5b** and **6b** was deduced after conversion to the corresponding 5-diethylphosphonooxazolidin-2-ones (**7** and **8**)[7] *via* amines **5c** and **6c** [1. H_2/$Pd(OH)_2$/MeOH; 2. carbonyldiimidazole (CDI) / N-methylmorphorine (NMM) / THF].[8]

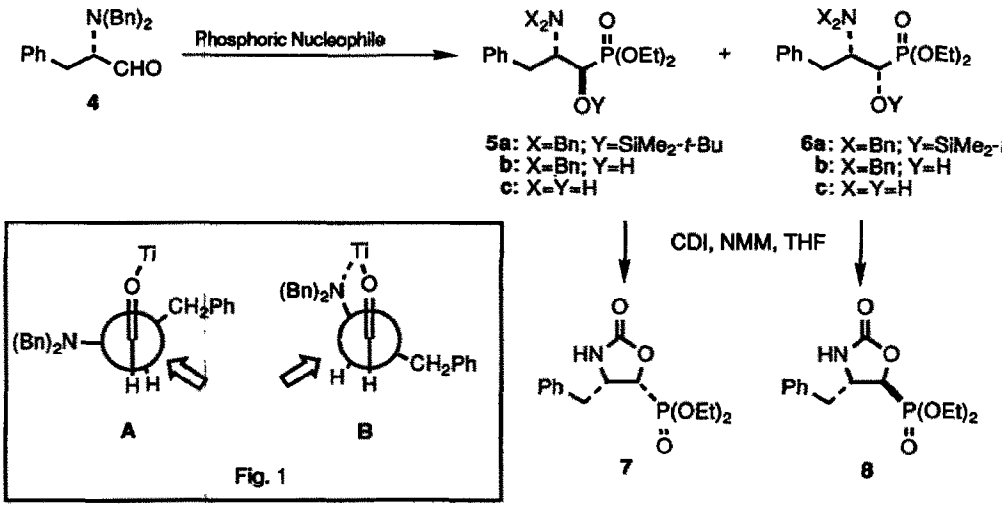

Fig. 1

In an effort to achieve high diastereoselectivity, next, we employed $TiCl_4$ as a catalyst to promote the reactions. Stereoselective hydrophosphonylation reactions of **4** using the Lewis acid and phosphoric nucleophiles are summerized in Table 1. The reaction of **4** with silylphosphite (**3**) and triethyl phosphite in CH_2Cl_2 at –78 °C in the presence of 1.2 equiv. of $TiCl_4$ gave the *erythro* isomer (**5b**) *via* the non-chelate complex (**A**) in excellent and modest diastereoselectivity, respectively (entry 1 and 3, Table 1).[9a] The stereochemical outcome of the present $TiCl_4$-mediated hydrophosphonylation is interesting from a mechanistic point of view, because $TiCl_4$-induced hydrocyanation of **4** using Me_3SiCN gave the chelation product as reported by Reetz.[10] These differences in stereochemical course might arise from the higher nucleophilicity of tri-valent phosphorus than that of Me_3SiCN. Although direct evidences for thermodynamical stability and relative reactivity of the non-chelate and chelate complexes (**A** and **B**) are not available at the present, the non-chelate complex (**A**) can be assumed to be less reactive than the chelate complex (**B**)[11] but to be of major equilibrium concentration among these complexes (Fig. 1).[12] The *erythro* selectivity obtained by above reactions might be attributed to the fact that tri-valent phosphorus are enough highly nucleophilic to capture the major and less reactive complex (**A**). Diastereo changeover depending on nucleophilicity was also observed by Mikami and co-workers in Lewis acid mediated carbon-carbon bond formation using dibenzylamino aldehyde.[13] The above explanantion also supports the remarkably high diastereoselectivity observed in the reaction with silylphosphite **3** which is a more reactive nucleophile than triethyl phosphite due to activation by hyperconjugation arising from β-silicon atom.[14]

Table 1 Stereoselective hydrophosphonylation of **4** catalyzed by $TiCl_4$[a]

Entry	Phosphoric nucleophile[b]	Lewis acid (equiv.)	Reaction temp.(h)	**5b/6b**[c]	Yield(%)
1[e]	*t*-$BuMe_2SiOP(OEt)_2$ (**3**)	$TiCl_4$ (1.2)	–78 °C (2 h)	>98 : <2	86[d]
2[e]	**3**	$TiCl_4$ (3.0)	–78 °C (2 h)	68 : 32	60
3	$P(OEt)_3$	$TiCl_4$ (1.2)	–78 °C (1 h)	81 : 19	45
4	$HP(O)(OEt)_2$ (**9**)	$TiCl_4$ (1.2)	–45 °C (18 h)	54 : 46	29
5	**9**	$TiCl_4$ (3.0)	–45 °C (18 h)	7 : 93	46[d]

a) All reactions were carried out in CH_2Cl_2 on 2 mmol scale. b) One point two equivalents of nucleophile was used unless stated otherwise. c) Determined by $^{31}P\{^1H\}$- and ^1H-Nmr analysis of crude reaction mixture. d) Isolated yield of major diastereomer. e) Siloxy adducts (**5a** and **6a**) were not produced from this reaction.

Diethyl phosphite (**9**) should be a less reactive nucleophile than **3** and triethyl phosphite because of its favoured of existence as the penta-valent phosphonate tautomer and would induce the reaction through chelate-complex (**B**) under proper conditions. Upon treatment of **4** with diethyl phosphite in the presence of excess (3 equiv.) of $TiCl_4$, the *threo* isomer (**6b**) was obtained in high diastereoselectivity (93 : 7) as expected (entry 5).[9b] However when 1.2 equiv. of $TiCl_4$ were used, no diasteroselectivity was observed and yield of the adducts decreased siginificantly (entry 4). This difference may be caused by the fact that one equivalent of $TiCl_4$ was used for complexation with diethyl phosphite while another equivalent of the acid acted as chelator. Apparently, the stereochemical course of the reaction was not only determined by amount of the Lewis acid, but also by the nucleophilic nature of phosphorus, since the reaction of silylphosphite **3** in the presence of excess of $TiCl_4$ gave the non-chelation product as major diastereomer (entry 2). The results described above showed that diethyl phosphite would be capable of reacting with more reactive chelate complex (**B**) but not with the less reactive non-chelate complex (**A**) under the provided conditions (Fig. 1).[11,12]

During the formation of the phosphorus to carbon bond in above reaction, no racemization of α-amino aldehyde takes place. This was confirmed by nmr analysis of the Mosher esters of **5b** and **6b** derived from both (+)- and (-)-α-methoxy-α-(trifluoromethyl)phenylacetic acids in all cases.

In conclusion, simple tuning of the nucleophilic nature of phosphorus is valuable for the stereocontrolled synthesis of enantiomerically pure β-amino-α-hydoxyphosphonic acids through Lewis acid-mediated hydrophosphonylation of α-amino aldehydes and the method should be applicable to the synthesis of peptidomimetic inhibitors contaning phosphoric bioisosteres.

References and Notes

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6. M. Reetz, M. W. Drewes, and A. Schmitz, *Angew. Chem. Int. Ed. Engl.*, **1987**, *26*, 1141.
7. All new compounds gave satisfactory spectroscopic and analytical data. Selected spectroscopic and physical data for **5b**, **6b**, **7** and **8** as follows. ^{1}H- and ^{31}P{^{1}H}-Nmr ($CDCl_3$) were recorded at 300 and 161 MHz, respectively. Chemical shifts for ^{31}P-Nmr were reported relative to $HP(O)(OEt)_2$ (7.0 ppm) as interenal reference. **5b**: CIMS m/z 468(MH^+); ^{1}H-Nmr δ 7.29-7.05 (15H, m), 4.39 (1H, br d, *J*=10 Hz, disappeared upon addition of D_2O), 4.29-4.01(5H, m), 3.91 (2H, d, *J*=14 Hz), 3.58 (2H, d, *J*=14 Hz), 3.45-3.32 (1H, m), 3.15-3.02 (2H, m), 1.29 (3H, t, *J*=7.1 Hz), 1.25(3H, t, *J*=7.1 Hz); ^{31}P{^{1}H}-Nmr δ 23.85. **6b**: CIMS m/z 468 (MH^+); ^{1}H-Nmr δ 7.45-7.35 (4H, m), 7.35-7.19 (7H, m), 7.15-6.98 (4H, m), 4.95 (1H, d, *J*=18 Hz, disappeared upon addition of D_2O), 4.21-4.01 (2H, m), 3.95-3.80 (2H, m), 3.80-3.70 (2H, m), 3.53-3.28 (3H, m), 3.00 (1H, dd, *J*=10.5, 14.3 Hz), 1.29 (3H, t, *J*=7.14 Hz), 1.12 (3H, t, *J*=7.14 Hz); ^{31}P{^{1}H}-Nmr δ 23.14. **7**: an oil; $[\alpha]_D^{20}$-47.5 (c 1.0, $CHCl_3$); MS *m/z* 313(M^+); ^{1}H-Nmr δ 7.38–7.25 (4H, m), 7.26-7.19 (1H, m), 4.19 (1H, br s), 4.87 (1H, dd, *J*=4.2, 7.95 Hz), 4.39-4.19 (5H, m), 3.29 (1H, dd, *J*=2.86, 13.5 Hz), 3.01 (1H, dd, *J*=11.9, 13.5 Hz), 1.42 (3H, t, *J*=7.14 Hz), 1.41 (3H, t, *J*=7.08 Hz); ^{31}P{^{1}H}-Nmr δ 13.70. **8**: an oil; $[\alpha]_D^{20}$-61.5 (c 1.3, $CHCl_3$); MS *m/z* 313(M^+); ^{1}H-Nmr δ 7.38-7.25 (3H, m), 7.20 (1H, br d, *J*=6.81 Hz), 5.30 (1H, br s), 4.45 (1H, d, *J*=6.03 Hz), 4.35-4.20 (1H, m), 4.25-4.16 (1H, m), 3.05 (1H, dd, *J*= 4.4, 13.5 Hz), 2.82 (1H, dd, *J*=8.79, 13.5 Hz), 1.35 (6H, t, *J*=7.08 Hz); ^{31}P{^{1}H}-Nmr δ 15.85.
8. The structural assignments for **7** and **8** were made by their ^{1}H- and ^{13}C-Nmr: Signal due to H-5 for *cis* oxazolidin-2-one (**7**) appeared at δ 4.87 ($J_{4,5}$=4.2 Hz), but that for *trans* **8** resonated at δ 4.45 ($J_{4,5}$= ca. 0). Their chemical shifts and $J_{4,5}$ values consist with those ($J_{cis}>J_{trans}$; $\delta_{cis}>\delta_{trans}$) normally observed for 4,5-disubstituted oxazolidin-2-ones; R. Polt, M. A. Peterson, and L. DeYoung, *J. Org. Chem.*, **1992**, *57*, 5469 and see ref. 2. Chemical shifts of benzylic carbons (δ 37.92 for **7** and δ 42.12 for **8**) also support these structural assignments.[2]
9. a) No diastereoselectivity was observed when Et_2AlCl and **3** were used as Lewis acid and phosphoric nucleophile, respectively. b) Modest *erythro* selectivity (82 : 18) was obtained by the reaction with Et_2AlCl under the identical conditions; The details of these results will be discussed in full paper.
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12. Reetz suggests that the non chelate complex (A) are likely to be involved in an 1 : 1 mixture of **4** and $TiCl_4$ based on nmr experiments and the chelate complex (B) opens rather readily due to the results of both weaker N-Ti bonding and steric interaction between the chlorine ligands and benzyl groups on the five member rings: See ref. 4 and 10.
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