JOC*Article*

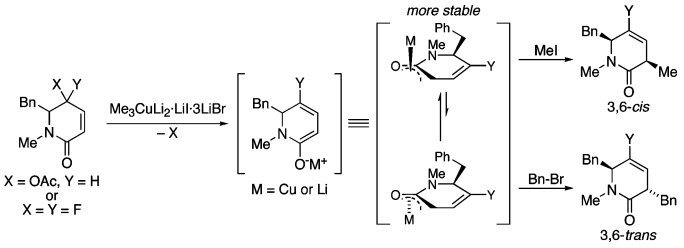
# Synthesis of (*Z*)-Alkene and (*E*)-Fluoroalkene-Containing Diketopiperazine Mimetics Utilizing Organocopper-Mediated Reduction−Alkylation and Diastereoselectivity Examination Using DFT Calculations

Ayumu Niida,[†] Makiko Mizumoto,[†] Tetsuo Narumi,[†] Eriko Inokuchi,[†] Shinya Oishi,[†] Hiroaki Ohno,[†] Akira Otaka,[†,‡] Kazuo Kitaura,[†] and Nobutaka Fujii*,[†]

*Graduate School of Pharmaceutical Sciences, Kyoto University, Sakyo-ku, Kyoto 606-8501, Japan, and Graduate School of Pharmaceutical Sciences, The University of Tokushima, Tokushima 770-8505, Japan*

*nfujii@pharm.kyoto-u.ac.jp*

*Received January 30, 2006*




We have carefully examined the organocopper-mediated reduction−alkylation of $\gamma$-acetoxy or $\gamma,\gamma$-difluoro-$\alpha,\beta$-unsaturated-$\delta$-lactams for the synthesis of (*Z*)-alkene- or (*E*)-fluoroalkene-containing diketopiperazine mimetics. Reduction of acetates **2**, **12**, **14**, and difluorolactam **18** with higher-order cuprate reagents ($Me_3CuLi_2$·LiI·3LiBr), followed by trapping the resulting metal dienolate with an electrophile in a one-pot procedure gave $\alpha$-alkylated-$\beta,\gamma$-unsaturated-$\delta$-lactams in good yields. Because of side-chain steric repulsion, we found that alkylation using relatively large electrophiles such as BnBr gave mostly 3,6-trans isomers by kinetic trapping of metal enolates. On the other hand, MeI-mediated alkylations predominantly provided the unexpected 3,6-cis isomers despite the presence of a bulky benzyl side chain. Based on density functional theory calculations, we concluded that formation of the 3,6-cis isomers was due to the occurrence of oxa-$\pi$-allyllithium complexes **29** and **31**.

## Introduction

2,5-Diketopiperazines, the smallest possible cyclic peptides consisting of two $\alpha$-amino acid residues, are often identified as common structural motifs in a large number of natural and artificial bioactive compounds.[1] This highly constrained scaffold is likely to serve as a privileged platform in medicinal chemistry. The mimetics of 2,5-diketopiperazines could be novel scaffolds for expanding the structural diversity of molecular libraries. During the past decade, we have engaged in the development of synthetic methodologies for (*E*)-alkene dipeptide isosteres[2] as potential *trans*-peptide bond equivalents along with their application to biologically active peptides.[3−5] More recently, we developed efficient synthetic strategies for (*Z*)-fluoroalkene dipeptide isosteres possessing electrostatically favorable (*Z*)-fluoroalkene units in comparison with the simple (*E*)-alkenes.[6,7] On the basis of our research on alkene-type dipeptide isosteres, we envisioned that 3,6-dihydropiridin-2-ones could function as potential 2,5-diketopiperazine mimetics in which a *cis*-peptide bond has been replaced with a structurally similar (*Z*)-alkene[8] or (*E*)-fluoroalkene unit (Figure 1).

* Corresponding author. Phone: +81-75-753-4551. Fax: +81-75-753-4570.
[†] Kyoto University.
[‡] The University of Tokushima.

(1) (a) Bauer, K.; Gräf, K. J.; Faivre-Bauman, A.; Beier, S.; Tixier-Vidal, A.; Kleinkauf, H. *Nature* **1978**, *274*, 174. (b) Shimazaki, N.; Shima, I.; Hemmi, K.; Tsurumi, Y.; Hashimoto, M. *Chem. Pharm. Bull.* **1987**, *35*, 3527. (c) Prasad, C. *Peptides* **1995**, *16*, 151. (d) Weng, J. H.; Bado, A.; Garbay, C.; Roques, B. P. *Regul. Pept.* **1996**, *65*, 3. (e) Kanoh, K.; Kohno, S.; Katada, J.; Takahashi, J.; Uno, I.; Hayashi, Y. *Bioorg. Med. Chem.* **1999**, *7*, 1451. (f) Folkes, A.; Roe, M. B.; Sohal, S.; Golec, J.; Faint, R.; Brooks, T.; Charlton, P. *Bioorg. Med. Chem. Lett.* **2001**, *11*, 2589. (g) Donkor, I. O.; Sanders, M. L. *Bioorg. Med. Chem. Lett.* **2001**, *11*, 2647. (h) Maeda, K.; Nakata, H.; Koh, Y.; Miyakawa, T.; Ogata, H.; Takeoka, Y.; Shibayama, S.; Sagawa, K.; Fukushima, D.; Moravek, J.; Koyanagi, Y.; Mitsuya, H. *J. Virol.* **2004**, *78*, 8654. (i) Nam, N.-H.; Ye, G.; Sun, G.; Parang, K. *J. Med. Chem.* **2004**, *47*, 3131. (j) Borthwick, A. D.; Davies, D. E.; Exall, A. M.; Livermore, D. G.; Sollis, S. L.; Nerozzi, F.; Allen, M. J.; Perren, M.; Shabbir, S. S.; Woollard, P. M.; Wyatt, P. G. *J. Med. Chem.* **2005**, *48*, 6956.

10.1021/jo060202z CCC: $33.50 
Published on Web 05/02/2006

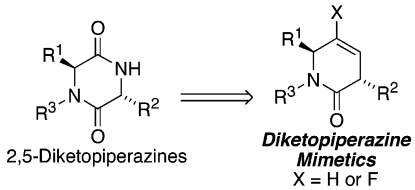
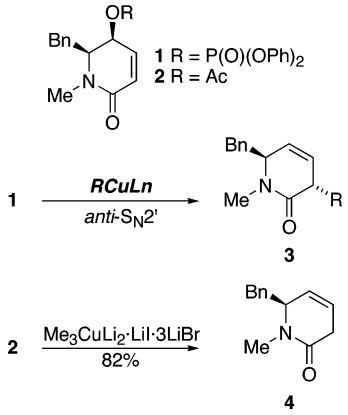



**FIGURE 1.** Diketopiperazine mimetics containing (*Z*)-alkene or (*E*)-fluoroalkene units as *cis*-peptide bond equivalents.

Recently, we reported a stereoselective methodology to prepare (*Z*)-alkene-containing diketopiperazine mimetics utilizing organocopper-mediated *anti*-$S_N2'$ reactions of $\gamma$-phosphoryloxy-$\alpha,\beta$-unsaturated-$\delta$-lactams. Regio- and stereoselective *anti*-$S_N2'$ reactions of phosphate **1** using various organocopper reagents proceeded smoothly to yield highly functionalized diketopiperazine mimetics possessing the desired $\beta,\gamma$-alkene unit (Scheme 1).[9] This method enables the establishment of a chiral center at the $\alpha$-position, and it is useful for the divergent synthesis of alkene-type diketopiperazine mimetics.

In the course of the above study, acetate **2** proved to be susceptible to reduction with an organocopper reagent, whereas **2** is an inappropriate substrate for the organocopper-mediated *anti*-$S_N2'$ reaction. Treatment of **2** with $Me_3CuLi_2$·LiI·3LiBr

**SCHEME 1**




followed by quenching with aqueous acid afforded a reduced product **4** in a high yield.[10] It has also been reported that treatment of $\gamma,\gamma$-difluoro-$\alpha,\beta$-enoates with higher-order cuprates gives the reduction products. Applications of this reaction to the synthesis of (*Z*)-fluoroalkene dipeptide isosteres as *trans*-amide bond mimetics have previously been described by us[6,11] and others.[12] Two consecutive single electron transfers from higher-order cuprates to these substrates could be involved in this reduction.[6,11b,13] The metal dienolate intermediate **5** could be trapped by electrophiles such as alkyl halides to provide $\alpha$-substituted diketopiperazine mimetics **6** (Scheme 2). We envisioned that the organocopper-mediated reduction−alkylation of $\gamma$-acetoxy- or $\gamma,\gamma$-difluoro-$\alpha,\beta$-unsaturated-$\delta$-lactams could be used for the key step in constructing an $\alpha$-chiral center of (*Z*)-alkene- or (*E*)-fluoroalkene-containing diketopiperazine mimetics. However, systematic studies on the reduction−alkylation

(2) (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, Y.; Uyehara, T.; Yamamoto, Y. *J. Org. Chem.* **1991**, *56*, 4370. (c) 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. (d) Oishi, S.; Tamamura, H.; Yamashita, M.; Odagaki, Y.; Hamanaka, N.; Otaka, A.; Fujii, N. *J. Chem. Soc., Perkin Trans. 1* **2001**, 2445. (e) Otaka, A.; Katagiri, F.; Kinoshita, T.; Odagaki, Y.; Oishi, S.; Tamamura, H.; Hamanaka, N.; Fujii, N. *J. Org. Chem.* **2002**, *67*, 6152. (f) Oishi, S.; Niida, A.; Kamano, T.; Miwa, Y.; Taga, T.; Odagaki, Y.; Hamanaka, N.; Yamamoto, M.; Ajito, K.; Tamamura, H.; Otaka, A.; Fujii, N. *J. Chem. Soc., Perkin Trans. 1* **2002**, 1786.

(3) (a) Fujimoto, K.; Doi, R.; Hosotani, R.; Wada, M.; Lee, J.-U.; Koshiba, T.; Ibuka, T.; Habashita, H.; Nakai, K.; Fujii, N.; Imamura, M. *Life Sci.* **1997**, *60*, 29. (b) Kawaguchi, M.; Hosotani, R.; Ohishi, S.; Fujii, N.; Tulachan, S. S.; Koizumi, M.; Toyoda, E.; Masui, T.; Nakajima, S.; Tsuji, S.; Ida, J.; Fujimoto, K.; Wada, M.; Doi, R.; Imamura, M. *Biochem. Biophys. Res. Commun.* **2001**, *288*, 711. (c) Tamamura, H.; Hiramatsu, K.; Miyamoto, K.; Omagari, A.; Oishi, S.; Nakashima, H.; Yamamoto, N.; Kuroda, Y.; Nakagawa, T.; Otaka, A.; Fujii, N. *Bioorg. Med. Chem. Lett.* **2002**, *12*, 923. (d) Oishi, S.; Kamano, T.; Niida, A.; Odagaki, Y.; Hamanaka, N.; Yamamoto, M.; Ajito, K.; Tamamura, H.; Otaka, A.; Fujii, N. *J. Org. Chem.* **2002**, *67*, 6162. (e) Tamamura, H.; Koh, Y.; Ueda, S.; Sasaki, Y.; Yamasaki, T.; Aoki, M.; Maeda, K.; Watai, Y.; Arikuni, H.; Otaka, A.; Mitsuya, H.; Fujii, N. *J. Med. Chem.* **2003**, *46*, 1764. (f) Tamamura, H.; Hiramatsu, K.; Ueda, S.; Wang, Z.; Kusano, S.; Terakubo, S.; Trent, J. O.; Peiper, S. C.; Yamamoto, N.; Nakashima, H.; Otaka, A.; Fujii, N. *J. Med. Chem.* **2005**, *48*, 380.

(4) For alkene dipeptide isosteres, see: (a) Christos, T. E.; Arvanitis, A.; Cain, G. A.; Johnson, A. L.; Pottorf, R. S.; Tam, S. W.; Schmidt, W. K. *Bioorg. Med. Chem. Lett.* **1993**, *3*, 1035. (b) Bohnstedt, A. C.; Prasad, J. V. N. V.; Rich, D. H. *Tetrahedron Lett.* **1993**, *34*, 5217. (c) Wai, J. S.; Bamberger, D. L.; Fisher, T. E.; Graham, S. L.; Smith, R. L.; Gibbs, J. B.; Mosser, S. D.; Oliff, A. I.; Pompliano, D. L.; Rands, E.; Kohl, N. E. *Bioorg. Med. Chem.* **1994**, *2*, 939. (d) Vasbinder, M. M.; Jarvo, E. R.; Miller, S. J. *Angew. Chem., Int. Ed.* **2001**, *40*, 2824. (e) Wipf, P.; Xiao, J. *Org. Lett.* **2005**, *7*, 103. (f) Jenkins, C. L.; Vasbinder, M. M.; Miller, S. J.; Raines, R. T. *Org. Lett.* **2005**, *7*, 2619.

(5) For amide bond isosteres, see: (a) Wipf, P.; Henninger, T. C.; Geib, S. J. *J. Org. Chem.* **1998**, *63*, 6088. (b) Mutahi, M.; Nittoli, T.; Guo, L.; Sieburth, S. M. *J. Am. Chem. Soc.* **2002**, *124*, 7363. (c) Melendez, R. E.; Lubell, W. D. *J. Am. Chem. Soc.* **2004**, *126*, 6759. (d) Wang, X. J.; Xu, B.; Mullins, A. B.; Neiler, F. K.; Etzkorn, F. A. *J. Am. Chem. Soc.* **2004**, *126*, 15533. (e) Wipf, P.; Stephenson, C. R. J. *Org. Lett.* **2005**, *7*, 1137. (f) Xiao, J.; Weisblum, B.; Wipf, P. *J. Am. Chem. Soc.* **2005**, *127*, 5742.

(6) Otaka, A.; Watanabe, J.; Yukimasa, A.; Sasaki, Y.; Watanabe, H.; Kinoshita, T.; Oishi, S.; Tamamura, H.; Fujii, N. *J. Org. Chem.* **2004**, *69*, 1634.

(7) For fluoroalkene isosteres, see: (a) Abraham, R. J.; Ellison, S. L. R.; Schonholzer, P.; Thomas, W. A. *Tetrahedron* **1986**, *42*, 2101. (b) Allmendinger, T.; Furet, P.; Hungerbühler, E. *Tetrahedron Lett.* **1990**, *31*, 7297. (c) Allmendinger, T.; Felder, E.; Hungerbühler, E. *Tetrahedron Lett.* **1990**, *31*, 7301. (d) Boros, L. G.; De Corte, B.; Gimi, R. H.; Welch, J. T.; Wu, Y.; Handschumacher, R. E. *Tetrahedron Lett.* **1994**, *35*, 6033. (e) Bartlett, P. A.; Otake, A. *J. Org. Chem.* **1995**, *60*, 3107. (f) Welch, J. T.; Allmendinger, T. In *Peptidomimetics Protocols*; Kazmierski, W. M., Ed.; Human Press: Totowa, NJ, 1999; pp 357−384. (g) Der Veken, P. V.; Senten, K.; Kertèsz, I.; De Meester, I.; Lambeir, A.-M.; Maes, M.-B.; Scharpé, S.; Haemers, A.; Augustyns, K. *J. Med. Chem.* **2005**, *48*, 1768.

(8) For the synthesis of 3,6-dihydropyridine-2-one, see: (a) Knight, J. G.; Ainge, S. W.; Harm, A. M.; Harwood, S. J.; Maughan, H. I.; Armour, D. R.; Hollinshead, D. M.; Jaxa-Chamiec, A. A. *J. Am. Chem. Soc.* **2000**, *122*, 2944. (b) Boucard, V.; Sauriat-Dorizon, H.; Guibé, F. *Tetrahedron* **2002**, *58*, 7275. (c) Knight, J. G.; Tchabanenko, K. *Tetrahedron* **2002**, *58*, 6659. (d) Anderson, T. F.; Knight, J. G.; Tchabanenko, K. *Tetrahedron Lett.* **2003**, *44*, 757.

(9) Niida, A.; Oishi, S.; Sasaki, Y.; Mizumoto, M.; Tamamura, H.; Fujii, N.; Otaka, A. *Tetrahedron Lett.* **2005**, *46*, 4183.

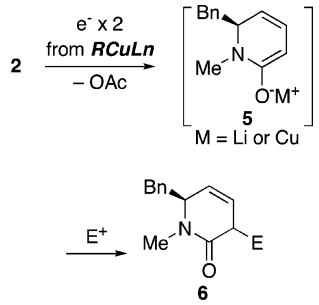
(10) For the organocopper-mediated reduction of $\gamma$-substituted-$\alpha,\beta$-enoates, see: (a) Ibuka, T.; Aoyagi, T.; Yoneda, F. *J. Chem. Soc., Chem. Commun.* **1985**, 527. (b) Ibuka, T.; Aoyagi, T.; Yamamoto, Y. *Chem. Pharm. Bull.* **1986**, *34*, 2417. (c) Takano, S.; Sekiguchi, Y.; Ogasawara, K. *J. Chem. Soc., Chem. Commun.* **1988**, 449. (d) Fujii, N.; Habashita, H.; Shigemori, N.; Otaka, A.; Ibuka, T.; Tanaka, M.; Yamamoto, Y. *Tetrahedron Lett.* **1991**, *32*, 4969. (e) Ibuka, T.; Yoshizawa, H.; Habashita, H.; Fujii, N.; Chounan, Y.; Tanaka, M.; Yamamoto, Y. *Tetrahedron Lett.* **1992**, *33*, 3783.

(11) (a) Otaka, A.; Watanabe, H.; Mitsuyama, E.; Yukimasa, A.; Tamamura H.; Fujii, N. *Tetrahedron Lett.* **2001**, *42*, 285. (b) Otaka, A.; Watanabe, H.; Yukimasa, A.; Oishi, S.; Tamamura, H.; Fujii, N. *Tetrahedron Lett.* **2001**, *42*, 5443.

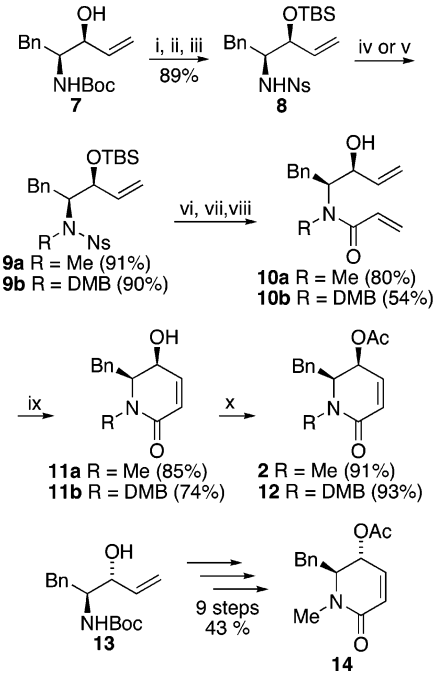
(12) Okada, M.; Nakamura, Y.; Saito, A.; Sato, A.; Horikawa, H.; Taguchi, T. *Chem. Lett.* **2002**, 28.

(13) (a) Chounan, Y.; Ibuka, T.; Yamamoto, Y. *J. Chem. Soc., Chem. Commun.* **1994**, 2003. (b) Chounan, Y.; Horino, H.; Ibuka, T.; Yamamoto, Y. *Bull. Chem. Soc. Jpn.* **1997**, *70*, 1953.

**SCHEME 2**



**SCHEME 3** [a]



[a] Reagents and conditions: (i) 4 M HCl−dioxane; (ii) Ns-Cl, 2,4,6-collidine, $CHCl_3$; (iii) TBSOTf, 2,6-lutidine, $CH_2Cl_2$; (iv) MeI, $K_2CO_3$, DMF; (v) DMBOH, $PPh_3$, DEAD, THF; (vi) $HSCH_2CO_2H$, LiOH, DMF; (vii) $CH_2$═CHCOCl, $Et_3N$, $CH_2Cl_2$; (viii) tetrabutylammonium fluoride (TBAF), THF; (ix) Grubbs' second-generation catalyst, $CH_2Cl_2$; (x) $Ac_2O$, DMAP, pyridine, $CHCl_3$. Abbreviations: Ns, 2-nitrobenzenesulfonyl; TBS, *tert*-butyldimethylsilyl; DMB, 2,4-dimethoxybenzyl.

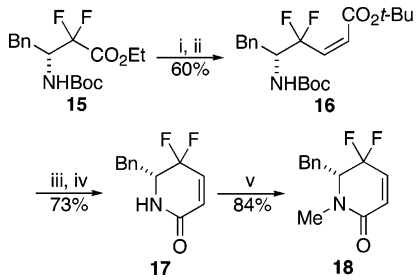
sequence of these lactams have yet to be carried out. In this paper, we report the application of organocopper-mediated reduction−alkylation sequences to the synthesis of (*Z*)-alkene- or (*E*)-fluoroalkene-containing diketopiperazine mimetics, where unexpected diastereoselectivity in the alkylation step was observed. Density functional theory (DFT) calculations were also carried out to attempt to address the diastereoselectivity in this alkylation step.

## Results and Discussion

Synthesis of the requisite substrate, *N*-alkyl-$\gamma$-activated-$\alpha,\beta$-unsaturated-$\delta$-lactams for organocopper-mediated reduction−alkylation is summarized in Schemes 3 and 4. Conversion of the *N*-protecting group of the chiral allyl alcohol **7**[14] to *N*-Ns (Ns = 2-nitrobenzenesulfonyl),[15] followed by *O*-protection with a TBS group gave the *N*-Ns amide derivative **8**. Treatment of

(14) Hanson, G. J.; Lindberg, T. *J. Org. Chem.* **1985**, *50*, 5399.

**SCHEME 4** [a]



[a] Reagents and conditions: (i) DIBAL-H, $CH_2Cl_2$−toluene; (ii) $(o\text{-MePhO})_2P(O)CH_2CO_2t\text{-Bu}$, NaI, DBU, THF; (iii) 4 M HCl−dioxane; (iv) 1-ethyl-3-[3-(dimethylamino)propyl]carbodiimide (EDC), HOAt, $(i\text{-Pr})_2NEt$, DMF; (v) MeI, NaH, THF.

**8** with MeI in the presence of $K_2CO_3$ afforded *N*-methyl sulfonamide **9a**. The corresponding *N*-DMB (2,4-dimethoxybenzyl) derivative **9b** was also synthesized by treatment of **8** with DMBOH under Mitsunobu conditions[16] to examine the effects of *N*-substitution against organocopper-mediated reduction−alkylation. After removal of the Ns group by treatment with thiolate anion under basic conditions, the resulting secondary amines were acylated with acryloyl chloride. Subsequent deprotection of *O*-TBS with TBAF followed by a ring-closing metathesis reaction of the resulting **10** with Grubbs' second-generation catalyst[17] proceeded smoothly at room temperature to yield *N*-alkyl-$\gamma$-hydroxy-$\alpha,\beta$-unsaturated-$\delta$-lactams **11**. Treatment of **11** with $Ac_2O$ in the presence of pyridine and a catalytic amount of DMAP gave acetates **2** and **12**. Acetate **14**, corresponding to the diastereomer of **2** at the $\gamma$-position, was also synthesized from allyl alcohol **13**[14] by a sequence of reactions identical to those used for the preparation of **2**.

The chiral $\beta$-amino acid ester **15**,[6] which could be synthesized using a Reformatsky−Honda reaction,[18] was chosen as a starting material for the preparation of *N*-methyl-$\gamma,\gamma$-difluoro-$\alpha,\beta$-unsaturated-$\delta$-lactam **18**. After treatment of **15** with DIBAL-H, the resulting aldehyde was subjected to (*Z*)-selective Horner−Wadsworth−Emmons reaction[19] to afford the (*Z*)-enoate **16** in 60% yield along with 15% of the isolated (*E*)-isomer. After removal of the Boc and *t*-Bu groups of **16** using 4 M HCl in dioxane, the resulting amino acid was cyclized with EDC to yield $\delta$-lactam **17**. Treatment of lactam **17** with MeI and NaH gave the desired $\gamma,\gamma$-difluoro-*N*-methyl-$\alpha,\beta$-unsaturated-$\delta$-lactam **18**.

Next we examined the organocopper-mediated reduction−alkylation of acetates **2**, **12**, and **14** for the preparation of diketopiperazine mimetics (Table 1). After reduction of acetate **2** with $Me_3CuLi_2{\cdot}LiI{\cdot}3LiBr$ at −78 °C for 20 min, the reaction mixture was treated with MeI to yield the $\alpha$-methylated diketopiperazine mimetics **19** in a good yield (entry 1). Contrary to our expectation that this alkylation would favor the predominant formation of 3,6-trans isomers as a result of steric repulsion

(15) (a) Fukuyama, T.; Jow, C.-K.; Cheung, M. *Tetrahedron Lett.* **1995**, *36*, 6373. (b) Hidai, Y.; Kan, T.; Fukuyama, T. *Chem. Pharm. Bull.* **2000**, *48*, 1570.

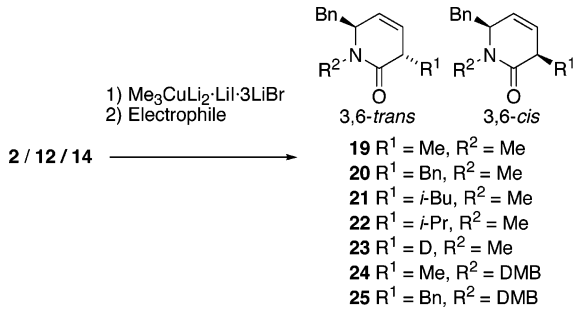
(16) Lin, X.; Dorr, H.; Nuss, J. M. *Tetrahedron Lett.* **2000**, *41*, 3309.

(17) (a) Scholl, M.; Ding, S.; Lee, C. W.; Grubbs, R. H. *Org. Lett.* **1999**, *1*, 953. (b) Arisawa, M.; Theeraladanon, C.; Nishida, A.; Nakagawa, M. *Tetrahedron Lett.* **2001**, *42*, 8029.

(18) Honda, T.; Wakabayashi, H.; Kanai, K. *Chem. Pharm. Bull.* **2002**, *50*, 307.

(19) Ando, K.; Oishi, T.; Hirama, M.; Ohno, H.; Ibuka, T. *J. Org. Chem.* **2000**, *65*, 4745.

**TABLE 1. Organocopper-Mediated Reduction−Alkylation of *γ*-Acetoxy-α,*β*-unsaturated-*δ*-lactams 2, 12, and 14**



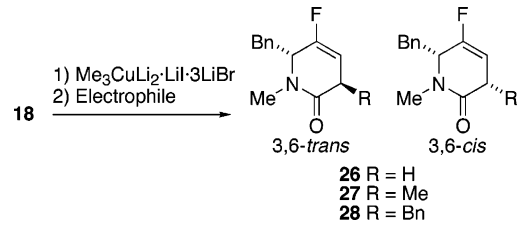

| entry | substrate | electrophile[a] | alkylation conditions[b] | products[c] (%) | trans/cis[d] |
|---|---|---|---|---|---|
| 1 | **2** | MeI | 0 °C, 3 h | **19** (68) | 15:85 |
| 2 | **2** | BnBr | −78 °C, 2.5 h | **20** (80) | 90:10 |
| 3 | **2** | *i*-BuI | 0 °C, 2 h | **21** (71) | 86:14 |
| 4 | **2** | *i*-PrI | 0 °C, 3 h | **22** (56) | 100: 0 |
| 5 | **2** | $D_2O$ (excess) | | **23** (81) | 15:85[e] |
| 6 | **14** | MeI | 0 °C, 3 h | **19** (81) | 21:79 |
| 7 | **14** | BnBr | −78 °C, 3 h | **20** (94) | 88:12 |
| 8 | **12** | MeI | 0 °C, 3 h | **24** (75) | 13:87 |
| 9 | **12** | BnBr | −78 °C, 3 h | **25** (73) | 74:26 |

[a] Eight equivalents were used, except for entry 5. [b] Reduction was carried out with $Me_3CuLi_2$·LiI·3LiBr (2 equiv) in THF−$Et_2O$ (4:1) at −78 °C for 20 min before alkylation. [c] Combined isolated yields. [d] Ratios were calculated from isolated yields of both isomers. [e] Ratio was determined by $^1H$ NMR experiments.

between the substrate benzyl group and the incoming electrophile, the use of MeI as the electrophile gave the 3,6-*cis*-**19** as the main product (trans/cis = 15:85). On the other hand, alkylation with Bn−Br or *i*-BuI afforded the α-substituted diketopiperazine mimetics **20** and **21**, respectively, in good yields, with the expected high 3,6-trans selectivity (entries 2 and 3). By using *i*-PrI, *trans*-**22** was isolated as a sole product (entry 4). Quenching the reaction with $D_2O$ preferentially gave the 3,6-*cis*-α-deuteriodiketopiperazine mimetics **23** (trans/cis = 15:85). Therefore, in this reduction−alkylation system, relatively bulky substituents such as Bn, *i*-Bu, and *i*-Pr groups were introduced with 3,6-trans diastereoselectivity, while small substituents such as Me and D tended to be introduced with high 3,6-cis selectivity.[20]

The diastereomeric substrate **14** gave similar results to those observed in the reaction of the acetate **2**: alkylation with MeI proceeded in a cis-selective manner, while the Bn group was introduced with predominantly trans selectivity (entries 6 and 7). Thus, the configuration of the leaving group relative to the benzyl substituent of **2** and **14** does not affect the diastereoselectivity of the alkylation step. These results suggest that the reactions of both acetate **2** and acetate **14** proceed via the same intermediates. The reactions of *N*-DMB acetate **12** with

**TABLE 2. Organocopper-Mediated Reduction−Alkylation of *γ*,*γ*-Difluoro-α,*β*-unsaturated-*δ*-lactam 18**




| entry | electrophile[a] | alkylation conditions[b] | solvent | products[d] (%) | trans/cis[e] |
|---|---|---|---|---|---|
| 1 | $H^+$ | | THF/$Et_2O$ (4:1) | **26** (77) | |
| 2 | MeI | 0 °C, 2 h | THF/$Et_2O$ (4:1) | **27** (60) | 50:50 |
| 3 | MeI | 0 °C, 2 h | $Et_2O$ | **27** (61) | 20:80 |
| 4 | MeOTf | 0 °C, 2 h | THF/$Et_2O$ (4:1) | **27** (75) | 50:50 |
| 5 | MeOTf | −78 °C, 2 h | $Et_2O$ | **27** (86) | 20:80 |
| 6 | BnBr | −78 °C, 2 h | THF/$Et_2O$ (4:1) | **28** (61) | 100:0 |
| 7 | BnBr | −78 °C, 2 h | $Et_2O$ | **28** (46) | 100:0 |
| 8 | MeI | 0 °C, 2 h[c] | THF/$Et_2O$ (4:1) | **27** (77) | 50:50 |
| 9 | MeI | 0 °C, 2 h[c] | $Et_2O$ | **27** (62) | 20:80 |

[a] Eight equivalents were used. [b] Reduction was carried out with $Me_3CuLi_2$·LiI·3LiBr (2 equiv) at −78 °C for 30 min before alkylation, except for entries 8 and 9. [c] *n*-$Bu_3CuLi_2$·LiI (2 equiv) was used as the reducing reagent. [d] Combined isolated yields. [e] Ratios were calculated from the isolated yields of both isomers.

$Me_3CuLi_2$·LiI·3LiBr and alkyl halides proceeded with diastereoselectivities similar to those observed in the reaction of *N*-methyl acetates **2** and **14** to yield diketopiperazine mimetics **24** and **25**.[21] These could be important precursors for (*Z*)-alkene dipeptide isosteres (entries 8 and 9).[8b] The results indicate that *N*-alkyl substituents do not affect the diastereoselectivity of alkylation.

Next, we examined the reaction of *γ*,*γ*-difluoro-α,*β*-unsaturated-*δ*-lactam **18** in the organocopper-mediated reduction−alkylation system (Table 2). Initially, it was confirmed that the organocopper-mediated reduction proceeded smoothly to yield lactam **26** (entry 1). In the same THF−$Et_2O$ (4:1) solvent system as that used in the reduction−alkylation of acetates, alkylation with MeI yielded (*E*)-fluoroalkene-containing diketopiperazine mimetics **27** without diastereoselectivity (entry 2, trans/cis = 1:1). Of note, the use of $Et_2O$ as the reaction solvent dramatically affected the product balance to yield *cis*-**27** as the main product (trans/cis = 20:80, entry 3). The use of MeOTf instead of MeI improved the chemical yield of **27**, but this did not affect the cis diastereoselectivity in $Et_2O$ (entries 4 and 5). In contrast, benzylation gave only *trans*-**27**, regardless of the solvent employed (entries 6 and 7).[22,23] To probe the involvement of the organocopper species in the diastereoselectivity of the reduction−alkylation sequence, *n*-$Bu_3CuLi_2$·LiI was used in

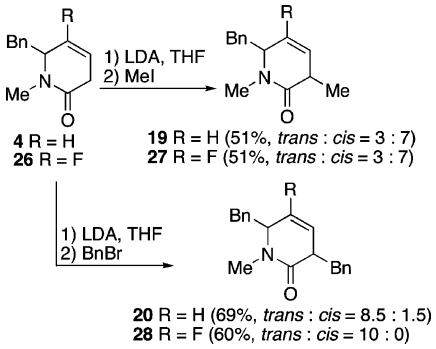
(20) The absolute configurations of *cis*-**19** or *trans*-**20** were determined to be (3*R*,6*S*) or (3*S*,6*S*) by X-ray analysis. On the basis of these results, the relative configuration of the corresponding diastereomer *trans*-**19** or *cis*-**20** was assigned. $^1H$ NMR measurements of these diastereomeric pairs indicated that the α-protons (3-position) of the 3,6-trans compounds appeared about 0.6 ppm upfield from the corresponding α-protons of the 3,6-cis isomers as a result of the anisotropic effect of the side chain phenyl ring. Structures of **21**, **22**, and **23** were determined on the basis of the observed α-proton chemical shifts: *trans*-**21** (2.07 ppm), *trans*-**22** (2.14 ppm), *trans*-**23** (2.12 ppm) vs *cis*-**21** (2.76 ppm), *cis*-**22** (2.81 ppm, obtained in ref 9), and *cis*-**23** (2.65 ppm). These assignments were supported by the experiments on organocopper-mediated *anti*-$S_N2'$ reactions of phosphate derivatives. See ref 9.

(21) Relative configurations of **25** could be assigned by the data of ref 8b. Structures of the diastereomeric pair of **24** were determined by the observed chemical shift of the α-proton in $^1H$ NMR experiments: *trans*-**24** (2.24 ppm) or *trans*-**25** (2.46 ppm) vs *cis*-**24** (2.85 ppm) or *cis*-**25** (3.13 ppm).

(22) It was confirmed that *trans*-**27** does not isomerize to *cis*-**27** at 0 °C for 2 h under the presence of $Me_3CuLi_2$·LiI·3LiBr in $Et_2O$.

(23) Two α-protons of **26** were detected at 1.87 and 2.57 ppm in $^1H$ NMR measurements. The proton at 1.87 ppm is likely to be affected by the anisotropic effect of the side chain phenyl ring, as in the case of alkene-series compounds. The structures of each of the isomers of **27** were assigned on the basis of the α-proton chemical shift: *trans*-**27** (1.90 ppm) vs *cis*-**27** (2.78 ppm). Compound **28** was assigned as a 3,6-trans isomer because the observed α-proton chemical shift (2.14 ppm) was similar to *trans*-**27** or the upfield proton of **26**.

**SCHEME 5**




place of MeLi-derived organocopper as a reducing agent. This showed that reduction with *n*-$Bu_3CuLi_2$·LiI followed by alkylation with MeI also afforded the same results as those observed using $Me_3CuLi_2$·LiI·3LiBr (entries 8 and 9). From these results, we speculated that potential involvement of the organocopper alkyl moiety in the alkylation diastereoselectivity could be excluded.

To determine whether the metal dienolate (Cu or Li enolate) played a critical role in the reaction mechanism, we next examined alkylation of the Li dienolate (Scheme 5). Deprotonation of the reduction products **4** and **26** with LDA was carried out, followed by electrophilic trapping of the Li dienolate with MeI or BnBr.[8d] In these reactions, trends similar to those in the organocopper-mediated reduction−alkylation sequence were observed, where methylation proceeded with high cis selectivity, while benzylation gave predominantly trans isomers.

On the basis of these results, we realized that diastereoselectivity in the organocopper-mediated reduction−alkylation was determined at the alkylation step of the metal dienolate (Cu or Li). Additionally, because essentially no differences were observed in the alkylation diastereoselectivity between Li and putative Cu dienolates, we performed DFT calculations[24] on the lithium dienolates using the Gaussian 98 program[25] to probe the mechanism leading to diastereoselectivity. Reactions of the lithium dienolates from lactam **4** and fluorolactam **26** with MeBr were chosen as model systems.

First, we examined local energy minima structures of lithium dienolates from lactam **4** at the B3LYP/6-31G(d) level. The X-ray analyses of *cis*-**19** and *trans*-**20** revealed that the re-face of the lactam ring is covered by the side chain phenyl ring, as depicted in Figure 2.[26] Therefore, we performed calculations,

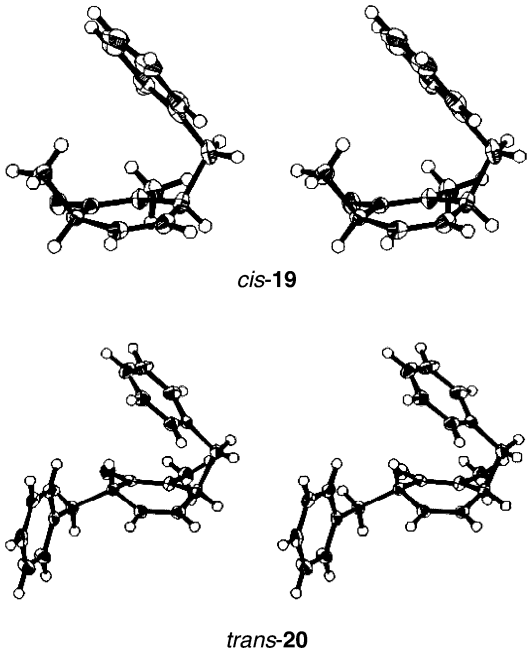



**FIGURE 2.** ORTEP diagrams for the X-ray structures of *cis*-**19** and *trans*-**20** (stereoviews).

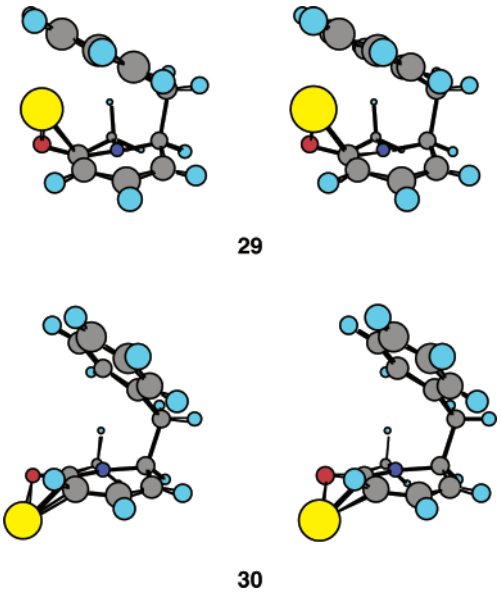



**FIGURE 3.** Optimized geometries of oxa-$\pi$-allyllithium complexes **29** and **30** in the gas phase at the B3LYP/6-31G(d) level (stereoviews).

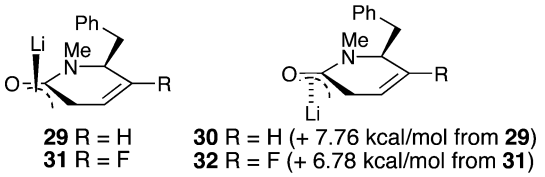
focusing particular attention on the phenyl ring orientation. As a result, two oxa-$\pi$-allyllithium complexes **29** and **30** were optimized as local minima reaction intermediates (Figure 3). Calculations of the fluoro counterparts, which were obtained from initial structures derived from **29** and **30**, gave similar oxa-$\pi$-allyllithium complexes **31** and **32**, respectively, as local minima structures.[27] Relative energies of these intermediates are shown in Figure 4. It was found that oxa-$\pi$-allyllithium complexes **29** and **31**, having the lithium cation on the same

(24) (a) Seminario, J. M., Politzer, P., Eds. *Modern Density Functional Theory. A Tool for Chemistry*; Elsevier: New York, 1995; Vol. 2 (Theoretical and Computational Chemistry). (b) Koch, W.; Holthausen, M. C. *A Chemist's Guide to Density Functional Theory*; Wiley-VCH: Weinheim, Germany, 2000.

(25) Frisch, M. J.; Trucks, G. W.; Schlegel, H. B.; Scuseria, G. E.; Robb, M. A.; Cheeseman, J. R.; Zakrzewski, V. G.; Montgomery, J. A., Jr.; Stratmann, R. E.; Burant, J. C.; Dapprich, S.; Millam, J. M.; Daniels, A. D.; Kudin, K. N.; Strain, M. C.; Farkas, O.; Tomasi, J.; Barone, V.; Cossi, M.; Cammi, R.; Mennucci, B.; Pomelli, C.; Adamo, C.; Clifford, S.; Ochterski, J.; Petersson, G. A.; Ayala, P. Y.; Cui, Q.; Morokuma, K.; Malick, D. K.; Rabuck, A. D.; Raghavachari, K.; Foresman, J. B.; Cioslowski, J.; Ortiz, J. V.; Stefanov, B. B.; Liu, G.; Liashenko, A.; Piskorz, P.; Komaromi, I.; Gomperts, R.; Martin, R. L.; Fox, D. J.; Keith, T.; Al-Laham, M. A.; Peng, C. Y.; Nanayakkara, A.; Gonzalez, C.; Challacombe, M.; Gill, P. M. W.; Johnson, B. G.; Chen, W.; Wong, M. W.; Andres, J. L.; Head-Gordon, M.; Replogle, E. S.; Pople, J. A. *Gaussian 98*, revision A.11; Gaussian, Inc.: Pittsburgh, PA, 2001.

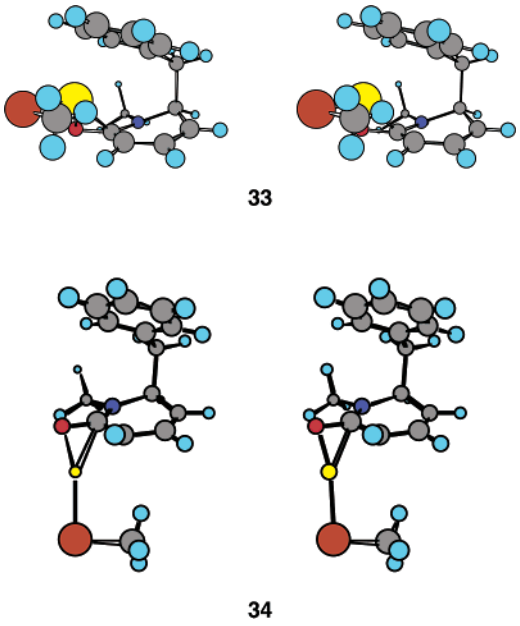
(26) The α-proton of *trans*-**20** is supposed to be affected by the anisotropic effect of the phenyl ring in the X-ray structure. This supports the reliability of the above structure determinations.

(27) For examples of the oxa-$\pi$-allyllithium complex in theoretical studies, see: (a) Lynch, T. J.; Newcomb, M.; Bergbreiter, D. E.; Hall, M. B. *J. Org. Chem.* **1980**, *45*, 5005. (b) Lambert, C.; Schleyer, P. v. R. *Angew. Chem., Int. Ed. Engl.* **1994**, *33*, 1129. (c) Kremer, T.; Schleyer, P. v. R. *Organometallics* **1997**, *16*, 737. (d) Abbotto, A.; Streitwieser, A.; Schleyer, P. v. R. *J. Am. Chem. Soc.* **1997**, *119*, 11255.




**29** R = H **30** R = H (+ 7.76 kcal/mol from **29**)
**31** R = F **32** R = F (+ 6.78 kcal/mol from **31**)

**FIGURE 4.** Relative energies of oxa-$\pi$-allyl complexes **29**−**32** in the gas phase at the B3LYP/6-31G(d) level.



**33**

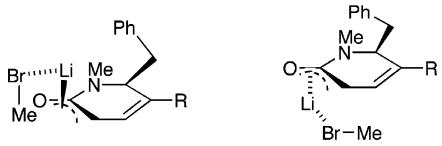
**34**

**FIGURE 5.** Optimized geometries of complexes **33** and **34** in the gas phase at the B3LYP/6-31G(d) level (stereoviews).

face of the benzyl side chain, were significantly more stable as compared to the complexes **30** or **32** having the lithium cation on the opposite face of the benzyl group, respectively (energy difference: R = H, 7.76 kcal/mol; R = F, 6.78 kcal/mol). A cation $\pi$-like interaction[28] between the lithium cation and the phenyl ring is likely to contribute to stabilization of the complexes **29** and **31** over **30** and **32**, respectively. Calculated charge distributions of the lithium atoms were estimated as follows: **29** (+0.261) versus **30** (+0.379) and **31** (+0.269) versus **32** (+0.387). These results suggested that the lithium cation interacts with the phenyl ring $\pi$-electrons.

Next, we carried out DFT calculations on the coordinated complexes with MeBr-derived oxa-$\pi$-allyllithium intermediates **29**−**32**.[29] Local minima structures **33**−**36** were optimized, and the relative energies were calculated at the B3LYP/6-31G(d) level (Figures 5 and 6). The relative energies of complexes **33** and **35**, which were formed from the stable oxa-$\pi$-allyllithium complexes **29** or **31**, were lower than those of complexes **34** and **36**, derived from intermediates **30** and **32** (energy difference: R=H, 4.27 kcal/mol; R=F, 3.30 kcal/mol).

From these calculations we derived a plausible explanation for the observed diastereoselectivity in the organocopper-mediated reduction−alkylation system, as shown in Figure 7. After reduction of the lactams **2** and **18** with $Me_3CuLi_2$·LiI·




**33** R = H **34** R = H (+ 4.27 kcal/mol from **33**)
**35** R = F **36** R = F (+ 3.30 kcal/mol from **35**)

**FIGURE 6.** Relative energies of complexes **33**−**36** in the gas phase at the B3LYP/6-31G(d) level.

3LiBr, the thermodynamically stable oxa-$\pi$-allylmetal complex **A** exists as the preferred reaction intermediate. The coordination of MeI with **A** gives complex **C**, which is a precursor intermediate of the 3,6-cis isomers. Such a route, via thermodynamically more stable intermediates **A** and **C** leading to the 3,6-cis isomers, is thought to be preferable over alternate routes in the reaction of the resulting metal dienolate with MeI or $D_2O$. In contrast, the approach of bulky alkyl halides from the same side of the benzyl side chain would be difficult due to steric repulsion. DFT calculations of complexes coordinated with *i*-PrBr were performed next, and the results are shown in Figure 8. The calculations indicated that complex **37**, derived from the $\pi$-allyllithium intermediate **29**, is thermodynamically more stable than complex **38**, derived from **30**. However, the subsequent alkylation step might be disturbed by the steric hindrance of the *i*-Pr group (Figure 9). This implies that electrophilic trapping with bulky alkyl halides such as *i*-PrI could be controlled in the final step of the alkylation to yield 3,6-trans isomers as the main products.

To demonstrate the importance of the phenyl ring on the stabilization of oxa-$\pi$-allyllithium complexes, such as **29**, we carried out DFT calculations on alanine derivatives. Two oxa-$\pi$-allyllithium complexes **39** and **40** were optimized at the B3LYP/6-31G(d) level (Figure 10). In this case, complex **40**, having a lithium atom on the opposite face of the methyl side chain, was slightly more stable as compared to complex **39**. It is clear that the interaction of the lithium cation with the phenyl ring plays an important role in the stabilization of the phenylalanine-derived complexes **29** and **31**.

To verify the above DFT calculations, we carried out an organocopper-mediated reduction−alkylation of the alanine-derived substrate **41**[30] with MeI (Scheme 6). The predominant product of the reaction was 3,6-*cis*-**42**.[31] Furthermore, we performed DFT calculations on plausible oxa-$\pi$-allyllithium complexes **43** and **44** and found that complex **44**, which is a precursor of *trans*-**42**, is thermodynamically more stable than complex **43** by 2.42 kcal/mol (Figure 11). This energy difference is not responsible for the observed cis selectivity. These results suggest that, in the methylation of the alanine-derived dienolate **43**/**44**, other factors such as aggregate formation of metal dienolate or activation energy on the methylation step may contribute to the diastereoselectivity.[32]

Finally, single-point energy calculations that included solvent effects (polarizable continuum model; PCM)[33] of optimized structures **29**−**36** were performed to address the issue of differential selectivity with lactam **18**, depending on the solvents. Energy differences based on calculated relative energy at the B3LYP/6-31G(d) level in $Et_2O$ or THF model systems are shown in Table 3. No significant changes of energy differences

(28) (a) Ma, J. C.; Dougherty, D. A. *Chem. Rev.* **1997**, *97*, 1303. (b) Gokel, G. W.; Barbour, L. J.; Ferdani, R.; Hu, J. *Acc. Chem. Res.* **2002**, *35*, 878.

(29) Pratt, L. M.; Nguyên, N. V.; Ramachandran, B. *J. Org. Chem.* **2005**, *70*, 4279.

(30) Compound **41** was synthesized by a procedure similar to the preparation of acetate **2**. See Supporting Information.

(31) For structure determination of **42**, see Supporting Information.

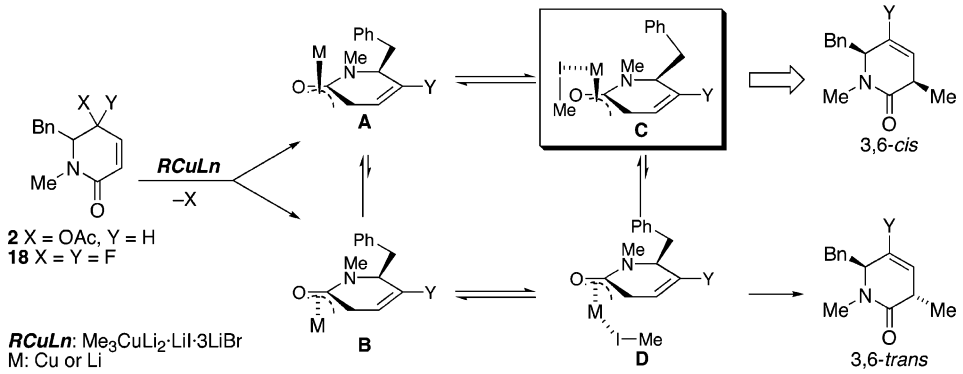



**FIGURE 7.** Plausible explanation for the unexpected cis selectivity of MeI in an organocopper-mediated reduction−alkylation system.

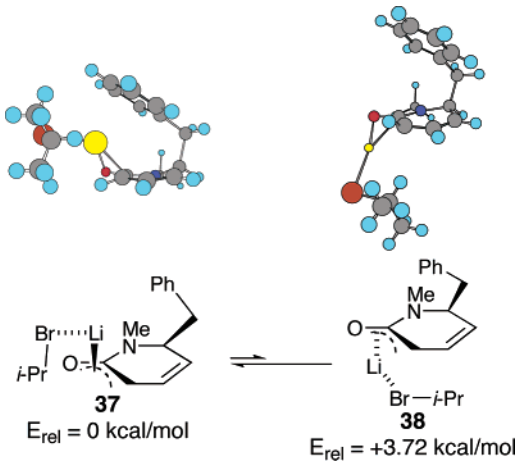



**FIGURE 8.** Optimized geometries of complexes **37** and **38** and their relative energies in the gas phase at the B3LYP/6-31G(d) level.

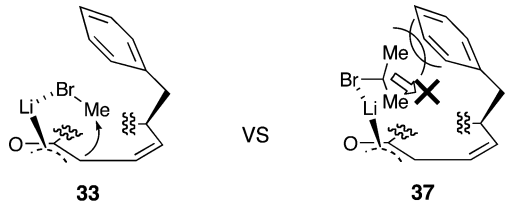
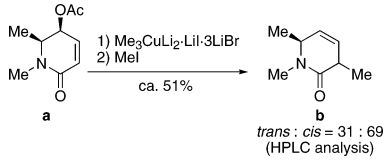



**FIGURE 9.** Comparison of complexes **33** and **37** in the alkylation step.

between **29**, **31**, **33** and **30**, **32**, **34**, respectively, were observed in any phase. It is worth noting that the energy difference between the fluorinated intermediates **35** and **36** in THF was 1.30 kcal/mol, which is significantly smaller as compared to that of the corresponding alkene-type intermediates **33** and **34**

(32) The organocopper-mediated reduction−alkylation of *N*-methylalanine-derived substrate **a** was also performed. This reaction proceeded smoothly to yield α-methylated product **b**. HPLC analysis of the reaction mixture indicated that the predominant product of this reaction was the 3,6-cis isomer, as in the case of the reaction of acetate **41**. We could not completely purify the product **b** and determine precise chemical yields as a result of its highly volatile nature.



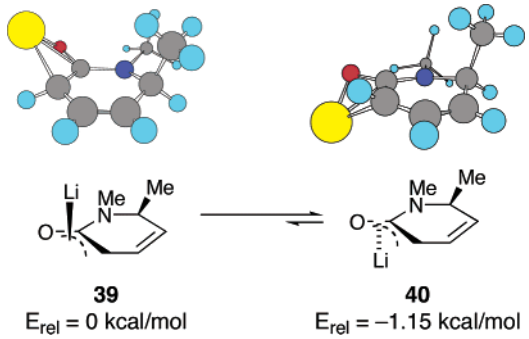




**FIGURE 10.** Optimized geometries of complexes **39** and **40** in the gas phase at the B3LYP/6−31(d) level.

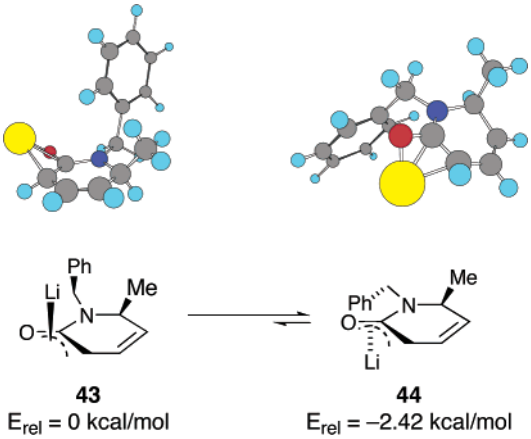
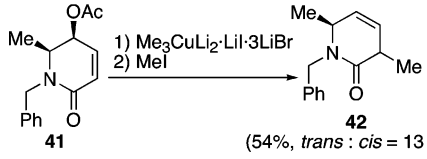



**FIGURE 11.** Optimized geometries of complexes **43** and **44** in the gas phase at the B3LYP/6−31(d) level.

**SCHEME 6**




in THF (3.39 kcal/mol) or $Et_2O$ (3.37 kcal/mol). On the basis of these data, the observed diastereoselectivity in the alkylation of the difluorolactam **18** with MeI can be attributed to a small

(33) For the PCM, see: (a) Tomasi, J.; Persico, M. *Chem. Rev.* **1994**, *94*, 2027. (b) Barone, V.; Cossi, M.; Tomasi, J. *J. Comput. Chem.* **1998**, *19*, 404.

**TABLE 3. Energy Differences between Corresponding Intermediates in the Gas Phase, $Et_2O$, or THF, as Estimated by Single-Point Energy Calculations Using the PCM at the B3LYP/6-31G(d) Level**

| | $\Delta E_{rel}$ (kcal/mol) | | | |
|---|---|---|---|---|
| phase | $E_{rel}$**30** − $E_{rel}$**29** | $E_{rel}$**32** − $E_{rel}$**31** | $E_{rel}$**34** − $E_{rel}$**33** | $E_{rel}$**36** − $E_{rel}$**35** |
| gas | +7.76 | +6.78 | +4.27 | +3.30 |
| $Et_2O$[a] | +5.93 | +4.62 | +3.37 | +1.78 |
| THF[a] | +6.28 | +4.74 | +3.39 | +1.30 |

[a] Single-point energy calculations were performed without geometry optimization under the PCM.

energy difference between **C** and **D**, as shown in Figure 7. Furthermore, the larger energy differences between **C** and **D** in THF could be an important controlling factor for the predominant formation of the 3,6-cis products via intermediate **C**.

## Conclusion

Taken together, the work reported herein demonstrates the applicability of organocopper-mediated reduction−alkylation methodology for the preparation of (*Z*)-alkene or (*E*)-fluoroalkene diketopiperazine mimetics. In this reaction system, relatively bulky alkyl halides such as Bn-Br gave 3,6-trans isomers as main products, while the reaction with MeI resulted in predominant formation of the 3,6-cis isomers. DFT calculations suggested that oxa-$\pi$-allyllithium complexes **29** and **31**, which are stabilized by cation $\pi$-like interactions between the neighboring phenyl ring of the lactam ring side chain and the lithium cation, could be important reaction intermediates affecting diastereoselectivity.

## Experimental Section

**General Method.** Melting points are uncorrected. Chemical shifts of the compounds, of which $^1$H and $^{13}$C NMR spectra were recorded in $CDCl_3$, are reported in parts per million downfield from $Me_4Si$ (s = singlet, d = doublet, dd = double doublet, ddd = doublet of double doublet, t = triplet, dt = double triplet, dtd = doublet of triple doublet, m = multiplet). $^{19}$F NMR spectra were referenced to the internal $CFCl_3$ ($\delta$ 0.00 ppm). For flash chromatographies, Wakosil C-300 (silica gel for column chromatography, Wako) was employed.

**(3*S*,4*S*)-3-[(*tert*-Butyl)dimethylsiloxy]-4-[*N*-(2-nitrobenzenesulfonyl)amino]-5-phenylpent-1-en (8).** The allyl alcohol **7** (6.0 g, 21.6 mmol) was dissolved in 4 M HCl−dioxane (30 mL), and the mixture was stirred for 1.5 h at room temperature. Concentration under reduced pressure gave an oily residue, which was dissolved in $CHCl_3$ (20 mL). 2,4,6-Collidine (5.98 mL, 45.3 mmol) and a solution of 2-nitrobenzenesulfonyl chloride (5.03 g, 22.7 mmol) in $CHCl_3$ (10 mL) were added to the above solution at 0 °C, and the mixture was stirred for 5 h at room temperature. Saturated citric acid (10 mL) was added to the mixture at 0 °C, and the mixture was extracted with EtOAc. The extract was washed successively with saturated citric acid, brine, saturated $NaHCO_3$, and brine and dried over $MgSO_4$. Concentration under reduced pressure gave an oily residue, which was dissolved in $CH_2Cl_2$ (40 mL). 2,6-lutidine (6.54 mL, 56.2 mmol) and TBSOTf (6.44 mL, 28.1 mmol) were added to the above solution at 0 °C, and the mixture was stirred overnight at room temperature. Saturated $NaHCO_3$ (15 mL) was added to the mixture at 0 °C, and the mixture was extracted with EtOAc. The extract was washed successively with saturated citric acid, brine, saturated $NaHCO_3$, and brine and dried over $MgSO_4$. Concentration under reduced pressure followed by flash chromatography over silica gel with *n*-hexanes−EtOAc (6:1) gave the title compound **8** (9.24 g, 89.5% yield) as colorless crystals: mp 77−79 °C; $[\alpha]^{28}_D$ +40.5 (*c* 1.06, $CHCl_3$); $^1$H NMR (270 MHz, $CDCl_3$) $\delta$ 0.06 (s, 3H), 0.13 (s, 3H), 0.97 (s, 9H), 2.58 (dd, *J* = 13.8, 9.2 Hz, 1H), 2.99 (dd, *J* = 13.8, 5.6 Hz, 1H), 3.63−3.75 (m, 1H), 4.25−4.33 (m, 1H), 5.02 (dt, *J* = 10.5, 1.3 Hz, 1H), 5.18 (dt, *J* = 17.1, 1.3 Hz, 1H), 5.70 (d, *J* = 7.6 Hz, 1H), 5.78 (ddd, *J* = 16.8, 10.2, 5.9 Hz, 1H), 6.95−7.05 (m, 5H), 7.45−7.80 (m, 4H); $^{13}$C NMR (100 MHz, $CDCl_3$) $\delta$ −4.8, −4.2, 18.1, 25.8, 37.6, 62.0, 74.4, 116.8, 125.3, 126.5, 128.2, 129.0, 129.9, 132.6, 132.7, 135.0, 136.9, 137.5, 147.1. Anal. Calcd for $C_{23}H_{32}N_2O_5SSi$: C, 57.95; H, 6.77; N, 5.88. Found: C, 57.79; H, 6.61; N, 5.84.

**(3*S*,4*S*)-3-[(*tert*-Butyl)dimethylsiloxy]-4-[*N*-methyl-*N*-(2-nitrobenzenesulfonyl)amino]-5-phenylpent-1-en (9a).** To a stirred solution of sulfonamide **8** (500 mg, 1.05 mmol) in DMF (5 mL) was added $K_2CO_3$ (724 mg, 5.24 mmol) and MeI at 0 °C. After stirring the mixture for 1 h at room temperature, the mixture was extracted with EtOAc. The extract was washed with brine and dried over $MgSO_4$. Concentration under reduced pressure, followed by flash chromatography over silica gel with *n*-hexanes−EtOAc (6:1), gave the title compound **9a** (507 mg, 98.6%) as colorless crystals: mp 74−75 °C; $[\alpha]^{33}_D$ −49.8 (*c* 1.02, $CHCl_3$); $^1$H NMR (270 MHz, $CDCl_3$) $\delta$ 0.03 (s, 3H), 0.08 (s, 3H), 0.95 (s, 9H), 2.80 (dd, *J* = 14.1, 8.7 Hz, 1H), 3.08 (s, 3H), 3.11 (dd, *J* = 13.8, 6.2 Hz, 1H), 4.12−4.24 (m, 1H), 4.32−4.24 (m, 1H), 5.08 (d, *J* = 10.5, Hz, 1H), 5.19 (dt, *J* = 17.1, 1.3 Hz, 1H), 5.90 (ddd, *J* = 17.1, 10.2, 6.9 Hz, 1H), 7.07−7.18 (m, 5H), 7.25−7.55 (m, 4H); $^{13}$C NMR (100 MHz, $CDCl_3$) $\delta$ −4.8, −3.7, 18.3, 26.1, 31.6, 33.9, 64.1, 75.9, 117.1, 123.6, 126.4, 128.3, 128.9, 130.3, 131.1, 132.5, 133.0, 137.9, 147.8. Anal. Calcd for $C_{24}H_{34}N_2O_5SSi$: C, 58.75; H, 6.98; N, 5.71. Found: C, 58.71; H, 7.05; N, 5.69.

**(3*S*,4*S*)-3-[(*tert*-Butyl)dimethylsiloxy]-4-[*N*-(2,4-dimethoxybenzyl)-*N*-(2-nitrobenzenesulfonyl)-amino]-5-phenylpent-1-en (9b).** To a stirred solution containing the sulfonamide **8** (200 mg 0.419 mmol), 2,4-dimethoxybenzyl alcohol (247 mg, 1.47 mmol), and $PPh_3$ (385 mg, 1.47 mmol) in THF (4 mL) was added dropwise DEAD in toluene (40% solution, 660 $\mu$L, 1.47 mmol) at 0 °C under argon, and the mixture was stirred overnight at room temperature. Concentration under reduced pressure followed by flash chromatography over silica gel with *n*-hexanes−EtOAc (5:1) gave the title compound **9b** (238 mg, 90.6% yield) as a colorless oil: $[\alpha]^{28}_D$ −87.5 (*c* 0.38, $CHCl_3$); $^1$H NMR (270 MHz, $CDCl_3$) $\delta$ −0.01 (s, 6H), 0.91 (s, 9H), 3.15 (d, *J* = 7.2 Hz, 2H), 3.67 (s, 3H), 3.81 (s, 3H), 4.23 (dd, *J* = 7.2, 3.3 Hz, 1H), 4.37 (dt, *J* = 7.2, 3.3 Hz, 1H), 4.65 (d, *J* = 15.8 Hz, 1H), 4.86 (d, *J* = 15.8 Hz, 1H), 4.95−5.10 (m, 2H), 5.83 (ddd, *J* = 17.1, 10.0, 7.3 Hz, 1H), 6.17 (d, *J* = 2.7 Hz, 1H), 6.32 (dd, *J* = 8.5, 2.3 Hz, 1H), 7.14−7.58 (m, 10H); $^{13}$C NMR (100 MHz, $CDCl_3$) $\delta$ −4.7, −3.4, 18.3, 26.1, 35.2, 45.2, 54.8, 55.4, 64.8, 66.6, 75.5, 97.7, 98.3, 103.6, 116.9, 117.4, 123.5, 126.1, 128.1, 129.2, 130.0, 130.9, 131.2, 131.6, 132.0, 135.0, 138.2, 138.5, 147.2, 157.9, 160.2; HRMS (FAB) *m*/*z* calcd for $C_{32}H_{43}N_2O_7SSi$ ($MH^+$), 627.2560; found, 627.2575.

**(3*S*,4*S*)-4-(*N*-Acryloyl-*N*-methylamino)-3-[(*tert*-butyl)dimethylsiloxy]-5-phenylpent-1-en (*O*-TBS Derivative of 10a).** To a stirred solution of the *N*-Me-sulfonamide **9a** (507 mg, 1.03 mmol) in DMF (3.6 mL) was added $LiOH\cdot H_2O$ (260 mg, 6.20 mmol) and $HSCH_2CO_2H$ (216 $\mu$L, 1.26 mmol) at 0 °C, and the mixture was stirred for 2 h at room temperature. The mixture was extracted with EtOAc. The extract was washed with saturated $NaHCO_3$ and dried over $MgSO_4$. Concentration under reduced pressure gave oily residues, which was dissolved in $CH_2Cl_2$ (5 mL). $Et_3N$ (720 $\mu$L, 5.17 mmol) and acryloyl chloride (336 $\mu$L, 1.01 mmol) were added dropwise to the above solution at −20 °C, and the mixture was stirred for 1.5 h at 0 °C under argon. Saturated $NaHCO_3$ (2 mL) was added to the above mixture at 0 °C, and the mixture was extracted with EtOAc. The extract was washed successively with saturated citric acid, brine, saturated $NaHCO_3$, and brine and dried over $MgSO_4$. Concentration under reduced pressure, followed by flash chromatography over silica gel with *n*-hexanes−EtOAc (6:1), gave the title compound *O*-TBS-**10a** (316 mg, 83.8% yield) as a colorless oil (rotamer mixture): $[\alpha]^{33}_D$ −51.3 (*c* 0.94, $CHCl_3$);

$^1$H NMR (600 MHz at 323 K, $CDCl_3$) $\delta$ 0.04 (s, 6H), 0.06 (s, 3H), 0.07 (s, 3H), 0.88 (s, 9H), 0.92 (9H), 2.81 (dd, $J$ = 14.3, 10.6 Hz, 1H), 2.84−2.90 (m, 1H), 2.87 (s, 3H), 2.91−2.97 (m, 1H), 2.94 (s, 3H), 3.02−3.08 (m, 1H), 4.02 (ddd, $J$ = 10.4, 6.2, 4.1 Hz, 1H), 4.20 (t, $J$ = 6.8 Hz, 1H), 4.40−4.50 (m, 1H), 4.65−4.80 (m, 1H), 5.15 (d, $J$ = 10.4 Hz, 1H), 5.24−5.30 (m, 3H), 5.33 (dd, $J$ = 10.8, 1.8 Hz, 1H), 5.52 (dd, $J$ = 10.5, 2.0 Hz, 1H), 5.75−5.90 (m, 3H), 6.10 (dd, $J$ = 16.8, 2.0 Hz, 1H), 6.18 (dd, $J$ = 17.0, 10.8 Hz, 1H), 6.36 (dd, $J$ = 16.8, 10.5 Hz, 1H), 7.05−7.26 (m, 10H); $^{13}$C NMR (100 MHz, $CDCl_3$) $\delta$ −5.0, −4.9, −4.1, −3.9, 17.9, 18.0, 25.5, 25.6, 25.8, 28.3, 34.1, 34.8, 63.5, 73.6, 75.0, 75.4, 115.6, 117.4, 125.2, 125.8, 126.1, 126.2, 126.7, 127.9, 128.2, 128.4, 128.6, 129.0, 137.4, 138.0, 138.2, 138.4, 166.6, 168.2; HRMS (FAB) *m*/*z* calcd for $C_{21}H_{34}NO_2Si$ ($MH^+$), 360.2359; found, 360.2352.

**(3*S*,4*S*)-4-(*N*-Acryloyl-*N*-methylamino)-5-phenylpent-1-en-3-ol (10a).** The acrylamide *O*-TBS-**10a** (116 mg, 0.322 mmol) was dissolved in 1.0 M TBAF in THF (1 mL) at 0 °C, and the mixture was stirred for 3 h at room temperature. The mixture was extracted with EtOAc. The extract was washed with brine and dried over $MgSO_4$. Concentration under reduced pressure, followed by flash chromatography over silica gel with *n*-hexanes−EtOAc (3:1), gave the title compound **10a** (78.2 mg, 98.9% yield) as a colorless oil (rotamer mixture): $[\alpha]^{29}_D$ −92.2 (*c* 1.58, $CHCl_3$); $^1$H NMR (600 MHz, $CDCl_3$) $\delta$ 2.75 (s, 3H), 2.78 (dd, $J$ = 14.4, 10.5 Hz, 0.3H), 2.94 (dd, $J$ = 14.2, 4.1 Hz, 0.3H), 2.97 (s, 0.9H), 3.06 (dd, $J$ = 14.0, 5.5 Hz, 1H), 3.10−3.30 (m, 1H), 4.01 (ddd, $J$ = 10.9, 7.4, 4.2 Hz, 0.3H), 4.22 (t, $J$ = 7.2 Hz, 0.3H), 4.26 (m, 1H), 5.16 (d, $J$ = 10.5 Hz, 1H), 5.31 (d, $J$ = 10.3 Hz, 0.3H), 5.37 (dt, $J$ = 17.1, 1.4 Hz, 1H), 5.35−5.45 (m, 0.6H), 5.66 (dd, $J$ = 10.4, 1.7 Hz, 1H), 5.80−5.90 (m, 1.6H), 6.16 (dd, $J$ = 16.9, 10.8 Hz, 0.3H), 6.24 (dd, $J$ = 16.7, 1.3 Hz, 1H), 6.38 (dd, $J$ = 16.8, 10.4 Hz, 1H), 7.00−7.30 (m, 6.5H); $^{13}$C NMR (100 MHz, $CDCl_3$) $\delta$ 28.1, 34.4, 34.9, 63.5, 73.5, 73.8, 115.6, 118.4, 126.0, 126.2, 126.5, 128.1, 128.2, 128.3, 128.4, 128.6, 128.7, 128.8, 137.3, 138.4, 168.0, 168.6; HRMS (FAB) *m*/*z* calcd for $C_{15}H_{20}NO_2$ ($MH^+$), 246.1494; found, 246.1490.

**(3*S*,4*S*)-4-[*N*-Acryloyl-*N*-(2,4-dimethoxybenzyl)amino]-3-[(*tert*-butyl)dimethylsiloxy]-5-phenylpent-1-en (*O*-TBS Derivative of 10b).** By the use of a procedure identical with that described for the preparation of *O*-TBS-**10a** from **9a**, the *N*-DMB sulfonamide **9b** (159 mg, 0.253 mmol) was converted into the title compound *O*-TBS-**10b** (76.2 mg, 60.7% yield) as a colorless oil (rotamer mixture): $[\alpha]^{29}_D$ −67.7 (*c* 0.33, $CHCl_3$); $^1$H NMR (600 MHz, $CDCl_3$, major isomer at 320 K) $\delta$ 0.02 (s, 3H), 0.03 (s, 3H), 0.91 (s, 9H), 2.88 (dd, $J$ = 14.5, 5.5 Hz, 1H), 3.12 (m, 1H), 3.71 (s, 3H), 3.75 (s, 3H), 3.83 (m, 1H), 4.42 (d, $J$ = 17.8 Hz, 1H), 4.63 (m, 1H), 4.74 (d, $J$ = 17.7 Hz, 1H), 5.14 (d, $J$ = 10.3 Hz, 1H), 5.25 (d, $J$ = 17.1 Hz, 1H), 5.49 (dd, $J$ = 10.2, 1.7 Hz, 1H), 5.83 (ddd, $J$ = 17.1, 10.3, 6.8 Hz, 1H), 6.16 (dd, $J$ = 8.2, 1.6 Hz, 1H), 6.28−6.34 (m, 2H), 6.41 (dd, $J$ = 16.0, 10.0 Hz, 1H), 6.54 (d, $J$ = 8.3 Hz, 1H), 6.95−7.20 (m, 5H); $^{13}$C NMR (100 MHz, $CDCl_3$) $\delta$ −4.9, −4.0, −3.6, 18.0, 25.7, 34.7, 54.7, 55.2, 75.4, 97.9, 103.2, 116.3, 125.7, 127.3, 128.0, 128.1, 128.3, 128.5, 128.8, 129.0, 129.3, 138.9, 139.3, 157.2, 159.7, 167.9; HRMS (FAB) *m*/*z* calcd for $C_{29}H_{42}NO_4Si$ ($MH^+$), 496.2883; found, 496.2871.

**(3*S*,4*S*)-4-[*N*-Acryloyl-*N*-(2,4-dimethoxybenzyl)amino]-5-phenylpent-1-en-3-ol (10b).** By the use of a procedure identical with that described for the preparation of **10a** from *O*-TBS-**10a**, the acrylamide *O*-TBS-**10b** (103 mg, 0.207 mmol) was converted into the title compound **10b** (70.0 mg, 88.6% yield) as a colorless oil: $[\alpha]^{30}_D$ −65.2 (*c* 1.21, $CHCl_3$); $^1$H NMR (600 MHz, $CDCl_3$) $\delta$ 2.92 (dd, $J$ = 13.4, 7.2 Hz, 1H), 3.33 (dd, $J$ = 13.3, 7.9 Hz, 1H), 3.47 (m, 1H), 3.74 (s, 3H), 3.81 (s, 3H), 3.96 (m, 1H), 4.04 (m, 1H), 4.30 (d, $J$ = 15.6 Hz, 1H), 4.93 (d, $J$ = 10.4 Hz, 1H), 5.23 (d, $J$ = 17.0 Hz, 1H), 5.39 (m, 1H), 5.70 (dd, $J$ = 10.5, 1.5 Hz, 1H), 6.35 (dd, $J$ = 16.7, 1.9 Hz, 1H), 6.40−6.44 (m, 2H), 6.78 (dd, $J$ = 15.3, 10.6 Hz, 1H), 6.92 (d, $J$ = 8.7 Hz, 1H), 7.00−7.27 (m, 5H); $^{13}$C NMR (100 MHz, $CDCl_3$) $\delta$ 29.6, 34.7, 54.8, 55.4, 72.4, 98.5, 103.8, 114.3, 116.1, 126.2, 127.6, 128.3, 129.3, 129.4, 131.0, 138.6, 138.9, 158.8, 161.1, 168.9; HRMS (FAB) *m*/*z* calcd for $C_{23}H_{28}NO_4$ ($MH^+$), 382.2018; found, 382.2008.

**(5*S*,6*S*)-6-Benzyl-5,6-dihydro-5-hydroxy-1-methylpyridin-2-one (11a).** To a solution of the acrylamide **10a** (750 mg, 3.05 mmol) in $CH_2Cl_2$ (20 mL) was added Grubbs' second-generation catalyst (129 mg, 0.152 mmol), and the mixture was stirred for 6 h at room temperature under argon. Concentration under reduced pressure, followed by flash chromatography over silica gel with *n*-hexanes−EtOAc (1:1), gave the title compound **11a** (558 mg, 84.2% yield) as colorless crystals: mp 96−97 °C; $[\alpha]^{28}_D$ −137.1 (*c* 1.06, $CHCl_3$); $^1$H NMR (270 MHz, $CDCl_3$) $\delta$ 2.56 (s, 3H), 2.97 (dd, $J$ = 13.5, 9.2 Hz, 1H), 3.19 (dd, $J$ = 13.5, 4.6 Hz, 1H), 3.60−3.85 (m, 2H), 4.87 (m, 1H), 5.85 (d, $J$ = 9.8 Hz, 1H), 6.42 (d, $J$ = 9.8 Hz, 1H), 7.14−7.35 (m, 5H); $^{13}$C NMR (100 MHz, $CDCl_3$) $\delta$ 33.1, 35.1, 65.6, 66.7, 122.8, 126.2, 128.3, 129.2, 138.3, 143.7, 163.6. Anal. Calcd for $C_{13}H_{15}NO_2$: C, 71.87; H, 6.96; N, 6.45. Found: C, 71.69; H, 7.01; N, 6.37.

**(5*S*,6*S*)-6-Benzyl-5,6-dihydro-1-[(2,4-dimethoxy)benzyl]-5-hydroxypyridin-2-one (11b).** By the use of a procedure identical with that described for the preparation of **11a** from **10a**, the acrylamide **10b** (163 mg, 0.427 mmol) was converted into the title compound **11b** (111 mg, 73.6% yield) as colorless crystals: mp 118−120 °C; $[\alpha]^{22}_D$ −10.8 (*c* 0.65, $CHCl_3$); $^1$H NMR (400 MHz, $CDCl_3$) $\delta$ 2.93 (dd, $J$ = 13.4, 8.8 Hz, 1H), 3.07−3.17 (m, 1H), 3.17 (d, $J$ = 14.6 Hz, 1H), 3.20−3.42 (m, 1H), 3.69 (s, 3H), 3.74 (s, 3H), 3.79 (m, 1H), 4.68 (m, 1H), 4.82 (d, $J$ = 14.6 Hz, 1H), 5.81 (dd, $J$ = 9.8, 2.2 Hz, 1H), 6.27−6.42 (m, 3H), 6.91 (d, $J$ = 8.0 Hz, 1H), 7.10−7.34 (m, 5H); $^{13}$C NMR (100 MHz, $CDCl_3$) $\delta$ 33.0, 44.2, 55.0, 55.1, 61.8, 67.4, 76.6, 98.2, 103.8, 117.8, 123.1, 126.2, 128.3, 129.6, 130.8, 138.1, 143.6, 158.3, 160.1, 163.5. Anal. Calcd for $C_{21}H_{23}NO_4$: C, 71.37; H, 6.56; N, 3.96. Found: C, 71.33; H, 6.52; N, 3.96.

**(5*S*,6*S*)-5-Acetoxy-6-benzyl-5,6-dihydro-1-methylpyridin-2-one (2).** To a stirred solution of the alcohol **11a** (458 mg, 2.10 mmol), pyridine (3.39 mL, 21.0 mmol), and DMAP (25.6 mg, 0.21 mmol) in $CHCl_3$ (6 mL) was added dropwise $Ac_2O$ (1.98 mL, 3.68 mmol) at 0 °C, and the mixture was stirred for 1.5 h at 0 °C. $H_2O$ (6 mL) was added to the above mixture at 0 °C, and the mixture was extracted with EtOAc. The extract was washed successively with saturated citric acid, brine, saturated $NaHCO_3$, and brine and dried over $MgSO_4$. Concentration under reduced pressure, followed by flash chromatography over silica gel with *n*-hexanes−EtOAc (2:1), gave the title compound **2** (490 mg, 90.0% yield) as colorless crystals: mp 55−57 °C; $[\alpha]^{25}_D$ −129.0 (*c* 1.26, $CHCl_3$); $^1$H NMR (600 MHz, $CDCl_3$) $\delta$ 1.93 (s, 3H), 2.68 (s, 3H), 2.94 (dd, $J$ = 13.9, 7.4 Hz, 1H), 2.99 (dd, $J$ = 13.9, 6.2 Hz, 1H), 3.95−4.01 (m, 1H), 5.79 (dt, $J$ = 6.3, 2.3 Hz, 1H), 5.93 (dd, $J$ = 10.0, 2.5 Hz, 1H), 6.30 (dt, $J$ = 10.0, 1.8 Hz, 1H), 7.12−7.31 (m, 5H); $^{13}$C NMR (100 MHz, $CDCl_3$) $\delta$ 20.5, 33.8, 34.4, 61.7, 69.4, 125.2, 126.6, 128.6, 129.2, 137.6, 137.9, 162.8, 170.0. Anal. Calcd for $C_{15}H_{17}NO_3$: C, 69.48; H, 6.61; N, 5.40. Found: C, 69.39; H, 6.62; N, 5.33.

**(5*S*,6*S*)-5-Acetoxy-6-benzyl-5,6-dihydro-1-(2,4-dimethoxy)-benzylpyridin-2-one (12).** By the use of a procedure identical with that described for the preparation of **2** from **11a**, the alcohol **11b** (545 mg, 1.54 mmol) was converted into the title compound **12** (583 mg, 95.5% yield) as a colorless oil: $[\alpha]^{22}_D$ +18.1 (*c* 1.38, $CHCl_3$); $^1$H NMR (400 MHz, $CDCl_3$) $\delta$ 1.82 (s, 3H), 2.93 (dd, $J$ = 13.9, 7.3 Hz, 1H), 3.00 (dd, $J$ = 13.9, 6.6 Hz, 1H), 3.47 (d, $J$ = 14.4 Hz, 1H), 3.77 (s, 3H), 3.82 (s, 3H), 4.20 (m, 1H), 4.78 (d, $J$ = 14.4 Hz, 1H), 5.65 (dt, $J$ = 6.3, 2.2 Hz, 1H), 5.93 (dd, $J$ = 10.0, 2.4 Hz, 1H), 6.24 (dt, $J$ = 10.0, 1.8 Hz, 1H), 6.37−6.46 (m, 2H), 7.05−7.33 (m, 6H); $^{13}$C NMR (100 MHz, $CDCl_3$) $\delta$ 14.2, 20.5, 34.3, 44.7, 55.3, 58.8, 69.9, 98.2, 103.9, 117.6, 125.2, 126.2, 128.3, 129.1, 131.4, 137.8, 137.9, 158.3, 160.1, 162.4, 169.5; HRMS (FAB) *m*/*z* calcd for $C_{23}H_{26}NO_5$ ($MH^+$), 396.1811; found, 396.1819.

***tert*-Butyl (5*R*, 2*Z*)-5-[*N*-(*tert*-Butoxycarbonyl)amino]-4,4-difluoro-6-phenylhex-2-enoate (16).** To a solution of the ester **15** (623 mg, 1.81 mmol) in $CH_2Cl_2$ (20 mL) was added dropwise a

solution of DIBAL-H in toluene (1.0 M, 3.63 mL, 3.63 mmol) at −78 °C under argon, and the mixture was stirred for 30 min at −78 °C. The reaction was quenched with saturated citric acid and extracted with $Et_2O$. The extract was washed with saturated citric acid and brine and dried over $MgSO_4$. Concentration under reduced pressure gave an oily aldehyde, which was used immediately in the next step without purification. To a stirred solution of $(o\text{-MePhO})_2P(O)CH_2CO_2t\text{-Bu}$ (563 mg, 1.63 mmol) in THF (10 mL) were added NaI (299 mg, 2.00 mmol) and DBU (271 μL, 1.82 mmol) at 0 °C under argon. After stirring for 10 min, a solution of the above aldehyde in THF (10 mL) was added to the mixture at −78 °C, and the mixture was stirred for 2 h at 0 °C. The reaction was quenched with saturated $NH_4Cl$ and extracted with EtOAc. The extract was washed 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*-hexanes−EtOAc (14:1), gave the title compound **16** (440 mg, 61.1% yield) as a colorless oil and the (*E*)-isomer (102 mg, 14.2% yield). **Compound 16:** $[\alpha]^{23}_D$ −94.3 (*c* 0.05, $CHCl_3$); $^1$H NMR (400 MHz, $CDCl_3$) δ 1.29 (s, 9H) 1.52 (s, 9H), 2.71 (dd, *J* = 13.7, 11.0 Hz, 1H), 3.19 (d, *J* = 14.4, 1H), 4.47−4.68 (m, 1H), 4.85 (d, *J* = 9.5 Hz, 1H), 5.83−5.93 (m, 1H), 6.05 (d, *J* = 12.7 Hz, 1H), 7.17−7.33 (m, 5H); $^{13}$C NMR (100 MHz, $CDCl_3$) δ 27.9, 28.1, 34.5, 55.5 (dd, *J* = 31.4, 24.8 Hz), 79.7, 82.3, 120.0 (t, *J* = 246 Hz), 126.5, 128.3, 129.3, 130.6 (t, *J* = 28.1 Hz), 136.7, 155.1, 164.3; $^{19}$F NMR (376 MHz, $CDCl_3$) δ −107.4 (ddt, *J* = 250, 174, 16.5 Hz, 1F), −100.8 (dd, *J* = 331, 252 Hz, 1F); HRMS (FAB) *m*/*z* calcd for $C_{21}H_{30}F_2NO_4$ ($MH^+$), 398.2143; found, 398.2151.

**(6*R*)-6-Benzyl-5,5-difluoro-6-hydro-1*H*-pyridin-2-one (17).** The enoate **16** (150 mg, 0.377 mmol) was dissolved in 4 M HCl−dioxane (6 mL) at 0 °C, and the mixture was stirred for 1 h at room temperature. Concentration under reduced pressure gave oily residues that dissolved in DMF (6 mL). To the above mixture were successively added $(i\text{-Pr})_2$NEt (197 μL, 1.13 mmol), HOAt (154 mg, 1.13 mmol), and EDC·HCl (217 μg, 1.13 mmol) at 0 °C, and the mixture was stirred for 23 h at room temperature. After concentration under reduced pressure, the residue was extracted with EtOAc. The extract was washed 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*-hexanes−EtOAc (4:1), gave the title compound **17** (61.4 mg, 73.0% yield) as colorless crystals: mp 78−80 °C; $[\alpha]^{24}_D$ +78.4 (*c* 0.05, $CHCl_3$); $^1$H NMR (400 MHz, $CDCl_3$) δ 2.81 (dd, *J* = 13.9, 11.5 Hz, 1H), 3.29 (dd, *J* = 13.9, 3.2 Hz, 1H), 3.97−4.08 (m, 1H), 5.43 (s, 1H), 6.18 (ddd, *J* = 10.2, 2.2, 0.9 Hz, 1H), 6.59 (ddd, *J* = 10.2, 7.6, 3.2 Hz, 1H), 7.20−7.42 (m, 5H); $^{13}$C NMR (100 MHz, $CDCl_3$) δ 33.6 (d, *J* = 5.0 Hz), 57.4 (dd, *J* = 31.4, 27.1 Hz), 115.0 (dd, *J* = 244, 236 Hz), 127.4, 129.0, 129.2, 130.2 (d, *J* = 10.0 Hz), 133.8 (dd, *J* = 30.6, 27.3 Hz), 134.6, 162.7; $^{19}$F NMR (376 MHz, $CDCl_3$) δ −107.1 (d, *J* = 281 Hz, 1F), −105.1 (dd, *J* = 277, 18.6 Hz, 1F). Anal. Calcd for $C_{12}H_{11}NOF_2$: C, 64.57; H, 4.97; N, 6.27. Found: C, 64.65; H, 5.06; N, 6.25.

**(6*R*)-6-Benzyl-5,5-difluoro-6-hydro-1-methylpyridin-2-one (18).** To a suspension of NaH (60% oil suspension, 5.6 mg, 0.140 mmol) in THF (0.75 mL) was added the lactam **17** (26.7 mg, 0.120 mmol) in THF (0.75 mL) at 0 °C under argon. After stirring for 2 h at 0 °C, MeI (15 μL, 0.241 mmol) was added to the above mixture, and the resulting mixture was stirred for 2 h at room temperature. The reaction was quenched with $H_2O$ (3 mL) at 0 °C and extracted with EtOAc. The extract was washed with brine and dried over $MgSO_4$. Concentration under reduced pressure, followed by flash chromatography over silica gel with *n*-hexanes−EtOAc (1:3), gave the title compound **18** (23.9 mg, 84.0% yield) as colorless crystals: mp 48−50 °C; $[\alpha]^{25}_D$ −16.6 (*c* 0.06, $CHCl_3$); $^1$H NMR (400 MHz, $CDCl_3$) δ 2.71 (s, 3H), 2.89 (dd, *J* = 13.9, 8.1 Hz, 1H), 3.15 (dt, *J* = 13.9, 3.6 Hz, 1H), 3.89−3.95 (m, 1H), 6.04 (dt, *J* = 10.0, 2.9 Hz, 1H), 6.28 (ddt, *J* = 10.0, 8.5, 1.6 Hz, 1H), 7.12−7.32 (m, 5H); $^{13}$C NMR (100 MHz, $CDCl_3$) δ 35.0, 36.0 (d, *J* = 5.8 Hz), 66.2 (t, *J* = 28.1), 116.6 (dd, *J* = 242, 239 Hz), 127.3, 128.9, 129.6, 130.7 (dd, *J* = 12.4, 9.1 Hz), 131.3 (dd, *J* = 34.8, 22.3 Hz), 135.6, 161.0; $^{19}$F NMR (376 MHz, $CDCl_3$) δ −112.2 (dd, *J* = 275, 8.3 Hz, 1F), −85.4 (dd, *J* = 275, 14.4 Hz, 1F). Anal. Calcd for $C_{13}H_{13}NOF_2$: C, 65.81; H, 5.52; N, 5.90. Found: C, 65.65; H, 5.47; N, 5.83.

**General Procedure for the Organocopper-Mediated Reduction. Synthesis of (6*S*)-6-Benzyl-3,6-dihydro-1-methylpyridin-2-one (4).** To a suspension of CuI (220 mg, 1.15 mmol) in THF (4.5 mL) was added dropwise a solution of the MeLi·LiBr complex in $Et_2O$ (1.45 M, 2.38 mL, 3.46 mmol) at −78 °C under argon, and the mixture was stirred for 10 min at 0 °C. To the solution of organocopper reagent was added dropwise a solution of the acetate **2** (150 mg, 0.578 mmol) in THF (4.5 mL) at −78 °C, and the mixture was stirred for 20 min at −78 °C. The reaction was quenched at −78 °C by the addition of a 1:1 saturated $NH_4Cl$−28% $NH_4OH$ solution (20 mL), with additional stirring at room temperature for 30 min. The mixture was extracted with $Et_2O$, and the extract was washed with $H_2O$ and dried over $MgSO_4$. Concentration under reduced pressure, followed by flash chromatography over silica gel with *n*-hexanes−EtOAc (1:2), gave the title compound **4** (95.6 mg, 82.1% yield) as colorless crystals: mp 55−56 °C; $[\alpha]^{21}_D$ +262.6 (*c* 1.12, $CHCl_3$); $^1$H NMR (400 MHz, $CDCl_3$) δ 2.14 (d, *J* = 22.2 Hz, 1H), 2.68 (d, *J* = 21.7 Hz, 1H), 2.88 (dd, *J* = 13.4, 3.9 Hz, 1H), 2.94 (dd, *J* = 13.4, 6.6 Hz, 1H), 3.11 (s, 3H), 4.08−4.15 (m, 1H), 5.62−5.71 (m, 2H), 7.05−7.09 (m, 2H), 7.21−7.29 (m, 3H); $^{13}$C NMR (100 MHz, $CDCl_3$) δ 31.8, 32.9, 39.4, 61.4, 123.6, 124.8, 126.6, 128.1, 129.8, 135.6, 168.4. Anal. Calcd for $C_{13}H_{15}NO$: C, 77.58; H, 7.51; N, 6.96. Found: C, 77.43; H, 7.58; N, 6.89.

**General Procedure for the Organocopper-Mediated Reduction−Alkylation. Synthesis of (3*S*,6*S*)-6-Benzyl-3,6-dihydro-1,3-dimethylpyridin-2-one (*trans*-19) and (3*R*,6*S*)-6-Benzyl-3,6-dihydro-1,3-dimethylpyridin-2-one (*cis*-19).** To a suspension of CuI (77.3 mg, 0.406 mmol) in THF (1.5 mL) was added dropwise a solution of the MeLi·LiBr complex in $Et_2O$ (1.33 M, 915 μL, 1.22 mmol) at −78 °C under argon, and the mixture was stirred for 10 min at 0 °C. To the solution of organocopper reagent was added dropwise a solution of the acetate **2** (52.8 mg, 0.203 mmol) in THF (1.5 mL) at −78 °C, and the mixture was stirred for 20 min at −78 °C. To the above mixture was added MeI (101 μL, 1.62 mmol) at −78 °C, and the mixture was stirred for 3 h at 0 °C. The reaction was quenched at −78 °C by the addition of a 1:1 saturated $NH_4Cl$−28% $NH_4OH$ solution (2 mL), with additional stirring at room temperature for 30 min. The mixture was extracted with $Et_2O$, and the extract was washed with $H_2O$ and dried over $MgSO_4$. Concentration under reduced pressure, followed by flash chromatography over silica gel with *n*-hexanes−EtOAc (1:1), gave the title compound *trans*-**19** (4.4 mg, 10.1% yield) and *cis*-**19** (25.3 mg, 57.8% yield) in order of elution. ***trans*-19 (colorless oil):** $[\alpha]^{23}_D$ +231.9 (*c* 0.207, $CHCl_3$); $^1$H NMR (600 MHz, $CDCl_3$) δ 1.16 (d, *J* = 7.5 Hz, 3H), 2.11−2.17 (m, 1H), 2.88 (dd, *J* = 13.4, 3.7 Hz, 1H), 2.93 (dd, *J* = 13.5, 6.6 Hz, 1H), 3.08 (s, 3H), 4.08−4.14 (m, 1H), 5.55 (dd, *J* = 10.0, 2.1 Hz, 1H), 5.62 (ddd, *J* = 9.9, 4.3, 2.9 Hz, 1H), 7.05−7.32 (m, 5H); $^{13}$C NMR (100 MHz, $CDCl_3$) δ 17.7, 33.1, 34.9, 39.3, 61.6, 123.5, 126.3, 127.8, 129.5, 129.9, 135.5, 171.4; HRMS (FAB) *m*/*z* calcd for $C_{14}H_{18}NO$ ($MH^+$), 216.1388; found, 216.1389. ***cis*-19 (colorless crystals):** mp 134−135 °C; $[\alpha]^{22}_D$ +198.8 (*c* 0.51, $CHCl_3$); $^1$H NMR (600 MHz, $CDCl_3$) δ 0.68 (d, *J* = 7.4 Hz, 3H), 2.78 (m, 1H), 2.91 (d, *J* = 5.1 Hz, 2H), 3.10 (s, 3H), 4.00−4.13 (m, 1H), 5.57 (ddd, *J* = 10.1, 3.8, 0.6 Hz, 1H), 5.64 (ddd, *J* = 10.1, 4.1, 0.9 Hz, 1H), 7.00−7.30 (m, 5H); $^{13}$C NMR (100 MHz, $CDCl_3$) δ 19.2, 33.1, 36.4, 40.1, 61.5, 123.2, 126.8, 128.2, 129.2, 129.9, 135.8, 171.7. Anal. Calcd for $C_{14}H_{17}NO$: C, 78.10; H, 7.96; N, 6.51. Found: C, 77.80; H, 7.96; N, 6.35.

**(3*S*,6*S*)-3,6-Dibenzyl-3,6-dihydro-1-methylpyridin-2-one (*trans*-20) and (3*R*,6*S*)-3,6-Dibenzyl-3,6-dihydro-1-methylpyridin-2-one (*cis*-20).** By the use of a procedure identical with that described for the preparation of **19** from **2**, organocopper-mediated reduction

(−78 °C, 20 min)−alkylation with BnBr (176 μL, 1.48 mmol, −78 °C, 2.5 h) of acetate **2** (48.2 mg, 0.185 mmol) gave the title compound *trans*-**20** (38.9 mg, 72.1% yield) and *cis*-**20** (4.8 mg, 8.9% yield). ***trans*-20 (colorless crystals):** mp 78−80 °C; $[\alpha]^{23}_D$ +231.8 (*c* 0.37, $CHCl_3$); $^1$H NMR (600 MHz, $CDCl_3$) δ 2.41 (m, 1H), 2.72 (dd, *J* = 13.7, 9.3 Hz, 1H), 2.87 (d, *J* = 5.27 Hz, 2H), 3.08 (s, 3H), 3.24 (d, *J* = 13.7, 4.4 Hz, 1H), 3.98−4.02 (m, 1H), 5.50 (dd, *J* = 10.3, 2.0 Hz, 1H), 5.57 (ddd, *J* = 10.1, 4.1, 2.7 Hz, 1H), 7.02−7.27 (m, 10H); $^{13}$C NMR (100 MHz, $CDCl_3$) δ 33.2, 37.5, 39.5, 41.4, 61.4, 124.5, 126.1, 126.7, 126.9, 128.1, 128.2, 129.3, 129.8, 135.8, 139.1, 170.5. Anal. Calcd for $C_{20}H_{21}NO$: C, 82.44; H, 7.26; N, 4.81. Found: C, 82.34; H, 7.30; N, 4.70. ***cis*-20 (colorless oil):** $[\alpha]^{23}_D$ −15.2 (*c* 0.19, $CHCl_3$); $^1$H NMR (600 MHz, $CDCl_3$) δ 1.98 (dd, *J* = 13.1, 9.3 Hz, 1H), 2.13 (dd, *J* = 13.4, 7.7 Hz, 1H), 2.71 (dd, *J* = 13.4, 3.7 Hz, 1H), 3.07 (s, 3H), 3.06−3.12 (m, 1H), 3.96−4.05 (m, 1H), 5.48 (dd, *J* = 10.5, 3.7 Hz, 1H), 5.51 (dd, *J* = 10.7, 3.6 Hz, 1H), 7.10−7.33 (m, 10H); $^{13}$C NMR (100 MHz, $CDCl_3$) δ 33.2, 39.5, 40.0, 43.3, 61.6, 124.5, 126.2, 126.3, 126.7, 128.1, 128.3, 129.5, 129.8, 136.2, 138.5, 170.1; HRMS (FAB) *m*/*z* calcd for $C_{20}H_{22}NO$ ($MH^+$), 292.1701; found, 292.1695.

**(3*S*,6*S*)-6-Benzyl-3,6-dihydro-1-methyl-3-(2-methylpropyl)pyridin-2-one (*trans*-21) and (3*R*,6*S*)-6-Benzyl-3,6-dihydro-1-methyl-3-(2-methylpropyl)pyridin-2-one (*cis*-21).** By the use of a procedure identical with that described for the preparation of **19** from **2**, organocopper-mediated reduction (−78 °C, 20 min)−alkylation with *i*-BuI (152 μL, 1.31 mmol, 0 °C, 2 h) of acetate **2** (43.3 mg, 0.166 mmol) gave the title compound *trans*-**21** (26.0 mg, 60.8% yield) and *cis*-**21** (5.1 mg, 11.9% yield). ***trans*-21 (colorless oil):** $[\alpha]^{24}_D$ +159.8 (*c* 1.46, $CHCl_3$); $^1$H NMR (600 MHz, $CDCl_3$) δ 0.78 (d, *J* = 6.5 Hz, 3H), 0.82 (d, *J* = 6.5 Hz, 3H), 1.33 (ddd, *J* = 13.8, 8.8, 5.5 Hz, 1H), 1.64 (m, 1H), 1.72 (ddd, *J* = 13.5, 8.8, 4.7 Hz, 1H), 2.07 (m, 1H), 2.91 (d, *J* = 5.2 Hz, 2H), 3.08 (s, 3H), 4.08−4.13 (m, 1H), 5.63−5.65 (m, 2H), 7.06−7.10 (m, 2H), 7.20−7.28 (m, 3H); $^{13}$C NMR (100 MHz, $CDCl_3$) δ 21.6, 23.1, 25.3, 33.3, 38.1, 39.5, 40.3, 61.4, 124.0, 126.7, 128.2, 129.9, 135.9, 171.8; HRMS (FAB) *m*/*z* calcd for $C_{17}H_{24}NO$ ($MH^+$), 258.1858; found, 258.1859. ***cis*-21 (colorless oil):** $[\alpha]^{23}_D$ +42.6 (*c* 0.26, $CHCl_3$); $^1$H NMR (600 MHz, $CDCl_3$) δ 0.32 (ddd, *J* = 13.2, 9.9, 5.3 Hz, 1H), 0.76 (d, *J* = 6.6 Hz, 3H), 0.81 (d, *J* = 6.6 Hz, 3H), 1.17 (ddd, *J* = 13.2, 9.2, 5.5 Hz, 1H), 1.49−1.56 (m, 1H), 2.73−2,79 (m, 1H), 2.91 (d, *J* = 5.2 Hz, 2H), 3.08 (s, 3H), 4.07−4.12 (m, 1H), 5.61 (ddd, *J* = 10.2, 4.0, 0.5 Hz, 1H), 5.71 (ddd, *J* = 10.2, 4.4, 0.9 Hz, 1H), 7.04−7.08 (m, 2H), 7.19−7.29 (m, 3H); $^{13}$C NMR (100 MHz, $CDCl_3$) δ 21.2, 23.1, 24.9, 33.1, 39.4, 40.1, 43.5, 61.6, 123.7, 126.8, 127.6, 128.2, 130.0, 135.8, 171.7; HRMS (FAB) *m*/*z* calcd for $C_{17}H_{24}NO$ ($MH^+$), 258.1858; found, 258.1855.

**(3*S*,6*S*)-6-Benzyl-3,6-dihydro-1-methyl-3-(methylethyl)pyridin-2-one (*trans*-22).** By the use of a procedure identical with that described for the preparation of **19** from **2**, organocopper-mediated reduction (−78 °C, 20 min)−alkylation with *i*-PrI (143 μL, 1.44 mmol, 0 °C, 3 h) of acetate **2** (46.7 mg, 0.180 mmol) gave the title compound *trans*-**22** (26 mg, 55,9% yield) as a colorless oil: $[\alpha]^{24}_D$ +1.91 (*c* 0.52, $CHCl_3$); $^1$H NMR (600 MHz, $CDCl_3$) δ 0.68 (d, *J* = 6.8 Hz, 3H), 0.89 (d, *J* = 7.1 Hz, 3H), 2.11−2.15 (m, 1H), 2.47−2.54 (m, 1H), 2.88 (dd, *J* = 13.4, 6.9 Hz, 1H), 2.93 (dd, *J* = 13.4, 3.6 Hz, 1H), 3.10 (s, 3H), 4.10−4.15 (m, 1H), 5.61 (ddd, *J* = 10.3, 1.5, 1.0 Hz, 1H), 5.71 (ddd, *J* = 10.3, 3.5, 3.0 Hz, 1H), 7.07−7.28 (m, 5H); $^{13}$C NMR (100 MHz, $CDCl_3$) δ 17.6, 19.9, 29.1, 33.1, 39.6, 45.6, 61.0, 123.9, 125.3, 126.3, 127.8, 129.5, 135.6, 170.4; HRMS (FAB) *m*/*z* calcd for $C_{16}H_{22}NO$ ($MH^+$), 244.1701; found, 244.1694.

**(6*S*)-6-Benzyl-3-deuterio-3,6-dihydro-1-methylpyridin-2-one (23).** By the use of a procedure identical with that described for the preparation of **4** from **2**, after reduction of acetate **2** (25.5 mg, 0.098 mmol) with $Me_3CuLi_2$·LiI·3LiBr at −78 °C for 20 min, treatment of the mixture with $D_2O$ (3 mL) gave the title compound **23** (16.0 mg, 80.7% yield) as a diastereomixture. The ratio of diastereomers was determined by $^1$H NMR experiments (trans/cis = 15:85). **Compound 23:** $^1$H NMR (600 MHz, $CDCl_3$) δ 2.12 (m, 0.15H), 2.65 (m, 0.85H), 2.88 (dd, *J* = 13.5, 3.6 Hz, 1H), 2.93 (dd, *J* = 13.5, 6.6 Hz, 1H), 3.10 (s, 3H), 4.10−4.13 (m, 1H), 5.64−5.69 (m, 2H), 7.03−7.09 (m, 2H), 7.20−7.28 (m, 3H); HRMS (FAB) *m*/*z* calcd for $C_{13}H_{15}DNO$ ($MH^+$), 203.1294; found, 203.1296.

**(3*S*,6*S*)-6-Benzyl-3,6-dihydro-1-(2,4-dimethoxy)benzyl-3-methylpyridin-2-one (*trans*-24) and (3*R*,6*S*)-6-Benzyl-3,6-dihydro-1-(2,4-dimethoxy)benzyl-3-methylpyridin-2-one (*cis*-24).** By the use of a procedure identical with that described for the preparation of **19** from **2**, organocopper-mediated reduction (−78 °C, 20 min)−alkylation with MeI (63.4 μL, 1.02 mmol, 0 °C, 3 h) of acetate **12** (50.4 mg, 0.127 mmol) gave the title compound *trans*-**24** (4.6 mg, 10.3% yield) and *cis*-**24** (28.8 mg, 64.5% yield). ***trans*-24 (colorless oil):** $[\alpha]^{20}_D$ −15.6 (*c* 0.26, $CHCl_3$); $^1$H NMR (400 MHz, $CDCl_3$) δ 1.20 (d, *J* = 7.5 Hz, 3H), 2.19−2.28 (m, 1H), 2.86−2.97 (m, 2H), 3.79 (s, 3H), 3.84 (s, 3H), 4.00−4.13 (m, 1H), 4.27 (d, *J* = 15.1 Hz, 1H), 5.32 (d, *J* = 15.1 Hz, 1H), 5.52−5.61 (m, 2H), 6.39−6.52 (m, 2H), 7.03−7.33 (m, 6H); $^{13}$C NMR (100 MHz, $CDCl_3$) δ 17.9, 35.2, 39.3, 40.8, 55.4, 58.0, 98.3, 104.3, 117.8, 124.6, 126.5, 128.1, 129.9, 130.2, 136.4, 158.5, 160.1, 172.1; HRMS (FAB) *m*/*z* calcd for $C_{22}H_{26}NO_3$ ($MH^+$), 352.1913; found, 352.1906. ***cis*-24:** $[\alpha]^{21}_D$ −1.45 (*c* 1.37, $CHCl_3$); $^1$H NMR (400 MHz, $CDCl_3$) δ 0.79 (d, *J* = 7.5 Hz, 3H), 2.80−2.90 (m, 1H), 2.91 (dd, *J* = 13.1, 7.3 Hz, 1H), 2.97 (dd, *J* = 13.4, 3.9 Hz, 1H), 3.79 (s, 3H), 3.84 (s, 3H), 4.06−4.16 (m, 1H), 4.30 (d, *J* = 14.9 Hz, 1H), 5.35 (d, *J* = 14.9 Hz, 1H), 5.51 (dd, *J* = 10.0, 4.1 Hz, 1H), 5.63 (dd, *J* = 10.0, 4.1 Hz, 1H), 6.41−6.50 (m, 2H), 7.02−7.10 (m, 2H), 7.15−7.30 (m, 4H); $^{13}$C NMR (100 MHz, $CDCl_3$) δ 19.3, 29.7, 36.9, 40.4, 55.4, 57.8, 98.3, 104.4, 117.7, 123.9, 126.6, 128.1, 128.8, 130.0, 130.6, 136.4, 158.6, 160.2, 172.1; HRMS (FAB) *m*/*z* calcd for $C_{22}H_{26}NO_3$ ($MH^+$), 352.1913; found, 352.1919.

**(3*S*,6*S*)-3,6-Dibenzyl-3,6-dihydro-1-(2,4-dimethoxy)benzylpyridin-2-one (*trans*-25) and (3*R*,6*S*)-3,6-Dibenzyl-3,6-dihydro-1-(2,4-dimethoxy)benzylpyridin-2-one (*cis*-25).** By the use of a procedure identical with that described for the preparation of **19** from **2**, organocopper-mediated reduction (−78 °C, 20 min)−alkylation with BnBr (120 μL, 1.01 mmol, −78 °C, 3 h) of acetate **12** (50.4 mg, 0.127 mmol) gave the title compound *trans*-**25** (29.2 mg, 53.7% yield) and *cis*-**25** (10.3 mg, 18.9% yield). Compound *cis*-**25** was identical to the compound characterized by Guibé et al. (ref 8b). ***trans*-25 (colorless oil):** $[\alpha]^{23}_D$ +77.9 (*c* 0.68, $CHCl_3$); $^1$H NMR (400 MHz, $CDCl_3$) δ 2.42−2.50 (m, 1H), 2.87 (dd, *J* = 13.6, 8.5 Hz, 1H), 2.87−3.00 (m, 2H), 3.18 (dd, *J* = 13.6, 4.4 Hz, 1H), 3.79 (s, 3H), 3.81 (s, 3H), 3.95−4.05 (m, 1H), 4.27 (d, *J* = 14.8 Hz, 1H), 5.33 (d, *J* = 15.1 Hz, 1H), 5.49−5.60 (m, 2H), 6.37 (dd, *J* = 8.6, 2.4 Hz, 1H), 6.44 (d, *J* = 2.2 Hz, 1H), 6.88 (d, *J* = 8.3 Hz, 1H), 7.00−7.12 (m, 4H), 7.13−7.27 (m, 6H); $^{13}$C NMR (100 MHz, $CDCl_3$) δ 37.3, 39.3, 40.8, 41.5, 55.3, 57.8, 98.2, 104.4, 117.5, 125.2, 125.9, 126.5, 127.2, 128.0, 128.1, 129.5, 129.8, 129.9, 136.2, 139.2, 158.4, 160.0, 170.5; HRMS (FAB) *m*/*z* calcd for $C_{28}H_{30}NO_3$ ($MH^+$), 428.2226; found, 428.2219.

**(6*R*)-6-Benzyl-3,6-dihydro-5-fluoro-1-methylpyridin-2-one (26).** By the use of a procedure identical with that described for the preparation of **4** from **2**, organocopper-mediated reduction of lactam **18** (23.2 mg, 0.0978 mmol) with $Me_3CuLi_2$·LiI·3LiBr (2 equiv) at −78 °C for 30 min gave the title compound **26** (16.5 mg, 76.8% yield) as a colorless oil: $[\alpha]^{24}_D$ −13.3 (*c* 0.08, $CHCl_3$); $^1$H NMR (400 MHz, $CDCl_3$) δ 1.87 (ddt, *J* = 20.9, 4.8, 3.4 Hz, 1H), 2.57 (dtd, *J* = 20.9, 5.4, 2.0 Hz, 1H), 2.95 (ddd, *J* = 14.1, 3.2, 1.3 Hz, 1H), 3.09 (s, 3H), 3.14 (dd, *J* = 14.1, 4.2 Hz, 1H), 4.14−4.24 (m, 1H), 5.13 (ddd, *J* = 13.6, 5.1, 2.4 Hz, 1H), 7.04−7.10 (m, 2H), 7.23−7.31 (m, 3H); $^{13}$C NMR (100 MHz, $CDCl_3$) δ 29.1 (d, *J* = 8.3 Hz), 33.0, 35.8, 59.8 (d, *J* = 34.7 Hz), 99.9 (d, *J* = 15.7 Hz), 127.2, 128.2, 130.0, 134.0, 152.8 (d, *J* = 253 Hz), 167.9; $^{19}$F NMR (376 MHz, $CDCl_3$) δ −118.2 (dd, *J* = 14.4, 6.2 Hz, 1F); HRMS (FAB) *m*/*z* calcd for $C_{13}H_{15}FNO$ ($MH^+$), 220.1138; found, 220.1135.

**(3*R*,6*R*)-6-Benzyl-3,6-dihydro-5-fluoro-1,3-dimethylpyridin-2-one (*trans*-27) and (3*S*,6*R*)-6-Benzyl-3,6-dihydro-5-fluoro-1,3-dimethylpyridin-2-one (*cis*-27).** By the use of a procedure identical with that described for the preparation of **19** from **2**, organocopper-

mediated reduction (−78 °C, 30 min)−alkylation with MeI (62.2 μL, 1.44 mmol, 0 °C, 2 h) of the lactam **18** (46.7 mg, 0.180 mmol) in $Et_2O$ gave the title compound *trans*-**27** (2.7 mg, 9.2% yield) and *cis*-**27** (15.0 mg, 51.1% yield). ***trans*-27 (colorless oil):** $[\alpha]^{25}_D$ +44.4 (*c* 0.05, $CHCl_3$); $^1$H NMR (400 MHz, $CDCl_3$) δ 1.10 (d, *J* = 7.6 Hz, 3H), 1.87−1.92 (m, 1H), 2.94 (ddd, *J* = 14.2, 2.9, 0.9 Hz, 1H), 3.08 (s, 3H), 3.15 (dd, *J* = 14.2, 4.2 Hz, 1H), 4.19 (m, 1H), 5.05 (dd, *J* = 14.2, 2.4 Hz, 1H), 7.02−7.10 (m, 2H), 7.22−7.30 (m, 3H); $^{13}$C NMR (100 MHz, $CDCl_3$) δ 18.7, 32.9 (d, *J* = 8.3 Hz), 33.1, 35.7 (d, *J* = 2.5 Hz), 60.2 (d, *J* = 34.8 Hz), 106.2 (d, *J* = 12.4 Hz), 127.2, 128.3, 130.0, 134.2, 152.4 (d, *J* = 254 Hz), 171.2; $^{19}$F NMR (376 MHz, $CDCl_3$) δ −119.5 (d, *J* = 14.4 Hz, 1F); HRMS (FAB) *m*/*z* calcd for $C_{14}H_{17}FNO$ ($MH^+$), 234.1294; found, 234.1291. ***cis*-27:** $[\alpha]^{25}_D$ +21.7 (*c* 0.05, $CHCl_3$); $^1$H NMR (400 MHz, $CDCl_3$) δ 0.35 (d, *J* = 7.6 Hz, 3H), 2.75−2.81 (m, 1H), 2.94 (ddd, *J* = 14.4, 4.4, 2.0 Hz, 1H), 3.10 (s, 3H), 3.12 (dd, *J* = 14.4, 4.1 Hz, 1H), 4.20 (dt, *J* = 6.6, 3.2 Hz, 1H), 5.16 (dd, *J* = 14.6, 4.4 Hz, 1H), 7.02−7.08 (m, 2H), 7.19−7.33 (m, 3H); $^{13}$C NMR (100 MHz, $CDCl_3$) δ 18.9 (d, *J* = 1.6 Hz), 33.1, 34.7 (d, *J* = 8.3 Hz), 35.6 (d, *J* = 2.5 Hz), 59.8 (d, *J* = 34.8 Hz), 105.7 (d, *J* = 12.4 Hz), 127.2, 128.3, 130.2, 134.2, 152.0 (d, *J* = 252 Hz), 170.9; $^{19}$F NMR (376 MHz, $CDCl_3$) δ −120.4 (d, *J* = 14.5 Hz, 1F); HRMS (FAB) *m*/*z* calcd for $C_{14}H_{17}FNO$ ($MH^+$), 234.1294; found, 234.1299.

**(3*R*,6*R*)-3,6-Dibenzyl-3,6-dihydro-5-fluoro-1-methylpyridin-2-one (28).** By the use of a procedure identical with that described for the preparation of **19** from **2**, organocopper-mediated reduction (−78 °C, 30 min)−alkylation with BnBr (191 μL, 1.61 mmol, −78 °C, 2 h) of lactam **18** (47.8 mg, 0.201 mmol) gave the title compound **28** (38.1 mg, 61.3% yield) as a colorless oil: $[\alpha]^{26}_D$ +15.2 (*c* 0.07, $CHCl_3$); $^1$H NMR (400 MHz, $CDCl_3$) δ 2.12−2.16 (m, 1H), 2.61 (dd, *J* = 13.7, 9.5 Hz, 1H), 2.89 (ddd, *J* = 13.9, 2.9, 1.0 Hz, 1H), 3.07 (s, 3H), 3.11 (dd, *J* = 14.1, 4.2 Hz, 1H), 3.15 (ddd, *J* = 13.7, 4.1, 1.4 Hz, 1H), 4.09 (dt, *J* = 7.1, 4.2 Hz, 1H), 4.98 (dd, *J* = 14.6, 2.7 Hz, 1H), 6.98−7.06 (m, 4H), 7.12−7.28 (m, 6H); $^{13}$C NMR (100 MHz, $CDCl_3$) δ 33.2, 35.7 (d, *J* = 3.3 Hz), 38.3, 39.6 (d, *J* = 7.4 Hz), 59.8 (d, *J* = 34.8 Hz), 103.4 (d, *J* = 14.1 Hz), 126.3, 127.1, 128.3, 129.2, 129.9, 134.1, 138.4, 152.7 (d, *J* = 255 Hz), 169.7; $^{19}$F NMR (376 MHz, $CDCl_3$) δ −117.7 (d, *J* = 14.5 Hz, 1F); HRMS (FAB) *m*/*z* calcd for $C_{20}H_{21}FNO$ ($MH^+$), 310.1607; found, 310.1607.

**General Procedure for the Alkylation of β,γ-Unsaturated-δ-Lactam with LDA/Alkyl Halide System.** To a solition of $(i\text{-Pr})_2NH$ (45.3 μL, 0.322 mmol) in THF (1.25 mL) was added *n*-BuLi in hexane (1.6 M, 170 μL, 0.273 mmol) at −78 °C under argon. After stirring for 20 min at −78 °C, lactam **4** (50 mg, 0.248 mmol) in THF (0.75 mL) was added dropwise to the above mixture and stirred for 30 min at −78 °C. To the above mixture, MeI (30.9 μL, 0.496 mmol) was added, and the mixture was stirred at −78 °C for 2 h, then at 0 °C for 1 h. The reaction was quenched with saturated aq $NH_4Cl$, followed by the usual workup, to yield *trans*-**19** (8.4 mg, 15.7% yield) and *cis*-**19** (35.6% yield).

**(6*S*)-1-Benzyl-3,6-dihydro-3,6-dimethylpyridine-2-one (42).** By use of a procedure identical with that described for the preparation of **19** from **2**, organocopper-mediated reduction (−78 °C, 20 min)−alkylation with MeI (191 μL, 1.61 mmol, −78 °C, 2 h then 0 °C, 1 h) of lactam **41** (47.9 mg, 0.184 mmol) gave the title compound **42** (21.4 mg, 54.0% combined yield, trans/cis = 13:87). The diastereo ratio was determined by $^1$H NMR. Each isomer was separated by repetitious flash chromatography and characterized. **(3*R*,6*S*)-1-Benzyl-3,6-dihydro-3,6-dimethylpyridine-2-one (*cis*-42).** A colorless oil: $[\alpha]^{26}_D$ −103.3 (*c* 0.41, $CHCl_3$); $^1$H NMR (400 MHz, $CDCl_3$) δ 1.26 (d, *J* = 6.6 Hz, 3H), 1.36 (d, *J* = 7.3 Hz, 3H), 3.00−3.12 (m, 1H), 3.78−3.90 (m, 1H), 4.06 (d, *J* = 15.4 Hz, 1H), 5.40 (d, *J* = 15.1 Hz, 1H), 5.63 (dd, *J* = 10.0, 3.6 Hz, 1H), 5.74 (dd, *J* = 10.0, 4.4, 0.9 Hz, 1H), 7.20−7.35 (m, 5H); $^{13}$C NMR (100 MHz, $CDCl_3$) δ 20.8, 21.5, 36.9, 46.6, 52.6, 126.4, 127.2, 127.7, 128.5, 137.2, 171.8; HRMS (FAB) *m*/*z* calcd for $C_{14}H_{18}NO$ ($MH^+$), 216.1388; found, 216.1383. **(3*S*,6*S*)-1-Benzyl-3,6-dihydro-3,6-dimethylpyridine-2-one (*trans*-42).** A colorless oil: $[\alpha]^{19}_D$ −58.9 (*c* 0.21, $CHCl_3$); $^1$H NMR (400 MHz, $CDCl_3$) δ 1.24 (d, *J* = 6.6 Hz, 3H), 1.39 (d, *J* = 7.6 Hz, 3H), 2.98−3.10 (m, 1H), 3.80−3.92 (m, 2H), 4.05 (d, *J* = 15.4 Hz, 1H), 5.41 (d, *J* = 15.4 Hz, 1H), 5.62−5.69 (m, 2H), 7.19−7.40 (m, 5H); $^{13}$C NMR (100 MHz, $CDCl_3$) δ 18.5, 20.2, 35.3, 46.5, 52.8, 126.7, 127.2, 127.5, 128.0, 128.5, 137.4, 171.5; HRMS (FAB) *m*/*z* calcd for $C_{14}H_{18}NO$ ($MH^+$), 216.1388; found, 216.1396.

**DFT Calculations.** DFT calculations were carried out on a SGI Origin 3800 system within the Gaussian 98 package. All geometry optimizations were performed by the B3LYP/6-31G(d) method. It was confirmed that all optimized structures have no imaginary frequencies by the frequency analysis at the B3LYP/6-31G(d) level. It was also confirmed that optimization of complex **34** at the B3LYP/6-31G(d,p) level gave a similar structure as in the case of the use of B3LYP/6-31G(d) method.

**Acknowledgment.** We thank Dr. Motoo Shiro, Rigaku International Corporation, Japan, and Dr. Terrence R. Burke Jr., NCI, NIH, USA, for X-ray analysis and for proofreading this manuscript, respectively. Computation time was provided by the Supercomputer Laboratory, Institute for Chemical Research, Kyoto University. This research was supported in part by 21st Century COE Program "Knowledge Information Infrastructure for Genome Science" a Grant-in-Aid for Scientific Research from the Ministry of Education, Culture, Sports, Science and Technology, Japan, and the Japan Health Science Foundation. A.N. is grateful for Research Fellowships of the JSPS for Young Scientists.

**Supporting Information Available:** Synthesis of acetate **14** and the alanine-derived substrate **41**. Structure determination of mimetics **42**. CIF files of *cis*-**19** and *trans*-**20**. Stereoviews, optimized coordinates, and energies of oxa-π-allyl complexes. This material is available free of charge via the Internet at http://pubs.acs.org.

JO060202Z