ORGANIC LETTERS

2002
Vol. 4, No. 7
1055−1058

Diastereoselective Synthesis of ψ[(*E*)-CMe═CH]- and ψ[(*E*)-CMe═CMe]-Type Dipeptide Isosteres Based on Organocopper-Mediated *anti*-S_N2' Reaction

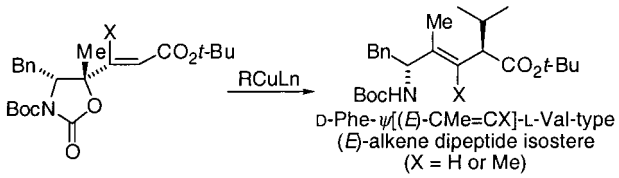
Shinya Oishi,[†] Ayumu Niida,[†] Takae Kamano,[†] Yoshihiko Odagaki,[‡] Hirokazu Tamamura,[†] Akira Otaka,[†] Nobuyuki Hamanaka,[‡] and Nobutaka Fujii*,[†]

Graduate School of Pharmaceutical Sciences, Kyoto University, Sakyo-ku, Kyoto, 606-8501, Japan, and Minase Research Institute, Ono Pharmaceutical Co. Ltd., Mishima-gun, Osaka 618-8585, Japan

nfujii@pharm.kyoto-u.ac.jp

Received September 28, 2001

ABSTRACT



A straightforward synthetic route for the synthesis of diastereomerically pure ψ[(*E*)-CMe═CH]- and ψ[(*E*)-CMe═CMe]-type dipeptide isosteres was developed on the basis of regio- and stereoselective *anti*-S_N2' alkylation of 3-(*N*-Boc-5-methyl-4-substituted-oxazolidin-2-on-5-yl)acrylates with organocopper reagents.

β-Turn substructures on the surface of bioactive peptides and proteins very often participate in important molecular recognition. This motif represents an intensive target for development of new pharmaceuticals in medicinal chemistry.[1] Many β-turn mimetics have been developed and evaluated for restriction and stabilization of active conformations.[2,3] (*E*)-Alkene dipeptide isosteres (EADIs) corresponding to (L,D)- and (D,L)-type dipeptides are potential mimetics of the type II and II′ β-turn motifs, respectively. Gellman et al. previously reported that a Gly-ψ[(*E*)-CMe═CMe]-Gly type EADI promotes β-hairpin formation in CH_2Cl_2 in a flexible linear peptide backbone.[4] In addition, Wipf et al. recently reported that ψ[(*E*)-CMe═CH]-type EADIs promote the formation of β-turns in the solid state as a result of restriction of φ,ψ-dihedral angles by $A^{1,2}$- and $A^{1,3}$-strains.[5] However, synthesis of these agents is likely to be limited to Ala-ψ[(*E*)-CMe═CH]-Xaa-type EADIs since requisite chiral epoxides corresponding to diverse amino acids are not easily

[†] Kyoto University.
[‡] Ono Pharmaceutical Co., Ltd.

(1) Rose, G. D.; Gierasch, L. M.; Smith, J. A. *Advances in Protein Chemistry*; Academic Press: New York, 1985; pp 1−109.

(2) (a) Chen, S.; Chrusciel, R. A.; Nakanishi, H.; Raktabutr, A.; Johnson, M. E.; Sato, A.; Weiner, D.; Hoxie, J.; Saragovi, H. U.; Greene, M. I.; Kahn, M. *Proc. Natl. Acad. Sci. U.S.A.* **1992**, *89*, 5872. (b) Etzkorn, F. A.; Guo, T.; Lipton, M. A.; Goldberg, S. D.; Bartlett, P. A. *J. Am. Chem. Soc.* **1994**, *116*, 10412. (c) Gillespie, P.; Cicariello, J.; Olson, G. L. *Biopolymers* **1997**, *43*, 191. (d) Fink, B. E.; Kym, P. R.; Katzenellenbogen, J. A. *J. Am. Chem. Soc.* **1998**, *120*, 4334. (e) Johannesson, P.; Lindeberg, G.; Tong, W.; Gogoll, A.; Karlén, A.; Hallberg, A. *J. Med. Chem.* **1999**, *42*, 601. (f) Khalil, E. M.; Ojala, W. H.; Pradhan, A.; Nair, V. D.; Gleason, W. B.; Mishra, R. K.; Johnson, R. L. *J. Med. Chem.* **1999**, *42*, 628. (g) Eguchi, M.; Lee, M. S.; Nakanishi, H.; Stasiak, M.; Lovell, S.; Kahn, M. *J. Am. Chem. Soc.* **1999**, *121*, 12204. (h) Kim, H.-O.; Nakanishi, H.; Lee, M. S.; Kahn, M. *Org. Lett.* **2000**, *2*, 301. (i) Estiarte, M. A.; Rubiralta, M.; Diez, A.; Thormann, M.; Giralt, E. *J. Org. Chem.* **2000**, *65*, 6992. (j) Golebiowski, A.; Klopfenstein, S. R.; Shao, X.; Chen, J. J.; Colson, A.-O.; Grieb, A. L.; Russell, A. F. *Org. Lett.* **2000**, *2*, 2615. (k) Smith, A. B., III; Wang, W.; Sprengeler, P. A.; Hirschmann, R. *J. Am. Chem. Soc.* **2000**, *122*, 11037. (l) Alonso, E.; López-Ortiz, F.; Del Pozo, C.; Peralta, E.; Macías, A.; González, J. *J. Org. Chem.* **2001**, *66*, 6333.

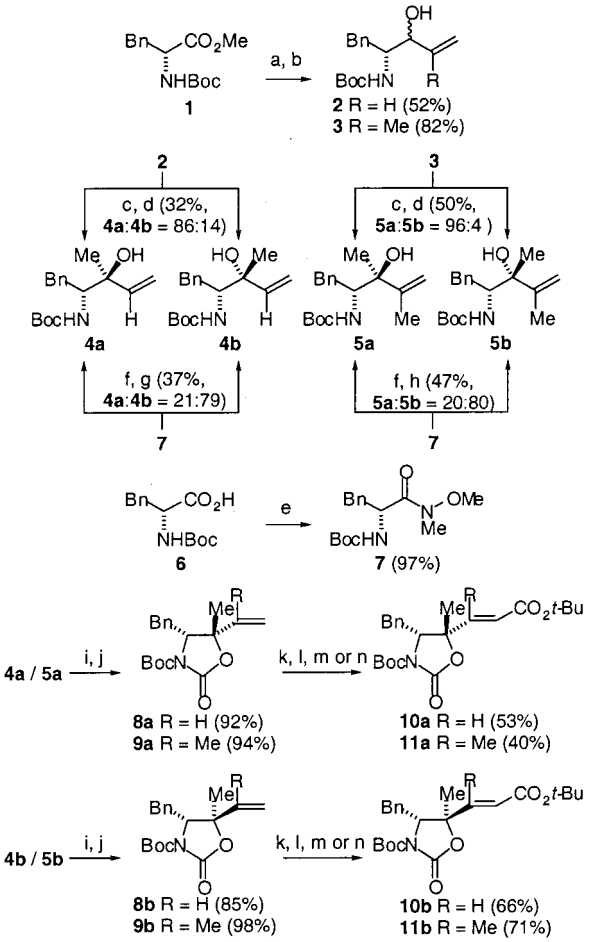
10.1021/ol016835b CCC: $22.00
Published on Web 03/05/2002

available. In this communication, we describe an alternative practical synthesis of ψ[(*E*)-CMe=CH]- and ψ[(*E*)-CMe=CMe]-type dipeptide isosteres from a chiral amino acid utilizing organocopper-mediated regio- and stereoselective *anti*-S_N2' alkylation of oxazolidinone derivatives.

We and others previously reported that ψ[(*E*)-CH=CH]-type EADIs are efficiently synthesized via organocopper-mediated regio- and stereoselective alkylation of α,β-unsaturated esters containing a leaving group at the γ-position. This includes γ-mesyloxy-α,β-unsaturated esters[6] and *N*-activated β-aziridino-α,β-unsaturated esters,[5,7] which are easily constructed from chiral amino alcohol derivatives. On the other hand, if γ-methylated α,β-unsaturated esters are to be used in the same manner for the synthesis of ψ[(*E*)-CMe=CX]-type EADIs (X = H or Me), activation of tertiary alcohols for the construction of key S_N2' substrates as the corresponding mesylates or *N*-activated aziridines is potentially problematic. Thus, we attempted to develop a new process for the synthesis of ψ[(*E*)-CMe=CX]-type EADIs based on organocopper-mediated S_N2' reactions of β-oxazolidinonyl-α,β-unsaturated esters as key substrates.

To make our synthetic methodology generally applicable to diverse ψ[(*E*)-CMe=CX]-type EADIs, we chose chiral amino acid derivatives **1** and **6** as the starting materials (Scheme 1).[8] Initially, ester **1** was converted to allyl alcohols **2** or **3** by successive treatment with DIBAL-H and vinyl or isopropenyl Grignard reagents. Swern oxidation of **2** and **3** followed by treatment with methyl Grignard reagent in the presence of $CeCl_3$ yielded *anti*-isomers of the respective allyl alcohols **4a** and **5a** as major products (**4a**:**4b** = 86:14; **5a**:**5b** = 96:4).[9] Their *syn*-isomer **4b** or **5b** was preferentially obtained by treatment of the methyl ketone, which was prepared from Weinreb's amide **7**, with vinyl or isopropenyl Grignard reagent in the presence of $CeCl_3$ (**4a**:**4b** = 21:79; **5a**:**5b** = 20:80).[9] Cyclization by sodium hydride of allyl alcohols **4a,b** and **5a,b**, followed by *N*-protection by a Boc group, afforded oxazolidin-2-ones **8a,b** and **9a,b**, respectively, in which the hydroxy groups of **4a,b** and **5a,b** were converted to leaving groups with apparent protecting groups as carbamates. After ozonolysis of 5-vinyloxazolidin-2-ones **8a,b** and subsequent reductive treatment with dimethyl sulfide, Horner−Wadsworth−Emmons reaction (HWE reaction) of the resulting aldehydes yielded α,β-unsaturated esters **10a,b** in *E*-selective manner. The β-methylated derivatives **11a,b** were prepared by Wittig reaction of the ketones in moderate yields, which were obtained following ozonolysis and consecutive reductive treatment of 5-isopropenyloxazo-

Scheme 1[a]



[a] (a) DIBAL-H, CH_2Cl_2/toluene. (b) CH_2=$CRMgBr{\cdot}ZnCl_2{\cdot}LiCl$, THF. (c) $(COCl)_2$, DMSO, DIEA, CH_2Cl_2. (d) MeMgCl, $CeCl_3$, THF. (e) $MeONHMe{\cdot}HCl$, DCC, DIEA, DMF. (f) MeMgCl, THF. (g) CH_2=CHMgBr, $CeCl_3$, THF. (h) CH_2=CMeMgBr, $CeCl_3$, THF. (i) NaH, THF. (j) Boc_2O. (k) O_3 gas, EtOAc. (l) DMS. (m) $(EtO)_2P(O)CH_2CO_2t$-Bu, LiCl, DIEA, MeCN. (n) Ph_3P=$CHCO_2t$-Bu, $CHCl_3$.

(3) For recent reviews of peptidomimetics, see: (a) Peptide Secondary Structure Mimetics. *Tetrahedron* (Symposia-in-print, no. 50; Kahn, M., Ed.) **1993**, *49*, 3444. (b) Hanessian, S.; McNaughton-Smith, G.; Lombart, H.-G.; Lubell, W. D. *Tetrahedron* **1997**, *53*, 12789. (c) *Peptidomimetics Protocols*; Kazmierski, W. M., Ed.; Humana Press: Totowa, NJ, 1999. (d) Hruby, V. J.; Balse, P. M. *Curr. Med. Chem.* **2000**, *7*, 945. (e) Kim, H.-O.; Kahn, M. *Comb. Chem. High Throughput Screening* **2000**, *3*, 167.

(4) Gardner, R. R.; Liang, G.-B.; Gellman, S. H. *J. Am. Chem. Soc.* **1995**, *117*, 3280.

(5) (a) Wipf, P.; Fritch, P. C. *J. Org. Chem.* **1994**, *59*, 4875. (b) Wipf, P.; Henninger, T. C.; Geib, S. J. *J. Org. Chem.* **1998**, *63*, 6088.

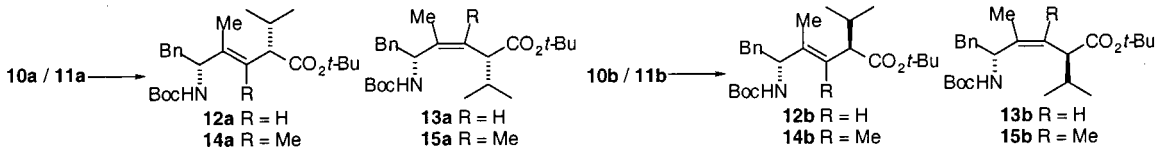
(6) (a) Ibuka, T.; Habashita, H.; Funakoshi, S.; Fujii, N.; Oguchi, Y.; Uyehara, T.; Yamamoto, Y. *Angew. Chem., Int. Ed. Engl.* **1990**, *29*, 801. (b) Ibuka, T.; Habashita, H.; Otaka, A.; Fujii, N.; Oguchi, T.; Uyehara, T.; Yamamoto, Y. *J. Org. Chem.* **1991**, *56*, 4370.

(7) (a) Ibuka, T.; Nakai, K.; Habashita, H.; Hotta, Y.; Fujii, N.; Mimura, N.; Miwa, Y.; Taga, T.; Yamamoto, Y. *Angew. Chem., Int. Ed. Engl.* **1994**, *33*, 652. (b) Fujii, N.; Nakai, K.; Tamamura, H.; Otaka, A.; Mimura, N.; Miwa, Y.; Taga, T.; Yamamoto, Y.; Ibuka, T. *J. Chem. Soc., Perkin Trans. 1* **1995**, 1359. (c) Wipf, P.; Henninger, T. C. *J. Org. Chem.* **1997**, *62*, 1586. (d) Tamamura, H.; Yamashita, M.; Nakajima, Y.; Sakano, K.; Otaka, A.; Ohno, H.; Ibuka, T.; Fujii, N. *J. Chem. Soc., Perkin Trans. 1* **1999**, 2983. (e) Oishi, S.; Tamamura, H.; Yamashita, M.; Odagaki, Y.; Hamanaka, N.; Otaka, A.; Fujii, N. *J. Chem. Soc., Perkin Trans. 1* **2001**, 2445.

(8) D-Phenylalanine derivatives **1** and **6** were utilized for the synthesis of D-Phe-ψ[(*E*)-CMe=CX]-D/L-Val-type EADIs as a model case in this communication. A dipeptide, D-Phe-L-Val, accommodates in the $(i+1)-(i+2)$ position in the type II′ β-turn substructure of the cyclic RGD pentapeptide, *cyclo*(-Arg-Gly-Asp-D-Phe-Val-), previously reported: Haubner, R.; Finsinger, D.; Kessler, H. *Angew. Chem., Int. Ed. Engl.* **1997**, *36*, 1374.

(9) The diastereomerically pure allyl alcohols **4a** and **5a,b** were readily purified by recrystallization from the diastereomixture, respectively. The *syn*-allyl alcohol **4b** could not be isolated in this step, and thus the diastereomixture, which contained the *syn*-allyl alcohol **4b** as a major isomer, was converted into the corresponding oxazolidin-2-one derivative **8b**. The diastereomerically pure oxazolidin-2-one **8b** was purified by recrystallization.

Table 1. Organocyanocuprate-Mediated Alkylation of β-(Oxazolidin-2-on-5-yl)-α,β-unsaturated Esters **10a,b** and **11a,b**



entry	substrate	reagent	condition	yield (%)[a]	product ratio[b]
1	**10a**	*i*-PrCu(CN)MgCl·BF_3·2LiCl (4 equiv)	−78 °C, 30 min	95	**12a**:**13a** = 100:0
2	**10a**	*i*-Pr_2Cu(CN)$(MgCl)_2$·BF_3·2LiCl (4 equiv)	−78 °C, 30 min	95	**12a**:**13a** = 100:0
3	**10b**	*i*-PrCu(CN)MgCl·BF_3·2LiCl (4.2 equiv)	−78 °C, 30 min	99	**12b**:**13b** = 68:32
4	**10b**	*i*-Pr_2Cu(CN)$(MgCl)_2$·BF_3·2LiCl (4.2 equiv)	−78 °C, 30 min	85	**12b**:**13b** = 79:21
5	**11a**	*i*-PrCu(CN)MgCl·BF_3·2LiCl (4 equiv)	−78 °C, 30 min, then 0 °C, 3 h	*c*	
6	**11a**	*i*-Pr_2Cu(CN)$(MgCl)_2$·BF_3·2LiCl (4 equiv)	−78 °C, 30 min, then 0 °C, 3 h	48	**14a**:**15a** = 76:24
7	**11a**	*i*-Pr_2Cu(CN)$(MgCl)_2$·BF_3·2LiCl (6 equiv)	−78 °C, 30 min, then 0 °C, 3 h	73	**14a**:**15a** = 75:25
8	**11a**	*i*-Pr_3Cu(CN)$(MgCl)_3$·BF_3·2LiCl (4 equiv)	−78 °C, 30 min, then 0 °C, 3 h	77	**14a**:**15a** = 68:32
9	**11b**	*i*-PrCu(CN)MgCl·BF_3·2LiCl (4 equiv)	−78 °C, 30 min, then 0 °C, 3 h	*c*	
10	**11b**	*i*-Pr_2Cu(CN)$(MgCl)_2$·BF_3·2LiCl (4 equiv)	−78 °C, 30 min, then 0 °C, 3 h	95	**14b**:**15b** = 79:21

[a] Combined isolated yields. [b] Ratio was determined by RP-HPLC. [c] The starting material was recovered.

lidin-2-ones **9a,b**. Relative configurations of **10a,b** and **11a,b** were determined by ^{1}H NMR measurements.

The leaving-group ability of carbamate functionality in β-(oxazolidin-2-on-5-yl)-α,β-unsaturated esters **10a,b** and **11a,b** is presumed to be insufficient for alkylation with organocyanocuprates as compared to that of mesylates or *N*-activated aziridines in key intermediates for ψ[(*E*)-CH═CH]-type EADIs. In practice, MeCu(CN)Li·LiBr or its BF_3 complex was not effective for the alkylation of 5-vinyloxazolidin-2-one. However, the alkylation by more active "higher-order" cyanocuprates, Me_2Cu(CN)Li_2·BF_3·LiBr, proceeded excellently.[10] On the basis of precedent investigations, we evaluated alkylation of oxazolidin-2-ones **10a,b** and **11a,b** by cyanocuprates prepared from copper cyanide and available Grignard reagents (Table 1). Treatment of *cis*-isomer **10a** with *i*-PrCu(CN)MgCl·BF_3·2LiCl or *i*-Pr_2Cu(CN)$(MgCl)_2$·BF_3·2LiCl in THF at − 78 °C for 30 min gave only the *E*-isomer of an *anti*-S_N2' product (D-Phe-ψ[(*E*)-CMe═CH]-D-Val) **12a** in excellent yield (entries 1 and 2). In the case of *trans*-isomer **10b**, the expected *anti*-S_N2' products, D-Phe-ψ[(*E*)-CMe═CH]-L-Val **12b** and D-Phe-ψ[(*Z*)-CMe═CH]-D-Val **13b**, were obtained by *i*-PrCu(CN)MgCl·BF_3·2LiCl (**12b**:**13b** = 68:32, entry 3). Employment of the more active reagent, *i*-Pr_2Cu(CN)$(MgCl)_2$·BF_3·2LiCl, similarly yielded **12b** and **13b** with higher *E*-selectivity (**12b**:**13b** = 79:21, entry 4).

Interestingly, the reactivities of β-methylated substrates **11a,b** to organocopper reagents were more sluggish than those of **10a,b**. Each reaction of **11a** or **11b** by the "lower-order" *i*-PrCu(CN)MgCl·BF_3·2LiCl gave no product, and the starting material was recovered (entries 5 and 9). Alkylation of the *cis*-isomer **11a** with 4 equiv of the higher-order reagent *i*-Pr_2Cu(CN)$(MgCl)_2$·BF_3·2LiCl yielded not only the expected *E*-isomer of *anti*-S_N2' product (D-Phe-ψ[(*E*)-CMe═CMe]-D-Val) **14a** but also its *Z*-isomer (D-Phe-ψ[(*Z*)-CMe═CMe]-L-Val) **15a** in low combined yield (48%, entry 6). The chemical yield was significantly improved by use of 6 equiv of the same reagent or 4 equiv of *i*-Pr_3Cu(CN)$(MgCl)_3$·BF_3·2LiCl, although a trace amount of the starting material **11a** still remained and the production of *Z*-isomer **15a** was not suppressed (entries 7 and 8). The *trans*-isomer **11b** was converted by *i*-Pr_2Cu(CN)$(MgCl)_2$·BF_3·2LiCl to D-Phe-ψ[(*E*)-CMe═CMe]-L-Val **14b** as a major product with concomitant formation of a small amount of D-Phe-ψ[(*Z*)-CMe═CMe]-D-Val **15b** (**14b**:**15b** = 79:21, entry 10). All products were purified by flash chromatography over silica gel, and the optical purity of each product was estimated as >99% by ^{1}H NMR spectra. Olefinic geometry of all products **12a**−**15a** and **12b**−**15b** were established by ^{1}H NMR, and stereochemistries of the α-alkyl groups of the products were determined by circular dichroism measurements.[11] X-ray analyses of **13b** and **14b** also supported these analyses.

In summary, we have found that alkylation of β-(oxazolidin-2-on-5-yl)-α,β-unsaturated esters by several organocopper reagents proceeds regio- and stereoselectively via *anti*-S_N2' mechanisms to give mainly *E*-isomers of the α-alkylated products. The alkylation was successfully applied to the stereoselective synthesis of ψ[(*E*)-CMe═CH]- and ψ[(*E*)-CMe═CMe]-type EADIs from a chiral amino acid.

Acknowledgment. We thank Dr. Terrence R. Burke, Jr., NCI, NIH, for valuable discussions. This work was supported by Grant-in-Aid for Scientific Research from the Ministry of Education, Culture, Sports, Science, and Technology, Japan, and the Japan Health Science Foundation. S.O. is grateful for Research Fellowships of the JSPS for Young Scientists.

(10) Ibuka, T.; Suzuki, K.; Habashita, H.; Otaka, A.; Tamamura, H.; Mimura, N.; Miwa, Y.; Taga, T.; Fujii, N. *J. Chem. Soc., Chem. Commun.* **1994**, 2151.

(11) Ibuka, T.; Habashita, H.; Funakoshi, S.; Fujii, N.; Baba, K.; Kozawa, M.; Oguchi, Y.; Uyehara, T.; Yamamoto, Y. *Tetrahedron: Asymmetry* **1990**, *1*, 389.

Supporting Information Available: Selected experimental procedures, ^{1}H NMR spectra for all new compounds, CD spectra of **12a**−**15a** and **12b**−**15b**, and crystal structure of **13b** and **14b**. This material is available free of charge via the Internet at http://pubs.acs.org.

OL016835B