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Synthesis of Amide-Type Fluoroalkene Dipeptide Isosteres by an Intramolecular Redox Reaction

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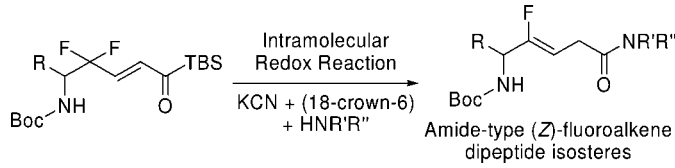

We previously achieved NHC-mediated preparation of ester-type fluoroalkene dipeptide isosteres (ES-FADIs, **4**) by an intramolecular redox reaction. In the present study, a cyanide ion-mediated reaction was successfully applied to the conversions of γ,γ-difluoro-α,β-enoylsilane **1** or **2** to amide-type fluoroalkene isosteres (AM-FADIs, **5** or **6**). The use of catalytic cyanide ion allowed synthesis of chiral auxiliary incorporated FADI **15b** which was then subjected to a diastereoselective α-alkylation reaction to yield α-substituted FADIs **17**. Furthermore, the presented amidation protocol was used for straightforward incorporation of FADI into peptidyl resin.

Introduction

In a precedent article,[1] the *N*-heterocyclic carbene (NHC)[2]-mediated synthesis of ester-type fluoroalkene dipeptide isosteres[3,4] (ES-FADIs, **4**) was addressed. Incorporation of FADIs into the peptide backbone requires the conversion of ES-FADI **4** to the corresponding active acyl component, whereby hydrolysis of the ester followed by activation of the resulting carboxy group is involved.[5] The fact that synthesis of ES-FADI **4** from γ,γ-difluoro-α,β-enoylsilane **1** or **2** (or enals) is accomplished by the NHC-mediated intramolecular redox reaction in the presence of an appropriate alcohol such as EtOH indicates that replacement of the alcohol with amines should result in the formation of amide-type FADIs (AM-FADI **5** or **6**; Figure 1).

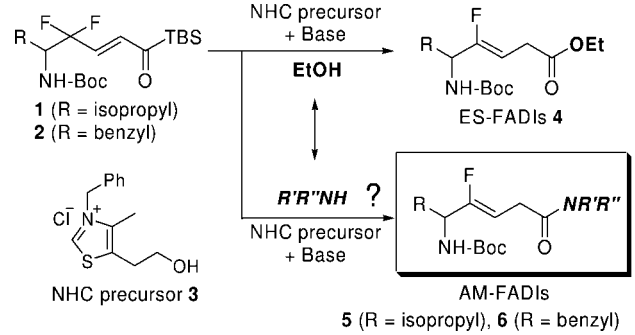

FIGURE 1. Envisioned synthesis of amide-type fluoroalkene dipeptide isosteres (AM-FADIs).

Therefore, we examined the synthesis of AM-FADIs with an intramolecular redox reaction leading to the straightforward incorporation of FADIs into peptides. On the basis of the knowledge obtained in the study on synthesis of AM-FADIs, we attempted to prepare a chiral auxiliary-possessing FADI with practical use in the auxiliary-guided stereoselective α-alkylations.

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(1) Yamaki, Y.; Shigenaga, A.; Tomita, K.; Narumi, T.; Fujii, N.; Otaka, A. *J. Org. Chem.* **2009**, *74*, 3272–3277.

(2) Much recent literature about the NHC-mediated reactions are listed in ref 1.

(3) For some recent reviews for FADIs, see: (a) Welch, J. T.; Allmendinger, T. In *Peptidomimetics Protocols*; Kazmierski, W. M., Ed.; Humana Press: Totowa, NJ, 1999; pp 357−384. (b) Couve-Bonnaire, S.; Cahard, D.; Pannecoucke, X. *Org. Biomol. Chem.* **2007**, *5*, 1151–1157.

(4) Recent examples of the synthesis of FADIs are listed in ref 1.

(5) Some recent examples of the incorporation of FADIs into peptides, see: (a) Niida, A.; Tomita, K.; Mizumoto, M.; Tanigaki, H.; Terada, T.; Oishi, S.; Otaka, A.; Inui, K.; Fujii, N. *Org. Lett.* **2006**, *8*, 613–616. (b) Tomita, K.; Narumi, T.; Niida, A.; Oishi, S.; Ohno, H.; Fujii, N. *Biopolymers* **2007**, *88*, 272–278. (c) Lamy, C.; Hofmann, J.; Parrot-Lopez, H.; Goekjian, P. *Tetrahedron Lett.* **2007**, *48*, 6177–6180. (d) Narumi, T.; Tomita, K.; Inokuchi, E.; Kobayashi, K.; Oishi, S.; Ohno, H.; Fujii, N. *Tetrahedron* **2008**, *64*, 4332–4346.

(6) (a) Vora, H. U.; Rovis, T. *J. Am. Chem. Soc.* **2007**, *129*, 13796–13797. (b) Bode, J. W.; Sohn, S. S. *J. Am. Chem. Soc.* **2007**, *129*, 13798–13799.

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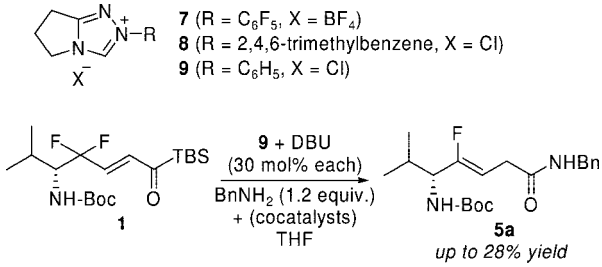


FIGURE 2. Triazolium precatalysts.

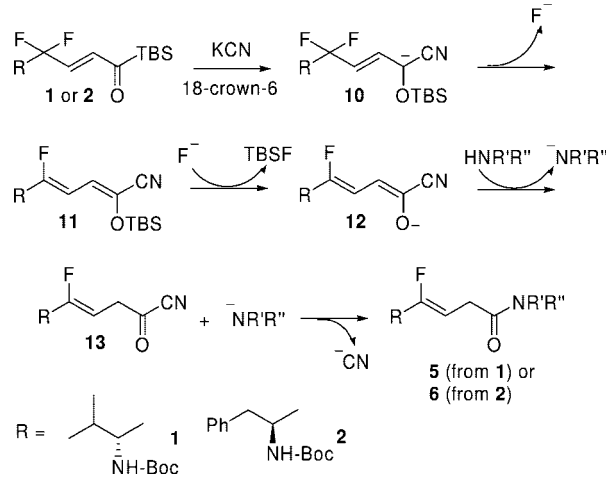
Results and Discussion

The fact that the NHC derived from thiazolium salt **3** was the catalyst used for the preparation of ES-FADI **4** prompted us to utilize NHC in the presence of amines targeting the preparation of AM-FADIs. First, the attempted reaction of γ,γ-difluoro-α,β-enoylsilane **1** with **3** in the presence of 1,8-diazabicyclo[5,4,0]undec-7-ene (DBU) resulted in failure to afford the desired material. Recently, Rovis and Vora and Bode and Sohn reported that triazolium salts **7** and **8** were effective precatalysts for the NHC-mediated oxidation of aldehydes to amides.[6] On the basis of these reports, we also attempted to use triazolium salt **9** (Figure 2).

Reaction of enoylsilane **1** with benzyl amine in the presence of triazolium salt **9** and DBU (30 mol % each) in THF at room temperature afforded the desired AM-FADI **5a** in 15% isolated yield with the accompanying 1,4-adduct of benzyl amine (19%). Analogous with the fact that NHC-mediated synthesis of ES-FADIs proceeds more efficiently at elevated temperature, the reaction was conducted at 70 °C to give **5a** in 28% yield. Aiming to further increase the yield of the desired material **5a**, we attempted to fine-tune the reaction conditions utilizing additives[6,7] such as HOAt,[8] imidazole, or DMAP; however, all trials offered no improvement in the amidation reaction. All cases examined here were complicated by the competing 1,4-addition of benzyl amine and the formation of unidentified materials.[9] Therefore, we speculated that the complete conversion of enoylsilane **1** to the active acyl equivalent followed by addition of amines would lead to the formation of **5a** in improved yield. The use of a stoichiometric amount of NHC prior to the addition of amines was evaluated to achieve complete conversion. Starting enoylsilane **1** disappeared with treatment with precatalyst **9** (1.0 equiv) in the presence of DBU (1.0 equiv); however, subsequent addition of benzyl amine to the resulting reaction mixture did not afford desired **5a** in satisfactory yield.

Consequently, the applicability of a cyanide anion alternate to NHCs in the synthesis of AM-FADIs was next examined.[10−13] We expected that the envisioned reaction would first give silyl-protected cyanohydrin carbanion **10** via nucleophilic attack of the cyanide ion to acylsilanes followed by Brook rearrangement.[14] Then the resulting negative charge would move into the π-electron system to give silyl fluorodienol ether **11** via the pushing out of one fluorine atom. Attack of the liberated fluoride ion to the silyl group followed by protonation with amines should give acyl cyanide **13**, whereby synthesis of AM-FADIs would be achieved (Scheme 1).

SCHEME 1



To ensure the complete internal conversion of the enoylsilanes to the corresponding cyano dienolate anion **12** as a precursor for acyl cyanide **13**, we subjected enoylsilane **1** or **2** to a reaction with potassium cyanide (1.05 equiv) in the presence of 18-crown-6 (1.05 equiv) followed by the addition of amines including amino esters. Results are summarized in Table 1.

The use of cyanide anion gave satisfactory results in the preparation of AM-FADIs as shown in Table 1. Dependent on the increase in soluble KCN, disappearance of the starting material **1** occurred efficiently to give the corresponding acyl cyanide precursor (enolate anion **12**) which was converted to acyl cyanide **13** upon protonation by subsequently added amines. Acylation of benzyl amine with the resulting cyanide in Et_2O progressed at a faster rate than in THF to afford amide **5a** (Table 1, entries 1−4). The use of *n*-Bu_4NCN as an easily soluble cyanide source in organic solvents allowed enoylsilane **1** to be consumed rapidly (within 1 min) to lead to the formation of **5a** at −78 °C (entry 5). Reactions of enoylsilane (**1** or **2**) with amino acid derivatives, even with a sterically hindered valine derivative, also proceeded efficiently to yield tripeptide mimetics (**5b**, **5c**, and **5d** or **6b**, **6c**, and **6d**, respectively) with high (*Z*)-selectivity (entries 6−11).[15] The reaction in DMF without 18-crown-6 completed to give peptidomimetic **5b** in quantitative

(7) Addition of additives such as HOAt,[6a] DMAP, or imidazole[6b] is indispensable for the NHC-catalyzed redox amidation of aldehydes with amines.

(8) Carpino, L. A. *J. Am. Chem. Soc.* **1993**, *115*, 4397–4398.

(9) The NHC-mediated reaction of enals with amines needs the slow addition of amines into the reaction mixtures.[6b] We also tried this protocol not to obtain the desired material in high yield.

(10) Cyanide anion-mediated conversion of α-reducible aldehydes to esters, see: (a) Roedig, A.; Hagedorn, F. *Liebigs Ann. Chem.* **1965**, *683*, 30–41. (b) Yoshida, K.; Nomura, S.; Ban, Y. *Tetrahedron Lett.* **1985**, *41*, 5495–5501.

(11) Direct conversion of aldehydes to esters and amides using acetone cyanohydrin was reported, see: Victor Paul Raj, I.; Sudalai, A. *Tetrahedron Lett.* **2005**, *46*, 8303–8306.

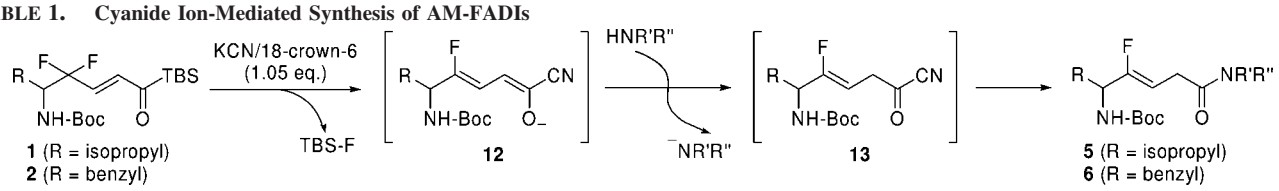
(12) For review on acyl cyanides, see: Hünig, S.; Schaller, R. *Angew. Chem., Int. Ed.* **1982**, *21*, 36–49.

(13) Some recent examples of reaction of acylsilanes with cyanide anion, see: (a) Reich, H. J.; Holtan, R. C.; Bolm, C. *J. Am. Chem. Soc.* **1990**, *112*, 5609–5617. (b) Takeda, K.; Ohnishi, Y. *Tetrahedron Lett.* **2000**, *41*, 4169–4172. (c) Saleur, D.; Bouillon, J.-P.; Portella, C. *Tetrahedron Lett.* **2001**, *42*, 6535–6537. (d) Tanaka, K.; Takeda, K. *Tetrahedron Lett.* **2004**, *45*, 7859–7861. (e) Tanaka, K.; Masu, H.; Yamaguchi, K.; Takeda, K. *Tetrahedron Lett.* **2005**, *46*, 6429–6432.

(14) For reviews on the Brook rearrangement, see: (a) Brook, A. G.; Bassindale, A. R. In *Rearrangements in Ground and Excited States*; de Mayo, P., Ed.; Academic Press: New York, 1980; pp 149−221. (b) Brook, A. G. *Acc. Chem. Res.* **1974**, *7*, 77–84. (c) Moser, W. H. *Tetrahedron* **2001**, *57*, 2065–2084.

(15) In our system, reactions conducted at temperatures from 0 to 70 °C generally gave approximately 95(*Z*):5(*E*)-diastereomeric mixture. The ratio was easily determined by the NMR measurement of crude samples. (*Z*)-Fluoroalkene compounds have coupling constants of $^3J_{HF} = 35.3-37.0$. (*E*)-Fluoroalkenes have smaller coupling constants of $^3J_{HF} = 20.0-21.2$. Compounds possessing (*E*)-geometry were obtained as (*Z*)/(*E*)-mixture, and further purification was not conducted in this study.

TABLE 1. Cyanide Ion-Mediated Synthesis of AM-FADIs



entry[a]	silane	amine (equiv)	solvent	temp (°C)	time[b] (h)	product (yield %[c] (*Z*:*E*)[d])
1	**1**	$BnNH_2$ (1.05)	Et_2O	0	2	**5a** (82 (92:8))
2	**1**	$BnNH_2$ (1.05)	THF	0	7.5	**5a** (73 (95:5))
3	**1**	$BnNH_2$ (5.0)	Et_2O	0	2.5	**5a** (89 (93:7))
4	**1**	$BnNH_2$ (5.0)	THF	0	7.5	**5a** (85 (95:5))
5[e]	**1**	$BnNH_2$ (5.0)	THF	−78	12	**5a** (95 (100:0))
6	**1**	H-Gly-OEt[g] (5.0)	THF	0	2	**5b** (93 (94:6))
7	**1**	H-Val-OMe[g] (5.0)	THF	0	3	**5c** (90 (94:6))
8	**1**	H-Pro-OMe[g] (5.0)	THF	0	3	**5d** (84 (96:4))
9	**2**	H-Gly-OEt[g] (5.0)	THF	0	2	**6b** (93 (95:5))
10	**2**	H-Val-OMe[g] (5.0)	THF	0	4.5	**6c** (88 (94:6))
11	**2**	H-Pro-OMe[g] (5.0)	THF	0	2.5	**6d** (88 (95:5))
12[f]	**1**	H-Gly-OEt[g] (5.0)	DMF	0	2	**5b** (quant. (95:5))

[a] Prior to the addition of amines, reaction mixtures containing acylsilane, KCN, and 18-crown-6 were stirred at 0 °C until acylsilane disappeared (ca. 0.5−1 h). [b] Reaction time after addition of amines. [c] Combined yield. [d] *E*/*Z* ratios were determined by NMR analysis. [e] Instead of KCN/18-crown-6, 2 equiv of *n*-Bu_4NCN was used. In this case, no (*E*)-isomer was detected. [f] Reaction was performed without 18-crown-6. [g] In situ formed amines from the corresponding HCl salts and Et_3N were used.

SCHEME 2

yield (entry 12). The results obtained here encouraged us to evaluate the straightforward incorporation of FADIs into peptides by solid-phase peptide synthesis, reported later in this study.

Next we tried to incorporate α-substitution in AM-FADIs. Direct/one-pot α-alkylation of the possible dienolate intermediate **12** resulting from the treatment of enoylsilanes with KCN/18-crown-6 was attempted. Reaction of **1** with KCN/18-crown-6 in THF at −78 °C followed by the addition of allyl bromide and benzyl amine sequentially afforded the exclusively *O*-allylated product **14** in 89% isolated yield (Scheme 2). Transformation to tin enolates by the addition of Bu_3SnCl, Ph_3SnCl, or Ph_3SnCl/HMPA to the dienolate solution gave no desired α-allylated product with the accompanying *O*-allylated product and α-nonsubstituted benzyl amide **5a** in varying ratios.

Although other possible procedures based on the direct/one-pot strategy were ruled out, we decided to explore other strategies where the synthesis of AM-FADIs with amide-type chiral auxiliaries such as oxazolidinone (**HXa**)[16] or sultam (**HXb**)[17] and subsequent chiral auxiliary-guided alkylation were involved. We first examined the preparation of chiral auxiliary **X**-possessing FADIs (**X**-FADI **15**). Examination of the reactions is summarized in Table 2.

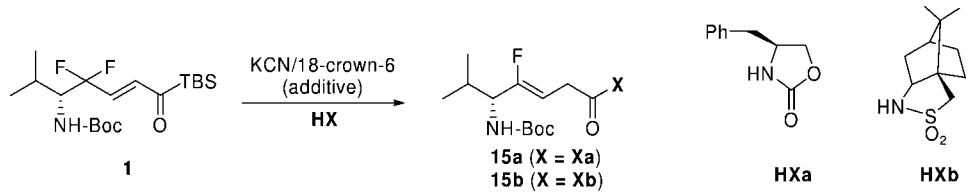
Evans' oxazolidinone **HXa** was first selected as an incorporated auxiliary. The reaction of enoylsilane **1** with a stoichiometric amount of KCN/18-crown-6 (1.05 equiv each) in THF at 0 °C with stirring until the starting material disappeared followed by addition of oxazolidinone (**HXa**) afforded the desired auxiliary-containing FADI **15a**, albeit in low chemical yield (37%, Table 2, entry 1). The reaction at an elevated temperature did not improve the chemical yield. Addition of such additives that promote the acylation of the auxiliary was also not so effective (Table 2, entries 3−6). On the basis of these results, we envisioned that the reason for the low chemical yields was attributable to the stoichiometric amount of cyanide anion as shown in Scheme 3.

A reaction with a stoichiometric amount of cyanide anion followed by 1,2-Brook rearrangement and a subsequent redox reaction consumed the starting enoylsilane **1** to give dienolate **12**, which, upon protonation by a chiral auxiliary, resulted in the formation of acyl cyanide **13** and the nucleophilic amide anion of the auxiliary. To the resulting acyl cyanide **13**, two courses of reactions are possible: one is the nucleophilic attack of the auxiliary anion to give desired FADI **15a**; the other is the reaction with DMAP to give acyl-DMAP **16** which has higher reactivity to the auxiliary anion than the acyl cyanide **13**. Therefore, preferential formation of the acyl-DMAP seemed to be the one critical issue to achieve high chemical yield in the preparation of the FADIs. Using a stoichiometric amount of the cyanide anion, the regenerated anion was involved in the reversed reaction from **16** to **13**, which probably attributed to the low chemical yield. On the other hand, if a catalytic amount of cyanide anion was used, we speculated that the regenerated cyanide anion resulting from the reaction of the acyl cyanide with DMAP could preferentially attack the remaining enoylsilane **1** to lead to the unequivocal involvement of the acyl-DMAP **16** in the acylation of the auxiliary. On the basis of this assumption, a reaction using a catalytic amount of cyanide anion was attempted. Treatment of **1** with KCN/18-crown-6 (0.1 equiv each) and the oxazolidinone **HXa** in the presence of DMAP in THF (0.1 M concentration) gave the **Xa**-FADI **15a** in moderate yield (59%). Increasing the concentrations of the reactants from 0.1 to 0.3 M improved the chemical yield (64%). A reaction with Oppolzer's sultam **HXb** with catalytic KCN completed in 2 h to yield the desired **Xb**-FADI **15b** in 95% isolated yield, whereas the stoichiometric reaction gave **15b** in 44% yield (Table 2, entries 9 and 10).

(16) (a) Evans, D. A.; Bartoli, J.; Shih, T. L. *J. Am. Chem. Soc.* **1981**, *103*, 2127–2129. (b) Evans, D. A.; Ennis, M. D.; Le, T.; Mandel, N.; Mandel, G. *J. Am. Chem. Soc.* **1984**, *106*, 1154–1156. (c) Evans, D. A.; Britton, T. C. *J. Am. Chem. Soc.* **1987**, *109*, 6881–6883.

(17) (a) Oppolzer, W.; Chapuis, C.; Bernardinelli, G. *Helv. Chim. Acta* **1984**, *67*, 1397–1401. (b) Oppolzer, W.; Mills, R. J.; Reglier, M. *Tetrahedron Lett.* **1986**, *27*, 183–186. (c) Oppolzer, W. *Tetrahedron* **1987**, *43*, 1969–2004.

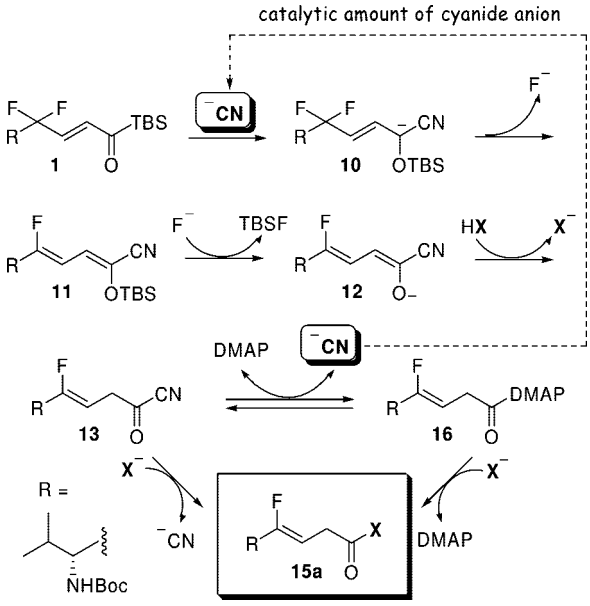
TABLE 2. Cyanide Ion-Mediated Synthesis of Chiral Auxiliary-Possessing FADIs



entry	auxiliary	KCN (equiv)	additive	time (h)	temp. (°C)	yield[a] (*Z*:*E*[b])
1	**HXa**	1.05		18	40	37
2	**HXa**	1.05		18	70	26 (94:6)
3	**HXa**	1.05	imidazole (1.1)	18	40	35 (95:5)
4	**HXa**	1.05	DMAP (1.1)	18	40	39 (95:5)
5	**HXa**	1.05	DMAP (10)	18	40	43 (95:5)
6	**HXa**	1.05	HOAt (1.1)	18	40	[d]
7	**HXa**	0.1	DMAP (1.1)	20	40	59 ([c])
8	**HXa**	0.1	DMAP (1.1)	11	40	68 (92:8)
9	**HXb**	1.05	DMAP (1.1)	20	40	44 ([c])
10	**HXb**	0.1	DMAP (1.1)	2	40	95 (93:7)

[a] Combined yield of (*Z*)- and (*E*)-isomers. [b] *E*/*Z* ratios were determined by NMR analyses. [c] Not determined. [d] No desired product was obtained.

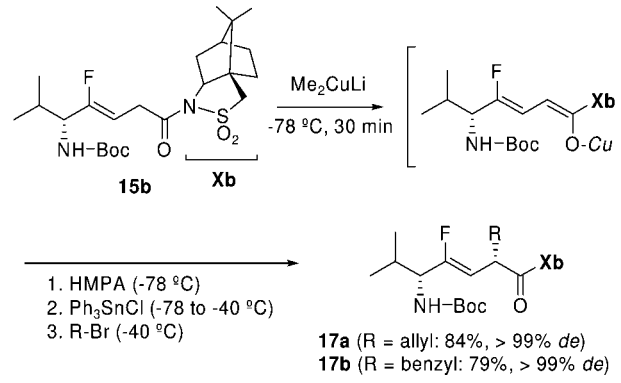
SCHEME 3



Having the chiral auxiliary-incorporated FADI in high chemical yield, we next examined the chiral auxiliary-guided incorporation of a substitution at the α-position of the FADI **15**. Initially attempted aldol reactions of **15b** utilizing titanium[18]- or borane-enolate[19] did not afford satisfactory results to our demands.[20] Additionally, Na- or Li-enolate for α-alkylation was proven to decompose.

Here, we became interested in the synthesis of α-substituted FADIs by the reaction of γ,γ-difluoro-α,β-enoylsultam with an organocopper followed by α-alkylation via transmetalation from the resulting Cu-enolate to a corresponding Sn-enolate.[21] Treatment of the auxiliary-possessing FADI with an organocopper reagent followed by a sequence of reactions consisting of conversion to Sn-enolate and α-alkylation was next evaluated (Scheme 4). The reaction of **15b** with Gillman cuprate ($Me_2CuLi\cdot LiI\cdot LiBr$) followed by the subsequent addition of Ph_3SnCl/HMPA and allylbromide or benzyl bromide yielded the α-alkylated product **17** in a highly diastereoselective manner.[22]

SCHEME 4



Next, we turned our attention to the straightforward incorporation of FADIs into the peptide backbone by solid phase protocols. As a model peptide, we selected a nociceptin/orphanin FQ (N/OFQ) analogue.[23] The N/OFQ is a neuropeptide characterized by the following sequence: H-Phe-Gly-Gly-Phe-Thr-Gly-Ala-Arg-Lys-Ser-Ala-Arg-Lys-Leu-Ala-Asn-Gln-OH. This neuropeptide modulates several biological functions at the peripheral and central levels by selectively activating an ORL1 (opioid receptor-like **1**) receptor. Extensive efforts to develop the receptor antagonist have continued, where an N/OFQ analogue possessing *N*-terminal Phe-Ψ[CH_2−NH]-Gly isostere ((Phe[1]Ψ(CH_2−NH)Gly[2])N/OFQ(1−13)-NH_2, **18**) is known to

(18) (a) Saksena, A. K.; Girijavallabhan, V. M.; Wang, H.; Liu, Y.-T.; Pike, R. E.; Ganguly, A. K. *Tetrahedron Lett.* **1996**, *36*, 5657–5660. (b) Watson, R. J.; Batty, D.; Baxter, A. D.; Hannah, D. R.; Owen, D. A.; Montana, J. G. *Tetrahedron Lett.* **2002**, *43*, 683–685. (c) Bandur, N. G.; Harms, K.; Koert, U. *Synthesis* **2007**, *17*, 2720–2730. (d) Beshore, D. C.; Smith, A. B., III. *J. Am. Chem. Soc.* **2007**, *129*, 4148–4149.

(19) (a) Oppolzer, W.; Blagg, J.; Rodriguez, I.; Walther, E. *J. Am. Chem. Soc.* **1990**, *112*, 2767–2772. (b) Wu, Y.; Liao, X.; Wang, R.; Xie, X.-S.; De Brabander, J. K. *J. Am. Chem. Soc.* **2002**, *124*, 3245–3253. (c) Fraser, B.; Permutter, P. *J. Chem. Soc., Perkin Trans. 1* **2002**, 2896–2899.

(20) Hydroxymethylation is a useful transformation for the preparation of a wide variety of FADIs. Reaction with paraformaldehyde or trioxane under various conditions did not always lead to the reproducible result. No synthetically useful result was obtained.

(21) Narumi, T.; Niida, A.; Tomita, K.; Oishi, S.; Otaka, A.; Ohno, H.; Fujii, N. *Chem. Commun.* **2006**, 4720–4722.

(22) No α-epimers were detected in the crude materials.

(23) For a recent review on the nociceptin/orphanin FQ peptide (N/OFQ), see: Lambert, D. G. *Nat. Rev. Drug Discovery* **2008**, *7*, 694–710.

exhibit partial agonistic activity.[24] We were interested in the replacement of the *N*-terminal reduced amide isoster unit in **18** with FADI (PheΨ(CF═CH)Gly).

Standard Fmoc-based solid phase protocols on the Rink amide resin gave the protected peptide chain **19** corresponding to N/OFQ(3−13), on which the Boc-protected FADI corresponding to the L-Phe-Gly sequence was introduced under the reaction conditions mentioned below. Conversion of the dienolate anion such as **12** to the acyl cyanide requires the presence of an appropriate proton source. Excessively added amines worked as both proton sources and nucleophiles in the experiment shown in Table 1. In the case of solid phase peptide synthesis, excess carboxy components are used for amines on resin, and therefore, a proton source which promotes amidation is necessary. For this purpose, the general amidation promoter, 1-hydroxybenzotriazole (HOBt), was used. Conversion of enoylsilane **2** (5 equiv to the resin) to the corresponding dienolate was effected by treatment with KCN (5.25 equiv) in DMF at room temperature for 30 min. Then, reaction of the peptidyl resin with the resulting mixture in the presence of HOBt was performed under microwave irradiation conditions (12 min at 100 °C, measured by the internal infrared sensor of the microwave apparatus).[25] The attempted reaction proceeded smoothly in 12 min to yield the protected resin corresponding to N/OFQ (1−13) analogue **20**. Deprotection of the completed resin with TFA−thioanisole−*m*-cresol−EDT−H_2O (80:5:5:5:5, v/v) at room temperature for 1 h gave crude deprotected (Phe[1]Ψ(CF═CH)Gly[2])N/OFQ(1−13)-NH_2 **20**. HPLC analysis of crude peptides indicated that the straightforward incorporation of the FADI unit was efficiently achieved (Figure 3). HPLC purified N/OFQ analogue **20** was subjected to the ligand−receptor competitive binding assay using COS-7 cells expressing the human ORL1 receptor.[26] Compared with reference analogue **18**, peptide **20** exhibited a 10-fold high binding affinity (**18**, IC_{50} 32.2 nM vs **20**, 3.34 nM) although the affinity was less than that of nociceptin itself (0.73 nM).

In conclusion, synthesis of amide-type FADIs (AM-FADIs) from the enoylsilanes was accomplished by the intramolecular redox reaction mediated by the cyanide anion in the presence of a wide variety of amines. This redox type amidation protocol was successfully applied to the synthesis of chiral auxiliary-incorporated FADIs, which was then used for stereoselective incorporation of α-substituent. Straightforward incorporation of FADIs into peptidyl resin was also accomplished by reductive amidation protocols under microwave irradiation conditions.

Experimental Section

Benzyl (5*R*,3*Z*)-5-[*N*-(*tert*-Butoxycarbonyl)amino]-4-fluoro-6-methylhept-3-eneamide (5a) from 1 (Table 1, entries 1−5). To a solution of KCN (7.8 mg, 0.12 mmol) and 18-crown-6 (32 mg, 0.12 mmol) in solvent (entry 1, Et_2O, 1.0 mL; entry 2, THF, 1.0 mL; entry 3, Et_2O, 0.5 mL; entry 4, THF, 0.5 mL) was added substrate **1** (45 mg, 0.11 mmol) in solvent (entry 1, Et_2O, 1.0 mL; entry 2, THF, 1.0 mL; entry 3, Et_2O, 0.5 mL; entry 4, THF, 0.5 mL) at 0 °C with additional stirring at this temperature for 1−2 h. After complete consumption of starting material **1**, benzylamine (13 μL, 0.12 mmol for entries 1 and 2 or 48 μL, 0.57 mmol for entries 3 and 4) was added to the reaction mixture at 0 °C. After being stirred at 0 °C for the period indicated in Table 1, the reaction was quenched by the addition of saturated $NaHCO_3$(aq) and extracted with Et_2O. The extract was washed with 1 M HCl, saturated $NaHCO_3$(aq), and brine and dried over $MgSO_4$. Concentration under reduced pressure followed by column chromatography on silica gel with EtOAc−*n*-hexane (1:4) gave the title compound **5a** and its (*E*)-isomer (entry 1) or their mixture (entries 2−4). Entry 1: (*Z*):(*E*) = 92:8 (88:12) in 82% combined yield (ratio in parenthesis indicates the (*Z*)/(*E*) ratio of isolated materials). Entry 2: (*Z*):(*E*) = 95:5 in 73% combined yield. Entry 3: (*Z*):(*E*) = 93:7 in 89% combined yield. Entry 4: (*Z*):(*E*) = 95:5 in 85% combined yield.

For entry 5, 2 equiv of *n*-Bu_4NCN were used for the cyanide ion source for 30 min at −78 °C. Then, at −78 °C, a procedure similar to that described above was applied for the preparation of **5a**.

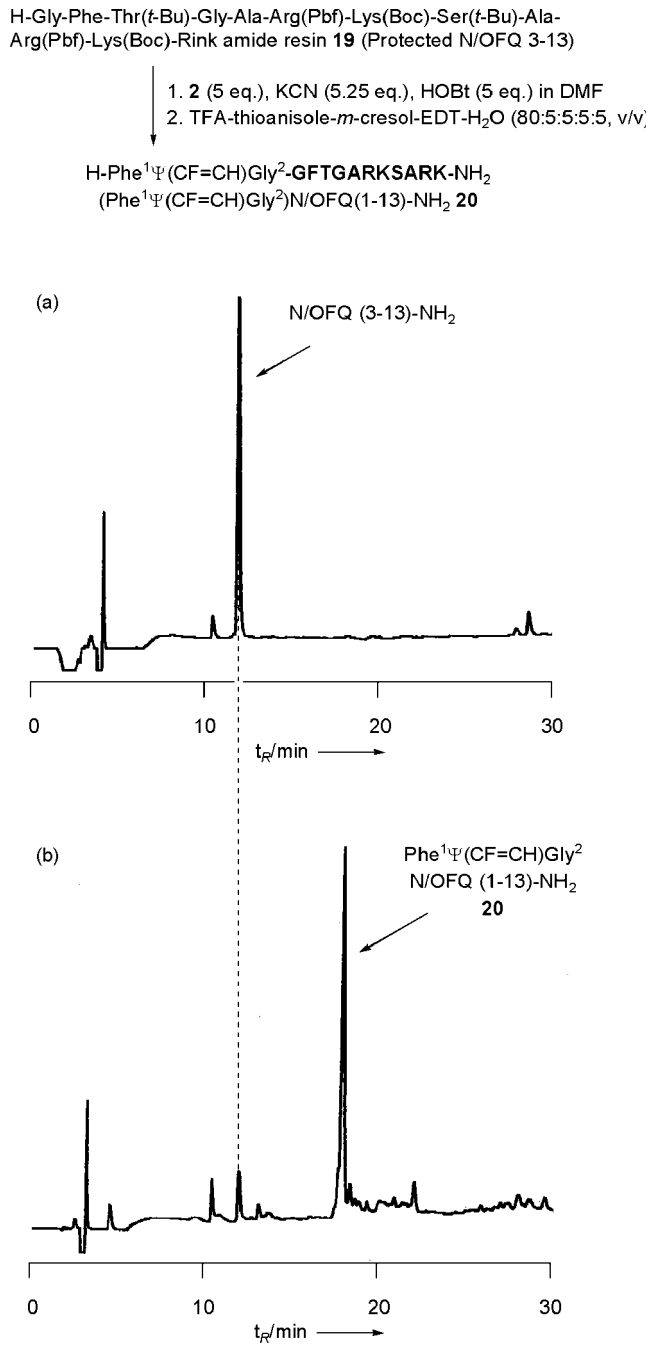


FIGURE 3. Synthesis of N/OFQ analogue **20** and HPLC examination of the straightforward incorporation of FADI into peptidyl resin.

(24) Guerrini, R.; Calo, G.; Rizzi, A.; Bigoni, R.; Bianchi, C.; Salvadori, S.; Regoli, D. *Br. J. Pharmacol.* **1998**, *123*, 163–165.
(25) For a recent review on microwave irradiation, see: Kappe, C. O. *Chem. Soc. Rev.* **2008**, *37*, 1127–1139.
(26) Li, J.; Isozaki, K.; Okada, K.; Matsushima, A.; Nose, T.; Costa, T.; Shimohigashi, Y. *Bioorg. Med. Chem.* **2008**, *16*, 2635–2644.

5a: white powder, mp 116−117 °C. $[\alpha]_D^{26}$ + 1.1 (*c* 1.24, $CHCl_3$). ^1H NMR (400 MHz, $CDCl_3$, δ): 0.94 (d, J = 6.8 Hz, 3H), 0.95 (d, J = 6.8 Hz, 3H), 1.38 (s, 9H), 1.89 (sext, J = 6.8 Hz, 1H), 3.03 (dd, J = 7.8 and 16.6 Hz, 1H), 3.15 (dd, J = 7.8 and 16.6 Hz, 1H), 3.86 (dt, J = 7.8 and 20.8 Hz, 1H), 4.41 (dd, J = 5.8 and 14.8 Hz, 1H), 4.46 (dd, J = 5.8 and 14.8 Hz, 1H), 4.69 (d, J = 6.4 Hz, 1H), 4.99 (dt, J = 7.8 and 36.4 Hz, 1H), 6.42 (br s, 1H), 7.23−7.33 (m, 5H). ^{13}C NMR (75 MHz, $CDCl_3$, δ): 18.3, 19.2, 28.1, 29.6, 31.2 (d, 5.0 Hz), 43.4, 57.8 (d, J = 27.8 Hz), 79.7, 100.3 (d, J = 13.6 Hz), 127.2, 127.5, 128.4, 138.2, 155.3, 159.6 (d, J = 260.3 Hz), 170.0. HRMS (ESI), *m*/*z*: (M + Na^+) calcd for $C_{20}H_{29}FN_2NaO_3$, 387.2060; found, 387.2053. Anal. Calcd for $C_{20}H_{29}FN_2O_3$: C, 65.91; H, 8.02; N, 7.69. Found: C, 65.94; H, 8.12; N, 7.58.

(*E*)-isomer of **5a**: colorless oil. ^1H NMR (400 MHz, $CDCl_3$, δ): 0.93 (d, J = 6.8 Hz, 3H), 1.03 (d, J = 6.8 Hz, 3H), 1.30 (s, 9H), 1.83 (dsext, J = 6.8 and 9.0 Hz, 1H), 2.87 (dt, J = 4.4 and 14.0 Hz, 1H), 3.22 (ddd, J = 2.4, 12.0, and 14.0 Hz, 1H), 4.06 (dt, J = 9.0 and 29.6 Hz, 1H), 4.33 (dd, J = 6.0 and 15.2 Hz, 1H), 4.48 (dd, J = 6.0 and 15.2 Hz, 1H), 4.79 (d, J = 8.0 Hz, 1H), 5.40 (ddd, J = 5.2, 12.0, and 20.4 Hz, 1H), 7.21−7.32 (m, 5H), 7.48 (br s, 1H).

General Procedure for the Synthesis of Tripeptide Mimetics (Table 1, entries 6−12). To a solution of KCN (7.8 mg, 0.12 mmol) and 18-crown-6 (32 mg, 0.12 mmol) in solvent (0.5 mL of Et_2O, THF, or DMF in the absence of 18-crown-6) was added enoylsilane **1** or **2** (0.11 mmol) at 0 °C with additional stirring at this temperature until complete consumption of the starting material. To the reaction mixture was added a mixture of amino ester hydrochloride (0.57 mmol) and triethylamine (79 μL, 0.57 mmol) in solvent (0.5 mL of Et_2O, THF, or DMF) at 0 °C. After being stirring at this temperature for the period indicated in Table 1, the reaction was quenched by the addition of $NaHCO_3$(aq) and extracted with Et_2O. The resulting organic layer was washed with 1 M HCl, saturated $NaHCO_3$(aq), and brine and dried over $MgSO_4$. Condensation under reduced pressure followed by column chromatography over silica gel with EtOAc−*n*-hexane (1:2) gave pure (*Z*)- and (*E*)-isomers of FADI-containing tripeptide mimetics or pure (*Z*)-isomer and (*Z*)/(*E*)-mixture.

Entry 5: Boc-D-Val-Ψ[(*Z*)CF═CH]-Gly-Gly-OEt (**5b**), (*E*)-isomer of **5b** = 92:8, 62% combined yield.

5b: white powder, mp 89−90 °C. $[\alpha]_D^{26}$ + 14.9 (*c* 1.02, $CHCl_3$). ^1H NMR (400 MHz, $CDCl_3$, δ): 0.97 (d, J = 6.8 Hz, 6H), 1.28 (t, J = 7.2 Hz, 3H), 1.44 (s, 9H), 1.92 (sext, J = 6.8 Hz, 1H), 3.06 (dd, J = 7.8 and 16.6 Hz, 1H), 3.14 (dd, J = 7.8 and 16.6 Hz, 1H), 3.92 (dt, J = 7.8 and 20.4 Hz, 1H), 4.00 (d, J = 5.2 Hz, 2H), 4.20 (q, J = 7.2 Hz, 2H), 4.76 (d, J = 7.8 Hz, 1H), 5.01 (dt, J = 7.8 and 36.4 Hz, 1H), 6.49 (br s, 1H). ^{13}C NMR (75 MHz, $CDCl_3$, δ): 14.0, 18.3, 19.2, 28.2, 29.7, 30.9 (d, 5.0 Hz), 41.3, 57.7 (d, J = 27.2 Hz), 61.3, 79.7, 99.9 (d, J = 13.0 Hz), 155.3, 159.8 (d, J = 260.3 Hz), 169.6, 170.3. HRMS (ESI), *m*/*z*: (M + Na^+) calcd for $C_{17}H_{29}FN_2NaO_5$, 383.1958; found, 383.1963. Anal. Calcd for $C_{17}H_{29}FN_2O_5$: C, 56.65; H, 8.11; N, 7.77. Found: C, 56.42; H, 8.05; N, 7.74.

(*E*)-isomer of **5b**: colorless oil. ^1H NMR (400 MHz, $CDCl_3$, δ): 0.95 (d, J = 6.8 Hz, 3H), 1.04 (d, J = 6.8 Hz), 1.27 (t, J = 7.2 Hz), 1.45 (s, 9H), 1.85 (dsext, J = 6.8 and 8.8 Hz, 1H), 2.89 (ddd, J = 4.0, 6.0, and 14.4 Hz, 1H), 3.22 (ddd, J = 2.0, 11.4, and 14.4 Hz, 1H), 3.96 (dd, J = 6.0 and 9.2 Hz, 2H), 3.89−4.24 (m, 1H), 4.8 (q, J = 7.2 Hz, 2H), 4.83 (d, J = 8.4 Hz, 1H), 4.38 (ddd, J = 6.0, 11.4, and 20.8 Hz, 1H), 7.39 (br s, 1H).

Entry 6: **5b**, (*E*)-isomer of **5b** = 94:6, 93% combined yield.

Entry 7: Boc-D-Val-Ψ[(*Z*)CF═CH]-Gly-Val-OMe (**5c**), (*E*)-isomer of **5c** = 94:6, 90% combined yield.

5c: white powder, mp 97−99 °C. $[\alpha]_D^{26}$ + 35.8 (*c* 1.05, $CHCl_3$). ^1H NMR (400 MHz, $CDCl_3$, δ): 0.90 (d, J = 6.8 Hz, 3H), 0.93 (d, J = 6.8 Hz, 3H), 0.96 (d, J = 6.8 Hz, 3H), 0.97 (d, J = 6.8 Hz, 3H), 1.44 (s, 9H), 1.93 (sext, J = 6.8 Hz, 1H), 2.16 (sext, J = 6.8 Hz, 1H), 3.09 (d, J = 7.6 Hz, 2H), 3.73 (s, 3H), 3.98 (dt, J = 8.2 and 20.0 Hz, 1H), 4.53 (dd, J = 5.2 and 8.4 Hz, 1H), 4.74 (d, J = 8.2 Hz, 1H), 5.02 (dt, J = 7.6 and 36.4 Hz, 1H), 6.15 (br d, J = 7.6 Hz, 1H). ^{13}C NMR (75 MHz, $CDCl_3$, δ): 17.8, 18.2, 18.8, 19.3, 28.3, 29.6, 31.1, 31.3 (d, J = 5.0 Hz), 52.0, 57.1, 57.3 (d, J = 27.8 Hz), 79.8, 99.8 (d, J = 13.6 Hz), 155.2, 160.1 (d, J = 259.7 Hz), 169.9, 170.3. HRMS (ESI), *m*/*z*: (M + Na^+) calcd for $C_{19}H_{33}FN_2NaO_5$, 411.2271; found, 411.2263. Anal. Calcd for $C_{19}H_{33}FN_2O_5$: C, 58.74; H, 8.56; N, 7.21. Found: C, 58.44; H, 8.45; N, 6.97.

(*E*)-isomer of **5c**: colorless oil. ^1H NMR (400 MHz, $CDCl_3$, δ): 0.95 (d, J = 6.8 Hz, 6H), 1.04 (d, J = 6.4 Hz, 6H), 1.43 (s, 9H), 1.85 (dsext, J = 6.4 and 8.8 Hz, 1H), 2.18 (sext, J = 6.8 Hz, 1H), 2.94 (ddd, J = 3.0, 6.0, and 15.4 Hz, 2H), 3.22 (dd, J = 10.4 and 15.4 Hz, 3H), 3.70 (s, 3H), 4.08 (dt, J = 8.6 and 30.0 Hz, 1H), 4.49 (dd, J = 5.6 and 8.8 Hz, 1H), 4.79 (d, J = 8.6 Hz, 1H), 5.35 (ddd, J = 6.0, 10.4, and 20.4 Hz, 1H), 6.79 (d, J = 8.0 Hz, 1H).

Entry 8: Boc-D-Val-Ψ[(*Z*)CF═CH]-Gly-Pro-OEt (**5d**), (*E*)-isomer of **5d** = 96:4, 84% combined yield.

5d: colorless oil. $[\alpha]_D^{26}$ − 21.9 (*c* 3.09, $CHCl_3$). ^1H NMR (400 MHz, $CDCl_3$, δ): 0.93 (d, J = 6.8 Hz, 3H), 0.95 (d, J = 6.8 Hz, 3H), 1.44 (s, 9H), 1.90−2.21 (m, 5H), 2.92 (dd, J = 6.0 and 17.2 Hz, 1H, minor rotamer), 3.07−3.16 (m, 1H), 3.22 (dd, J = 7.0 and 17.2 Hz, 1H), 3.49−3.59 (m, 1H), 3.61−3.68 (br, 1H), 3.72 (s, 3H, major rotamer), 3.76 (s, 3H, minor rotamer), 4.03 (hept, J = 9.2 Hz, 1H), 4.44 (dd, J = 2.6 and 8.6 Hz, 1H, minor rotamer), 4.49 (dd, J = 2.8 and 8.6 Hz, 1H, major rotamer), 4.70 (d, J = 9.2 Hz, 1H), 5.09 (dt, J = 37.6 and 7.0 Hz, 1H). ^{13}C NMR (75 MHz, $CDCl_3$, δ, rotamer): 17.9, 19.2, 22.5, 24.7, 28.3, 29.2, 29.7 (d, J = 3.7 Hz), 29.7 (d, J = 4.4 Hz), 30.1, 46.5, 46.9, 52.2 (major rotamer), 52.6, 57.0 (d, J = 29.0 Hz), 58.7, 59.3, 79.6, 99.7 (d, J = 13.7 Hz), 155.2, 158.7 (d, J = 257.8 Hz), 169.0, 172.5, 172.7. HRMS (ESI), *m*/*z*: (M + Na^+) calcd for $C_{19}H_{31}FN_2NaO_5$, 409.2115; found, 409.2115.

(*E*)-isomer of **5d**: colorless oil. ^1H NMR (400 MHz, $CDCl_3$, δ): 0.93 (d, J = 6.8, 3H), 0.99 (d, J = 6.8 Hz, 3H), 1.44 (s, 9H), 1.82−2.21 (m, 5H), 2.90 (dd, J = 6.8 and 16.8 Hz, 1H, minor rotamer), 3.07−3.16 (m, 2H), 3.53 (m, 1H), 3.68 (br s, 1H), 3.61−3.68 (br, 1H), 3.72 (s, 3H, major rotamer), 3.78 (s, 3H, minor rotamer), 4.15 (dt, J = 9.2 and 30.0 Hz, 1H), 4.48 (dd, J = 3.2 and 8.4 Hz, 1H), 4.85 (d, J = 9.2 Hz, 1H), 5.44 (dt, J = 6.8 and 21.2 Hz, 1H).

Entry 9: Boc-L-Phe-Ψ[(*Z*)CF═CH]-Gly-Gly-OEt (**6b**), (*E*)-isomer of **6b** = 95:5, 93% combined yield.

6b: white powder, mp 64−65 °C. $[\alpha]_D^{22}$ + 6.3 (*c* 1.04, $CHCl_3$). ^1H NMR (400 MHz, $CDCl_3$, δ): 1.28 (t, J = 7.0 Hz, 3H), 1.40 (s, 9H), 2.96 (d, J = 7.2 Hz, 2H), 3.03 (d, J = 7.6 Hz, 2H), 3.90 (d, J = 5.6 Hz, 1H), 4.20 (q, J = 7.0 Hz, 2H), 4.43 (m, 1H), 4.79 (m, 1H), 4.86 (dt, J = 7.6 and 35.6 Hz, 1H), 6.06 (br s, 1H), 7.18−7.31 (m, 5H). ^{13}C NMR (75 MHz, $CDCl_3$, δ): 14.1, 28.2, 31.0, 38.1, 41.3, 53.1 (d, J = 29.1 Hz), 61.4, 80.1, 100.2 (d, J = 13.0 Hz), 126.8, 128.6, 129.2, 136.4, 154.8, 159.4 (d, J = 259.6 Hz), 169.6, 170.0. HRMS (ESI), *m*/*z*: (M + Na^+) calcd for $C_{21}H_{29}FN_2NaO_5$, 431.1958; found, 431.1974.

(*E*)-isomer of **6b**: colorless oil. ^1H NMR (400 MHz, $CDCl_3$, δ): 1.26 (t, J = 7.0 Hz, 3H), 1.42 (s, 9H), 2.51 (dd, J = 4.4 and 15.2 Hz, 1H), 2.82−2.99 (m, 3H), 3.80 (dd, J = 5.2 and 17.6 Hz, 1H), 3.90 (dd, J = 5.6 and 17.6 Hz, 1H), 4.17 (q, J = 7.0 Hz, 2H), 4.66 (m, 1H), 4.79 (br d, J = 7.2 Hz, 1H), 5.24 (ddd, J = 6.8, 10.0, and 20.0 Hz, 1H), 6.84 (br s, 1H), 7.20−7.31 (m, 5H).

Entry 10: Boc-L-Phe-Ψ[(*Z*)CF═CH]-Gly-Val-OMe (**6c**), (*E*)-isomer of **6c** = 94:6 (determined by NMR measurement of the crude materials), 88% combined yield.

6c: white powder, mp 118−120 °C. $[\alpha]_D^{26}$ + 13.9 (*c* 1.04, $CHCl_3$). ^1H NMR (400 MHz, $CDCl_3$, δ): 0.89 (d, J = 6.8 Hz, 3H), 0.92 (d, J = 6.8 Hz, 3H), 1.38 (s, 9H), 2.14 (dsept, J = 5.6 and 6.8 Hz, 1H), 2.88−3.11 (m,, 4H), 3.73 (s, 3H), 4.48−4.51 (m, 1H), 4.50 (dd, J = 5.6 and 8.8 Hz, 1H), 4.71 (br s, 1 H), 4.93 (dt, J = 7.2 and 36.4 Hz, 1H), 6.09 (br s, 1H), 7.17−7.31 (m, 5H). ^{13}C NMR (75 MHz, $CDCl_3$, δ): 17.9, 18.9, 28.2, 31.1, 31.3 (d, J = 4.7 Hz),

38.4, 52.1, 52.7 (d, J = 31.5 Hz), 57.2, 80.0, 99.8 (d, J = 13.1 Hz), 126.9, 128. 5, 129.2, 136.3, 154.7, 159.6 (d, J = 259.0 Hz), 169.7, 172.3. HRMS (ESI), m/z: (M + Na^+) calcd for $C_{23}H_{33}FN_2NaO_5$, 459.2271; found, 459.2252.

(*E*)-isomer of **6c**: colorless oil. ^{1}H NMR (400 MHz, $CDCl_3$, δ): 0.89 (d, J = 6.8 Hz, 3H), 0.92 (d, J = 6.8 Hz, 3H), 1.42 (s, 9H), 2.13 (sept, J = 6.0 Hz, 1H), 2.86−3.11 (m, 4H), 3.68 (s, 3H), 4.42 (dd, J = 5.6 and 8.8 Hz, 1H), 4.51−4.67 (m, 1H), 4.71 (br d, J = 6.4 Hz, 1H), 5.22 (ddd, J = 5.6, 10.7, and 20.0 Hz, 1H), 6.66 (br d, J = 8.8 Hz 1H), 7.17−7.31 (m, 5H).

Entry 11: Boc-L-Phe-Ψ[(*Z*)CF═CH]-Gly-Pro-OMe (**6d**), (*E*)-isomer of **6d** = 95:5 (determined by NMR measurement of the crude materials), 88% combined yield.

6d: colorless oil. $[\alpha]_D^{26}$ − 33.0 (c 1.07, $CHCl_3$). ^{1}H NMR (400 MHz, $CDCl_3$, δ): 1.37 (s, 9H), 1.97−2.19 (m, 5H), 2.88 (m, 1H), 2.99 (dd, J = 6.4 and 14.4 Hz, 1H), 3.07 (dd, J = 6.2 and 16.4 Hz, 1H), 3.19 (dd, J = 7.6 and 17.2 Hz, 1H), 3.42−3.49 (m, 1H), 3.56−3.60 (m, 1H), 3.72 (s, 3H, major rotamer), 3.77 (s, 3H, minor rotamer), 4.37 (dd, J = 3.0 and 8.4 Hz, 1H, minor rotamer), 4.45 (dd, J = 3.6 and 8.4 Hz, 1H, major rotamer), 4.65 (br, 1H), 5.03 (dt, J = 6.4 and 37.6 Hz, 1H). ^{13}C NMR (75 MHz, $CDCl_3$, δ, rotamer): 22.5, 24.7, 28.2, 29.2, 29.7, 29.7 (d, J = 4.4 Hz), 31.5, 38.6, 46.5, 46.9, 52.2, 52.6, 58.7, 59.3, 79.8, 99.7 (d, J = 11.8 Hz), 126.7, 128.4, 129.3, 136.6, 154.7, 158.5 (d, J = 256.5 Hz), 168.8, 172.3. HRMS (ESI), m/z: (M + Na^+) calcd for $C_{23}H_{31}FN_2NaO_5$, 457.2115; found, 457.2131.

(*E*)-isomer of **6d**: Characteristic signal for (*E*)-isomer. ^{1}H NMR (400 MHz, $CDCl_3$ δ): 5.36 (dt, J = 20.8 and 7.2 Hz, 1H).

Entry 12: **5b**, (*E*)-isomer of **5b** = 95:5 (determined by NMR measurement of the crude materials); 100% combined yield.

***O*-Allylated Diene 14.** Conversion of enoylsilane **1** to dienolate **12** was performed by the procedure described above. To the resulting mixture was added ally bromide (5.0 equiv) with stirring at 0 °C for 2 h. Then benzyl amine (5.0 equiv) was added to the mixture. After 2 h reaction at 0 °C, usual workup procedures were applied to the isolation of the products (89% isolated yield). Obtained products were proven to be a mixture of diastereomers at the diene part of the *O*-allylated diene by NMR measurement. Compound **14**: colorless oil. ^{1}H NMR (400 MHz, $CDCl_3$, δ): 0.95 (d, J = 6.8 Hz, 6H), 1.45 (s, 9H, major isomer), 1.46 (s, 9H, minor isomer), 1.94 (sept, J = 6.8 Hz, 1H), 3.85 (br s, 1H, minor isomer), 4.03 (dt, J = 20.2 and 8.8 Hz, 1H), 4.41 (d, J = 5.2 Hz, 1H, minor isomer), 4.51 (d, J = 5.6 Hz, 1H, major isomer), 4.73 (br d, J = 8.8 Hz, 1H), 5.04 (d, J = 10.0 Hz, 1H, minor isomer), 5.11 (d, J = 17.2 Hz, 1H, minor isomer), 5.33 (d, J = 10.0 Hz, 1H, major isomer), 5.40 (d, J = 17.2 Hz, 1H, major isomer), 5.69 (dd, J = 12.0 and 33.2 Hz, 1H, minor isomer), 5.80−5.96 (m, 2H), 6.27 (d, J = 11.2 Hz, 1H, major isomer), 6.43 (d, J = 11.2 Hz, 1H, minor isomer). ^{13}C NMR (75 MHz, $CDCl_3$, δ): 19.0, 19.3, 28.3, 30.3, 57.5 (d, J = 24.8 Hz), 71.1, 72.1, 80.0, 100.4 (d, J = 9.9 Hz), 114.6, 116.2 (d, J = 6.2 Hz), 119.4, 119.8, 126.8 (d, J = 5.6 Hz), 131.3, 131.7, 155.1, 161.2 (d, J = 273.8 Hz). HRMS (ESI), m/z: (M + H^+) calcd for $C_{17}H_{26}FN_2O_3$, 325.1927; found, 325.1927.

(4*R*,5′*R*,3′*Z*)-5′-{[*N*-(*tert*-Butoxycarbonyl)amino]-4′-fluoro-6′-methylhept-3′-enoyl}-4-benzyl-2-oxazolidinone (15a; Table 2, entry 8). To a mixture of KCN (2.0 mg, 0.030 mmol), 18-crown-6 (8.0 mg, 0.030 mmol), and **1** (117 mg, 0.300 mmol) in THF (0.5 mL) was added a solution of (4*R*)-benzyl-2-oxazolidinone (266 mg, 1.50 mmol) and DMAP (40 mg, 0.33 mmol) in THF (0.5 mL) at 0 °C under argon. After being stirred at 40 °C for 11 h, the reaction was quenched by the addition of saturated $NaHCO_3$(aq) and extracted with Et_2O. The extract was washed with brine and dried over $MgSO_4$. Removal of solvent under reduced pressure followed by column chromatography over silica gel with EtOAc−*n*-hexane (1:4) gave the title compound **15a** as white powder: mp 97−100 °C. $[\alpha]_D^{21}$ − 23.0 (c 1.19, $CHCl_3$). ^{1}H NMR (400 MHz, $CDCl_3$, δ): 0.95 (d, J = 6.4 Hz, 3H), 0.98 (d, J = 6.8 Hz, 3H), 1.45 (s, 9H), 1.93 (sext, J = 6.8 Hz, 1H), 2.78 (dd, J = 9.6 and 13.6 Hz, 1H), 3.30 (dd, J = 3.0 and 13.6 Hz, 1H), 3.74 (dd, J = 6.8 and 18.0 Hz, 1H), 3.80 (dd, J = 6.8 and 18.0 Hz, 1H), 4.04 (dt, J = 9.0 and 21.2 Hz, 1H), 4.17−4.24 (m, 2H), 4.67 (m, 1H), 4.75 (d, J = 9.0 Hz, 1H), 5.10 (dt, J = 6.8 and 36.8 Hz, 1H), 7.19−7.36 (m, 5H). ^{13}C NMR (75 MHz, $CDCl_3$, δ): 18.2, 19.3, 28.3, 30.9 (d, 5.0 Hz), 37.7, 55.1, 57.3 (d, J = 27.2 Hz), 66.3, 79.7, 98.5 (d, J = 13.0 Hz), 127.3, 128.9, 129.4, 135.1, 153.3, 155.2, 159.4 (d, J = 260.1 Hz), 170.3. HRMS (ESI), m/z: (M + Na^+) calcd for $C_{23}H_{31}FN_2NaO_5$, 457.2115; found, 457.2109.

(1*R*,5′*R*,3′*Z*)-5′-{[*N*-(*tert*-Butoxycarbonyl)amino]-4′-fluoro-6′-methylhept-3′-enoyl}bornane-10,2-sultam (15b; Table 2, entry 10). To a mixture of KCN (1.0 mg, 0.015 mmol), 18-crown-6 (4.0 mg, 0.015 mmol), and **1** (59 mg, 0.15 mmol) in THF (0.5 mL) was added a solution of (1*R*)-bornane-10,2-sultam (34 mg, 0.16 mmol) and DMAP (20 mg, 0.17 mmol) in THF (0.5 mL) at 0 °C under argon atmosphere. The reaction was stirred at 40 °C for 2 h and then quenched with saturated $NaHCO_3$(aq). The mixture was extracted with Et_2O, and the resulting extract was washed with brine. After being dried over $MgSO_4$, the extract was condensed under reduced pressure to give residues. Column chromatographical purification over silica gel with EtOAc−*n*-hexane (1:4) gave the title compound **15b** as white powder (67.1 mg, 95%): mp 57−60 °C. $[\alpha]_D^{21}$ + 95.9 (c 1.05, $CHCl_3$). ^{1}H NMR (400 MHz, $CDCl_3$, δ): 0.94 (d, J = 6.8 Hz, 3H), 0.95 (d, J = 6.8 Hz, 3H), 0.97 (s, 3H), 1.15 (s, 3H), 1.28−1.44 (m, 2H), 1.44 (s, 9H), 1.87−1.92 (m, 4H), 2.03− 2.12 (m, 2H), 3.44 (d, J = 14.0 Hz, 1H), 3.49−3.56 (m, 2H), 3.62 (dd, J = 6.8 and 18.4 Hz, 1H), 3.86 (dd, J = 5.2 and 7.2 Hz, 1H), 3.99 (dt, J = 8.8 and 20.4 Hz, 1H), 4.72 (d, J = 8.8 Hz, 1H), 5.04 (dt, J = 6.8 and 36.8 Hz, 1H). ^{13}C NMR (75 MHz, $CDCl_3$, δ): 18.2, 19.3, 19.8, 20.8, 26.4, 28.3, 30.3, 30.5 (d, J = 5.0 Hz), 32.8, 38.3, 44.6, 47.8, 48.5, 52.8, 57.1, 57.2 (d, J = 25.4 Hz), 65.3, 79.6, 98.4 (d, J = 12.4 Hz), 155.2, 159.3 (d, J = 260.3 Hz), 169.0. HRMS (ESI), m/z: (M + Na^+) calcd for $C_{23}H_{37}FN_2NaO_5S$, 495.2305; found, 495.2298.

(1*R*,5′*R*,2′*S*,3′*Z*)-{5′-[*N*-(*tert*-Butoxycarbonyl)amino]-4′-fluoro-6′-methylhept-2′-(prop-2″-enyl)-3′-enoyl}bornane-10,2-sultam (17a). To a suspension of CuI (66 mg, 0.35 mmol) in THF (1.0 mL) was added dropwise a solution of MeLi·LiBr complex in Et_2O (1.5 M, 0.46 mL, 0.69 mmol) at −78 °C under argon, and the mixture was stirred for 10 min at 0 °C. To the resulting organocopper reagent was added dropwise a solution of the *N*-enoyl sultam **15b** (40 mg, 0.085 mmol) in THF (1.5 mL) at −78 °C. The mixture was stirred for 30 min at −78 °C, and HMPA (24 μL, 1.4 mmol) was added dropwise to the mixture. After stirring for 30 min at −78 °C, a solution of triphenyltin chloride (67 mg, 0.17 mmol) in THF (1.5 mL) was added dropwise; the mixture was then stirred for 30 min at −40 °C, and allyl bromide (59 μL, 0.70 mmol) was added dropwise. The mixture was stirred for 20 h at −40 °C. The reaction was quenched at −40 °C by addition of a 1:1 saturated NH_4Cl, 28% NH_4OH solution with additional stirring at room temperature for 30 min. The mixture was extracted with Et_2O, and the extract was washed with brine and dried over $MgSO_4$. Concentration under reduced pressure followed by column chromatography over silica gel with EtOAc−*n*-hexane (1:5) gave the title compound **17a** (37 mg, 84%) as colorless oil. $[\alpha]_D^{20}$ 73.47 (c 1.11, $CHCl_3$). ^{1}H NMR (400 MHz, $CDCl_3$, δ): 0.92 (d, J = 6.4 Hz, 3H), 0.93 (d, J = 6.4 Hz, 3H), 0.97 (s, 3H), 1.16 (s, 3H), 1.24−1.40 (m, 2H), 1.44 (s, 9H), 1.85−1.91 (m, 4H), 2.03−2.08 (m, 2H), 2.36 (m, 1H), 2.53 (m, 1H), 3.43 (d, J = 13.6 Hz, 1H), 3.50 (d, J = 13.6 Hz, 1H), 3.87−3.97 (m, 2H), 4.21 (dt, J = 7.0 and 8.0 Hz, 1H), 4.71 (d, J = 9.2 Hz, 1H), 4.90−5.02 (m, 1H), 5.01 (d, J = 9.2 Hz, 1H), 5.07 (d, J = 17.2 Hz, 1H), 5.71−5.81 (m, 1H). ^{13}C NMR (75 MHz, $CDCl_3$, δ): 18.6, 19.3, 19.9, 20.8, 26.4, 28.3, 30.3, 32.8, 38.3, 38.6, 40.7, 44.6, 47.7, 48.3, 53.1, 57.6 (d, J = 25.4 Hz), 65.2, 79.6, 104.1 (d, J = 11.8 Hz), 117.8, 134.0, 155.1, 158.0 (d, J = 260.3 Hz), 172.5. HRMS (ESI), m/z: (M + Na^+) calcd for $C_{26}H_{41}FN_2NaO_5S$, 535.2618; found, 535.2611.

(1*R*,2′*S*,5′*R*,3′*Z*)-{2′-Benzyl-5′-[*N*-(*tert*-butoxycarbonyl)amino]-4′-fluoro-6′-methylhept-3′-enoyl}bornane-10,2-sultam (17b). Experimental procedures identical to those used for the preparation of

17a were employed. Forty milligrams (0.085 mmol) of **15b** was converted to the title compound **17b** (38 mg, 79%) as a colorless oil. $[\alpha]_D^{21}$ 67.3 (*c* 1.14, $CHCl_3$). ^1H NMR (400 MHz, $CDCl_3$, δ): 0.71 (s, 1H), 0.86−0.90 (m, 6H), 0.88 (s, 3H), 1.25−1.36 (m, 2H), 1.45 (s, 9H), 1.74−1.85 (m, 5H), 1.93−1.98 (m, 1H), 2.79 (dd, J = 7.2 and 13.2 Hz, 1H), 3.11 (dd, J = 8.0 and 13.2 Hz, 1H), 3.36 (d, J = 14.0 Hz, 1H), 3.41 (d, J = 14.0 Hz, 1H), 3.78 (br, 1H), 3.90 (dt, J = 9.0 and 24.0 Hz, 1H), 4.45 (dt, J = 8.4 and 7.2 Hz, 1H), 4.64 (d, J = 9.0 Hz, 1H), 4.97 (dd, J = 9.2 and 36.0 Hz, 1H), 7.14−7.26 (m, 5H). ^{13}C NMR (75 MHz, $CDCl_3$, δ): 18.5, 19.1, 19.8, 20.5, 26.4, 28.3, 30.4, 32.7, 38.2, 40.4, 43.0 (d, J = 3.1 Hz), 44.6, 47.6, 48.1, 53.0, 57.6 (d, J = 26.0 Hz), 65.0, 79.5, 104.3 (d, J = 12.4 Hz), 127.1, 128.2, 129.5, 137.5, 155.1, 158.2 (d, J = 259.8 Hz), 172.3. HRMS (ESI), *m*/*z*: ($M + Na^+$) calcd for $C_{30}H_{43}FN_2NaO_5S$, 585.2761; found, 585.2774.

Synthesis of Protected Peptide Resin [N/OFQ(3−13)-NH_2] (19). Protected peptide resin was manually constructed by Fmoc-based solid-phase synthesis. Fmoc deprotection was achieved by 20% piperidine in DMF (10 min). Fmoc-amino acids were coupled by treatment with 3 equiv of reagents [Fmoc-amino acid, diisopropylcarbodiimide (DIPCDI), and HOBt·H_2O] to free amino groups on the resin in DMF for 2 h.

[Phe^1-Ψ(CF=CH)-Gly^2]Nociceptin(1−13)-NH_2 (20). After preactivation of acylsilane **2** (10.6 mg, 0.021 mmol) with KCN (1.60 mg, 0.022 mmol) in DMF (0.10 mL) for 30 min, the protected peptide resin **19** (51.0 mg, 4.25 μmol) in a microwave vial (0.2−0.5 mL) was treated with the resulting activated species and HOBt·H_2O (3.2 mg, 0.02 mmol) in DMF (0.10 mL). The vial was equipped with a magnetic stir bar and capped with a rubber septum. The above mixture was shaken vigorously and then heated in the microwave for 12 min at 100 °C (as measured by the IR sensor of the microwave apparatus). Then the vessel was cooled, and the resin was washed with DMF and CH_2Cl_2. The resulting protected peptidyl resin (10 mg) was treated with thioanisole (25 μL)-TFA (400 μL) in the presence of *m*-cresol (25 μL), 1,2-ethanedithiol (25 μL), and H_2O (25 μL) at room temperature for 2 h. After removal of resin by filtration, ice-cold dry Et_2O was added to the residue. The resulting powder was collected by centrifugation and then washed three times with ice-cold dry Et_2O. The crude peptide was dissolved in 0.1% TFA(aq) solution (400 μL) and analyzed by HPLC. Analytical HPLC condition: linear gradient of solvent B in solvent A, 2−40% over 30 min. Retention time = 17.9 min. MS (ESI-IT): ($M + 2H^+$) calcd for $C_{62}H_{104}FN_{21}O_{14}$, 691.9; found, 692.0. As reference peptides in HPLC analysis, N/OFQ(3−13)-NH_2 was obtained after deprotection identical to those employed for peptide **20**.

N/OFQ(3−13)-NH_2. Analytical HPLC condition: linear gradient of solvent B in solvent A, 2−40% over 30 min. Retention time = 11.9 min. MS (ESI-IT): ($M + 2H^+$) calcd for $C_{50}H_{90}N_{20}O_{13}$, 589.4; found, 589.5.

Receptor-Binding Assay. The receptor-binding assay with cell membranes was conducted in a 96-well format according to literature.[26] The receptor-binding potencies of synthetic peptides were assessed by the radio-ligand ([^{3}H]nociceptin) receptor-binding assay using COS-7 cell membrane preparations expressing human ORL1-Ga fusion receptors. The binding potency of each peptide was estimated as the IC_{50} value, the peptide concentration at which the half-maximal inhibition is achieved.

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Supporting Information Available: Copies of ^1H NMR and ^{13}C NMR spectra of compounds **5a**, **5b**, **5c**, **5d**, **6b**, **6c**, **6d**, **14**, **15a**, **15b**, **17a**, and **17b**. This material is available free of charge via the Internet at http://pubs.acs.org.

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