Pergamon

Tetrahedron Letters 42 (2001) 5443–5446

TETRAHEDRON LETTERS

New access to α-substituted (*Z*)-fluoroalkene dipeptide isosteres utilizing organocopper reagents under 'reduction–oxidative alkylation (R–OA)' conditions

Akira Otaka,* Hideaki Watanabe, Akira Yukimasa, Shinya Oishi, Hirokazu Tamamura and Nobutaka Fujii

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

Received 12 March 2001; revised 25 May 2001; accepted 8 June 2001

Abstract—(*Z*)-Fluoroalkene dipeptide isosteres serve as potential dipeptide mimetics. The present paper reports a new access to α-substituted (*Z*)-fluoroalkene isosteres utilizing an organocopper-mediated 'reduction–oxidative alkylation (R–OA)' reaction.

Dipeptide isosteres possessing nonhydrolyzable scaffolds as replacements for scissile peptide bonds, represent important constituents in peptidomimetics for medicinal and/or biological use.[1] Among these, (*E*)-alkene dipeptide isosteres,[2] Xaa1-Ψ[(*E*)-CH=CH]-Xaa2 (**1**), feature three dimensional structures closely approximating parent peptide bonds; however, certain intrinsic properties of amide bonds such as dipole interaction and hydrogen bonding are lacking. Therefore, (*Z*)-fluoroalkene dipeptide isosteres,[3] Xaa1-Ψ[(*Z*)-CF=CH]-Xaa2 (**2**), have gained significant attention as potentially more suitable mimetics for (*E*)-alkene type isosteres (Fig. 1). Allmendinger et al.[4] employed aldol reactions of α-fluoro-α,β-unsaturated aldehydes with ester enolates, followed by introduction of nitrogen functionality via an Overman rearrangement, for the synthesis of fluoroalkene isosteres. They demonstrated that a substance P analogue containing a Phe-Ψ[(*Z*)-CF=CH]-Gly unit, exhibited potency comparable to the natural ligand, whereas the (*E*)-alkene counterpart did not.[4b] Other synthetic methodologies using fluoroolefination reactions of aldehydes or ketones with α-fluoroacetate derivatives have also been reported.[5]

During the course of our investigations on the synthesis of nonhydrolyzable phosphothreonine mimetics,[6] we found that reaction of γ-phosphono-γ,γ-difluoro-α,β-enoates with organocopper reagents afforded reduction products, γ-phosphono-γ-fluoro-β,γ-enoates.[7] Subsequently we applied the organocopper-mediated reduction[8] to the synthesis of Xaa-Gly type (*Z*)-fluoroalkene dipeptide isosteres (Scheme 1).[9] Although

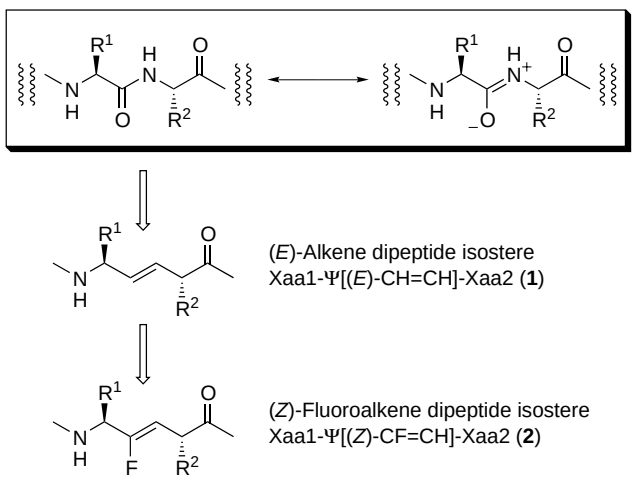
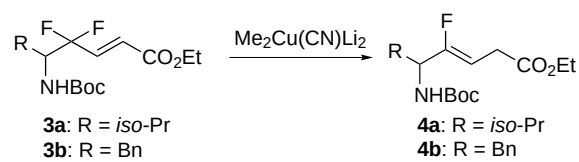


Figure 1. Peptide bond and its alkene-type isosteres.



Scheme 1. Synthesis of Xaa-Gly-type isosteres.

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

0040-4039/01/$ - see front matter © 2001 Elsevier Science Ltd. All rights reserved.
PII: S0040-4039(01)01010-3

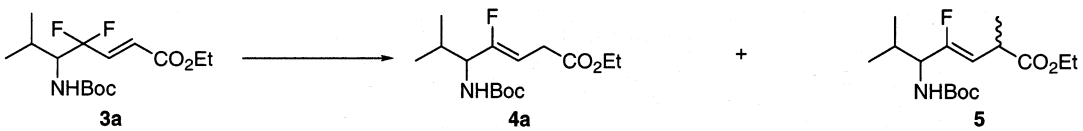
such copper-mediated methodologies provide new access to the fluoroalkene isosteres, the resulting products were limited to Xaa-Gly types. In this communication, we examined the feasibility of copper-mediated procedures for the synthesis of α-substituted (*Z*)-fluoroalkene dipeptide isosteres.

First, organocopper reagents[10] including $Me_2Cu(CN)Li_2{\cdot}2LiBr{\cdot}2LiCl$,[11] which was used for quantitative conversion of **3** to **4**, were examined in terms of α-alkylation as well as reduction (Table 1). Except for $Me_2Cu(CN)Li_2$, methyl copper reagents were not effective for both α-alkylation and reduction. Other RLi (R = *n*-Bu, and *sec*-Bu) derived higher order cyano cuprates ($R_2Cu(CN)Li_2{\cdot}2LiCl$) showed reactivity similar to that of $Me_2Cu(CN)Li_2$. Modification of $Me_2Cu(CN)Li_2$ with addition of $AlCl_3$ in Et_2O[12] changed the reaction outcome so that trace amount of α-alkylated product **5** was formed; however, these conditions are of no use for α-alkylation. Successive treatment of the $Me_2Cu(CN)Li_2$ reaction mixture with MeI afforded **5** in 81% isolated yield without diastereofacial selectivity at α-position.[8a]

Next, we explored methodology for α-alkylation based on reaction mechanisms of the reduction. Recently, Yamamoto et al. reported that single electron transfer (SET) from MeCuLn (Ln = ligand) to a substrate, is involved with highly electrophilic trimethoxycarbonylethylene in the formation of corresponding reduction products.[13] In this process, single electron transfer to the substrate give stable Cu(I) or Cu(II) intermediate which are quenched with H^+ to yield the reduction product. Alternatively oxidation with O_2 to unstable Cu(III) species, affords the Me substituted product via reductive elimination.[14] This work prompted us to envision that the formation of reduction products from highly electrophilic γ,γ-difluoro-α,β-enoates with organocopper reagents, would be likely to proceed via the SET mechanism (Table 2). Treatment of **3a** with $Me_2Cu(CN)Li_2{\cdot}2LiBr{\cdot}2LiCl$ in Et_2O-THF at −78°C under an Ar atmosphere for 4 min, followed by reaction under an O_2 atmosphere at −78°C for 20 min, proceeded nonstereoselectively to afford the corresponding α-methylated product **5** in 64% isolated yield, accompanied by corresponding carboxylic acid derivative resulting from deprotection of the ethyl ester.[15] The use of higher species ($Me_3Cu(CN)Li_3$) suppressed the formation of the carboxylic acid, and improved the yield (74%). Reaction with other alkyl copper reagents derived from *n*-BuLi or *sec*-BuLi, followed by O_2 oxidation, gave the α-substituted products (**6** or **7**) in moderate yields.

As shown in Scheme 2, formation of the alkylated products may be attributable to generation of Cu(II) **10** or Cu(I) **11** intermediates respectively, resulting from combination of radical **8** or anion **9** species with organocopper reagents, followed by O_2-induced reductive elimination. Therefore, the initial reduction step would proceed via a SET mechanism.[7b] In this report stereoselective alkylation at the α-position has not been

Table 1. Examination of various organocopper reagents for the preparation of fluoroalkene isosteres[a]



Entry	Reagent[b,c] (solvent)	Conditions	Products[d] (isolated yield %)
1	$Me_2Cu(CN)Li_2{\cdot}2LiBr{\cdot}2LiCl$ (THF:Et_2O = 4:1)	−78°C, 10 min	**4a** (95)
2	$MeCu(CN)Li{\cdot}LiBr{\cdot}LiCl$ (THF:Et_2O = 7:1)	−78°C, 1 h then −15°C, 20 min	**3a** (94)
3	$Me_2Zn{\cdot}2LiBr{\cdot}2LiCl$, 20 mol% CuCN (THF:$Et_2O$ = 1:1)	−78°C, 1 h then −15°C, 30 min	**3a** (55)
4	$MeZnCl{\cdot}Mg(Br)Cl{\cdot}2LiCl$, 10 mol% $Cu(acac)_2$ (THF:Et_2O = 6:1)	0°C, 1 h	**3a** (83)
5	$Me_2Cu(CN)(MgCl)_2{\cdot}2LiCl$ (THF)	−78°C, 20 min then −40°C, 1 h	**3a** (40), **4a** (45)
6	$Me_2CuLi{\cdot}LiI$ (THF:Et_2O = 4:1)	−78°C, 20 min	**3a** (11), **4a** (65)
7	*n*-$Bu_2Cu(CN)Li_2{\cdot}2LiCl$ (THF:hexane = 4:1)	−78°C, 20 min	**4a** (95)
8	*sec*-$Bu_2Cu(CN)Li_2{\cdot}2LiCl$ (THF:hexane = 5:2)	−78°C, 30 min	**4a** (93)
9	*tert*-$Bu_2Cu(CN)Li_2{\cdot}2LiCl$ (THF:pentane = 4:1)	−78°C, 30 min	**4a** (71), **4a′** (16)[f]
10	$Me_2Cu(CN)Li_2{\cdot}2LiBr{\cdot}2LiCl{\cdot}AlCl_3$ (THF:Et_2O = 5:4)	−78°C, 1 h then −15°C, 30 min	**3a** (53), **4a** (41), **5** (trace)
11	$Me_2Cu(CN)Li_2{\cdot}2LiBr{\cdot}2LiCl$ then MeI (THF:Et_2O = 4:1)	−78°C, 10 min then −40°C, 30 min[e]	**5** (81)

[a] Precursor **3a** is racemic.

[b] Four equiv. were used.

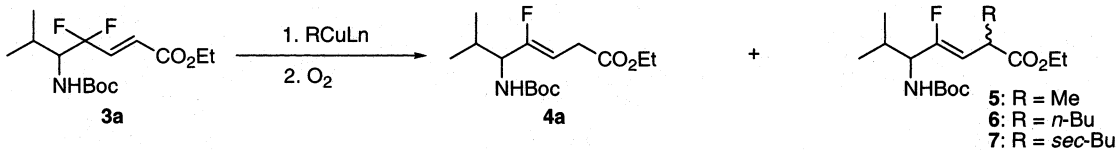
[c] $Me_2Cu(CN)Li_2$ and $MeCu(CN)Li$ were prepared as LiBr complexes from $CuCN{\cdot}2LiCl$ in THF and $MeLi{\cdot}LiBr$ in Et_2O. Me_2Zn was prepared as the LiBr complex from $ZnCl_2$ and $MeLi{\cdot}LiBr$ in Et_2O (Ref. 2f,h). $MeZnCl{\cdot}Mg(Br)Cl{\cdot}2LiCl$ was prepared from LiCl in THF, $ZnCl_2$ in Et_2O and MeMgBr in THF (Ref. 2c). $Me_2Cu(CN)(MgCl)_2$ was prepared from $CuCN{\cdot}2LiCl$ and MeMgCl in THF. $R_2Cu(CN)Li_2$ (R = *n*-Bu, *sec*-Bu, *tert*-Bu) were prepared from $CuCN{\cdot}2LiCl$ in THF and RLi in hexane (or pentane).

[d] All new compounds were characterized by ^1H NMR and elemental compositions were determined by high-resolution mass spectrometry.

[e] After addition of MeI.

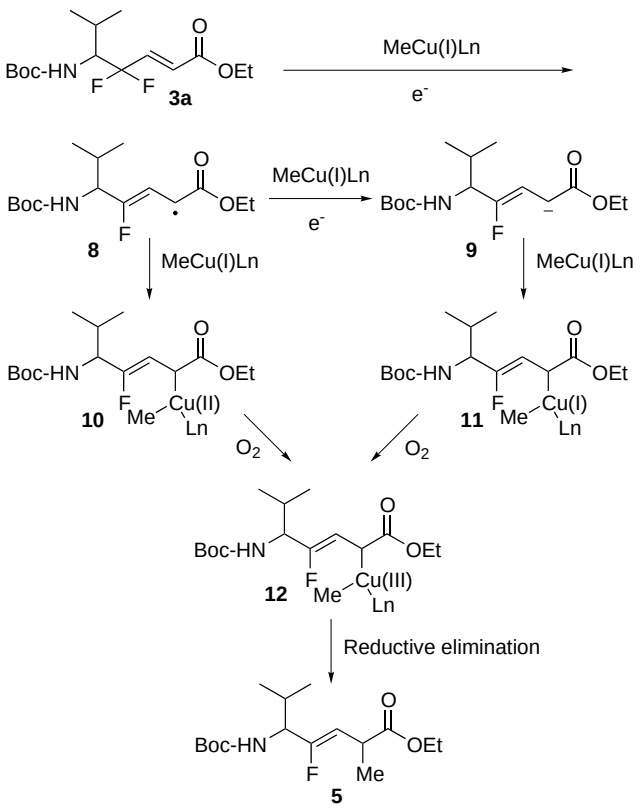
[f] (*E*)-Isomer of **4a**, the ratio of **4a** and **4a′** was determined by ^1H NMR.

Table 2. Examination of α-alkylation utilizing reduction–oxidative alkylation reactions



Entry	Reagent[a,b]	Conditions (reduction then oxidation)	Products[c] (isolated yield %)		
			Cmpd[d]	**4a**	**3a**
1	$Me_2Cu(CN)Li_2{\cdot}2LiBr{\cdot}2LiCl$	−78°C, 4 min then −78°C, 20 min	**5** (64)	Trace	–[e]
2	$n\text{-}Bu_2Cu(CN)Li_2{\cdot}2LiCl$	−78°C, 5 min then −78°C, 30 min	**6** (54)	11	–[e]
3	$sec\text{-}Bu_2Cu(CN)Li_2{\cdot}2LiCl$	−78°C, 7 min then −78°C, 30 min	**7** (45)	28	–[e]
4	$tert\text{-}Bu_2Cu(CN)Li_2{\cdot}2LiCl$	−78°C, 4 min then −78°C, 20 min	–[e]	81[f]	9
5	$Me_2CuLi{\cdot}LiI$	−78°C, 5 min then −78°C, 20 min	**5** (32)	14	6
6	$Me_2Cu(CN)(MgCl)_2{\cdot}2LiCl$	−40°C, 1 h then −40°C, 20 min	**5** (6)	16	37
7	$Me_3Cu(CN)Li_3{\cdot}2LiCl{\cdot}3LiBr$	−78°C, 8 min then −78°C, 20 min	**5** (74)	3	–[e]
8	$n\text{-}Bu_3Cu(CN)Li_3{\cdot}2LiCl$	−78°C, 8 min then −78°C, 20 min	**6** (30)	27	–[e]
9	$sec\text{-}Bu_3Cu(CN)Li_3{\cdot}2LiCl$	−78°C, 8 min then −78°C, 20 min	**7** (14)	30	–[e]

[a] Four equiv. were used.
[b] See footnotes in Table 1. $R_3Cu(CN)Li_3{\cdot}2LiCl$ (R = Me, *n*-Bu, *sec*-Bu) were prepared from CuCN·2LiCl in THF and RLi (MeLi·LiBr in Et_2O, *n*-BuLi in hexane or *sec*-BuLi in hexane).
[c] All new compounds were characterized by ^{1}H-NMR, and elemental compositions were determined by high-resolution mass spectrometry.
[d] Substituted products.
[e] Not detected.
[f] (*Z*)-Isomer 69%, (*E*)-isomer 12%.



Scheme 2. Plausible mechanism for α-alkylation via reduction–oxidative alkylation.

achieved. However, formation of **10** or **11** under a chiral environment created by a reagent such as a chiral auxiliary could provide a way for stereoselective induction.

In summary, we have developed a new route to α-substituted fluoroalkene dipeptide isosteres using reduction–oxidative alkylation (R–OA) reactions with organocopper reagents. Present results are the first example of the synthesis of alkene-type dipeptide isosteres utilizing R–OA reactions. Further studies to optimize reaction conditions, as well as investigation of stereoselective introduction of α-substituents, are now in progress.

Acknowledgements

We thank Dr. Terrence R. Burke, Jr., NCI, NIH, Frederick, MD 21702-1201, for proofing the manuscript and providing useful comments. This work was supported in part by The Japan Health Sciences Foundation and Grants-in Aid for Scientific Research from the Ministry of Education, Science and Culture of Japan.

References

1. For recent reviews, see: *Peptidomimetics Protocols*, Kazmierski, W. M., Ed.; Humana Press: Totowa, NJ, 1999.
2. (*E*)-Alkene isostere: (a) Ibuka, T.; Habashita, H.; Funakoshi, S.; Fujii, N.; Baba, K.; Kozawa, M.; Oguchi, Y.; Uyehara, T. Yamamoto, Y. *Tetrahedron Asymmetry* **1990**, *1*, 389–394; (b) Ibuka, T.; Habashita, H.; Otaka, A.; Fujii, N.; Oguchi, Y.; Uyehara, T.; Yamamoto, Y. *J. Org. Chem.* **1991**, *56*, 4370–4382; (c) Fujii, N.; Nakai, K.; Habashita, H.; Yoshizawa, H.; Ibuka, T.; Garrido, F.;

Mann, A.; Chounan, Y.; Yamamoto, Y. *Tetrahedron Lett*. **1993**, *34*, 4227–4230; (d) Daly, M. J.; Ward, R. A.; Thompson, D. A.; Procter, G. *Tetrahedron Lett*. **1995**, *36*, 7545–7548; (e) Kessler, H.; Kranz, M. *Tetrahedron Lett*. **1996**, *37*, 5359–5362; (f) 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*, 652–654; (g) Wipf, P.; Fritch, P. C. *J. Org. Chem*. **1994**, *59*, 4875–4886; (h) 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**, 1359–1371; (i) Wipf, P.; Henninger, T. C. *J. Org. Chem*. **1997**, *62*, 1586–1587; (j) Tamamura, H.; Yamashita, M.; Muramatsu, H.; Ohno, H.; Ibuka, T.; Otaka, A.; Fujii, N. *Chem. Commun*. **1997**, 2327–2328; (k) Tamamura, H.; Yamashita, M.; Nakajima, Y.; Sakano, K.; Otaka, A.; Ohno, H.; Ibuka, T.; Fujii, N. *J. Chem. Soc., Perkin Trans. 1* **1999**, 2983–2996; (l) Henninger, T. C.; Wipf, P. In Ref. 1, 125–136.

3. Welch, J. T.; Allmendinger, T. In Ref. 1, 357–384.
4. (a) Allmendinger, T.; Furet, P.; Hungerbühler, E. *Tetrahedron Lett*. **1990**, *31*, 7297–7300; (b) Allmendinger, T.; Felder, E.; Hungerbühler, E. *Tetrahedron Lett*. **1990**, *31*, 7301–7304.
5. (a) Boros, L. G.; De Corte, B.; Gimi, R. H.; Welch, J. T.; Wu, Y.; Handschumacher, R. E. *Tetrahedron Lett*. **1994**, *35*, 6033–6036; (b) Bartlett, P. A.; Otake, A. *J. Org. Chem*. **1995**, *60*, 3107–3111; (c) Welch, J. T.; Lin, J. *Tetrahedron* **1996**, *52*, 291–304.
6. Otaka, A.; Mitsuyama, E.; Kinoshita, T.; Tamamura, H.; Fujii, N. *J. Org. Chem*. **2000**, *65*, 4888–4899.
7. Otaka, A.; Mitsuyama, E.; Watanabe, H.; Tamamura, H.; Fujii, N. *Chem. Commun*. **2000**, 1081-1082. Kitazume's group investigated organocopper-mediated reduction of a γ,γ,γ-trifluoro-α,β-enoate, see: (b) Yamazaki, T.; Shinohara, N.; Kitazume, T.; Sato, S. *J. Fluorine Chemistry* **1999**, *97*, 91–96.
8. For copper-mediated reduction of γ-substituted-α,β-enoates, see: (a) Ibuka, T.; Aoyagi, T.; Yamamoto, Y. *Chem. Pharm. Bull*. **1986**, *34*, 2417–2427; (b) Fujii, N.; Habashita, H.; Shigemori, N.; Otaka, A.; Ibuka, T.; Tanaka, M.; Yamamoto, Y. *Tetrahedron Lett*. **1991**, *32*, 4969–4972; (c) Ibuka, T.; Yoshizawa, H.; Habashita, H.; Fujii, N.; Chounan, Y.; Tanaka, M.; Yamamoto, Y. *Tetrahedron Lett*. **1992**, *33*, 3783–3786.
9. Otaka, A.; Watanabe, H.; Mitsuyama, E.; Yukimasa, A.; Tamamura, H.; Fujii, N. *Tetrahedron Lett*. **2001**, *42*, 285–287.
10. For recent reviews, see: (a) Nakamura, E.; Mori, S. *Angew. Chem., Int. Ed*. **2000**, *39*, 3750–3771. (b) *Organocopper Reagents, A Practical Approach*; Taylor, R. J. K., Ed.; Oxford University Press: Oxford, 1994 and references cited threrein.
11. Although reagents prepared from CuCN and 2 equiv. of RLi may be represented as $R_2CuLi{\cdot}LiCN$ by analogy to Gilman reagents, $R_2CuLi{\cdot}LiI$ for the cuprates prepared from CuI and 2 equiv. of RLi as suggested by Dr Bertz and others, the constitutional formula $R_2Cu(CN)Li_2$ has been used throughout this paper as a matter of convenience. We are not concerned about the exact structure, but watch the reactive species as a reagent system. For recent discussion about the structures, see: (a) Lipshutz, B. H.; James, B. *J. Org. Chem*. **1994**, *59*, 7585–7587. (b) Bertz, S. H.; Nilsson, K.; Davidsson, Ö.; Snyder, J. P. *Angew. Chem., Int. Ed*. **1998**, *37*, 314–317. (c) Boche, G.; Bosold, F.; Marsch, M.; Harms, K. *Angew., Chem. Int. Ed*. **1998**, *37*, 1684–1686. (d) Kronenburg, C. M. P.; Jastrzebski, J. T. B. H.; Spek, A. L.; van Koten, G. *J. Am. Chem. Soc*. **1998**, *120*, 9688–9689 and references cited therein.
12. Ibuka, T.; Yamamoto, Y. In Ref. 10b, 143–158.
13. (a) Chounan, Y.; Ibuka, T.; Yamamoto, Y. *J. Chem. Soc., Chem. Commun*. **1994**, 2003–2004; (b) Chounan, Y.; Horino, H.; Ibuka, T.; Yamamoto, Y. *Bull. Chem. Soc. Jpn*. **1997**, *70*, 1953–1959.
14. For an oxidative ligand coupling of organocopper reagents, see: (a) Lipshutz, B. H.; Siegmann, K.; Garcia, E. *J. Am. Chem. Soc*. **1991**, *113*, 8161–8162. (b) Lipshutz, B. H.; Siegmann, K.; Garcia, E.; Kayser, F. *J. Am. Chem. Soc*. **1993**, *115*, 9276–9282. (c) Kabir, S. M. H.; Iyoda, M. *Chem. Commun*. **2000**, 2329–2330.
15. **Typical experiment:** To a solution of CuCN (84 mg, 0.93 mmol) and LiCl (79 mg, 1.87 mmol) in THF (2.4 mL) was added MeLi·LiBr in Et_2O (1.5 M, 1.25 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, **3a**[9] (75 mg, 0.23 mmol) in THF (2.1 mL) was added. After the mixture was stirred at −78°C for 4 min (yellow solution), the Ar balloon was changed to an O_2 balloon, and the reaction was continued at −78°C for 20 min (reddish brown solution). Then, sat. NH_4Cl −28% NH_4OH solution was added to quenched the reaction. After usual work-up followed by flash chromatographic purification (EtOAc:hexanes = 1:4), a diastereomeric mixture (1:1) of **5** (47 mg, 65% yield) was obtained as a colorless oil: HRMS (FAB) m/z calcd for $C_{16}H_{29}NO_4N$ (MH^+) 318.2080, found 318.2088; ^1H NMR (270 MHz, $CDCl_3$) for each diastereomer: δ 0.94 (d, J = 6.6 Hz, 6H), 1.24 (t, J = 7.3 Hz, 3H), 1.26 (d, J = 7.3 Hz, 3H), 1.45 (s, 9H), 1.87 (dq, J = 13.5, 6.9 Hz, 1H), 3.52 (dq, J = 9.6, 6.9 Hz, 1H), 3.83–4.00 (m, 1H), 4.13 (q, J = 7.3 Hz, 2H), 4.73 (d, J = 8.6 Hz, 1H), 4.88 (dd, J = 36.6, 9.6 Hz, 1H); δ 0.93 (d, J = 6.6 Hz, 3H), 0.94 (d, J = 6.6 Hz, 3H), 1.25 (t, J = 7.3 Hz, 3H), 1.26 (d, J = 6.6 Hz, 3H), 1.45 (s, 9H), 1.82–1.98 (m, 1H), 3.52 (dq, J = 9.2, 7.3 Hz, 1H), 3.90–4.06 (m, 1H), 4.13 (q, J = 7.3, 2H), 4.70 (d, J = 8.2, 1H), 4.92 (dd, J = 36.6, 9.2 Hz, 1H).