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STEREOSELECTIVE INTRAMOLECULAR CYCLIZATION OF ISOPENTENYL BENZAMIDE VIA π-ALLYLPALLADIUM COMPLEX CATALYZED BY Pd(0)

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Abstract – An efficient procedure was developed to synthesize oxazoline as key intermediate in the total synthesis of (+)-lactacystin using palladium(0)-catalyzed intramolecular cyclization of isopentenyl benzamide via a π–allylpalladium complex. A convenient and efficient method was developed for the synthesis of the optically pure α-amino-β-hydroxy acid.

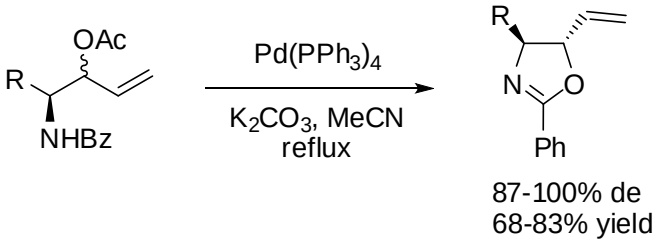
INTRODUCTION

The palladium(0)-catalyzed intramolecular cyclization of a benzamide through a π-allylpalladium(II) complex is useful for the synthesis of highly functionalized compounds, particularly when chirality transfer is involved.

In previous papers, we described a new palladium(0)-catalyzed procedure for the stereoselective formation of an oxazoline ring from a homoallylic amide having a benzoyl substituent as an *N*-protection group. The most significant point of this method is that it is based on *trans*-oxazoline ring formation in palladium(0)-catalyzed conditions (Scheme 1).[1] We have also been exploring the utility of enantiopure oxazoline as a chiral building block for the stereocontrolled syntheses of natural products.[2]

To extend the scope of this method, we replaced the vinyl group with isopropenyl group as testing in view of its selectivity in the formation of the corresponding oxazoline.

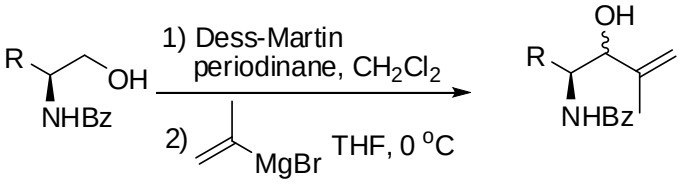
Based on our previous research, we anticipated that the palladium(0)-catalyzed oxazoline formation of isopentenyl benzamide might proceed with high stereoselectivity.



Scheme 1. Palladium(0)-catalyzed oxazoline formation

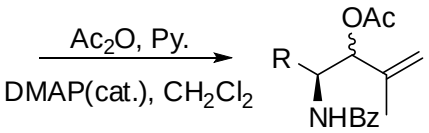
RESULTS AND DISCUSSION

Our initial efforts in the synthesis of the requisite isopentenyl benzamide commenced with the protected *N*-benzoyl amino alcohols **1a-e** as shown in Scheme 2. Oxidation of the alcohols **1a-e** with Dess-Martin periodinane gave the corresponding aldehydes, which were reacted with isopropenylmagnesium bromide in THF at 0 °C to afford secondary 2-isobutenyl alcohols **2a-d** as 1.09-1.57:1 mixtures of *syn/anti* isomers (^{1}H NMR).



1a R=benzyl
1b R=4-methoxylbenzyl
1c R=isopropyl
1d R=isobutyl
1e R=*tert*-butyldimethylsilyloxymethyl

2a R=benzyl (74%)
2b R=4-methoxylbenzyl (69%)
2c R=isopropyl (70%)
2d R=isobutyl (68%)
2e R=*tert*-butyldimethylsilyloxymethyl (75%)

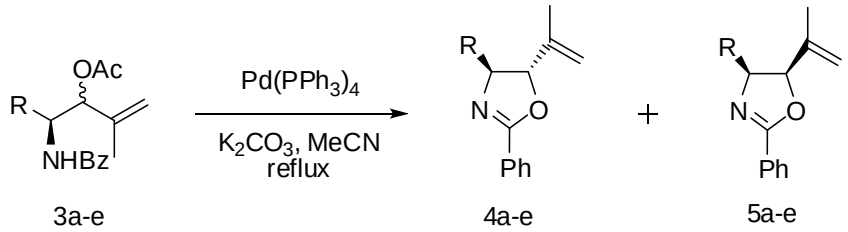


3a R=benzyl (97%)
3b R=4-methoxylbenzyl (96%)
3c R=isopropyl (98%)
3d R=isobutyl (98%)
3e R=*tert*-butyldimethylsilyloxymethyl (99%)

Scheme 2

Acetylation of the hydroxyl group yielded the corresponding acetates **3a-e**. Under the same conditions [$Pd(PPh_3)_4$, K_2CO_3, in CH_3CN] used in the formation of oxazolines, the intramolecular cyclization of isobutenylic acetates afforded the designed *trans*-oxazolines in good yields. (Table 1)

Table 1. Palladium(0)-Catalyzed Oxazoline Formation Reaction of Isobutenylic Acetates 3a-e



3a-e 4a-e 5a-e

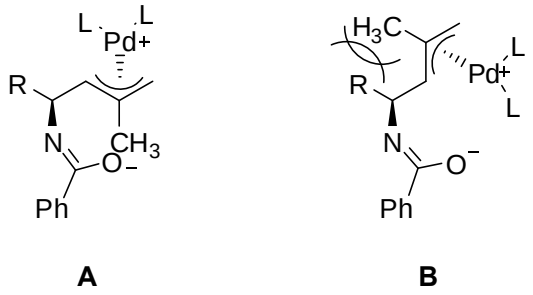
Substrate	Time(h)	Yield(%)[a]	Ratio(4:5)[b]
3a	24	69	17:1
3b	24	71	16:1
3c	24	70	16:1
3d	24	72	13:1
3e	24	75	>20:1

Reaction conditions: $Pd(PPh_3)_4$ (5 mol%), K_2CO_3 (2 equiv), MeCN, reflux. [a]Yields refer to isolated and chromatographically pure products. [b] Ratios were determined by ^1H NMR.

The stereochemistry of the oxazoline obtained above was elucidated by the ^1H NMR data. The J values ($J_{4,5}$ = 5.9-7.0 Hz) observed in all oxazolines **4a-e** clearly indicate that the conpounds possess the assigned trans structures.

It is reasonable to assume that the palladium(0)-catalyzed oxazoline ring formation reaction proceeded via π-allylpalladium complex that arose from the secondary allylic acetates.

The high stereoselectivity of the cyclization of **3a-e** may arise due to differences in the steric interactions between the bulky R group and the methyl group of the π-allylpalladium complex in transition states A and B. Consequently, cyclization proceeds through the more favored transition state A as shown in Figure 1.



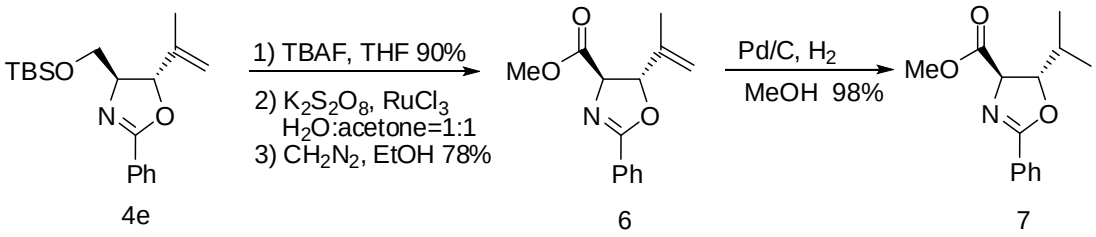
A **B**

Figure 1

This change in the diastereoselectivity of oxazoline ring formation is predominantly controlled by steric repulsion between R groups and the methyl group.

There is excellent evidence for the diastereoselectivity ratios reported herein and the ratios from palladium(0)-catalyzed oxazoline ring formation of allyl and homoallyl benzamide.[1b]

Deprotection of the silyl ether **4e** with tetrabutylammonium fluoride gave the corresponding primary alcohol in 90% yield. Oxidation of the primary alcohol with potassium persulfate and ruthenium(III) chloride hydrate in a 1:1 mixture of H_2O/CH_3CN gave the corresponding carboxylic acid, which was treated with diazomethane in EtOH to afford ester **6**. Reduction of ester **6** in MeOH was catalyzed by Pd/C under 70 psi of H_2 at ambient temperature. Under these conditions, the *trans*-oxazoline **7** was produced. The optical rotation of **7** {$[\alpha]_D^{25}$ = -107.81 (c = 1.0, $CHCl_3$)} was in good agreement with the reported value, which also conclusively proved the stereochemical assignment[5a] (Scheme 3).



Scheme 3

(+)-Lactacystin **8**, a potent proteasome inhibitor, was isolated from the fermentation broth of *Streptomyces sp.* OM-6519 by Omura *et al*. (-)-Clasto-lactacystin (also known as Omuralide **9**) is the cell-permeable and biologically active form of **7**.

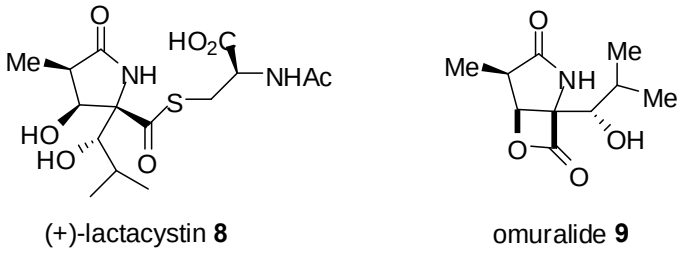


Figure 2. (+)-Lactacystin and Omuralide.

The combination of these potent biological activities and their novel structures has widely increased the interest of the synthetic community. The first complete synthesis of (+)-lactacystin **8** was reported by Corey and coworkers in 1992,[3] and a number of synthetic approaches have been reported in the past several years.[4]

Many of the published procedures have recently used oxazoline **7** as a key intermediate in the total syntheses of (+)-lactacystin and omuralide.[5]

CONCLUSION

An efficient procedure for synthesizing oxazoline **7** as a key intermediate for the total synthesis of (+)-lactacystin was developed using the palladium(0)-catalyzed intramolecular cyclization of isopentenyl benzamide via a π–allylpalladium complex. A convenient and efficient method was developed for the synthesis of the optically pure α-amino-β-hydroxy acid.

Indeed, such synthetic strategies have successfully been applied to the syntheses of *trans*-oxazolines, and these have prompted research into the development of an oxazoline synthesis method that is practical and adaptable for relatively large-scale production.

EXPERIMENTAL

1. General methods

Optical rotations were measured on a JASCO DIP 1020 digital polarimeter. ^{1}H NMR spectra were recorded on a Varian inova FT-NMR at 500 MHz in $CDCl_3$. ^{13}C NMR spectra were recorded at 125 MHz in $CDCl_3$. Chemical shifts are reported as δ values in ppm relative to $CHCl_3$ (7.26) in $CDCl_3$. IR spectra were measured on a Bruker FT-IR spectrometer. Mass spectral data were obtained from the Korea Basic Science Institute (Daegu) on a Jeol JMS 700 high resolution mass spectrometer. Flash chromatography was executed with Merck Kiesegel 60 (230-400 mesh) using mixtures of EtOAc and hexane as eluents. Ethyl acetate and hexane were dried and purified by distillation prior to use. Tetrahydrofuran (THF) and Et_2O were distilled over sodium and benzophenone (indicator). Methylene chloride (CH_2Cl_2) was shaken with concentrated sulfuric acid, dried over potassium carbonate, and distilled. Commercially available compounds were used without further purification.

2. General procedure for 2-Isobutenyl alcohols 2

To a solution of Dess-Martin periodinane (9.65 g, 22.76 mmol, 1.5 equiv) in CH_2Cl_2 (50 mL) at 25 °C was added a solution of alcohol **1** (15.17 mmol, 1.0 equiv) in CH_2Cl_2 (75 mL). The reaction mixture was stirred for 2 h at 25 °C, after which time TLC analysis indicated complete reaction. The reaction mixture was diluted with ether (150 mL) and poured into saturated aqueous $NaHCO_3$ (300 mL) containing $Na_2S_2O_3$ (39.53g, 159.29 mmol, 10.5 equiv). The mixture was stirred to dissolve the solid, and the layers were separated. The ether layer was extracted with saturated aqueous $NaHCO_3$ (150 mL) and with water (150 mL), then dried ($MgSO_4$) and filtered. The filtrate was concentrated *in vacuo* to give crude aldehyde. This aldehyde was immediately employed in the next step without further purification. To a stirred solution of crude aldehyde in THF (75 mL) at 0 °C was added a solution of isopropenylmagnesium bromide (1.0 M in THF, 75.85 mL, 75.85 mmol, 5.0 equiv). After being stirred for 1 h, the reaction mixture was washed with saturated aqueous NH_4Cl (30 mL×2), brine (30 mL×2), dried with $MgSO_4$ and

evaporated *in vacuo*. Purification by silica gel chromatography (EtOAc / hexane =1/2) gave **2**.

2.1. (*S*)-*N*-(3-Hydroxy-4-methyl-1-phenylpent-4-en-2-yl)benzamide, 2a

74% yield, *syn/anti* = 1.26/1, white solid. IR (neat): 3336, 2966, 1639 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$): δ = 1.69 (s, 1.5H), 1.86 (s, 1.5H), 2.59 (s, 0.5H), 2.73 (s, 0.5H), 2.91 (dd, *J* = 9.0, 14.0 Hz, 0.5H), 3.00-3.04 (m, 1H), 3.11 (dd, *J* = 7.0, 13.5 Hz, 0.5H), 4.09 (d, *J* = 9.0 Hz, 0.5H), 4.32 (d, *J* = 3.0 Hz, 0.5H), 4.47 (ddd, *J* = 3.0, 7.5, 16.0 Hz, 0.5H), 4.53 (ddd, *J* = 4.5, 8.5, 13.5 Hz, 0.5H), 4.91 (dd, *J* = 1.5, 2.5 Hz, 0.5H), 5.02 (dd, *J* = 1.5, 2.5 Hz, 0.5H), 5.06 (d, *J* = 1.0 Hz, 0.5H), 5.12 (d, *J* = 1.0 Hz, 0.5H), 6.22 (d, *J* = 8.5 Hz,0.5H), 6.45 (d, *J* = 8.5 Hz, 0.5H), 7.18-7.33 (m, 5H), 7.36-7.49 (m, 2H), 7.58-7.68 (m, 2H) ^{13}C NMR (125 MHz, $CDCl_3$): δ 19.30, 19.35, 34.34, 38.43, 53.22, 53.57, 74.78, 111.45, 112.68, 126.75, 126.84, 127.07, 127.14, 128.77, 128.79, 128.87, 129.55, 131.66, 131.73, 1379, 134.89, 138.40, 138.44, 145.08, 145.84, 167.90, 168.00; HRMS(EI, 70eV) calcd for $C_{19}H_{21}NO_2$(M+1) 295.1572; found 295.1577.

2.2. (*S*)-*N*-[3-Hydroxy-1-(4-methoxyphenyl)-4-methylpent-4-en-2-yl]benzamide, 2b

69% yield, *syn/anti* = 1.17/1, white solid. IR (neat): 3350, 2933, 1639 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$): δ = 1.68 (s, 1.5H). 1.84 (s, 1.5H), 2.85 (dd, *J* = 9.0, 15.0Hz, 0.5H), 2.94-2.98 (m, 1H), 3.03 (dd, *J* = 6.5, 14.0 Hz, 1H), 3.76 (s, 1.5H), 3.79 (s, 1.5H), 4.08 (d, *J* = 10.0Hz, 0.5H), 4.29 (d, *J* = 4.0 Hz, 0.5H), 4.40 (ddd, *J* = 3.0, 6.5, 18.0 Hz, 0.5H), 4.49 (ddd, *J* = 4.0, 8.5, 13.5 Hz, 0.5H), 4.89 (d, *J* = 1.0 Hz, 0.5H), 5.00 (d, *J* = 1.0 Hz, 0.5H), 5.05 (d, *J* = 1.0 Hz, 0.5H), 5.11 (d, *J* = 1.0 Hz, 0.5H), 6.28 (d, *J* = 7.5 Hz, 0.5H), 6.51 (d, *J* = 7.5 Hz, 0.5H), 6.78-6.85 (m, 2H), 7.12-7.24 (m, 2H), 7.35-7.48 (m, 3H), 7.60-7.69 (m, 2H),; ^{13}C NMR (125 MHz, $CDCl_3$): δ 19.31, 19.35, 33.45, 37.52, 53.44, 53.58, 55.44, 55.47, 74.43, 111.40, 112.63, 114.17, 114.26, 127.12, 127.19, 128.74, 128.76, 130.38, 130.50, 130.55, 131.63, 131.69, 134.79, 134.89, 145.11, 145.88, 158.45, 158.52, 167.94, 168.09; HRMS (EI, 70eV) calcd for $C_{20}H_{23}NO_3$ (M+1) 325.1678; found 325.1677.

2.3. (*S*)-*N*-(4-Hydroxy-2,5-dimethylhex-5-en-3-yl)benzamide, 2c

70% yield, *syn/anti* = 1.57/1, colorless needles. IR (neat): 3351, 2961, 1640 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$): δ = 0.98-1.25 (m, 6H), 1.78 (s, 1.5H), 1.81 (s, 1.5H), 2.02-2.09 (m, 0.5H), 2.11-2.18 (m, 0.5H), 2.22 (d ,*J* = 4.0 Hz, 0.5H), 2.29 (d, *J* = 3.0 Hz, 0.5H), 3.99 (ddd, *J* = 3.0, 7.5, 10.0 Hz, 0.5H), 4.23 (dd, *J* = 4.0, 5.5 Hz, 0.5H), 4.29 (ddd, *J* = 4.5, 6.0, 10.0 Hz, 0.5H), 4.33 (m, 0.5H), 4.88 (d, *J* = 1.5 Hz, 0.5H), 4.96 (d, *J* = 1.5 Hz, 0.5H), 5.01 (d, *J* = 1.5 Hz, 0.5H), 5.04 (d, *J* = 1.5, 0.5H), 6.13 (d, *J* = 9.0 Hz, 0.5H), 6.41 (d, *J* = 9.0 Hz, 0.5H), 7.40-7.52 (m, 3H), 7.74-7.76 (m, 2H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 17.49, 18.64, 19.45, 19.63, 20.23, 21.37, 28.19, 30.48, 56.02, 56.98, 74.43, 110.99, 113.10, 127.10, 127.17, 128.75, 128.86, 131.52, 131.69, 135.14, 145.92, 146.43, 168.05, 168.26; HRMS (EI, 70eV) calcd for $C_{15}H_{21}NO_2$ (M+1) 247.1572; found 247.1570.

2.4. (*S*)-*N*-(3-Hydroxy-2,6-dimethylhept-1-en-4-yl)benzamide, 2d

68% yield, *syn/anti* =1.20/1, colorless needles. IR (neat): 3338, 2954, 1638 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$): δ = 0.92-1.03 (m, 6H), 1.25-1.32 (m, 0.5H), 1.43-1.50 (m, 0.5H), 1.62-1.74 (m, 1H), 1.80 (s, 3H), 4.10 (d, *J* = 3.5 Hz, 0.5H), 4.26 (d, 9.5 Hz, 0.5H),4.38 (ddt, *J* = 3.5, 5.0, 9.5 Hz, 0.5H), 4.43 (ddt, *J* = 3.0, 6.0, 9.0 Hz, 0.5H), 4.89 (d, *J* = 1.0 Hz, 0.5H), 4.98 (d, *J* = 1.0 Hz, 0.5H), 5.00 (d, *J* = 1.0 Hz, 0.5H), 5.07 (d, *J* = 1.0 Hz, 0.5H), 6.29 (d, *J* = 9.0 Hz, 0.5H), 6.37 (d, *J* = 9.0 Hz, 0.5H), 7.39-7.52 (m, 3H), 7.73-9.68 (m, 2H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 19.25, 19.74, 21.86, 22.56, 23.35, 24.04, 25.07, 25.32, 37.20, 41.90, 50.20, 50.43, 111.61, 127.22, 128.68, 128.75, 131.55, 131.67, 134.81, 134.93, 145.06, 145.85, 167.92, 168.33; HRMS (EI, 70eV) calcd for $C_{16}H_{23}NO_2$ (M+1) 261.1729; found 261.1729.

2.5. (*S*)-*N*-[1-(*tert*-Butyldimethylsilyloxy)-3-hydroxy-4-methylpent-4-en-2-yl]benzamide, 2e

75% yield, *syn/anti* = 1.09/1, colorless oil. IR (neat): 3327, 2930, 1643 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$): δ = 0.02-0.12 (m, 6H), 0.91 (s, 9H), 1.70 (s, 1.5H), 1.82 (s, 1.5H), 3.72 (s, 0.5H), 3.76 (d, *J* = 8.0 Hz, 0.5H), 3.87 (dd, *J* = 4.5, 10.0 Hz, 0.5H), 3.90 (dd, *J* = 3.5, 10.0 Hz, 0.5H), 4.01-4.04 (m, 1H), 4.24-4.29 (m, 1.5H), 4.51 (m, 0.5H), 4.95 (d, *J* = 1.5Hz, 0.5H), 5.06 (d, *J* = 1.5Hz, 0.5H), 5.14 (d, *J* = 1.5Hz, 0.5H), 5.17 (d, *J* = 1.5Hz, 0.5H), 6.72 (d, *J* = 8.0 Hz, 0.5H), 6.95 (d, *J* = 7.5 Hz, 0.5H), 7.40-7.55 (m, 3H), 7.75-7.81 (m, 2H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 5.31, 5.45, 18.27, 18.33, 19.14, 19.34, 25.98, 26.02, 51.22, 51.98, 63.20, 64.95, 75.25, 111.89, 112.28, 127.13, 128.76, 128.82, 131.71, 131.77, 134.65, 134.70, 144.33, 144.88, 167.33, 167.88; HRMS (EI, 70eV) calcd for $C_{19}H_{31}NO_3Si$ (M+1) 349.5416; found 349.5417.

3. General procedure for Benzamides 3

Acetic anhydride (1.24 mL, 13.18 mmol, 1.1 equiv.), pyridine (1.07 mL, 13.18 mmol, 1.1 equiv) and DMAP (147 mg, 1.20 mmol, 0.1 equiv.) were added to a stirred solution of alcohol **2** (11.98 mmol, 1.0 equiv.) in CH_2Cl_2 (50 mL) and stirring was continued for 12 h. The reaction mixture was washed with 1 N HCl (50 mL x 2), saturated aqueous $NaHCO_3$ solution (50 mL x 2), and brine (50 mL x 2); dried with $MgSO_4$; and evaporated *in vacuo*. The resulting substance was purified by silica gel column chromatography (EtOAc/ hexane = 1/2) and gave isobutenylic acetate **3**.

3.1. (*S*)-4-Benzamido-2-methyl-5-phenylpent-1-en-3-yl acetate, 3a

97% yield, *syn/anti* = 1.33/1, colorless oil. IR (neat): 3300, 2932, 1737, 1644 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$): δ = 1.63 (s, 1.5H), 1.77 (s, 1.5H), 2.10 (s, 3H), 2.83 (dd, *J* = 8.5, 14.5 Hz, 0.5H), 2.92 (ddd, *J* = 6.5, 13.5, 20.5 Hz, 1H), 3.09 (dd, *J* = 5.0, 14.5 Hz, 0.5H), 4.72-4.79 (m, 1H), 4.92 (d, *J* = 1.0 Hz, 0.5H), 4.95 (d, *J* = 1.0Hz, 0.5H), 5.01 (m, 1H), 5.22 (d, *J* = 4.0 Hz, 0.5H), 5.35 (d, *J* = 6.0 Hz, 0.5H), 5.92 (d, *J* = 9.0 Hz, 0.5H), 6.20 (d, *J* = 9.0 Hz, 0.5H), 7.18-7.30 (m, 5H), 7.35-7.50 (m, 3H), 7.56-7.58 (m, 1H), 7.66-7.68 (m, 1H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 19.14, 19.35, 21.19, 21.28, 35.78, 38.62, 50.83, 51.44, 113.39, 114.62, 126.91, 126.99, 127.04, 128.79, 128.82, 128.86, 128.87, 129.51, 131.70, 131.72, 134.83,

134.86, 137.31, 137.48, 141.23, 141.32, 167.22, 167.31, 170.06, 170.22; HRMS(EI, 70eV) calcd for $C_{21}H_{23}NO_3$(M+1) 337.1678; found 337.1677.

3.2. (*S*)-4-Benzamido-5-(4-methoxyphenyl)-2-methylpent-1-en-3-yl acetate, 3b

96% yield, *syn/anti* = 1.28/1, colorless oil. IR (neat): 3305, 2942, 1737, 1644 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$): δ = 1.76 (s, 1.5H), 1.85 (s, 1.5H), 2.12 (s, 1.5H), 2.13 (s, 1.5H), 3.03 (dd, *J* = 5.0, 14.5 Hz, 0.5H), 3.76 (s, 1.5H), 3.78 (s, 1.5H), 4.68-4.72 (m, 1H), 4.92 (d, *J* = 1.0 Hz, 0.5H), 4.94 (d, *J* = 1.0 Hz, 0.5H) 5.00 (d, *J* = 1.0 Hz, 0.5H), 5.01 (d, *J* = 1.0 Hz, 0.5H) 5.21 (d, *J* = 3.5 Hz, 0.5H), 5.31 (d, *J* = 6.0 Hz, 0.5H), 5.88 (d ,*J* = 9.0 Hz, 0.5H), 6.17 (d, *J* = 9.5 Hz, 0.5H), 6.80-6.84 (m, 2H), 7.09-7.14 (m, 2H), 7.37-7.51 (m, 3H), 7.58-7.59 (m. 1H), 7.67-7.69 (m, 1H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 19.08, 19.37, 21.21, 21.31, 31.13, 34.82, 37.69, 50.81, 51.60, 55.46, 76.67, 78.36, 113.31, 114.25, 114.31, 114.70, 126.99, 127.05, 128.83, 128.86, 129.27, 130.49, 130.52, 131.70, 134.84, 134.89, 141.27, 141.38, 158.63, 158.70, 167.15, 167.28, 170.07, 170.21; HRMS (EI, 70eV) calcd for $C_{22}H_{25}NO_4$ (M+1) 367.1784; found 367.1786.

3.3. (*S*)-4-Benzamido-2,5-dimethylhex-1-en-3-yl acetate, 3c

98% yield, *syn/anti* = 1.57/1, colorless needles. IR (neat): 3316, 2964, 1737, 1650 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$): δ = 093-1.03 (m, 12H), 1.80-1.87 (m, 7H), 2.01-2.05 (m, 1H), 2.09 (s, 6H), 4.32 (ddd, *J* = 5.0, 6.0, 11.0 Hz, 1H), 4.48 (ddd, *J* = 4.0,7.0,11.0 Hz, 1H), 4.92 (m, 1H), 4.99 (d, *J* = 1.0 Hz, 0.5H), 5.02 (d, *J* = 1.0 Hz, 0.5H), 5.29 (d, *J* = 8.0 Hz, 1H), 4.45 (d, *J* = 4.5 Hz, 1H), 5.85 (d, *J* = 10.5 Hz, 1H), 6.08 (d, *J* = 10.0Hz, 1H), 7.42-7.46 (m, 4H), 7.49-7.52 (m, 2H), 7.70-7.75 (m, 4H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 16.65, 18.46, 18.55, 19.25, 20.25, 20.82, 21.23, 21.35, 28.48, 30.27, 53.81, 55.33, 76.58, 113.21, 115.70, 127.03, 127.07, 128.87, 128.91, 131.66, 131.72, 135.05, 141.65, 141.90, 167.78, 170.31; HRMS (EI, 70eV) calcd for $C_{17}H_{23}NO_3$ (M+1) 289.1678; found 289.1681.

3.4. (*S*)-4-Benzamido-2,6-dimethylhept-1-en-3-yl acetate, 3d

98% yield, *syn/anti* = 1.19/1, colorless needles. IR (neat): 3303, 2955, 1738, 1642,cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$): δ = 0.93-0.99 (m, 6H),1.32-1.46 (m, 2H), 1.65-1.71 (m, 1H), 1.85 (s, 3H), 2.08 (s, 1.5H), 2.11 (s, 1.5H), 4.56 (4.5, 9.5, 14.5 Hz, 0.5H), 4.63 (ddd, *J* = 5.0, 5.0, 10.0 Hz, 0.5H), 4.95 (m, 2H), 5.26 (dd, *J* = 4.5, 8.0 Hz, 1H), 5.97 (d, *J* = 9.5 Hz, 0.5H), 6.03 (d, *J* = 9.0 Hz, 0.5H), 7.41-7.44 (m, 2H), 7.47-7.51 (m, 1H), 7.71-7.74 (m, 2H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 19.25, 19.73, 21.20, 21.27, 21.80, 22.38, 23.48, 23.97, 25.05, 25.13, 38.99, 41.95, 48.58, 78.77, 79.56, 113.45, 113.63, 127.07, 127.09, 128.85, 131.66, 131.71, 134.92, 141.30, 141.42, 167.23, 16741, 170.41, 170.47; HRMS (EI, 70eV) calcd for $C_{18}H_{25}NO_3$ (M+1) 303.1834; found 303.1832.

3.5. (*S*)-4-Benzamido-5-(*tert*-butyldimethylsilyloxy)-2-methylpent-1-en-3-yl acetate, 3e

99% yield, *syn/anti* = 1.09/1, colorless oil. IR (neat): 3322, 2931, 1745, 1646 cm^{-1}, ^1H NMR (500 MHz, $CDCl_3$): δ = 0.02-0.05 (m, 6H), 0.91 (s, 9H), 1.80 (s, 1.5H), 1.84 (s, 1.5H), 2.04 (s, 1.5H), 2.09 (s, 1.5H),

3.65 (dd, *J* = 5.5, 10.5 Hz, 0.5H), 3.73 (dd, *J* = 3.5, 7.0Hz, 0.5H), 3.76 (dd, *J* = 3.5, 6.0 Hz, 0.5H), 3.86 (dd, *J* = 3.0, 10.0 Hz, 0.5H), 4.49-4.51 (m, 1H), 4.99-5.06 (m, 2H), 5.37 (d, *J* = 8.5 Hz, 0.5H), 5.61 (d, *J* = 7.0 Hz, 0.5H), 6.42 (d, *J* = 8.0 Hz, 0.5H), 6.45 (d, *J* = 9.0 Hz, 0.5H) 7.41-7.52 (m, 3H), 7.70-7.75 (m, 2H); ^{13}C NMR (125 MHz, $CDCl_3$): δ; 3.36 5.35 18.39 19.02 21.21 25.90 50.86 51.72 61.43 62.02 76.07 114.97 115.87 127 27 128 90 131.93 134.63 141.38 167.02 167.33 169.86 170.63;HRMS (EI, 70eV) calcd for $C_{21}H_{32}NO_4Si$ (M+1) 391.5822; found 391.5827.

4. General procedure for Oxazolines 4

To a stirred solution of isobutenylic acetate (0.42 g, 1.06 mmol) and K_2CO_3 (0.44 g, 3.18 mmol, 3.0 equiv) in MeCN (20 mL) was added $Pd(PPh_3)_4$ (6.1 mg, 0.05 mmol, 0.05 equiv) under an argon atmosphere. The solution was refluxed for 24 h, whereupon it was cooled to rt and the catalyst was removed by filtration over a pad of silica. The filtrate was concentrated under reduced pressure to give the crude product, which was purified by silica gel chromatography (EtOAc/hexane = 1/20).

4.1. (4*S*,5*S*)-4-Benzyl-2-phenyl-5-(prop-1-en-2-yl)-4,5-dihydrooxazole, 4a

74% yield, colorless oil. $[\alpha]_D^{25}$ +11.88 (c 1.0, $CHCl_3$); IR (neat): 2924, 1649 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$): δ = 1.51 (s, 1H), 2.76 (dd, *J* = 8.5, 13.5 Hz, 1H), 3.21 (dd, *J* = 5.5, 13.5 Hz, 1H), 4.24 (dt, *J* = 6.0, 8.0 Hz, 1H), 4.71 (d, *J* = 6.5 Hz, 1H), 4.73 (m, 2H), 7.20-7.31 (m, 5H), 7.39-7.43 (m, 2H), 7.46-7.49 (m, 1H), 7.97-7.99 (m, 2H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 16.82, 42.40, 73.11, 86.81, 112.12, 126.80 128.03 128.55 128.60 128.71 129.91 131.61 137.85 143.32 163.45 ; HRMS (EI, 70eV) calcd for $C_{19}H_{19}NO$ (M+1) 277.1467; found 277.1465.

4.2. (4*S*,5*S*)-4-(4-Methoxybenzyl)-2-phenyl-5-(prop-1-en-2-yl)-4,5-dihydrooxazole, 4b

74% yield, colorless oil. $[\alpha]_D^{25}$ +57.16 (c 1.0, $CHCl_3$); IR (neat): 2924, 1649 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$): δ = 1.53 (s, 1H), 2.76 (dd, *J* = 8.5, 13.5 Hz, 1H), 3.21 (dd, *J* = 5.5, 13.5 Hz, 1H), 3.79 (s, 1H), 4.20 (dt, *J* = 5.5, 8.5 Hz, 1H), 4.71 (d, *J* = 6.0 Hz, 1H), 4.75 (t, *J* = 1.0 Hz, 1H), 4.76 (t, *J* = 1.0 Hz, 1H), 6.83-6.86 (m, 2H), 7.17-7.20 (m, 2H), 7.40-7.51 (m, 3H), 7.97-7.99 (m, 2H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 16.88, 41.41, 55.50, 73.22, 76.69, 86.73, 112.08, 114.10, 127.00, 128.02, 128.53, 128.59, 129.85, 130.85, 131.59, 143.36, 158.56, 163.37; HRMS (EI, 70eV) calcd for $C_{20}H_{21}NO_2$ (M+1) 307.1572; found 307.1574.

4.3. (4*S*,5*S*)-4-Isopropyl-2-phenyl-5-(prop-1-en-2-yl)-4,5-dihydrooxazole, 4c

74% yield, colorless oil. $[\alpha]_D^{25}$ -46.32 (c 1.0, $CHCl_3$); IR (neat): 2959, 1652 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$): δ = 0.97-1.03 (m, 6H), 1.73 (s, 3H), 1.91 (dt, *J* = 6.0, 10.0 Hz, 1H), 3.83 (dd, *J* = 5.5, 6.0 Hz, 1H), 4.75 (d, *J* = 6.0Hz, 1H), 4.88 (dd, *J* = 1,5, 3.0 Hz, 1H), 5.02 (t, *J* = 1.5 Hz,1H), 7.39-7.42 (m, 2H), 7.45-7.49 (m, 1H), 7.98-8.00 (m, 2H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 16.82, 18.45, 18.90, 33.15, 85.31, 112.55, 128.11, 128.53, 128.54, 131.44, 144.28, 162.81; HRMS (EI, 70eV) calcd for $C_{15}H_{19}NO$ (M+1)

229.1467; found 229.1468.

4.4. (4*S*,5*S*)-4-Isobutyl-2-phenyl-5-(prop-1-en-2-yl)-4,5-dihydrooxazole, 4d

74% yield, colorless oil. $[\alpha]_D^{25}$ -53.20 (c 1.0, $CHCl_3$); IR (neat): 2950, 1650 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$): δ = 0.96-1.00 (m, 6H), 1.41 (ddd, *J* = 7.0, 7.0, 10.5 Hz, 1H), 1.65 (ddd, *J* = 7.0, 7.0, 10.5 Hz, 1H), 1.75 (s, 1H), 1.89-1.97 (m, 1H), 4.03 (dd, *J* = 7.0, 14.0 Hz, 1H), 4.61 (d, *J* = 7.0 Hz, 1H), 4.91 (t, d = 1.5 Hz, 1H), 5.03 (d, *J* = 1.0 Hz, 1H), 7.38-7.42 (m, 2H), 7.45-7.48 (m, 1H), 7.96-7.98 (m, 2H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 16.90, 23.02, 23.10, 25.17, 46.32, 69.78, 88.92, 112.80, 128.22, 128.48, 128.53, 131.42, 143.62, 162.81; HRMS (EI, 70eV) calcd for $C_{16}H_{21}NO$ (M+1) 243.1623; found 243.1626.

4.5. (4*S*,5*S*)-4-((*tert*-Butyldimethylsilyloxy)methyl)-2-phenyl-5-(prop-1-en-2-yl)-4,5-dihydrooxazole, 4e

75% yield, colorless oil. $[\alpha]_D^{25}$ +2.4 (c 1.2, $CHCl_3$); IR (neat): 2930, 1649 cm^{-1}, ^1H NMR (500 MHz, $CDCl_3$): δ = 0.03 (s, 3H), 0.07 (s, 3H), 0.85 (s, 9H), 1.74 (s, 3H), 3.66 (*J* = 10.2Hz, 6.7Hz, 1H), 3.89 (dd, *J* = 10.2Hz, 3.8Hz), 1H),4.05 (dt, *J* = 6.4Hz, 3.8Hz, 1H), 4.88 (t, *J* = 1.4Hz, 1H), 4.97 (d, *J* = 5.9Hz, 1H), 5.04 (t, *J* = 0.7Hz, 1H), 7.51-7.38(m, 3H), 8.01-7.95 (m, 2H). ^{13}C NMR (125 MHz, $CDCl_3$): δ 5.10, 5.09, 17.22, 18.45, 26.04, 65.24, 73.39, 85.21, 111.86, 128.02, 128.52, 131.55, 143.75, 164.27; HRMS (EI, 70eV) calcd for $C_{19}H_{29}NO_2Si$ (M+1) 331.5289; found 331.5267.

5. (4*R*,5*S*)-Methyl 2-phenyl-5-(prop-1-en-2-yl)-4,5-dihydrooxazole-4-carboxylate, 6

To a solution of oxazoline **4e** (1.0 g, 3.0 mmol) in THF (15 mL) was added a solution of tetrabutylammonium fluoride (1 M in THF, 0.96 mL, 3.3 mmol, 1.1 equiv). After being stirred for 4 h, AcOEt (20 mL) and saturated aqueous NH_4Cl solution (5 mL) was added and the mixture was diluted with water (20 mL). The aqueous layer was extracted with AcOEt (20 mL × 2). The combined organic layers were dried with $MgSO_4$ and concentrated. The residue was chromatographed on silica gel (EtOAc/hexane =1/2) gave primary alcohol (0.59 g, 90%) as a white solid. $[\alpha]_D^{25}$ -51.76 (c 1.0, $CHCl_3$); IR (neat): 3199, 2919, 1645 cm-'; ^1H NMR (500 MHz, $CDCl_3$): δ 1.74 (S, 3H), 3.66 (dd, *J* = 4.0, 12.5 Hz, 1H), 4.05 (m, 2H), 4.94 (t, *J* = 1.5 Hz, 1H), 4.99 (d, *J* = 8.0 Hz, 1H), 5.08 (ddd, *J* = 1.0, 1.0, 1.5 Hz, 1H), 7.34 (m, 2H), 7.45 (m, 1H), 7.85 (m, 2H) ; ^{13}C NMR (125 MHz, $CDCl_3$): δ 16.94, 64.07, 73.09, 84.66, 113.09, 127.31, 128.52, 131.77, 143.01, 165.17; HRMS(EI, 70eV) calcd for $C_{13}H_{15}NO_2Si$ (M+1) 217.1103; found 217.1100.

A solution of potassium persulfate (1.1 g, 4.06 mmol, 2.17 equiv.) was dissolved in 1N KOH solution (83 mL), this solution was added to a solution of primary alcohol (0.42 g, 1.92 mmol) in biphasic water/acetonitrile (1/1) (40 mL). $RuCl_3$ hydrate (88 mg, 0.42 mmol, 0.2 equiv.) was then added to the solution under magnetic stirring. The resulting mixture was stirred at room temperature for 24 h. At the end of the reaction, the mixture was extracted with Et_2O (5×50 mL). The combined extracts were dried

with anhydrous Na_2SO_4, and the solvent was removed by evaporation under reduced pressure to give the crude product. To the stirred solution of the above the crude product in Et_2O (15 mL), an ethereal solution of diazomethane was added dropwise until the reaction mixture turned yellow. The mixture was stirred for 1 h at room temperature. Evaporation of solvents yielded crude compound. The residue was chromatographed on silica gel (EtOAc/hexane = 1/6) gave the compound **6** (0.37 g , 78%) as a colorless oil; $[\alpha]_D^{25}$ -63.18 (c 1.0, $CHCl_3$); IR (neat): 2923, 1743, 1644, 1444 cm^{-1}; 1H-NMR (500 MHz, $CDCl_3$) δ 1.77 (s, 3H), 3.84(s, 3H), 4.63-4.64 (d, 7.0 Hz, 1H), 4.68 (dd, *J* = 1.0 Hz, 1H), 4.68 (dd, *J* = 1.0 Hz, 1H), 5.30-5.32 (d, *J* = 7.5 Hz, 1H), 7.41 (m, 2H), 7.51 (m, 1H), 8.03(m, 2H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 17.04, 53.04, 73.48, 85.13, 113.78, 127.15, 128.64, 128.87, 132.18, 141.95, 165.87, 171.75; HRMS (EI, 70eV) calcd for $C_{14}H_{15}NO_3$ (M+1) 245.1052; found 245.1050.

6. (4*R*,5*S*)-Methyl 5-isopropyl-2-phenyl-4,5-dihydrooxazole-4-carboxylate, 7

To a solution of **6** (100 mg, 4.08 mmol) in MeOH (2 mL) was added 20 mg of 10% Pd/C, and the reaction mixture was vigorously shaken under an atmosphere of hydrogen for 8 h at room temperature. The reaction mixture was filtered through Celite pad, concentrated *in vacuo*, and purified by column chromatography over silica gel (EtOAc/hexane =1/6) gave **7** (86 mg, 98%) as a colorless oil; $[\alpha]_D^{25}$ -107.81 (c 1.0, $CHCl_3$); IR (neat): 2959, 1743, 1645, 1450, 1343 cm^{-1}; 1H-NMR (500 MHz, $CDCl_3$) δ 1.00 (d, *J* = 7.0 Hz, 3H), 1.03 (d, *J* = 6.5 Hz, 3H), 1.96 (m, 1H), 3.81 (s, 3H), 4.57 (d, 7.0 Hz, 1H), 4.68 (dd, *J* = 6.5, 7.0 Hz, 1H), 7.41 (m, 2H), 7.50 (m, 1H), 8.00 (m, 2H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 17.52, 17.64, 32.67, 52.91, 71.56, 87.44, 127.45, 128.57, 128.79, 132.01, 165.60, 172.31; HRMS (EI, 70eV) calcd for $C_{14}H_{17}NO_3$ (M+1) 247.1208; found 247.1212.

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