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General Asymmetric Synthesis of Hydroxymethylene and Hydroxyethylene Peptide Isosteres

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Abstract. The Lewis acid-promoted coupling reactions of (*5R, 6S*)-2-acetoxy-4-(benzyloxycarbonyl)-5,6-diphenyl-2,3,5,6-tetrahydro-4H-1,4-oxazines (**11a-e**, and **21**), which are prepared easily from (+)-(*5R, 6S*)-4-(benzyloxycarbonyl)-5,6-diphenyl-2,3,5,6-tetrahydro-4H-1,4-oxazin-2-one (**9**), with allyltrimethylsilane proceeded to give the corresponding coupling products with moderate to excellent stereoselectivity in good yields. These coupling products (**13a, b,** and **d**) were converted to hydroxymethylene- (**25a, b,** and **d**) and hydroxyethylene (**28**) peptide isosteres.

Introduction

Recently, much attention is being devoted to the design and synthesis of non-scissile peptide mimics.[1] For example, (-)-Statine (**1**), which is an unusual β-hydroxy-γ-amino acid, is a core constituent of the natural peptide Pepstatin (**2**) discovered by Umezawa in 1970.[2] This substance, produced by various *Streptomyces* sp., was demonstrated to be a potent inhibitor of aspartic proteases such as, pepsin, renin and cathepsin D. The amino acid (**1**) is an isosteric mimic of the typical tetrahedral transition state (**3**) for peptide bond hydrolysis and constitutes the conceptual framework upon which the general area of peptidomimetics are based.

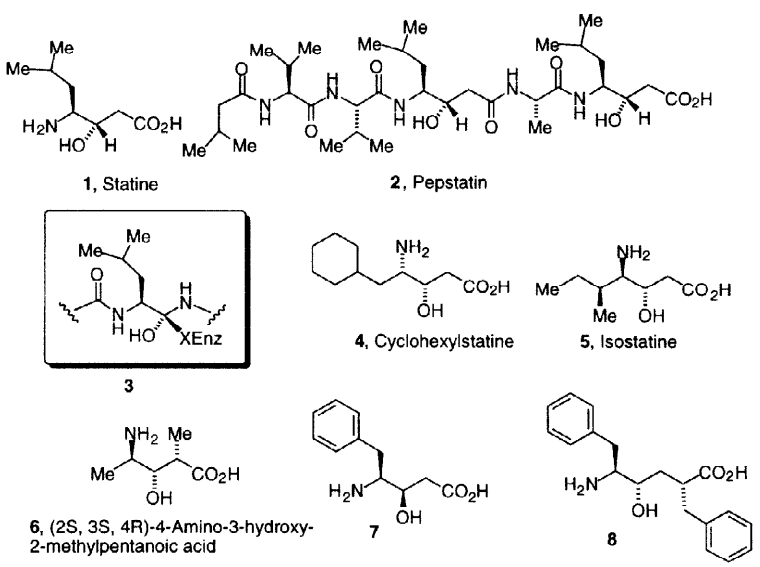

Figure 1

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Intensive work on statine analogs bearing the *syn* (*threo*) relative configuration, has led to the development of cyclohexylstatine, a key building block of renin inhibitors.[3] Examples of the corresponding *anti* (*erythro*) series can be found in isostatine (**5**), a component of the natural cytotoxic cyclodepsipeptides the didemnins A-C[4] and (2*S*, 3*S*, 4*R*)-4-amino-3-hydroxy-2-methylpentanoic acid (**6**), the core structural linker of bleomycin A_2 and blenoxane.[5]

Furthermore, several β-hydroxy-γ-amino acids have been found to be components of other biologically active peptides. For example, simple β-hydroxy-γ-amino acids such as (*R*)-4-amino-3-hydroxybutanoic acid (GABOB)[6] and (*R*)-carnitine[7] display interesting biological activities. (*R*)-GABOB is a neuromodulator of the mammalian central nervous system and has been found to be a hypotensive drug. On the other hand, (*R*)-carnitine is an essential substance in fatty acid metabolism in mammals. Hapalosin,[8] isolated from *Hapalosiphon welwitschii* W. & S. West, contains the β-hydroxy-γ-amino acid (**7**) and possesses better p-glycoprotein-mediated multidrug resistance reversing activities than verapamil. Another example, SB- 203386, has been found to be a potent HIV protease inhibitor, which has the β-hydroxy-δ-amino acid component (**8**) (Figure 1).[9] The importance of this large and growing class of amino acids prompted us to develop a general and flexible asymmetric synthesis of β-hydroxy-γ and δ-amino acids, which are regarded as hydroxymethylene and hydroxyethylene peptide isosteres. Here, we report additional observations on the conversion of commercially available oxazinones into various peptide isosteres.

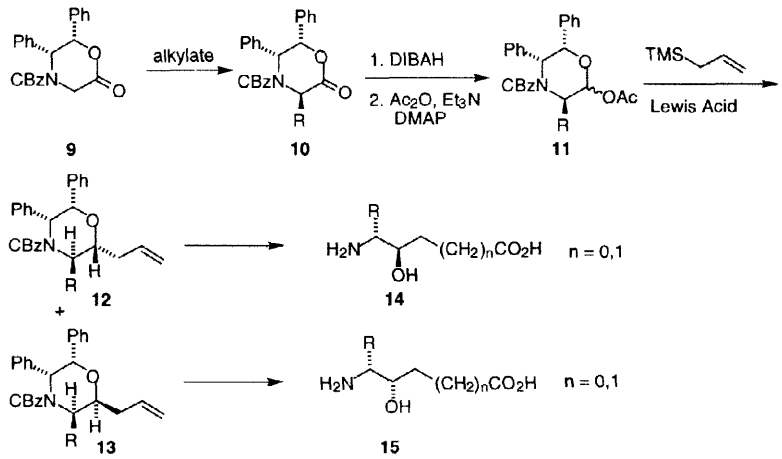
In a preliminary paper,[10] we reported the asymmetric synthesis of (-)-Statine (**1**) and a few related analogs *via* the coupling reaction of hemi-acetal **11** with the ketene silyl acetal of methyl acetate as a key step. This reaction proceeded with moderate stereoselectivity, which was followed by hydrolysis and Birch reduction to give the desired β-hydroxy-γ-amino acids in moderate to good yields. In continuing these studies, we have recently found that the coupling reaction of these hemi-acetals with allylsilanes provides a superior entry to peptide isosteres.

Results and Discussion

The synthetic approach is depicted in Scheme 1. The key hemi-acetals (**11**) were prepared from (+)-(5*R*, 6*S*)-4-(benzyloxycarbonyl)-5,6-diphenyl-2,3,5,6-tetrahydro-4H-1,4-oxazine-2-one (**9**) generally *via* enolate alkylation followed by reduction and acylation according to the method previously reported by our group.[10] The Lewis acid-mediated coupling reactions of hemi-acetals[11] and glucals[12] with allylsilanes, which are known as the Sakurai and Ferrier reactions, respectively, have been described. These reactions proceed stereoselectively *via* the generation of an incipient oxocarbenium ion followed by nucleophilic capture. Similarly, in the presence of an appropriate Lewis acid, the hemi-acetals (**11**) couple with allylsilanes to afford the corresponding coupling products **12** and **13**. Finally, these coupling products can be converted to β-hydroxy-γ-amino acids and γ-hydroxy-δ-amino acids.

First, we carried out the preparation of several hemi-acetal substrates. Alkylation of oxazinone **9** was carried out in according to the procedures previously described.[13] The diastereochemically pure monoalkylated products **10b-e** were reduced with diisobutylaluminum hydride (DIBAH) to the corresponding

lactols, followed by acetylation with a combination of acetic anhydride, triethylamine, and a catalytic amount of 4-dimethylaminopyridine (DMAP) in methylene chloride to give the corresponding hemi-acetals (**11a-e**) in good yields (Table 1).



Scheme 1

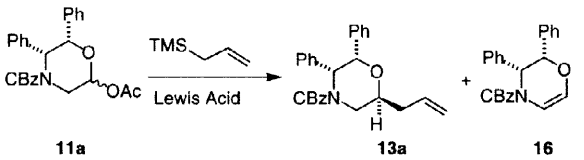
Table 1

Entry	susbstrate	R	10 (yield %)	11 (yield%) & ratio
1	a	H	-	78 (68:32)
2	b	Me	88	76 (3:2)
3	c	Et	80	75 (36:64)
4	d	i-Bu	75	82 (3:2)
5	e	Bn	77	93 (63:37)

Among the acetals that we have prepared, only **11c** could be readily separated by silica gel chromatography into the two diastereomeric acetals (**11c**α and **11c**β, epimeric at the hemi-acetal stereogenic center). The relative configuration of these isomers was assigned by ^{1}H nmr on the basis of ^{1}H-^{1}H differential nOe's. The use of these isomers will be discussed below.

First, to determine the optimum reaction conditions, we examined the coupling reaction of the α-unsubstituted acetal **11a** with allyltrimethylsilane as shown in Scheme 2 and Table 2. When methylene chloride and boron trifluoride etherate were used as a solvent and Lewis acid, respectively, the elimination product (**16**) was the predominant product (entry 1 in Table 2). The use of relatively weak Lewis acids such as zinc chloride and diethylaluminum chloride and solvents such as THF and DMF were not effective (entries 4, 5, 10 and 12, Table 2) resulting in significant recovery of the starting material.

However, we found that when acetonitrile was employed as a solvent, the desired coupling product **13a** could be obtained in high yield with no detectable production of the diastereomer **12a**. The determination of the absolute configuration of compound **13a** was established on the basis of ^{1}H-^{1}H differential nOe's. Of the conditions examined, the best results were obtained with BF_3-Et_2O in acteonitrile at -15 °C.



Scheme 2

Table 2. Reactions with acetal **11a** and allyltrimethylsilane.

Entry	Lewis Acid	Solvent	temp. °C	time (min)	13a	16	11a[b]
1	BF_3-Et_2O	CH_2Cl_2	0→ rt	60	19[a]	77	0
2	BF_3-Et_2O	MeCN	0	10	99[a]	trace	0
3	BF_3-Et_2O	toluene	0→ rt	60	19[a]	75[a]	0
4	BF_3-Et_2O	THF	0→ rt	60	0	0	99
5	BF_3-Et_2O	DMF	0→ rt	60	0	0	99
6	BF_3-Et_2O	MeCN	rt	10	98[a]	trace	0
7	BF_3-Et_2O	MeCN	-15	10	98	0	0
8	BF_3-Et_2O	MeCN	-30	30	18	0	81
9	$TiCl_4$	MeCN	0→ rt	60	99	0	0
10	Et_2AlCl	MeCN	0→ rt	60	63[a]	10[a]	24
11	Et_2AlCl	MeCN	0→ rt	60	99	trace	0
12	$ZnCl_2$	MeCN	0→ rt	60	0	0	10

[a]As compound **12a** was not easy to separate from **16** by silica gel chromatography, the ratios were determined by ^1H nmr analysis. [b] Recovery of the starting material **11a**.

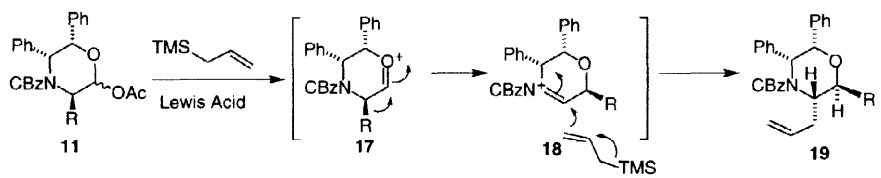
Next, we investigated the coupling reactions of the α-substituted acetals (**11b-e**) with allyltrimethylsilane under various conditions (Table 3). When the reaction conditions (entry 7, Table 2) optimized in the coupling reactions for the acetal (**11a**) with allyltrimethylsilane were employed on substrate **11b**, isomer **13b** was produced exclusively in 61 % yield (entry 3, Table 3). On the other hand, with either titanium tetrachloride (entry 1, Table 3) or tin tetrachloride (entry 4, Table 3) were employed as a Lewis acid in methylene chloride, two readily separable diastereomers (**12b** and **13b**) were produced, with **13b** being the predominant stereoisomer. The relative configuration of these diastereomers were determined on the basis of ^1H-^1H differential nOe's.

Similar treatment of substrate **11c** with $TiCl_4$ in methylene chloride at low temperature, gave predominantly isomer **12c** (Table 3, entry 6) in nearly quantitative yield. Under the same conditions, **11d** gave **12d** as the exclusive product in 90% yield and **11e** gave **12e** in 75% yield plus a new and unexpected compound identified as **19e** in 21% yield. The structure of this substance was rigorously confirmed by a single crystal X-ray analysis (Figure 2). The formation of substance **19e** can be rationalized by invoking that the incipient oxocarbenium ion **17**, generated from **11**, must undergo a suprafacial 1,2-alkyl migration giving the iminium ion **18** which is then trapped by the allyltrimethyl silane yielding the observed product **19** (Scheme 3)

It was then found that this unusual migration/trapping product could be produced in high yield for substrates **11c-e** using BF_3-Et_2O as the Lewis acid (Table 3, entries 7, 9 and 11). Based on the observed relative stereochemical assignments for **19c-e**, which as above, were assigned on the basis of ^1H-^1H differential nOe's, the allyl moiety must approach iminium ion **18** from the *same face* as the phenyl groups and *anti-* to the R group.

Table 3. Lewis acid-mediated couplings to **11b-e**.

Entry	Substrate	Lewis Acid	Solvent	temp. °C	12 (yield %)	13 (yield %)	19 (yield %)
1	**11b**	$TiCl_4$	CH_2Cl_2	-78 → 0	24	76	-
2	**11b**	$TiCl_4$	MeCN	-40→ 0	-	21	-
3	**11b**	BF_3-Et_2O	MeCN	-40→ 0	-	61	-
4	**11b**	$SnCl_4$	CH_2Cl_2	-78 → 0	19	62	-
5	**11b**	$EtAlCl_2$	MeCN	0 → rt	-	28	-
6	**11c**	$TiCl_4$	CH_2Cl_2	-78 → 0	78	22	-
7	**11c**	BF_3-Et_2O	MeCN	-15	-	-	79
8	**11d**	$TiCl_4$	CH_2Cl_2	-78 → -23	90	-	-
9	**11d**	BF_3-Et_2O	MeCN	-15	-	-	87
10	**11e**	$TiCl_4$	CH_2Cl_2	-78 → 0	75	-	21
11	**11e**	BF_3-Et_2O	MeCN	-15	-	-	83



Scheme 3

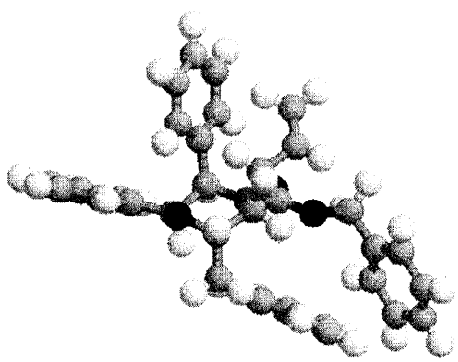
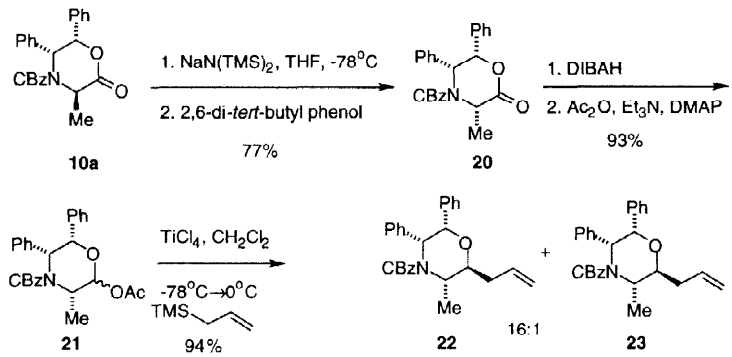


Figure 2. Stereodiagram of **19e** as determined by single crystal X-ray analysis. Spheres are of fixed, arbitrary radius.

Based on these observations and the high degree of stereoselectivity observed for substrate **11a**, it would appear that the α-R group and the phenyl rings of the heterocycle are exerting a stereochemical bias but in

opposite directions. The bulkier the α-R group, the greater the preponderance of isomer **12**, which is the result of nucleophilic attack on the face opposite to the R group (compare entries 1 and 8, Table 3).

These considerations prompted us to try to epimerize the stereogenic center bearing the R group, such that all of the substituents on the heterocycle would be disposed on the same face and should strongly favor attack from the opposite, unhindered face. This could be accomplished as shown in Scheme 4.



Scheme 4

Treatment of **10a** with sodium hexamethyldisilyl amide in THF at low temperature followed by quenching the enolate with 2,6-di-*tert*-butyl phenol gave the all-*syn* diastereomer **20** in 77% isolated yield. Conversion of this substance as above to the acetal **21** proceeded in high yield. Condensation of **21** with allyltrimethyl silane in the presence of $TiCl_4$ gave the desired coupling products (**22** and **23**) in 94% yield as a 16:1 ratio favoring the expected isomer **22**. Although we have not yet examined this approach on the more sterically hindered substrates **10c-e**, it is reasonable to expect that even higher levels of stereoselectivity can be expected for substrates bearing more highly branched R groups possessing the all-*syn*-configuration.

As mentioned above, we were able to separate the individual acetal diastereomers of **11c**. Subjecting each of these isomers (**11cα** and **11cβ**) separately to the Lewis acid-mediated allylation reaction, the coupling products **12c** and **13c** were produced in comparable ratios and yields to that of the mixture.

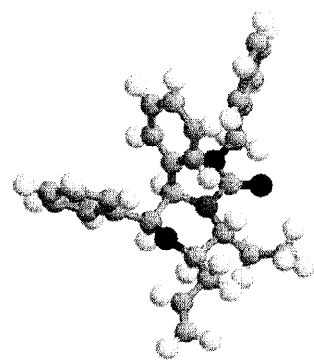
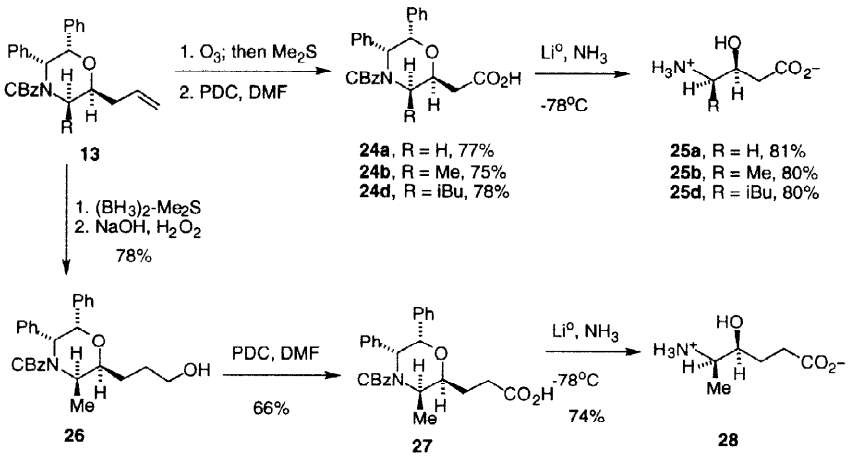


Figure 3. Stereodiagram of **12c** as determined by single crystal X-ray analysis. Spheres are of fixed, arbitrary radius.

The structure and relative stereochemical assignments for the coupling products **12c** and **13c** were assigned by ^{1}H nmr and for **12c**, a single crystal X-ray analysis (Figure 3) further confirmed these assignments. This result strongly supports the notion that these reactions proceed *via* initial generation of the oxocarbenium ion **17** followed by nucleophilic capture.

The final transformation of the coupling products (**13a**, **b**, and **d**) to hydroxymethylene- and hydroxyethylene peptide isosteres has been accomplished as shown in Scheme 5.



Scheme 5

Compounds **13a**, **13b** and **13d** were oxidized[14] by sequential treatment with ozone followed by PDC in DMF to afford the carboxylic acids **24** in 75-78% yields. Subsequent dissolving metal reduction gave the hydroxymethylene peptide isosteres **25a**, **25b** and **25d** in 80-81% yields. To illustrate the flexibility of this approach for making both the hydroxymethylene and hydroxyethylene peptide isosteres from the same substrate, compound **13b** was subjected to hydroboration/oxidation to give the primary alcohol **26** in good yield. Treatment of **26** with PDC in DMF afforded the acid **27** which was subsequently converted to the corresponding hydroxyethylene peptide isostere **28**.

Conclusion

In this paper, we have revealed that the Lewis acid-mediated coupling reaction of the acetals, (+)-(5*R*, 6*S*)-2-acetoxy-4-(benzyloxycarbonyl)-5,6-diphenyl-2,3,5,6-tetrahydro-4H-1,4-oxazine (**11a-e**, and **21**), with allyltrimethylsilane proceeded with moderate to excellent stereoselectivity to give the corresponding coupling products. Several of these coupling products were converted to the corresponding hydroxymethylene- and hydroxyethylene peptide isosteres. Since we have previously demonstrated a range of C-C bond-forming reactions to convert oxazinones **9** into the α-functionalized oxazinones **10**,[15,16] and that both enantiomers of **9** are commercially available,[17] this methodology offers a versatile and flexible approach for the synthesis of this important class of peptide mimics. Efforts are underway to extend the approach illustrated herein to crotyl and related silane and stannane couplings which present the opportunity to construct three contiguous stereogenic centers on these templates. In addition, efforts to clarify the fundamental stereoelectronic and steric parameters

governing the coupling reactions to these oxocarbenium species are under study and will be reported on in due course.

Acknowledgment. This work was supported by the National Science Foundation. We are very grateful to Dr. Chris Rithner for measuring ^{1}H-^{1}H differential nOe and Susie Miller for X-Ray crystallographic analysis.

Experimental

Melting points were determined in open-ended capillary tubes on a Mel-Temp apparatus and are uncorrected. ^{1}H (300 MHz) and ^{13}C (75 MHz)-NMR spectra were obtained on a Brucker ACE-300 spectrometer. Chemical shifts are reported in parts per million downfield from the internal standard. Infrared spectra were recorded on a Perkin Elmer 1600 FTIR and were recorded as λ_{max} in cm^{-1}. Optical rotations were obtained on a Rudolph Research automatic polarimeter Autopol III. Specific rotation $[\alpha]_D^{25}$ are reported in degrees per decimeter at 25 °C and the concentration (*c*) is given in grams per 100 mL in the specified solvent. Elemental analyses were performed by M-H-W Laboratories, Phoenix, AZ and are accurate to within the calculated values by ± 0.3 %. Mass spectra were obtained on a V.G. Micromass Ltd. Model 16F spectrometer or were carried out by UCR Mass Spectrometry Facility, Department of Chemistry, University of California at Riverside, CA.

Column chromatography and flash chromatography were performed with Merck silica gel Kieselgel 60 (230-400 mesh). Radial chromatography was carried out with a Harrison Research Chromatotron Model 7924 using Merck silica gel Kieselgel 60 PF-254 containing gypsum; 2 and 4 mm plates were used as needed. Preparative thin layer chromatography (PTLC) was carried out with Merck Kieselgel 60 F254 precoated glass (either 0.25 or 0.50 mm).

The lactones **10b**,[15] **10d**,[10] **10e**,[15] and the acetates **11b**[10] and **11d**[10] were prepared according to the reported procedures.

Ethylation of (5*R*, 6*S*)-4-(benzyloxycarbonyl)-5,6-diphenyl-2,3,5,6-tetrahydro-4H-1,4-oxazin-2-one (9) with ethyl iodide: (3*R*, 5*R*, 6*S*)-4-(benzyloxycarbonyl)-5,6-diphenyl-3-ethyl-2,3,5,6-tetrahydro-4H-1,4-oxazin-2-one (10c). To a solution of compound (+)-**9** (2.0 g, 5.17 mmol), EtI (4.1 mL, 51.7 mmol), HMPA (10 mL), and dry THF (100 mL), 1.0 M NaN(TMS)$_2$ in THF (7.76 mL, 7.76 mmol) was added dropwise at -78 °C under an Ar atmosphere. After the resulting solution was stirred at the same temperature for 40 min, the reaction mixture was poured into EtOAc (200 mL). The organic layer was washed with water (150 mL x 2) and sat. NaCl (150 mL x 1), dried over anhydrous $MgSO_4$, filtered, concentrated, and purified by silica gel flash chromatography (eluted with Hexanes : EtOAc = 6 : 1) to give compound **11** (colorless solid, 1.71 g, 80 % yield from compound (+)-**9**. Colorless needles (hexanes/CH_2Cl_2), mp 168-169 °C. $[\alpha]_D^{25}$ = +63.6° (CH_2Cl_2, *c* = 1.49). ^{1}H NMR (300 MHz) (393 K, DMSO-d_6) δ TMS: 1.07 (3H, t, J = 7.4 Hz), 2.23-2.07 (2H, m), 4.74 (1H, dd, J = 8.6 Hz, 5.8 Hz), 4.95 (1H, d, J = 12.6 Hz), 5.01 (1H, d, 12.7 Hz), 5.27 (1H, d, J = 3.1 Hz), 6.15 (1H, d, J = 3.1 Hz), 6.58 (2H, d, J = 7.1 Hz), 7.03-7.24 (13H, m). ^{13}C NMR (75 MHz) (393 K, DMSO- d_6) δ: 9.4, 26.7, 58.0, 59.6, 66.2, 77.7, 125.7, 125.8, 126.6, 126.7, 126.8, 126.9, 127.0, 127.4, 134.1, 135.5, 135.7, 153.1, 167.5. IR (KBr): 1842, 1752 (C=O) cm^{-1}. MS (FAB+): 416 (M^++H). Anal. calcd. for $C_{26}H_{25}NO_4$: C, 75.16; H, 6.06; N, 3.37. Found: C, 75.24; H, 5.89; N, 3.20.

General Procedure for Preparation of Hemi-acetals (11a, 11cα, 11cβ, and 11e): To a dry CH_2Cl_2solution (100 mL) of **10** (7.48 mmol), 1.0 M DIBAH in hexanes (11.2 mL, 11.2 mmol) was added dropwise at -78 °C under an Ar atmosphere. After the resulting solution was stirred at the same temperature for 1 hr, H_2O (20 mL) was added to the reaction mixture. Then the reaction mixture was stirred at room temperature for 30 min, filtered through ®Celite 545 to afford a filtrate, which was washed with sat. NaCl (50 mL x 2), dried over anhydrous $MgSO_4$, filtered, concentrated. A mixture of the residue (6.8 mmol), 4-dimethylaminopyridine (cat. amount), Et_3N (1.89 mL, 13.6 mmol), Ac_2O (1.89 mL, 13.6 mL), and dry CH_2Cl_2 (40 mL) was stirred at 0 °C for 10 min and room temperature for 20 min. Then, H_2O (10 mL) was added. The organic layer was separated and washed with H_2O (20 mL x 1) and sat. NaCl (20 mL x 1), dried over $MgSO_4$, concentrated *in vacuo* to give an oil, which was purified by silica gel flash chromatography (eluted with Hexane : AcOEt = 6 : 1) to give the corresponding hemi-acetals.

(2*R* and *S*, 5*R*, 6*S*)-2-Acetoxy-4-(benzyloxycarbonyl)-5, 6-diphenyl-2, 3, 5, 6-tetrahydro-4H-1,4-oxazine (11a) (Diastereomer mixture). The diastereomer ratio (68 : 32) was determined on the basis of ^{1}H NMR analysis.

(colorless amorphous solid, 78 % yield from compound (+)-**9**. Mp 50-52 °C. $[\alpha]_D^{25}$ = -58.4° (CH_2Cl_2, *c* = 0.63). ^1H NMR (300 MHz) (393 K, DMSO- d_6) δ TMS: (major isomer) 2.14 (3H, s), 3.26 (1H, dd, J = 13.2 Hz, 9.0 Hz), 4.13 (1H, dd, J = 13.2 Hz, 3.6 Hz), 5.16 (1H, d, J = 12.3 Hz), 5.32 (1H, d, J = 3.6 Hz), 5.34 (1H, d, J = 3.9 Hz), 6.02 (1H, dd, J = 9.0 Hz, 3.3 Hz). (minor isomer) 2.03 (3H, s), 3.64 (1H, dd, J = 14.7 Hz, 3.3 Hz), 3.99 (1H, ddd, J = 14.6 Hz, 2.0 Hz, 0.6 Hz), 5.19 (1H, d, J = 13.0 Hz), 5.43 (1H, d, J = 3.9 Hz), 5.59 (1H, d, J = 3.6 Hz), 6.38 (1H, m). (mixed signals) 5.10 (1H, d, J = 12.9 Hz), 7.09-7.32 (15H, m). IR (KBr): 1754, 1701 (C=O) cm^{-1}. MS (FAB+): 432 (M^++H), 373 (M^+-OAc). Anal. calcd. for $C_{26}H_{25}NO_5$: C, 72.37; H, 5.84; N, 3.25. Found: C, 72.18; H, 5.85; N, 3.30.

(*2R, 3R, 5R, 6S*)-2-Acetoxy-4-(benzyloxycarbonyl)-5,6-diphenyl-3-ethyl-2,3,5,6-tetrahydro-4H-1,4-oxazine (11cα). Major diastereomer (colorless solid, 49 % yield from compound **10c**). $[\alpha]_D^{25}$ = +132.0° (CH_2Cl_2, *c* = 0.62). ^1H NMR (300 MHz) (393 K, DMSO- d_6) δ TMS: 1.02 (3H, t, J = 7.5 Hz), 2.11 (3H, s), 1.88-2.15 (2H, m), 4.13 (1H, ddd, J = 9.0 Hz, 6.0 Hz, 2.1 Hz), 4.90 (1H, d, J = 12.6 Hz), 4.95 (1H, d, J = 12.6 Hz), 5.12 (1H, d, J = 4.2 Hz), 5.55 (1H, d, J = 3.6 Hz), 6.25 (1H, d, J = 2.4 Hz), 6.91-7.03 (9H, m), 7.09-7.14 (3H, m), 7.18-7.23 (3H, m). IR (NaCl, neat): 1746, 1701 (C=O) cm^{-1}. MS (FAB+): 460 (M^++H), 400 (M^+-OAc). Anal. calcd for $C_{28}H_{29}NO_5$: C, 73.18; H, 6.36; N, 3.05. Found: C, 73.39; H, 6.51; N, 3.02.

(*2S, 3R, 5R, 6S*)-2-Acetoxy-4-(benzyloxycarbonyl)-5,6-diphenyl-3-ethyl-2,3,5,6-tetrahydro-4H-1,4-oxazine (11cβ). Minor diastereomer (colorless viscous oil, 27 % yield from compound **10c**). Colorless crystals ($^iPr_2O$), mp 99-101 °C. $[\alpha]_D^{25}$ = -3.1° (CH_2Cl_2, *c* = 0.80). ^1H NMR (300 MHz) (393 K, DMSO- d_6) δ TMS: 0.96 (3H, t, J = 7.5 Hz), 1.89-2.11 (2H, m), 2.04 (3H, s), 4.27 (1H, td, J = 6.6 Hz, 4.8 Hz), 4.97 (1H, d, J = 12.9 Hz), 5.02 (1H, d, J = 12.6 Hz), 5.25 (1H, d, J = 3.6 Hz), 5.60 (1H, d, J = 3.6 Hz), 6.52 (1H, d, J = 4.8 Hz), 6.90-6.93 (2H, m), 7.02-7.14 (10H, m), 7.23-7.25 (3H, m). IR (KBr): 1744, 1707 (C=O) cm^{-1}. MS (FAB+): 460 (M^++H), 400 (M^+-OAc). Anal. calcd for $C_{28}H_{29}NO_5$: C, 73.18; H, 6.36; N, 3.05. Found: C, 73.34; H, 6.44; N, 3.10.

(*2R and S, 3R, 5R, 6S*)-2-Acetoxy-3-benzyl-4-(benzyloxycarbonyl)-5,6-diphenyl-2,3,5,6-tetrahydro-4H-1,4-oxazine (11e) (Diastereomer mixture). The diastereomer ratio (63 : 37) was determined on the basis of ^1H-NMR analysis (colorless amorphous solid, 93 % yield from compound **10e**). Mp 55-57 °C. $[\alpha]_D^{25}$ = +98.2° (CH_2Cl_2, *c* = 0.73). ^1H NMR (300 MHz) (393 K, DMSO- d_6) δ TMS: (major isomer) 1.98 (3H, s), 4.48 (1H, ddd, J = 7.6 Hz, 6.3 Hz, 1.8 Hz), 4.89 (1H, d, J = 12.6 Hz), 4.95 (1H, d, J = 12.6 Hz), 5.14 (1H, d, J = 4.2 Hz), 5.55 (1H, d, J = 4.2 Hz), 6.24 (1H, d, J = 1.8 Hz). (minor isomer) 1.92 (3H, s), 4.77 (1H, ddd, J = 7.5 Hz, 5.4 Hz, 4.5 Hz), 4.87 (1H, d, J = 12.6 Hz), 4.94 (1H, d, J = 12.3), 5.22 (1H, d, J = 3.6 Hz), 5.63 (1H, d, J = 3.6 Hz), 6.53 (1H, d, J = 5.1 Hz). (mixed peaks) 3.24-3.40 (2H, m), 6.87-7.37 (20H, m). IR (KBr): 1752, 1702 (C=O) cm^{-1}. MS (FAB+): 522 (M^++H), 462 (M^+-OAc). Anal. calcd. for $C_{33}H_{31}NO_5$: C, 75.99; H, 5.99; N, 2.69. Found: C, 75.99; H, 5.78; N, 2.75.

Lewis acid-Promoted Coupling Reactions of Hemi-acetals with Allyltrimethylsilane: General Procedure for Preparation of the Coupling Products.

a) Borontrifluoride diethyl etherate. To a CH_3CN solution (3 mL) of hemi-acetal (0.25 mmol), allyltrimethylsilane (1.25 mmol), BF_3•OEt_2 (0.50 mmol) was added at -15 °C under an Ar atmosphere. The reaction mixture was stirred at the same temperature until the starting hemi-acetal could not be detected on TLC. After the reaction, sat. $NaHCO_3$ (10 mL) was added, stirred for 20 min at room temperature, and diluted with AcOEt (15 mL). The organic layer was separated, and the aqueous phase was extracted with AcOEt (10 mL x 2). The combined organic layer was washed with sat. NaCl (15 mL x 3), dried over anhydrous $MgSO_4$, filtered, and evaporated under reduced pressure to give an oily residue, which was purified by silica gel radial chromatography or PTLC to give the corresponding coupling product.

b) Titanium tetrachloride. To a CH_2Cl_2 solution (3 mL) of hemi-acetal (0.25 mmol), allyltrimethylsilane (1.25 mmol), and 1.0 M $TiCl_4$ in CH_2Cl_2 (0.50 mL, 0.50 mmol) were added at -78 °C under an Ar atmosphere. The reaction mixture was stirred at the same temperature for 10 min and then at 0 °C until the starting hemi-acetal could not be detected on TLC. After the reaction was complete, sat. $NaHCO_3$ (10 mL) was added, stirred for 20 min at room temperature, and diluted with CH_2Cl_2 (15 mL). The organic layer was separated, and the aqueous phase was extracted with CH_2Cl_2 (10 mL x 2). The combined organic layer was washed with sat. NaCl (15 mL x 3), dried over anhydrous $MgSO_4$, filtered, and evaporated under reduced pressure to give an oily residue, which was purified by using silica gel radial chromatography or PTLC to give the corresponding coupling product.

(2*S*, 5*R*, 6*S*)-4-(benzyloxycarbonyl)-5,6-diphenyl-2-(2-propenyl)-1, 2, 5, 6-tetrahydro-4H-1,4-oxazine (13a). (98 % yield from compound **11a**) Colorless viscous oil. $[\alpha]_D^{25}$ = -95.0° (CH_2Cl_2, *c* = 0.13). ^{1}H NMR (300 MHz) (393 K, DMSO- d_6) δ TMS: 2.40-2.50 (1H, m), 2.55-2.65 (1H, m), 3.61 (1H, dd, J = 13.8 Hz, 4.8 Hz), 3.76 (1H, dd, J = 13.7 Hz, 3.9 Hz), 4.37 (1H, ddt, J = 7.0 Hz, 4.0 Hz, 4.0 Hz), 5.04 (1H, ddt, J = 10.2 Hz, 2.1 Hz, 1.2 Hz), 5.07 (1H, d, J = 12.6 Hz), 5.11 (1H, ddd, J = 18.0 Hz, 3.6 Hz, 1.5 Hz), 5.15 (1H, d, J = 12.9 Hz), 5.32 (1H, d, J = 3.6 Hz), 5.39 (1H, d, J = 3.6 Hz), 5.84 (1H, ddt, J = 17.1 Hz, 10.5 Hz, 6.6 Hz), 7.05-7.32 (15H, m). ^{13}C NMR (75 MHz) (393 K, DMSO- d_6) δ: 34.3, 40.4, 58.3, 66.2, 71.1, 71.5, 116.8, 125.4, 126.2, 126.5, 127.0, 127.1, 127.3, 127.8, 128.8, 133.9, 136.3, 136.6, 138.4, 154.6. IR (NaCl, neat): 1698 (C=O) cm^{-1}. MS (FAB+): 414 (M^++H). HRMS calcd. for $C_{27}H_{28}NO_3$ (M^++H): 414.2069. Found: 414.2069.

(2*R*, 3*R*, 5*R*, 6*S*)-4-(benzyloxycarbonyl)-5,6-diphenyl-3-methyl-2-(2-propenyl)-1, 2, 5, 6-tetrahydro-4H-1,4-oxazine (12b). (24 % yield from compound **11b**) Colorless viscous oil. $[\alpha]_D^{25}$ = +53.2° (CH_2Cl_2, *c* = 0.71). ^{1}H NMR (300 MHz) (393 K, DMSO- d_6) δ TMS: 1.40 (3H, d, J = 5.7 Hz), 2.58 (2H, m), 3.71 (1H, qd, J = 6.3 Hz, 4.2 Hz), 3.79 (1H, dt, J = 8.1 Hz, 6.0 Hz), 4.80 (1H, d, J = 12.9 Hz), 4.89 (1H, d, J = 12.6 Hz), 5.03 (1H, d, J = 3.6 Hz), 5.05 (1H, d, J = 3.6 Hz), 5.11 (1H, ddt, J = 10.4 Hz, 2.1 Hz, 0.9 Hz), 5.19 (1H, ddt, J = 17.1 Hz, 2.1 Hz, 1.5 Hz), 5.98 (1H, ddt, J = 17.3 Hz, 9.9 Hz, 6.9 Hz), 6.83-6.86 (2H, m), 6.94-7.07 (9H, m), 7.17-7.21 (4H, m). ^{13}C NMR (75 MHz) (393 K, DMSO- d_6) δ: 19.78, 37.59, 49.6, 60.63, 65.81, 77.57, 80.59, 117.0, 125.4, 125.9, 126.3, 126.5, 126.9, 127.0, 127.1, 128.1, 133.9, 136.0, 138.0, 138.6, 155.6. IR (NaCl, neat): 1704 (C=O) cm^{-1}. MS (FAB+): 428 (M^++H). HRMS calcd. for $C_{28}H_{30}NO_3$ (M^++H): 428.2226. Found: 428.2230.

(2*S*, 3*R*, 5*R*, 6*S*)-4-(benzyloxycarbonyl)-5,6-diphenyl-3-methyl-2-(2-propenyl)-1, 2, 5, 6-tetrahydro-4H-1,4-oxazine (13b). (76% yield from compound **11b**) Colorless viscous oil. $[\alpha]_D^{25}$ = +42.0° (CH_2Cl_2, *c* = 2.43). ^{1}H NMR (300 MHz) (393 K, DMSO- d_6) δ TMS: 1.45 (3H, d, J = 6.6 Hz), 2.23-2.44 (2H, m), 4.30 (1H, qdd, J = 6.6 Hz, 3.6 Hz, 0.6 Hz), 4.62 (1H, ddd, J = 7.7 Hz, 6.2 Hz, 3.6 Hz), 4.97 (1H, d, J = 12.9 Hz), 5.08 (1H, ddt, J = 10.5 Hz, 3.3 Hz, 1.5 Hz), 5.08 (1H, d, J = 12.6 Hz), 5.15 (1H, ddt, J = 17.3 Hz, 3.5 Hz, 1.5 Hz), 5.23 (1H, d, J = 3.9 Hz), 5.63 (1H, d, J = 3.9 Hz), 5.87 (1H, dddd, J = 17.4 Hz, 10.2 Hz, 7.2 Hz, 6.0 Hz), 6.70-6.73 (2H, m), 6.98-7.07 (5H, m), 7.15-7.23 (8H, m). ^{13}C NMR (75 MHz) (393 K, DMSO- d_6) δ: 16.01, 36.46, 49.96, 61.12, 65.85, 72.95, 74.61, 116.7, 126.2, 126.7, 126.8, 127.1, 127.4, 127.7, 133.9, 136.3, 138.4, 138.9, 154.0. IR (NaCl, neat): 1698 (C=O) cm^{-1}. MS (FAB+): 428 (M^++H). HRMS calcd. for $C_{28}H_{30}NO_3$ (M^++H): 428.2226. Found: 428.2231.

(2*R*, 3*R*, 5*R*, 6*S*)-4-(benzyloxycarbonyl)-5,6-diphenyl-3-ethyl-2-(2-propenyl)-1, 2, 5, 6-tetrahydro-4H-1,4-oxazine (12c). (78 % yield from compound **11c**). Colorless needles (Hexanes), mp 84-85 °C. $[\alpha]_D^{25}$ = +93.4° (CH_2Cl_2, *c* = 0.41). ^{1}H NMR (300 MHz) (393 K, DMSO- d_6) δ TMS: 0.91 (3H, t, J = 7.4 Hz), 1.69-1.83 (1H, m), 1.96-2.01 (1H, m), 2.57 (2H, dddd, J = 6.9 Hz, 5.7 Hz, 1.2 Hz, 1.2 Hz), 3.82 (1H, dt, J = 6.6 Hz, 4.2 Hz), 3.92 (1H, dt, J = 6.6 Hz, 5.7 Hz), 4.81 (1H, d, J = 12.3 Hz), 4.92 (1H, d, J = 12.6 Hz), 5.04 (1H, d, J = 3.6 Hz), 5.08 (1H, d, J = 3.6 Hz), 5.12 (1H, ddt, J = 10.2 Hz, 1.8 Hz, 0.9 Hz), 5.20 (1H, ddd, J = 17.3 Hz, 3.6 Hz, 1.5 Hz), 5.99 (1H, ddt, J = 17.3 Hz, 10.5 Hz, 6.9 Hz), 6.86-6.89 (2H, m), 6.93-7.08 (10H, m), 7.18-7.22 (3H, m). IR (KBr): 1710 (C=O) cm^{-1}. MS (FAB+): 442 (M^++H). HRMS calcd. for $C_{29}H_{32}NO_3$ (M^++H): 442.2382. Found: 442.2389.

(2*S*, 3*R*, 5*R*, 6*S*)-4-(benzyloxycarbonyl)-5,6-diphenyl-3-ethyl-2-(2-propenyl)-1, 2, 5, 6-tetrahydro-4H-1,4-oxazine (13c). (22 % yield from compound **11c**). Colorless viscous oil. $[\alpha]_D^{25}$ = +51.4° (CH_2Cl_2, *c* = 0.35). ^{1}H NMR (300 MHz) (393 K, DMSO- d_6) δ TMS: 1.04 (3H, t, J = 7.5 Hz), 1.72-1.89 (1H, m), 1.96-2.11 (1H, m), 2.29-2.48 (2H, m), 4.18 (1H, ddd, J = 6.6 Hz, 6.6 Hz, 3.3 Hz), 4.62 (1H, ddd, J = 8.0 Hz, 6.0 Hz, 3.3 Hz), 4.98 (2H, s), 5.07 (1H, dddd, J = 10.4 Hz, 1.8 Hz, 1.2 Hz, 1.2 Hz), 5.13 (1H, dddd, J = 17.3 Hz, 1.8 Hz, 1.5 Hz, 1.5 Hz), 5.23 (1H, d, J = 3.6 Hz), 5.49 (1H, d, J = 3.6 Hz), 5.89 (1H, dddd, J = 16.8 Hz, 10.8 Hz, 6.3 Hz, 6.3 Hz), 6.76-6.79 (2H, m), 6.97-7.24 (13H, m). IR (NaCl, neat): 1704 (C=O) cm^{-1}. MS (FAB+): 442 (M^++H). HRMS calcd. for $C_{29}H_{32}NO_3$ (M^++H): 442.2382. Found: 442.2387.

(2*S*, 3*S*, 5*R*, 6*S*)-4-(benzyloxycarbonyl)-5,6-diphenyl-2-ethyl-3-(2-propenyl)-1, 2, 5, 6-tetrahydro-4H-1,4-oxazine (19c). (79 % yield from compound **11c**). Colorless viscous oil. $[\alpha]_D^{25}$ = -113.0° (CH_2Cl_2, *c* = 0.83). ^{1}H NMR (300 MHz) (393 K, DMSO- d_6) δ TMS: 0.91 (3H, t, J = 7.4 Hz), 1.55-1.96 (1H, m), 1.88-2.07 (2H, m), 2.16-2.27 (1H, m), 3.92-4.01 (2H, m), 4.58 (1H, ddt, J = 17.1 Hz, 2.1 Hz, 1.8 Hz), 4.77 (1H, ddt, J = 10.2 Hz, 2.1 Hz, 1.2 Hz), 5.18 (1H, d, J = 12.6 Hz), 5.25 (1H, d, J = 12.6 Hz), 5.26 (1H, d, J = 3.9 Hz), 5.45 (1H, ddt, J = 17.4 Hz, 10.5

Hz, 6.9 Hz), 5.68 (1H, d, J = 3.9 Hz), 6.99-7.46 (15H, m). IR (NaCl, neat): 1694 (C=O) cm^{-1}. MS (FAB+): 442 (M^++H). HRMS calcd. for $C_{29}H_{32}NO_3$ (M^++H): 442.2382. Found: 442.2379.

(2*R*, 3*R*, 5*R*, 6*S*)-4-(benzyloxycarbonyl)-5,6-diphenyl-3-iso-butyl-2-(2-propenyl)-1, 2, 5, 6-tetrahydro-4H-1,4-oxazine (12d). (90 % yield from compound **11d**). Colorless viscous oil. $[\alpha]_D^{25}$ = +37.7° (CH_2Cl_2, *c* = 1.69). ^1H NMR (300 MHz) (340K, C_6D_6) δ TMS: 1.35 (3H, d, J = 6.6 Hz), 1.57 (3H, d, J = 6.6 Hz), 2.07 (1H, ddd, J = 13.2 Hz, 6.9 Hz, 6.9 Hz), 2.22-2.36 (1H, m), 2.67 (1H, ddd, J = 13.2 Hz, 6.6 Hz, 6.6 Hz), 3.10 (2H, ddd, J = 7.2 Hz, 7.2 Hz, 1.2 Hz), 4.49 (1H, ddd, J = 6.3 Hz, 6.3 Hz, 6.3 Hz), 4.63 (1H, td, J = 6.9 Hz, 6.9 Hz), 5.59 (1H, d, J = 12.6 Hz), 5.64 (1H, d, J = 3.6 Hz); 5.65 (1H, d, J = 12.3 Hz), 5.70 (1H, m), 5.76 (1H, ddt, J = 17.4 Hz, 1.8 Hz, 1.5 Hz), 5.98 (1H, d, J = 3.3 Hz), 6.64 (1H, ddd, J = 17.0 Hz, 10.5 Hz, 6.9 Hz), 7.50-7.82 (15H, m). IR (NaCl, neat): 1700 (C=O) cm^{-1}. MS (EI): 469 (M^+), 454 (M^+-Me), 428 (M^+-C_3H_5). HRMS calcd. for $C_{31}H_{35}NO_3$ (M^+): 469.2617. Found: 469.2614.

(2*S*, 3*S*, 5*R*, 6*S*)-4-(benzyloxycarbonyl)-5,6-diphenyl-2-iso-butyl-3-(2-propenyl)-1, 2, 5, 6-tetrahydro-4H-1,4-oxazine (19d). (87 % yield from compound **11d**). Colorless viscous oil. $[\alpha]_D^{25}$ = -35.7 ° (CH_2Cl_2, *c* = 0.89). ^1H NMR (300 MHz) (393K, DMSO- d_6) δ TMS: 0.91 (3H, d, J = 6.7 Hz), 0.96 (3H, d, J = 6.6 Hz), 1.32-1.41 (1H, m), 1.60-1.70 (1H, m), 1.91-2.07 (2H, m), 2.17-2.28 (1H, m), 3.95 (1H, dd, J = 8.7 Hz, 8.4 Hz), 4.14 (1H, dd, J = 9.0 Hz, 6.0 Hz), 4.59 (1H, m), 4.78 (1H, m), 5.18 (1H, d, J = 12.6 Hz), 5.26 (1H, d, J = 12.6 Hz), 5.29 (1H, d, J = 3.9 Hz), 5.38-5.52 (1H, m), 5.70 (1H, d, J = 3.9 Hz), 6.99-7.47 (15H, m). IR (NaCl, neat): 1692 (C=O) cm^{-1}. MS (CI): 470 (M^++H), 428 (M^+-C_3H_5). HRMS calcd. for $C_{31}H_{36}NO_3$ (M^++H): 470.2695. Found: 470.2701.

(2*R*, 3*R*, 5*R*, 6*S*)-2-Benzyl-4-(benzyloxycarbonyl)-5,6-diphenyl-3-(2-propenyl)-1, 2, 5, 6-tetrahydro-4H-1,4-oxazine (12e). (75 % yield from compound **11e**). Colorless viscous oil. $[\alpha]_D^{25}$ = +66.4 ° (CH_2Cl_2, *c* = 0.25). ^1H NMR (300 MHz) (393K, DMSO- d_6) δ TMS: 2.26-2.48 (2H, m), 3.22 (2H, d, J = 6.0 Hz), 4.11 (1H, dt, J = 6.9 Hz, 5.3 Hz), 4.27 (1H, dd, J = 6.0 Hz, 6.0 Hz), 4.83 (1H, d, J = 12.3 Hz), 4.89 (1H, d, J = 3.6 Hz), 4.94 (1H, d, J = 3.6 Hz), 4.96 (1H, d, J = 12.9 Hz), 5.01-5.03 (1H, m), 5.06-5.08 (1H, m), 5.81 (1H, ddt, J = 17.9 Hz, 9.8 Hz, 6.9 Hz), 6.83-6.91 (4H, m), 6.95-7.10 (8H, m), 7.21-7.35 (8H, m). IR (NaCl, neat): 1695 (C=O) cm^{-1}. MS (FAB+): 504 (M^++H). HRMS calcd. for $C_{34}H_{34}NO_3$ (M^++H): 504.2539. Found: 504.2540.

(2*S*, 3*S*, 5*R*, 6*S*)-2-Benzyl-4-(benzyloxycarbonyl)-5,6-diphenyl-3-(2-propenyl)-1, 2, 5, 6-tetrahydro-4H-1,4-oxazine (19e). (83 % yield from compound **11e**). Colorless needles ($^iPr_2O$), mp 110-111 °C. $[\alpha]_D^{25}$ = -143.0° (CH_2Cl_2, *c* = 0.39). ^1H NMR (300 MHz) (393 K, DMSO- d_6) δ TMS: 1.93-2.04 (1H, m), 2.09-2.20 (1H, m), 3.04 (1H, dd, J = 14.0 Hz, 7.2 Hz), 3.20 (1H, dd, J = 14.0 Hz, 7.2 Hz), 4.11 (1H, dd, J = 7.2 Hz, 7.2 Hz), 4.31 (1H, dd, J = 7.2 Hz, 7.2 Hz), 4.45 (1H, ddt, J = 17.1 Hz, 1.8 Hz, 1.5 Hz), 4.67 (1H, ddt, J = 10.2 Hz, 2.1 Hz, 1.2 Hz), 5.21-5.34 (1H, m), 5.20 (1H, d, J = 12.6 Hz), 5.30 (1H, d, J = 12.3 Hz), 5.51 (1H, d, J = 4.5 Hz), 5.77 (1H, d, J = 4.2 Hz), 7.02-7.48 (20 H, m). IR (NaCl, neat): 1676 (C=O) cm^{-1}. MS (FAB+): 504 (M^++H), 462 (M^+-C_3H_5). HRMS calcd. for $C_{34}H_{34}NO_3$ (M^++H): 504.2539. Found: 504.2532.

Preparation of elimination product (5*R*, 6*S*)-4-(benzyloxycarbonyl)-5,6-diphenyl-5, 6-dihydro-4H-1,4-oxazine (16). To a CH_2Cl_2 solution (10 mL) of hemi-acetal (**11a**) (0.431 g, 1.0 mmol), BF_3•OEt_2 (0.14 mL, 0.156 g, 1.1 mmol) was added at 0 °C under an Ar atmosphere. The reaction mixture was stirred at the same temperature for 1 h. After the reaction was complete, sat. $NaHCO_3$ (15 mL) was added, stirred for 20 min at room temperature, and diluted with CH_2Cl_2 (15 mL). The organic layer was separated, and the aqueous phase was extracted with CH_2Cl_2 (15 mL x 2). The combined organic layer was washed with sat. NaCl (15 mL x 3), dried over anhydrous $MgSO_4$, filtered, and evaporated under reduced pressure to give an oily residue, which was purified by silica gel flash chromatography (eluted with Hexanes : EtOAc = 15 : 1) to give compound **16** (0.26 g, 70 % yield from compound **11a**) as a colorless solid. Mp 62-64 °C. $[\alpha]_D^{25}$ = +150.0° (CH_2Cl_2, *c* = 0.78). ^1H NMR (300 MHz) (393 K, DMSO- d_6) δ TMS: 5.08 (1H, d, J = 12.6 Hz), 5.15 (1H, d, J = 12.6 Hz), 5.26 (1H, d, J = 2.9 Hz), 5.36 (1H, d, J = 2.9 Hz), 6.37 (1H, d, J = 4.9 Hz), 6.65 (1H, dd, J = 4.9 Hz, 1.1 Hz), 6.89-6.92 (2H, m), 7.05-7.29 (13H, m). IR (KBr): 1704 (C=O) cm^{-1}. MS (FAB+): 371 (M^+). HRMS calcd. for $C_{24}H_{21}NO_3$ (M^+): 371.1521. Found: 371.1525.

Epimerization of C-3 methyl group of lactone 10a: Preparation of (*3S, 5R, 6S*)-4-(benzyloxycarbonyl)-5,6-diphenyl-3-methyl-2,3,5,6-tetrahydro-4H-1,4-oxazin-2-one (20). To a THF solution (20 mL) of compound (+)-**10a** (0.100 g, 0.25 mmol) and 15-crown-5 (0.33 g, 1.5 mmol), 1.0 M $NaN(TMS)_2$ in THF (0.38 mL, 0.38 mmol) was added dropwise at -78 °C under an Ar atmosphere. After the resulting mixture was stirred at -78 °C for 10 min, 2,6-di-*tert*-butylphenol (0.062 g, 0.3 mmol) in THF (2 mL) was added at the same temperature. The mixture was stirred at -78 °C for 30 min. To the mixture, sat. NH_4Cl (15 mL) was added and separated. The aqueous layer was extracted with AcOEt (10 mL x 2). The combined organic layer was washed with sat. NaCl (20 mL x 3), dried over $MgSO_4$, and evaporated under reduced pressure to give an oily residue, which was purified by silica gel radial chromatography (eluted with Hexanes : AcOEt = 4 : 1) to give compound **20** (0.077 g, 77 % yield from compound (+)-**10a**) as a colorless viscous oil. $[\alpha]_D^{25}$ = -78.2° (CH_2Cl_2, *c* = 1.10). ^1H NMR (300 MHz) (393 K, DMSO- d_6) δ TMS: 1.38 (3H, d, J = 6.9 Hz), 4.88 (1H, q, J = 6.9 Hz), 5.22 (2H, s), 5.70(1H, d, J = 3.0 Hz), 6.16 (1H, d, J = 3.3 Hz), 7.00-7.04 (2H, m), 7.13-7.38 (13 H, m). ^{13}C NMR (75 MHz) (393 K, DMSO- d_6) δ: 17.97, 50.43, 57.14, 66.64, 79.69, 124.9, 126.8, 127.0, 127.1, 127.2, 127.3, 127.4, 127.5, 127.6, 127.9, 134.9, 135.8, 153.6, 168.6. IR (KBr): 1748, 1702 (C=O) cm^{-1}. MS (FAB+): 402 (M^++H). HRMS calcd. for $C_{25}H_{24}NO_4$ (M^++H): 402.1705. Found: 402.1720.

Preparation of (*2R and S, 3S, 5R, 6S*)-2-Acetoxy-4-(benzyloxycarbonyl)-5, 6-diphenyl-3-methyl-2, 3, 5, 6-tetrahydro-4H-1,4-oxazine (21) (Diastereomer mixture). To a dry CH_2Cl_2 solution (30 mL) of compound **20** (0.801 g, 2.01 mmol), 1.0 M DIBAH in hexanes (3.02 mL, 3.02 mmol) was added dropwise at -78 °C under an Ar atmosphere. After the resulting solution was stirred at the temperature for 1 hr, H_2O (10 mL) was added to a reaction mixture at the same temperature. Then the reaction mixture was stirred at room temperature for 30 min, filtered through ®Celite 545 to afford a filtrate, which was washed with sat. NaCl (25 mL x 2), dried over anhydrous $MgSO_4$, filtered, concentrated to give an amorphous solid. A mixture of the residue (0.806 g, 2.01 mmol), 4-dimethylaminopyridine (catalytic amount), Et_3N (0.56 mL, 4.02 mmol), Ac_2O (0.41 g, 4.02 mmol), and dry CH_2Cl_2 (17 mL) was stirred at 0 °C for 10 min and room temperature for 20 min. H_2O (5 mL) was added. The organic layer was separated and washed with H_2O (10 mL x 1) and sat. NaCl (10 mL x 1), dried over $MgSO_4$, concentrated *in vacuo* to give an oil, which was purified by silica gel flash chromatography (eluted with Hexane : AcOEt = 5 : 1) to give compound **21** (0.836 g, 93 % from compound **20**) as a colorless amorphous solid. Diastereomer ratio (41 : 59) was determined on the basis of ^1H -NMR spectrum of compound **21**. Mp 42-44 °C. $[\alpha]_D^{25}$ = -175.1° (CH_2Cl_2, *c* = 0.62). ^1H NMR (300 MHz) (393 K, DMSO- d_6) δ TMS: (major isomer) 1.06 (3H, d, J = 7.2 Hz), 2.05 (3H, s), 4.26 (1H, qd, J = 7.2 Hz, 0.6 Hz), 5.20 (1H, d, J = 12.6), 5.27 (1H, d, J = 12.6 Hz), 5.68 (1H, d, J = 3.6 Hz), 6.12 (1H, d, J = 0.6 Hz). (minor isomer) 0.96 (3H, d J = 7.2 Hz), 2.14 (3H, s), 4.41 (1H, qd, J = 6.9 Hz, 4.2 Hz), 5.21 (2H, s), 5.38 (1H, d, J = 4.1 Hz), 6.04 (1H, d, J = 3.9 Hz). (mixed peaks) 5.61 (1H, d, J = 3.9 Hz), 7.01-7.43 (15H, m). IR (KBr): 1750, 1696 (C=O) cm^{-1}. MS (FAB+): 446 (M^++H). HRMS (FAB+) calcd. for $C_{27}H_{28}NO_5$ (M^++H): 446.1967. Found: 446.1974.

Titanium(IV) Chloride-Mediated Coupling Reaction of Hemi-acetal 21 with Allyltrimetrhylsilane: (*2S, 3S, 5R, 6S*)-4-(benzyloxycarbonyl)-5,6-diphenyl-3-methyl-2-(2-propenyl)-1, 2, 5, 6-tetrahydro-4H-1,4-oxazine (22). To a CH_2Cl_2 solution (3 mL) of hemi-acetal **21** (0.114 g, 0.25 mmol) and allyltrimethylsilane (0.2 mL, 1.25 mmol), 1.0 M $TiCl_4$ in CH_2Cl_2 (0.50 mL, 0.50 mmol) was added at -78 °C under an Ar atmosphere. The reaction mixture was stirred at the same temperature for 10 min and then at 0 ° for 10 min. After the reaction, sat. $NaHCO_3$ (10 mL) was added, stirred for 20 min at room temperature, and diluted with CH_2Cl_2 (15 mL). The organic layer was separated, and the aqueous phase was extracted with CH_2Cl_2 (10 mL x 2). The combined organic layer was washed with sat. NaCl (15 mL x 3), dried over anhydrous $MgSO_4$, filtered, and evaporated under reduced pressure to give an oily residue, which was purified by using silica gel radial chromatography (eluted with Hexane : AcOEt = 15 : 1) to give a major coupling product **22** (0.093 g, 87 % from compound **21**) as a colorless viscous oil. $[\alpha]_D^{25}$ = -199° (CH_2Cl_2, *c* = 0.3). ^1H NMR (300 MHz) (393 K, DMSO- d_6) δ: TMS: 0.99 (3H, d, J = 7.1 Hz), 2.42-2.52 (1H, m), 2.59 (1H, m), 4.01-4.13 (2H, m), 5.01-5.13 (2H, m), 5.19 (1H, d, J = 12.3 Hz), 5.25 (1H, d, J = 12.6 Hz), 5.33 (1H, d, J = 3.9 Hz), 5.65 (1H, d, J = 3.9 Hz), 5.89 (1H, ddt, J = 17.1 Hz, 10.2 Hz, 6.9 Hz), 7.00-7.41 (15H, m). IR (NaCl, neat):1694 (C=O) cm^{-1}. MS (EI): 427 (M^+), 386 (M^+-C_3H_5). Anal calcd. for $C_{28}H_{29}NO_3$: C, 78.66; H, 6.84; N, 3.28. Found: C, 78.47, H, 6.72, N, 3.34.

General Procedure for Preparation of Carboxylic acids (24a, b, and d) *via* Ozonolysis. A mixture of the coupling product (1.07 mmol), absolute MeOH (5 mL), and dry CH_2Cl_2 (2.5 mL) was bubbled with O_3 at -78 °C until the color of solution turned to blue (*ca.* 5 min). After the reaction mixture was then bubbled with Ar gas

for 5 min at the same temperature, Me_2S (2 mL) was added carefully. The solvent was evaporated under reduced pressure to give an oily residue, which was diluted with Et_2O (15 mL), washed with H_2O (10 mL x 3), and dried over anhydrous $MgSO_4$. The solvent was evaporated under reduced pressure to give the crude carboxaldehyde, which was employed to the next reaction without further purification. A mixture of the crude carboxaldehyde (0.24 mmol), PDC (0.84 mmol), and DMF (0.8 mL) was stirred at room temperature for 12 h under an Ar atmosphere. After the reaction, the resulting mixture was poured into H_2O (10 mL) and extracted with CH_2Cl_2 (10 mL x 3). The extract was washed with 5 % HCl (15 mL x 2), and sat. NaCl (15 mL x 3), dried over anhydrous $MgSO_4$, filtered, and evaporated under reduced pressure to give a residue, which was purified by silica gel flash chromatography (eluted with CH_2Cl_2:MeOH = 20:1) to give the corresponding carboxylic acid.

(2*S*, 5*R*, 6*S*)-2-(4-benzyloxycarbonyl-5,6-diphenyl-1, 2, 5, 6-tetrahydro-4H-1,4-oxazin-2-yl)acetic acid (24a). (77 % yield from compound **13a**) Colorless amorphous solid, mp 67-69 °C. $[\alpha]_D^{25}$ = -102° (CH_2Cl_2, *c* = 0.4). ^{1}H NMR (300 MHz) (393 K, DMSO- d_6) δ TMS: 2.71 (2H, d, J = 6.6 Hz), 3.72 (1H, dd, J = 13.8 Hz, 4.8 Hz), 3.88 (1H, dd, J = 13.7 Hz, 3.9 Hz), 4.72-4.78 (1H, m), 5.10 (1H, d, J = 12.9 Hz), 5.16 (1H, d, J = 12.6 Hz), 5.32 (1H, d, J = 3.6 Hz), 5.43 (1H, d, J = 3.3 Hz), 7.09-7.36 (15H, m). IR (KBr): 3036 (OH), 1733, 1703 (C=O) cm^{-1}. MS (FAB+): 432 (M^++H), 388 (M^+-CO_2). HRMS Calcd. for $C_{26}H_{26}NO_5$ (M^++H): 432.1811. Found: 432.1804.

(2*S*, 3*R*, 5*R*, 6*S*)-2-(4-benzyloxycarbonyl-5,6-diphenyl-3-methyl-1, 2, 5, 6-tetrahydro-4H-1,4-oxazin-2-yl)acetic acid (24b). (75 % yield from compound **13b**) Colorless amorphous solid, mp 79-81 °C. $[\alpha]_D^{25}$ = +56.4° (CH_2Cl_2, *c* = 0.59). ^{1}H NMR (300 MHz) (393 K, DMSO- d_6) δ TMS: 1.48 (3H, d, J = 6.6 Hz), 2.59 (2H, d, J = 6.6 Hz), 4.44 (1H, qd, J = 6.6 Hz, 3.5 Hz), 5.03 (1H, td, J = 6.6 Hz, 3.6 Hz), 5.03 (1H, d, J = 12.6 Hz), 5.11 (1H, d, J = 12.9 Hz), 5.29 (1H, d, J = 4.2 Hz), 5.65 (1H, d, J = 3.9 Hz), 6.80-6.83 (2H, m), 7.01-7.28 (13H, m). IR (KBr): 3063 (OH), 1736, 1701 (C=O) cm^{-1}. MS (FAB+): 446 (M^++H), 402 (M^+-CO_2). HRMS Calcd. for $C_{27}H_{28}NO_5$ (M^++H):. 446.1967. Found: 446.1962.

(2*S*, 3*R*, 5*R*, 6*S*)-2-(4-benzyloxycarbonyl-5,6-diphenyl-3-isobutyl-1, 2, 5, 6-tetrahydro-4H-1,4-oxazin-2-yl)acetic acid (24d). (75 % yield from compound **13d**) Colorless amorphous solid, mp 61-63 °C. $[\alpha]_D^{25}$ = +23.5° (CH_2Cl_2, *c* = 0.37). ^{1}H NMR (300 MHz) (300 K, DMSO- d_6) δ TMS: 0.66 (3H, d, J = 6.0 Hz), 0.81 (3H, d, J = 6.0 Hz), 1.50-1.65 (2H, m), 1.81 (1H, m), 2.69-2.71 (2H, m), 3.84 (1H, td, J = 6.5 Hz, 6.0 Hz), 4.27 (1H, dt, J = 6.6 Hz, 5.9 Hz), 4.97 (2H, s), 5.18 (1H, d, J = 3.6 Hz), 5.20 (1H, d, J = 3.6 Hz), 6.97-7.27 (15H, m). IR (KBr):1734, 1709 (C=O) cm^{-1}. MS (EI): 487 (M^+), 430 (M^+-C_4H_9). HRMS Calcd. for $C_{30}H_{33}NO_5$ (M^+): 487.2359. Found: 487.2350.

Hydroboration of the Coupling Product 13b: (2*S*, 3*R*, 5*R*, 6*S*)-4-(Benzyloxycarbonyl)-5,6-diphenyl-2-hydroxypropyl-2,3,5,6-tetrahydro-4H-1,4-oxazine (26). To a THF solution (5 mL) of the coupling product **13** (0.217 g, 0.51 mmol), 2.0 M Borane dimethylsulfide complex in THF (0.26 mL, 0.52 mmol) was added at 0 °C. Then the resulting mixture was stirred at room temperature for 12 h, and recooled to 0 °C. To the reaction mixture, MeOH (5 drops), 3M NaOH (2 mL), and 30 % H_2O_2 (2 mL) was added, successively. After being gently refluxed for 1 hr, the mixture was extracted with Et_2O (10 mL x 3). The organic phase was washed with sat. NaCl (15 mL x 3), dried over $MgSO_4$, filtered, and evaporated under reduced pressure to give a viscous oil, which was purified by silica gel flash chromatography (eluted with Hexanes:AcOEt = 2:3) to give compound **26** (colorless viscous oil, 0.18 g, 78% yield from compound (+)-**13**). Colorless viscous oil. $[\alpha]_D^{25}$ = +64.0° (CH_2Cl_2, *c* = 0.42). ^{1}H NMR (300 MHz) (393 K, DMSO- d_6) δ TMS 1.46 (3H, d, J = 7.2 Hz), 1.52-1.72 (4H, m), 3.49 (2H, t, J = 6.3 Hz), 3.69 (1H, brs), 4.34 (1H, qd, J = 6.6 Hz, 3.5 Hz), 4.57 (1H, m), 5.02 (1H, d, J = 12.9 Hz), 5.10 (1H, d, J = 12.9 Hz), 5.27 (1H, d, J = 4.2 Hz), 5.62 (1H, d, J = 4.2 Hz), 6.79 (2H, dd, J = 7.7 Hz, 1.7 Hz), 7.00-7.28 (13H, m). IR (NaCl, neat): 3460 (OH), 1698 (C=O) cm^{-1}. MS (FAB+): 446 (M^++H). HRMS Calcd. for $C_{28}H_{32}NO_4$ (M^++H): 446.2331. Found: 446.2325.

Oxidation of Alcohol 26: (2*S*, 3*R*, 5*R*, 6*S*)-3-(4-Benzyloxycarbonyl-5,6-diphenyl-3-methyl-2,3,5,6-tetrahydro-4H-1,4-oxazin-2-yl)propanoic acid (27). A mixture of compound **26** (0.15 g, 0.33 mmol), PDC (0.46 g, 1.23 mmol), and DMF (1.5 mL) was stirred at room temperature for 12 h under an Ar atmosphere. After the reaction, the resulting mixture was poured into H_2O (10 mL) and extracted with CH_2Cl_2 (10 mL x 3). The extract was washed with 5 % HCl (15 mL x 2), and sat. NaCl (15 mL x 3), dried with anhydrous $MgSO_4$, filtered, and evaporated under reduced pressure to give a residue, which was purified by silica gel flash chromatography (eluted with CH_2Cl_2:MeOH = 20:1) to give compound **27** (colorless amorphous solid, 0.10 g,

66 % yield from compound (+)-**26**). Colorless amorphous solid, mp 67-68 °C $[\alpha]_D^{2.5}$ = +52.8° (CH_2Cl_2, *c* = 0.38). ^{1}H NMR (300 MHz) (393 K, DMSO- d_6) δ TMS 1.47 (3H, d, J = 6.6 Hz), 1.79-1.92 (2H, m), 2.35-2.43 (2H, m), 4.33 (1H, qd, J = 6.6 Hz, 3.6 Hz), 4.58-4.63 (1H, m), 5.01 (1H, d, J = 12.9 Hz), 6.00 (1H, d, J = 12.6 Hz), 5.27 (1H, d, J = 3.9 Hz), 5.62 (1H, d, J = 4.2 Hz), 6.79 (2H, d, J = 7.5 Hz), 6.99-7.28 (13H, m). IR (KBr): 3031 (OH), 1730, 1703 (C=O) cm^{-1}. MS (FAB+): 460 (M^++H). HRMS Calcd. for $C_{28}H_{30}NO_5$ (M^++H): 460.2124. Found: 460.2120.

General Procedure for Birch Reduction: Preparation of Hydroxymetylene and Hydroxyethylene Peptide Isosteres (25a, b, d, and 28). To a solution of Li^0 (0.05 g, 7.14 mmol atom) in liq. NH_3 (10 mL, distilled from Na^0), a THF solution (5 mL) of carboxylic acid (0.30 mmol) and *tert*-BuOH (0.11 g, 1.51 mmol) was added dropwise at -78 °C. The reaction mixture was stirred at the same temperature for 10 min, and then at -33 °C for 40 min. To the reaction mixture, excess NH_4Cl was added. The mixture was concentrated to give a residue. H_2O (4 mL) was added to the residue and make it pH 2~3 by adding 4N HCl. The aqueous solution was washed with Et_2O (10 mL x 3). The aqueous phase was concentrated under reduced pressure at room temperature until the volume was 2 mL. The residue was purified by ion exchange chromatography (®Dowex 50WX-100, eluted with 0.1N NH_4OH) to give the corresponding amino acid.

(*3S*)-4-Amino-3-hydroxybutyric acid (25a). (81 % yield from compound **24a**) Colorless amorphous solid, mp 208-210 °C (lit. mp 212-214[6b]). $[\alpha]_D^{2.5}$ = +21° (H_2O, *c* = 0.18). ($[\alpha]_D^{2.5}$ = +20.7° (H_2O, *c* = 1.9)[6b]). ^{1}H and ^{13}C NMR, IR, MS of the synthetic compound **25a** were identical with those of the authentic sample reported by Yang *et al.*[6b]

(*3S, 4R*)-4-Amino-3-hydroxypentanoic acid (25b). (80 % yield from compound **24b**) Colorless amorphous solid, mp 187-188 °C. $[\alpha]_D^{2.5}$ = +6.9 ° (H_2O, *c* = 0.18). ^{1}H NMR (300 MHz) (300 K, D_2O) δ 1.22 (3H, d, J = 7.2 Hz), 2.39 (2H, d, J = 6.6 Hz), 3.39-3.47 (1H, m), 4.16-4.21 (1H, m). ^{13}C NMR (75 MHz) (300 K, D_2O-CD_3OD) δ: 12.8, 41.7, 51.9, 69.7, 179.6. IR (KBr): 3483 (OH), 1569 (COO^-) cm^{-1}. MS (EI): 133 (M^+), 115 (M^+-H_2O). HRMS (FAB+) Calcd. for $C_5H_{12}NO_3$ (M^++H): 134.0817. Found: 134.0817.

(*3S, 4R*)-4-Amino-3-hydroxy-6-methylheptanoic acid (25d). (80 % yield from compound **24d**) Colorless amorphous solid, mp 194-195 °C. $[\alpha]_D^{2.5}$ = +19.8° (H_2O, *c* = 0.51). ($[\alpha]_D^{2.5}$ and mp of (*3S, 4S*)-statine are reported as -18.9° (H_2O, *c* = 0.424) and mp 199-201 °C).[2a] ^{1}H NMR (300 MHz) (300 K, D_2O) δ 0.84 (3H, d, J = 5.4 Hz), 0.86 (3H, d, J = 6.3 Hz), 1.41 (2H, dd, J = 7.5 Hz, 7.5 Hz), 1.62 (1H, m), 2.32 (1H, dd, J = 15.5 Hz, 7.5 Hz), 2.46 (1H, dd, J = 15.3 Hz, 5.1 Hz), 3.16 (1H, ddd, J = 7.5 Hz, 6.3 Hz, 6.3 Hz), 3.92 (1H, dt, J = 7.5 Hz, 5.4 Hz). ^{13}C NMR (75 MHz) (300 K, D_2O-CD_3OD) δ: 22.0, 23.1, 24.9, 39.6, 42.4, 54.7, 69.3, 179.7. IR (KBr): 3197 (OH), 1559 (COO^-) cm^{-1}. MS (EI): 157 (M^+-H_2O). HRMS (FAB+) Calcd. for $C_8H_{18}NO_3$ (M^++H): 176.1287. Found: 176.1292.

(*4S, 5R*)-5-Amino-4-hydroxyhexanoic acid (28). (74 % yield from compound **27**) Colorless amorphous solid, mp 155-156 °C. $[\alpha]_D^{2.5}$ = +5.0° (H_2O, *c* = 0.44). ^{1}H NMR (300 MHz) (300 K, D_2O) δ 1.22 (3H, d, J = 6.9 Hz), 1.57-1.79 (2H, m), 2.18-2.37 (2H, m), 3.37 (1H, qd, J = 6.9 Hz, 3.3 Hz), 3.75 (1H, td, J= 8.7 Hz, 3.3 Hz). ^{13}C NMR (75 MHz) (300 K, D_2O-CD_3OD) δ: 12.4, 29.8, 34.7, 52.0, 71.7, 183.2. IR (KBr):): 3375 (OH), 1560 (COO^-) cm^{-1}. MS (EI): 129 (M^+-H_2O). HRMS (FAB+) Calcd. for $C_6H_{14}NO_3$ (M^++H): 148.0974. Found: 148.0977.

References and Footnotes

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