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Stereoselective Synthesis of 3,6-Disubstituted-3,6-dihydropyridin-2-ones as Potential Diketopiperazine Mimetics Using Organocopper-Mediated *anti*-S_N2' Reactions and Their Use in the Preparation of Low-Molecule CXCR4 Antagonists

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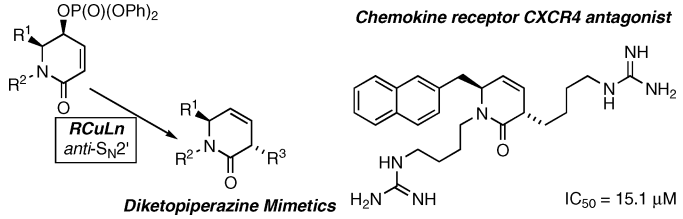

Organocopper-mediated *anti*-S_N2' reactions of γ-phosphoryloxy-α,β-unsaturated-δ-lactams were used to prepare highly functionalized diketopiperazine mimetics. The substrate phosphates **24**, **32**, and **47** were prepared from α-amino acid-derived allylic alcohols **10** by a sequence of reactions that included ring-closing metathesis. In the reactions of phosphates with organocopper reagents, the addition of LiCl dramatically improved *anti*-S_N2' selectivity, indicating that an organocopper cluster containing lithium chloride plays an important role in the determination of regioselectivity. This reaction system was applied to the preparation of novel low molecular weight CXCR4-chemokine receptor antagonists.

Introduction

The replacement of a peptide bond in biologically active peptides with a non-hydrolyzable unit is a promising approach for peptide-lead drug discovery. (*E*)-Alkene dipeptide isosteres (EADIs) represent amide-bond mimetics that possess excellent structural homology and resistance to proteases.[1] Over the past decade, we have engaged in the development of efficient stereoselective methodology for the preparation of EADIs utilizing organocopper-mediated transformations along with their application to biologically active peptides.[2,3] Piperazine-2,5-dione (diketopiperazine: DKP) derivatives **1** represent the smallest cyclic peptides consisting of two α-amino acid residues. This well-organized structure is widely seen in compounds of biological or medicinal interest. Therefore, it seemed logical that the DKP nucleus could serve as a drug template with appropriately arrayed pharmacophores (Figure 1).[4] On the basis of our studies on EADIs, we envisioned that the replacement of a DKP *cis*-amide bond with structurally similar (*Z*)-alkene units could provide DKP mimetics **2** as novel starting points for creating drug-like structures (Figure 2).

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† Kyoto University.
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(1) 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.

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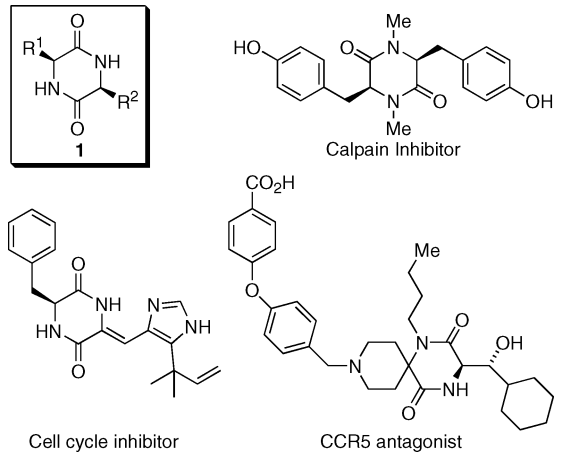


FIGURE 1. General structure of 2,5-diketopiperazine and biologically active derivatives.

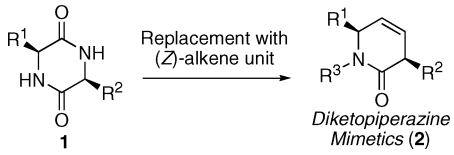
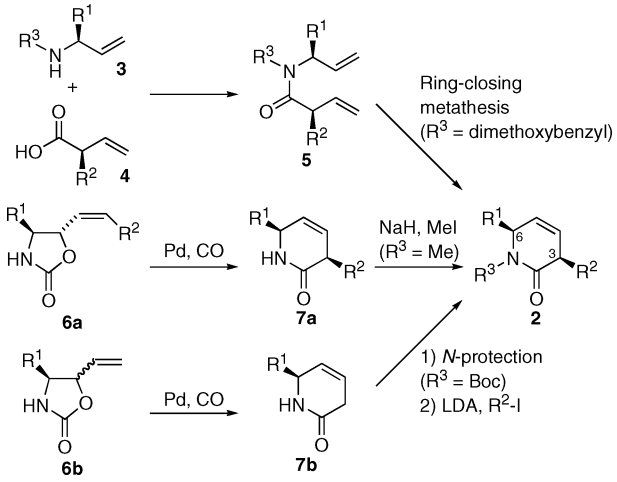


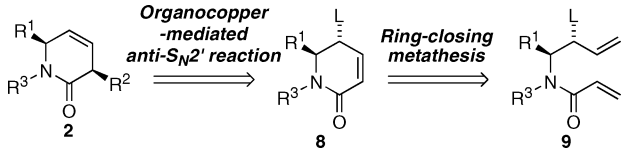
FIGURE 2. Design of diketopiperazine mimetics.

However, to our knowledge, there have been only a few reports in which 3,6-disubstituted-3,6-dihydropyridin-2-ones (DKP mimetics **2**) having side-chain functionalities have been synthesized in stereoselective fashions. These include synthetic protocols that employ the ring-closing metathesis or palladium-catalyzed carbonylation as key reactions (Scheme 1). Ring-closing metathesis of bisolefinic amide **5** with Grubbs' ruthenium alkylidene complexes yielded the desired DKP mimetics **2**, where the stereochemical outcome depends on the stereochemistry of the requisite metathesis substrate **5**, which was obtained by coupling between enantiomerically pure 1-substituted prop-2-enylamines **3** and 2-substituted but-3-enoic acids **4**.[5] Alternatively, Knight et al. have reported the enantioselective synthesis of 3,6-dihydro-1*H*-pyridin-2-ones **7** by Pd-catalyzed decarboxylative carbonylation of 5-vinyloxazolidin-2-ones **6**,

SCHEME 1. Previous Synthetic Routes for the Preparation of Diketopiperazine Mimetics



SCHEME 2. Retrosynthetic Analysis of Diketopiperazine Mimetics Prepared by an Organocopper-Mediated *anti*-S_N2' Reaction[a]



[a] L = leaving group.

which were synthesized from the corresponding α-amino aldehydes.[6] The stereochemistry at the 6-position was derived from that of the precursor α-amino aldehyde. The stereoselective introduction of substituents at the 3-position was achieved in two ways. One way involves the Pd-catalyzed reaction of 5-(alk-1-enyl)oxazolidinones **6a** to provide 3,6-disubstituted analogues **7a**;[6a,b] however, this requires long reaction times, and the product yields were rather low. To circumvent these problems, a two-step protocol consisting of the Pd-catalyzed synthesis of the 6-substituted pyridinones **7b** followed by an enolate alkylation (**7b** to **2**) was developed.[6c] In this methodology, the nature of both the electrophiles incoming to the enolate and the substituent on the nitrogen affect the diastereoselection at the 3-position.

Our approach for the stereoselective preparation of DKP mimetics **2** is shown in Scheme 2. We envisioned that the γ-activated-α,β-unsaturated lactams **8** could be converted into the corresponding dihydropyridinone derivatives **2** by an organocopper-mediated *anti*-S_N2' reaction. A Ru-catalyzed olefin metathesis[7] reaction is suitable for the synthesis of key substrates

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(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.

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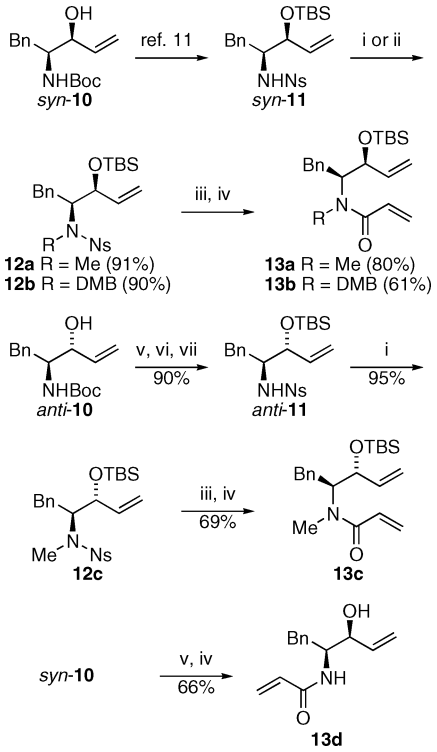
8, in terms of compatibility with various functional groups.[8] The amide nitrogen should be appropriately protected by a group such as Me or dimethoxybenzyl (DMB) to raise the proportion of conformers with *cis*-amide geometry, which is necessary for facile olefin metathesis.[9] We present herein the efficient conversion of γ-oxygenated-α,β-unsaturated-δ-lactams **8** to DKP mimetics **2** using organocopper-mediated *anti*-S_N2' reactions. This novel methodology was applied to the synthesis of low molecular weight CXCR4 antagonists on the basis of the DKP mimetic structure.[10]

Results and Discussion

Our synthesis started from the known *N*-Ns-*O*-TBS protected *syn*-1,2-amino alcohol *syn*-**11**[11] (Ns: 2-nitrobenzenesulfonyl; TBS: *tert*-butyldimethylsilyl) derived from allylic alcohol *syn*-**10**[12] (Scheme 3). The silyl ether *syn*-**11** was subjected to *N*-modification either with MeI, K_2CO_3, or with DMB−OH, Ph_3P, and DEAD (Mitsunobu conditions) to afford *N*-Me **12a** and *N*-DMB **12b** derivatives, respectively.[13] After removal of the Ns group of **12** by treatment with thiolate anion under basic conditions, the resulting secondary amines were acylated with acryloyl chloride to yield the metathesis substrates **13**. The corresponding diastereomer **13c** was synthesized from *N*-Boc protected *anti*-1,2-amino alcohol *anti*-**10**[12] by a sequence of reactions identical to those used for the preparation of **13a**. Nonalkylated derivative **13d** was also synthesized.

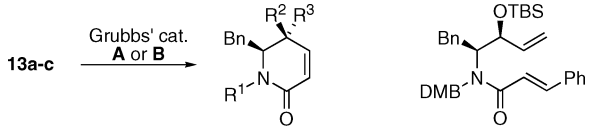
The attempted olefin metathesis of **13a**−**c** with Grubbs' Ru catalyst **A**[14] resulted in low cyclization yields (Table 1, entries 1−4). The use of the second-generation catalyst **B**[15] improved the yields (entries 5−7), although long reaction times under reflux were required. Ring-closing metathesis of **13** with catalyst **B** gave the benzylidene derivative **15** as a side product. This prompted us to postulate that the low reactivity of the substrates may be partly attributed to the presence of the bulky TBS group. Therefore, TBS-deprotected derivatives **16a**−**c**, obtained in high yields by the treatment of **13a**−**c** with TBAF (88−99%), were subjected to the metathesis reaction with catalyst **A** or **B** (Table 2). Although the reaction with catalyst **A** did not afford satisfactory results (entries 1 and 2), ring-closure with catalyst **B** proceeded smoothly at room temperature to yield the desired cyclized compounds **17a**−**c** in good yields (entries 3−6). Even for substrate **13d**, which lacked an *N*-alkyl substituent, the catalyst **B** afforded the cyclized product **17d** in a moderate yield (entry 7).

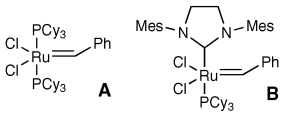
SCHEME 3. Synthesis of Requisite Substrates for Ring-Closing Metathesis[a]



[a] Reagents and conditions: (i) MeI, K_2CO_3, DMF; (ii) DMB-OH, PPh_3, DEAD, THF; (iii) $HSCH_2CO_2H$, LiOH, DMF; (iv) CH_2═$CHCOCl$, Et_3N, CH_2Cl_2; (v) 4 M HCl in dioxane; (vi) Ns-Cl, 2,4,6-collidine, $CHCl_3$; (vii) TBSOTf, 2,6-lutidine, CH_2Cl_2.

TABLE 1. Ring-Closing Metathesis of *O*-TBS-Protected Acrylamide Derivatives





entry	substrate	cat. (equiv)	conditions[a]	product[b,c] (yield, %)
1	**13a**	**A** (0.6)	rt, 48 h	**14a** (trace)
2	**13a**	**A** (0.6)	reflux, 36 h	**14a** (37)
3	**13b**	**A** (0.1)	reflux, 36 h	**14b** (10)
4	**13c**	**A** (0.6)	reflux, 36 h	**14c** (30)
5	**13a**	**B** (0.6)	rt, 36 h	**14a** (57)
6	**13a**	**B** (0.6)	reflux, 48 h	**14a** (61)
7	**13b**	**B** (0.6)	reflux, 36 h	**14b** (29)

[a] CH_2Cl_2 was used as solvent. [b] Isolated yield. [c] Starting materials were recovered, except for entry 6.

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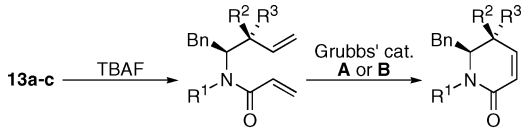
TABLE 2. Ring-Closing Metathesis of Acrylamides Containing Allylic Alcohol Moieties

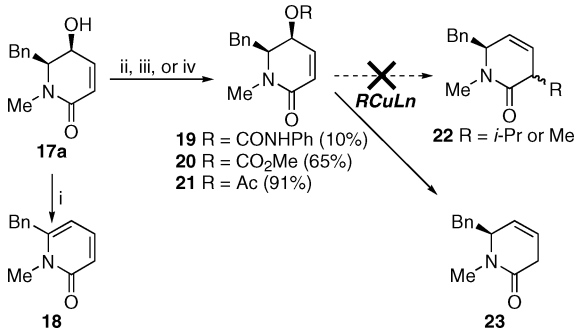


a-series (R^1 = Me; R^2 = OH; R^3 = H)
b-series (R^1 = DMB; R^2 = OH; R^3 = H)
c-series (R^1 = Me; R^2 = H; R^3 = OH)
d-series (R^1 = H; R^2 = OH; R^3 = H)

entry	substrate	cat. (equiv)	conditions[a]	product[b] (yield, %)
1	**16a**	**A** (0.15)	rt, 12 h	**17a** (trace)[c]
2	**16b**	**A** (0.15)	reflux, 12 h	**17b** (31)[c]
3	**16a**	**B** (0.15)	rt, 12 h	**17a** (74)
4	**16a**	**B** (0.05)	rt, 6 h	**17a** (84)
5	**16b**	**B** (0.15)	rt, 12 h	**17b** (74)
6	**16c**	**B** (0.15)	rt, 12 h	**17c** (84)
7	**13d**	**B** (0.15)	rt, 12 h	**17d** (53)

[a] CH_2Cl_2 was used as solvent. [b] Isolated yield. [c] Starting materials were recovered.

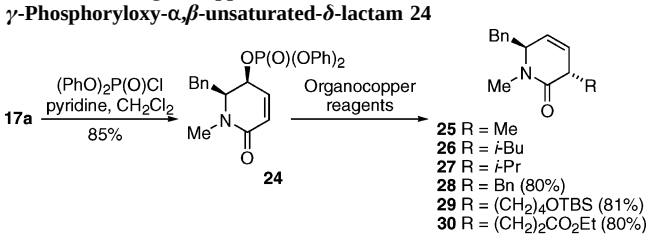
SCHEME 4. Attempted Conversion of 17a to γ-Activated Derivatives Followed by Organocopper-Mediated Reactions[a]

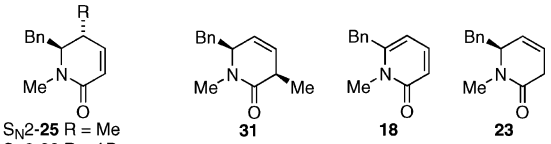


[a] Reagents and conditions: (i) MsCl, pyridine, CH_2Cl_2; (ii) $ClCO_2Me$, DMAP, pyridine, CH_2Cl_2; (iii) PhNCO, $BF_3{\cdot}Et_2O$, Et_2O; (iv) Ac_2O, DMAP, pyridine, $CHCl_3$. RCuLn: see text.

Next, we examined the activation of the γ-hydroxyl group of **17a** (Scheme 4). Generally, the use of γ-mesyloxy groups is suitable for the organocopper-mediated reaction of acyclic (*E*)-α,β-enoates to prepare EADIs in satisfactory yield.[2] However, the reaction of **17a** with Ms-Cl-pyridine resulted in the formation of the pyridinone derivative **18**. Thus, we examined alternative substrates having a less electron-withdrawing *O*-activating group, including carbonate,[16] carbamate,[17] and acetate[18] derivatives. These compounds were obtained in low to excellent yields (carbamate **19**, 10%; carbonate **20**, 65%; acetate **21**, 91%). However, attempted reactions of these compounds with organocopper reagents [*i*-PrCu(CN)MgCl·BF_3·2LiCl or *i*-Pr_2Cu-(CN)$(MgCl)_2$·BF_3·2LiCl][2e] for the preparation of S_N2' alkylation product **22** led to the recovery of starting materials along with the formation of the undesired reduced product **23**. The treatment of the easily obtainable acetate **21** with Gilman-type (Me_2CuLi_2·LiI·2LiBr) and "higher-order" (Me_3CuLi_2·LiI·3LiBr) cuprate gave the reduction product **23** in 42 and 82% yields, respectively, without the formation of the desired *anti*-S_N2' product. The use of "lower-order" organocopper reagent (MeCu·LiI·LiBr) resulted in 86% recovery of the starting material.

TABLE 3. Organocopper-mediated Reactions of γ-Phosphoryloxy-α,β-unsaturated-δ-lactam 24





entry	organocopper reagent[a,b,c]	product(s) (isolated yield, %)
1	Me_3CuLi_2·LiI·3LiBr	**25** (35), S_N2-**25** (10), **31** (3), **23** (23)
2	Me_2CuLi·LiI·2LiBr	**25** (67), S_N2-**25** (8), **31** (5), **23** (5)
3	MeCu·LiI·LiBr	**25** (83)
4	MeCuI·MgCl	**25** (24), S_N2-**25** (40)
5	MeCuI·MgCl·2LiCl	**25** (93)
6	MeCu(CN)·MgCl·2LiCl	**25** (77), S_N2-**25** (trace)
7	MeCu(CN)·MgCl·2LiCl·BF_3	**25** (55), S_N2-**25** (7)
8	$Me_2Cu(CN){\cdot}(MgCl)_2{\cdot}2LiCl{\cdot}BF_3$	S_N2-**25** (11), **23** (17)
9	*i*-BuCu·2LiI[d]	**26** (63), S_N2-**26** (13)
10	*i*-BuCu·2LiI·2LiCl[d]	**26** (82)
11	*i*-PrCuI·MgCl·2LiCl[e]	**27** (trace), S_N2-**27** (trace), **18** (62)
12	*i*-PrCu(CN)·MgCl·2LiCl	**27** (84), S_N2-**27** (8)
13	*i*-PrCu(CN)·MgCl·2LiCl·BF_3	**27** (59), S_N2-**27** (12)
14	*i*-PrCu(CN)·MgCl·2LiCl·$5BF_3$	**27** (36), S_N2-**27** (45)

[a] Two equivalents of reagents were used, except for entry 8 (4 equiv). [b] THF or a mixed solvent consisting of THF and Et_2O (or Et_2O−*n*-pentane) was used. [c] Reactions were carried out at −78 °C for 20 min, except for entry 11. [d] Alkyllithium for the preparation of the organocopper reagent was obtained from the reaction of the corresponding alkyl iodide and a pentane solution of *tert*-butyllithium (See the Supporting Information). [e] Reaction at −78 °C for 20 min then at 0 °C for 40 min.

Because allylic phosphates have also been documented to undergo highly stereoselective *anti*-S_N2' reactions with organocopper reagents,[19] we next examined the feasibility of using γ-phosphoryloxy-α,β-unsaturated-δ-lactams for the preparation of disubstituted DKP mimetics (Table 3). The reaction of **17a** with diphenylphosphoryl chloride in the presence of pyridine proceeded smoothly to give the phosphate derivative **24** in 85% yield as an activated compound, which was stable below 4 °C. Upon standing at room temperature, the phosphates were gradually converted to the pyridinone derivative **18**.

First, the reaction of phosphate **24** with MeLi·LiBr complex-derived organocopper-reagents was investigated. Contrary to the finding that the reaction of acetate **21** with MeLi·LiBr-derived reagents did not afford any S_N2' alkylated product, the phosphate **24** was converted into mixtures containing the desired *anti*-

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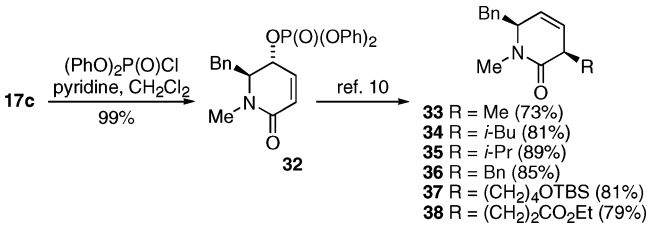
S_N2' product in varying ratios, depending on the organocopper reagents employed (Table 3, entries 1 and 2). It should be noted that the reaction of **24** with MeCu·LiI·LiBr in THF−Et_2O at −78 °C for 20 min proceeded smoothly to afford **25** in 83% isolated yield, without other accompanying products (Table 3, entry 3).[20]

On the basis of these results, we speculated that "lower-order" reagent systems such as MeCu·MX, prepared from a 1:1 mixture of organometallic reagent and copper salt, affected the *anti*-S_N2' conversion of the phosphate. Being encouraged by these results, we next examined Grignard reagent (MeMgCl) as an alkyl source for the organocopper reagents. Unexpectedly, the treatment of phosphate **24** with MeCuI·MgCl, formed from equimolar amounts of MeMgCl and CuI, gave a mixture of S_N2 (S_N2-**25**: 40%) and *anti*-S_N2'(**25**: 24%) products (Table 3, entry 4). In contrast, the addition of the lithium salts (LiCl) dramatically improved the selectivity to produce the desired *anti*-S_N2' compound **25** in 93% isolated yield (Table 3, entry 5). This indicated that using "lower-order" reagents in the presence of lithium salts provides a suitable system for the *anti*-S_N2' reaction of γ-phosphoryloxy-α,β-unsaturated-δ-lactams. Recently, a mixture of CuCN and LiCl (1:2, mole ratio), which is a soluble copper complex in THF, was successfully applied to a wide range of organocopper-mediated transformations.[21] In our present work, the use of a CuCN·2LiCl complex gave the desired compound **25** in 77% yield with an accompanying small amount of S_N2 product (Table 3, entry 6). It is well-documented that the addition of Lewis acids such as BF_3·Et_2O or TMSCl to organocopper-mediated reactions improves the chemical yields or regioselectivity.[22] However, inclusion of BF_3·Et_2O in the CuCN-mediated reaction of the phosphate **24** led to an increase in S_N2 product (Table 3, entry 7). The corresponding reaction with "higher order" cyanocuprate−BF_3 [$Me_2Cu(CN)$·$(MgCl)_2$·2LiCl·BF_3] was unsuccessful, resulting in a complex mixture without formation of the desired *anti*-S_N2' product (Table 3, entry 8).

Next, the introduction of other alkyl groups using various organometallic reagents was investigated. The reaction of phosphate **24** with organocopper reagents prepared from *i*-BuLi and CuI (1:1 ratio) gave the desired *anti*-S_N2' product **26** (63% yield) along with a small amount of S_N2-**26** (13%; Table 3, entry 9). As expected, the addition of LiCl to *i*-BuCu·2LiI completely suppressed the formation of S_N2-**26** (Table 3, entry 10). In sharp contrast, the reaction with the copper reagent derived from *i*-PrMgCl and CuI did not proceed at −78 °C. When the reaction was conducted at room temperature, pyridinone derivative **18** was obtained in 62% isolated yield (Table 3, entry 11). This was probably due both to steric hindrance and to higher basicity of the reagent having a secondary carbon center. On the other hand, use of CuCN·2LiCl in combination with *i*-PrMgCl afforded the desired *anti*-S_N2' product **27** (Table 3, entry 12). Generally, CuCN-based reagents have been reported to exhibit higher soft nucleophilic character than reagents prepared using other copper salts including CuI.[23] These may be more suitable for S_N2' reactions of **24** with the copper reagents having an *i*-Pr group. An increased formation of the S_N2 product was observed when the reaction with *i*-PrCu(CN)·MgCl·2LiCl was conducted in the presence of BF_3·Et_2O (Table 3, entries 13 and 14), as in the case of MeCu(CN)·MgCl·2LiCl. Other diketopiperazine mimetics **28**−**30**, containing phenyl, hydroxyl, and ester functional groups, respectively, were also synthesized by use of organocopper-mediated *anti*-S_N2' reactions.[10] We have confirmed that organocopper-mediated reactions of 5,6-*trans*-phosphate **32** derived from lactam **17c** proceeded smoothly in an *anti*-S_N2' manner to yield 3,6-*cis*-diketopiperazine mimetics **33**−**38** (Scheme 5).[10,24] In all cases, no detectable amounts of S_N2 products were observed. This is probably due to the presence of a benzyl group, which effectively prevents the access of organocopper reagent to the γ-position from the opposite side of the leaving group.

SCHEME 5. Organocopper-Mediated *anti*-S_N2' Reaction of 5,6-*trans*-Phosphate 32



The involvement of lithium salts is likely to be crucial for the preferential formation of *anti*-S_N2' products (e.g., Table 3, entry 4 vs 5). We hypothesized that cluster-like structures consisting of organocopper and lithium salts were responsible for determining regioselectivity. The importance of cluster structures of organocopper and lithium salts is well-documented in organocopper chemistry.[25] Of note, in conjugate additions to α,β-unsaturated carbonyl compounds using organocuprates, including Me_2CuLi·LiX (X = I or CN), a "trap and bite" mechanism has been postulated and supported by theoretical investigations (Figure 3).[26] According to this mechanism, organocuprate cluster reagent **39** traps the substrate by coordinating with a carbonyl group, followed by the opening of the cluster to form the "biting" structure **40**. This results in C−C bond formation by subsequent reductive elimination. It has been

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(20) Generally, an increase in MeLi, a copper salt ratio, improved the electron-donating activity of the reagents. The reactivity of MeLi-derived organocopper reagents toward the acetate **21** reflects this nature. Organocopper reagents possessing highly reducing potency proved to be unsuitable for the *anti*-S_N2' reaction of the phosphate **24**. See: Chounan, Y.; Horino, H.; Ibuka, T.; Yamamoto, Y. *Bull. Chem. Soc. Jpn.* **1997**, *70*, 1953.

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(24) Relative configurations of the resulting DKP mimetics **25**−**30** and **32**−**37** were determined based on X-ray and ^1H NMR analyses. In ^1H NMR measurements, upfield shifts of α-protons of 3,6-trans derivatives, which were probably caused by an anisotropic effect of the side-chain phenyl ring, were observed (see the Supporting Information).

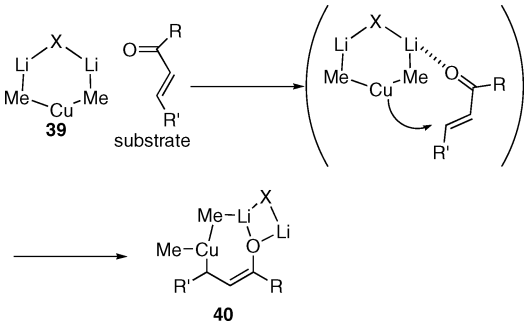

FIGURE 3. Conjugate addition of organocuprates to α,β-unsaturated carbonyl compounds via a "trap and bite" mechanism.

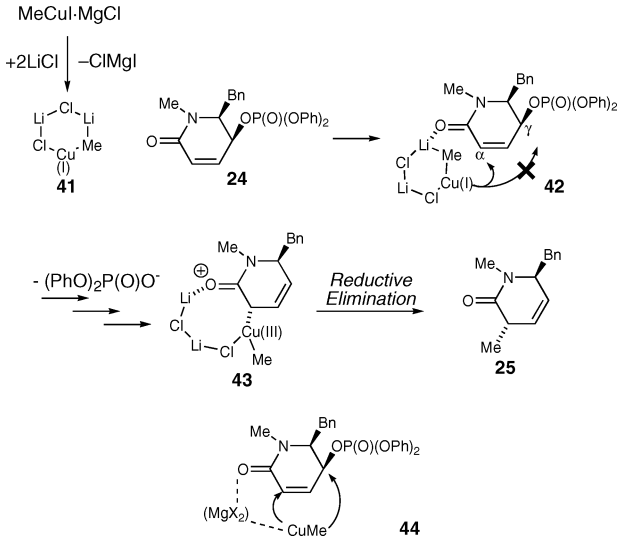

FIGURE 4. Potential mechanism for *anti*-S_N2' selectivity induced by the inclusion of LiCl in the reaction of MeCuI·MgCl.

proposed that similar reaction mechanisms are involved in S_N2 reactions of organocuprates.[27]

It is tempting to envisage the reaction mechanism of lithium-induced *anti*-S_N2' selectivity, as shown in Figure 4. According to this model, MeCuI·MgCl is initially converted to the cluster **41** by the addition of lithium chloride. The formation of the cluster **41** may be adequate because **41** has been identified as a reaction product in a theoretical study on the S_N2 reaction of organocuprates by Nakamura et al.[27] The cluster **41** approaches the phosphate **24** while coordinating the carbonyl oxygen with a lithium atom to form complex **42**. The resulting complex **42** is then preferentially converted to the Cu(III) complex **43** with an *anti*-S_N2' interaction of the intramolecular organocopper moiety. Rapid reductive elimination of **43** results predominantly in the formation of the *anti*-S_N2' product **25**. It is hypothesized that magnesium salts cannot induce the formation of the cluster structure such as **41** for electrostatic and structural reasons. Therefore, both the α- and γ-carbons would be attacked by "MeCu" without coordination between the organocopper species and the carbonyl oxygen, leading to a mixture of *anti*-S_N2' and S_N2 products (Figure 4, **44**). The reactivity of CN-containing organocopper cluster reagents may differ from that of cluster **41**. Decreased regioselectivity induced by BF_3·Et_2O may result from decomposition of the organocopper cluster or disruption of interactions between the organocopper species and the carbonyl oxygen.

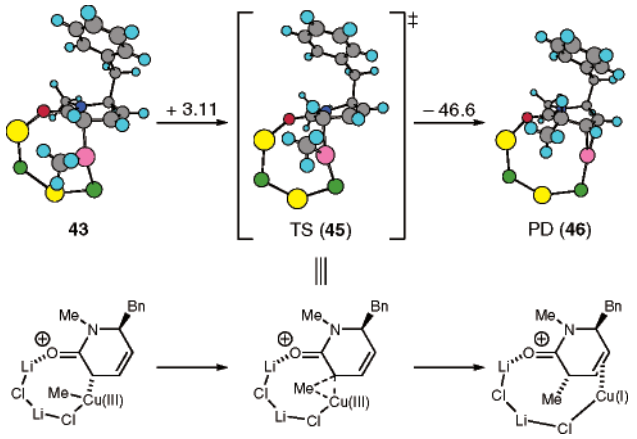

FIGURE 5. Optimized geometries of complex **43**, TS (**45**) and PD (**46**) in the gas phase at the B3LYP/631A level. The energy changes in kcal/mol are given above the arrows.

We performed density functional theory (DFT)[28] calculations on the basis of the plausible route from **43** to **25** (Figure 5). As shown in Figure 5, these calculations confirm that reductive elimination of complex **43** proceeds smoothly via transition state **45** with a reasonable activation energy (3.11 kcal/mol) to yield complex **46**, which leads to the *anti*-S_N2' product **25**. These results support the above explanation for the improvement of *anti*-S_N2' selectivity induced by LiCl.

Next, organocopper-mediated *anti*-S_N2' reactions of *N*-DMB-phosphate derivative **47** were carried out. (Scheme 6). All reactions proceeded smoothly to afford the *anti*-S_N2' products **48**−**50**.[29] After removal of the DMB group under acidic conditions, the resulting lactams were converted into the corresponding (*Z*)-alkene dipeptide isosteres using Guibé's methodology.[5a] These represent *cis*-peptide bond equivalents,[11] indicating that our novel synthetic methodology for the preparation of DKP mimetics may also afford a potential strategy for the stereoselective synthesis of (*Z*)-alkene dipeptide isosteres.

Encouraged by this methodology for the stereoselective preparation of diketopiperazine mimetics, we conducted the

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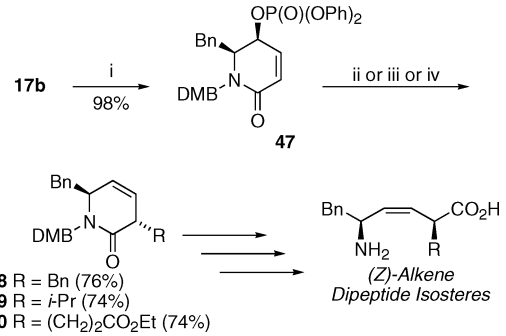
SCHEME 6. Organocopper-Mediated *anti*-S_N2' Reaction of *N*-DMB Derivative 47[a]



[a] Reagents and conditions: (i) $(PhO)_2P(O)Cl$, pyridine, CH_2Cl_2; (ii) BnCuI·MgCl·2LiCl, THF, −78 °C, 20 min; (iii) *i*-PrCu(CN)·MgCl·2LiCl, THF, −78 °C, 20 min; (iv) BrZnCu(CN)·$CH_2CH_2CO_2Et$, THF, 0 °C, 60 min.

synthesis of a biologically relevant DKP mimetic designed as a CXCR4-chemokine receptor antagonist (Scheme 7). CXCR4 is a seven-transmembrane G-protein-coupled receptor, which is involved in HIV infection, cancer metastasis, and other disease processes.[30] Thus, CXCR4 is thought to be an attractive therapeutic target for these problematic diseases.[31] Recently, we identified a cyclic pentapeptide, *cyclo*-(-Nal-Gly-D-Tyr-Arg-Arg-), possessing strong CXCR4 antagonistic activity.[32] In this peptide, guanidyl and naphthyl side chains proved to be especially important pharmacophores for the antagonistic activity. We hypothesized that DKP mimetics having guanidine and naphthalene moieties such as **62** could exhibit CXCR4 antagonistic activity. The synthesis of **62** started from L-2-naphthylalanine **51**, which was converted to *N*-Boc-protected methyl ester **52** (esterification with $SOCl_2$ and MeOH, followed by *N*-protection). After reduction of the ester **52**, the resulting aldehyde was treated with vinyl Grignard reagent in the presence of zinc and lithium salts to yield the *syn*-allylic alcohol **53** along with a small amount of the anti isomer. Following Boc deprotection of **53**, *O*-TBS protected Ns-amide **54** was synthesized by a procedure identical to that used to prepare **12**. *N*-Alkylation of **54** with $BocNHCH_2(CH_2)_2CH_2I$[33] yielded amide **55**, which was converted to phosphate **58** by a sequence of reactions, including ring-closing metathesis. The reaction of phosphate **58** with $TBSOCH_2(CH_2)_2CH_2Cu(CN)Li·LiI·2LiCl$ proceeded smoothly in an *anti*-S_N2' manner[34] to afford the alkylated product **59** as the sole product. After removal of the TBS group with H_2SiF_6, the resulting alcohol **60** was subjected to guanidylation with 1,3-bis(*tert*-butoxycarbonyl)guanidine under Mitsunobu conditions[35] to afford compound **61**. *N*-Boc deprotection of **61** followed by guanidylation[8d] of the resulting amine and HPLC purification yielded the desired DKP mimetic **62**, which showed significant CXCR4 antagonistic activity (IC_{50} = 15.1 μM). Although the antagonistic activity of mimetic **62** has yet to reach the level for clinical usage, the 3,6-dihydropyridin-2-one could be a potential scaffold for the development of novel low molecular weight CXCR4 antagonists.

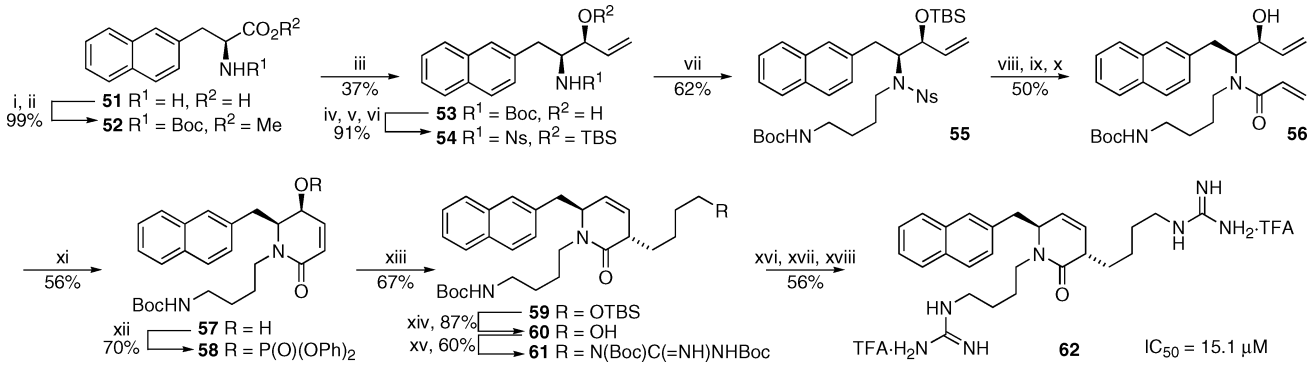
Conclusion

In conclusion, regio- and stereoselective alkylations of γ-phosphoryloxy-α,β-unsaturated-δ-lactams with organocopper reagents were carefully examined for the synthesis of highly functionalized DKP mimetics. Organocopper reagents, which were prepared from equimolar amounts of an organometallic (Li, Mg or Zn) reagent and a copper salt in the presence of LiCl, proved to be suitable for these transformations. This reaction system features several advantages for the diversity-oriented synthesis of DKP mimetics in terms of available organocopper reagents, stereoselectivity, and tolerance of functional groups. Dramatic improvement of regioselectivity induced by LiCl in the reaction of MeCuI·MgCl can be rationalized by a "trap and bite" mechanism in which organocopper cluster structures containing LiCl are responsible for determining regioselectivity. Such a hypothesis was supported by a DFT calculation. Finally, compound **62**, a potential lead for the development of low molecule CXCR4 antagonists was synthesized by a reaction sequence utilizing an organocopper-mediated *anti*-S_N2' reaction of phosphate **58**. Details of the reaction mechanisms involving organocopper cluster formation are currently being investigated.

Experimental Section

(3*S*,4*S*)-3-[(*tert*-Butyl)dimethylsiloxy]-4-[*N*-methyl-*N*-(2-nitrobenzenesulfonyl)amino]-5-phenylpent-1-en (12a). To a stirred solution of sulfonamide *syn*-**11** (500 mg, 1.05 mmol) in DMF (5

SCHEME 7. Synthesis of a Biologically Relevant DKP Mimetic 62 Designed as a CXCR4-Chemokine Receptor Antagonist[a]



[a] Reagents and conditions: (i) $SOCl_2$, MeOH; (ii) Boc_2O, (*i*-Pr)$_2$NEt, $CHCl_3$; (iii) DIBAL-H, CH_2Cl_2−toluene then CH_2=$CHMgCl$, $ZnCl_2$, LiCl, THF; (iv) 4 M HCl−dioxane; (v) Ns-Cl, 2,4,6-collidine, $CHCl_3$; (vi) TBSOTf, 2,6-lutidine, CH_2Cl_2; (vii) $BocNHCH_2(CH_2)_2CH_2I$, K_2CO_3, DMF; (viii) $HSCH_2CO_2H$, $LiOH·H_2O$, DMF; (ix) CH_2=$CHCOCl$, Et_3N, CH_2Cl_2; (x) TBAF, THF; (xi) Grubbs' cat. second generation, CH_2Cl_2; (xii) $(PhO)_2P(O)Cl$, pyridine, CH_2Cl_2; (xiii) $TBSOCH_2(CH_2)_2CH_2Cu(CN)Li·LiI·2LiCl$, *n*-pentane-THF; (xiv) H_2SiF_6, CH_3CN; (xv) 1,3-bis(*tert*-butoxycarbonyl)guanidine, PPh_3, diisopropyl azodicarboxylate, THF; (xvi) 95% aq CF_3CO_2H; (xvii) 1*H*-pyrazole-1-carboxamidine hydrochloride, (*i*-Pr)$_2$NEt, DMF; (xviii) RP-HPLC purification. Abbreviation: TFA, trifluoroacetic acid.

mL) were 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 whole 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 **12a** (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, $CDCl_3$) δ 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, $CDCl_3$) δ −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*)-4-(*N*-Acryloyl-*N*-methylamino)-3-[(*tert*-butyl)dimethylsiloxy]-5-phenylpent-1-en (13a). To a stirred solution of the *N*-Me-sulfonamide **12a** (507 mg, 1.03 mmol) in DMF (3.6 mL) were added $LiOH\cdot H_2O$ (260 mg, 6.20 mmol) and $HSCH_2CO_2H$ (216 μL, 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 that were dissolved in CH_2Cl_2 (5 mL). Et_3N (720 μL, 5.17 mmol) and acryloyl chloride (336 μL, 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 whole 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 **13a** (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, $CDCl_3$) δ 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, $CDCl_3$) δ −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 (16a). The acrylamide **13a** (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 **16a** (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, $CDCl_3$) δ 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, $CDCl_3$) δ 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.

(5*S*,6*S*)-6-Benzyl-5,6-dihydro-5-hydroxy-1-methylpyridin-2-one (17a). To a solution of the acrylamide **16a** (750 mg, 3.05 mmol) in CH_2Cl_2 (20 mL) was added Grubbs' catalyst second generation (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 **17a** (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, $CDCl_3$) δ 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, $CDCl_3$) δ 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-5-diphenylphosphoryloxy-1-methylpyridine-2-one (24). To a solution of the alcohol **17a** (450 mg, 2.07 mmol) and pyridine (1.33 mL, 16.5 mmol) in CH_2Cl_2 (7.5 mL) was added dropwise diphenylphosphoryl chloride (1.72 mL, 8.28 mmol) at 0 °C, and the mixture was stirred at 0 °C for 4 h. H_2O (10 mL) was added to the above mixture, and the whole was extracted with EtOAc. The extract was washed successively with saturated citric acid, brine, saturated $NaHCO_3$, and brine and dried

(29) Relative configurations of **48** and **49** were assigned as 3,6-trans derivatives based on the published data (ref 5). The observed chemical shifts of the α-protons of **48** and **49** (2.45 and 2.16 ppm, respectively) were nearly identical to those of the corresponding *N*-methyl derivatives **27** and **28** (2.41 and 2.14 ppm, respectively). We also confirmed that the α-proton of the corresponding 3,6-cis diastereomer of **48** appeared downfield (3.16 ppm) in comparison with **48**, as in the cases of *N*-methyl derivatives. The α-proton chemical shift of **50** was 2.29 ppm, which is similar to that of the corresponding *N*-methyl-3,6-trans derivative **30** (2.21 ppm). Based on these data, compound **50** was assigned as 3,6-trans.

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(34) In ^{1}H NMR experiments, the α-proton of compound **59** was detected at higher field (2.20 ppm) in comparison with that of the corresponding diastereomer (2.72 ppm). This can be rationalized by the anisotropic effect of the naphthalene ring, as in the case of phenylalanine-derived compounds. Based on these data, the relative configuration of **59** was assigned as 3,6-trans. See the Supporting Information.

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over $MgSO_4$. Concentration under reduced pressure followed by flash chromatography over silica gel with *n*-hexanes−EtOAc (1:1) gave the title compound **24** (790 mg, 84.8% yield) as a colorless oil: $[\alpha]^{26}_D$ −25.8 (*c* 0.28, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.46 (s, 3H), 2.92 (dd, J = 13.6, 7.2 Hz, 1H), 3.00 (dd, J = 13.6, 3.0 Hz, 1H), 3.83 (m, 1H), 5.69 (m, 1H), 5.88 (dd, J = 10.0, 0.8 Hz, 1H), 6.29 (dt, J = 10.0, 1.6 Hz, 1H), 7.00−7.07 (m, 2H), 7.17−7.44 (m, 13H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 33.3, 34.8, 63.2, 63.3, 73.5, 73.6, 119.5, 119.6, 119.7, 125.0, 125.4, 126.3, 128.2, 129.0, 129.5, 136.8, 137.0, 137.1, 149.7, 149.8, 161.9; HRMS (FAB) *m*/*z* calcd for $C_{25}H_{25}NO_5P$ (MH^+), 450.1470; found, 450.1462.

General Procedure for the Organocopper-Mediated *anti*-S_N2' Reaction of γ-Phosphoryloxy-α,β-unsaturated-δ-lactams. Synthesis of (3*S*,6*S*)-6-Benzyl-3,6-dihydro-1,3-dimethylpyridin-2-one (25). To a solution of CuI (37.3 mg, 0.196 mmol) and anhydrous LiCl (16.6 mg) in THF (0.75 mL) was added dropwise a solution of MeMgCl in THF (3.0 M, 65.3 μL, 0.196 mmol) at −78 °C under argon, and the mixture was stirred for 10 min at 0 °C. To the above mixture, was added dropwise a solution of the lactam **24** (44.1 mg, 0.0981 mmol) in THF (0.75 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 (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 **25** (19.6 mg, 92.8% yield) as a colorless oil: $[\alpha]^{23}_D$ +231.9 (*c* 0.21, $CHCl_3$); ^{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 = 10.1, 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.

(5*R*,6*S*)-6-Benzyl-5,6-dihydro-1,5-dimethylpyridin-2-one (S_N2-25). A colorless oil: $[\alpha]^{24}_D$ −212.0 (*c* 0.49, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.05 (d, J = 7.1 Hz, 3H), 2.31 (m, 1H), 2.73 (dd, J = 13.4, 9.0 Hz, 1H), 2.91 (s, 3H), 3.00 (dd, J = 13.4, 5.8 Hz, 1H), 3.31 (m, 1H), 5.93 (d, J = 9.8 Hz, 1H), 6.45 (ddd, J = 9.8, 6.1, 1.7 Hz, 1H), 7.07−7.40 (m, 5H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 18.8, 31.5, 34.5, 38.3, 66.6, 123.6, 126.7, 128.7, 129.2, 137.8, 142.7, 163.2; HRMS (FAB) *m*/*z* calcd for $C_{14}H_{18}NO$ (MH^+), 216.1388; found, 216.1393.

(3*S*,6*S*)-1-{4-[(*tert*-Butoxycarbonyl)amino]butyl}-3-{4-[(*tert*-butyl)dimethylsiloxy]butyl}-3,6-dihydro-6-[(2-naphthyl)methyl]-pyridin-2-one (59). By use of a procedure identical with that described for the preparation of **29** from **24**, treatment of the phosphate **58** (196 mg, 0.300 mmol) with $TBSOCH_2(CH_2)_2CH_2$-Cu(CN)Li·LiI·2LiCl (4 equiv) at −78 °C for 1 h gave the title compound **59** (120 mg, 67.2% yield) as a colorless oil: $[\alpha]^{23}_D$ +80.3 (*c* 1.06, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.00 (s, 6H), 0.85 (s, 9H), 1.11−1.23 (m, 2H), 1.43 (s, 9H), 1.38−1.72 (m, 8H), 2.14−2.25 (m, 1H), 2.93−3.23 (m, 5H), 3.45−3.59 (m, 2H), 4.04−4.27 (m, 2H), 4.64−4.76 (m, 1H), 5.58 (dd, J = 10.0, 2.0 Hz, 1H), 5.64−5.75 (m, 1H), 7.17−7.30 (m, 1H), 7.40−7.60 (m, 3H), 7.70−7.86 (m, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ −5.3, 18.3, 22.0, 24.7, 25.9, 27.5, 28.4, 31.1, 32.7, 39.9, 40.0, 40.3, 44.4, 59.0, 62.9, 79.0, 125.1, 125.6, 126.0, 127.5, 127.6, 127.7, 127.9, 128.3, 128.5, 132.1, 133.2, 133.7, 156.0, 170.7; HRMS (FAB) *m*/*z* calcd for $C_{35}H_{55}N_2O_4Si$ (MH^+), 595.3931; found, 595.3939.

(3*S*,6*S*)-1-{4-[(*tert*-Butoxycarbonyl)amino]butyl}-3,6-dihydro-3-(4-hydroxy)butyl-6-[(2-naphthyl)methyl]pyridin-2-one (60). To a solution of the lactam **59** (102 mg, 0.172 mmol) in CH_3CN (1.7 mL) was added a solution of H_2SiF_6 in H_2O (3.23 M, 11.0 μL, 0.0357 mmol) at 0 °C, and the mixture was stirred for 1 h at 0 °C. Saturated aq K_2CO_3 (2 mL) was added to the above mixture, and the whole was extracted with Et_2O. The extract was washed successively with saturated K_2CO_3 and 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 **60** (69.8 mg, 87.2% yield) as a colorless oil: $[\alpha]^{24}_D$ +142.3 (*c* 1.14, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.12−1.35 (m, 4H), 1.43 (s, 9H), 1.39−1.56 (m, 4H), 1.58−1.73 (m, 2H), 1.73−1.88 (m, 1H), 2.15−2.25 (m, 1H), 2.95−3.11 (m, 3H), 3.08−3.22 (m, 2H), 3.50−3.65 (m, 2H), 4.10−4.28 (m, 2H), 4.80−4.94 (m, 1H), 5.57 (dd, J = 10.0, 2.0 Hz, 1H), 5.63−5.78 (m, 1H), 7.18−7.30 (m, 1H), 7.40−7.60 (m, 3H), 7.70−7.85 (m, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 21.7, 24.7, 27.5, 28.4, 30.5, 32.2, 39.9, 40.0, 40.1, 44.3, 59.0, 62.2, 79.0, 125.2, 125.6, 126.0, 127.5, 127.6, 127.7, 127.9, 128.5, 128.6, 132.1, 133.2, 133.6, 156.1, 171.0; HRMS (FAB) *m*/*z* calcd for $C_{29}H_{41}N_2O_4$ (MH^+), 481.3066; found, 481.3060.

(3*S*,6*S*)-3-{4-{[*N*,*N*-Bis(*tert*-butoxycarbonyl)guanidino]}butyl}-1-{4-[(*tert*-butoxycarbonyl)amino]butyl}-3,6-dihydro-6-[(2-naphthyl)methyl]pyridin-2-one (61). To a solution of the alcohol **60** (62.6 mg, 0.183 mmol), PPh_3 (144 mg, 0.548 mmol), and 1,3-bis(*tert*-butoxycarbonyl)guanidine (142 mg, 0.548 mmol) in THF (0.98 mL) was added dropwise a solution of diisopropyl azodicarboxylate in toluene (1.9 M, 288 mL, 0.548 mmol) at 0 °C under argon, and the mixture was stirred for 12 h at room temperature. Concentration under reduced pressure followed by flash chromatography over silica gel with *n*-hexanes−EtOAc (3:1) gave the title compound **61** (66.8 mg, 50.7% yield) as a colorless oil: $[\alpha]^{24}_D$ +103.3 (*c* 0.79, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.07−1.69 (m, 37H), 2.17−2.25 (m, 1H), 2.94−3.26 (m, 5H), 3.67−3.95 (m, 2H), 4.13 (m, 1H), 4.17−4.27 (m, 1H), 4.74−4.89 (m, 1H), 5.58 (dd, J = 10.0, 1.6 Hz, 1H), 5.66−5.77 (m, 1H), 7.17−7.28 (m, 1H), 7.38−7.60 (m, 3H), 7.69−7.86 (m, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 22.9, 24.8, 27.6, 28.0, 28.3, 28.4, 28.7, 31.0, 39.9, 40.1, 40.2, 44.3, 44.4, 59.0, 83.5, 125.1, 125.6, 126.0, 127.5, 127.7, 127.9, 128.3, 128.6, 132.1, 133.2, 133.6, 155.1, 156.0, 160.6, 163.8, 170.6; HRMS (FAB) *m*/*z* calcd for $C_{40}H_{60}N_5O_7$ (MH^+), 722.4493; found, 722.4482.

(3*S*,6*S*)-1,3-Bis(4-guanidinobutyl)-3,6-dihydro-6-[(2-naphthyl)-methyl]pyridin-2-one Trifluoroacetate (62). The lactam **61** (47.8 mg, 0.0662 mmol) was dissolved in 95% aq TFA (1.2 mL), and the mixture was stirred for 4 h at room temperature. Concentration under reduced pressure gave an oily residue, which was dissolved in DMF (0.1 mL). 1*H*-pyrazole-1-carboxamidine hydrochloride (29.1 mg, 0.198 mmol) and $(i\text{-Pr})_2NEt$ (210 μL, 1.23 mmol) was added to the above mixture at 0 °C, and the mixture was stirred overnight at room temperature. Concentration under reduced pressure and purification by preparative HPLC gave the title compound **62** (15.4 mg, 33.6% yield) as a freeze-dried powder: $[\alpha]^{21}_D$ +132.5 (*c* 0.35, CH_3OH); ^{1}H NMR (400 MHz, CD_3OD) δ 1.04−1.19 (m, 2H), 1.30−1.40 (m, 2H), 1.54−1.74 (m, 5H), 2.96−3.08 (m, 3H), 3.14−3.30 (m, 4H), 4.02−4.15 (m, 1H), 4.36−4.45 (m, 1H), 5.59 (dd, J = 9.8, 2.0 Hz, 1H), 5.87−5.96 (m, 1H), 7.21−7.28 (m, 1H), 7.37−7.49 (m, 2H), 7.56 (s, 1H), 7.70−7.84 (m, 3H); ^{13}C NMR (100 MHz, CD_3OD) δ 23.9, 25.7, 27.3, 29.6, 31.6, 39.7, 40.6, 40.9, 42.1, 45.5, 60.5, 126.8, 126.9, 127.1, 128.4, 128.6, 129.2, 129.7, 130.3, 133.7, 134.7, 134.8, 158.5, 158.6, 162.7, 178.6; HRMS (FAB) *m*/*z* calcd for $C_{26}H_{38}N_7O$ (MH^+), 464.3138; found, 464.3147.

Density Functional Theory (DFT) Calculation. DFT calculations were carried out on a SGI Origin 3800 system within the Gaussian 98 package.[36] Geometry optimizations were performed by the B3LYP hybrid functional[37] with the basis set denoted as B3LYP/631A, which consists of the Ahlrichs all-electron SVP basis set[38] for Cu and 6-31G(d)[39] for the rest. The geometry of the transition state (**45**) was optimized by QST2 transition state search from the optimized structures **43** and **46**. The number of imaginary frequencies of these optimized structures was confirmed by frequency analysis (**43** and **46**, 0; **45**, 1).

[^{125}I]-SDF-1 Binding and Displacement. Stable CHO cell transfectants expressing CXCR4 variants were prepared as described previously.[40] CHO transfectants were harvested by treatment with trypsin-EDTA, allowed to recover in complete growth medium

(MEM-α, 100 μg/mL penicillin, 100 μg/mL streptomycin, 0.25 μg/mL amphotericin B, 10% (v/v)) for 4 to 5 h, and then washed in cold binding buffer (PBS containing 2 mg/mL BSA). For ligand binding, the cells were resuspended in binding buffer at 1×10^7 cells/mL, and 100 μL aliquots were incubated with 0.1 nM of [^{125}I]-SDF-1 (PerkinElmer Life Sciences) for 2 h on ice under constant agitation. Free and bound radioactivity were separated by centrifugation of the cells through an oil cushion, and bound radioactivity was measured with a gammma-counter (Cobra, Packard, Downers Grove, IL). Inhibitory activity of compound **62** was determined based on the inhibition of [^{125}I]-SDF-1-binding to CXCR4 transfectants (IC_{50}).

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Supporting Information Available: Experimental details. Alternative synthetic route of S_N2-**25**. Determination of the relative configuration of **53** and **59**. ORTEP diagrams and CIF files for X-ray structures of **28** and **33**. Optimized coordinates and energies of complexes **43**, **45**, and **46**. ^{1}H and ^{13}C NMR spectra of representative compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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