Pergamon

Tetrahedron Letters 42 (2001) 5033–5036

TETRAHEDRON LETTERS

Diastereoselective synthesis of chiral β-amino-α-hydroxy-*H*-phosphinates through hydrophosphinylation of α-amino aldehydes

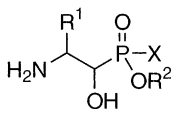
Takehiro Yamagishi, Kenji Suemune, Tsutomu Yokomatsu* and Shiroshi Shibuya

School of Pharmacy, Tokyo University of Pharmacy and Life Science, 1432-1 Horinouchi, Hachioji, Tokyo 192-0392, Japan

Received 20 April 2001; revised 21 May 2001; accepted 25 May 2001

Abstract—A stereodivergent synthesis of β-amino-α-hydroxy-*H*-phosphinates was achieved by ALB-catalyzed hydrophosphinylation of *N*,*N*-dibenzyl-α-amino aldehydes tuning the chirality of the catalyst.

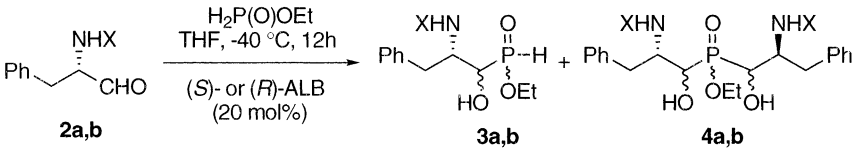
The β-amino-α-hydroxyphosphinic acids **1** serve as the key intermediates for the synthesis of potent inhibitors of human renin and HIV protease (Fig. 1).[1,2] Stereogenic carbon–phosphorus bond formation processes are of great interest in stereoselective synthetic sequences of the β-amino alcohol moiety by the reaction of α-amino aldehydes with phosphinic nucleophiles, since the stereochemistry of β-amino alcohol is known to be an important factor to show highly potent protease inhibitory activity. The initial synthetic route to this class of compounds, which followed the classical protocol through the reaction of *N*-Boc-α-amino aldehyde with phosphinic nucleophiles in situ generated from alkyl-*H*-phosphinate (HPO(OMe)(Et)) with conventional reagents in combination of TMSCl and an amine, resulted in a formation of the desired β-amino-α-hydroxyphosphinic acid derivatives but without diastereoselectivity.[1]



1: X = alkyl or H

Figure 1.

Aiming at a highly diastereoselective approach to β-amino-α-hydroxy-*H*-phosphinic acids (**1**: X = H), we envisaged the use of alkyl phosphinate (H_2PO_2R) with a chiral AlLibis(binaphtoxide) (ALB)[3] catalyst would give rise to a formation of β-amino-α-hydroxy-*H*-phosphinic acids with either *anti*- or *syn*-stereoselectivity. Recently, we found that the enantioselective synthesis of α-hydroxy-*H*-phosphinates as well as α,α′-dihydroxyphosphinates could be achieved by the reaction of



2a,b **3a,b** **4a,b**

a: X = Cbz; **b**: X = Boc

substrate	ALB	yield (%) of **3**	yield (%) of **4**
2a	(*S*)-ALB	23	11
2a	(*R*)-ALB	27	13
2b	(*S*)-ALB	26	15

Scheme 1.

Keywords: diastereoselection; phosphinic acids; derivatives.

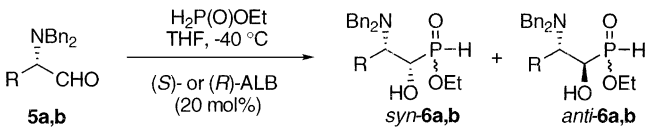
* Corresponding author. Tel./fax: +81-426-76-3239; e-mail: yokomatu@ps.toyaku.ac.jp

0040-4039/01/$ - see front matter
PII: S0040-4039(01)00911-X

aldehydes with alkyl phosphinate activated by ALB.[4] In this paper, we wish to report our experimental results on chiral ALB-catalyzed hydrophosphinylation of *N*,*N*-dibenzyl-α-amino aldehydes[5] with ethyl phosphinate,[6] generated from anhydrous phosphinic acid and triethyl orthoformate in situ, with a high level of diastereofacial selectivity. The stereochemical outcome of the reaction can be controlled in either *anti*- or *syn*-selective manner by tuning the chirality of ALB.

First, we attempted the ALB-catalyzed hydrophosphinylation of *N*-CBz-L-phenylalaninal **2a**[7] and *N*-Boc-L-phenylalaninal **2b**[8] with ethyl phosphinate (Scheme 1). When **2a** was treated with ethyl phosphinate in THF in the presence of (*S*)-ALB (20 mol%), generated from (*S*)-binaphthol, at −40°C for 12 h, adducts **3a** and **4a** were produced in 23 and 11% yield, respectively. On analyzing the ^{1}H (400 MHz) and ^{31}P (162 MHz) spectrum of the products, there is no evidence that the reaction proceeded in a diastereoselective manner.[9] The diastereoselectivity was not improved when the reaction was conducted with (*R*)-ALB under the same condition. Also, the reaction of **2b** catalyzed by (*S*)-ALB afforded **3b** and **4b** without stereoselectivity. The formation of **4a**,**b** takes place by the activation of the H-phosphinate group of **3a**,**b** with ALB, followed by the addition to the α-amino aldehydes.[10]

Table 1. Hydrophosphinylation of **5a**,**b** with ethyl phosphinate in the presence of ALB



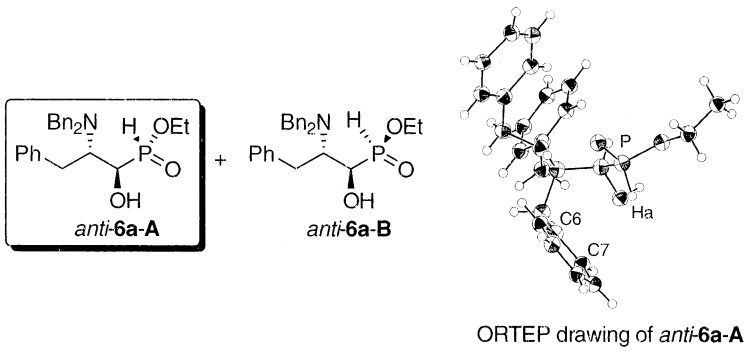
Entry[a]	Substrate	ALB	*syn*:*anti*	Yield (%)[b]
1	**5a**	(*S*)-ALB	6:94	56
2	**5a**	(*R*)-ALB	87:13	66
3	**5b**	(*S*)-ALB	2:98	71
4	**5b**	(*R*)-ALB	94:6	54

[a] All reactions were carried out for 12 h.
[b] Combined yields of *syn*- and *anti*-isomers.

To obtain β-amino-α-hydroxy-*H*-phosphinates in a highly diastereoselective manner, we next examined the hydrophosphinylation of *N*,*N*-dibenzyl-α-amino aldehydes **5a**,**b** in the presence of a catalytic amount of ALB (Table 1). The excellent ability of the dibenzyl protective group of **5a**,**b** for the diastereoselective alkylation through non-chelation control has been demonstrated.[5] Moreover, the dibenzyl protective group might give rise to steric hindrance around the H-phosphinate functionality of the adducts and would suppress the formation of the dimeric side-products corresponding to **4a**,**b**.

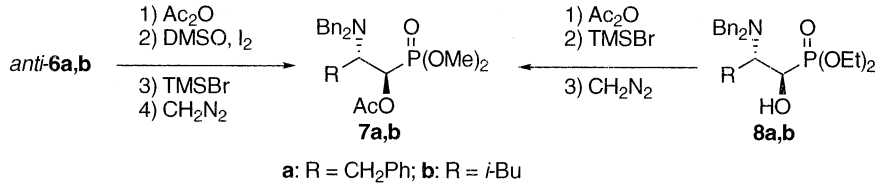
As we expected, treatment of ethyl phosphinate with *N*,*N*-dibenzyl-L-phenylalaninal **5a** and *N*,*N*-dibenzyl-L-leucinal **5b** in the presence of ALB (20 mol%) for 12 h afforded the corresponding hydrophosphinylation products in moderate yields without formation of detectable side products (entries 1–4).[11] An intriguing result was revealed upon analyzing the diastereoselectivities of the products. In the reaction of **5a** with (*S*)-ALB, high *anti*-selectivity (*syn*-**6a**:*anti*-**6a** = 6:94) was observed (entry 1).[12] On the other hand, hydrophosphinylation of **5a** in the presence of (*R*)-ALB proceeded with inversed stereoselection to give *syn*-**6a** in a ratio of 87:13 (entry 2). Also, when the reaction of **5b** was carried out with (*S*)- or (*R*)-ALB, either *anti*-**6b** or *syn*-**6b** could be obtained in high stereoselectivity (entries 3 and 4).[13] In the above-mentioned cases, diastereofacial selectivity was found to be controlled predominantly by the chirality of the asymmetric catalyst rather than that of the α-amino aldehydes. As observed in Table 1, the diastereoselectivity of the hydrophosphinylation with (*S*)-ALB is generally higher than that with (*R*)-ALB.[14]

The products *anti*-**6a**,**b** and *syn*-**6a**,**b** were obtained as a 1:1 mixture of diastereoisomers arising from the chirality of the phosphinate group. The diastereomerically pure *anti*-**6a**-**A** (mp: 149–150°C) was isolated from the mixture (*anti*-**6a**-**A** and *anti*-**6a**-**B**) upon recrystallization from ethyl acetate. The relative stereochemistry of *anti*-**6a**-**A** was confirmed unambiguously by X-ray crystallographic analysis (Fig. 2).[15,16] In the X-ray crystal structure, the proton Ha of the phosphinate group appeared to be sterically shielded by the neighboring hydroxy and ethyloxy groups as well as the phenyl group. It is noteworthy that Ha located close to the



ORTEP drawing of *anti*-**6a**-**A**

Figure 2.



Scheme 2.

phenyl group, showing the distance of Ha–C6 and Ha–C7 to be 2.89 and 2.88 Å, respectively. The steric surroundings of the P–H moiety in *anti*-**6a** would be important for circumventing the interaction with ALB, thus preventing its nucleophilic reactivity to aldehydes.

The stereochemistry of *anti*-**6a**,**b** was also confirmed after converting to β-amino-α-acetoxyphosphonate **7a**,**b** through sequential acetylation, oxidation, deesterification and methyl esterification (Scheme 2). The ^{1}H NMR spectra of **7a**,**b** were identical with those of the authentic specimens derived from the known β-amino-α-hydroxyphosphonate **8a**,**b**[17] through acetylation, deesterification followed by methyl esterification. The optical purity of **7a** derived from *anti*-**6a** was determined to be 99% ee by HPLC analysis on a chiral phase (DAICEL CHIRALPAK OD column, hexane:EtOH = 20:1). Therefore, it was proved that no racemization of *N*,*N*-dibenzyl-α-amino aldehydes took place during the hydrophosphinylation.

In conclusion, we have developed a diastereoselective synthesis of β-amino-α-hydroxy-*H*-phosphinates through hydrophosphinylation of *N*,*N*-dibenzyl-α-amino aldehydes catalyzed by ALB. Both *syn* and *anti*-β-amino-α-hydroxy-*H*-phosphinate could be prepared selectively by tuning the chirality of ALB. Further application of the present hydrophosphinylation methodology to the synthesis of biologically active compounds is under investigation.

Acknowledgements

The authors wish to thank Mr. Haruhiko Fukaya (the analytical center of this university) for the X-ray crystallographic analysis.

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9. ^{1}H and ^{31}P NMR spectroscopic analysis has been successfully applied to determine the diastereomeric excess of chiral phosphonate derivatives, see: (a) Yokomatsu, T.; Yamagishi, T.; Shibuya, S. *J. Chem. Soc., Perkin Trans. 1* **1997**, 1527; (b) Hammerschmidt, F.; Li, Y.-F. *Tetrahedron* **1994**, *50*, 10253; (c) Kozlowski, J. K.; Rath, N. P.; Spilling, C. D. *Tetrahedron* **1995**, *51*, 6385.
10. Previously, we have found the ALB-catalyzed reaction of methyl phosphinate with 2.2 equivalents of benzaldehyde resulted in exclusive formation of the corresponding dimeric product. See Ref. 4.
11. The moderate yields of products might be due to partial hydrolysis of the ethyl phopshinate functionality during the work up.
12. A pair of doublets due to the diastereomeric phosphinate protons of *syn*-**6a** was observed at δ 7.15 (d, J = 561.7 Hz) and 7.03 (d, J = 560.3 Hz), whereas the corresponding signals of *anti*-**6a** resonated at δ 6.68 (d with small splits, J = 549.5 Hz) and 6.53 (d with small splits, J = 558.0 Hz) in their ^{1}H NMR (400 MHz, CD_3OD) spectra. The *syn*/*anti* ratio was determined by relative ratio of integral area for these signals.
13. The ratio was determined by ^{31}P NMR (162 MHz, CD_3OD) analysis of the crude products. The diastereomeric phosphorus atoms of *syn*-**6b** resonated at δ 43.64 and 41.92; the corresponding signals of *anti*-**6b** appeared at δ 40.32 and 39.00.
14. We also examined reactions of **5a** with ethyl phosphinate using 1.5 equivalents of an achiral base such as BuLi, NaH, La(O-*i*-Pr)$_3$ and Et_3N. It was found that only Et_3N could promote the reaction to afford a mixture of *syn*-**6a** and *anti*-**6a** in 43% yield with a low level of diastereoselectivity (23:77). Thus, the high chemical yields and diastereoselectivities, observed when the binaphthol-modified heterobimetallic complex was employed, may be accounted for by the simultaneous activation of both aldehydes and ethyl phosphinate with ALB.[3]
15. X-Ray crystal data of *anti*-**6a**-**A** were collected by a Mac-Science MXC18 diffractometer. The structure was solved by a direct method using SIR-92 (Altomare, 1994)[18] and refined with a full matrix least-squares method. Molecular formula = $C_{25}H_{30}NO_3P$, M_r = 423.50, orthorhombic, space group = $P2_12_12_1$, a = 16.725 (4), b = 12.170 (2), c = 11.434 (3) Å, V = 2327.2 (9) Å^3, T = 298 K, Z = 4, D_x = 1.208 Mg m^{-3}, (Mo-Kα) = 0.71073 Å, μ = 1.375 mm^{-1}, R = 0.083 over 2658 independent reflections.

16. 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 160271. Copies of the data can be obtained, free of charge, on application to CCDC, 12 Union Road, Cambridge CB2 1EZ, UK [fax: +44(0)-1223-336033 or e-mail: deposit@ccdc.cam.ac.uk].
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