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Synthesis of (*Z*)-fluoroalkene dipeptide isosteres utilizing organocopper-mediated reduction of γ,γ-difluoro-α,β-enoates

Akira Otaka,* Hideaki Watanabe, Etsuko Mitsuyama, Akira Yukimasa, Hirokazu Tamamura and Nobutaka Fujii

Graduate School of Pharmaceutical Sciences, Kyoto University, Sakyo-ku, Kyoto 606-8501, Japan

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Abstract—γ,γ-Difluoro-α,β-enoates are reduced with organocopper reagents to afford the corresponding γ-fluoro-β,γ-enoates. This organocopper-mediated reduction was applied to the synthesis of (*Z*)-fluoroalkene dipeptide isosteres.

Replacement of scissile amide bonds in peptides with the corresponding nonhydrolyzable cognates, has gained much attention in medicinal and organic chemistry,[1] and it has facilitated the development of peptide-based drugs. Extensive synthetic studies on dipeptide mimetics possessing nonhydrolyzable peptide bond analogues have been reported by others, and we have also been engaged in the synthesis of (*E*)-alkene dipeptide isosteres using organocopper-mediated S_N2' reactions.[2] Although such (*E*)-alkene isosteres closely approximate parent peptide bonds in three-dimensional structure, they lack corresponding hydrogen bonding or dipolar interactions. Therefore, fluoro-[3] or trifluomethylalkene[4] dipeptide isosteres have been proposed as potentially better alkene mimetics, and much effort has been directed toward their synthesis (Fig. 1).

In the course of our synthetic studies on difluoromethylphosphono pThr (phosphothreonine) mimetics,[5] we found that reaction of 3-(diethylphosphonodifluoromethyl)but-2-enoate with methyl copper reagents affords an organocopper-mediated reduction product, α-fluorovinylphosphonate.[6] This finding is the first example of copper-mediated reduction of molecules containing the γ,γ-difluoro-α,β-enoate moiety where one fluorine works as a leaving group. We speculated that this organocopper-mediated reaction should be applicable to molecules possessing substituents other than the phosphono group, to afford γ-fluoro-β,γ-enoates. This hypothesis encouraged us to examine the feasibility of this unprecedented reduction to the synthesis of fluoroalkene dipeptide isosteres.

We chose α,α-difluoro-β-hydroxy esters **2** as potential precursors, and anticipated subjecting these to a sequence of reactions consisting of copper-mediated reduction followed by transformation of the hydroxy group to an amino functionality, which would lead to desired fluoroalkene isosteres (Scheme 1).

Reaction of aldehydes with $BrZnCF_2CO_2Et$ in THF afforded the α,α-difluoro-β-hydroxy esters **2**. Protection of the hydroxy group with TBSOTf–2,6-lutidine, followed by DIBAL-H reduction and subsequent Horner–

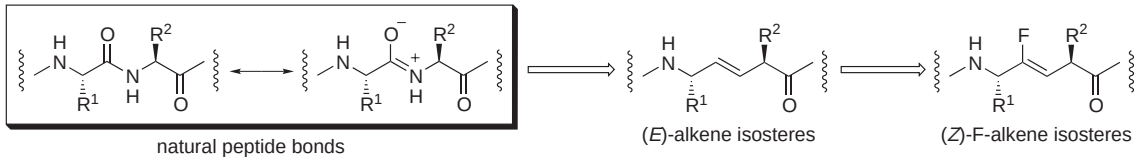

Figure 1. Peptide bonds and their alkene-type isosteres.

Keywords: fluoroalkene; dipeptide isosteres; organocopper-mediated reduction.
* Corresponding author. Tel.: +81-75-753-4571; fax: +81-75-753-4570; e-mail: aotaka@pharm.kyoto-u.ac.jp

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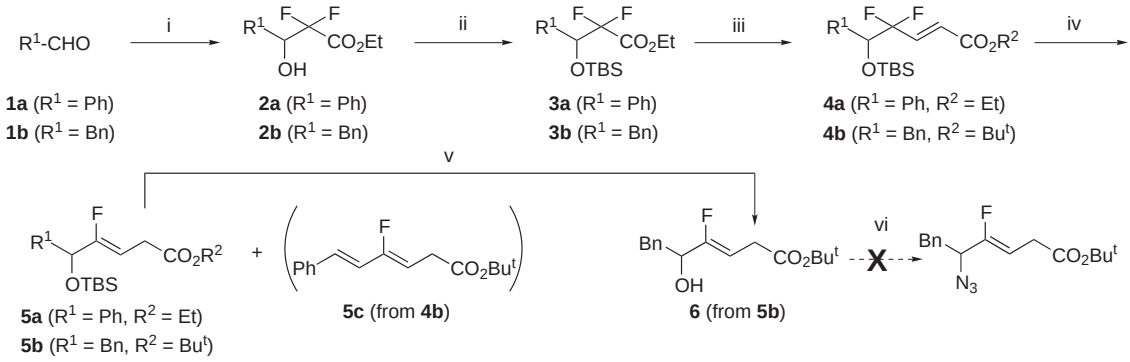


Scheme 1. (i) $BrZnCF_2CO_2Et$, THF; (ii) TBSOTf, 2,6-lutidine, CH_2Cl_2; (iii) DIBAL-H, CH_2Cl_2–toluene, then $(EtO)_2P(O)CH_2CO_2Et$ (or Bu^t), LiCl, diisopropylethylamine, CH_3CN; (iv) $Me_2Cu(CN)Li_2{\cdot}2LiBr{\cdot}2LiCl$, THF–$Et_2O$; (v) TBAF, THF; (vi) MsCl, pyridine, DMAP, CH_2Cl_2, then NaN_3, DMF or Ph_3P, DEAD, diphenylphosphoryl azide, THF.

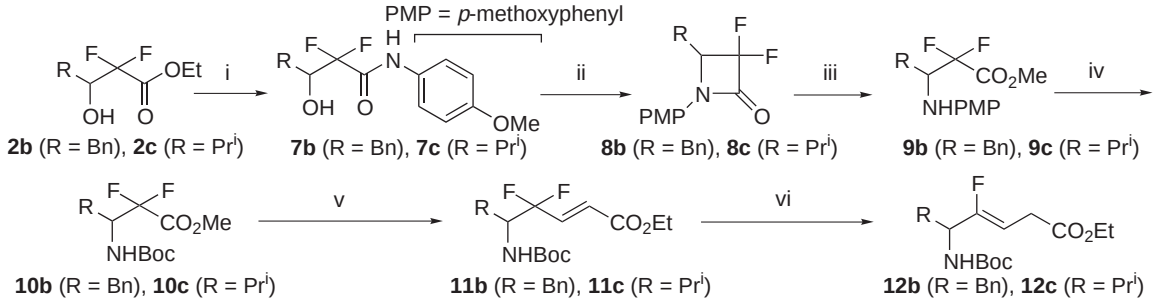
Wadsworth–Emmons (HWE) olefination of the resulting aldehydes, gave the requisite enoates **4** possessing (*E*)-geometry. Reduction of phenyl-substituted enoate **4a** with $Me_2Cu(CN)Li_2{\cdot}2LiBr{\cdot}2LiCl$ (4 equiv., which was the most effective organocopper reducing reagent in our previous study[6]), in THF–Et_2O at −78°C for 15 min, yielded the corresponding reduction product **5a** possessing (*Z*)-fluoroalkene geometry† in 96% yield. On the other hand, similar reaction of benzyl-substituted enoate **4b**, gave a mixture of desired reduction product **5b** and fluorodiene **5c** (**5b**: **5c** = 4:1). Furthermore, attempted transformation of the hydroxy functionality in reduction product **6** to an azide group using an S_N2-azide replacement (MsCl–base, then NaN_3) or Mitsunobu reaction (Ph_3P–DEAD–diphenylphosphoryl azide)[7] met with failure. Similarly, intermolecular azide replacement of α,α-difluoro-β-hydroxy esters **2** resulted in no satisfactory result. These results necessitated an alternative synthetic approach (Scheme 2), wherein we planned to introduce an amino group via intramolecular Mitsunobu reaction[8] prior to undertaking essentially the same sequence of reactions, involving organocopper-mediated reduction as stated above.

Starting from the α,α-difluoro-β-hydroxy esters **2b** or **2c**, treatment with NaOH in THF–H_2O, followed by coupling of *p*-anisidine using bis(2-oxo-3-oxazolidinyl)-phosphinic chloride and diisopropylethylamine, provided the corresponding α,α-difluoro-β-hydroxy amides **7**. Intramolecular Mitsunobu reaction of **7** with Ph_3P–DEAD in THF, gave β-lactams **8**. Ring-opening of **8** with NaOH in THF–H_2O, followed by esterification, afforded *p*-methoxyphenyl (PMP)-protected α,α-difluoro-β-amino esters **9**. Removal of the PMP group with CAN in MeCN–H_2O and subsequent introduction of the Boc-protecting group, gave Boc-protected α,α-difluoro-β-amino esters **10**. Reduction of **10** to the corresponding aldehydes with DIBAL-H (2 equiv.) in CH_2Cl_2–toluene at −78°C, followed by HWE reaction, gave δ-amino-γ,γ-difluoro-α,β-enoates **11** possessing (*E*)-geometry. Reduction of **11b** with $Me_2Cu(CN)Li_2{\cdot}2LiBr{\cdot}2LiCl$ (4 equiv.)‡ in THF–Et_2O at −78°C for 15 min, proceeded unequivocally to yield the desired (*Z*)-fluoroalkene dipeptide isostere,† Boc–Phe-Ψ[(*Z*)-CF=CH]-Gly–OEt (**12b**) in 85% isolated yield without formation of the fluorodiene. Similarly, **11c** was subjected to the organocopper-mediated reduction to give Boc–Val-Ψ[(*Z*)-CF=CH]-Gly–OEt (**12c**) in 95% yield. Utilization of the second synthetic route is crucial for introduction of the amino group and suppression of undesired fluorodiene formation.

Allmendingers' pioneering study on fluoroalkene isosteres, employed aldol reaction of α-fluoro-α,β-unsaturated aldehydes with ester enolates, followed by the introduction of nitrogen functionality by an Overman rearrangement.[3] Alternatively, synthetic methodologies employing fluoroolefination reactions of aldehydes or ketones with α-fluoroacetate derivatives, have also been reported.[9] Conceptually distinct from the above published methodologies, our presented protocol is new due to its strategy of using organocopper-mediated reduction. Since enantioselective syntheses of Boc-protected δ-amino-γ,γ-difluoro-α,β-enoate[10] and α,α-difluoro-β-hydroxy ester[11] have been reported, our methodology extends to the synthesis of enantiomerically pure versions. In conclusion, methodology has been presented herein which utilizes organocopper-mediated reduction to provide access to fluoroalkene dipeptidomimetics. Additional studies to extend this methodology to other Xaa–Ψ[(*Z*)-CF=CH]-Gly type isosteres (in this study Xaa = Phe or Val) and stereoselevtive versions, are currently underway and will be reported in due course.

† Coupling constants of **5a**, **5b**, **12b** and **12c** ($^3J_{HF}$ = 35.0, 36.5, 36.7 and 36.6 Hz, respectively) are consistent with those of α-fluorovinyl groups possessing a (*Z*)-configuration ($^3J_{HF\,cis}$ = 33–38 Hz).[3]

‡ To a solution of CuCN (59 mg, 0.66 mmol) and LiCl (56 mg, 1.32 mmol) in THF (1.7 ml) was added MeLi·LiBr in Et_2O (1.5 M, 0.88 ml) at −78°C. The mixture was allowed to warm to 0°C and stirred at this temperature for 1–2 min. After re-cooling to −78°C, **11b** (60 mg, 0.17 mmol) in THF (1.5 ml) was added. After being stirred at −78°C for 15 min, the reaction was quenched by addition of sat. NH_4Cl–28% NH_4OH solution. After usual work-up followed by flash chromatographic purification, 48 mg (85% yield) of compound **12b** was obtained.



Scheme 2. (i) NaOH, THF–H_2O, then bis(2-oxo-3-oxazolidinyl)-phosphinic chloride, *p*-anisidine, diisopropylethylamine, CH_2Cl_2; (ii) Ph_3P, DEAD, THF; (iii) NaOH, THF–H_2O, then H_2SO_4, MeOH; (iv) CAN, MeCN–H_2O, then $(Boc)_2O$, THF; (v) DIBAL-H, CH_2Cl_2–toluene, then $(EtO)_2P(O)CH_2CO_2Et$, LiCl, diisopropylethylamine, CH_3CN; (vi) $Me_2Cu(CN)Li_2{\cdot}2LiBr{\cdot}2LiCl$, THF–$Et_2O$.

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