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Diastereoselective Synthesis of ψ[(*E*)-CH=CMe]- and ψ[(*Z*)-CH=CMe]-Type Dipeptide Isosteres by Organocopper-Mediated *anti*-S_N2' Reaction

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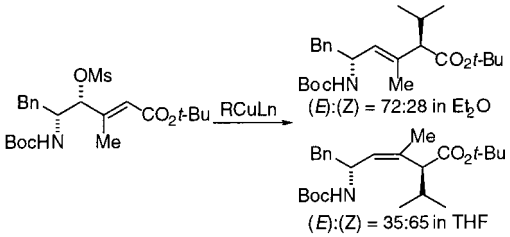
ABSTRACT



Acyclic ψ[(*E*)-CH=CMe]- and ψ[(*Z*)-CH=CMe]-type dipeptide isosteres were efficiently synthesized. In a key reaction, α-alkylation of γ-mesyloxy-β-methyl-α,β-unsaturated esters with organocyanocuprates in diethyl ether or tetrahydrofuran preferentially afforded the ψ[(*E*)-CH=CMe]- or ψ[(*Z*)-CH=CMe]-isomer, respectively, via *anti*-S_N2' mechanism.

Bioisosteres of natural amino acids and dipeptides are useful tools for investigation of molecular recognition including receptor/ligand and enzyme/substrate interactions, and they represent diverse elements of practical value for constructing chemical libraries in medicinal chemistry.[1] (*E*)-Alkene dipeptide isosteres (EADIs) are examples of structures having modified peptide backbones, which are designed to provide resistance to biodegradation[2] and conformational restriction of a β-turn substructures,[3] etc. We and others have reported the stereoselective synthesis of EADIs mediated by organocopper reagents[4] and their application to bioactive peptides.[2,5] For instance, we recently synthesized an EADI-containing cyclic RGD pseudopeptide **3** and evaluated its biological activities.[6] A D-Phe-ψ[(*E*)-CH=CH]-L-Val isostere was

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incorporated as an equivalent to the $(i+1)-(i+2)$ position in the type II′ β-turn substructure of the cyclic RGD pentapeptide **1** reported by Kessler et al. (Figure 1).[7] In the

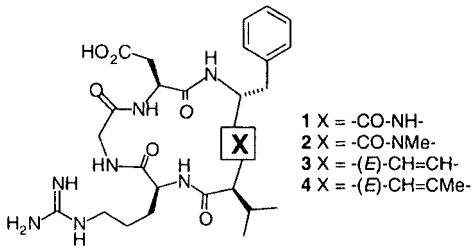


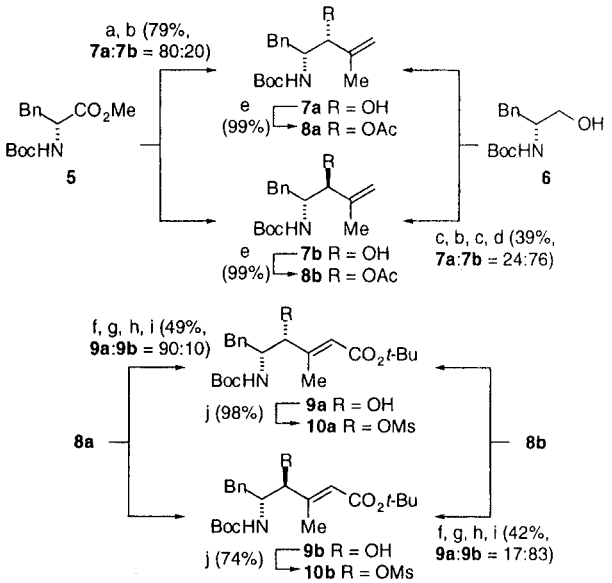
Figure 1. Cyclic RGD peptides **1** and **2** by Kessler et al. and EADI-containing cyclic RGD pseudopeptides **3** and **4**.

inhibition assay of vitronectin-$\alpha_v\beta_3$ integrin binding, the potency of pseudopeptide **3** was higher than that of **1** and nearly equal to that of the improved cyclic peptide **2**.[8]

While the reason for the high activity of the pseudopeptide **3** has not been elucidated yet, incorporation of the D-Phe-ψ[(*E*)-CH=CH]-L-Val moiety may convert the peptide backbone to a more active form, as well as *N*-methylvaline. Thus, we designed the pseudopeptide **4** containing the D-Phe-ψ[(*E*)-CH=CMe]-L-Val moiety in order to rationally investigate the effect of both the *N*-methylvaline and the (*E*)-alkene moiety. Synthesis of **4** required preparation of this unique dipeptide isostere. In this communication, we describe the first unequivocal synthesis of a ψ[(*E*)-CH=CMe]-type dipeptide isostere and its ψ[(*Z*)-CH=CMe]-congener, which is inherently an unanticipated product, obtained with organocopper reagents.

Synthesis of ψ[(*E*)-CH=CMe]-Type Dipeptide Isostere Precursors. Synthesis of key intermediate, γ-mesyloxy-α,β-unsaturated esters **10**, started from D-phenylalanine derivative **5** or D-phenylalaninol derivative **6**. This provided a generalized synthetic strategy toward ψ[(*E*)-CH=CMe]-type dipeptide isosteres from chiral amino acids (Scheme 1). A *syn*-allyl alcohol **7a** was stereoselectively prepared by reduction of Boc-D-Phe-OMe **5** with DIBAL-H at −78 °C in CH_2Cl_2/toluene, followed by treatment with isopropenyl Grignard

Scheme 1[a]



[a] (a) DIBAL-H, CH_2Cl_2/toluene. (b) CH_2=CMeMgCl·$ZnCl_2$·LiCl, THF. (c) $(COCl)_2$, DMSO, DIEA, CH_2Cl_2. (d) $Zn(BH_4)_2$, Et_2O. (e) Ac_2O, pyridine, DMAP, $CHCl_3$. (f) O_3, EtOAc. (g) DMS. (h) Ph_3P=$CHCO_2t$-Bu, $CHCl_3$, reflux. (i) Na_2CO_3, MeOH. (j) MsCl, TEA, THF.

reagent (*syn*:*anti* = 80:20). Alternatively, an *anti*-allyl alcohol **7b** was preferentially afforded by reduction of the enone (obtained by Swern oxidation of a diastereomixture of allyl alcohols **7a** and **7b**) with $Zn(BH_4)_2$ in Et_2O (*syn*:*anti* = 24:76).[9] The diastereomerically pure alcohols **7a** and **7b** could be separated by flash chromatography over silica gel followed by recrystallization, respectively.

After protection of hydroxyl groups, acetates **8a** and **8b** were converted to α,β-unsaturated esters. Ozonolysis of **8a** followed by reductive treatment with dimethyl sulfide and successive Wittig reaction with Ph_3P=$CHCO_2t$-Bu gave γ-acetoxy-α,β-unsaturated esters. Deprotection of acetyl groups yielded two isomers of the γ-hydroxy-α,β-unsaturated esters. Unexpectedly, the resulting minor isomer was not the (*Z*)-isomer of *syn*-α,β-unsaturated esters **9a** but rather the *anti*-(*E*)-isomer **9b**, which apparently originated as a result of epimerization at the chiral center of the acetoxy group (**9a**:**9b** = 90:10). Even in the case of the acetate **8b**, both isomers of α,β-unsaturated esters **9a** and **9b** were obtained in similar manner (**9a**:**9b** = 17:83). Each isomer of esters **9a** and **9b** was readily purified by flash chromatography. The *E* geometry and the relative configuration of the hydroxy groups of α,β-unsaturated esters **9a** and **9b** were established by ^{1}H NMR analysis of the corresponding acetonides.[10] Esters **9a** and **9b** were converted into the respective mesylates **10a** and **10b**.

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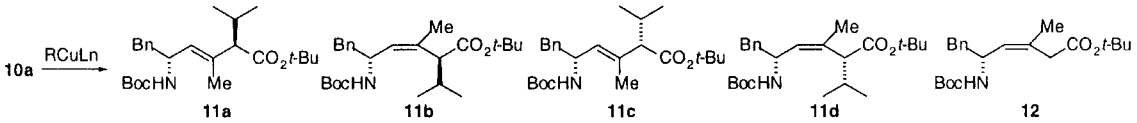
Table 1. Alkylation of *syn*-γ-Mesyloxy-β-methyl-α,β-unsaturated Ester **10a** with Organocyanocuprates



entry	reagent[a]	additive[b]	solvent	condition	product ratio[c] **11a**:**11b**:**11c**+**11d**[d]:**12**	yield[e] (%)
1	*i*-PrCu(CN)MgCl·BF_3		THF	0 °C, 0.5 h	40:51: -[g]:9	82
2	*i*-Pr_2Cu(CN)$(MgCl)_2$·BF_3		THF	−78 °C, 0.5 h	35:64: -[g]:1	94
3	*i*-Pr_2Cu(CN)$(MgCl)_2$·BF_3	HMPA	THF	−78 °C, 0.5 h	28:71: -[g]:1	91
4	*i*-Pr_2Cu(CN)$(MgCl)_2$·BF_3	TMEDA	THF	−78 °C, 0.5 h	27:72: -[g]:1	92
5	*i*-Pr_2Cu(CN)$(MgCl)_2$	18-crown-6	THF	−78 °C, 0.5 h	25:73: -[g]:1	86
6	*i*-PrCu(CN)MgCl·BF_3		Et_2O	0 °C, 3 h	36:63: -[g]:1	15[h]
7	*i*-Pr_2Cu(CN)$(MgCl)_2$·BF_3		Et_2O	−78 °C, 0.5 h	46:27:26:1	90
8	*i*-Pr_2Cu(CN)$(MgCl)_2$·BF_3	HMPA	Et_2O	−78 °C, 0.5 h, then 0 °C, 0.5 h	70:27: -[g]:3	93
9	*i*-Pr_2Cu(CN)$(MgCl)_2$·BF_3	TMEDA	Et_2O	−78 °C, 0.5 h	44:25:28:3	81
10	*i*-Pr_2Cu(CN)$(MgCl)_2$	18-crown-6	Et_2O	−78 °C, 0.5 h	14:84: -[g]:2	93
11	*i*-Pr_2Cu(CN)$(MgCl)_2$·BF_3	THF	Et_2O	−78 °C, 0.5 h	43:42:12:3	97
12	*i*-Pr_2Cu(CN)$(MgCl)_2$·BF_3		Et_2O/THF[f]	−78 °C, 0.5 h	37:62: -[g]:1	87

[a] All reactions were carried out with 4 molar equiv of reagent. [b] 4 molar equiv. [c] Product ratios were determined by HPLC and ^{1}H NMR. [d] Containing a small amount of an unknown product. [e] Combined yield. [f] Et_2O/THF = 7:3. [g] Although we cannot conclusively rule out its presence, we failed to isolate the corresponding product. [h] The starting material was recovered (77%).

Synthesis of ψ[(*E*)-CH=CMe]- and ψ[(*Z*)-CH=CMe]-Type Dipeptide Isosteres. Alkylation of γ-Mesyloxy-β-methyl-α,β-unsaturated Esters with Organocyanocuprates. In the synthesis of chiral α-alkyl-β,γ-unsaturated esters[11a] and chiral α,α-dialkyl-β,γ-unsaturated esters[11b] and its application to the synthesis of ψ[(*E*)-CH=CH]-type dipeptide isosteres,[4a] the regio- and stereochemical outcomes of organocopper-mediated alkylation of γ-mesyloxy-α,β-unsaturated esters are fully documented. Alkylation proceeds through an *anti*-S_N2' mechanism, and all products are exclusively of *E*-geometry. As such, it was our expectation that ψ[(*E*)-CH=CMe]-type dipeptide isosteres would be easily prepared from γ-mesyloxy-β-methyl-α,β-unsaturated esters such as **10a** and **10b**.

However, treatment of **10a** with a "lower-order" organocyanocuprate-BF_3 complex, *i*-PrCu(CN)MgCl·BF_3, in THF, which is the usual condition for preparation of ψ[(*E*)-CH=CH]-type dipeptide isosteres, gave D-Phe-ψ[(*Z*)-CH=CMe]-D-Val-type dipeptide isostere **11b** as a major product, along with the expected D-Phe-ψ[(*E*)-CH=CMe]-L-Val-type dipeptide isostere **11a** (**11a**:**11b** = 44:56, Table 1, entry 1).[12] A "higher-order" cyanocuprate-BF_3 complex, *i*-Pr_2Cu(CN)-$(MgCl)_2$·BF_3 (which gave only reductive products in the case of alkylation of β-aziridinyl-α,β-unsaturated esters[4d]), also yielded **11b** with higher *Z*-selectivity (**11a**:**11b** = 35:65, entry 2). Several additives (HMPA, TMEDA, 18-crown-6), which were intended to improve *E*-selectivity, further increased *Z*-selectivity (entries 3−5).

Next, we investigated conditions using only Et_2O as solvent. We originally thought this to be unsuitable for the alkylation because of sluggishness.[4,11] Treatment with *i*-PrCu-(CN)MgCl·BF_3 afforded a mixture of S_N2'-alkylated products in low yield (15%), and the substrate **10a** was recovered (77%, entry 6). The more reactive "higher-order" reagent *i*-Pr_2Cu(CN)$(MgCl)_2$·BF_3 in Et_2O gave alkylated products in excellent yield (90%) with concomitant formation of *anti*- and *syn*-S_N2' products[4b] (*anti*-S_N2':*syn*-S_N2' = 74:26), and the *E*-ratio of the isomers was remarkably increased (**11a**:**11b** = 63:37) compared with the reaction in THF (entry 7). In addition, various additives were examined (entries 8−10), including HMPA, which proved to suppress formation of *syn*-S_N2' products, **11c** and **11d**, and apparently improved the overall yield of the D-Phe-ψ[(*E*)-CH=CMe]-L-Val-type dipeptide isostere **11a** (**11a**:**11b** = 72:28, entry 8). In contrast, addition of 18-crown-6 decreased the formation of the *E*-isomer **11a** (entry 10).

To evaluate solvent effects on selectivity, alkylation in mixed solvents of Et_2O and THF was examined (entries 11 and 12). Addition of 4 equiv of THF in Et_2O decreased *E*-selectivity (**11a**:**11b** = 51:49), and a 7:3 mixture of Et_2O and THF yielded a ratio of **11a** and **11b** products similar to that using THF alone (**11a**:**11b** = 37:63). Taken together, cyclic ethers such as THF and 18-crown-6 probably affected the *Z*-selectivity in alkylation for reasons that are unclear.

Alkylation of the *anti*-isomer **10b** with organocyanocuprates was also investigated similarly (Table 2). In THF, both *i*-PrCu(CN)MgCl·BF_3 and *i*-Pr_2Cu(CN)$(MgCl)_2$·BF_3 provided **11c** and **11d** *Z*-selectively (entries 1 and 2). Whereas treatment of **10b** with *i*-PrCu(CN)MgCl·BF_3 in Et_2O resulted in recovered substrate with no conversion to products (entry 3), *i*-Pr_2Cu(CN)$(MgCl)_2$·BF_3 in Et_2O gave a D-Phe-ψ[(*Z*)-CH=CMe]-L-Val-type dipeptide isostere **11d** as a main

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Table 2. Alkylation of *anti*-γ-Mesyloxy-β-methyl-α,β-unsaturated Ester **10b** with Organocyanocuprates

entry	reagent[a,b]	solvent	product ratio[c] **11c**:**11d**:**11a**+**11b**:**12**	yield[d] (%)
1	*e*	THF	27:69: -[g]:4	65
2	*f*	THF	41:54: -[g]:5	87
3	*e*	Et_2O		*h*
4	*f*	Et_2O	7:41:26:26	68

[a] Reactions in entries 1, 3, and 4 were carried out at −78 °C, 0.5 h then 0 °C, 3 h with 4 molar equiv of reagent. [b] Reaction in entry 2 was carried out at −78 °C, 0.5 h with 4 molar equiv of reagent. [c] Product ratios were determined by HPLC and ^{1}H NMR. [d] Combined yield. [e] *i*-PrCu(CN)-MgCl·BF_3. [f] *i*-$Pr_2Cu(CN)(MgCl)_2$·BF_3. [g] Although we cannot conclusively rule out its presence, we failed to isolate the corresponding product. [h] The starting material was recovered.

product with a considerable amount of a D-Phe-ψ[(*Z*)-CH═CMe]-Gly-type dipeptide isostere **12** (entry 4).

The olefinic geometries of **11a**−**d** were established by NOE experiment, and the stereochemistry of **11a**−**d** was determined by circular dichroism in a fashion analogous to the determination of the α-alkyl group configuration in acyclic α-alkyl-β,γ-unsaturated esters.[13] Whereas **11a** and **11d** had negative Cotton effects around 220 nm, **11b** and **11c** exhibited positive Cotton effects as expected. Thus, the alkylated products **11a**−**d** were identified as the (2*R*,3*E*)-, (2*S*,3*Z*)-, (2*S*,3*E*)-, (2*R*,3*Z*)-isomers, respectively. The absolute configuration of **11d** was also confirmed by X-ray analysis.

A plausible reaction mechanism is depicted in Figure 2. The predominant formation of the (2*R*,3*E*)-isomer **11a** and (2*S*,3*Z*)-isomer **11b** from **10a** and of (2*S*,3*E*)-isomer **11c** and (2*R*,3*Z*)-isomer **11d** from **10b** suggested that the products were obtained via *anti*-S_N2' alkylation as in the case of

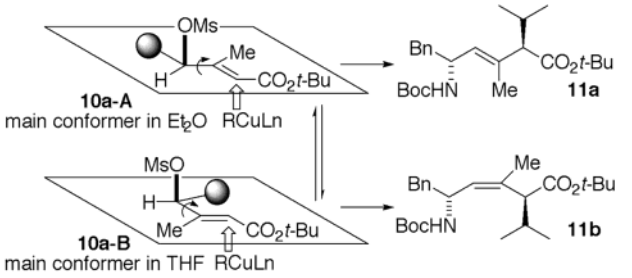

Figure 2. Plausible mechanism for the stereoselective alkylation of *syn*-γ-mesyloxy-β-methyl-α,β-unsaturated ester **10a**.

β-unsubstituted substrates.[4,11] The products **11a** and **11b** are presumably formed via conformer **10a-A** and conformer **10a-B**, respectively. The ratio of products is assumed to be determined by the population of these conformers in the transition state.[14]

In conclusion, we have accomplished the synthesis of ψ[(*E*)-CH═CMe]- and ψ[(*Z*)-CH═CMe]-type dipeptide isosteres via organocopper-mediated alkylation with solvent-dependent geometric selectivity. These isosteres may afford valuable tools for restriction of peptide bonds to *trans*- and *cis*-conformation, respectively. They may be vital for the evaluation of effects of *N*-methylamino acids on conformation of peptides.

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Supporting Information Available: Selected experimental procedures, ^{1}H NMR spectra for all new compounds, CD spectra of **11a**−**d**, and crystal structure of **11d**. This material is available free of charge via the Internet at http://pubs.acs.org.

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