ORGANIC LETTERS

2008
Vol. 10, No. 19
4347−4350

Diastereoselective Synthesis of α,β′-Disubstituted Aminomethyl(2-carboxyethyl)phosphinates as Phosphinyl Dipeptide Isosteres

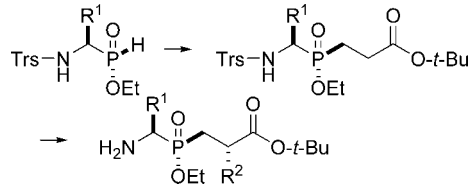
Takehiro Yamagishi, Hiroyuki Ichikawa, Terumitsu Haruki, and Tsutomu Yokomatsu*

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

yokomatu@ps.toyaku.ac.jp

Received July 29, 2008

ABSTRACT



A new and efficient method has been developed for the diastereoselective synthesis of unnatural dipeptide analogues containing the metabolically stable phosphinic moiety, $NH_2XaaΨ[P(O)OHCH_2]XaaOH$, which mimics the transition state of tetrahedral geometry of a scissile peptide bond in hydrolysis by protease. The method is based upon stereospecific Michael addition of stereodefined α-aminoalkyl-*H*-phosphinates to acrylates and subsequent diastereoselective alkylation at the *β′*-position of the resulting Michael adducts.

The backbone modification of bioactive peptides with replacement of a scissile peptide bond in enzymatic hydrolysis is a well-established strategy for developing protease inhibitors.[1] Among the known isosteric modifications, several studies have demonstrated that the use of phosphinyl dipeptide isosteres (PDIs) can be a very effective approach for the development of highly potent and selective inhibitors of various Zn metalloproteases.[2] PDIs contain the metabolically stable phosphinic moiety, $NH_2XaaΨ[P(O)OHCH_2]XaaOH$, which mimics the transition state for tetrahedral geometry of a scissile peptide bond during enzymatic hydrolysis (Figure 1). Although PDIs are of considerable interest as a dipeptide building block in medicinal chemistry, their application to the modification of bioactive peptides is limited due to the paucity of methods for preparing PDIs in a highly stereocontrolled manner.

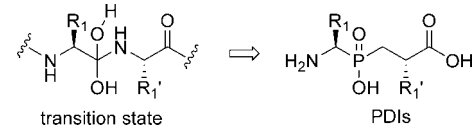


Figure 1. Structure of PDIs and transition states in the hydrolysis of dipeptides.

Classical methods for the synthesis of PDIs rely on the Michael addition of N-protected silyl aminoalkylphosphinates to α-substituted acrylate derivatives, followed by diastereo-

(1) For reviews, see: (a) Leung, D.; Abbenante, G.; Fairlie, D. P. *J. Med. Chem.* **2000**, *43*, 305–341. (b) Babine, R. E.; Bender, S. L. *Chem. Rev.* **1997**, *97*, 1359–1472.

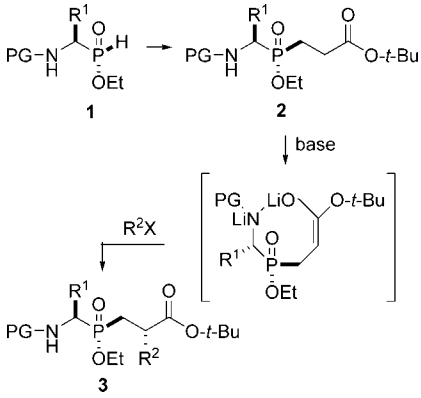
(2) (a) Collinsová, M.; Jirácek, J. *Curr. Med. Chem.* **2000**, *7*, 629. (b) Yiotakis, A.; Geogiadis, D.; Matziari, M.; Makaritis, A.; Dive, V. *Curr. Org. Chem.* **2004**, *8*, 1135. (c) Natchev, I. A. *Tetrahedron* **1991**, *47*, 1239. (d) Moree, W. J.; van der Marel, G. A.; van Boom, J. H.; Liskamp, R. M. J. *Tetrahedron* **1993**, *49*, 11055. (e) Mucha, A.; Kafarski, P.; Plenat, F.; Cristau, H.-J. *Tetrahedron* **1994**, *50*, 12743. (f) Li, B.; Cai, S.; Du, D.-M.; Xu, J. *Org. Lett.* **2007**, *9*, 2257.

10.1021/ol801743d CCC: $40.75
Published on Web 09/10/2008

selective protonation of the intermediate enolates.[3] Alternatively, diastereoselective reduction of dehydroalanyl phosphinyl peptide analogues with an asymmetric catalyst has been applied.[4] In these reactions, a mixture of four stereoisomers is usually formed upon using a racemic aminoalkylphosphinate as a starting material. The separation of the mixture[5] is necessary to isolate an individual diastereoisomer showing the desired biological activity. Therefore, there is room for the development of more stereoselective methods for the preparation of PDIs.

We have recently developed a general method for the stereoselective synthesis of α-aminoalkyl-*H*-phosphinates **1** through alkylation of aminomethylphosphinate derivatives having a bulky 1,1-diethoxyethyl functionality connected to a phosphorus atom.[6,7] In this method, the stereogenic center at the α-carbon is highly controlled by the phosphorus chirality.[6,7] Asymmetric synthesis of this class of compounds has also been successful through the same sequence utilizing optically active aminomethylphosphinates.[8] Thus, our investigations focused on developing a general method for the diastereoselective synthesis of α,β′-disubstituted aminomethyl(2-carboxyethyl)phosphinate derivatives **3**, useful for the synthesis of PDIs, starting from highly stereodefined α-aminoalkyl-*H*-phosphinates **1** (Scheme 1).

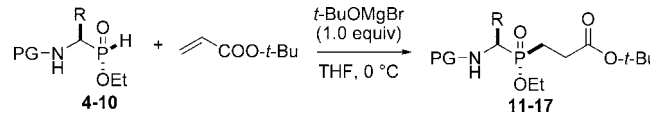
Scheme 1. Strategy for Stereoselective Synthesis of PDI Derivatives



Our strategy for stereoselective synthesis of **3** is based on the following two critical reactions: (1) Michael addition of **1** to acrylates without a loss of the phosphorus chirality and (2) stereoselective alkylation of lithium enolates of the resulting Michael adduct **2** under the influence of the phosphorus chirality. In the second reaction, *cis*-lithium enolates bearing a cyclic chelated structure might be favorably generated,[9] and alkylation of the enolate is expected to proceed in a highly diastereoselective manner induced by the chirality of the phosphorus atom (Scheme 1). Herein, we communicate our results.

According to the strategy, we first examined the Michael addition of racemic α-aminoalkyl-*H*-phosphinates **4**−**10**, prepared according to our previously reported method,[6] to acrylates without a loss of phosphorus chirality (Table 1).

Table 1. Michael Addition of **4**−**10** to *t*-Butyl Acrylate[a]



entry	substrate	product	yield[b] (%)
1	**4** (PG = Cbz, R = Bn)	**11**	93
2	**5** (PG = Bz, R = Bn)	**12**	78
3	**6** (PG = Boc, R = Bn)	**13**	90
4	**7** (PG = Ts, R = Bn)	**14**	83
5	**8** (PG = Trs, R = Bn)	**15**	92
6	**9** (PG = Trs, R = *i*-Bu)	**16**	67
7	**10** (PG = Trs, R = H)	**17**	99

[a] Reactions were carried out for 2−6 h. [b] Isolated yield.

Han and Zhao have recently established a magnesium alkoxide-catalyzed Michael addition of P-chiral *H*-phosphinates to electron-deficient alkenes, which proceeded in a stereospecific manner with retention of phosphorus stereochemistry.[10] Thus, the Michael reaction of Ts-amide **7** to *t*-butyl acrylate was examined using the conditions of Han and Zhao (entry 4) because a large amount of Ts-amide **7** is readily prepared. Accordingly, Ts-amide **7** was treated with *t*-butyl acrylate in the presence of *t*-BuOMgBr (10 mol %) at 0 °C in THF. Although this reaction provided the desired adduct **14** as a single isomer as expected, chemical yield was quite low (10%). However, the yield was significantly improved to 83% upon utilizing 1 equiv of *t*-BuOMgBr

(3) For selected examples, see: (a) Makaritis, A.; Georgiadis, D.; Dive, V.; Yiotakis, A. *Chem.−Eur. J.* **2003**, *9*, 2079. (b) Liu, X.; Hu, X. E.; Tian, X.; Mazur, A.; Ebetino, F. H. *J. Organomet. Chem.* **2002**, *646*, 212–222. (c) Cristau, H.-J.; Coulombeau, A.; Genevois-Borella, A.; Pirat, J.-L. *Tetrahedron Lett.* **2001**, *42*, 4491. (d) Chen, H.; Noble, F.; Mothe, A.; Meudal, H.; Coric, P.; Danascimento, S.; Roques, B. P.; George, P.; Fournie-Zaluski, M.-C. *J. Med. Chem.* **2000**, *43*, 1398. (e) Allen, M. C.; Fuhrer, W.; Tuck, B.; Wade, R.; Wood, J. M. *J. Med. Chem.* **1989**, *32*, 1652.

(4) Parsons, W. H.; Patchett, A. A.; Bull, H. G.; Schoen, W. R.; Taub, D.; Davidson, J.; Combs, P. L.; Springer, J. P.; Gadebusch, H.; Weissberger, B.; Valiant, M. E.; Mellin, T. N.; Busch, R. D. *J. Med. Chem.* **1988**, *31*, 1772.

(5) The method to separate inidividual phosphinic dipeptide stereoisomers using HPLC was reported, see: Mucha, A.; Lammerhofer, M.; Lindner, W.; Pawelczak, M.; Kafarski, P. *Bioorg. Med. Chem. Lett.* **2008**, *18*, 1550.

(6) Yamagishi, T.; Haruki, T.; Yokomatsu, T. *Tetrahedron* **2006**, *62*, 9210.

(7) For application of our methodology to the synthesis of α,α′-diaminophosphinates and α-amino-α′-hydroxyphosphinates, see: (a) Kaboudin, B.; Haruki, T.; Yamagishi, T.; Yokomatsu, T. *Tetrahedron* **2007**, *63*, 8199. (b) Kaboudin, B.; Haruki, T.; Yamagishi, T.; Yokomatsu, T. *Synthesis* **2007**, 3226.

(8) Haruki, T.; Yamagishi, T.; Yokomatsu, T. *Tetrahedron: Asymmetry* **2007**, *18*, 2886.

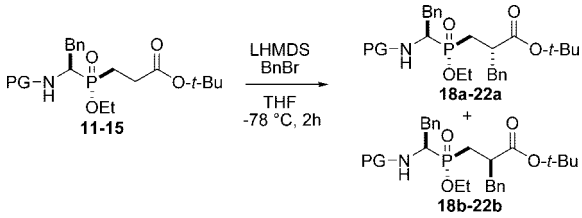
(9) Alkylation of lithiun enolates derived from γ-amino esters and δ-hydroxy esters was reported to proceed with high diastereoselectivity. In these cases, selectivity were rationalized by *cis*-enolates bearing a cyclic chelated structure. Reactions of γ-amino esters: (a) Hanessian, S.; Schaum, R. *Tetrahedron Lett.* **1997**, *38*, 163. (b) Hanessian, S.; Margarita, R. *Tetrahedron Lett.* **1998**, *39*, 5887. Reactions of δ-hydroxy esters: (c) Narasaka, K.; Ukaji, Y. *Chem. Lett.* **1986**, *59*, 81. (d) Narasaka, K.; Ukaji, Y.; Watanabe, K. *Chem. Lett.* **1986**, *59*, 1755. (e) Narasaka, K.; Ukaji, Y.; Watanabe, K. *Chem. Lett.* **1987**, *60*, 1457.

(10) Han, L.-B.; Zhao, C.-Q. *J. Org. Chem.* **2005**, *70*, 10121.

(entry 4). The stereochemistry of **14** was ascertained by single-crystal X-ray analysis, suggesting the stereochemistry at the phosphorus atom was retained without epimerization in accordance with Han's report.[10] Through this methodology, α-aminoalkyl(2-carboxyethyl)phosphinates **11**−**13** and **15**−**17** bearing Bz, Boc, Cbz, and 2,4,6-triisopropylbenzenesulfonyl (Trs) groups on the nitrogen atom could be prepared without a loss of phosphorus chirality in good yields, respectively (entries 1−7).

Having requisite **11**−**17** in hand, alkylations of their enolates with benzyl bromide (BnBr) as a model electrophile were next investigated to determine the influence of the nitrogen protecting group (PG) on diastereoselectivity (Table 2). Thus, compound **11** having a conventional Cbz protecting

Table 2. Reactions of **11**−**15** with Benzyl Bromide



entry	substrate	product	dr(**a**:**b**)[a]	yield[b] (%)
1	**11** (PG = Cbz)	**18**	1.1:1	93
2	**12** (PG = Bz)	**19**	3.4:1	78
3	**13** (PG = Boc)	**20**	4.5:1	90
4	**14** (PG = Ts)	**21**	4.0:1	83
5	**15** (PG = Trs)	**22**	21:1	92

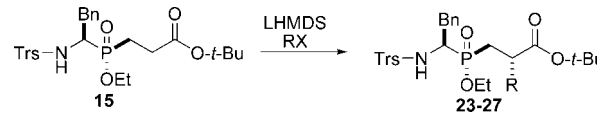
[a] Determined by ^{31}P NMR analysis. [b] Combined yield of each isomer.

group was treated with LHMDS (3 equiv) in THF at −78 °C, and the resulting enolate was alkylated with BnBr (3.2 equiv) at the same temperature. This alkylation reaction was completed within 2 h to give a 1.1:1 mixture of **18a** and **18b** in 93% yield (entry 1). Modest diastereoselectivity (3.4:1 to 4.5:1) was observed when substrates **12**−**14** bearing Bz, Boc, and a Ts protecting group, respectively, were alkylated under the same conditions (entries 2−4).[11] It is noteworthy that a bulky Trs protecting group of **15** markedly influenced diastereoselectivity, and **22a** was preferably produced in an excellent diastereoselectivity (21:1) in a 92% yield under the same conditions (entry 5). Determination of the stereochemistry of alkylation product **21a** was accomplished by X-ray crystallographic analysis. The stereochemistries of **18a**−**20a** and **22a** were inferred based on their analogous spectroscopic data (^{1}H NMR and ^{31}P NMR) to those of **21a**.

(11) A similar benzylation of **14** was also attempted using LiCl (6 equiv) as an additive, which has previously been elucidated to enhance the reactivity of lithium enolates and have an influence on the diastereoselectivity of their alkylation reactions by changing the aggregated states. However, the selectivity was deteriorated to **21a**:**21b** = 3:1. For LiCl-mediated reactions of lithium enolates with electrophiles, see: (a) Seebach, D.; Grundler, H.; Shoda, S.-I. *Helv. Chim. Acta* **1991**, *74*, 197. (b) Myers, A. G.; Gleason, J. L.; Yoon, T.; Kung, D. W. *J. Am. Chem. Soc.* **1997**, *119*, 656. (c) Myers, A. G.; Yang, B. H.; Chen, H.; McKinstry, L.; Kopecky, D. J.; Gleason, J. L. *J. Am. Chem. Soc.* **1997**, *119*, 6496. (d) Lee, J.; Choi, W. B.; Lynch, J. E.; Volante, R. P.; Reider, P. J. *Tetrahedron Lett.* **1998**, *39*, 3679.

To elucidate the scope of this methodology, alkylations of the lithium enolate generated from **15** with several electrophiles were examined (Table 3). Reactions with

Table 3. Reactions of **15** with Several Electrophiles



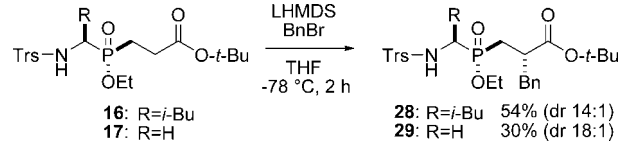
entry	RX	temp (°C)	product	dr[a]	yield[b] (%)
1	MeI	−78	**23**	24:1	82
2	allylBr	−78	**24**	21:1	83
3	methallylBr	−78	**25**	29:1	69
4	*i*-BuI	−78 to rt	**26**	14:1	62
5	propargylCl	−78 to −20	**27**	17:1	84

[a] Determined by ^{31}P NMR analysis. [b] Isolated yield.

relatively active alkyl halides including methyl iodide, allyl bromide, and methallyl bromide proceeded at −78 °C to give alkylation products **23**−**25** in good yields (entries 1−3). However, increasing the temperature from −78 °C to rt or −20 °C was necessary in reactions using *i*-butyl iodide and propargyl chloride (entries 4 and 5). In all cases, excellent diastereoselectivity (14:1−29:1) was observed (entries 1−5). Recently, a propargyl side chain at the P1′ position proved to be a versatile functionality for divergent synthesis of phosphinic peptides bearing an isoxazole ring, which is expected to interact favorably with the S1′ pocket of metalloproteases.[3a] However, highly stereoselective synthesis of phosphinic dipeptide units having a propargyl side chain at the P1′ position is a difficult task as seen in a previous study.[3a] Therefore, the remarkably high diastereoselectivity (17:1) observed in the alkylation with propargyl chloride is noteworthy (entry 5).

To survey the origin of the high diastereoselectivity, diastereoselectivity for benzylation of **17** having no stereogenic center at the α-position was analyzed in comparison with that of **16**, which possesses a bulky *i*-butyl group at the α-position (Scheme 2). Our survey revealed that dias-

Scheme 2

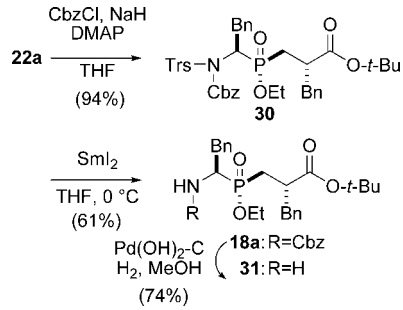


tereoselectivity might be highly dependent upon the chirality at the phosphorus atom rather than the α-position, since both reactions provided desired benzylation products **28** and **29** in high diastereoselectivity (14:1 vs 18:1) without significant differences.

Before incorporating α,β′-disubstituted aminomethyl(2-carboxyethyl)phosphinates obtained into a peptide sequence,

the N-terminal protecting group must be removed. Thus, deprotection of the Trs group of **22a** was examined (Scheme 3). Although the reported deprotection protocols using (1) sodium with liquid NH_3,[12] (2) SmI_2,[13] and (3) 4,4-di-*tert*-butylbiphenyl with lithium[14] were applied, a desired free amine product could not be obtained in each case. However, facile removal of the Trs group was achieved through application of the Knowles method.[15] Accordingly, **22a** was carbamated with CbzCl, and the resulting carbamate **30** was treated with SmI_2 in THF to give **18a** in a modest overall yield. Finally, hydrogenolysis of **18a** over Pearlman's catalyst provided free amine **31** in a 74% yield.

Scheme 3



In summary, we have developed a novel method for the stereoselective synthesis of α,β′-disubstituted aminomethyl(2-carboxyethyl)phosphinates starting from α-aminoalkyl-*H*-phosphinates having high diastereomerical purity. The feature of this method is that all stereogenic centers are highly controlled by the chirality of the phosphorus atom. Since both enantiomers of α-aminoalkyl-*H*-phosphinates are now available in high optical purity,[8] the present method is applicable to the synthesis of optically active α,β′-disubstituted aminomethyl(2-carboxyethyl)phosphinate derivatives. Synthesis of the optically active analogues and their incorporation to a peptide sequence as a phosphinyl dipeptide isostere are now in progress.

Acknowledgment. This work was partially supported by a grant for private universities from The Promotion and Mutual Aid Corporation for Private Schools of Japan and the Ministry of Education, Culture, Sports, Science, and Technology. The authors wish to thank Mr. Haruhiko Fukaya (the analytical center of this university) for the X-ray crystallographic analysis.

Supporting Information Available: Experimental procedures and full spectroscopic data for all new compounds, and X-ray analysis data for compounds **14** and **21a**. This material is available free of charge via the Internet at http://pubs.acs.org.

OL801743D

(12) Roemmele, R. C.; Rapoport, H. *J. Org. Chem.* **1988**, *53*, 2367.
(13) Vedejs, E.; Lin, S. *J. Org. Chem.* **1994**, *59*, 1602.
(14) Neipp, C. E.; Humphrey, J. M.; Martin, S. F. *J. Org. Chem.* **2001**, *66*, 531.
(15) For SmI_2-mediated removal of the sulfonyl group of *N*-benzoyl benzenesulfonamide derivatives, see: Knowles, H.; Parsons, A. F.; Pettifer, R. M. *Synlett.* **1997**, 271.