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Stereoselective intramolecular cyclization of γ-allylbenzamide via π–allylpalladium complex catalyzed by Pd(0)

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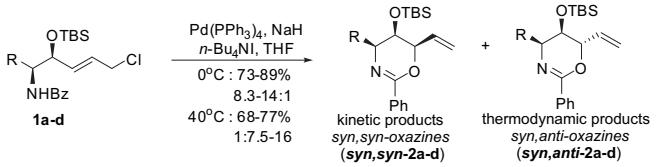
ABSTRACT

An efficient procedure for synthesizing oxazines was developed by the palladium(0)-catalyzed intramolecular cyclization of a benzamide through a π-allylpalladium (II) complex. Interestingly, the diastereoselectivity of oxazine ring formation was dominantly controlled by the bulkiness of various protecting groups on the secondary alcohols.

1. Introduction

In our previous papers,[1–3] we described a procedure for highly stereoselective formation of oxazines from γ–allyl amides having a benzoyl substituent as *N*-protecting group in the presence of $Pd(PPh_3)_4$, NaH, and *n*-Bu_4NI in THF. Unlike in other palladium-catalyzed reactions, the diastereoselectivity of oxazine ring formation is predominantly controlled by the temperature. Our study of intramolecular oxazine formation from **1a–d** shows that the stereoselectivity of these cyclizations can be critically dependent upon whether the reaction temperature results in kinetic or thermodynamic control of the products (Scheme 1). Oxazines *syn*,*syn*-**2a–d** required conditions giving kinetic control (0 °C), whereas *syn*,*anti*-**2a–d** are observed under thermodynamic control (40 °C).

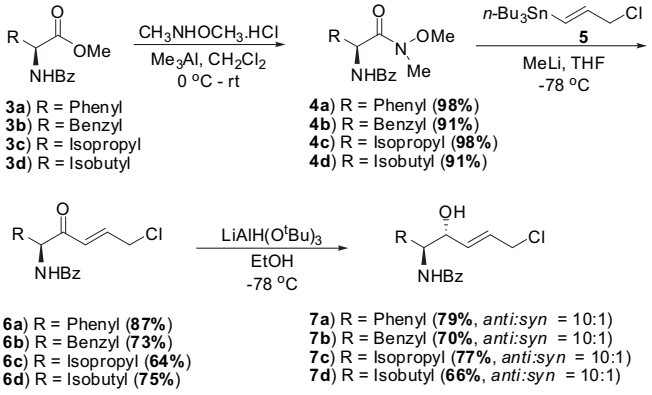


Scheme 1. Palladium catalyzed oxazine formation.

To extend the scope of this method, we replaced the *syn*-aminoalcohols with *anti*-aminoalcohols, which are interesting because of their selectivity in the formation of corresponding oxazines. This paper discusses the results of stereoselective intramolecular oxazine formation.

2. Results and discussion

The requisite cyclization precursor was prepared in high yield from the commercially available *N*-benzoyl leucine methyl ester **3d** by the three-step sequence shown in Scheme 2.



Scheme 2.

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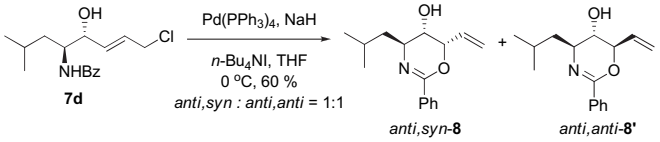
The synthesis of **7d** commenced with preparation of the Weinreb amide **4d** from ester **3d** by treatment of *N*,*O*-dimethylhydroxylamine in the presence of trimethylaluminum in 91% yield.[4] Reaction of the Weinreb amide **4d** with vinyltin **5** and MeLi in THF at −78 °C gave the α,β–unsaturated ketone **6d** in 75% yield. Chelating-controlled hydride reduction of **6d** using LiAlH(*t*-BuO)$_3$ yielded *anti*-alcohol **7d** with excellent stereoselectivity (*anti*/*syn*=10:1, as determined by ^{1}H NMR).[5–9]

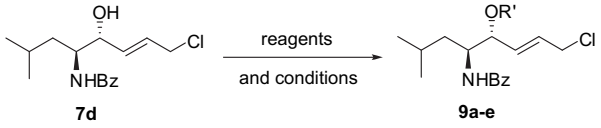
Under the same conditions [Pd(PPh$_3$)$_4$, NaH, and *n*-Bu$_4$NI in THF at 0 °C] that were used in the formation of oxazines (*syn*,*syn*-**2a**–**d** and *syn*,*anti*-**2a**–**d**, Scheme 1),[1] the intramolecular cyclization of allyl chloride **7d** afford oxazines **8** and **8′** as a 1:1 *syn*/*anti* mixture (as determined by ^{1}H NMR) in moderate yield (Scheme 3).†



Scheme 3. Palladium catalyzed oxazine formation.

Based on our previous research, we anticipated that the palladium(0)-catalyzed oxazine formation of γ-allylbenzamide with various alcohol protection substitutes might proceed with high stereoselectivity.[1–3] In order to investigate the influence of the bulkiness of the protection group, these reaction conditions were extended to other substrates used to investigate the influence of the R′ group on selectivity. These substrates were simply prepared under the reaction conditions shown in Table 1.

Table 1
Preparation of various alcohol protection cyclization precursors



Substrate	R′	Reagents	Temp (°C)	Time (h)	Yield[a] (%)
9a	Me	MeI, NaH, THF	0-rt	2	73
9b	Bn	BnBr, NaH, THF	rt	2	70
9c	MeOCH$_2$	MOMCl, TEA, CH$_2$Cl$_2$	0-rt	24	80
9d	BnOCH$_2$	BOMCl, TEA, CH$_2$Cl$_2$	0	3	76
9e	TBS	TBSCl, Imid, DMF	rt	2	95

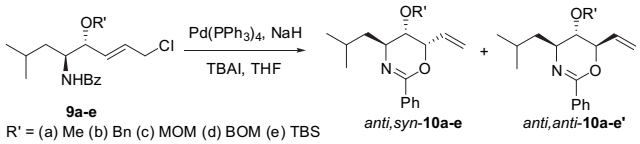
[a] Yield refer to the isolated products.

The reaction of **9a**–**e**, which had methyl, benzyl, methoxymethyl, benzyloxymethyl, and *tert*-butyldimethylsilyl as the protection groups with NaH and *n*-Bu$_4$NI in the presence of Pd(PPh$_3$)$_4$ in THF at 0 °C afforded the *anti*,*syn*-oxazines **10a**–**e** as the major products along with minor amounts of the *anti*,*anti*-oxazine products **10a**–**e**′. The results are summarized in Table 2.

The diastereoselectivity decreased with sterically less bulky groups, such as methyl, benzyl, methoxymethyl, and benzyloxymethyl (entries 1–4, Table 2). The diastereoselectivity was improved to >30:1 when R′ was the TBS group (entry 5). It is clear from these experiments that steric bulkiness at the R′ groups highly influences the level of diastereoselectivity (Table 2).

† The ratio of oxazines **8** and **8′** from the reaction of **7d** under above condition [Pd(PPh$_3$)$_4$, NaH, and *n*-Bu$_4$NI in THF] at higher temperature (such as room temperature or 40 °C) was a 1:1 *syn*/*anti* mixture in a lower yield. Later, we tested the cyclization reaction of **9a**–**e** at 40 °C and the same result ratio (1:1 *syn*/*anti* mixtures) at a lower yield for **10a**–**e** and **10a**–**e**′ as determined by TLC. These experiments show that the stereoselectivity of these cyclizations of *anti*-aminoalcohols moieties **7a**–**d** and **9a**–**e** is not depended on the reaction temperature.

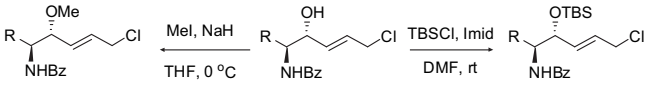
Table 2
Oxazine formation catalyzed by Pd(0)[a]



Entry	Substrate	Temp (°C)	Time (h)	Yield[b] (%)	Ratio[c] (*anti*,*syn*/*anti*,*anti*)
1	**9a**	0	5	51	6:1
2	**9b**	0	5	70	5:1
3	**9c**	0	5	76	8:1
4	**9d**	0	5	90	15:1
5	**9e**	0	5	65	>30:1

[a] Reaction conditions: Pd(PPh$_3$)$_4$ (0.2 equiv), NaH (2 equiv), *n*-Bu$_4$NI (1 equiv), and THF.
[b] Yield refers to the isolated and mixed products.
[c] Ratio was determined by ^{1}H NMR of *anti*,*syn*-oxazines and *anti*,*anti*-oxazines.

These reaction conditions were then extended to other substrates in order to investigate the influence of the R′ groups on the reactivity. The substrates were synthesized according to the procedure shown in Scheme 4. This method afforded high diastereoselectivity and chemical yield.



11a) R = phenyl: 63%
11b) R = benzyl: 57%
11c) R = isopropyl: 57%

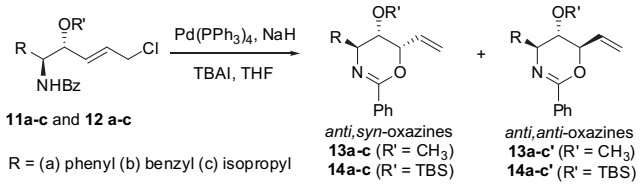
7a) R = phenyl
7b) R = benzyl
7c) R = isopropyl

12a) R = phenyl: 85%
12b) R = benzyl: 95%
12c) R = isopropyl: 82%

Scheme 4.

The reaction of **11a**–**c** and **12a**–**c**, which have phenyl, benzyl, and isopropyl as substituent groups and methyl or TBS protecting groups on the secondary alcohol, with NaH, *n*-Bu$_4$NI in presence of Pd(PPh$_3$)$_4$ in THF at 0 °C afforded the *anti*,*syn*-oxazines, **13a**–**c** and **14a**–**c**, as the major products, along with minor amounts of the *anti*,*anti*-oxazine products, **13a**–**c**′ and **14a**–**c**′. The results are summarized in Table 3.

Table 3
Oxazine formation catalyzed by Pd(0)[a]

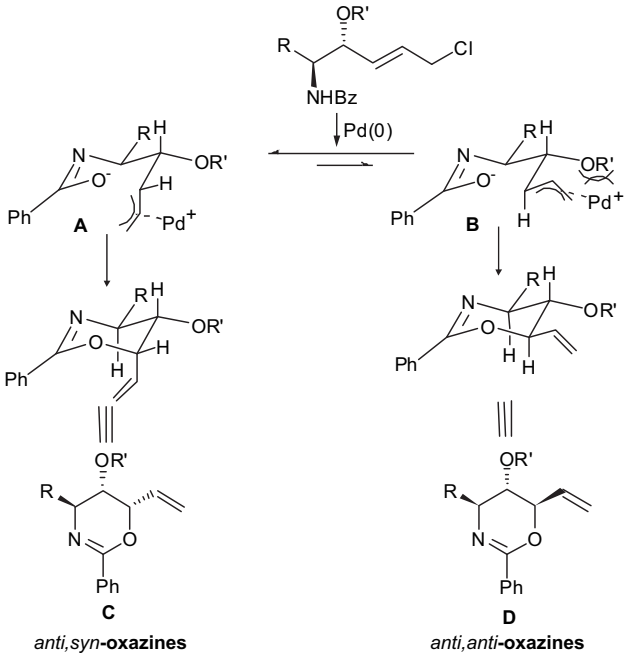


Entry	Substrate	Temp (°C)	Time (h)	Yield[b] (%)	Ratio[c] (*anti*,*syn*/*anti*,*anti*)
1	**11a**	0	5	62	2:1
2	**12a**	0	5	57	13:1
3	**11b**	0	5	65	3:1
4	**12b**	0	5	65	12:1
5	**11c**	0	5	58	4:1
6	**12c**	0	5	57	13:1

[a] Reaction conditions: Pd(PPh$_3$)$_4$ (0.2 equiv), NaH (2 equiv), *n*-Bu$_4$NI (1 equiv), and THF.
[b] Yield refers to the isolated and mixed products.
[c] Ratio was determined by ^{1}H NMR of *anti*,*syn*-oxazines and *anti*,*anti*-oxazines.

The diastereoselectivity of oxazine ring formation is dominantly controlled by the bulkiness of R′. This result verified that the bulky TBS group plays an important role in determining the stereoselectivity during oxazine formation. Upon extensive examination of R′, we found that reaction of **12a**–**c** using TBS as the protection group gave the desired diastereomer as the major compound with high diastereoselectivity and in good yield.

One possible explanation for the stereoselective formation of **C** or **D** is as follows (Scheme 5). The chair-like transition states **A** and **B**, which have OR′ in an equatorial orientation, are proposed to explain the stereochemical outcome of the cyclization. The initial π-allylpalladium complexes **A** and **B** were equilibrated by π–σ–π isomerization.[10,11] Although the axially disposed π-allylpalladium complex in transition state **A** might suffer from a non-bonding *gauche* repulsion with OR′, the transition state **B** appears to be further destabilized by non-bonded steric repulsion between the equatorial π-allylpalladium complex and OR′. The stereoselectivity of cyclization may also arise from differences in steric interactions between the bulky R′ group and the π-allylpalladium complex in the transition states **A** and **B**. Consequently, cyclization proceeds through the more favored transition state **A** as shown in Scheme 5.



Scheme 5.

To verify the stereochemical outcome at the newly generated stereocenter C-6, the NOE spectra of the oxazine were studied under the assumption that there must be a NOE difference between the two isomers **A** and **B**. This technique has been mentioned in previous reports. [1,‡]

The stereochemistries of the oxazines were elucidated by ^{1}H NMR, as shown in Table 4.

‡ The assignment of relative configuration was confirmed by observation of the larger NOE enhancement for *anti*,*syn*-oxazines **10a**, **10e** and *anti*,*anti*-oxazine **10a**′ as shown below: in the *anti*,*syn*-oxazines case, for compound **10a** and **10e**: there is NOE between H-5 and H-6, but no NOE effective between H-4 and H-6; in the *anti*,*anti*-oxazine case, for compound **10a**′: there are 1.59% between H-4 and H-6, 0. 37% between H-5 and H-6.

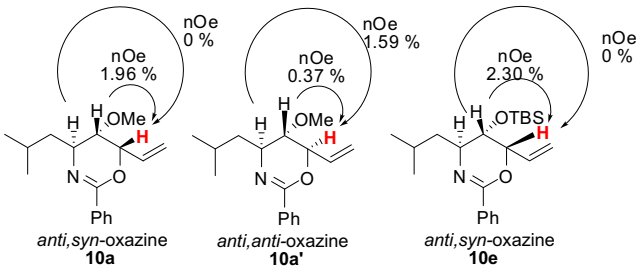
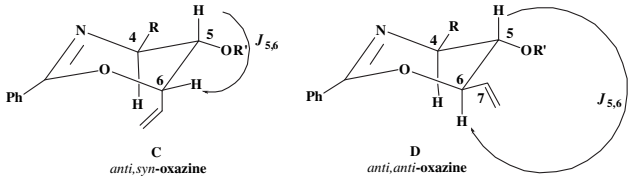


Table 4
^{1}H NMR ($CDCl_3$) coupling constants of oxazines

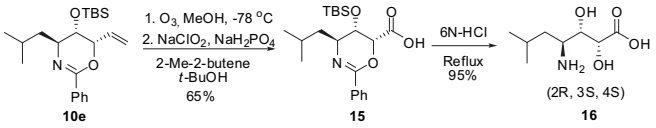


Substrate	R	R′	Isomer	$J_{5,6}$
10a	Isobutyl	Me	C	3.5
10a′	Isobutyl	Me	D	9.0
10e	Isobutyl	TBS	C	2.5
13a	Phenyl	Me	C	4.0
13a′	Phenyl	Me	D	8.5
14a	Phenyl	TBS	C	4.5
13b	Benzyl	Me	C	3.5
13b′	Benzyl	Me	D	8.0
14b	Benzyl	TBS	C	3.0
13c	Isopropyl	Me	C	4.5
13c′	Isopropyl	Me	D	7.5
14c	Isopropyl	TBS	C	4.0

The relative configuration of each diastereomer of the oxazine products obtained after the silica gel column separation was determined by comparing their coupling constants (Table 4). Small coupling constants of $J_{5,6}$=2.5–4.5 Hz, as in *anti*,*syn*-oxazine (**C**), are caused by the axial–equatorial relationship between the two adjacent protons in six-membered rings. The large coupling constants of $J_{5,6}$=7.5–9.0 Hz, as in *anti*,*anti*-oxazine (**D**), are typically due to the diaxial relationship between the two adjacent protons in six-membered rings.

In addition, the coupling constants of the newly generated chiral center (H_5–H_6) of **C** have similar values of 2.5–4.5 Hz compared to those previously reported for *syn*,*syn*-oxazine compounds. In contrast, the coupling constants of the newly generated chiral center (H_5–H_6) of **D** have the same values of 7.5–9.0 Hz as the *syn*,*anti*-isomer.

We utilized this method for the synthesis of α-hydroxy statine **16**.[12] Ozonolysis of the terminal olefin of oxazine **10e** gave the corresponding aldehyde, and further oxidation with sodium chlorite afforded acid **15** in 65% yield (Scheme 6). Deprotection of silyl ether and oxazine cleavage with 6 N-HCl at reflux temperature gave α-hydroxy statine **16** in excellent yield.



Scheme 6.

3. Conclusion

This study examined the stereoselective intramolecular oxazine formation by palladium(0). Diastereoselectivity of oxazine ring formation is dominantly controlled by the bulkiness of R′. Also, there is excellent correlation between the diastereoselectivity ratio and the bulkiness of R′ in the palladium(0)-catalyzed oxazine ring formation. A means of stereoselectively generating an alcohol moiety in the γ-position of the amine is important from a synthetic point of view. The mildness of the reaction, the simplicity of the procedure, and rather high de values offer a convenient and efficient method for the synthesis of optically pure oxazines. Further applications of this formation catalyzed by Pd(0) will be reported in due course.

4. Experimental section

4.1. General methods and materials

Optical rotations were measured on a polarimeter in the solvent specified. ^{1}H NMR and ^{13}C NMR spectra were recorded on FT-NMR 125, or 500 MHz spectrometers. Chemical shifts values are reported in parts per million relative to TMS or $CDCl_3$ as an internal standard and coupling constants in Hertz. IR spectra were measured on a FTIR spectrometer. Mass spectral data were obtained from the Korea Basic Science Institute (Daegu) on Jeol JMS 700 high resolution mass spectrometer. Flash chromatography was executed using mixtures of ethyl acetate and hexane as eluents. Unless otherwise noted, all non-aqueous reactions were carried out under an argon atmosphere with commercial grade reagents and solvents. Tetrahydrofuran (THF) was distilled over sodium and benzophenone (indicator). Methylene chloride (CH_2Cl_2) was distilled from calcium hydride.

4.2. General procedure for synthesis of Weinreb amides (4a–d)

To a solution of *N*,*O*-dimethylhydroxylamine hydrochloride (3.0 equiv) in CH_2Cl_2 was added trimethylaluminum (2 M solution in hexane, 3.0 equiv) at 0 °C (Caution: CH_4 evolution). The mixture was stirred for 30 min at room temperature. Subsequently, a solution of methyl ester (**3a–d**) (1.0 equiv) in CH_2Cl_2 was added dropwise. The mixture was stirred at room temperature for 1 h, after, which time TLC analysis indicated complete reaction. The reaction mixture was cooled to 0 °C and carefully quenched with 10% sodium potassium tartarate. After being stirred for 1 h at room temperature, the resulting suspension was filtered through Celite pad, washed with CH_2Cl_2. The filtrate was concentrated in vacuo to give the crude product, which upon purification by column chromatography on silica gel gave the Weinreb amide **4a–d** as a white solid.

*4.2.1. (S)-N-(2-(Methoxy(methyl)amino)-2-oxo-1-phenylethyl)benzamide (**4a**).* Yield 98%; as a white solid; mp=101–103 °C; R_f=0.2 (ethyl acetate/hexanes=1/2); IR (neat) ν_{max}: 1515, 1650, 1688, 2358, 3618, 3740, 3851 cm^{-1}; $[\alpha]_D^{25}$ +93.23 (*c* 1.0, $CHCl_3$); ^{1}H NMR ($CDCl_3$, 300 MHz) δ 3.25 (s, 3H), 3.51 (s, 3H), 6.23 (d, *J*=7.5 Hz), 7.31–7.55 (m, 8H), 7.58 (d, *J*=7.2 Hz, 1H-NH), 7.84–7.86 (m, 2H); ^{13}C NMR ($CDCl_3$, 125 Hz) δ 32.6, 54.5, 61.4, 127.4, 128.3, 128.5, 128.7, 129.1, 131.9, 134.2, 137.9, 166.5, 171.2; HRMS calcd for $C_{17}H_{19}O_3N_2$ (M^++H) 299.1396; found, 299.1399.

*4.2.2. (S)-N-(1-(Methoxy(methyl)amino)-1-oxo-3-phenylpropan-2-yl)benzamide (**4b**).* Yield 91% as a white solid; mp=115–116 °C; R_f=0.4 (ethyl acetate/hexanes=1/2); IR (neat) ν_{max}: 704, 1295, 1533, 1646, 2936, 3328 cm^{-1}; $[\alpha]_D^{25}$ +38.74 (*c* 1.0, $CHCl_3$); ^{1}H NMR ($CDCl_3$, 300 MHz) δ 3.15 (dd, *J*=6.3, 13.5 Hz, 1H), 3.25–3.31 (m, 4H), 3.78 (s, 3H), 5.49–5.52 (m, 1H), 6.86 (d, *J*=7.5, 1H-NH), 7.22–7.36 (m, 5H), 7.43–7.56 (m, 3H), 7.77–7.80 (m, 2H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 32.4, 38.4, 51.1, 51.9, 127.2, 127.3, 128.7, 129.7, 131.8, 134.3, 136.8, 167.1, 172.2; HRMS calcd for $C_{18}H_{21}O_3N_2$ (M^++H) 313.1552; found, 313.1550.

*4.2.3. (S)-N-(1-(Methoxy(methyl)amino)-3-methyl-1-oxobutan-2-yl)benzamide (**4c**).* Yield 98%; as a white solid; mp=92–94 °C; R_f=0.5 (ethyl acetate/hexanes=1/2); IR (neat) ν_{max}: 706, 1174, 1319, 1527, 1643, 2966, 3322 cm^{-1}; $[\alpha]_D^{25}$ +33.85 (*c* 1.0, $CHCl_3$); ^{1}H NMR ($CDCl_3$, 300 MHz) δ 0.398–1.02 (m, 6H), 2.12–2.19 (m, 1H), 3.21 (s, 3H), 3.81 (s, 3H), 5.15 (dd, *J*=7.5, 15.5 Hz, 1H), 6.94 (d, *J*=6.0 Hz, 1H-NH), 7.36–7.49 (m, 3H), 7.77–7.81 (m, 2H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 22.3, 23.8, 35.9, 36.2, 58.3, 65.9, 131.4, 132.8, 135.8, 138.6, 171.6, 176.8; HRMS calcd for $C_{14}H_{21}O_3N_2$ (M^++H) 265.1552; found, 265.1555.

*4.2.4. (S)-N-(1-(Methoxy(methyl)amino)-4-methyl-1-oxopentan-2-yl)benzamide (**4d**).* Yield 91%; as a white solid; mp=95–96 °C; R_f=0.3 (ethyl acetate/hexanes=1/2); IR (neat) ν_{max}: 998, 1069, 1456, 2921, 3306 cm^{-1}; $[\alpha]_D^{25}$ −25.36 (*c* 1.0, $CHCl_3$); ^{1}H NMR ($CDCl_3$, 300 MHz) δ 0.93–1.01 (m, 6H), 1.57–1.64 (m, 2H), 1.73–1.78 (m, 1H), 3.22 (s, 3H), 3.85 (s, 3H), 5.28 (t, *J*=2.1, 2.4 Hz, 1H), 7.02 (d, *J*=5.4, 1H-NH), 7.36–7.46 (m, 3H), 7.78–7.80 (m, 2H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 21.9, 23.6, 25.2, 32.4, 42.2, 48.4, 61.9, 127.3, 127.4, 128.6, 131.7, 134.3, 167.4, 173.7; HRMS calcd for $C_{15}H_{23}O_3N_2$ (M^++H) 279.1709; found, 279.1710.

4.3. General procedure for synthesis of amino ketones (6a–d)

Vinyltin **5** (3.0 equiv) was dissolved in dry THF (0.1 M) and cooled to −78 °C. MeLi (1.6 M solution in hexanes, 3.0 equiv) was added dropwise. The mixture was stirred for 30 min at same temperature. Subsequently, a solution of amide **4a–d** (1.0 equiv) in dry THF (0.1 M) was added dropwise and stirring was allowed to continue for 30 min, after which time TLC analysis indicated complete reaction. The reaction was quenched by aqueous saturated NH_4Cl then warmed to room temperature. The layers were separated and the aqueous layer was extracted with ethyl acetate. The combined organic layer washed with satd $NaHCO_3$ solution, brine, dried with $MgSO_4$, and filtered. The filtrate was concentrated in vacuo. The resulting substance was purified by silica gel column chromatography gave the amino ketone **6a–d** as white wax materials.

*4.3.1. (S,E)-N-(5-Chloro-2-oxo-1-phenylpent-3-enyl)benzamide (**6a**).* Yield 87%; as a wax material; R_f=0.5 (ethyl acetate/hexanes=1/2); IR (neat) ν_{max}: 1332, 1516, 1645, 2358, 3404, 3740, 3852 cm^{-1}; $[\alpha]_D^{25}$ +242.68 (*c* 1.0, $CHCl_3$); ^{1}H NMR ($CDCl_3$, 300 MHz) δ 4.16 (dd, *J*=1.5, 6.0 Hz, 2H), 5.97 (d, *J*=6.3 Hz, 1H), 6.46 (d, *J*=12.9 Hz, 1H), 7.05–7.10 (m, 1H), 7.40–7.50 (m, 8H), 7.54 (d, *J*=7.2 Hz, 1H-NH), 7.85–7.88 (m, 2H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 42.9, 62.6, 127.4, 127.9, 128.7, 128.8, 129.1, 129.6, 132.1, 133.9, 136.1, 142.4, 166.6, 193.9; HRMS calcd for $C_{18}H_{17}O_2NCl$ (M^++H) 314.0948; found, 314.0948.

*4.3.2. (S,E)-N-(6-Chloro-3-oxo-1-phenylhex-4-en-2-yl)benzamide (**6b**).* Yield 73%; as a wax material; R_f=0.7 (ethyl acetate/hexanes=1/2); IR (neat) ν_{max}: 680, 1524, 1643, 1700, 2358, 3618, 3681, 3740, 3852 cm^{-1}; $[\alpha]_D^{25}$ +59.67 (*c* 1.0, $CHCl_3$); ^{1}H NMR ($CDCl_3$, 300 MHz) δ 3.23 (m, 2H), 4.22 (dd, *J*=1.8, 5.7 Hz, 2H), 6.52 (ddd, *J*=1.8, 1.8, 16.0 Hz, 1H), 6.92 (d, *J*=6.6 Hz, 1H-NH), 6.99–7.19 (m, 1H), 7.25–7.29 (m, 2H), 7.30–7.37 (m, 4H), 7.45–7.51 (m, 2H), 7.53–7.59 (m, 2H), 7.75–7.81 (m, 1H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 37.8, 42.9, 58.5, 127.0, 127.4, 128.6, 128.8, 128.9, 129.1, 129.5, 132.0, 134.2, 135.8, 132.3, 167.1, 196.7; HRMS calcd for $C_{19}H_{19}O_2NCl$ (M^++H) 328.1104; found, 328.1100.

*4.3.3. (S,E)-N-(7-Chloro-2-methyl-4-oxohept-5-en-3-yl)benzamide (**6c**).* Yield 64%; as a wax material; R_f=0.5 (ethyl acetate/hexanes=1/4); IR (neat) ν_{max}: 703, 1524, 1645, 1709, 2358, 2965, 3681, 3740, 3852 cm^{-1}; $[\alpha]_D^{25}$ +86.69 (*c* 1.0, $CHCl_3$); ^{1}H NMR ($CDCl_3$, 300 MHz) δ 0.94 (d, *J*=6.9 Hz, 3H), 1.12 (d, *J*=6.6 Hz, 3H), 2.32–2.38 (m, 1H), 4.28 (dd, *J*=1.8, 6.0 Hz, 2H), 5.14 (dd, *J*=4.2, 4.2 Hz, 1H), 6.59 (ddd, *J*=1.8, 1.8, 13.8 Hz, 1H), 6.89 (d, *J*=7.8 Hz, 1H), 7.04–7.14 (m, 1H), 7.46–7.59 (m, 3H), 7.85–7.89 (m, 2H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 21.5, 24.3, 35.4, 47.1, 65.8, 131.4, 132.9, 133.2, 136.1, 138.5, 146.1, 171.8, 201.9; HRMS calcd for $C_{15}H_{19}O_2NCl$ (M^++H) 280.1104; found, 280.1100.

*4.3.4. (S,E)-N-(8-Chloro-2-methyl-5-oxooct-6-en-4-yl)benzamide (**6d**).* Yield 60%; as a wax material; R_f=0.2 (Ethyl acetate/

Hexane=1/4); IR (neat) ν_{max}: 1040, 1294, 1530, 1642, 1714, 2358, 2954, 3307, 3740, 3852 cm^{-1}; $[\alpha]_D^{25}$ +20.85 (*c* 1.0, $CHCl_3$); ^1H NMR ($CDCl_3$, 300 MHz) δ 0.97 (d, *J*=6.3 Hz, 3H), 1.06 (d, *J*=6.0 Hz, 3H), 1.53–1.62 (m, 1H), 1.69–1.82 (m, 2H), 4.23 (dd, *J*=1.5, 6.0 Hz, 2H), 5.12–5.19 (m, 1H), 6.55 (ddd, *J*=1.5, 1.5, 15.5 Hz, 1H), 6.99 (d, *J*=8.4 Hz, 1H-NH), 7.06 (ddd, *J*=6.0, 6.0, 15.3 Hz, 1H), 7.403–7.54 (m, 3H), 7.81–7.84 (m, 2H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 22.3, 23.6, 41.4, 42.9, 55.9, 127.3, 128.6, 128.8, 131.9, 134.2, 141.9, 167.5, 198.3; HRMS calcd for $C_{16}H_{21}O_2NCl$ (M^++H) 294.1261; found, 294.1255.

4.4. General procedure for synthesis of amino alcohols (7a–d)

To a solution of amino ketone **6a**–**d** (1.0 equiv) in ethanol (0.1 M) was added lithium tri-*tert*-butoxyaluminohydride (1 N solution in THF, 2.0 equiv) at −78 °C. After the reaction mixture was stirred at the same temperature for 4 h, 10% aqueous solution of citric acid was added. The resulting mixture was warmed to room temperature and extracted with ethyl acetate. The organic layers were combined, washed with brine, dried over $MgSO_4$, filtered, and concentrated in vacuo to give the crude products. Column chromatography on silica gel gave amino alcohol **7a**–**d** as colorless oil or a white solid.

*4.4.1. N-((1S,2R,E)-5-Chloro-2-hydroxy-1-phenylpent-3-enyl)benzamide (**7a**).* Yield 79%; as a white solid; mp=152–153 °C; R_f=0.15 (ethyl acetate/hexanes=1/2); IR (neat) ν_{max}: 1321, 1533, 1637, 2357, 3304 cm^{-1}; $[\alpha]_D^{25}$ −3.38 (*c* 1.0, $CHCl_3$); ^1H NMR ($CDCl_3$, 300 MHz) δ 2.90 (d, *J*=6.0 Hz, 1H), 4.06 (d, *J*=6.9 Hz, 2H), 4.64–4.66 (m, 1H), 5.38 (dd, *J*=3.6, 7.5 Hz, 1H), 5.77 (dd, *J*=6.0, 15.0 Hz, 1H), 5.95 (ddd, *J*=1.2, 6.3, 7.5 Hz, 1H), 6.89 (d, *J*=6.9 Hz, 1H-NH), 7.30–7.59 (m, 8H), 7.83–7.86 (m, 2H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 44.2, 58.9, 74.6, 127.3, 127.8, 128.3, 128.9, 129.0, 129.2, 129.3 132.1, 132.9, 134.3, 137.7, 167.8; HRMS calcd for $C_{18}H_{19}O_2NCl$ (M^++H) 316.1104; found, 316.1100.

*4.4.2. N-((2S,3R,E)-6-Chloro-3-hydroxy-1-phenylhex-4-en-2-yl)benzamide (**7b**).* Yield 70%; as a white solid; mp=169–170 °C; R_f=0.4 (ethyl acetate/hexanes=1/1); IR (neat) ν_{max}: 1532, 1642, 1701, 2358, 3279, 3618, 3681, 3740, 3852 cm^{-1}; $[\alpha]_D^{25}$ −63.44 (*c* 1.0, $CHCl_3$); ^1H NMR (CD_3OD, 300 MHz) δ 2.80 (dd, *J*=6.0, 8.4 Hz, 1H), 3.03 (d, *J*=8.4 Hz, 1H), 4.12–4.23 (m, 4H), 5.60 (ddd, *J*=4.2, 4.5, 9.0 Hz, 1H), 5.96 (ddd, *J*=2.4, 4.5, 4.5 Hz, 1H), 7.11–7.13 (m, 1H), 7.15–7.29 (m, 4H), 7.39–7.57 (m, 3H), 7.67–7.76 (m, 2H), 8.16–8.18 (m, 1H); ^{13}C NMR (CD_3OD, 125 MHz) δ 35.7, 45.7, 56.25, 73.3, 126.5, 127.2, 127.8, 127.9, 127.9, 128.7, 128.8, 129.8, 131.6, 135.6, 137.0, 140.4, 166.9; HRMS calcd for $C_{19}H_{21}O_2NCl$ (M^++H) 330.1261; found, 330.1262.

*4.4.3. N-((3S,4R,E)-7-Chloro-4-hydroxy-2-methylhept-5-en-3-yl)benzamide (**7c**).* Yield 77%; as a white solid; mp=84–85 °C; R_f=0.2 (ethyl acetate/hexanes=1/4); IR (neat) ν_{max}: 696, 1525, 1643, 1700, 2358, 2961, 3353, 3681, 3851 cm^{-1}; $[\alpha]_D^{25}$ −66.35 (*c* 1.0, $CHCl_3$); ^1H NMR ($CDCl_3$, 300 MHz) δ 1.05–1.12 (m, 6H), 1.91–2.06 (m, 1H), 3.69 (br, 1H), 4.08 (d, *J*=6.6 Hz, 2H), 4.11–4.18 (m, 1H), 4.49 (br, 1H), 5.89 (dd, *J*=6.0, 12.0 Hz, 1H), 6.01 (ddd, *J*=1.2, 6.0, 15.0 Hz, 1H), 6.21 (d, *J*=9.0 Hz, 1H-NH) 7.42–7.57 (m, 3H), 7.77–7.82 (m, 2H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 19.1, 19.4, 29.5, 44.6, 72.8, 127.3, 128.8, 128.9, 132.0, 133.2, 134.5, 169.4; HRMS calcd for $C_{15}H_{21}O_2NCl$ (M^++H) 282.1261; found, 282.1258.

*4.4.4. N-((4S,5R,E)-8-Chloro-5-hydroxy-2-methyloct-6-en-4-yl)benzamide (**7d**).* Yield 66%; as a white solid; mp=125–126 °C; R_f=0.4 (ethyl acetate/hexanes=1/2); IR (neat) ν_{max}: 1075, 1533, 1636, 2358, 2950, 3297, 3740, 3852 cm^{-1}; $[\alpha]_D^{25}$ −64.46 (*c* 1.0, $CHCl_3$); ^1H NMR ($CDCl_3$, 300 MHz) δ 0.94–0.97 (m, 6H), 1.36–1.41 (m, 1H), 1.46–1.52 (m, 1H), 1.66–1.71 (m, 1H), 3.91 (d, *J*=2.4 Hz, 1H-OH), 4.06 (d, *J*=4.2 Hz, 2H), 4.35 (ddd, *J*=2.1, 2.4, 7.2 Hz, 1H), 5.83 (dd, *J*=3.0, 9.0 Hz, 1H), 5.94–5.99 (m, 1H), 6.34 (d, *J*=5.1 Hz, 1H-NH), 7.39–7.42 (m, 2H), 7.48–7.52 (m, 1H), 7.74–7.76 (m, 2H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 22.0, 23.7, 25.3, 53.5, 74.8, 127.3, 128.5, 128.9, 131.9, 133.5, 134.4, 168.9; HRMS calcd for $C_{16}H_{23}O_2NCl$ (M^++H) 296.1417; found, 296.1420.

4.5. General procedure for alcohol protection (with methyl group)

NaH (60% dispersion in mineral oil, 3.0 equiv) was added to a stirring solution of amino alcohol **7a**–**d** (1.0 equiv) in THF (0.1 M) at 0 °C. After 10 min, MeI (3.0 equiv) was added dropwise and the reaction mixture was warmed to room temperature. After 2 h, the reaction mixture was quenched by adding H_2O and Et_2O was added. The phases were separated and the aqueous phase was extracted twice with Et_2O. The combined organic layers were washed with brine, dried, and concentrated. Flash column chromatography of the crude material yielded methyl ether **9a**, **11a**–**c** as a colorless oil.

*4.5.1. N-((1S,2R,E)-5-Chloro-2-methoxy-1-phenylpent-3-enyl)benzamide (**11a**).* Yield 63%; as a colorless oil; R_f=0.4 (ethyl acetate/hexanes=1/2); IR (neat) ν_{max}: 1099, 1527, 1638, 1724, 2354, 3620, 3678, 3740, 3854 cm^{-1}; $[\alpha]_D^{25}$ 18.42 (*c* 0.5, $CHCl_3$); ^1H NMR ($CDCl_3$, 300 MHz) δ 3.41 (s, 3H), 4.04 (d, *J*=6.6 hz, 2H), 4.13–4.21 (m, 1H), 5.30–5.59 (m, 2H), 5.94–6.09 (m, 1H), 7.00 (d. *J*=8.1 Hz, 1H-NH), 7.31–7.58 (m, 8H), 7.23–7.86 (m, 2H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 31.2, 44.0, 56.5, 57.3, 83.2, 127.1, 127.3, 127.8, 128.3, 128.8, 128.8, 129.7, 131.5, 131.8, 134.8, 137.3, 138.4, 166.7; HRMS calcd for $C_{19}H_{21}O_2NCl$ (M^++H) 330.1261; found, 330.1263.

*4.5.2. N-((2S,3R,E)-6-Chloro-3-methoxy-1-phenylhex-4-en-2-yl)benzamide (**11b**).* Yield 57%; as a colorless oil; R_f=0.5 (ethyl acetate/hexanes=1/2); IR (neat) ν_{max}: 1100, 1532, 1642, 1701, 2358, 3618, 3681, 3740, 3852 cm^{-1}; $[\alpha]_D^{25}$ −16.91 (*c* 0.5, $CHCl_3$); ^1H NMR ($CDCl_3$, 300 MHz) δ 2.97 (dd, *J*=5.0, 9.0 Hz, 1H), 3.04 (dd, *J*=3.0, 9.0 Hz, 1H), 3.36 (s, 3H), 3.86 (dd, *J*=3.0, 3.5 Hz, 1H), 4.01–4.11 (m, 2H), 4.52–4.58 (m, 1H), 5.78 (dd, *J*=4.2, 9.3 Hz, 1H), 5.93–5.98 (m, 1H), 6.17 (d, *J*=5.1 Hz, 1H-NH), 7.20–7.31 (m, 5H), 7.33–7.49 (m, 3H), 7.62–7.66 (m, 2H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 35.38, 44.18, 53.73, 57.44, 82.47, 126.77, 127.05, 127.08, 127.14, 128.75, 128.80, 128.83, 129.50, 130.75, 131.62, 131.96, 134.99, 138.06, 167.23; HRMS calcd for $C_{20}H_{23}O_2NCl$ (M^++H) 344.1417; found, 344.1419.

*4.5.3. N-((3S,4R,E)-7-Chloro-4-methoxy-2-methylhept-5-en-3-yl)benzamide (**11c**).* Yield 57%; as a colorless oil; R_f=0.4 (ethyl acetate/hexanes=1/2); IR (neat) ν_{max}: 1093, 1261, 1610, 1720, 2355, 2960, 3615, 3682, 3740, 3855 cm^{-1}; $[\alpha]_D^{25}$ 5.68 (*c* 1.0, $CHCl_3$); ^1H NMR ($CDCl_3$, 300 MHz) δ 0.99–1.14 (m, 6H), 2.08–2.14 (m, 1H), 3.34 (s, 3H), 3.80 (dd, *J*=6.3, 6.6 Hz, 1H), 4.10 (d, *J*=6.6 Hz, 2H), 4.23–4.30 (m, 1H), 5.80 (dd, *J*=6.9, 9.3 Hz, 1H), 5.91–5.97 (m, 1H), 6.17 (d, *J*=9.3 Hz, 1H-NH), 7.43–7.55 (m, 3H), 7.77–7.82 (m, 2H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 17.8, 20.8, 28.8, 44.3, 56.3, 57.3, 82.3, 127.1, 127.2, 128.8, 128.9, 130.6, 131.7, 131.8, 132.2, 135.20, 167.8; HRMS calcd for $C_{16}H_{23}O_2NCl$ (M^++H) 296.1417; found, 296.1414.

*4.5.4. N-((4S,5R,E)-8-Chloro-5-methoxy-2-methyloct-6-en-4-yl)benzamide (**9a**).* Yield 73%; as a colorless oil; R_f=0.4 (ethyl acetate/hexanes=1/3); IR (neat) ν_{max}: 1462, 1525, 1642, 1688, 2357, 2948, 3618, 3680, 3740, 3851 cm^{-1}; $[\alpha]_D^{25}$ −32.76 (*c* 1.0, $CHCl_3$); ^1H NMR ($CDCl_3$, 300 MHz) δ 0.92–1.06 (m, 6H), 1.38–1.59 (m, 2H), 1.63–1.74 (m, 1H), 3.34 (s, 3H), 3.84 (dd, *J*=3.9, 6.6 Hz, 1H), 4.11 (d, *J*=6.6 Hz, 2H), 4.33–4.39 (m, 1H), 5.73–5.84 (m, 1H), 5.89–5.98 (m, 1H), 6.33 (d, *J*=9.3 Hz, 1H-NH), 7.31–7.55 (m, 3H), 0, 7.79–7.81 (m, 2H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 21.9, 23.9, 25.2, 38.4, 44.2, 51.2, 57.6, 83.9,

126.8, 127.0, 127.2, 128.8, 129.9, 131.6, 132.0, 135.0, 167.2; HRMS calcd for $C_{17}H_{25}O_2NCl$ (M^++H) 310.1574; found, 310.1574.

4.6. General procedure for alcohol protection (with *tert*-butyldimethylsilyl group)

Imidazole (1.2 equiv) and *tert*-butyldimethyl chlorosilane (1.2 equiv) were added to a stirred solution of alcohol **7a–d** (1.0 equiv) in DMF (0.1 M) at room temperature. And stirring was allowed to continue for 2 h. The reaction mixture was quenched with H_2O, extracted twice with Ethyl acetate. The organic layer was washed with brine, dried with $MgSO_4$, and evaporated in vacuo. Purification by silica gel chromatography gave silyl ether **9e**, **12a–c** as a white solid.

*4.6.1. N-((1S,2R,E)-2-(tert-Butyldimethylsilyloxy)-5-chloro-1-phenylpent-3-enyl)-benzamide (**12a**).* Yield 85%; as a white solid; mp=105–107 °C; R_f=0.3 (ethyl acetate/hexanes=1/8); IR (neat) ν_{max}: 1083, 1255, 1533, 1639, 2358, 2857, 2942, 3291, 3741, 3852 cm^{-1}; $[\alpha]_D^{25}$ −0.27 (*c* 1.0, $CHCl_3$); ^1H NMR ($CDCl_3$, 300 MHz) δ 0.10 (d, *J*=3.6 Hz, 6H), 0.94–0.96 (m, 9H), 4.03 (dd, *J*=1.2, 6.6 Hz, 2H), 4.70 (dd, *J*=4.8, 5.4 Hz, 1H), 5.25 (dd, *J*=4.2, 8.1 Hz, 1H), 5.59 (ddd, *J*=0.6, 6.0, 15.3 Hz, 1H), 6.81 (d, *J*=7.8 Hz, 1H-NH), 7.31–7.42 (m, 5H), 7.46–7.55 (m, 3H), 7.81–7.85 (m, 2H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ −4.7, −4.1, 18.4, 26.1, 44.3, 58.6, 74.8, 127.1, 127.9, 128.1, 128.6, 128.7, 128.9, 131.8, 134.2, 134.7, 138.4, 166.9; HRMS calcd for $C_{24}H_{33}O_2NClSi$ (M^++H) 430.1969; found, 430.1967.

*4.6.2. N-((2S,3R,E)-3-(tert-Butyldimethylsilyloxy)-6-chloro-1-phenylhex-4-en-2-yl)benzamide (**12b**).* Yield 95%; as a white solid; mp=120–122 °C; R_f=0.7 (ethyl acetate/hexanes=1/4); IR (neat) ν_{max}: 1082, 1548, 1640, 1700, 2357, 2858, 2952, 3281, 3681, 3740, 3852 cm^{-1}; $[\alpha]_D^{25}$ −23.05 (*c* 1.0, $CHCl_3$); ^1H NMR ($CDCl_3$, 300 MHz) δ −0.1 to 0.09 (m, 6H), 0.91–0.98 (m, 6H), 2.93 (dd, *J*=5.5, 9.0 Hz, 1H), 3.03 (dd, *J*=4.5, 9.0 Hz, 1H), 4.08 (d, *J*=3.9 Hz, 2H), 4.43–4.48 (m, 1H), 4.54 (t, *J*=2.4, 2.4 Hz, 1H), 5.89–6.00 (m, 2H), 6.07 (d, *J*=5.1 Hz, 1H-NH), 7.20–7.34 (m, 5H), 7.38–7.49 (m, 3H), 7.60–7.71 (m, 2H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ −4.8, −4.0, 18.4, 26.1, 34.9, 44.4, 55.5, 73.5, 126.7, 126.9, 128.2, 128.8, 128.8, 129.37, 131.6, 134.8, 134.9, 138.4, 167.2; HRMS calcd for $C_{25}H_{35}O_2NClSi$ (M^++H) 444.2126; found, 444.2120.

*4.6.3. N-((3S,4R,E)-4-(tert-Butyldimethylsilyloxy)-7-chloro-2-methylhept-5-en-3-yl)benzamide (**12c**).* Yield 82%; as a white solid; mp=110–112 °C; R_f=0.2 (ethyl acetate/hexanes=1/6); IR (neat) ν_{max}: 697, 1086, 1532, 1642, 2358, 2862, 2956, 3303, 3740 cm^{-1}; $[\alpha]_D^{25}$ −9.08 (*c* 1.0, $CHCl_3$); ^1H NMR ($CDCl_3$, 300 MHz) δ 0.032–0.072 (m, 6H), 0.90–0.95 (m, 9H), 1.02–1.05 (m, 6H), 2.06–2.10 (m, 1H), 4.09–4.17 (m, 3H), 4.41 (dd, *J*=4.2, 4.8 Hz, 1H), 5.91–5.93 (m, 2H), 6.11 (d, *J*=9.9 Hz, 1H-NH), 7.44–7.53 (m, 3H), 7.77–7.81 (m, 2H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ −4.8, −3.9, 18.0, 18.3, 21.2, 26.0, 26.1, 28.7, 44.5, 58.1, 73.6, 126.9, 128.1, 128.8, 128.9, 131.6, 131.6, 134.9, 135.3, 167.6; HRMS calcd for $C_{21}H_{35}O_2NClSi$ (M^++H) 396.2126; found, 396.2127.

*4.6.4. N-((4S,5R,E)-5-(tert-Butyldimethylsilyloxy)-8-chloro-2-methyloct-6-en-4-yl)benzamide (**9e**).* Yield 95%; as white solid; mp=127–128 °C; R_f=0.4 (ethyl acetate/hexanes=1/10); IR (neat) ν_{max}: 1084, 1642, 1547, 1641, 1688, 2357, 2949, 3296, 3618, 3681, 3740, 3851 cm^{-1}; $[\alpha]_D^{25}$ −10.51 (*c* 1.0, $CHCl_3$); ^1H NMR ($CDCl_3$, 300 MHz) δ −0.024 to 0.04 (m, 6H), 0.87–0.98 (m, 15H), 1.37–1.42 (m, 1H), 1.45–1.52 (m, 1H), 1.65–1.70 (m, 1H), 1.09 (d, *J*=4.2 Hz, 2H), 4.22–4.28 (m, 1H), 4.43 (t, *J*=2.4 Hz, 1H), 5.84 (dd, *J*=3.0, 9.0 Hz, 1H), 5.92 (ddd, *J*=4.2, 4.5, 9.0 Hz, 1H), 6.03 (d, *J*=5.7 Hz, 1H-NH), 7.28–7.53 (m, 3H), 7.76–7.78 (m, 2H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ −4.7, −4.1, 18.4, 21.9, 23.9, 25.2, 25.9, 26.1, 38.0, 44.5, 42.7, 126.9, 127.9, 128.8, 131.6, 134.9, 134.9, 167.0; HRMS calcd for $C_{22}H_{37}O_2NClSi$ (M^++H) 410.2282; found, 410.2277.

4.7. Protection of alcohol with benzyl, methyoxymethyl and benzyloxymethyl groups

*4.7.1. N-((4S,5R,E)-5-(Benzyloxy)-8-chloro-2-methyloct-6-en-4-yl)-benzamide (**9b**).* A solution of alcohol **7d** (1.0 mmol) in tetrahydrofuran (5 mL) was added to a rapidly stirred suspension of sodium hydride (60%, 100 mg, 2.5 mmol) in tetrahydrofuran (10 mL). After the reaction mixture was stirred at room temperature for 10 min, a solution of benzyl bromide (1.16 mmol) in tetrahydrofuran (2 mL) was added. The reaction mixture was stirred at room temperature for 2 h, and poured into aqueous ammonium chloride solution (15%, 2 mL), and concentrated under reduced pressure. The residue was extracted with ethyl acetate (3×20 mL). The combined organic layers were washed with brine, dried, filtered, and evaporated to afford crude product under reduced pressure. Purification on silica gel afforded benzyl ether product **9b**; Yield 70%; as a white solid; mp=118–120 °C; R_f=0.4 (ethyl acetate/hexanes=1/4); IR (neat) ν_{max}: 1079, 1279, 1532, 1642, 2358, 2953, 3305, 3681, 3741, 3852 cm^{-1}; $[\alpha]_D^{25}$ −50.21 (*c* 1.0, $CHCl_3$); ^1H NMR ($CDCl_3$, 300 MHz) δ 0.93 (d, *J*=6.6 Hz, 6H), 1.42–1.64 (m, 3H), 4.05–4.12 (m, 3H), 4.32–4.36 (m, 2H), 4.65 (d, *J*=12.0 Hz, 1H), 5.77–5.85 (m, 1H), 5.93–6.01 (m, 1H), 6.13 (d, *J*=9.5 Hz, 1H-NH), 7.24–7.49 (m, 8H), 7.64–7.67 (m, 2H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 21.8, 24.0, 25.2, 38.2, 44.3, 51.2, 71.4, 81.2, 127.1, 128.0, 128.1, 128.7, 128.6, 130.2, 131.6, 132.2, 134.9, 138.3 167.1; HRMS calcd for $C_{23}H_{29}O_2NCl$ (M^++H) 386.1887; found, 386.1887.

*4.7.2. N-((4S,5R,E)-8-Chloro-5-(methoxymethoxy)-2-methyloct-6-en-4-yl)benzamide (**9c**).* To a solution of amino alcohol **7d** (1.0 equiv) in anhydrous CH_2Cl_2 (20 mL) was added *N*,*N*-diisopropylethylamine (4.0 equiv) and MOMCl (2.0 equiv) dropwise at 0 °C under N_2. The reaction mixture was stirred at room temperature for 24 h. After the starting material disappeared, saturated aqueous $NaHCO_3$ (10 mL) was added to quench the reaction. The layers were separated, and the aqueous layer was extracted with CH_2Cl_2 (20 mL×3). The combined organic layers were washed with brine (20 mL×3), dried ($MgSO_4$), and concentrated. The residue was purified by flash column chromatography on silica gel gave the MOM-protective product **9c**; Yield 90%; as a white solid; mp=107–109 °C; R_f=0.35 (ethyl acetate/hexanes=1/4); IR (neat) ν_{max}: 1542, 1636, 1688, 2358, 2952, 3311, 3681, 3740, 3852 cm^{-1}; $[\alpha]_D^{25}$ −55.07 (*c* 1.0, $CHCl_3$); ^1H NMR ($CDCl_3$, 300 MHz) δ 0.95–1.01 (m, 6H), 1.41–1.55 (m, 2H), 1.68–1.71 (m, 1H), 3.37 (s, 3H), 4.10 (d, *J*=4.2 Hz, 2H), 4.27 (dd, *J*=3.0, 5.0 Hz, 1H), 4.36–4.40 (m, 1H), 4.66 (s, 2H), 5.80 (ddd, *J*=1.0, 5.0, 15.5 Hz, H), 5.94–5.99 (m, 1H), 6.47 (d, *J*=9.5 Hz, 1H-NH), 7.43–7.52 (m, 3H), 7.79–7.81 (m, 2H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 21.9, 23.9, 25.2, 38.7, 44.3, 51.1, 56.0, 80.1, 95.8, 127.1, 128.8, 129.8, 131.6, 131.9, 134.9, 167.1; HRMS calcd for $C_{18}H_{27}O_3NCl$ (M^++H) 340.1679; found, 340.1679.

*4.7.3. N-((4S,5R,E)-5-(Benzyloxymethoxy)-8-chloro-2-methyloct-6-en-4-yl)-benzamide (**9d**).* To a solution of amino alcohol **7d** in THF (6.0 mL) were added DIEA (0.83 mL, 4.7 mmol) and BOMCl (0.73 mL, 4.7 mmol). After being stirred for 3 h at 60 °C, the solution was cooled and diluted with ethyl acetate(100 mL). The organic layer was washed with brine (50 mL×3), dried ($MgSO_4$), and concentrated. The residue was purified on a column of silica gel to yield BOM-protective product **9d**; Yield 76%; as a white solid; mp=119–121 °C; R_f=0.4 (Ethyl acetate/Hexane=1/4); IR (neat) ν_{max}: 1032, 1532, 1640, 2358, 2953, 3309, 3740, 3852 cm^{-1}; $[\alpha]_D^{25}$ −51.87 (*c*=1.0, $CHCl_3$); ^1H NMR ($CDCl_3$, 300 MHz) δ 0.94–1.00 (m, 6H), 1.43–1.48 (m, 1H), 1.52–1.58 (m, 1H), 1.67–1.71 (m, 1H), 4.09 (d, *J*=4.2 Hz, 2H), 4.33 (dd, *J*=3.0, 5.0 Hz, 1H), 4.39–4.44 (m, 1H), 4.55 (d, *J*=6.9 Hz,

1H), 4.69 (d, *J*=6.3 Hz, 1H), 4.77 (d, *J*=4.2 Hz, 1H), 4.86–4.88 (m, 1H), 5.82 (dd, *J*=3.9, 9.3 Hz, 1H), 5.98 (ddd, *J*=4.2, 4.2, 8.4 Hz, 1H), 6.53 (d, *J*=5.7 Hz, 1H), 7.28–7.49 (m, 8H), 7.73–7.75 (m, 2H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 21.9, 23.9, 25.2, 38.7, 44.3, 51.1, 70.5, 80.6, 94.2, 127.1, 127.2, 127.8, 128.1, 128.7, 128.7, 128.7, 129.9, 131.6, 131.9, 134.8, 137.6, 167.2; HRMS calcd for $C_{24}H_{31}O_3NCl$ (M^++H) 416.1992; found, 416.1987.

4.8. General procedure for oxazine formation

NaH(60% in mineral oil, 2 equiv) and *n*-Bu_4NI (1.0 equiv) were added to a stirred solution of methyl ether or silyl ether (1.0 equiv) in dry THF(0.05 M) at 0 °C. After being stirred for 5 min, Pd $(PPh_3)_4$ (0.2 equiv) was added to a mixture and stirring was allowed to continue for 5 h. at same temperature. The reaction mixture was filtered through a pad of silica and then evaporated under reduced pressure to give the crude product. Purification of this material by silica gel chromatography gave mixtures of *anti*,*anti*/*anti*,*syn*-oxazines.

*4.8.1. (4S,5S,6S)-4-Isobutyl-2-phenyl-6-vinyl-5,6-dihydro-4H-1,3-oxazin-5-ol (**8**).* Yield 62%; ratio *anti*,*syn*/*anti*,*anti*=2/1; as a colorless oil; R_f=0.4 (ethyl acetate/hexanes=1/6); IR (neat) ν_{max}: 926, 1082, 1265, 1330, 1460, 1653, 1721, 2922, 3385 cm^{-1}; $[\alpha]_D^{25}$ −35.93 (*c* 1.0, $CHCl_3$); ^{1}H NMR ($CDCl_3$, 300 MHz) δ 0.99–1.12 (m, 6H), 1.42–1.58 (m, 2H), 2.01–2.13 (m, 1H), 3.67–3.72 (m, 1H), 3.79 (br, 1H), 4.76 (ddd, *J*=2.0, 2.1, 3.5 Hz, 1H), 5.52 (ddd, *J*=1.5, 1.5, 10.5 Hz, 1H), 5.62 (ddd, *J*=1.5, 1.5, 17.5 Hz, 1H), 6.08 (ddd, *J*=5.1, 10.5, 17.5 Hz, 1H), 7.39–7.52 (m, 3H), 7.75–7.77 (m, 1H), 8.03–8.07 (m, 1H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 22.9, 23.1, 25.1, 31.2, 45.9, 46.3, 66.0, 66.7, 73.7, 74.7, 87.2, 87.6, 118.0, 119.0, 127.5, 128.5, 131.5, 131.6, 135.3, 162.3; HRMS calcd for $C_{16}H_{21}O_2N$ (M^++H) 259.1572; found, 259.1570.

*4.8.2. (4S,5S,6R)-4-Isobutyl-2-phenyl-6-vinyl-5,6-dihydro-4H-1,3-oxazin-5-ol (**8′**).* Yield 62%; ratio *anti*,*syn*/*anti*,*anti*=2/1; as a colorless oil; R_f=0.5 (ethyl acetate/hexanes=1/6); IR (neat) ν_{max}: 928, 1076, 1275, 1330, 1456, 1646, 1713, 2954, 3380 cm^{-1}; $[\alpha]_D^{25}$ 5.66 (*c* 0.5, $CHCl_3$); ^{1}H NMR ($CDCl_3$, 300 MHz) δ 1.05–1.10 (m, 6H), 1.37–1.46 (m, 1H), 1.71–1.78 (m, 1H), 1.21–1.28 (m, 1H), 3.34 (ddd, *J*=3.9, 4.5, 8.4 Hz, 1H), 3.50 (ddd, *J*=3.6, 7.5, 11.0 Hz, 1H), 4.42 (dd, *J*=6.8, 9.2 Hz, 5.57) (ddd, *J*=1.2, 1.5, 9.5 Hz, 2H), 6.06 (ddd, *J*=6.8, 9.5, 17.5 Hz, 1H), 7.38–7.47 (m, 3H), 7.34–7.77 (m, 1H), 8.00–8.03 (m, 1H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 22.2, 24.2, 24.5, 30.0, 43.8, 57.3, 70.6, 79.5, 116.5, 120.3, 127.7, 128.2, 130.7, 133.4, 134.4, 152.8; HRMS calcd for $C_{16}H_{21}O_2N$ (M^++H) 259.1572; found, 259.1568.

*4.8.3. (4S,5S,6S)-4-isobutyl-5-methoxy-2-phenyl-6-vinyl-5,6-dihydro-4H-1,3-oxazine (**10a**).* Yield 51%; ratio *anti*,*syn*/*anti*,*anti*=6/1; as a colorless oil; R_f=0.4 (ethyl acetate/hexanes=1/20); IR (neat) ν_{max}: 931, 1109, 1284, 1366, 1455, 1657, 1738, 2950 cm^{-1}; $[\alpha]_D^{25}$ −84.74 (*c* 1.0, $CHCl_3$); ^{1}H NMR ($CDCl_3$, 300 MHz) δ 1.08 (d, *J*=6.9 Hz, 6H), 1.50 (t, *J*=6.9, 7.2 Hz, 2H), 2.11–2.20 (m, 1H), 3.32 (dd, *J*=3.5, 5.0 Hz, 1H), 3.51 (s, 3H), 3.68 (ddd, *J*=3.5, 5.1, 10.3 Hz, 1H), 4.87 (ddd, *J*=1.5, 3.5, 7.0 Hz, 1H), 5.41 (ddd, *J*=1.2, 1.2, 11.7 Hz, 1H), 5.48 (ddd, *J*=1.2, 1.2, 17.0 Hz, 1H), 6.13 (ddd, *J*=5.4, 10.6, 17.2 Hz, 1H), 7.38–7.46 (m, 3H), 8.03–8.06 (m, 2H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 22.7, 23,7, 24.9, 44.9, 52.4, 57.8, 73.7, 78.1, 117.9, 127.6, 128.2, 130.6, 133.6, 133.9, 152.8; HRMS calcd for $C_{17}H_{24}O_2N$ (M^++H) 274.1807; found, 274.1812.

*4.8.4. (4S,5S,6R)-4-isobutyl-5-methoxy-2-phenyl-6-vinyl-5,6-dihydro-4H-1,3-oxazine (**10a′**).* Yield 51%; ratio *anti*,*syn*/*anti*,*anti*=6/1; as a colorless oil; R_f=0.5 (ethyl acetate/hexanes=1/20); IR (neat) ν_{max}: 930, 1109, 1280, 1366, 1454, 1656, 1721, 2942 cm^{-1}; $[\alpha]_D^{25}$ −88.39 (*c* 1.0, $CHCl_3$); ^{1}H NMR ($CDCl_3$, 300 MHz) δ 1.06–1.10 (m, 6H), 1.37–1.46 (m, 1H), 1.64–1.72 (m, 1H), 2.27–2.32 (m, 1H), 2.92 (t, *J*=8.4, 8.7 Hz, 1H), 3.48–3.52 (m, 1H), 3.56 (s, 3H), 4.49 (ddd, *J*=1.5, 6.0, 9.0 Hz, 1H), 5.44 (ddd, *J*=1.2, 1.5, 10.5 Hz, 1H), 5.61 (ddd, *J*=1.2, 1.5. 17.0 Hz, 1H), 6.12 (ddd, *J*=6.0, 10.5, 17.0 Hz, 1H), 7.38–7.46 (m, 3H), 8.01–8.04 (m, 2H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ: 22.2, 24.3, 24.6, 43.8, 56.8, 60.6, 78.1, 81.1, 118.45, 127.7, 128.2, 130.6, 133.5, 135.0, 152.7; HRMS calcd for $C_{17}H_{23}O_2N$ (M^+) 273.1729; found, 273.1730.

*4.8.5. (4S,5S,6S)-5-(Benzyloxy)-4-isobutyl-2-phenyl-6-vinyl-5,6-dihydro-4H-1,3-oxazine (**10b**).* Yield 70%; ratio *anti*,*syn*/*anti*,*anti*=5/1; as a colorless oil; R_f=0.4 (Ethyl acetate/Hexane=1/20); IR (neat) ν_{max}: 9.29, 1025, 1102, 1282, 1455, 1657, 2950, 3744 cm^{-1}; $[\alpha]_D^{25}$ −70.21 (*c* 0.5, $CHCl_3$); ^{1}H NMR ($CDCl_3$, 300 MHz) δ 0.96–1.06 (m, 6H), 1.41–1.50 (m, 2H), 2.06–2.11 (m, 1H), 3.50–3.51 (m, 1H), 3.67 (dd, *J*=3.5, 7.5 Hz, 1H), 4.64–4.79 (m, 2H), 5.40 (ddd, *J*=4.5, 5.5, 14.5 Hz, 2H), 6.13 (ddd, *J*=3.3, 6.6, 10.0 Hz, 1H), 7.31–7.44 (m, 8H), 8.01–8.03 (m, 2H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 22.8, 23.8, 24.8, 44.8, 52.8, 72.1, 74.0, 75.6, 117.9, 127.6, 127.8, 128.1, 128.2, 128.2, 128.7, 128.7, 130.6, 130.7, 133.5, 133.8, 134.9, 138.1, 138.2, 152.8; HRMS calcd for $C_{23}H_{28}O_2N$ (M^++H) 350.2120; found, 350.2124.

*4.8.6. (4S,5S,6R)-5-(Benzyloxy)-4-isobutyl-2-phenyl-6-vinyl-5,6-dihydro-4H-1,3-oxazine (**10b′**).* Yield 70%; ratio *anti*,*syn*/*anti*,*anti*=5/1; as a colorless oil; R_f=0.42 (ethyl acetate/hexanes=1/20); IR (neat) ν_{max}: 929, 1027, 1102, 1280, 1461, 1658, 2944, 3750 cm^{-1} $[\alpha]_D^{25}$ −40.80 (*c* 1.0, $CHCl_3$); ^{1}H NMR ($CDCl_3$, 300 MHz) δ 0.89–1.05 (m, 6H), 1.34–1.37 (m, 1H), 1.58–1.67 (m, 1H), 2.17–2.24 (m, 1H), 3.15 (t, *J*=8.5 Hz, 1H), 3.55 (ddd, *J*=3.6, 7.5, 11.0 Hz, 1H), 4.52 (dd, *J*=6.3, 8.6 Hz, 1H), 4.61 (d, *J*=11.0 Hz, 1H), 4.73 (d, *J*=11.0 Hz, 1H), 5.41 (dt, *J*=1.4, 1.4, 10.5 Hz, 1H), 5.58 (dt, *J*=1.4, 1.4, 17.2 Hz, 1H), 6.10 (ddd, *J*=6.3, 10.0, 16.3 Hz, 1H), 7.33–7.39 (m, 8H), 7.96–7.99 (m, 2H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 22.7, 23.7, 24.8, 44.7, 52.8, 72.1, 74.0, 75.6, 118.0, 127.6, 128.1, 128.2, 128.2, 128.7, 130.7, 133.7, 133.8, 138.1, 138.2, 152.8; HRMS calcd for $C_{23}H_{28}O_2N$ (M^++H) 350.2120; found, 350.2115.

*4.8.7. (4S,5S,6S)-4-Isobutyl-5-(methoxymethoxy)-2-phenyl-6-vinyl-5,6-dihydro-4H-1,3-oxazine (**10c**).* Yield 80%; ratio *anti*,*syn*/*anti*, *anti*=8/1; as a colorless oil; R_f=0.16 (ethyl acetate/hexanes=1/20); IR (neat) ν_{max}: 1038, 1110, 1217, 1367, 1459, 1526, 1656, 1738, 2358, 2950, 3742, 3850 cm^{-1}; $[\alpha]_D^{25}$ −54.59 (*c* 0.5, $CHCl_3$); ^{1}H NMR ($CDCl_3$, 300 MHz) δ 0.94 (d, *J*=6.0 Hz, 6H), 1.46–1.52 (m, 2H), 2.11–2.13 (m, 1H), 3.46 (s, 3H), 3.68 (t, *J*=1.5, 6.3 Hz, 1H), 3.74 (ddd, *J*=1.5, 3.0, 6.0 Hz, 1H), 4.78 (dd, *J*=6.9, 19.0 Hz, 2H), 4.85 (ddd, *J*=1.5, 1.5, 5.0 Hz, 1H), 5.42 (ddd, *J*=1.5, 1.5, 9.5 Hz, 1H), 5.51 (ddd, *J*=1.2, 1.5, 16.0 Hz, 1H), 6.14 (ddd, *J*=5.4, 10.5, 17.5 Hz, 1H), 7.38–7.49 (m, 3H), 8.02–8.06 (m, 2H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 22.7, 22.9, 29.9, 43.4, 44.9, 53.4, 56.1, 74.1, 74.3, 78.3, 118.1, 127.6, 127.7, 128.2, 130.7, 133.8, 152.9; HRMS calcd for $C_{18}H_{26}O_3N$ (M^++H) 304.1913; found, 304.1912.

*4.8.8. (4S,5S,6R)-4-Isobutyl-5-(methoxymethoxy)-2-phenyl-6-vinyl-5,6-dihydro-4H-1,3-oxazine (**10c′**).* Yield 80%; ratio *anti*,*syn*/*anti*, *anti*=8/1; as a colorless oil; R_f=0.2 (ethyl acetate/hexanes=1/20); IR (neat) ν_{max}: 1032, 1111, 1218, 1366, 1455, 1526, 1657, 1722, 2357, 2949, 3748, 3850 cm^{-1}; $[\alpha]_D^{25}$ −127.01 (*c* 1.0, $CHCl_3$); ^{1}H NMR ($CDCl_3$, 300 MHz) δ 0.99–1.03 (m, 6H), 1.35–1.40 (m. 1H), 1.60–1.69 (m, 1H), 2.17–2.25 (m, 1H), 3.32 (t, *J*=8.0 Hz, 1H), 3.42 (s, 3H), 3.51 (ddd, *J*=3.6, 4.0, 11.0 Hz, 1H), 4.48 (dd, *J*=6.6, 8.2 Hz, 1H), 4.68 (d, *J*=6.9 Hz, 1H), 4.75 (d, *J*=6.9 Hz, 1H), 5.38 (dt, *J*=1.3, 1.3, 10.5 Hz, 1H), 5.52 (dt, *J*=1.5, 1.5, 17.0 Hz, 1H), 6.02 (ddd, *J*=6.5, 10.5, 17.0 Hz, 1H), 7.35–7.39 (m, 3H), 7.95–7.99 (m, 2H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 22.1, 24.3, 24.6, 43.4, 56.5, 56.7, 78.3, 97.8, 119.1, 127.7, 128.2, 130.6, 133.4, 134.7, 152.9; HRMS calcd for $C_{18}H_{26}O_3N$ (M^++H) 304.1913; found, 304.1914.

*4.8.9. (4S,5S,6S)-5-(Benzyloxymethoxy)-4-isobutyl-2-phenyl-6-vinyl-5,6-dihydro-4H-1,3-oxazine (**10d**).* Yield 90%; ratio *anti*,*syn*/*anti*,*anti*=15/1; as a colorless oil; R_f=0.2 (ethyl acetate/hexanes=1/20); IR (neat) ν_{max}: 1042, 1113, 1516, 1655, 2951, 3672, 3744, 3841 cm^{-1}; $[\alpha]_D^{25}$ −50.25 (*c* 0.5, $CHCl_3$); ^{1}H NMR ($CDCl_3$, 300 MHz) δ 0.89–0.96 (m, 6H), 1.48–1.52 (m, 2H), 2.11–2.16 (m, 1H), 3.70–3.76

(m, 1H), 3.84 (dd, *J*=3.0, 4.5 Hz, 1H), 4.70 (dd, *J*=11.7, 22.0 Hz, 1H), 4.86–4.95 (m, 2H), 5.43 (ddd, *J*=1.5, 1.5, 9.0 Hz, 1H), 5.52 (ddd, *J*=1.6, 1.6, 16.0 Hz, 1H), 6.16 (ddd, *J*=5.4, 10.5, 17.0 Hz, 1H), 7.30–7.49 (m, 8H), 8.04–8.07 (m, 2H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 22.8, 23.7, 24.9, 45.0, 53.5, 70.2, 74.3, 94.3, 118.2, 127.6, 127.8, 127.9, 128.1, 128.1, 128.2, 128.8, 130.6, 133.8, 137.8, 152.9; HRMS calcd for $C_{24}H_{30}O_3N$ (M^++H) 380.2226; found, 380.2231.

*4.8.10. (4S,5S,6R)-5-(Benzyloxymethoxy)-4-isobutyl-2-phenyl-6-vinyl-5,6-dihydro-4H-1,3-oxazine (**10d′**).* Yield 90%; ratio *anti*,*syn*/*anti*,*anti*=15/1; as a colorless oil; R_f=0.21 (ethyl acetate/hexanes=1/20); IR (neat) ν_{max}: 1042, 1113, 1515, 1658, 2944, 3672, 3746, 3845 cm^{-1}; $[\alpha]_D^{25}$ −11.86 (*c* 1.0, $CHCl_3$); ^{1}H NMR ($CDCl_3$, 300 MHz) δ 0.92–1.01 (m, 6H), 1.32–1.38 (m, 1H), 1.64–1.72 (m, 1H), 3.41 (t, *J*=8.0 Hz, 1H), 3.54 (ddd, *J*=3.6, 3.6, 10.5 Hz, 1H), 4.50 (dd, *J*=6.5, 8.0 Hz, 1H), 4.63 (d, *J*=12.0 Hz, 1H), 4.74 (d, *J*=12.0 Hz, 1H), 4.86 (m, 2H), 5.35 (dt, *J*=1.3, 1.3, 10.5 Hz, 1H), 5.52 (dt, *J*=1.4, 1.4, 17.3 Hz, 1H), 6.02 (ddd, *J*=6.5, 10.5, 17.3 Hz, 1H), 7.33–7.39 (m, 8H), 7.96–7.99 (m, 2H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 22.7, 23.6, 24.9, 44.9, 53.5, 70.1, 74.2, 94.2, 118.1, 127.6, 128.0, 128.1, 128.2, 128.7, 130.6, 133.8, 133.9, 137.8, 152.9; HRMS calcd for $C_{24}H_{30}O_3N$ (M^++H) 380.2226; found, 380.2225.

*4.8.11. (4S,5S,6S)-5-(tert-Butyldimethylsilyloxy)-4- isobutyl-2-phenyl-6-vinyl-5,6-dihydro-4H-1,3-oxazine (**10e**).* Yield 65%; ratio *anti*,*syn*/*anti*,*anti*=30/1; as a colorless oil; R_f=0.35 (ethyl acetate/hexanes=1/20); IR (neat) ν_{max}: 1115, 1259, 1462, 1513, 1655, 2928, 3680, 3742, 3852 cm^{-1}; $[\alpha]_D^{25}$ −61.54 (*c* 0.5, $CHCl_3$); ^{1}H NMR ($CDCl_3$, 300 MHz) δ 0.081–0.14 (m, 6H), 0.86–0.89 (m, 9H), 0.99–1.05 (m, 6H), 1.32–1.37 (m, 1H), 1.45–1.50 (m, 1H), 2.12–2.19 (m, 1H), 3.41 (ddd, *J*=3.0, 3.0, 6.0 Hz, 1H), 3.70 (t, *J*=2.4, 3.3 Hz, 1H), 4.72 (t, *J*=2.4, 3.0 Hz, 1H), 5.35 (t, *J*=7.2, 11.7 Hz, 12H), 6.07 (ddd, *J*=3.0, 6.3, 10.5 Hz, 1H), 7.37–7.44 (m, 3H), 7.99–8.01 (m, 2H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ −4.4, −4.1, 18.3, 22.5, 24.1, 24.7, 25.9, 44.4, 55.4, 69.9, 75.9, 117.5, 127.6, 128.2, 130.4, 133.7, 134.0, 152.1; HRMS calcd for $C_{22}H_{36}O_2NSi$ (M^++H) 374.2515; found, 374.2513.

*4.8.12. (4S,5S,6S)-5-Methoxy-2,4-diphenyl-6-vinyl-5,6-dihydro-4H-1,3-oxazine (**13a**).* Yield 62%; ratio *anti*,*syn*/*anti*,*anti*=2/1; as a colorless oil; R_f=0.32 (ethyl acetate/hexanes=1/20); IR (neat) ν_{max}: 699, 1115, 1270, 1531, 1653, 2356, 2928, 3354, 3732, 3850 cm^{-1}; $[\alpha]_D^{25}$ −16.36 (*c* 0.5, $CHCl_3$); ^{1}H NMR ($CDCl_3$, 300 MHz) δ 3.50 (s, 3H), 3.53 (dd, *J*=2.7, 3.9 Hz, 1H), 4.72 (ddd, *J*=1.2, 1.5, 4.8 Hz, 1H), 4.93 (d, *J*=3.9 Hz, 1H), 5.38–5.47 (m, 2H), 6.10 (ddd, *J*=5.4, 10.5, 17.4 Hz, 1H), 7.33–7.51 (m, 7H), 7.73–7.75 (m, 1H), 8.13–8.16 (m, 2H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 58.2, 58.5, 73.2, 79.7, 118.3, 127.4, 127.8, 127.8, 127.9, 127.9, 128.7, 130.9, 133.4, 135.47, 141.8, 155.2; HRMS calcd for $C_{19}H_{20}O_2N$ (M^++H) 294.1494; found, 294.1493.

*4.8.13. (4S,5S,6R)-5-Methoxy-2,4-diphenyl-6-vinyl-5,6-dihydro-4H-1,3-oxazine (**13a′**).* Yield 62%; ratio *anti*,*syn*/*anti*,*anti*=2/1; as a colorless oil; R_f=0.3 (ethyl acetate/hexanes=1/30); IR (neat) ν_{max}: 698, 1115, 1270, 1530, 1653, 2355, 2918, 3360, 3741, 3854 cm^{-1}; $[\alpha]_D^{25}$ −4.27 (*c* 1.0, $CHCl_3$); ^{1}H NMR ($CDCl_3$, 300 MHz) δ 3.06 (t, *J*=9.0 Hz, 1H), 3.13 (s, 3H), 4.61 (d, *J*=8.7 Hz, 1H), 4.66 (dd, *J*=6.0, 6.0 Hz, 1H), 5.43 (ddd, *J*=1.2, 1.5, 11.0 Hz, 1H), 5.64 (ddd, *J*=1.2, 1.2, 17.5 Hz, 1H), 6.10 (ddd, *J*=6.0, 11.0, 17.0 Hz, 1H), 7.31–7.53 (m, 8H), 8.09–8.13 (m, 2H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 58.2, 58.5, 73.2, 79.6, 118.3, 127.4, 127.8, 128.3, 128.7, 131.0, 133.4, 141.8, 155.2; HRMS calcd for $C_{19}H_{20}O_2N$ (M^++H) 294.1494; found, 294.1492.

*4.8.14. (4S,5S,6S)-5-(tert-Butyldimethylsilyloxy)-2,4-diphenyl-6-vinyl-5,6-dihydro-4H-1,3-oxazine (**14a**).* Yield 57%; ratio *anti*,*syn*/*anti*,*anti*=13/1; as a colorless oil; R_f=0.3 (ethyl acetate/hexanes=1/30); IR (neat) ν_{max}: 1117, 1512, 1655, 1739, 2375, 2944, 3742, 3850 cm^{-1}; $[\alpha]_D^{25}$ −40.22 (*c* 0.5, $CHCl_3$); ^{1}H NMR ($CDCl_3$, 300 MHz) δ −0.23 (s, 6H), 0.89–0.91 (m, 9H), 3.91 (dd, *J*=3.9, 6.6 Hz, 1H), 4.60 (d, *J*=6.9 Hz, 1H), 4.78 (ddd, *J*=2.0, 2.4, 5.9 Hz, 1H), 5.39 (ddd, *J*=1.5, 1.5, 4.5 Hz, 1H), 5.43 (ddd, *J*=1.2, 1.5, 4.5 Hz, 1H), 6.16 (ddd, *J*=4.5, 10.5, 17.7 Hz, 1H), 7.29–7.51 (m, 8H), 8.12–8.15 (m, 2H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ −5.2, −4.7, 18.2, 25.9, 61.6, 71.4, 75.8, 117.9, 127.5, 127.8, 128.3, 128.5, 130.9, 133.3, 133.6, 141.9, 154.3; HRMS calcd for $C_{24}H_{32}O_2NSi$ (M^++H) 394.2202; found, 394.2198.

*4.8.15. (4S,5S,6S)-4-Benzyl-5-methoxy-2-phenyl-6-vinyl-5,6-dihydro-4H-1,3-oxazine (**13b**).* Yield 65%; ratio *anti*,*syn*/*anti*,*anti*=3/1; as a colorless oil; R_f=0.3 (ethyl acetate/hexanes=1/20); IR (neat) ν_{max}: 772, 1109, 1217, 1516, 1651, 1739, 2357, 3678, 3742, 3850 cm^{-1}; $[\alpha]_D^{25}$ −4.72 (*c* 0.5, $CHCl_3$); ^{1}H NMR ($CDCl_3$, 300 MHz) δ 2.99 (dd, *J*=6.0, 13.5 Hz, 1H), 3.11 (dd, *J*=6.5, 13.5 Hz, 1H), 3.31 (dd, *J*=3.6, 5.4 Hz, 1H), 3.84 (dd, *J*=6.5, 12.5 Hz, 1H), 4.90 (ddd, *J*=1.8, 3.8, 7.0 Hz, 1H), 5.36–5.45 (m, 2H), 6.08 (ddd, *J*=5.5, 11.5, 18.5 Hz, 1H), 7.26–7.48 (m, 8H), 8.02–8.05 (m, 2H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 40.6, 55.5, 57.4, 73.5, 75.9, 118.0, 126.6, 127.6, 128.3, 128.5, 130.0, 130.7, 133.2, 133.5, 138.7, 153.4; HRMS calcd for $C_{20}H_{21}O_2N$ (M^+) 307.1572; found, 307.1568.

*4.8.16. (4S,5S,6R)-4-benzyl-5-methoxy-2-phenyl-6-vinyl-5,6-dihydro-4H-1,3-oxazine (**13b′**).* Yield 65%; ratio *anti*,*syn*/*anti*,*anti*=3/1; as a colorless oil; R_f=0.32 (ethyl acetate/hexanes=1/20); IR (neat) ν_{max}: 772, 1116, 1516, 1654, 3257, 3616, 3742, 3849 cm^{-1}; $[\alpha]_D^{25}$ −1.52 (*c* 0.5, $CHCl_3$); ^{1}H NMR ($CDCl_3$, 300 MHz) δ 2.91–3.02 (m, 2H), 3.25 (dd, *J*=5.0, 14.0 Hz, 1H), 3.79 (ddd, *J*=4.0, 4.5, 12.0 Hz, 1H), 4.50 (ddd, *J*=3.7, 6.6, 7.8 Hz, 1H), 5.44 (ddd, *J*=1.2, 1.2, 10.8 Hz, 1H), 5.60 (ddd, *J*=1.2, 1.5, 17.0 Hz, 1H), 6.08 (ddd, *J*=6.3, 10.5, 17.0 Hz, 1H), 7.26–7.47 (m, 8H), 7.99–8.05 (m, 2H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 40.6, 55.5, 57.4, 73.5, 75.8, 118.0, 126.6, 127.6, 128.3, 128.5, 130.0, 130.7, 133.1, 138.7, 153.4; HRMS calcd for $C_{20}H_{21}O_2N$ (M^+) 307.1572; found, 307.1568.

*4.8.17. (4S,5S,6S)-4-Benzyl-5-(tert-butyldimethylsilyloxy)-2-phenyl-6-vinyl-5,6-dihydro-4H-1,3-oxazine (**14b**).* Yield 65%; ratio *anti*,*syn*/*anti*,*anti*=12/1; as a colorless oil; R_f=0.4 (ethyl acetate/hexanes=1/20); IR (neat) ν_{max}: 772, 1034, 1518, 1695, 2354, 3673, 3743, 3848 cm^{-1}; $[\alpha]_D^{25}$ −0.94 (*c* 0.5, $CHCl_3$); ^{1}H NMR ($CDCl_3$, 300 MHz) δ 0.16 (d, *J*=9.0 Hz, 6H), 0.92–0.94 (m, 9H), 2.92–2.96 (m, 1H), 3.66 (ddd, *J*=6.0 Hz, 6.8 Hz, 14.0 Hz, 1H), 3.81 (ddd, *J*=3.0, 3.6, 5.0 Hz, 1H), 5.33 (ddd, *J*=1.2, 1.8, 7.8 Hz, 1H), 5.38 (ddd, *J*=1.5, 1.5, 14.4 Hz, 1H), 6.08 (ddd, *J*=4.8, 11.3, 18.0 Hz, 1H), 7.27–7.48 (m, 8H), 8.01–8.04 (m, 2H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ −4.5, −4.1, 18.3, 26.0, 26.3, 40.9, 59.4, 68.0, 75.7, 117.8, 126.3, 126.57, 127.6, 128.1, 128.3, 128.4, 128.6, 130.4, 133.6, 139.3, 153.1; HRMS calcd for $C_{25}H_{33}O_2NSi$ (M^+) 407.2281; found, 407.2274.

*4.8.18. (4S,5S,6S)-4-Isopropyl-5-methoxy-2-phenyl-6-vinyl-5,6-dihydro-4H-1,3-oxazine(**13c**).* Yield 58%; ratio *anti*,*syn*/*anti*,*anti*=4/1; as a colorless oil; R_f=0.4 (ethyl acetate/hexanes=1/20); IR (neat) ν_{max}: 772, 1113, 1520, 1654, 3672, 3742, 3847 cm^{-1}; $[\alpha]_D^{25}$ −45.74 (*c* 1.0, $CHCl_3$); ^{1}H NMR ($CDCl_3$, 300 MHz) δ 1.01 (d, *J*=6.6 Hz, 3H), 1.20 (d, *J*=9.3 Hz, 3H), 2.02–2.08 (m, 1H), 3.33 (ddd, *J*=3.65, 4.5, 4.5 Hz, 1H), 3.50–3.53 (m, 4H), 4.95–4.99 (m, 1H), 5.36–5.45 (m, 2H), 6.09 (ddd, *J*=5.1, 11.4, 18.0 Hz, 1H), 7.31–7.47 (m, 3H), 8.03–8.07 (m, 2H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 17.5, 20.3, 57.6, 59.1, 73.6, 75.2, 117.9, 125.8, 127.6, 128.2, 130.6, 133.0, 133.7, 152.8; HRMS calcd for $C_{16}H_{22}O_2N$ (M^++H) 260.1651; found, 260.1654.

*4.8.19. (4S,5S,6R)-4-Isopropyl-5-methoxy-2-phenyl-6-vinyl-5,6-dihydro-4H-1,3-oxazine (**13c′**).* Yield 58%; ratio *anti*,*syn*/*anti*,*anti*=4/1; as a colorless oil; R_f=0.42 (ethyl acetate/hexanes=1/20); IR (neat) ν_{max}: 780, 1112, 1520, 1661, 3670, 3760, 3850 cm^{-1}; $[\alpha]_D^{25}$ −2.00 (*c* 0.5, $CHCl_3$); ^{1}H NMR ($CDCl_3$, 300 MHz) δ 0.92 (d, *J*=6.9 Hz, 3H), 1.25 (d, *J*=6.6 Hz, 3H), 2.18–2.34 (m, 1H), 3.07 (t, *J*=9.0 Hz, 1H), 3.40 (dd, *J*=2.7, 10.0 Hz, 1H), 3.55 (s, 3H), 4.42 (ddd, *J*=4.0, 6.0, 7.5 Hz, 1H), 5.45 (dd, *J*=1.5, 7.5 Hz, 1H), 5.62 (dd, *J*=1.5, 17.0 Hz, 1H), 6.14 (ddd,

J=6.0, 10.5, 17.0 Hz, 1H), 7.38–7.49 (m, 3H), 8.01–8.04 (m, 2H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 16.3, 20.7, 29.2, 31.2, 60.5, 63.6, 78.2, 118.7, 127.7, 128.2, 130.6, 133.4, 134.9, 153.87; HRMS calcd for $C_{16}H_{22}O_2N$ (M^++H) 260.1651; found, 260.1650.

*4.8.20. (4S,5S,6S)-5-(tert-Butyldimethylsilyloxy)-4-isopropyl-2-phenyl-6-vinyl-5,6-dihydro-4H-1,3-oxazine (**14c**).* Yield 57%; ratio *anti*,*syn*/*anti*,*anti*=13/1; as a colorless oil; R_f=0.25 (ethyl acetate/hexanes=1/30); IR (neat) ν_{max}: 775, 1114, 1262, 1463, 1662, 2953, 3745 cm^{-1}; $[\alpha]_D^{25}$ −54.86 (*c* 0.5, $CHCl_3$); ^{1}H NMR ($CDCl_3$, 300 MHz) δ 0.14–0.20 (m, 6H), 0.93–0.99 (m, 12H), 1.24–1.26 (m, 3H), 2.02–2.10 (m, 1H), 3.24–3.28 (m, 1H), 3.94 (dd, J=4.8, 7.8 Hz, 1H), 4.83 (ddd, J=2.0, 2.5, 4.0 Hz, 1H), 5.34–5.41 (m, 2H), 6.08–6.18 (m, 1H), 7.38–7.50 (m, 3H), 8.06–8.08 (m, 2H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ −4.5, −3.9, 16.5, 18.2, 20.7, 25.9, 26.2, 28.8, 61.2, 66.7, 76.2, 117.3, 127.6, 127.7, 128.3, 130.5, 133.1, 133.8, 152.6; HRMS calcd for $C_{21}H_{34}O_2NSi$ (M^++H) 360.2359; found, 360.2359.

*4.8.21. (4S,5S,6R)-5-(tert-Butyldimethylsilyloxy)-4-isobutyl-2-phenyl-5,6-dihydro-4H-1,3-oxazine-6-carboxylic acid (**15**).* O_3 was bulbed through the solution of oxazine **10e** (0.50 g, 1.34 mmol) in methanol (50 mL) at −78 °C until pale blue (about 30 min), then Me_2S (0.5 mL) was added; the mixture was warmed to room temperature during 1 h and concentrated to a colorless oil, which was used directly. To the solution of the above residue in *t*-BuOH (21 mL) and H_2O (4.2 mL) at 0 °C, was added NaH_2PO_4 (313 mg, 2.01 mmol) and 2-methyl-2-butene (0.57 mL, 5.35 mmol), $NaClO_2$ (363 mg, 4.01 mmol, in three portions); the mixture was warmed to room temperature and stirred overnight. Saturated aqueous $Na_2S_2O_3$ solution(10 mL) was added to the reaction mixture and *t*-BuOH was removed in vacuo, the residue aqueous was acidified to pH 3–4 and extracted by CH_2Cl_2, the organic layer was washed by brine, dried over anhydrous Na_2SO_4, filtered and concentrated, the residue was purified by flash column chromatography to give the acid **15** (341 mg, 65%) as a white solid; mp: 125–127 °C; IR (neat) ν_{max} 3242, 2952, 2261, 1726, 1458, 1373, 1260, 1118, 846 cm^{-1}; $[\alpha]_D^{25}$ +4.78 (*c* 0.4, $CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$) δ −0.02–0.17 (m, 6H), 0.82–0.91 (m, 9H), 0.94–1.05 (m, 6H), 1.45–1.51 (m, 1H), 1.61–1.66 (m, 1H), 1.71–1.75 (m, 1H), 3.54 (ddd, J=3.5, 6.5, 10.0 Hz, 1H), 4.25 (t, J=6.5, 7.5 Hz, 1H), 4.78 (s, 1H-OH), 5.62 (d, J=7.5 Hz, 1H), 7.44–7.49 (m, 3H), 8.07–8.12 (m, 2H); ^{13}C NMR (125 MHz, $CDCl_3$) δ −4.7, −4.1, 18.1, 22.0, 23.6, 25.8, 43.2, 56.6, 77.9, 78.8, 128.6, 130.2, 133.6, 165.6, 170.5; HRMS calcd for $C_{21}H_{34}O_4NSi$ (M^++H) 392.2257; found, 392.2258.

*4.8.22. (2R,3S,4S)-4-Amino-2,3-dihydroxy-6-methyl-heptanoic acid (**16**).* To the acid **15** (96 mg, 0.25 mmol) in MeOH (3 mL) was added 6 N-HCl (3 mL) and the mixture was kept at room temperature for 5 h. After concentration under reduced pressure, the residue was dissolved in aqueous ammonium hydroxide (0.6 M; 1 mL) and chromatographed through a column of Dowex 50 W X8 (H^+) to give α-hydroxy statine **16** (45 mg, 95%) as a white solid; mp: 97–99 °C; IR (neat) ν_{max}: 37.36, 3393, 2956, 2550, 2357, 1605, 1507, 1379, 1062, cm^{-1}; $[\alpha]_D^{25}$ −3.2 (*c* 0.5, MeOH); ^{1}H NMR (500 MHz, D_2O) δ 0.88–0.92 (m, 6H), 1.56–1.58 (m, 2H), 1.66–1.71 (m, 1H), 3.49 (dd, J=7.0, 12.0 Hz, 1H), 4.07 (d, J=3.3 Hz, 1H), 4.15 (d, J=1.8 Hz, 1H); ^{13}C NMR (125 MHz, D_2O) δ 21.3, 22.2, 24.0, 53.9, 70.0, 72.4, 178.2; HRMS calcd for $C_8H_{18}O_4N$ (M^++H) 192.1236; found, 192.1233.

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Supplementary data

Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.tet.2010.01.075.

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