Regio- and stereoselective ring-opening of chiral 1,3-oxazolidin-2-one derivatives by organocopper reagents provides novel access to di-, tri- and tetra-substituted alkene dipeptide isosteres †

Shinya Oishi,[a] Ayumu Niida,[a] Takae Kamano,[a] Yoshihisa Miwa,[a] Tooru Taga,[a] Yoshihiko Odagaki,[b] Nobuyuki Hamanaka,[b] Mikio Yamamoto,[c] Keiichi Ajito,[c] Hirokazu Tamamura,[a] Akira Otaka[a] and Nobutaka Fujii*[a]

[a] *Graduate School of Pharmaceutical Sciences, Kyoto University, Sakyo-ku, Kyoto, 606-8501, Japan*
[b] *Minase Research Institute, Ono Pharmaceutical Co. Ltd., Mishima-gun, Osaka, 618-8585, Japan*
[c] *Pharmaceutical Research Center, Meiji Seika Kaisha, Ltd., Kohoku-ku, Yokohama, 222-0002, Japan*

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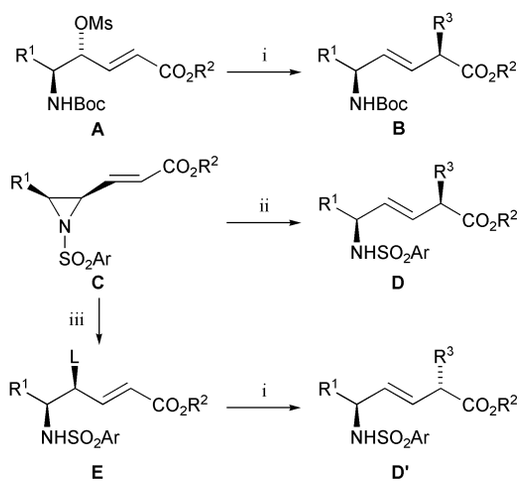
Organocopper-mediated alkylation of β-(*N*-Boc-2-oxo-1,3-oxazolidin-5-yl)-α,β-enoates has been intensively investigated. Alkylation proceeded regio- and stereoselectively by *anti*-S_N2' ring-opening to provide a new route to the synthesis of ψ[(*E*)-CH=CH]-, ψ[(*E*)-CMe=CH]- and ψ[(*E*)-CMe=CMe]- type alkene dipeptide isosteres from chiral amino acid derivatives. These resulting agents are potential mimetics of type II and type II′ β-turn substructure.

Introduction

Determination of bioactive conformations of peptides often allows identification of the spatial requirements involved in pharmacophore activities. This in turn provides valuable information for rational drug design of non-peptidic pharmaceuticals. For restriction of local and/or global conformation of bioactive peptides, a number of peptidomimetics have been developed, to aid in conformational structure–activity relationship studies.[1,2] Mimicry of the peptide backbone by replacement with functional units or addition of secondary-structure-promoting motifs represent effective strategies for conformational restriction of peptides. This can also be achieved through cyclization *via* covalent bond formation between side chains of neighbouring or distant residues. *E*-Alkene dipeptide isosteres (EADIs), based on the concept of ω-angle planarity, have been used as amide bond mimetics which are stable against specific/non-specific degradation and which serve as mechanistic probes lacking amide polarity.[3,4] In particular, (L,D)-type and (D,L)-type EADIs are thought to be potential surrogates of (*i* + 1)–(*i* + 2) dipeptides in type II and type II′ β-turns, respectively. Wipf *et al.* recently reported that, due to rigidity of φ- and ψ-dihedral angles, Xaa[1]-ψ[(*E*)-CMe=CH]-Xaa[2]- and Xaa[1]-ψ[(*Z*)-CCF_3=CH]-Xaa[2] -type EADIs having trisubstituted alkenes are more effective β-turn promoters in the solid state than Xaa[1]-ψ[(*E*)-CH=CH]-Xaa[2]-type EADIs having disubstituted alkenes, which lack heavy atoms corresponding to a carbonyl oxygen.[5] Gardner *et al.* have also shown that peptides containing a tetrasubstituted alkene such as a Gly-ψ[(*E*)-CMe=CMe]-Gly-type EADI, induce β-hairpin formation.[6]

We and others have developed practical methodologies for the stereoselective synthesis of EADIs starting from chiral amino acid derivatives (Scheme 1).[7–12] Herein, key reactions for the construction of side chain functionality at the α-position, utilize organocopper-mediated alkylation of α,β-enoates with a leaving group at the γ-position, to afford *E*-isomers of α-alkylated products regio- and stereoselectively. For example, treatment of γ-mesyloxy-α,β-enoates **A**[7,8] and *N*-activated γ,δ-epimino-α,β-enoates **C**[9,10] with organocopper reagents gives only *anti*-S_N2' products **B** and **D**, respectively. In addition, alkylation of γ-mesyloxy- or γ-chloro-α,β-enoates **E**, which can be obtained by MsOH- or HCl-treatment of *N*-activated γ,δ-epimino-α,β-enoates **C**, can also give *anti*-S_N2' products **D′**, which are diastereomers of **D**.[11] As such, 1,3-chirality transfer by organocopper-mediated alkylation offers an efficient approach for the synthesis of molecules having two remote chiral centres adjacent to an olefin such as Xaa[1]-ψ[(*E*)-CH=CH]-Xaa[2]-type EADIs.[13] We assumed that ψ[(*E*)-CMe=CH]- and ψ[(*E*)-CMe=CMe]-type EADIs could be synthesized



Scheme 1 R^1, R^2, R^3 = alkyl; L = OMs or Cl; Ms = methanesulfonyl. *Reagents*: i, $R^3Cu(CN)MgCl{\cdot}BF_3$; ii, $R^3Cu(CN)MgCl{\cdot}2LiCl$; iii, MsOH or HCl.

† Electronic supplementary information (ESI) available: synthetic procedures and characterization for **4a**,**b**, **5a**,**b**, **7b**, **8a**,**b**, **9a**,**b**, **10b**, **11a**,**b**, **12b**,**c**, **13b**, **14a**,**b**, **15**, **16a**,**b**, **17a**,**b**, **18**, **19b**, **20b**. See http://www.rsc.org/suppdata/p1/b2/b203482d/

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utilizing the same strategy as that used for the synthesis of ψ[(*E*)-CH=CH]-type EADIs. On the other hand, we inferred that γ-methylated γ-mesyloxy-α,β-enoates or γ-methylated γ,δ-epimino-α,β-enoates might not be obtainable through known synthetic schemes owing to difficulties in derivatization of the tertiary hydroxy group. As an example of this, a D-Ala-ψ[(*E*)-CMe=CH]-L-Ala-type EADI was prepared only in low overall yield by Wipf *et al.* from a chiral epoxide, wherein derivatization of the epoxide to a γ-methylated γ,δ-epimino-α,β-enoate was not efficient. Therefore, we sought to develop a new general synthesis of diverse ψ[(*E*)-CMe=CH]- and ψ[(*E*)-CMe=CMe]-type EADIs using organocopper-mediated alkylation of new key intermediates.[14]

Accordingly, 5-vinyl-1,3-oxazolidin-2-ones, having hydroxy groups protected and activated as cyclic carbamates, were subjected to various modifications using organometallic reagents with accompanying ring-opening and decarboxylation.[15–18] We had previously reported that alkylation of 5-vinyl-1,3-oxazolidin-2-ones with various organocopper reagents proceeds regio- and stereoselectively to give vinylglycine derivatives.[15] We further thought to examine the alkylation of β-(*N*-Boc-2-oxo-1,3-oxazolidin-5-yl)-α,β-enoates as an approach to precursors for the synthesis of EADIs. In this article, we report the organocopper-mediated alkylation of β-(*N*-Boc-2-oxo-1,3-oxazolidin-5-yl)-α,β-enoates to afford ψ[(*E*)-CH=CH]-type EADIs having disubstituted alkenes. We further report its application to the synthesis of ψ[(*E*)-CMe=CH]- and ψ[(*E*)-CMe=CMe]-type EADIs having multisubstituted alkenes.

Results and discussion

Synthesis of diastereomerically pure β-(*N*-Boc-2-oxo-1,3-oxazolidin-5-yl)-α,β-enoates

In the synthesis of EADIs based on the *anti*-S_N2' reaction of organocopper reagents, the chirality of the leaving group at the γ-position and the geometry of the olefin are responsible for the chirality of alkyl groups introduced at the product α-position. As such, the efficient synthesis of enantio- and diastereomerically pure substrates is critical. We therefore investigated the preparation of chiral β-(*N*-Boc-2-oxo-1,3-oxazolidin-5-yl)-α,β-enoates, including mono- and dimethylated derivatives. These were selected as chiral key intermediates for the preparation of diverse EADIs from α-amino alcohol or α-amino acid derivatives **1**–**3**[16,19,20] (Scheme 2 and 3). Vinyl and isopropenyl Grignard addition in the presence of anhydrous $CeCl_3$ to a methyl ketone, which was prepared by treatment of Weinreb amide **1** with MeMgCl, preferentially afforded the *syn*-allyl alcohols **4a** and **5a** (**4a** : **4b** = 79 : 21 and **5a** : **5b** = 80 : 20), respectively. Meanwhile, Swern oxidation of allyl alcohols **2** and **3** followed by addition of MeMgCl in the presence of $CeCl_3$ predominantly yielded *anti*-allyl alcohols **4b** and **5b** (**4a** : **4b** = 14 : 86 and **5a** : **5b** = 4 : 96), respectively. The ratio of isomers formed can be explained by chelation control during addition of alkenyl or methyl groups to methyl ketones or enones (Fig. 1). Each isomer of the allyl alcohols **4b** and **5a**,**b**

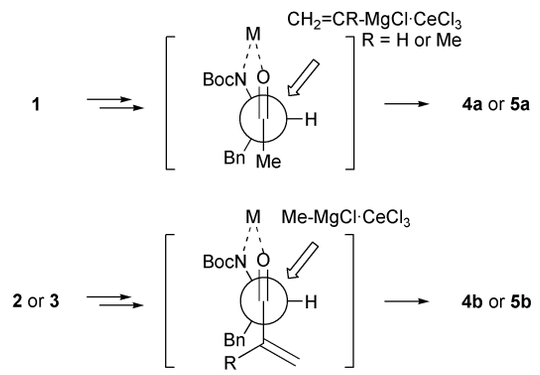
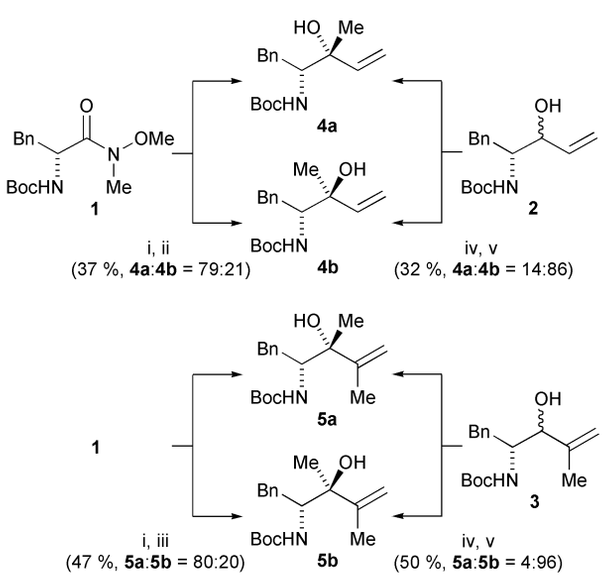


Fig. 1

was obtained as a single diastereomer following purification by flash chromatography and repeated recrystallization. The *syn*-allyl alcohol **4a** containing the minor isomer **4b** was used for next step without further purification.

Sodium hydride-mediated cyclization of allyl alcohols **6a**,**b**,[19] **4a**,**b** and **5a**,**b** followed by *N*-protection with $(Boc)_2O$ efficiently gave the respective 1,3-oxazolidin-2-ones **7a**,**b**, **8a**,**b** and **9a**,**b**. Removal of the minor isomer **8b** from **8a** was carried out at this step by repeated recrystallization. Ozone–dimethyl sulfide treatment of the 5-vinyl derivatives **7a**,**b**, **8a**,**b** followed by modified Horner–Wadsworth–Emmons reaction (HWE reaction)[21] gave α,β-enoates **10a**,**b** and **11a**,**b** *E*-selectively. β-Methylated analogues **12a**,**b** were also obtained *E*-selectively following Wittig reaction with $Ph_3P{=}CHCO_2Bu^t$ in $CHCl_3$ of methyl ketones prepared by ozonolysis and successive reductive treatment of 5-isopropenyl derivatives **9a**,**b**. Peterson olefination of the methyl ketone derived from **9b** gave an unexpected *Z*-isomer of α,β-enoates **12c**, although in low yield.

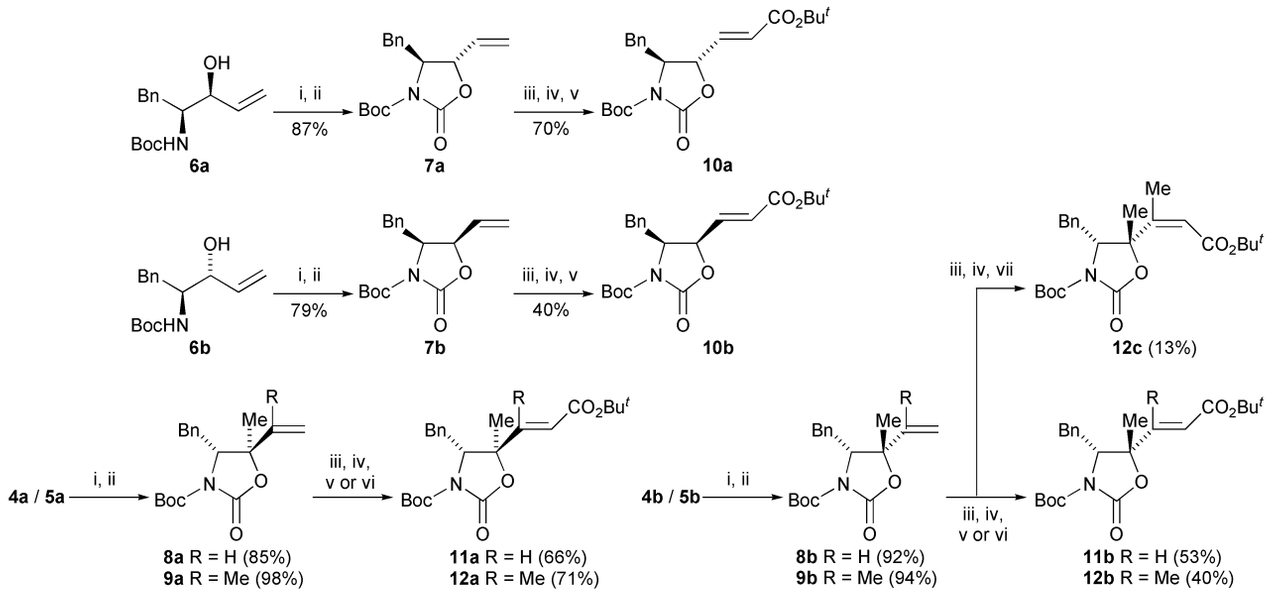
The 2*E*-geometry of **10a**,**b** and **11a**,**b** was established based on the large ^{1}H-coupling constants between the two olefinic protons (15.5–15.6 Hz). The geometry of **12a**,**b** was established by the absence of NOESY cross-peaks between the olefinic proton and the β-methyl protons, while the 2*Z*-geometry of **12c** was established by NOE enhancement (19%) of the olefinic proton resonance upon irradiation of the β-methyl protons. Relative configurations of 1,3-oxazolidin-2-ones **11a**,**b** were established by NOE experiments. No NOE enhancement of the 4-H resonance was observed by irradiation of the 5-methyl protons in the *trans*-isomer **11a**, while an NOE enhancement in the *cis*-isomer **11b** was observed (12%). The *trans*-configuration of **12a** was established by a NOESY cross-peak between the 5-methyl protons and one benzyl proton, while the *cis*-configuration of **12b** was established by cross-peaks between the 4-H proton and the 5-methyl protons.



Scheme 2 *Reagents*: i, MeMgCl, THF; ii, $CH_2{=}CH{-}MgCl$, $CeCl_3$, THF; iii, $CH_2{=}CMe{-}MgBr$, $CeCl_3$, THF; iv, $(COCl)_2$, DMSO, $(Pr^i)_2NEt$, CH_2Cl_2; v, MeMgCl, $CeCl_3$, THF.

Synthesis of ψ[(*E*)-CH=CH]-type EADIs by alkylation with ring-opening of β-(*N*-Boc-2-oxo-1,3-oxazolidin-5-yl)-α,β-enoates using organocopper reagents

For β-(*N*-Boc-2-oxo-1,3-oxazolidin-5-yl)-α,β-enoates, at least four alkylation sites are possible: S_N2-type substitution sites (Fig. 2, sites a and b) and a likely S_N2'-type substitution site



Scheme 3 *Reagents*: i, NaH, THF; ii, $(Boc)_2O$; iii, O_3 gas, EtOAc or CH_2Cl_2; iv, Me_2S; v, $(EtO)_2P(O)CH_2CO_2Bu^t$, LiCl, $(Pr^i)_2NEt$, MeCN; vi, $Ph_3P{=}CHCO_2Bu^t$, $CHCl_3$; vii, $Me_3SiCH_2CO_2Bu^t$, $(Cy)_2NLi$, THF.

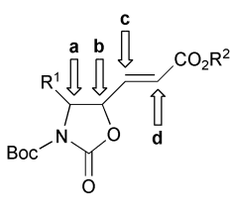
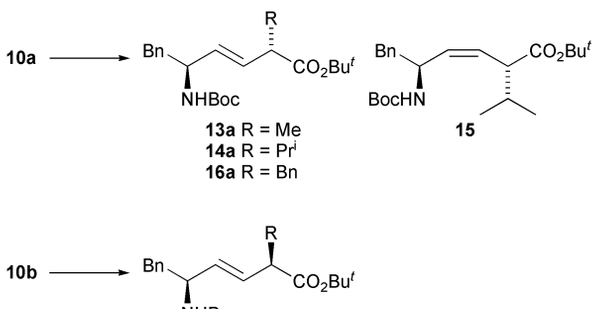


Fig. 2

(site d) with ring-opening, and a 1,4-addition site (site c). Alkylation of α,β-enoates having a leaving group at the γ-position is known to proceed principally *via* an S_N2' mechanism. However, we were afraid that 1,4-adducts might be obtained without ring-opening, due to the poor leaving-group ability of cyclic carbamates. Therefore we next investigated in detail alkylations of β-(*N*-Boc-2-oxo-1,3-oxazolidin-5-yl)-α,β-enoates **10a**,**b** by various organocopper reagents (Scheme 4 and



Scheme 4

Table 1). Here, expected α-alkylations of **10a**,**b** by an *anti*-S_N2' mechanism should give ψ[(*E*)-CH=CH]–type EADIs.

Treatment of *trans*-1,3-oxazolidin-2-one **10a** with either a methyl copper reagent (MeCu·LiI·LiBr) or Gilman-type reagent (Me_2CuLi·LiI·2LiBr) in THF gave a complex mixture of products (Table 1, entries 1 and 2). On the other hand, "lower-order" organocyanocuprate–BF_3 complexes prepared from methyl Grignard reagents [MeCu(CN)MgCl·BF_3·2LiCl] in THF at −78 °C for 30 min gave an α-alkylated product, L-Phe-ψ[(*E*)-CH=CH]-D-Ala **13a**, regio- and stereoselectively (entry 3). Other organocyanocuprate–BF_3 complexes [RCu(CN)MgCl·BF_3·2LiCl (R = Pr^i and Bn)] also provided the respective α-alkylated products, L-Phe-ψ[(*E*)-CH=CH]-D-Xaa **14a** and **16a** (Xaa = Val and Phe, respectively), in excellent yields (entries 4 and 6). Interestingly, unforeseen formation of the *Z*-isomer of the *anti*-S_N2' product, L-Phe-ψ[(*Z*)-CH=CH]-L-Val **15**, was observed only in the reaction of **10a** with $Pr^iCu(CN)MgCl·BF_3$·2LiCl (entry 4), although the reason for this is unclear.[22] An α-alkylated product **14a** and *Z*-isomer **15** were also afforded in moderate yields using a "higher-order" organocyanocuprate–BF_3 complex [$Pr^i_2Cu(CN)(MgCl)_2·BF_3$·2LiCl, entry 5). This is an inappropriate reagent for alkylation of *N*-activated β-aziridinyl-α,β-enoates, owing to the formation of unwanted reductive products.[9] Alkylation of *cis*-1,3-oxazolidin-2-one **10b** with the "lower-order" methyl cyanocuprate–BF_3 complex [MeCu(CN)Li·BF_3·LiBr] derived from methyllithium in THF–Et_2O, resulted in the production of small amounts of α-alkylated product **13b** with recovery of starting material **10b** (entry 7), whereas use of a "higher-order" complex [$Me_2Cu(CN)Li_2·BF_3$·2LiBr] gave a number of uncharacterized products (entry 8). In contrast, alkylation of **10b** proceeded favourably using organocyanocuprate–BF_3 complexes [RCu(CN)MgCl·BF_3·2LiCl, R = Me, Pr^i and Bn] derived from Grignard reagents, to afford L-Phe-ψ[(*E*)-CH=CH]-L-Xaa **13b**, **14b** and **16b** (Xaa = Ala, Val and Phe), respectively, in excellent yields (entries 9–11). This was similar to reactions of the *trans*-isomer **10a**. In contrast to the *trans*-isomer **10a** (entry 4), reaction of *cis*-1,3-oxazolidin-2-one **10b** with $Pr^iCu(CN)MgCl·BF_3$·2LiCl gave exclusively the *E*-isomer of the α-alkylated product **14b** without production of the *Z*-isomer (entry 10).

The regiochemistry of the resulting EADIs, **13a**,**b**, **14a**,**b** and **16a**,**b** was readily assigned by ^1H–^1H COSY spectra, large coupling constants between the olefinic protons (15.4–15.7 Hz) and/or comparison with the ^1H NMR spectrum of an authentic sample.[8] The stereochemical assignments of the α-alkyl groups in **13a**,**b**, **14a**,**b** and **16a**,**b** could be deduced from well-established organocopper-mediated *anti*-S_N2' alkylations. Additionally, the ^1H NMR spectrum of **14a** was in good accordance with that of the enantiomer[8] derived from another precursor. Based both on a 220 nm negative Cotton effect in its CD spectrum[23] and on regiochemical assignment by ^1H NMR spectroscopy, the α-adduct **15** was proved to be the *Z*-isomer of an *anti*-S_N2' product, L-Phe-ψ[(*Z*)-CH=CH]-L-Val-type isostere. As such, except for the formation of a *Z*-isomer **15** from **10a**, each reaction using organocopper reagents derived from Grignard reagents yielded the respective single diastereomers

Table 1 Alkylation of β-(*N*-Boc-2-oxo-1,3-oxazolidin-5-yl)-α,β-enoates **10a** and **10b** by organocopper reagents

Entry	Substrate	Reagent (4 eqiuv.)	Solvent	Conditions	Products (Yield %)
1	**10a**	MeCu·LiI·LiBr	THF–Et_2O (10 : 1)	−78 °C, 30 min, then 0 °C, 1 h	—[a]
2	**10a**	Me_2CuLi·LiI·2LiBr	THF–Et_2O (5 : 1)	−78 °C, 1 h	—[a]
3	**10a**	MeCu(CN)MgCl·BF_3·2LiCl	THF	−78 °C, 30 min	**13a** (77)
4	**10a**	$Pr^iCu(CN)MgCl·BF_3·2LiCl$	THF	−78°C, 30 min	**14a** (85) + **15** (14)[b]
5	**10a**	$Pr^i_2Cu(CN)(MgCl)_2·BF_3·2LiCl$	THF	−78 °C, 30 min	**14a** (50) + **15** (27)[b]
6	**10a**	BnCu(CN)MgCl·BF_3·2LiCl	THF	−78 °C, 30 min	**16a** (99)
7	**10b**	MeCu(CN)Li·BF_3·LiBr	THF–Et_2O (10 : 1)	−78 °C, 30 min, then 0 °C, 3 h	**13b** (24)[c]
8	**10b**	$Me_2Cu(CN)Li_2·BF_3$·2LiBr	THF–Et_2O (5 : 1)	−78 °C, 30 min	—[a]
9	**10b**	MeCu(CN)MgCl·BF_3·2LiCl	THF	−78 °C, 30 min	**13b** (90)
10	**10b**	$Pr^iCu(CN)MgCl·BF_3·2LiCl$	THF	−78 °C, 30 min	**14b** (96)
11	**10b**	BnCu(CN)MgCl·BF_3·2LiCl	THF	−78 °C, 30 min	**16b** (99)

[a] α-Alkylated products were not isolated. [b] The product ratios were determined by reverse phase HPLC. [c] The starting material was recovered (58%).

Table 2 Alkylation of mono- and dimethylated β-(*N*-Boc-2-oxo-1,3-oxazolidin-5-yl)-α,β-enoates **11a**,**b** and **12a**,**b** by organocopper reagents

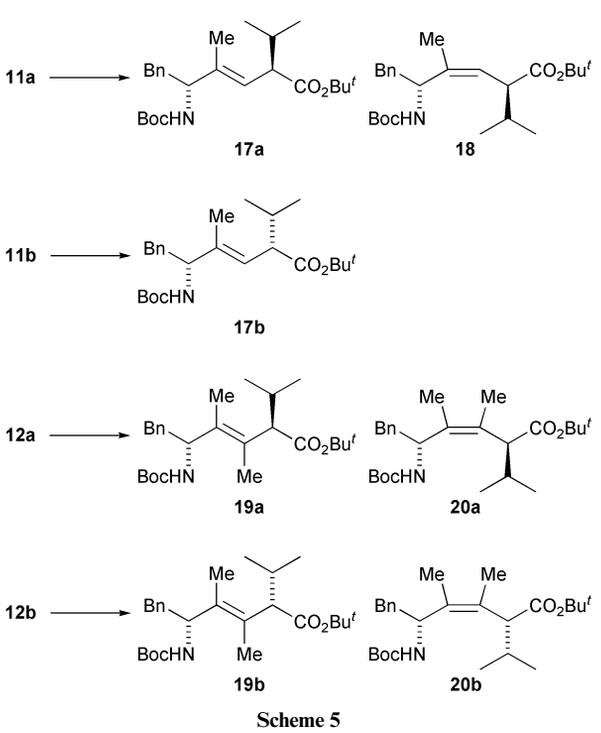
Entry	Substrate	Reagent	Conditions	Products (Yield %)
1	**11a**	$Pr^iCu(CN)MgCl·BF_3$ (4.2 equiv.)	−78 °C, 30 min	**17a** (70) + **18** (22)[a]
2	**11a**	$Pr^i_2Cu(CN)(MgCl)_2·BF_3$ (4.2 equiv.)	−78 °C, 30 min	**17a** (38) + **18** (26)[a]
3	**11a**	$Pr^iCu(CN)MgCl·BF_3·2LiCl$ (4.2 equiv.)	−78 °C, 30 min	**17a** (68) + **18** (31)[a]
4	**11a**	$Pr^i_2Cu(CN)(MgCl)_2·BF_3·2LiCl$ (4.2 equiv.)	−78 °C, 30 min	**17a** (58) + **18** (27)[a]
5	**11b**	$Pr^iCu(CN)MgCl·BF_3·2LiCl$ (4 equiv.)	−78 °C, 30 min	**17b** (95)
6	**11b**	$Pr^i_2Cu(CN)(MgCl)_2·BF_3·2LiCl$ (4 equiv.)	−78 °C, 30 min	**17b** (95)
7	**12a**	$Pr^iCu(CN)MgCl·BF_3·2LiCl$ (4 equiv.)	−78 °C, 30 min, then 0 °C, 3 h	—[b]
8	**12a**	$Pr^i_2Cu(CN)(MgCl)_2·BF_3·2LiCl$ (4 equiv.)	−78 °C, 30 min, then 0 °C, 3 h	**19a** (75) + **20a** (20)[a]
9	**12b**	$Pr^iCu(CN)MgCl·BF_3·2LiCl$ (4 equiv.)	−78 °C, 30 min, then 0 °C, 3 h	—[b]
10	**12b**	$Pr^i_2Cu(CN)(MgCl)_2·BF_3·2LiCl$ (4 equiv.)	−78 °C, 30 min, then 0 °C, 3 h	**19b** (37) + **20b** (11)[a]
11	**12b**	$Pr^i_2Cu(CN)(MgCl)_2·BF_3·2LiCl$ (6 equiv.)	−78 °C, 30 min, then 0 °C, 3 h	**19b** (55) + **20b** (19)[a]
12	**12b**	$Pr^i_3Cu(CN)(MgCl)_3·BF_3·2LiCl$ (4 equiv.)	−78 °C, 30 min, then 0 °C, 3 h	**19b** (52) + **20b** (25)[a]

[a] The product ratios were determined by reverse phase HPLC. [b] The starting material was recovered.

regio- and stereoselectively out of four possible α-alkylated products.

Synthesis of ψ[(*E*)-CMe=CH]- and ψ[(*E*)-CMe=CMe]-type alkene dipeptide isosteres *via* organocopper-mediated alkylation

To extend the application of regio- and stereoselective alkylation of β-(*N*-Boc-2-oxo-1,3-oxazolidin-5-yl)-α,β-enoates by organocopper reagents, we sought to synthesize ψ[(*E*)-CMe=CH]- and ψ[(*E*)-CMe=CMe]-type EADIs having multisubstituted alkenes (Scheme 5 and Table 2). As a model system, syntheses of D-Phe-ψ[(*E*)-CMe=CH]-L-Val-, D-Phe-ψ[(*E*)-CMe=CMe]-L-Val-type EADIs and their diastereomers were attempted. Such structures represent a potential (*i* + 1)–(*i* + 2) scaffold of type II′ β-turn found in the cyclic RGD peptide, *cyclo*(-Arg-Gly-Asp-D-Phe-Val-).[24] As employed for the synthesis of ψ[(*E*)-CH=CH]-type EADIs from 1,3-oxazolidin-2-ones **10a**,**b**, isopropylcyanocuprate–BF_3 complexes were prepared from Pr^iMgCl and used for alkylations.



Scheme 5

Similarly to the reaction of *trans*-1,3-oxazolidin-2-one **10a**, treatment of monomethylated (γ-methylated) *trans*-1,3-oxazolidin-2-one **11a** with $Pr^iCu(CN)MgCl·BF_3$ in THF at −78 °C for 30 min afforded α-alkylated products as both the *E*-isomer, D-Phe-ψ[(*E*)-CMe=CH]-L-Val **17a**, and the *Z*-isomer, D-Phe-ψ[(*Z*)-CMe=CH]-D-Val **18** (**17a** : **18** = 76 : 24, Table 2, entry 1). Additionally, reaction of **11a** with $Pr^i_2Cu(CN)(MgCl)_2·BF_3$ also gave α-alkylated products **17a** and **18** in low selectivity (entry 2). The use of LiCl-containing complexes such as $Pr^iCu(CN)MgCl·BF_3·2LiCl$ and $Pr^i_2Cu(CN)(MgCl)_2·BF_3·2LiCl$ in the reaction of **11a** somewhat improved the combined yield of α-alkylated products (entries 3 and 4).[25] From the *cis*-isomer **11b**, only the *E*-isomer of the α-alkylated product, D-Phe-ψ[(*E*)-CMe=CH]-D-Val **17b**, was obtained in excellent yields both by treatment with $Pr^iCu(CN)MgCl·BF_3·2LiCl$ and with $Pr^i_2Cu(CN)(MgCl)_2·BF_3·2LiCl$ in THF at −78 °C for 30 min (entries 5 and 6).

In contrast, dimethylated (β,γ-dimethylated) 1,3-oxazolidin-2-ones **12a**,**b** displayed different reactivity to organocopper reagents than those of the non-methylated **10a**,**b** and monomethylated ones **11a**,**b**. For both isomers of 1,3-oxazolidin-2-ones **12a**,**b**, no reaction was observed with the "lower-order" cyanocuprate–BF_3 complex [$Pr^iCu(CN)MgCl·BF_3·2LiCl$], rather, starting materials were recovered (entries 7 and 9). This was probably due to the low reactivity of the reagent. Alternatively, alkylation of *trans*-1,3-oxazolidin-2-one **12a** with the "higher-order" cyanocuprate–BF_3 complex [$Pr^i_2Cu(CN)(MgCl)_2·BF_3·2LiCl$] at −78 °C for 30 min then at 0 °C for 3 h, afforded two isomeric α-alkylated products, D-Phe-ψ[(*E*)-

CMe=CMe]-L-Val **19a** and D-Phe-ψ[(*Z*)-CMe=CMe]-D-Val **20a**. The selectivity of this reaction was similar to that in reactions of *trans*-1,3-oxazolidin-2-ones **10a** and **11a** (**19a** : **20a** = 79 : 21, entry 8). On the other hand, treatment of the *cis*-isomer **12b** with four equivalents of $Pr^i_2Cu(CN)(MgCl)_2\cdot BF_3\cdot 2LiCl$ gave both the expected *E*-isomer, D-Phe-ψ[(*E*)-CMe=CMe]-D-Val **19b**, as well as the *Z*-isomer, D-Phe-ψ[(*Z*)-CMe=CMe]-L-Val **20b**, in low yield (**19b** : **20b** = 76 : 24). Substrate **12b** was recovered in 13% yield (entry 10). Using six equivalents of the same reagent or four equivalents of $Pr^i_3Cu(CN)(MgCl)_3\cdot BF_3\cdot 2LiCl$ improved the combined yields of the reaction to 74 or 77%, respectively, although trace amounts of reactant **12b** still remained (entries 11 and 12).

Regiochemical assignments of EADIs **17a**,**b**, **18**, **19a**,**b** and **20a**,**b** were accurately established by ^1H NMR (^1H–^1H COSY, NOE experiments and NOESY). For example, an NOE enhancement of the olefinic proton signal upon irradiation of the 5-H resonance in the 3*E*-isomer **17a** (7%) as well as by irradiation of the 4-methyl proton signal in the 3*Z*-isomer **18** (15%) were observed. The presence of a cross-peak between the olefinic proton and the 5-H proton and the absence of a cross-peak between the olefinic proton and the 4-methyl protons in the NOESY spectrum of **17b**, suggested 3*E*-geometry. The lack of NOE enhancement of the 5-H proton signal of **19b** following irradiation of the 2-H proton signal, along with an NOE enhancement of the same signal of **20b** (14%), suggested that **19b** and **20b** had 3*E*- and 3*Z*-geometries, respectively. The stereochemistry of the α-alkyl groups of **17a**,**b**, **18**, **19a**,**b** and **20a**,**b** was established by the CD spectra.[23] EADIs **17a**, **19a** and **20b**, which showed negative Cotton effects, were regarded as 2*R*-isomers, while **17b**, **18**, **19b** and **20a**, which showed positive Cotton effects around 220 nm, were regarded as 2*S*-isomers. Crystal structures of **18**,‡ **19a**‡ and **19b** also supported these assignments. Based on the above, it was concluded that all α-alkylated products **17a**,**b**, **18**, **19a**,**b** and **20a**,**b** were obtained by organocopper-mediated *anti*-S_N2'-type alkylation.

A feasible mechanism for organocopper-mediated alkylation of β-(*N*-Boc-2-oxo-1,3-oxazolidin-5-yl)-α,β-enoates was inferred based on the precedence of γ-mesyloxy-α,β-enoates[7] or *N*-activated γ,δ-epimino-α,β-enoates[9] as shown in Fig. 3. Assuming direct alkylation by the organocopper reagents, examination of two possible conformers during the reaction facilitates interpretation of the diastereoselective formation of *E*- and *Z*-isomers. For example, alkylation of conformers **10a**,**b-A**, **11a**,**b-A** and **12a**,**b-A** can yield only *E*-isomers **13a**,**b**, **14a**,**b**, **16a**,**b**, **17a**,**b** and **19a**,**b**, while conformers **10a**,**b-B**, **11a**,**b-B** and **12a**,**b-B** would yield only *Z*-isomers such as **15**, **18** and **20a**,**b**. It might be supposed that the product ratios of *E*- and *Z*-isomers depend on the proportions of these two conformers, the stability of which is based on the *cis*/*trans*-configuration of the 1,3-oxazolidin-2-ones and the presence of methyl groups.[26] In addition, the unlikely formation of reactive conformers **12b-A** and **12b-B** of dimethylated *cis*-1,3-oxazolidin-2-one **12b** due to 1,3-allylic strain, may cause low reactivity to organocopper reagents. This could result in the production of *Z*-isomer **20b**, which does not occur with the non- and monomethylated substrates **10b** and **11b**. On the other hand, the formation of copper-π-allyl complexes as reactive intermediates such as **21a**–**d** cannot be ruled out. In such a mechanism, two complexes **21a** and **21b**, which can afford *E*- and *Z*-isomers of α-alkylated products, respectively, would be required to form from *trans*-1,3-oxazolidin-2-ones **10**–**12a** in a ratio dependent on their stability. Similarly, two complexes **21c** and **21d** should be formed from *cis*-1,3-oxazolidin-2-ones **10**–**12b**. In fact, in the alkylation of the non-methylated *trans*-1,3-oxazolidin-2-one **10a**, formation of the *Z*-isomer **15** of the α-alkylated product

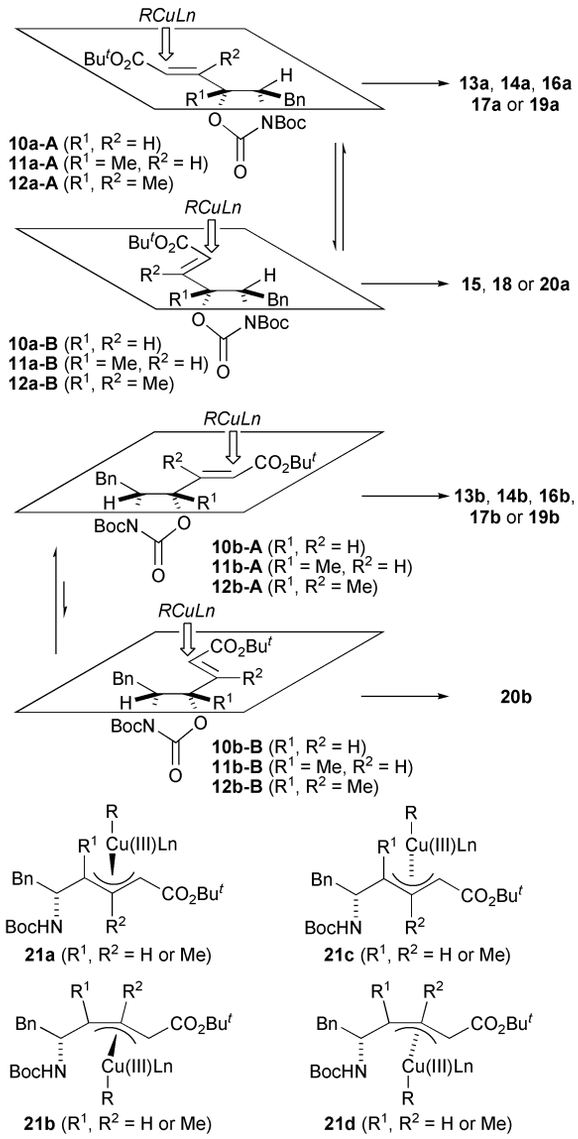


Fig. 3 Feasible reaction mechanism in the alkylation of β-(*N*-Boc-2-oxo-1,3-oxazolidin-5-yl)-α,β-enoates. R^1, R^2 = H or Me.[27]

was observed only by treatment with $Pr^iCu(CN)MgCl\cdot BF_3\cdot 2LiCl$ (but not the methyl and benzyl counterparts). Bulky alkyl groups such as an isopropyl group, may lead to favourable formation of other copper-π-allyl complexes such as **21b**, which can provide the *Z*-isomer **15**. In both mechanisms, organocopper-mediated alkylation of 1,3-oxazolidin-2-ones **10a**,**b**, **11a**,**b** and **12a**,**b** can afford only *anti*-S_N2'-type products.

In conclusion, we have found that alkylation of β-(*N*-Boc-2-oxo-1,3-oxazolidin-5-yl)-α,β-enoates with organocyanocuprates derived from Grignard reagents proceeds with ring-opening and decarboxylation to afford α-alkylated products in a regio- and stereoselective fashion. The stereochemistry at the α-positions of the α-alkylated products depends on the chirality of the 5-position of the 1,3-oxazolidin-2-one derivatives. The reactions proceed with complete *anti*-S_N2'-type chirality transfer regardless of *E*/*Z*-products. Finally, we have achieved the first synthesis of ψ[(*E*)-CMe=CH]- and ψ[(*E*)-CMe=CMe]-type alkene dipeptide isosteres starting from chiral amino acid derivatives by application of organocopper-mediated alkylation. To summarize, the reaction of 1,3-oxazolidin-2-one derivatives with organocopper reagents yields (L,D)-/(D,L)-type *E*- and (L,L)-/(D,D)-type *Z*-alkene isosteres from *trans*-starting material, while *cis*-isomers yield (L,L)-/(D,D)-type *E*- and (L,D)-/(D,L)-type *Z*-alkene isosteres.

‡ The crystal structures of **18** and **19a** were presented in the preliminary communication.[14]

Experimental

General

^{1}H NMR spectra were recorded using a JEOL EX-270, a Bruker AC 300 or a Bruker AM 600 spectrometer at 270, 300 or 600 MHz. Chemical shifts are reported in parts per million downfield from internal tetramethylsilane and coupling constants (J) are given in Hz. Nominal (LRMS) and exact mass (HRMS) spectra were recorded on a JEOL JMS-01SG-2 or JMS-HX/HX 110A mass spectrometer. Optical rotations were measured for samples in $CHCl_3$ with a Horiba high-sensitivity polarimeter SEPA-200 (Kyoto, Japan). CD spectra were recorded on a JASCO J-720 spectropolarimeter. The X-ray analysis was carried out on a Rigaku AFC5R-RU200 four-circle diffractometer. Melting points were measured on a hot stage melting point apparatus and are uncorrected. For flash chromatography, Silica Gel 60 H (silica gel for thin-layer chromatography, Merck) and Wakogel C-200 (silica gel for column chromatography) were employed. For HPLC separations, a Cosmosil 5C18-ARII analytical (4.6 × 250 mm) column was employed, and eluting products were detected by UV at 220 nm. A solvent system consisting of 0.1% TFA aqueous solution (v/v) and 0.1% TFA in MeCN (v/v) was used for HPLC elution.

(4*S*,5*S*)-4-Benzyl-*N*-(*tert*-butoxycarbonyl)-5-ethenyl-1,3-oxazolidin-2-one 7a

To a stirred suspension of NaH (1.58 g, 66.0 mmol) in dry THF (40 cm^3) was added dropwise a solution of the known allyl alcohol **6a**[19] (4.58 g, 16.5 mmol) in dry THF (60 cm^3) at 0 °C under argon, and the mixture was heated under reflux for 15 min. $(Boc)_2O$ (7.20 g, 33.0 mmol) was added to the mixture at 0 °C, and the mixture was stirred for 1.5 h with warming to room temperature. The mixture was poured into a saturated NH_4Cl solution at 0 °C, and the whole was extracted with EtOAc. The extract was washed successively with water, saturated $NaHCO_3$ and brine, and dried over $MgSO_4$. Concentration under reduced pressure followed by flash chromatography over silica gel with *n*-hexane–EtOAc (4 : 1) gave the title compound **7a** (4.36 g, 14.3 mmol, 87%) as colourless crystals, mp 89–91 °C [from *n*-hexane–Et_2O (3 : 1)] (Found: C, 67.39; H, 6.96; N, 4.50. $C_{17}H_{21}NO_4$ requires C, 67.31; H, 6.98; N, 4.62%); $[\alpha]_D^{21}$ −33.8 (*c* 0.708 in $CHCl_3$); δ_H (300 MHz; $CDCl_3$) 1.58 (9 H, s, CMe_3), 2.84 (1 H, dd, *J* 13.4 and 9.6, C*H*H), 3.34 (1 H, dd, *J* 13.4 and 3.6, CH*H*), 4.17 (1 H, dt, *J* 9.6 and 3.1, NCH), 4.62 (1 H, m, OCH), 5.10–5.21 (2 H, m, CH_2=), 5.62 (1 H, ddd, *J* 17.2, 10.4 and 5.6, CH=), 7.15–7.38 (5 H, m, Ph).

tert-Butyl (2*E*)-3-[(4*S*,5*S*)-4-benzyl-*N*-(*tert*-butoxycarbonyl)-2-oxo-1,3-oxazolidin-5-yl]prop-2-enoate 10a

Ozone gas was bubbled through a stirred solution of the 1,3-oxazolidin-2-one **7a** (4.26 g, 14.0 mmol) in EtOAc (150 cm^3) at −78 °C until a blue colour persisted. Me_2S (20.6 cm^3, 280 mmol) was added to the solution at −78 °C. After being stirred for 30 min at 0 °C, the mixture was dried over $MgSO_4$, and concentrated under reduced pressure to give the crude aldehyde, which was used for the next reaction without further purification. To a stirred suspension of LiCl (1.48 g, 35.1 mmol) in MeCN (50 cm^3) was added *tert*-butyl diethyl phosphonoacetate (8.34 cm^3, 35.1 mmol) and $(Pr^i)_2NEt$ (6.11 cm^3, 35.1 mmol) at 0 °C under argon. After 1 h, the above aldehyde in MeCN (35 cm^3) was added to the mixture at 0 °C, and the stirring was continued for 2 h. The mixture was concentrated under reduced pressure and extracted with EtOAc. The extract was washed successively with saturated citric acid, brine, 5% $NaHCO_3$ and brine, and dried over $MgSO_4$. Concentration under reduced pressure followed by flash chromatography over silica gel with *n*-hexane–EtOAc (6 : 1) gave the title compound **10a** (3.98 g, 9.86 mmol, 70%) as colourless crystals, mp 157–159 °C [from *n*-hexane–Et_2O (3 : 1)] (Found: C, 65.44; H, 7.21; N, 3.34. $C_{22}H_{29}NO_6$ requires C, 65.49; H, 7.24; N, 3.47%); $[\alpha]_D^{20}$ −74.7 (*c* 0.976 in $CHCl_3$); δ_H (300 MHz; $CDCl_3$) 1.44 (9 H, s, CMe_3), 1.59 (9 H, s, CMe_3), 2.82 (1 H, dd, *J* 13.4 and 9.8, C*H*H), 3.37 (1 H, dd, *J* 13.4 and 3.6, CH*H*), 4.22 (1 H, ddd, *J* 9.8, 3.5 and 2.9, NCH), 4.74 (1 H, ddd, *J* 4.5, 2.8 and 1.7, OCH), 5.86 (1 H, dd, *J* 15.6 and 1.7, CH=), 6.42 (1 H, dd, *J* 15.6 and 4.5, CH=), 7.15–7.40 (5 H, m, Ph).

tert-Butyl (2*E*)-3-[(4*R*,5*R*)-4-benzyl-*N*-(*tert*-butoxycarbonyl)-5-methyl-2-oxo-1,3-oxazolidin-5-yl]but-2-enoate 12a

By use of a procedure similar to that described for the successive treatment of the 1,3-oxazolidin-2-one **7a** with ozone gas and Me_2S, the 1,3-oxazolidin-2-one **9a** (3.33 g, 10.0 mmol) was converted into the corresponding ketone. To a solution of the above ketone in $CHCl_3$ (20 cm^3) was added Ph_3P=$CHCO_2Bu^t$ (11.3 g, 30.1 mmol), and the mixture was gently refluxed for 24 h. Concentration under reduced pressure followed by flash chromatography over silica gel with *n*-hexane–EtOAc (6 : 1) gave the title compound **12a** (3.08 g, 7.13 mmol, 71%) as colourless crystals, mp 158–159 °C [from *n*-hexane–Et_2O (3 : 1)]; (Found: C, 66.82; H, 7.71; N, 3.24. $C_{24}H_{33}NO_6$ requires C, 66.80; H, 7.71; N, 3.25%); $[\alpha]_D^{24}$ +78.3 (*c* 1.06 in $CHCl_3$); δ_H (300 MHz; $CDCl_3$) 1.40 (3 H, s, CMe), 1.45 (9 H, s, CMe_3), 1.47 (9 H, s, CMe_3), 1.90 (3 H, d, *J* 1.2, CMe), 2.98 (1 H, dd, *J* 14.3 and 9.1, C*H*H), 3.18 (1 H, dd, *J* 14.3 and 4.5, CH*H*), 4.48 (1 H, dd, *J* 9.1 and 4.5, CH), 5.95 (1 H, m, CH=), 7.23–7.38 (5 H, m, Ph).

General procedure for the synthesis of ψ[(*E*)-CH=CH]- and ψ[(*E*)-CMe=CH]-type alkene dipeptide isosteres *via* "lower-order" cyanocuprate-mediated alkylation: synthesis of *tert*-butyl (2*S*,5*S*,3*E*)-5-(*tert*-butoxycarbonylamino)-2-methyl-6-phenylhex-3-enoate (Boc-L-Phe-ψ[(*E*)-CH=CH]-D-Ala-OBu^t) 13a

To a stirred suspension of CuCN (44.4 mg, 0.496 mmol) and LiCl (42.0 mg, 0.992 mmol) in dry THF (1.5 cm^3) was added MeMgCl in dry THF (2.92 mol dm^{-3}, 0.169 cm^3, 0.496 mmol) under argon at −78 °C, and the mixture was stirred for 10 min at 0 °C. BF_3·Et_2O (0.0628 cm^3, 0.496 mmol) was added to the above mixture at −78 °C, and the mixture was stirred for 5 min. To the solution of organocopper reagent was added dropwise a solution of the ester **10a** (50.0 mg, 0.124 mmol) in dry THF (1.8 cm^3) at −78 °C. After being stirred for 30 min, the reaction mixture was quenched with a 1 : 1 saturated NH_4Cl-28% NH_4OH solution (2 cm^3). The mixture was extracted with Et_2O, and then the extract was washed with water, and dried over $MgSO_4$. Concentration under reduced pressure followed by flash chromatography over silica gel with *n*-hexane–EtOAc (15 : 1) yielded the title compound **13a** (36.1 mg, 0.0961 mmol, 77%) as colourless crystals, mp 64–66 °C [from *n*-hexane–Et_2O (10 : 1)]; (Found: C, 70.63; H, 8.83; N, 3.66. $C_{22}H_{33}NO_4$ requires C, 70.37; H, 8.86; N, 3.73%); $[\alpha]_D^{25}$ +19.2 (*c* 0.987 in $CHCl_3$); δ_H (600 MHz; $CDCl_3$) 1.14 (3 H, d, *J* 6.9, CMe), 1.40 (9 H, s, CMe_3), 1.41 (9 H, s, CMe_3), 2.79 (1 H, dd, *J* 13.3 and 6.9, C*H*H), 2.82–2.88 (1 H, m, CH*H*), 2.97 (1 H, dd, *J* 14.2 and 7.1, 2-H), 4.38 (1 H, m, 5-H), 4.45 (1 H, m, NH), 5.47 (1 H, dd, *J* 15.5 and 5.5, CH=), 5.57 (1 H, dd, *J* 15.5 and 7.5, CH=), 7.13–7.30 (5 H, m, Ph).

General procedure for the synthesis of ψ[(*E*)-CMe=CMe]-type alkene dipeptide isosteres *via* "higher-order" cyanocuprate-mediated alkylation: *tert*-butyl (2*R*,5*R*,3*E*)-5-(*tert*-butoxycarbonylamino)-2-isopropyl-3,4-dimethyl-6-phenylhex-3-enoate (Boc-D-Phe-ψ[(*E*)-CMe=CMe]-L-Val-OBu^t) 19a and *tert*-butyl (2*S*,5*R*,3*Z*)-5-(*tert*-butoxycarbonylamino)-2-isopropyl-3,4-dimethyl-6-phenylhex-3-enoate (Boc-D-Phe-ψ[(*Z*)-CMe=CMe]-D-Val-OBu^t) 20a

To a stirred solution of LiCl (32.2 mg, 0.760 mmol) and CuCN (34.0 mg, 0.380 mmol) in dry THF (1.5 cm^3) was added drop-

wise Pr^iMgCl (1.50 mol dm^{-3}, 0.506 cm^3, 0.760 mmol) in dry THF at −78 °C under argon, and the mixture was stirred for 10 min at 0 °C. $BF_3{\cdot}Et_2O$ (0.0481 cm^3, 0.380 mmol) was added to the mixture at −78 °C. After 5 min, to the above reagent was added dropwise a solution of the ester **12a** (41.0 mg, 0.0950 mmol) in dry THF (1.5 cm^3) at −78 °C, and stirring was continued for 30 min at −78 °C. The reaction was quenched with saturated NH_4Cl-28% NH_4OH (1 : 1, 2 cm^3), and the whole was extracted with Et_2O. The extract was washed with water, and dried over $MgSO_4$. Concentration under reduced pressure followed by flash chromatography over silica gel with *n*-hexane–EtOAc (25 : 1) gave the title compound **20a** (8.1 mg, 0.0187 mmol, 20%) and **19a** (30.8 mg, 0.0713 mmol, 75%), in order of elution.

Compound 19a. colourless crystals, mp 128–130 °C (from *n*-hexane); (Found: C, 72.40; H, 9.85; N, 3.26. $C_{26}H_{41}NO_4$ requires C, 72.35; H, 9.57; N, 3.25%); $\Delta\varepsilon$ = −36.54 (229 nm, isooctane); $[\alpha]_D^{26}$ −176.3 (*c* 0.726 in $CHCl_3$); δ_H (300 MHz; $CDCl_3$) 0.32 (3 H, d, *J* 6.2, CMe), 0.87 (3 H, d, *J* 6.3, CMe), 1.38 (9 H, s, CMe_3), 1.39 (9 H, s, CMe_3), 1.55 (3 H, s, CMe), 1.68 (3 H, m, CMe), 1.93 (1 H, m, CH), 2.66 (1 H, dd, *J* 13.3 and 8.8, C*H*H), 2.86–2.97 (2 H, m, CH*H* and 2-H), 4.70 (1 H, m, NH), 4.89 (1 H, m, 5-H), 7.12–7.28 (5 H, m, Ph).

Compound 20a. colourless crystals, mp 59–61 °C (from *n*-hexane); (Found: C, 72.25; H, 9.56; N, 3.12. $C_{26}H_{41}NO_4$ requires C, 72.35; H, 9.57; N, 3.25%); $\Delta\varepsilon$ = +32.47 (228 nm, isooctane); $[\alpha]_D^{26}$ +182.9 (*c* 1.72 in $CHCl_3$); δ_H (300 MHz; $CDCl_3$) 0.31 (3 H, d, *J* 6.1, CMe), 0.85 (3 H, d, *J* 6.3, CMe), 1.38 (9 H, s, CMe_3), 1.39 (9 H, s, CMe_3), 1.59 (3 H, d, *J* 0.9, CMe), 1.66 (3 H, d, *J* 0.9, CMe), 2.03 (1 H, m, CH), 2.78 (1 H, dd, *J* 13.3 and 7.4, C*H*H), 2.95–3.05 (2 H, m, CH*H* and 2-H), 4.53 (1 H, m, NH), 4.92 (1 H, m, 5-H), 7.12–7.28 (5 H, m, Ph).

Crystal structure determination of *tert*-Butyl (2*S*,5*R*,3*E*)-5-(*tert*-butoxycarbonylamino)-2-isopropyl-3,4-dimethyl-6-phenyl-hex-3-enoate (Boc-D-Phe-ψ[(*E*)-CMe=CMe]-D-Val-OBu′) 19b: crystal data §

$C_{26}H_{41}NO_4$, *M* = 431.62, monoclinic, *a* = 10.483(3), *b* = 10.019(2), *c* = 13.104(4) Å, *β* = 90.12(2)°, *U* = 1376.3(5) Å^3, *T* = 295 K, space group $P2_1$ (No. 4), *Z* = 2, μ(Cu-K*α*) = 0.55 mm^{-1}, 2229 reflections measured, 1897 [$I > 3.00\sigma(I)$] were used in all calculations. The final $R(F^2)$ was 0.061.

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§ The crystal data have been deposited at the Cambridge Crystallographic Data Centre. CCDC reference number 183665. See http://www.rsc.org/suppdata/p1/b2/b203482d/ for these data in .cif or other electronic format

References

1 For recent reviews of peptidomimetics, see: Peptide Secondary Structure Mimetics, *Tetrahedron* (Symposia-in-Print; No. 50, ed. M. Kahn), 1993, 49, 3433; S. Hanessian, G. McNaughton-Smith, H.-G. Lombart and W. D. Lubell, *Tetrahedron*, 1997, **53**, 12789; *Peptidomimetics Protocols*, ed. W. M. Kazmiersk, Humana Press, Totowa, New Jersey, 1999; V. J. Hruby and P. M. Balse, *Curr. Med. Chem.*, 2000, **7**, 945; H.-O. Kim and M. Kahn, *Combi. Chem. & High Throughput Screening*, 2000, **3**, 167; M. G. Bursavich and D. H. Rich, *J. Med. Chem.*, 2002, **45**, 541.

2 F. Polyak and W. D. Lubell, *J. Org. Chem.*, 1998, **63**, 5937; C. O. Ogbu, M. N. Qabar, P. D. Boatman, J. Urban, J. P. Meara, M. D. Ferguson, J. Tulinsky, C. Lum, S. Babu, M. A. Blaskovich, H. Nakanishi, F. Ruan, B. Cao, R. Minarik, T. Little, S. Nelson, M. Nguyen, A. Gall and M. Kahn, *Bioorg. Med. Chem. Lett.*, 1998, **8**, 2321; H.-O. Kim, H. Nakanishi, M. S. Lee and M. Kahn, *Org. Lett.*, 2000, **2**, 301; S. Hanessian, N. Moitessier and S. Wilmouth, *Tetrahedron*, 2000, **56**, 7643; A. B. Smith III, W. Wang, P. A. Sprengeler and R. Hirschmann, *J. Am. Chem. Soc.*, 2000, **122**, 11037; M. C. Hillier, J. P. Davidson and S. F. Martin, *J. Org. Chem.*, 2001, **66**, 1657; M. Eguchi, M. S. Lee, M. Stasiak and M. Kahn, *Tetrahedron Lett.*, 2001, **42**, 1237; N. Fuchi, T. Doi, T. Harada, J. Urban, B. Cao, M. Kahn and T. Takahashi, *Tetrahedron Lett.*, 2001, **42**, 1305; L. Belvisi, L. Colombo, M. Colombo, M. D. Giacomo, L. Manzoni, B. Vodopivec and C. Scolastico, *Tetrahedron*, 2001, **57**, 6463; E. Alonso, F. López-Ortiz, C. del Pozo, E. Peralta, A. Macías and J. González, *J. Org. Chem.*, 2001, **66**, 6333.

3 Y.-K. Shue, M. D. Tufano, G. M. Carrera Jr, H. Kopecka, S. L. Kuyper, M. W. Holladay, C. W. Lin, D. G. Witte, T. R. Miller, M. Stashko and A. M. Nadzan, *Bioorg. Med. Chem.*, 1993, **1**, 161; T. E. Christos, A. Arvanitis, G. A. Cain, A. L. Johnson, R. S. Pottorf, S. W. Tam and W. K. Schmidt, *Bioorg Med. Chem. Lett.*, 1993, **3**, 1035; A. C. Bohnstedt, J. V. N. V. Prasad and D. H. Rich, *Tetrahedron Lett.*, 1993, **34**, 5217; J. S. Wai, D. L. Bamberger, T. E. Fisher, S. L. Graham, R. L. Smith, J. B. Gibbs, S. D. Mosser, A. I. Oliff, D. L. Pompliano, E. Rands and N. E. Kohl, *Bioorg. Med. Chem.*, 1994, **2**, 939; M. Wada, R. Doi, R. Hosotani, S. Higashide, T. Ibuka, H. Habashita, K. Nakai, N. Fujii and M. Imamura, *Pancreas*, 1995, **10**, 301; P. A. Bartlett and A. Otake, *J. Org. Chem.*, 1995, **60**, 3107; K. Fujimoto, R. Doi, R. Hosotani, M. Wada, J.-U. Lee, T. Koshiba, T. Ibuka, H. Habashita, K. Nakai, N. Fujii and M. Imamura, *Life Sci.*, 1997, **60**, 29; K. Miyasaka, S. Kanai, M. Masuda, T. Ibuka, K. Nakai, N. Fujii and A. Funakoshi, *J. Auton. Nerv. Syst.*, 1997, **63**, 179; M. Kawaguchi, R. Hosotani, S. Ohishi, N. Fujii, S. S. Tulachan, M. Koizumi, E. Toyoda, T. Masui, S. Nakajima, S. Tsuji, J. Ida, K. Fujimoto, M. Wada, R. Doi and M. Imamura, *Biochem. Biophys. Res. Commun.*, 2001, **288**, 711; H. Tamamura, K. Hiramatsu, K. Miyamoto, A. Omagari, S. Oishi, H. Nakashima, N. Yamamoto, Y. Kuroda, T. Nakagawa, A. Otaka and N. Fujii, *Bioorg. Med. Chem. Lett.*, 2002, **12**, 923.

4 M. M. Vasbinder, E. R. Jarvo and S. J. Miller, *Angew. Chem., Int. Ed.*, 2001, **40**, 2824.

5 P. Wipf, T. C. Henninger and S. J. Geib, *J. Org. Chem.*, 1998, **63**, 6088.

6 R. R. Gardner, G.-B. Liang and S. H. Gellman, *J. Am. Chem. Soc.*, 1995, **117**, 3280; U. Schopfer, M. Stahl, T. Brandl and R. W. Hoffmann, *Angew. Chem., Int. Ed. Engl.*, 1997, **36**, 1745; R. R. Gardner, G.-B. Liang and S. H. Gellman, *J. Am. Chem. Soc.*, 1999, **121**, 1806.

7 T. Ibuka, H. Habashita, S. Funakoshi, N. Fujii, Y. Oguchi, T. Uyehara and Y. Yamamoto, *Angew. Chem., Int. Ed. Engl.*, 1990, **29**, 801; T. Ibuka, H. Habashita, A. Otaka, N. Fujii, Y. Oguchi, T. Uyehara and Y. Yamamoto, *J. Org. Chem.*, 1991, **56**, 4370; T. Ibuka, H. Yoshizawa, H. Habashita, N. Fujii, Y. Chounan, M. Tanaka and Y. Yamamoto, *Tetrahedron Lett.*, 1992, **33**, 3783; M. Noda, T. Ibuka, H. Habashita and N. Fujii, *Chem. Pharm. Bull.*, 1997, **45**, 1259.

8 S. Oishi, T. Kamano, A. Niida, M. Kawaguchi, R. Hosotani, M. Imamura, N. Yawata, K. Ajito, H. Tamamura, A. Otaka and N. Fujii, in *Peptide Science 2000*, ed. T. Shioiri, The Japanese Peptide Society, Osaka, 2001, p. 249.

9 T. Ibuka, K. Nakai, H. Habashita, Y. Hotta, N. Fujii, N. Mimura, Y. Miwa, T. Taga and Y. Yamamoto, *Angew. Chem., Int. Ed. Engl.*, 1994, **33**, 652; N. Fujii, K. Nakai, H. Tamamura, A. Otaka, N. Mimura, Y. Miwa, T. Taga, Y. Yamamoto and T. Ibuka, *J. Chem. Soc., Perkin Trans. 1*, 1995, 1359; T. Ibuka, N. Mimura, H. Ohno, K. Nakai, M. Akaji, H. Habashita, H. Tamamura, Y. Miwa, T. Taga, N. Fujii and Y. Yamamoto, *J. Org. Chem.*, 1997, **62**, 2982.

10 P. Wipf and P. C. Fritch, *J. Org. Chem.*, 1994, **59**, 4875; P. Wipf and T. C. Henninger, *J. Org. Chem.*, 1997, **62**, 1586.

11 H. Tamamura, M. Yamashita, H. Muramatsu, H. Ohno, T. Ibuka, A. Otaka and N. Fujii, *Chem. Commun.*, 1997, 2327; H. Tamamura, M. Yamashita, Y. Nakajima, K. Sakano, A. Otaka, H. Ohno, T. Ibuka and N. Fujii, *J. Chem. Soc., Perkin Trans. 1*, 1999, 2983; S. Oishi, H. Tamamura, M. Yamashita, Y. Odagaki, N. Hamanaka, A. Otaka and N. Fujii, *J. Chem. Soc., Perkin Trans. 1*, 2001, 2445.

12 N. Fujii, H. Habashita, N. Shigemori, A. Otaka, T. Ibuka, M. Tanaka and Y. Yamamoto, *Tetrahedron Lett.*, 1991, **32**, 4969; A. Otaka, H. Watanabe, E. Mitsuyama, A. Yukimasa,

H. Tamamura and N. Fujii, *Tetrahedron Lett.*, 2001, **42**, 285; A. Otaka, H. Watanabe, A. Yukimasa, S. Oishi, H. Tamamura and N. Fujii, *Tetrahedron Lett.*, 2001, **42**, 5443; S. Oishi, T. Kamano, A. Niida, Y. Odagaki, H. Tamamura, A. Otaka, N. Hamanaka and N. Fujii, *Org. Lett.*, 2002, **4**, 1051.
13 H. J. Mitchell, A. Nelson and S. Warren, *J. Chem. Soc., Perkin Trans. 1*, 1999, 1899.
14 A preliminary communication of this work has appeared: S. Oishi, A. Niida, T. Kamano, Y. Odagaki, H. Tamamura, A. Otaka, N. Hamanaka and N. Fujii, *Org. Lett.*, 2002, **4**, 1055.
15 T. Ibuka, K. Suzuki, H. Habashita, A. Otaka, H. Tamamura, N. Mimura, Y. Miwa, T. Taga and N. Fujii, *J. Chem. Soc., Chem. Commun.*, 1994, 2151.
16 T. Ibuka, N. Mimura, H. Aoyama, M. Akaji, H. Ohno, Y. Miwa, T. Taga, K. Nakai, H. Tamamura, N. Fujii and Y. Yamamoto, *J. Org. Chem.*, 1997, **62**, 999.
17 T. Xin, S. Okamoto and F. Sato, *Tetrahedron Lett.*, 1998, **39**, 6927.
18 J. G. Knight, S. W. Ainge, A. M. Harm, S. J. Harwood, H. I. Maughan, D. R. Armour, D. M. Hollinshead and A. A. Jaxa-Chamiec, *J. Am. Chem. Soc.*, 2000, **122**, 2944.
19 G. J. Hanson and T. Lindberg, *J. Org. Chem.*, 1985, **50**, 5399.
20 S. J. Hocart, M. V. Nekola and D. H. Coy, *J. Med. Chem.*, 1988, **31**, 1820.
21 M. A. Blanchette, W. Choy, J. T. Davis, A. P. Essenfeld, S. Masamune, W. R. Roush and T. Sakai, *Tetrahedron Lett.*, 1984, **25**, 2183.
22 A small amount of *Z*-isomer formation by organocopper-mediated alkylation has previously been reported: H. Yang, X. C. Sheng, E. M. Harrington, K. Ackermann, A. M. Garcia and M. D. Lewis, *J. Org Chem.*, 1999, **64**, 242.
23 T. Ibuka, H. Habashita, S. Funakoshi, N. Fujii, K. Baba, M. Kozawa, Y. Oguchi, T. Uyehara and Y. Yamamoto, *Tetrahedron: Asymmetry*, 1990, **1**, 389.
24 R. Haubner, D. Finsinger and H. Kessler, *Angew. Chem., Int. Ed. Engl.*, 1997, **36**, 1374.
25 G. Hallnemo and C. Ullenius, *Tetrahedron Lett.*, 1986, **27**, 395; B. H. Lipshutz, S. Whitney, J. A. Kozlowski and C. M. Breneman, *Tetrahedron Lett.*, 1986, **27**, 4273; B. H. Lipshutz, E. L. Ellsworth and S. H. Dimock, *J. Am. Chem. Soc.*, 1990, **112**, 5869.
26 In this plausible mechanism, the nearly equal rates in the direct alkylations of the two conformers of 1,3-oxazolidin-2-ones or in reactions *via* two copper–π-allyl complexes are assumed. Taking the Curtin–Hammett principle into consideration, product distribution may depend on the relative rates of reaction of the two conformers.
27 Enantiomers of **10a**,**b** are depicted for easy understanding.