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BF_3-Mediated *cis*-Selective Cycloaddition of *O*-Silyloxime with Alkenes

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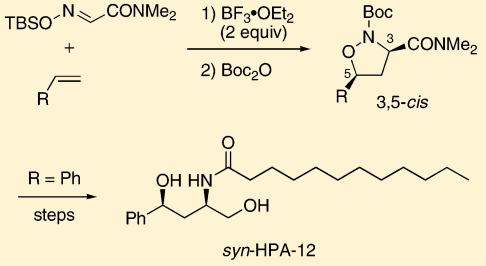
Supporting Information

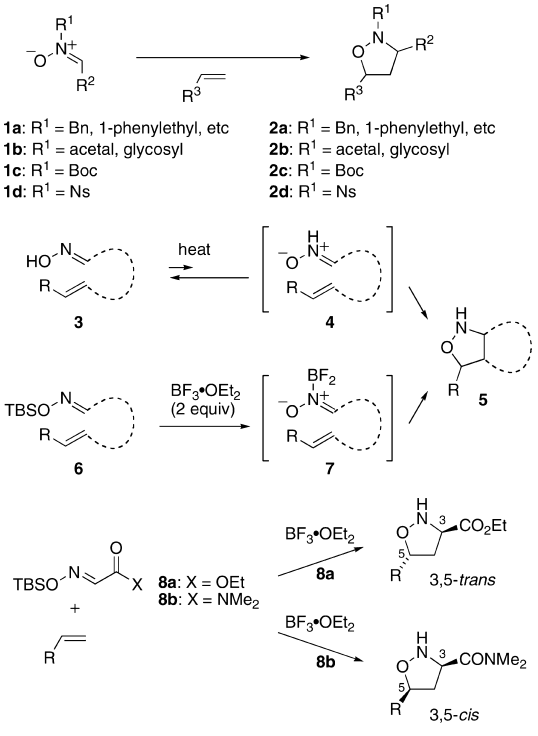
ABSTRACT: A *C*-amide-substituted *O*-silylated oxime, (*E*)-(*tert*-butyldimethylsiloxyimino)acetic acid *N*,*N*-dimethylamide (**8b**), on treatment with 2.2 equiv of BF_3·OEt_2, *in situ* generated boracyclic nitrone-type intermediate BF_3·**14**, which underwent cycloaddition with alkenes to give 3,5-*cis*-isoxazolidines as the major products. The mechanism was strongly supported by isolation of the reaction intermediate **14** that was characterized by X-ray diffraction and its further reaction. This cycloaddition was successfully applied to the synthesis of *syn*-HPA-12 known as an inhibitor of CERT that mediates the transport of ceramide.



Isoxazolidines have attracted much attention as the synthetic intermediates for 1,3-amino alcohols, and most of them have been synthesized by 1,3-dipolar cycloaddition of alkenes with *N*-benzylnitrone derivatives **1a** (Scheme 1).[1] After cycloaddition the benzyl groups of **2a** are usually removed by hydrogenolysis. However, N−O bonds of isoxazolidines **2a** are also labile under these conditions, hence chemoselective cleavage of either *N*-benzyl groups or N−O bond would be difficult. To overcome this problem, nitrones **1b** having acid-removable acetal-type substituents including glycosyl groups have been employed.[2] Recently, *N*-Boc[3] substituted and *N*-nosyl[4] substituted nitrones **1c** and **1d** were reported to provide isoxazolidines having electron-withdrawing protective groups that facilitate reductive cleavage of N−O bond and that can be readily removed. In this context, *N*-nonsubstituted isoxazolidines **5** would also be attractive since they can be protected with usual *N*-protective groups such as carbamate and sulfonyl groups. One of the simplest ways to synthesize *N*-nonsubstiuted isoxazolidines would be intramolecular oxime−olefin cycloadditions (IOOC) of oximes having olefin moieties **3** via *N*-nonsubstituted nitrones **4**.[5] However, most of these reactions require high temperature and long reaction periods. In contrast to IOOC, we reported that *O*-silylated oximes **6** having olefin moieties, on treatment BF_3·OEt_2, underwent intramolecular cycloaddition via *N*-boranonitrones **7** under very mild conditions.[6] More recently, it was also reported that intermolecular cycloaddition of *C*-ester substituted *O*-silylated oxime **8a** afforded 3,5-*trans*-cycloadducts as the major isomers.[7] In this paper, we would like to report that cycloaddition of *C*-amide substituted *O*-silylated oxime **8b** in the presence of BF_3·OEt_2 produces 3,5-*cis*-cycloadducts predominantly probably via complex BF_3·**14** (Scheme 3). The direct application of the present cycloaddition to the synthesis of *syn*-HPA-12 is also reported.

The starting *O*-silyl oxime **8b** was readily prepared from tartaric acid dimethyl amide (**9**) in 3 steps (Scheme 2). Thus, oxidative cleavage of **9** with periodic acid yielded aldehyde **10**.[8]

Scheme 1



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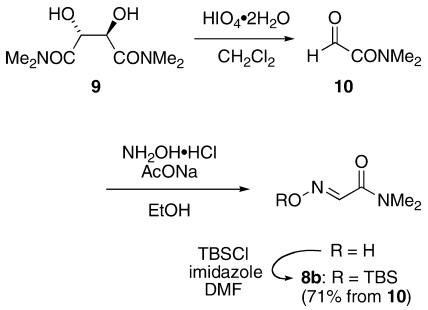
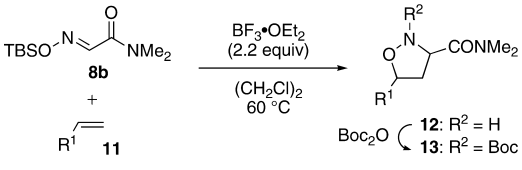
Scheme 2

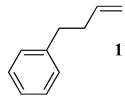


Aldehyde **10** was exposed to hydroxylamine leading to the oxime, hydroxyiminoacetic acid *N,N*-dimethylamide,[8] which was silylated with *tert*-butyldimethylcholorosilane under standard conditions to provide oxime **8b**.

The cycloadditions of *O*-silylated oxime **8b** with representative alkenes **11a**–**e** were next examined (Table 1). Heating

Table 1. BF_3·OEt_2-Mediated Cycloaddition of Oxime 8b with Alkenes 11



entry	Alkene **11**		Reaction Time	Yield (%) of **13** (*cis*:*trans*)
1		**11a**	30 h	99 (3.4:1)
2		**11b**	32 h	97 (*cis* only)
3		**11c**	46 h	87 (3.6:1)
4		**11d**	55 h	42 (*cis* only)
5		**11e**	55 h	72 (5.3:1)

oxime **8b** with alkene **11a**–**e** in the presence of 2.2 equiv of BF_3·OEt_2 at 60 °C in 1,2-dichloroethane induced cycloaddition affording isoxazolidines **12a**–**e**, which were isolated as Boc-protected isoxazolidines **13a**–**e** since NH-isoxazolidines **12a**–**e** showed broadened signals in their NMR spectra probably due to partial coupling NH with other protons. It was found that all reactions afforded *cis*-cycloadducts *cis*-**13a**–**e** as major products. Reaction of styrene (**11a**) proceeded almost quantitatively to give **13a** (entry 1). Aliphatic terminal alkenes **11b** and **11c** smoothly underwent cycloaddition to afford cycloaddcuts **13b** and **13c** in high yields (entries 2 and 3), whereas steric hindrance of branched alkene **11d** appeared to interfere with cycloaddition (entry 4). Cyclopentene (**11e**) also reacted with **8b** in the presence of 2.2 equiv of BF_3·OEt_2 to afford a 5.3:1 mixture of *cis*-**13e** and *trans*-**13e** after treatment of reaction mixture with Boc_2O (entry 5). The stereochemistries of the cycloadducts *cis*-**13a**, *cis*-**13b**, and *cis*-**13e** were confirmed on the basis of NOE experiments (Figure 1), and those of the other cycloadducts were deduced by comparison of their coupling constants with those of *cis*-**13a** and *cis*-**13b**.

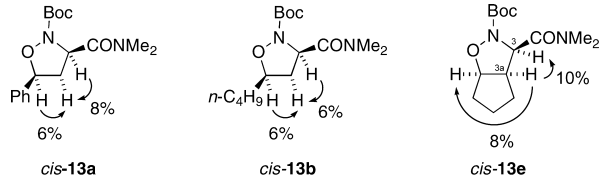
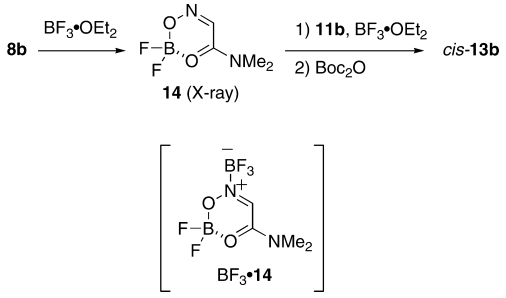


Figure 1. Selected NOEs of *cis*-**13a**, *cis*-**13b**, and *cis*-**13e**.

When oxime **8b** was mixed with BF_3·OEt_2, crystalline material precipitated, which dissolved gradually after addition of alkene **11**. So, the crystalline material was isolated and subjected to X-ray crystallography, which revealed that the crystalline material was six-membered boron-containing intermediate **14** (Scheme 3). With **14** in hand, we next examined

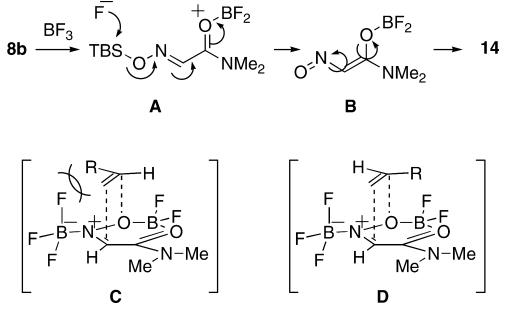
Scheme 3



the reactivity of the material. Thus, compound **14** was heated with alkene **11b** in 1,2-dichloroethane for 30 h. However, no reaction occurred, and then addition of 1 equiv of BF_3·OEt_2 induced cycloaddition to produce cycloadduct **13b** after extractive workup followed by Boc-protection. The crystallography and the subsequent experimentation strongly suggest that the active species of the present cycloaddition would be a complex of **14** with BF_3, most probably BF_3·**14** depicted in Scheme 3.

Strong Lewis basicity of amide-oxygen of **8b** may play a key role in the formation of **14** (Scheme 4). Amide-oxygen of oxime **8b**, the strongest Lewis base in **8b**, may coordinate with BF_3 to form complex **A**, in which Si–O bond and C=N double

Scheme 4



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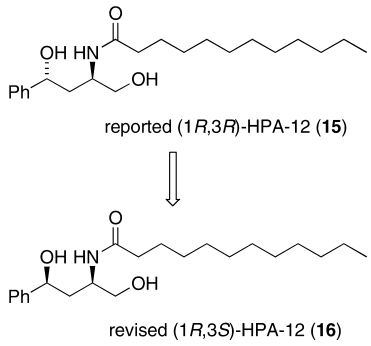
bond would be weakened by resonance effect. Hence, complex **A** released TBS-F to generate nitroso compound **B**, which, in turn, would cyclize to form boron-containing cyclic compound **14**.[9] The negatively charged BF_3 group of BF_3·**14** would induce a large nonbonded interaction with substituent R of alkene **11** (**C**), and hence the cycloaddition may proceed via **D** to afford *cis*-cycloadduct *cis*-**12**.

CERT,[10] a cytosolic protein, has been known to mediate the transport of ceramide from the endoplasmic reticulum to the Golgi apparatus in a nonvesicular manner. Recently, (1*R*,3*R*)-*N*-(3-hydroxy-1-hydroxymethyl-3-phenylpropyl) dodecamide (HPA-12) (**15**) was reported[11] as the first specific inhibitor for sphingomyelin synthesis in mammalian cells and a potential drug that inhibits the CERT-dependent pathway of ceramide trafficking in intact cells. More recently, the structure of HPA-12 was revised from the (1*R*,3*R*)-form (**15**) to the (1*R*,3*S*)-form (**16**) (Scheme 5).[12] Since then, (1*R*,3*S*)-**16** and its racemate *rac*-**16** have been good synthetic target molecules.[13,14] Thus, the present cycloaddition enable a facile synthesis of *rac*-**16**.

Scheme 5



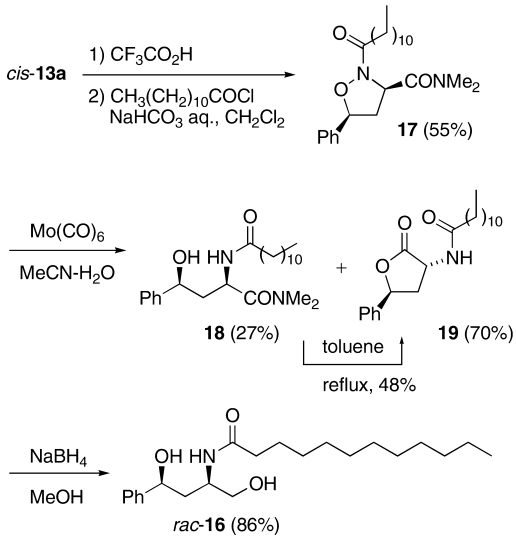
The Boc group of cycloadduct *cis*-**13a** obtained from silyl oxime **8b** and styrene (**11a**) was removed by treatment with CF_3CO_2H and the resulting *N*-nonsubstituted isoxazolidine was acylated with dodecanoyl chloride under Schotten-Baumann conditions to give *N*-acylated isoxazolidine **17** in 55% yield. Heating **17** with $Mo(CO)_6$ in MeCN−H_2O caused reductive cleavage of N−O bond to afford lactone **19** and 1,3-amino alcohol derivative **18**, which could be transformed to lactone **19** by heating in toluene. This lactonization enabled selective cleavage of one of two amide functionalities that usually resist hydride reduction or hydrolysis. Finally, the lactone **19** was reduced to alcohol with $NaBH_4$ to provide *syn*-HPA-12 (*rac*-**16**) (Scheme 6).

In conclusion, *C*-dimethylamide-substituted *O*-silyloxime **8b** underwent *cis*-selective cycloaddition with alkenes in the presence of 2.2 equiv of BF_3·OEt_2 to afford 3,5-*cis*-isoxazolidines predominantly. X-ray crystallography of the intermediate and additional experiment revealed that the reactive intermediate may be boracyclic complex. The cycloaddition was successfully applied to the synthesis of *syn*-HPA-12.

EXPERIMENTAL SECTION

Melting points are uncorrected. Infrared spectra (IR) were recorded with a FT-IR instrument. ^1H or ^{13}C NMR spectra were recorded at 300 or 75 MHz, respectively. The chemical shifts of ^1H NMR are expressed in ppm downfield from tetramethylsilane (δ = 0) as an internal standard ($CDCl_3$ solution). The chemical shifts of ^{13}C NMR

Scheme 6



are reported in ppm, relative to the central line of the triplet at 77.0 ppm for $CDCl_3$. High-resolution mass (HRMS) spectra using a fast atom bombardment (FAB) mode were obtained on a double-focusing high-resolution magnetic-sector mass analyzer and those using a electrospray ionization (ESI) mode were taken on a reflectron time-of-flight mass spectrometer. After extractive workup, organic layers were dried over anhydrous sodium sulfate or anhydrous magnesium sulfate and the solvent was removed by rotary evaporation under reduced pressure.

(*E*)-(*tert*-Butyldimethylsilyloxyimino)acetic Acid *N,N*-Dimethylamide (8b). To a stirred solution of *N,N*-dimethyl glyoxamide (**10**) (670.0 mg, 6.62 mmol) prepared from **9** by reported method[8] in EtOH (13 mL) was added NH_2OH·HCl (600 mg, 8.6 mmol) and AcONa (710 mg, 8.60 mmol) at room temperature, and the mixture was stirred for 4 h. The mixture was concentrated under reduced pressure to give a residue, which was chromatographed on silica gel (CH_2Cl_2−MeOH, 10:1) to afford a known oxime, hydroxyiminoacetic acid *N,N*-dimethylamide.[8] To a solution of the oxime prepared above (310 mg, 2.7 mmol) in DMF (1.8 mL) was added *tert*-butyldimethylchlorosilane (530 mg, 3.5 mmol) and imidazole (1.48 g, 2.17 mmol) at 0 °C and stirring was continued for 2 h. Water was added and the mixture was extracted with ether. The organic layer was washed with brine, dried (Na_2SO_4), and concentrated *in vacuo*. The residue was chromatographed on silica gel (hexane−AcOEt, 4:1) to give **8b** (441 mg, 71%) as a colorless oil. IR (KBr) 2930, 2858, 1647, 1599 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.75 (1H, s), 3.19 (3H, s), 3.04 (3H, s), 0.94 (9H, s), 0.19 (6H, s); ^{13}C NMR (75 MHz, $CDCl_3$) δ 162.5, 147.9, 37.9, 35.4, 25.6, 17.8, −5.6; HRMS (FAB) *m*/*z* calcd for $C_{10}H_{23}N_2O_2Si$ $[M + H]^+$ 231.1529, found 231.1538.

(3*R,5*S**)-3-(Dimethylcarbamoyl)-5-phenylisoxazolidine-2-carbamic Acid *tert*-Butyl Ester (*cis*-13a) and Its (3*R**,5*R**)-Isomer (*trans*-13a).** To a stirred solution of **8b** (100 mg, 0.43 mmol) and BF_3·OEt_2 (0.14 mL, 0.96 mmol) in 1,2-dichloroethane (4 mL) was added five 90 μL portions of **11a** every 5 min (total 0.45 mL, 4.3 mmol) at 60 °C to avoid polymerization of **11a**. The mixture was stirred at the same temperature for 30 h, and then an aqueous saturated solution of $NaHCO_3$ (1 mL) and ice−water were added. The whole was extracted with dichloromethane (10 mL × 3), and then the organic layer was dried (Na_2SO_4). To the solution was added di-*tert*-butyldicarbonate (Boc_2O, 0.3 mL, 1.30 mmol) at room temperature, and the mixture was stirred at the same temperature for 2 days. The mixture was concentrated *in vacuo*, and the residue was chromatographed on silica gel with hexane−AcOEt (2:1) to give *cis*-**13a** (107.5 mg, 77%) and *trans*-**13a** (31.9 mg, 22%). *cis*-**13a**: IR (KBr) 2926, 1736, 1709, 1657 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.55−7.52 (2H, m), 7.40−7.32 (3H, m), 5.22 (1H, dd, *J* = 9.0, 4.2 Hz), 4.85 (1H, dd, *J* = 9.0, 7.8 Hz), 3.21 (3H, s), 3.03 (3H, s), 2.96 (1H, ddd, *J* =

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12.3, 9.0, 4.2 Hz), 2.73 (1H, ddd, J = 12.3, 9.0, 7.8 Hz, spin saturation at δ = 5.22/6% NOE, spin saturation at δ = 4.85/8% NOE), 1.53 (9H, s); ^{13}C NMR (75 MHz, $CDCl_3$) δ 169.2, 157.8, 136.9, 128.7, 128.5, 127.7, 83.6, 82.8, 59.9, 38.9, 37.2, 36.6, 28.1; HRMS (FAB) m/z calcd for $C_{17}H_{25}N_2O_4$ $[M + H]^+$ 321.1814, found 321.1807. *trans*-**13a**: IR (KBr) 2928, 1734, 1697, 1655 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.45−7.42 (2H, m), 7.38−7.28 (3H, m), 5.51 (1H, dd, J = 7.5, 7.2 Hz), 5.20 (1H, dd, J = 7.2, 2.1 Hz), 3.18 (3H, s), 3.07 (1H, ddd, J = 12.3, 7.2, 2.7 Hz), 3.02 (3H, s), 2.34 (1H, dt, J = 12.3, 7.2 Hz), 1.43 (9H, s); ^{13}C NMR (75 MHz, $CDCl_3$) δ 168.9, 156.7, 139.3, 128.4, 128.1, 126.6, 82.6, 82.5, 59.2, 38.6, 37.3, 36.3, 28.1; HRMS (FAB) m/z calcd for $C_{17}H_{25}N_2O_4$ $[M + H]^+$ 321.1814, found 321.1817.

(3*R,5*R**)-5-Butyl-3-(dimethylcarbamoyl)isoxazolidine-2-carbamic Acid *tert*-Butyl Ester (*cis*-13b).** The crude material was obtained from **8b** (320 mg, 1.39 mmol), **11b** (1.17 mL, 13.9 mmol), $BF_3{\cdot}OEt_2$ (0.43 mL, 3.1 mmol), and Boc_2O (0.91 mL, 4.2 mmol) by a procedure similar to that for the preparation of **13a**. The crude material was chromatographed on silica gel (hexane−AcOEt, 4:1) to give *cis*-**13b** (408.7 mg, 97%). IR (KBr) 2934, 2874, 1736, 1709,1661 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 5.02 (1H, dd, J = 8.7, 4.8 Hz), 3.92 (1H, br quin, J = 6.9 Hz), 3.15 (3H, s), 2.98 (3H, s), 2.52−2.33 (2H, m), 1.79−1.60 (2H, m), 1.50 (9H, s), 1.43−1.20 (4H, m), 0.90 (3H, t, J = 6.9 Hz); ^{1}H NMR (300 MHz, C_6D_6) δ 4.92 (1H, dd, J = 8.7, 3.6 Hz), 3.87 (1H, m), 2.78−2.71 (1H, m), 2.71 (3H, s), 2.62 (3H, s), 1.99−1.83 (1H, m), 1.89−1.76 (1H, m, spin saturation at δ = 4.92/6% NOE, spin saturation at δ = 3.87/6% NOE), 1.66−1.54 (1H, m), 1.40 (9H, s), 1.36−1.14 (4H, m), 0.79 (3H, t, J = 6.9 Hz); ^{13}C NMR (75 MHz, $CDCl_3$) δ 169.2, 157.7, 82.4, 81.8, 59.7, 37.1, 36.5, 36.2, 32.0, 28.3, 28.1, 22.5, 13.9; HRMS (FAB) m/z calcd for $C_{15}H_{29}N_2O_4$ $[M + H]^+$ 301.2127, found 301.2126.

(3*R,5*R**)-3-(Dimethylcarbamoyl)-5-(2-phenylethyl)-isoxazolidine-2-carbamic Acid *tert*-Butyl Ester (*cis*-13c) and Its (3*R**,5*S**)-Isomer (*trans*-13c).** The crude material was obtained from **8b** (100 mg, 0.43 mmol), **11c** (0.57 mL, 4.3 mmol), $BF_3{\cdot}OEt_2$ (0.14 mL, 0.96 mmol), and Boc_2O (0.30 mL, 1.3 mmol) by a procedure similar to that for the preparation of **13a**. The crude material was chromatographed on silica gel (hexane−AcOEt, 1:1) to give *cis*-**13c** (102.3 mg, 68%) and *trans*-**13c** (28.5 mg, 19%). *cis*-**13c**: IR (KBr) 3026, 2934, 1734, 1705 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.31−7.18 (5H, m), 5.04 (1H, dd, J = 8.4, 3.9 Hz), 3.93 (1H, m), 3.15 (3H, s), 3.00 (3H, s), 2.86−2.67 (2H, m), 2.55−2.47 (1H, m), 2.38−2.31 (1H, m), 2.21−2.09 (1H, m, spin saturation at δ = 5.04/7% NOE, spin saturation at δ = 3.93/6% NOE), 2.02−1.89 (1H, m), 1.51 (9H, s); ^{13}C NMR (75 MHz, $CDCl_3$) δ 169.2, 157.6, 141.2, 128.5, 127.2, 125.8, 82.5, 80.4, 59.5, 37.1, 36.4, 35.9, 34.1, 32.2, 28.0, 19.4, 14.0; HRMS (FAB) m/z calcd for $C_{19}H_{29}N_2O_4$ $[M + H]^+$ 349.2127, found 349.2132. *trans*-**13d**: IR (KBr) 2936, 1734, 1697, 1655 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.29−7.18 (5H, m), 5.09 (1H, dd, J = 8.1, 2.4 Hz), 4.41 (1H, m), 3.14 (3H, s), 2.97 (3H, s), 2.87−2.79 (2H, m), 1.94−1.85 (2H, m), 1.81−1.72 (2H, m), 1.50 (9H, s); ^{13}C NMR (75 MHz, $CDCl_3$) δ 168.9, 157.4, 141.2, 128.4, 127.7, 125.9, 82.4, 81.0, 58.9, 37.2, 36.6, 36.3, 32.5, 28.1, 14.0. Two signals were not detected probably due to overlapping; HRMS (FAB) m/z calcd for $C_{19}H_{29}N_2O_4$ $[M + H]^+$ 349.2127, found 349.2118.

(3*R,5*S**)-5-Cyclohexyl-3-(dimethylcarbamoyl)-isoxazolidine-2-carbamic Acid *tert*-Butyl Ester (*cis*-13d).** The crude material was obtained from **8b** (100 mg, 0.43 mmol), **11d** (0.48 mL, 4.34 mmol), $BF_3{\cdot}OEt_2$ (0.14 mL, 0.96 mmol), and Boc_2O (0.30 mL, 1.3 mmol) by a procedure similar to that for the preparation of **13a**. The crude material was chromatographed on silica gel (hexane−AcOEt, 4:1) to give *cis*-**13d** (58.1 mg, 42%). IR (KBr) 2930, 2856, 1689, 1655 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 5.02 (1H, dd, J = 9.3, 4.8 Hz), 3.59 (1H, br q, J = 8.2 Hz), 3.15 (3H, s), 2.97 (3H, s), 2.55 (1H, ddd, J = 8.3, 4.8, 4.5 Hz), 2.36−2.26 (1H, m, spin saturation at δ = 5.02/6% NOE, spin saturation at δ = 3.59/7% NOE), 2.03−1.98 (1H, m), 1.74−1.64 (5H, m), 1.49 (9H, s), 1.31−1.02 (5H, m); ^{13}C NMR (75 MHz, $CDCl_3$) δ 169.3, 157.9, 86.0, 82.2, 59.4, 40.3, 37.1, 36.5, 34.3, 29.8, 29.0, 28.0, 26.3, 25.7, 25.3; HRMS (FAB) m/z calcd for $C_{17}H_{31}N_2O_4$ $[M + H]^+$ 327.2284, found 327.2285.

(3*R,3a*R**,6a*S**)-3-(Dimethylcarbamoyl)hexahydro-2*H*-cyclopent[d]isoxazole-2-carbamic Acid *tert*-Butyl Ester (*cis*-13e) and Its (3*R**,3a*R**,6a*R**)-Isomer (*trans*-13e).** The crude material was obtained from **8b** (100 mg, 0.43 mmol), **11e** (0.30 mL, 4.3 mmol), $BF_3{\cdot}OEt_2$ (0.14 mL, 0.96 mmol), and Boc_2O (0.30 mL, 1.3 mmol) by a procedure similar to that for the preparation of **13a**. The crude material was chromatographed on silica gel (hexane−AcOEt, 1:4) to give *cis*-**13e** (78.6 mg, 66%) and *trans*-**13e** (14.8 mg, 12%). *cis*-**13e**: IR (KBr) 2934, 2874, 1720, 1655 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 5.11 (1H, d, J = 9.9, Hz, spin saturation at δ = 3.25/10% NOE), 4.55 (1H, br t, J = 4.7 Hz, spin saturation at δ = 3.25/8% NOE) 3.30−3.20 (1H, m), 3.05 (3H, s), 3.00 (3H, s), 2.08−1.77 (2H, m), 1.63−1.51 (4H, m), 1.48 (9H, s); ^{13}C NMR (75 MHz, $CDCl_3$) δ 168.4, 87.2, 81.9, 63.0, 49.6, 36.6, 35.7, 30.1, 28.2, 27.6, 25.3; One carbonyl carbon could not be detected probably due to its broadened signal.; HRMS (FAB) m/z calcd for $C_{14}H_{25}N_2O_4$ $[M + H]^+$ 285.1814, found 285.1810. *trans*-**13d**: IR (KBr) 2961, 1734, 1697, 1653 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 4.86 (1H, td, J = 6.6, 3.0 Hz, spin saturation at δ = 3.45/4% NOE), 4.78 (1H, br s), 3.45 (1H, td, J = 10.8, 6.9 Hz) 3.14 (3H, s), 2.96 (3H, s), 1.98−1.68 (4H, m), 1.62−1.54 (2H, m), 1.50 (9H, s); ^{13}C NMR (75 MHz, $CDCl_3$) δ 168.8, 156.9, 87.8, 82.3, 65.6, 49.5, 37.2, 36.3, 33.1, 31.1, 28.2, 25.1; HRMS (FAB) m/z calcd for $C_{14}H_{25}N_2O_4$ $[M + H]^+$ 285.1814, found 285.1820.

(*Z*)-2-(Difluoroboryloxyimino)-*N*,*N*-dimethylacetamide (14). To a stirred solution of *O*-TBS oxime **8b** (350.0 mg, 1.52 mmol) in $(CH_2Cl)_2$ (10 mL) was added $BF_3{\cdot}OEt_2$ (0.42 mL, 3.34 mmol) at room temperature, then the mixture was stirred at 60 °C for 1 h. After cooling to room temperature, crystalline precipitates separated out. The mother liquor was removed by cannulation, and the precipitates were washed with CH_2Cl_2. Crystal data: $C_4H_7BF_2N_2O_2$; M = 163.93, monoclinic, a = 6.7266(9), b = 13.5479(19), c = 7.8299(11) Å, β = 105.2590(10)°, V = 688.39(16) Å3, T = 120 K, space group $P2(1)/n$, Z = 4, μ(Mo−Kα) = 0.154 mm^{-1}, The final R1 and wR2(F^2) was 0.0348 and 0.0922 (all data).

Reaction of 14 with 11b by Addition of $BF_3{\cdot}OEt_2$. To a suspension of **14** (35.2 mg, 0.22 mmol) in $(CH_2Cl)_2$ (2 mL) was added **11b** (0.27 mL, 2.2 mmol) and $BF_3{\cdot}OEt_2$ (0.030 mL, 0.23 mmol) at room temperature, and then the mixture was stirred at 60 °C for 2 h. After cooling, the reaction was diluted with an aqueous saturated solution of $NaHCO_3$ and extracted with CH_2Cl_2, dried (Na_2SO_4). To the extract, Boc_2O (0.15 mL, 0.64 mmol) was added for spontaneous protection of the product during concentration. The solvent was concentrated under reduced pressure to give the crude product, which was chromatographed on silica gel (hexane−AcOEt = 1:1) to afford **13b** (34.2 mg, 53%). ^{1}H NMR (300 MHz, $CDCl_3$) δ 5.02 (1H, dd, J = 8.7, 4.8 Hz), 3.92 (1H, br q, J = 6.9 Hz), 3.15 (3H, s), 2.98 (3H, s), 2.52−2.33 (2H, m), 1.79−1.60 (2H, m), 1.50 (9H, s), 1.43−1.20 (4H, m), 0.90 (3H, t, J = 6.9 Hz). This spectrum is identical with that obtained from the reaction of **14** and **11b** in the presence of 2.2 equiv of $BF_3{\cdot}OEt_2$.

(3*R,5*S**)-2-Dodecanoyl-*N*,*N*-dimethyl-5-phenylisoxazilidine-3-carboxamide (17).** A mixture of *cis*-**13a** (55 mg, 0.17 mmol) and CF_3CO_2H (0.4 mL, 5.1 mmol) in CH_2Cl_2 (1 mL) was stirred at room temperature for 2 h, and then the mixture was concentrated *in vacuo*. The residue was dissolved in a mixture of CH_2Cl_2 (1 mL) and an aqueous saturated solution of $NaHCO_3$ (1 mL). To the mixture was added dodecanoyl chloride (0.5 mL, 2.1 moL) at room temperature, then the mixture was stirred at the same conditions for 20 h. After workup, the crude product was chromatographed on silica gel (AcOEt−hexane, 3:1) to give **17** (37.1 mg, 55%). mp 44−45 °C (hexane); IR (KBr) 2918, 1645, 1440 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.55 (2H, dd, J = 7.7, 2.2 Hz), 7,43−7.34 (3H, m), 5.41 (1H, dd, J = 8.8, 5.9 Hz), 4.83 (1H, dd, J = 10.3, 7.3 Hz), 3.22 (3H, s), 3.02 (3H, s), 2.92−2.74 (2H, m), 2.60 (1H, td, J = 16.0, 7.2 Hz), 2.46 (1H, td, J = 16.0, 7.2 Hz), 1.69−1.59 (2H, m), 1.24 (16H, m), 0.87 (3H, t, J = 7.0 Hz); ^{13}C NMR (75 MHz, $CDCl_3$) δ 175.6, 169.1, 136.1, 129.1, 128.7, 127.5, 84.1, 55.9, 39.8, 37.2, 36.5, 33.8, 32.4, 31.9, 29.6, 29.4, 29.3, 29.3, 24.8, 24.5, 22.6, 14.1; HRMS (ESI$^+$) m/z calcd for $C_{24}H_{39}N_2O_3$ $[M + H]^+$ 403.2961, found 403.2941.

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***N*-[(3*R**,5*S**)-2-Oxo-5-phenyltetrahydrofuran-3-yl]-dodecanamide (19).** A mixture of **17** (25.0 mg, 0.0621 mmol) and $Mo(CO)_6$ (19.8 mg, 0.075 mmol) in CH_3CN-H_2O (10:1, 1.1 mL) was heated at reflux temperature for 21 h. After concentration, the residue was chromatographed on silica gel (AcOEt−hexane, 3:1) to give *N*-[(1*R**,3*S**)-1-dimethylamide-3-hydroxy-3-phenylpropyl] dodecanamide (**18**) (6.7 mg, 27%) and **19** (15.6 mg, 70%) . **18**: ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.40−7.26 (5H, m), 6.69 (1H, d, J = 7.7 Hz), 5.06 (1H, br q, J = 6.6 Hz), 4.83 (1H, dd, J = 7.7, 5.1 Hz), 3.01 (3H, s), 2.98 (3H, s), 2.34 (2H, t, J = 7.7 Hz), 2.20−2.03 (3H, m), 1.66−1.57 (2H, m), 1.26 (16H, br s), 0.88 (3H, t, J = 6.6 Hz). Compound **18** was immediately used for the conversion to compound **19**. Thus, compound **18** (6.7 mg) was heated in refluxing toluene (1 mL) for 24 h. After concentration, the residue was chromatographed on silica gel (AcOEt−hexane, 1:2) to give **19** (3.1 mg). The total yield of **19** was 18.7 mg (85%). **19**: mp 78.5−79.5 °C (hexane); IR (KBr) 3306, 2916, 1786, 1649, 1549, 1257, 1171 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.42−7.28 (5H, m), 5.97 (1H, d, J = 5.9 Hz), 5.75 (1H, dd, J = 8.4, 1.8 Hz), 4.52 (1H, ddd, J = 10.8, 9.0, 5.9 Hz), 2.91 (1H, ddd, J = 12.6, 9.0, 2.2 Hz), 2.59 (1H, ddd, J = 12.8, 10.8, 8.4 Hz), 2.24 (2H, t, J = 7.7 Hz), 1.66−1.61 (2H, m), 1.25 (16H, s), 0.88 (3H, t, J = 6.6 Hz); ^{13}C NMR (75 MHz, $CDCl_3$) δ 175.3, 173.6, 138.8, 128.9, 128.5, 124.9, 78.6, 48.3, 36.9, 36.1, 31.9, 29.6, 29.4, 29.3, 29.2, 25.4, 22.7, 14.1. Two signals were not detected probably due to overlapping; HRMS (ESI^+) m/z calcd for $C_{22}H_{34}NO_3$ $[M + H]^+$ 360.2539, found 360.2526.

[(1*R,3*S**)-3-Hydroxy-1-hydroxymethyl-3phenylpropyl]-dodecamide (*rac*-16).** To a solution of **15** (5.5 mg, 0.015 mmol) in MeOH (0.8 mL) was added $NaBH_4$ (0.8 mg, 0.02 mmol) at 0 °C, and the mixture was stirred at the same temperature for 30 min. After concentration, the residue was chromatographed on silica gel (CH_2Cl_2−MeOH, 40:1) to give ***rac*-16** (4.7 mg, 86%). IR (KBr) 3335, 2920, 1728, 1643, 1553, 1470, 1053 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.38−7.27 (5H, m), 6.36 (1H, d, J = 6.2 Hz), 4.83 (1H, dd, J = 8.8, 3.3 Hz), 4.12−4.03 (1H, m), 3.74−3.64 (2H, m), 2.91 (1H, br s), 2.18 (2H, t, J = 7.3 Hz), 2.07 (1H, ddd, J = 14.7, 5.5, 3.3 Hz), 1.94 (1H, ddd, J = 14.7, 8.8, 7.0 Hz), 1.66−1.57 (2H, m), 1.26 (16H, br s), 0.88 (3H, t, J = 7.0 Hz); ^{13}C NMR (75 MHz, $CDCl_3$) δ 174.3, 144.2, 128.7, 127.8, 125.5, 72.2, 66.0, 50.7, 40.6, 36.8, 31.9, 29.7, 29.6, 29.5, 29.4, 29.3, 29.3, 25.7, 22.7, 14.1; HRMS (ESI^+) m/z calcd for $C_{22}H_{38}NO_3$ $[M + H]^+$ 364.2852, found 364.2862.

■ ASSOCIATED CONTENT

Supporting Information

^{1}H NMR and ^{13}C NMR spectra of new compounds. X-ray data for compound **14**. CIF file. This material is available free of charge via the Internet at http://pubs.acs.org.

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Notes

The authors declare no competing financial interest.

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■ DEDICATION

This work is dedicated to Dr. Shiro Terashima, Former President of Sagami Chemical Research Center (Sagami Chemical Institute), on the occasion of his 77th birthday (KIJU).

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