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Synthesis of 2-Isoxazoline and α-Hydroxy Ketomethylene Dipeptide Isosteres

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Abstract—We have developed a simple and stereoselective method for synthesizing novel dipeptide isosteres using nitrile oxide cycloaddition as a key reaction. Employing this method, we have prepared efficiently various peptidomimetics containing 2-isoxazolines and α-hydroxy ketomethylene dipeptide isosteres.

Introduction

Peptides play important roles as hormones and neurotransmitters in biological systems. Modulation of the cell surface receptors by peptide agonists/antagonists and inhibition of the enzymes involved in key metabolic processes have important therapeutic implications.[1] Unfortunately, the use of native peptides for clinical applications has been limited by intrinsic properties of peptides such as metabolic instability.

In an effort to overcome these limitations, numerous modifications of peptide structure have been considered.[2] These modified structures are referred to as peptidomimetics. It is widely believed that such modifications will enhance the desirable properties and avoid undesirable properties of the native peptides. Many peptide analogues incorporating peptidomimetic components have exhibited improved pharmacological and pharmacokinetic properties, including bioactivity, selectivity, metabolic stability, absorption, and lower toxicity. Hence, the development of novel dipeptide isosteres possesses a great value in peptidomimetics.

We have introduced the asymmetric 1,3-dipolar nitrile oxide cycloaddition for the development of new dipeptide isosteres. In this way, we have prepared several peptidomimetics containing 2-isoxazoline rings and α-hydroxy ketomethylene dipeptide isosteres[3] (Scheme 1).

Results and Discussion

Synthesis of N-protected α-amino aldoxime

For the synthesis of 2-isoxazoline and α-hydroxy ketomethylene dipeptide isosteres, it is necessary to employ N-protected α-amino aldoximes from various amino acids as precursors of nitrile oxide dipoles.

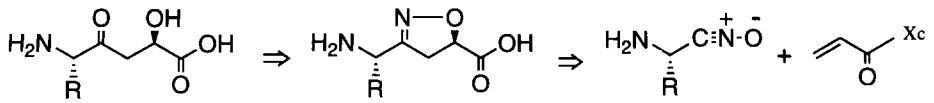
Key words: Dipeptide isostere, peptidomimetics, nitrile oxide cycloaddition, 2-isoxazoline, α-hydroxy ketomethylene.

In order to prepare the oximes, N-protected esters were reduced to the corresponding aldehydes. N-Protected α-amino aldehydes are important and versatile compounds in organic synthesis.[4] N-Protected α-amino aldehydes have been used mainly for the synthesis of peptide analogues, unusual amino acids and amino sugars. N-Protected α-amino aldehydes are relatively unstable both chemically and configurationally, particularly in solution.[5] In our experiments, α-amino aldehydes were prepared from N-protected α-amino esters by the method of diisobutylaluminum hydride (DIBAL) reduction.[6] The α-amino esters were converted to the corresponding α-amino aldehydes by DIBAL reduction under the conditions A [DIBAL(1.5 equiv), toluene, −78 °C, 1 h] or B [DIBAL(2.3 equiv), toluene, −78 °C, 5 min]. In most cases, we used method B to prepare the α-amino aldehydes. In order to check optical purity of the α-amino aldehydes, optical rotations of several α-amino aldehydes (Boc-L-alaninal, Boc-L-valinal, Boc-L-leucinal) were observed, and compared favorably with those of the literature.[5b] In the DIBAL reduction, we could find a small amount of the amino alcohols resulted from the over reduction.

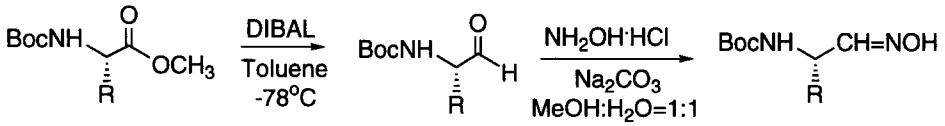
Due to relative instability of α-amino aldehydes, these compounds were directly transformed to the corresponding α-amino aldoximes. α-Amino aldehydes were dissolved in aqueous methanol and reacted with hydroxylamine, and sodium carbonate as a base to afford corresponding aldoximes in very good yield (Scheme 2). The aldoximes formed were mixtures of *E* and *Z* isomers in most cases, these isomers were used for the next reaction without further separation. The experimental results of the α-amino aldoxime formation are listed in Table 1.

Asymmetric 1,3-dipolar nitrile oxide cycloaddition

Asymmetric 1,3-dipolar nitrile oxide cycloadditions to chiral dipolarophiles provide versatile heterocyclic intermediates in optically active form.[7] N-Acryloyl



Scheme 1.



Scheme 2.

bornane-10,2-sultam[8] derived from Oppolzer's chiral camphorsultam[9] usually shows good π-face diastereoselectivities (ca. 90:10) in the nitrile oxide cycloaddition. The origin of π-face differentiation of the chiral auxiliary was suggested tentatively by the effect of the pyramidal nitrogen atom and the steric or electronic encumbrance of one of the sulfone oxygen. Recently, Kim et al.[10] reported the origin of the diastereofacial selectivity to chiral dipolarophiles. They suggested that diastereofacial selectivity in the nitrile oxide cycloaddition with the Oppolzer's chiral sultam originates not from conventional face shielding by sterically bulky groups, but mainly from face shielding due to Coulombic interaction (repulsion) between the dipolar oxygen and the sultam oxygens.

Asymmetric nitrile oxide cycloadditions with N-acryloyl camphor sultam using N-protected α-amino aldoximes as precursors were performed under the several conditions (Scheme 3). N-Protected α-amino aldoxime was reacted with N-chlorosuccinimide (NCS) in DMF for the formation of hydroximic chloride, which is the well known precursor of nitrile oxide in Huisgen method.[11] However, the yield of reaction was less satisfactory. Therefore, nitrile oxide was generated by one pot reaction with bromination of α-amino aldoxime by N-bromosuccinimide (NBS) followed by dehydrobromination by triethylamine. Cycloadditions using this method provided cycloadducts in 50–70% yield. Diastereomeric ratios of cycloadducts were determined by ^{1}H NMR using (−)Eu(hfc)$_3$ as a chiral shifting agent or by HPLC (silica gel column, 5 μm). The isomeric ratio of cycloadducts was ca. 90:10, the same as known cases. However, this method had a disadvantage that one isomer of the oximes did not reacted with NBS during the reactions. Finally, we employed sodium hypochlorite (NaOCl) as a reagent for nitrile oxide generation.[12] We used commercial bleach (typically contains >4% NaOCl) as a practical NaOCl reagent. The reactions were performed with slight excess of the oximes compared to the chiral dipolarophile for the improvement of reaction yields. Table 2 summarizes the experimental results of asymmetric dipolar cycloadditions.

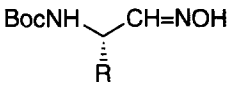
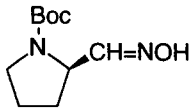
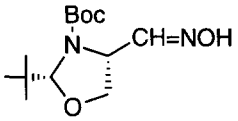
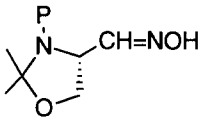
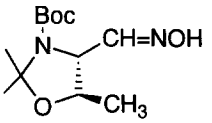
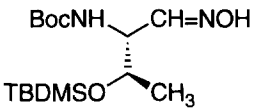
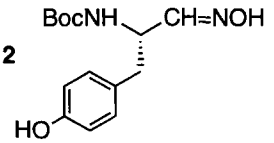
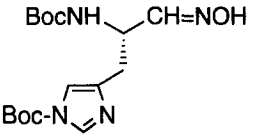
The absolute stereochemistry of the newly generated C12 stereogenic center of cycloadduct **20** was rigorously determined as *S* by X-ray crystallography (Fig. 1). The bond lengths and torsion angles which define the conformation of the dipeptide unit in **20** are given in Figure 1. The absolute stereochemistry of the cycloadduct **23** derived from antipodal (D)-camphorsultam was also determined by X-ray crystallography and then assigned the new chiral center as *R* (Fig. 2). The bond lengths and torsion angles in **23** are given in Figure 2. The stereochemistry of other major cycloadducts were tentatively assigned by analogy.

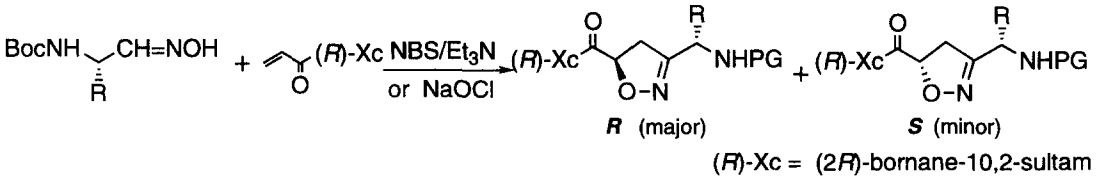
Synthesis of 2-isoxazoline dipeptide isostere

The cycloadducts **14–25** were converted to carboxylic acids by hydrolysis using LiOH and the chiral auxiliaries were also recovered. The carboxylic acids were esterified to give esters **26–35** in good yields (Scheme 4). Esterifications were performed by using one of the following methods; H_2SO_4/MeOH (Fisher esterification), CH_2N_2/Et_2O and $CH_3I/NaHCO_3$. The results are shown in Table 3.

These 2-isoxazoline dipeptide isosteres are new members of conformationally constrained dipeptide mimetics that restrict the ω_i and ϕ_{i+1} torsion angles in peptides. These systems are based on linking between i+1 side chain residue and carbonyl group in peptide bond. The ω_i and ϕ_{i+1} torsion angles in 2-isoxazolines are shown in Figure 1 and Figure 2. The

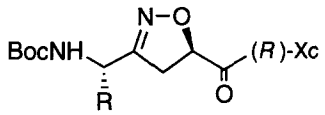
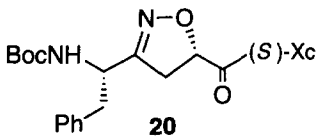
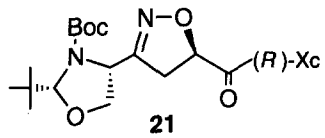
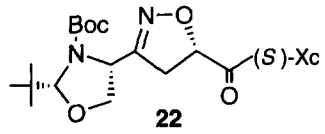
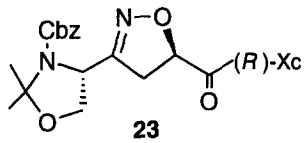
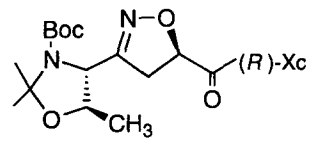
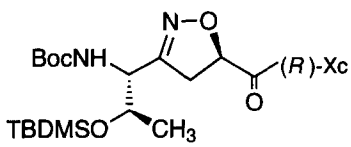
Table 1. Synthesis of N-protected α-amino aldoxime

amino acid	α-amino aldoxime		$[\alpha]_D$ (c, $CHCl_3$)	overall yield (%)
				
(Ala)	**1**	R=CH_3	-0.88 (1.14)	94
(Val)	**2**	R=$CH(CH_3)_2$	-9.27 (3.17)	94
(Leu)	**3**	R=$CH_2CH(CH_3)_2$	-27.4 (1.05)	83
(Phe)	**4**	R=CH_2Ph	-6.20 (1.85)	93
(Cha)	**5**	R=$CH_2C_6H_{11}$	-15.6 (1.00)	91
(Pro)	**6**		-47.4 (1.83)	95
(Ser)	**7**		-12.2 (1.00)	81
(Ser)				
	8	P=Cbz	-23.3 (1.84)	73
	9	P=Boc	-33.8 (1.13)	76
(Thr)	**10**		-25.4 (4.50)	81
(Thr)	**11**		+8.30 (4.01)	78
(Tyr)	**12**		+34.3 (1.69, CH_3OH)	83
(His)	**13**		+1.12 (1.07, CH_3OH)	76



Scheme 3.

Table 2. Asymmetric dipolar cycloaddition with N-acryloyl camphorsultam

α-amino aldoxime	major cycloadduct	method	ratio (major:minor)	yield (%)
				
1 (Ala)	**14** R=CH_3	b		80
2 (Val)	**15** R=$CH(CH_3)$	b		71
3 (Leu)	**16** R=$CH_2CH(CH_3)_2$	b		86
3 (Leu)	**16** R=$CH_2CH(CH_3)_2$	a	89 : 11	61
4 (Phe)	**17** R=CH_2Ph	b		79
4 (Phe)	**17** R=CH_2Ph	a	90 : 10	69
5 (Cha)	**18** R=$CH_2C_6H_{11}$	b		83
12 (Tyr)	**19** R=$CH_2PhOTBDMS$	b		80
4 (Phe)	 **20**	b		82
7 (Ser)	 **21**	a		57
7 (Ser)	 **22**	a	92 : 8	48
8 (Ser)	 **23**	a		66
10 (Thr)	 **24**	a		76
11 (Thr)	 **25**	a	91 : 9	44

Method a: (i) NBS; (ii) Et_3N, b: NaOCl (*R*)-Xc = (2*R*)-Bornane-10,2-sultam, (*S*)-Xc = (2 *S*)-Bornane-10,2-sultam

(*S*)-isoxazoline system holds these angles to $+167°$ and $-101°$ while the (*R*)-isoxazoline system restricts them to $-168°$ and $+100°$. These mimetics may be used as enzyme inhibitors and conformationally restricted peptide analogues. This type of peptide mimetics is present in natural cyclic peptides such as the cytotoxic peptides ascidiacyclamide and ulithiacyclamide.[13]

Synthesis of α-hydroxy ketomethylene dipeptide isosteres

2-Isoxazoline dipeptide isosteres were readily transformed to α-hydroxy ketomethylene dipeptide isostere (Scheme 5). Hydrogenolysis of the isoxazolines using Raney–nickel[14] followed by hydrolysis provided

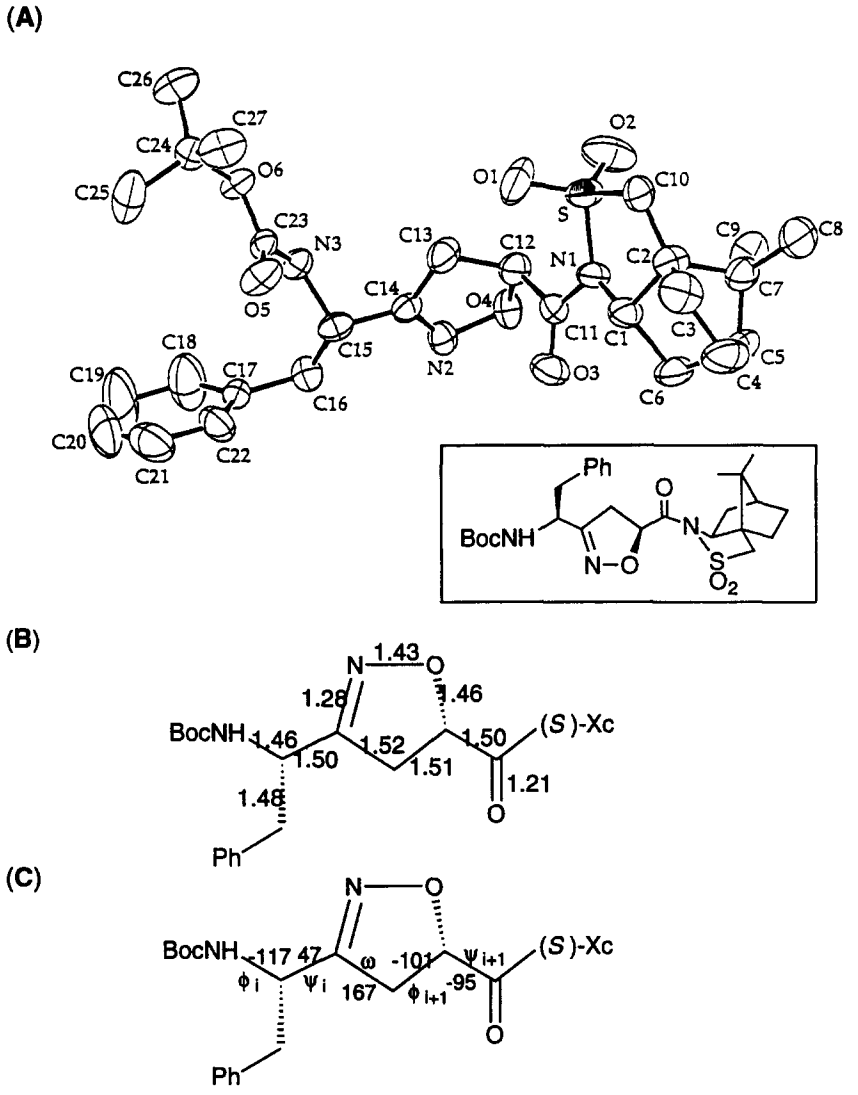


Figure 1. X-ray crystal structure (**A**) of cycloadduct **20**, bond length (Å, **B**), and torsion angle (deg, **C**) in the dipeptide unit for **20**.

β-hydroxy carbonyl compounds in good yields. In no case we were able to detect any loss of stereochemical purity. Thus, we could readily prepare the keto-methylene dipeptide isosteres with an additional stereogenic α-carbon center possessing the hydroxyl group. The experimental results are summarized in Table 4.

The absolute stereochemistry of the compound **41** was determined by X-ray crystallography (Fig. 3). The bond lengths of the dipeptide isostere **41** are given in Figure 3. The isostere was expected to reduce peptide backbone flexibility by the intramolecular hydrogen bonding between the hydroxyl group and the carbonyl oxygen. However, X-ray crystallographic study suggests that the hydroxyl group may form hydrogen bonding to the carbonyl oxygen of ester.

Application to enzyme inhibitors

Renin-angiotensin system (RAS) plays a central role in the regulation of blood pressure and electrolyte balance.[15] Angiotensin-converting enzyme (ACE) is a nonspecific dipeptidyl carboxypeptidase that generates the biologically active octapeptide angiotensin II from angiotensin I.[16] Angiotensin II is a potent vasoconstrictor. Several approaches to block the RAS have been studied for the treatment of essential hypertension and heart failure and ACE inhibitors have been used as antihypertensive agents. We reported novel ACE inhibitors of which 2-isoxazoline and α-hydroxy ketomethylene dipeptide isosteres were incorporated in the key moiety.[17]

Human immunodeficiency virus (HIV) is the causative agent of AIDS.[18] Understanding of the molecular events critical to virus replication has suggested several strategies for potential chemotherapeutic intervention.[19] Among them, blockage of the virally encoded protease has become a major target in the development for an effective anti-viral agent.[20] A general strategy for the design of HIV-1 protease inhibitors is based on the transition-state mimetic concept.[21] For the development of HIV-1 protease inhibitors, we

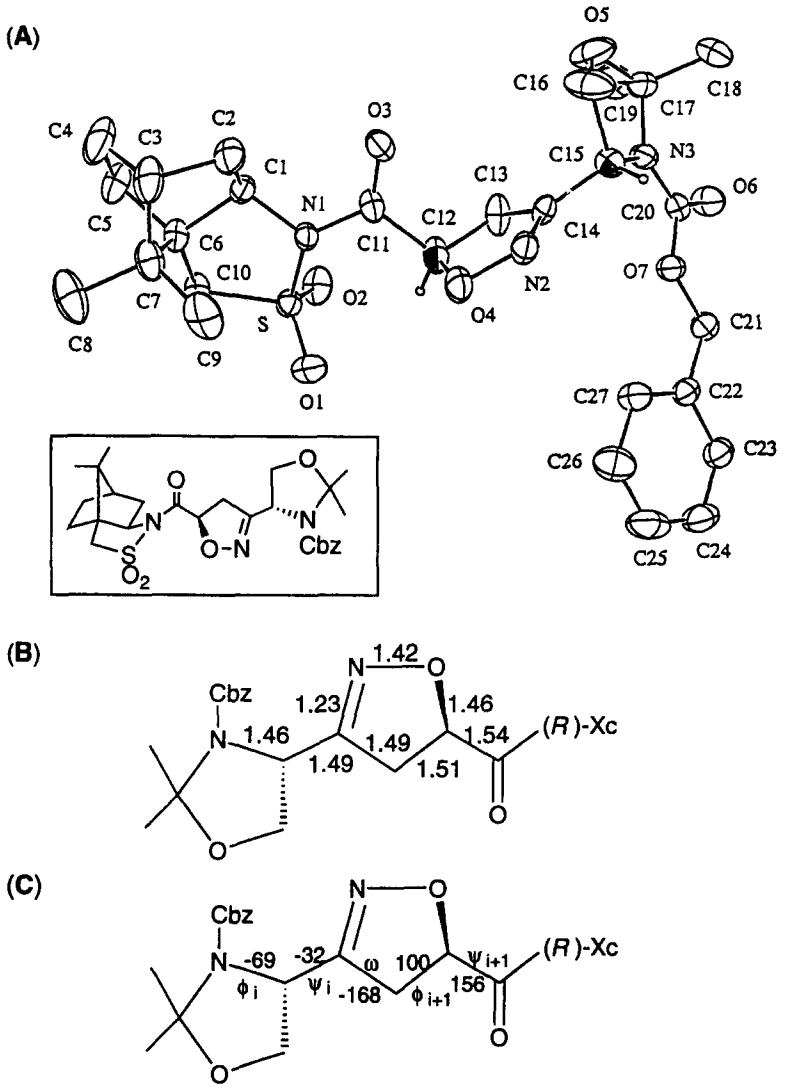
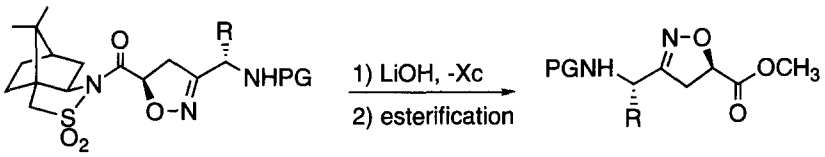


Figure 2. X-ray crystal structure (**A**) of cycloadduct **23**, bond length (Å, **B**), and torsion angle (deg, **C**) at the dipeptide unit for **23**.



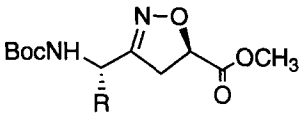
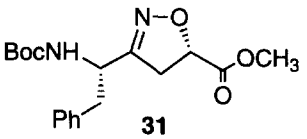
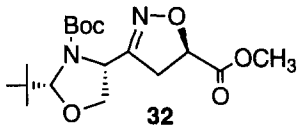
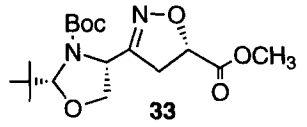
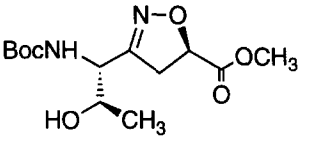
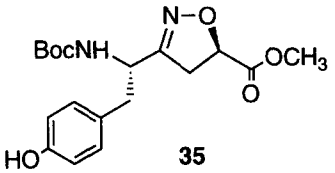
Scheme 4.

introduced novel dipeptide isosteres into the cleavage site of the substrate of the enzyme. The novel dipeptide isosteres possess key structural motifs; the hydroxyethylene transition state analogue and the 2-isoxazoline or isoxazole moiety instead of P_1' proline residue. The 2-isoxazoline containing compound **45** was shown to have the inhibitory activity ($IC_{50} = 18$ μM) (Fig. 4). Synthesis and inhibitory activities of other HIV-1 protease inhibitors will be reported in due course.

Conclusions

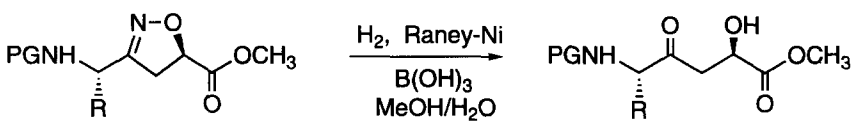
Employing asymmetric 1,3-dipolar nitrile oxide cycloaddition as a key reaction, we have developed a simple

Table 3. Synthesis of 2-isoxazoline isosteres

cycloadduct		isostere		$[\alpha]_D$ (c, $CHCl_3$)	overall yield (%)
					
14	(Ala)	**26**	$R=CH_3$	-185. 7 (1.05)	52
15	(Val)	**27**	$R=CH(CH_3)_2$ [a]	-145.9 (1.08)	67
16	(Leu)	**28**	$R=CH_2CH(CH_3)_2$	-163.4 (2.36)	76
17	(Phe)	**29**	$R=CH_2Ph$	-134.2 (0.86)	69
18	(Cha)	**30**	$R=CH_2C_6H_{11}$	-118.9 (2.93)	67
20	(Phe)	 **31**		+69.2 (1.06)	94
21	(Ser)	 **32**		-125.0 (1.27)	78
22	(Ser)	 **33**		+74.7 (1.10)	83
24	(Thr)	 **34**		-170.7 (1.07)	47
19	(Tyr)	 **35**		-140.1 (1.41)	66

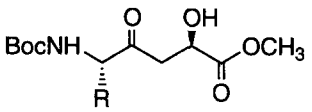
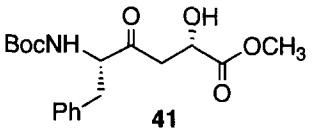
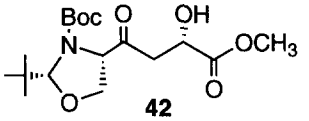
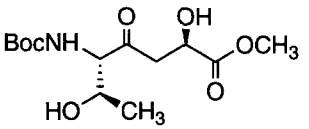
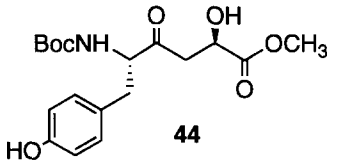
[a]ethyl ester

and stereoselective method for synthesizing novel peptidomimetics containing 2-isoxazolines and α-hydroxy ketomethylene dipeptide isosteres. These dipeptide isosteres reduce the conformational flexibility in the molecules and have some advantages in synthesis of the peptidomimetics. The dipeptide isosteres were applied to the synthesis of ACE inhibitors and HIV-1 protease inhibitors.



Scheme 5.

Table 4. Synthesis of α-hydroxy ketomethylene isosteres

isoxazoline isostere	ketomethylene isostere	$[\alpha]_D$ (c, $CHCl_3$)	yield (%)
			
26 (Ala)	**36** R=CH_3	+5.4 (2.00)	78
27 (Val)	**37** R=$CH(CH_3)_2$ [a]	+30.2 (2.92)	91
28 (Leu)	**38** R=$CH_2CH(CH_3)_2$	+2.0 (1.48)	92
29 (Phe)	**39** R=CH_2Ph	+18.4 (0.95)	94
30 (Cha)	**40** R=$CH_2C_6H_{11}$	+10.2 (2.44)	82
31 (Phe)	 **41**	+26.8 (1.00)	87
33 (Ser)	 **42**	-61.4 (1.43)	86
34 (Thr)	 **43**	-13.8 (0.88)	70
35 (Tyr)	 **44**	-24.6 (1.18, CH_3OH)	80

[a]ethyl ester

Experimental

General aspects

Most of reactions were carried out under an argon atmosphere with dried solvents unless otherwise stated. All commercial chemicals were used as obtained without further purification. Anhydrous solvents were obtained as follows: tetrahydrofuran, distillation from sodium/benzophenone; methylene chloride, toluene, dimethylformamide and pyridine, distillation from CaH_2.

Melting points were determined on a Thomas–Hoover capillary melting point apparatus and are uncorrected. Nuclear magnetic resonance (NMR) spectra were recorded on a Bruker AM 300 (300 MHz) spectrometer using tetramethylsilane as internal standard. Infrared (IR) spectra were obtained on a BOMEM model FT-IR M100-C15 spectrometer as neat. Mass spectra (EI or FAB) were recorded on a KRATOS MS 25 RFA system. High resolution MS was performed by the Inter-University Basic-Research Center, Seoul, Korea. Elemental analyses were performed by Galbraith Laboratories, Knoxville, U.S.A. Optical rotations were recorded on a JASCO DIP-360 polarimeter or Rudolph Autopol III polarimeter. Column chromatography was performed with E. Merck 240–400 mesh silica gel. Thin-layer chromatography (TLC) was carried out with E. Merck silica gel 60 F-254 plates and visualized with UV light and/or 20% solution of phosphomolybdic acid in EtOH.

General method 1: Preparation of N-protected α-amino aldoximes

To a precooled (−78 °C) solution of the corresponding protected amino ester (23 mmol) in dry toluene (40 mL) was added diisobutylaluminum hydride (36 mL of a 1.5 M solution in toluene, 53 mmol) dropwise over 30 min. Methanol (8 mL) was cautiously added 5 min

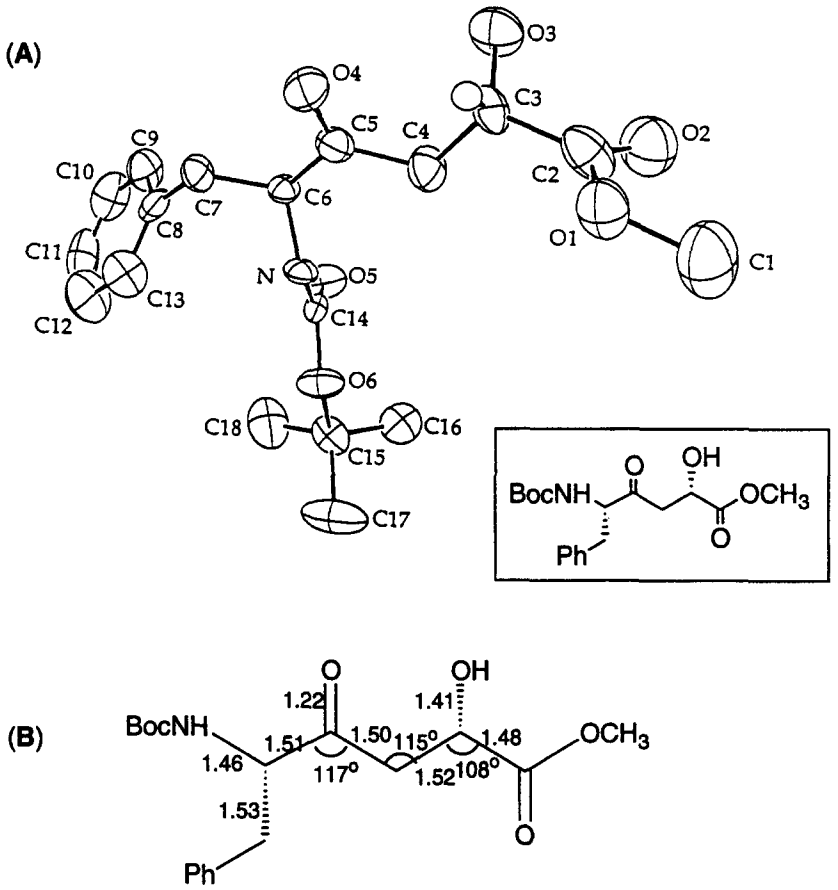
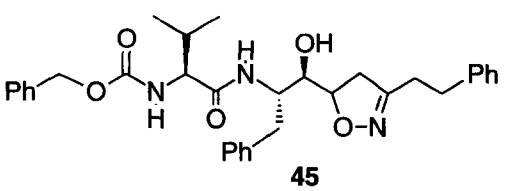


Figure 3. X-ray crystal structure (**A**), bond length (Å) and bond angle (deg, **B**) for the compound **41**.

later, and the mixture was poured into a precooled (O °C) 10% solution of citric acid (110 mL). After being stirred for 1–2 h, the mixture was extracted with ethyl acetate twice. The combined organic phase was washed with brine, dried over $MgSO_4$, filtered and concentrated in vacuo to give the corresponding amino aldehyde, which was immediately used in the next step without further purification.

To a precooled (4 °C) solution of above aldehyde in MeOH:H_2O (1:1 v/v, 100 mL) was added Na_2CO_3 (14 mmol) and NH_2OH·HCl (28 mmol). After being stirred for 6 h, the mixture was concentrated in vacuo to a half of the original volumes. The mixture was extracted with ethyl acetate and washed with brine, dried over $MgSO_4$, filtered and concentrated in vacuo to give the corresponding oximes. The oximes were purified by column chromatography and/or recrystallization.



45

Figure 4. HIV-1 protease inhibitor.

N-(*tert*-Butyloxycarbonyl)-L-alaninal oxime (1). The product was synthesized according to the general method 1 and recrystallized from ethyl acetate–hexane to give a white solid (yield 94%). R_f 0.26, 0.14 (C_6H_{14}:EtOAc, 3:1); IR (KBr, cm^{-1}) 3355, 2982, 1685, 1530, 1327, 1051; ^1H NMR (CD_3OD) δ 7.36 (d, J=4.4 Hz, 1H), 7.30 (br, 1H), 4.80 (br, 1H), 4.30 (br, 1H), 1.39 (s, 9H), 1.25 (d, J=6.8 Hz, 3H); ^{13}C NMR (CD_3OD) δ 157.9, 154.6, 80.5, 43.9, 29.0, 17.8; MS (*m/e*) 188 (M^+), 176, 132, 119, 97, 88, 72, 69, 60, 57, 54; mp 144.5–145.5 °C; $[\alpha]_D^{24}$ −0.88 (*c* 1.04; $CHCl_3$), $[\alpha]_D^{25}$ +58.3 (*c* 1.0; CH_3OH); Anal. calcd for $C_8H_{16}O_3N_2$: C, 51.05; H, 8.57; N, 14.88. Found: C, 51.11; H, 8.60; N, 14.68.

N-(*tert*-Butyloxycarbonyl)-L-valinal oxime (2). The product was synthesized according to the general method 1 and recrystallized from ethyl acetate–hexane to give a white solid (yield 94%). R_f 0.21, 0.10 (C_6H_{14}:EtOAc, 5:1); IR (KBr, cm^{-1}) 3344, 2969, 1682, 1526, 1315, 1174; ^1H NMR (CD_3OD) δ 6.52 (d, J=6.8 Hz, 1H), 4.66 (m, 1H), 1.91 (m, 1H), 1.43 (s, 9H), 0.93 (d, J=6.8 Hz, 3H), 0.91 (d, J=6.8 Hz, 3H); ^{13}C NMR (CD_3OD) δ 158.3, 152.0, 80.4, 52.4, 32.4, 29.0, 19.5, 18.9; mp 154–155 °C; $[\alpha]_D^{24}$ −9.3 (*c* 3.17; $CHCl_3$), $[\alpha]_D^{25}$ +62.5 (*c* 1.07; CH_3OH); Anal. calcd for

$C_{10}H_{20}O_3N_2$: C, 55.53; H, 9.32; N, 12.95. Found: C, 55.73; H, 9.73; N, 13.28.

N-(*tert*-Butyloxycarbonyl)-L-leucinal oxime (3). The product was synthesized according to the general method 1 and recrystallized from ethyl acetate–hexane to give a white solid (yield 83%). R_f 0.42, 0.25 (C_6H_{14}:EtOAc, 3:1); IR ($CHCl_3$, cm^{-1}) 3331, 2949, 1695, 1514, 1367, 1168; ^1H NMR ($CDCl_3$) δ 7.78 (br, 1H), 7.39 (d, J=4.8 Hz, 1H), 4.76 (br, 1H), 4.31 (br, 1H), 1.73–1.64 (m, 2H), 1.42 (s, 10H), 0.92 (d, J=6.3 Hz, 6H); MS (*m/e*) 230 (M^+), 175, 157, 130, 117, 86, 73, 57, 41; mp 150–151 °C; $[\alpha]_D^{25}$ −27.4 (*c* 1.0; $CHCl_3$); Anal. calcd for $C_{11}H_{22}O_3N_2$: C, 56.85; H, 9.63; N, 12.16. Found: C, 56.68; H, 9.65; N, 11.88.

N-(*tert*-Butyloxycarbonyl)-L-phenylalaninal oxime (4). The product was synthesized according to the general method 1 and recrystallized from ethyl acetate–hexane to give a white solid (yield 93%). R_f 0.28, 0.17 (C_6H_{14}:EtOAc, 3:1); IR ($CHCl_3$, cm^{-1}) 3338, 2977, 1690, 1506, 1367, 1253, 1168, 775; ^1H NMR ($CDCl_3$) δ [10.4, 8.11 (br, 1H)], [7.45 (d, J=4.1 Hz), 5.92 (br), (1H)], 7.33–7.12 (m, 5H), 5.08 (br, 1H), 4.55 (br, 1H), 3.04 (br, 2H), 1.42 (s, 9H); MS (*m/e*) 264 (M^+), 209, 191, 173, 163, 148, 130, 117, 91, 73, 57; mp 164.5–165.5 °C; $[\alpha]_D^{24}$ −6.2 (*c* 1.85; $CHCl_3$); Anal. calcd for $C_{14}H_{20}O_3N_2$: C, 63.62; H, 7.63; N, 10.60. Found: C, 64.04; H, 8.07; N, 10.57.

N-(*tert*-Butyloxycarbonyl)-L-cyclohexyalaninal oxime (5). The product was synthesized according to the general method 1 and recrystallized from ethyl acetate–hexane to give a white solid (yield 91%). R_f 0.46, 0.26 (C_6H_{14}:EtOAc, 3:1); IR ($CHCl_3$, cm^{-1}) 3357, 2851, 1708, 1509, 1256, 1011, 759; ^1H NMR ($CDCl_3$) δ 8.20 (br, 1H), 7.42 (d, J=4.9 Hz, 1H), 4.82 (br, 1H), 4.36 (br, 1H), 1.80–1.67 (m, 5H), 1.57–1.34 (m, 12H), 1.25–1.12 (m, 3H), 1.01–0.85 (m, 2H); mp 113–115 °C; $[\alpha]_D^{25}$ −15.6 (*c* 1.0; $CHCl_3$); Anal. calcd for $C_{14}H_{26}O_3N_2$: C, 62.19; H, 9.69; N, 10.36. Found: C, 61.95; H, 9.89; N, 10.21.

N-(*tert*-Butyloxycarbonyl)-L-prolinal oxime (6). The crude product was synthesized according to the general method 1 and purified by flash column chromatography on silica gel (C_6H_{14}:EtOAc, 3:1) to give the oxime as a clear oil (yield 95%). R_f 0.23 (C_6H_{14}:EtOAc, 3:1); IR ($CHCl_3$, cm^{-1}) 3326, 2974, 2881, 1677, 1406, 1168, 761; ^1H NMR ($CDCl_3$) δ [8.05, 7.80 (br, 1H)], [7.34, 6.68 (br, 1H), [4.83, 4.35 (br, 1H)], 3.59 (m, 2H), 2.25–1.78 (m, 4H), 1.42 (s, 9H); MS (*m/e*) 214 (M^+), 197, 158, 141, 114, 97, 70, 57, 41; $[\alpha]_D^{24}$ −47.4 (*c* 1.83; $CHCl_3$).

3-(*tert*-Butyloxycarbonyl) (*R*)-2-(*tert*-butyl) (*S*)-4-oxazolidine aldoxime (7). The product was synthesized according to the general method 1 and recrystallized from ethyl acetate–hexane to give a white solid (yield 81%). R_f 0.28 (C_6H_{14}:EtOAc, 4:1); IR ($CHCl_3$, cm^{-1}) 3373, 2968, 1700, 1362, 1169; ^1H NMR ($CDCl_3$) δ 7.91 (s, 1H), 7.57 (s, 1H), 7.48 (d, J=5.3 Hz, 1H), 6.97 (d, J=4.3 Hz, 1H), 5.04 (m, 3H), 4.68 (m, 1H), 4.38 (dd, J=8.7, 7.8 Hz, 1H), 3.93 (dd, J=8.9, 7.2 Hz, 1H), 1.45 (s, 9H), 0.91 (s, 9H); ^{13}C NMR ($CDCl_3$) δ 155.5, 153.4, 150.5, 97.1, 97.0, 81.3, 70.3, 68.6, 57.2, 54.9, 39.9, 37.4, 28.2, 26.2; MS (*m/e*) 273 (M^+), 215, 199, 173, 159, $[\alpha]_D^{25}$ −12.2 (*c* 1.0; $CHCl_3$); Anal. calcd for $C_{13}H_{24}O_4N_2$: C, 57.33; H, 8.88; N, 10.29. Found: C, 57.57; H, 9.11; N, 10.03.

3-Carbobenzoxy-2,2-dimethyl (*S*)-4-oxazolidine aldoxime (8). The crude product was synthesized according to the general method 1 and purified by flash column chromatography on silica gel (C_6H_{14}:EtOAc, 5:1) to give the oxime as a clear oil (yield 73%). R_f 0.32 (C_6H_{14}:EtOAc, 2:1); IR ($CHCl_3$, cm^{-1}) 3353, 2989, 1692, 1394, 1083, 753; ^1H NMR (C_6D_6, 73 °C) δ 7.49 (br, 1H), 7.38 (d, J=5.5 Hz, 1H), 7.26–7.05 (m, 5H), 5.07 (s, 3H), 4.37 (br, 1H), 3.94–3.79 (m, 1H), 3.73–3.59 (m, 1H), 1.59 (s, 3H), 1.46 (s, 3H); ^{13}C NMR (C_6D_6, 73 °C) δ 153.3, 149.7, 128.6, 128.3, 128.1, 127.7, 94.9, 67.2, 66.5, 56.6, 26.5, 24.3; MS (*m/e*) 278 (M^+), 263, 219, 135, 91, 65; $[\alpha]_D^{25}$ −23.3 (*c* 1.84; $CHCl_3$).

3-(*tert*-Butyloxycarbonyl)-2,2-dimethyl (*S*)-4-oxazolidine aldoxime (9). The crude product was synthesized according to the general method 1 and purified by flash column chromatography on silica gel (C_6H_{14}:EtOAc, 3:1) to give the oxime as a clear oil (yield 76%). R_f 0.23 (C_6H_{14}:EtOAc, 3:1); IR ($CHCl_3$, cm^{-1}) 3342, 2954, 1682, 1458, 1254, 1167; ^1H NMR ($CDCl_3$) δ [9.17, 8.89 (br, 1H)], [7.37, 6.77 (br d, 1H)], [4.98, 4.51 (br d, 1H)] 4.21–3.94 (m, 2H), 1.60–1.17 (m, 15H); MS (*m/e*) 245 (M^++1), 229, 189, 173, 145, 129, 113, 84, 70; $[\alpha]_D^{23}$ −33.8 (*c* 1.13; $CHCl_3$).

3-(*tert*-Butyloxycarbonyl)-2,2,5-trimethyl (*S*)-4-oxazolidine aldoxime (10). The product was synthesized according to the general method 1 and recrystallized from ethyl acetate–hexane to give a white solid (yield 81%). R_f 0.11 (C_6H_{14}:EtOAc, 5:1); IR ($CHCl_3$, cm^{-1}) 3370, 2980, 2935, 1690, 1386, 1254, 1131, 760; ^1H NMR (C_6D_6) δ 8.16 (s, 1H), 7.33 (d, J=5.7 Hz, 1H), 3.92 (dd, J=14.4, 7.5 Hz, 1H), 3.86 (m, 1H), 1.66 (s, 3H), 1.49 (s, 3H), 1.41 s, 9H), 1.14 (d, J=5.9 Hz, 3H); ^{13}C NMR (C_6D_6) δ 152.1, 150.4, 94.7, 80.3, 73.7, 63.3, 29.4, 27.1, 25.7, 16.6; MS (*m/e*) 258 (M^+), 243, 203, 187, 143, 84, 57, 43; mp 107–108.5 °C; $[\alpha]_D^{24}$ −25.4 (*c* 4.5; $CHCl_3$); Anal. calcd for $C_{12}H_{22}O_4N_2$: C, 55.79; H, 8.58; N, 10.85. Found: C, 55.52; H, 8.32; N, 10.67.

N-(*tert*-Butyloxycarbonyl)-*O*-(*tert*-butyldimethylsilyl)-L-threoninal oxime (11). The product was synthesized according to the general method 1 and purified by flash column chromatography on silica gel (C_6H_{14}:EtOAc, 10:1) to give the oxime as a clear oil (yield 78%). R_f 0.20 (C_6H_{14}:EtOAc, 5:1); IR ($CHCl_3$, cm^{-1}) 3345, 2926, 1700, 1489, 1377, 1253, 1169, 1006, 777; ^1H NMR ($CDCl_3$) δ 7.95 (br, 1H), 7.42 (d, J=3.9 Hz, 1H), 5.18 (br, 1H), 4.25 (m, 1H), 4.08 (m, 1H), 1.44 (s, 9H), 1.09 (d, J=6.2 Hz, 3H), 0.87 (s, 9H), 0.06 (s, 6H); ^{13}C NMR ($CDCl_3$) δ 155.8, 150.1, 0.00, 69.4, 55.7, 28.4, 25.8, 19.5, 17.9, −4.5, −4.6; MS (*m/e*) 332 (M^+), 277, 219, 159, 115, 83, 73, 57, 43; $[\alpha]_D^{24}$ +8.29 (*c* 4.01; $CHCl_3$).

N-(*tert*-Butyloxycarbonyl)-L-tyrosinal oxime (12). The product was synthesized according to the general method 1 and recrystallized from ethyl acetate–hexane to give a white solid (yield 83%). R_f 0.48, 0.37 (C_6H_{14}:EtOAc, 1:1); ^{1}H NMR (CD3OD) δ 7.28 (t, J=8.5 Hz, 2H), 6.69 (d, J=8.5 Hz, 2H), 6.58 (d, J=5.9 Hz, 5H), 4.90 (m, 1H), 4.30 (br, 1H), 2.94–2.68 (m, 2H), 1.35 (s, 9H); ^{13}C NMR (CD_3OD) δ (157.8, 157.3), (152.9, 151.4), 131.6, 130.1, 116.3, 80.5, 39.7, 37.9, 28.9; MS (*m/e*) 280 (M^+), 224, 163, 118, 107, 91, 73; mp 130–133 °C(dec); $[\alpha]_D^{22}$+34.3 (*c* 1.02;, CH_3OH)); Anal. calcd for $C_{14}H_{20}O_4N_2$: C, 59.97; H, 7.20; N, 9.99. Found: C, 59.05; H, 7.28; N, 9.50.

N^{α},N^{im}-Bis(*tert*-Butyloxycarbonyl)-L-histidinal oxime (13). The product was synthesized according to the general method 1 and recrystallized from ethyl acetate–hexane to give a white solid (yield 76%). R_f 0.33, 0.15 (C_6H_{14}:EtOAc, 1:1); ^{1}H NMR ($CDCl_3$) δ 9.82 (br, 1H), 8.02 (s, 1H), 7.50 (d, J=4.4 Hz, 1H), 7.18 (s, 1H), 5.72 (br, 1H), 4.58 (br, 1H), 2.98 (m, 2H), 1.59 (s, 9H),1.40 (s, 9H); ^{13}C NMR ($CDCl_3$) δ 156.1, 150.6, 147.5, 139.8, 137.3, 115.3, 86.3, 80.1, 50.7, 32.0, 28.9, 28.5; MS (*m/e*) 355 (M^++1), 299, 225, 182, 126, 82, 73; $[\alpha]_D^{24}$+1.12 (*c* 1.07; MeO); Anal. calcd for $C_{16}H_{26}O_5N_4$: C, 54.22; H, 7.39; N, 15.81. Found: C, 53.51; H, 7.35; N, 15.42.

General method 2: asymmetric 1,3-dipolar cycloaddition using NBS/Et_3N

To a precooled (0 °C) solution of NBS (2.3 mmol), pyridine (0.57 mmol) in THF (6 mL) was added oxime (1.9 mmol) in THF (6 mL). The resulting mixture was stirred at 50 °C for 1 h. N-Acryloyl camphor sultam (1.0 mmol) in toluene (60 mL) was added, and Et_3N (2.1 mmol) was added dropwise. After being stirred for 4 h, the mixture was extracted with ethyl acetate twice. The combined organic phase was washed with 5% $NaHCO_3$, H_2O, brine sequencely and dried over $MgSO_4$ and then concentrated to give a cycloadduct. The cycloadducts were purified by the flash column chromatography using silica gel.

General method 3: asymmetric 1,3-dipolar cycloaddition using NaOCl

To a precooled (0 °C) solution of N-acryloyl camphor sultam (4.7 mmol) in ethyl acetate (40 mL) was added dropwise an oxime (5.6 mmol) in ethyl acetate (40 mL), NaOCl (14 mmol) over 30 min. After stirring for 2 h, the mixture was extracted with ethyl acetate and washed with brine, dried over $MgSO_4$ and then concentrated. The residue was chromatographed on silica gel to give a cycloadducts.

3-[(1*S*)-N-(*tert*-Butyloxycarbonyl)aminoethyl]-5-[(2*R*)-(bornane-10,2-sultamyl)-N-carbonyl]-(5*R*)-Δ^2-isoxazoline (14). The product was synthesized according to the general method 3. Chromatography on silica gel (C_6H_{14}:EtOAc, 4:1) provided the cycloadduct **14** as a clear oil (yield 80%). R_f 0.17 (C_6H_{14}:EtOAc, 2:1); IR ($CHCl_3$, cm^{-1}) 3369, 2957, 1702, 1333, 1167, 760; ^{1}H NMR ($CDCl_3$) δ 5.53 (dd, J=6.8, 10.6 Hz, 1H), 4.96 (br, 1H), 4.55 (br, 1H), 3.93 (dd, J=5.0, 7.5 Hz, 1H), 3.54 (d, J=14.3 Hz, 1H), 3.45 (d, J=13.7 Hz, 1H), 3.45–3.16 (m, 2H), 3.08 (m, 1H), 2.18–2.04 (m, 2H), 1.99–1.87 (m, 3H), 1.44 (s, 9H), 1.41 (d, J=6.8 Hz, 3H), 1.18 (s, 2H), 1.12 (d, J=14.9 Hz, 1H), 0.98 (s, 2H), 0.93 (d, J=18.7 Hz, 1H); ^{13}C NMR ($CDCl_3$) δ 168.9, 160.1, 155.5, 81.6, 77.9, 67.7, 65.6, 53.5, 49.6, 48.2, 45.2, 38.6, 33.4, 28.9, 26.9, 21.5, 20.5, 19.6; $[\alpha]_D^{24}$ −190.7 (*c* 1.18; $CHCl_3$).

3-[(1*S*)-N-(*tert*-Butyloxycarbonyl)amino-2-methylpropyl]-5-[(2*R*)-(bornane-10,2-sultamyl)-N-carbonyl]-(5*R*)-Δ^2-isoxazoline (15). The product was synthesized according to the general method 3. Chromatography on silica gel (C_6H_{14}:EtOAc, 4:1) provided the cycloadduct **15** as a white solid (yield 71%). R_f 0.29 (C_6H_{14}:EtOAc, 2:1); IR ($CHCl_3$, cm^{-1}) 3361, 2959, 1702, 1507, 1334, 1168, 759; ^{1}H NMR ($CDCl_3$) δ 5.50 (dd, J=6.9, 10.7 Hz, 1H), 4.85 (br, 1H), 4.36 (br, 1H), 3.88 (dd, J=5.1, 7.6 Hz, 1H), 3.50 (d, J=13.8 Hz, 1H), 3.40 (d, J=13.8 Hz, 1H), 3.40–3.25 (m, 2H), 2.05 (m, 3H), 1.86 (m, 3H), 1.40 (s, 9H), 1.14 (s, 3H), 0.94 (m, 11H); ^{13}C NMR ($CDCl_3$) δ 169.1, 158.7, 156.1, 77.9, 65.9, 54.5, 53.6, 49.7, 48.5, 45.4, 40.6, 38.8, 33.5, 31.8, 28.9, 27.1, 21.5, 20.5, 20.0, 18.2; mp 195–198 °C (dec); MS (*m/e*) 484 (M^+), 384, 340, 185, 141, 109; $[\alpha]_D^{24}$ −191.7 (*c* 1.76; $CHCl_3$).

3-[(1*S*)-N-(*tert*-Butyloxycarbonyl)amino-3-methylbutyl]-5-[(2*R*)-(bornane-10,2-sultamyl)-N-carbonyl]-(5*R*)-Δ^2-isoxazoline (16). The product was synthesized according to the general method 2. Chromatography on silica gel (C_6H_{14}:EtOAc, 4:1) provided the cycloadduct **16** as a clear oil (yield 61%). Using the general method 3, the cycloadduct **16** was provided after chromatography (yield 86%). R_f 0.18 (C_6H_{14}:EtOAc, 3:1); IR ($CHCl_3$, cm^{-1}) 3358, 2947, 1701, 1509, 1334, 1167, 758; ^{1}H NMR ($CDCl_3$) δ 5.47 (dd, J=6.9, 10.9 Hz, 1H), 4.61 (br, 1H), 4.50 (br, 1H), 3.88 (dd, J=5.0, 7.6 Hz, 1H), 3.48 (d, J=13.8 Hz, 1H), 3.41 (d, J=13.7 Hz, 1H), 3.37–3.06 (m, 2H), 2.11–1.99 (m, 2H), 1.91–1.85 (m, 3H), 1.72–1.58 (m, 3H), 1.55–1.28 (m, 12H), 1.15 (s, 3H), 0.95 (s, 3H), 0.91 (d, J=6.3 Hz, 6H); ^{13}C NMR ($CDCl_3$) δ 166.4, 159.1, 155.1, 80.0, 77.2, 65.3, 62.9, 52.9, 49.0, 47.8, 44.8, 42.1, 39.0, 38.1, 32.9, 31.9, 28.3, 26.6, 26.4, 24.6, 22.8, 22.0, 20.6, 19.8; MS (*m/e*) 442 (M^+−55), 398, 340, 199, 155, 130, 86, 57; $[\alpha]_D^{30}$ −160.7 (*c* 2.1; $CHCl_3$).

3-[(1*S*)-N-(*tert*-Butyloxycarbonyl)amino-2-phenylethyl]-5-[(2*R*)-(bornane-10,2-sultamyl)-N-carbonyl]-(5*R*)-Δ^2-isoxazoline (17). The product was synthesized according to the general method 2. Chromatography on silica gel (C_6H_{14}:EtOAc, 4:1) provided the cycloadduct **17** as a clear oil (yield 69%). Using the general method 3, the cycloadduct **17** was provided after chromatography (yield 79%). The product was recrystallized from ethyl acetate–hexane to give a white solid. R_f 0.14 (C_6H_{14}:EtOAc, 3:1); IR ($CHCl_3$, cm^{-1}) 3367, 2960, 1702, 1505, 1334, 1167, 756; ^{1}H NMR ($CDCl_3$) δ 7.29–7.17 (m, 5H), 5.45 (dd, J=6.9, 10.9 Hz,

1H), 4.83 (br, 1H), 4.69 (br, 1H), 3.88 (dd, J=5.0, 7.7 Hz, 1H), 3.48 (d, J=13.8 Hz, 1H), 3.38 (d, J=13.8 Hz, 1H), 3.30 (dd, J=9.7, 17.4 Hz, 1H), 3.16–2.96 (m, 4H), 2.14–2.0 (m, 2H), 1.88 (m, 3H), 1.60–1.39 (m, 12H), 1.16 (s, 3H), 0.95 (s, 3H); ^{13}C NMR ($CDCl_3$) δ 168.2, 158.5, 154.7, 136.6, 129.5, 129.4, 126.8, 79.9, 77.4, 65.3, 52.9, 49.0, 47.7, 44.8, 39.7, 39.5, 38.1, 32.9, 28.2, 26.4, 20.8, 19.8; MS (*m/e*) 531 (M^+), 475, 432, 384, 340, 163, 135, 97, 91, 57; mp 183–185 °C; $[\alpha]_D^{24}$ −198.6 (*c* 2.4; $CHCl_3$); Anal. calcd for $C_{27}H_{37}O_6N_3S$: C, 60.99; H, 7.01; N, 7.90. Found: C, 61.40; H, 6.88; N, 7.91.

3-[(1*S*)-N-(*tert*-Butyloxycarbonyl)amino-2-cyclohexylethyl]-5-[(2*R*)-(bornane-10,2-sultamyl)-N-carbonyl]-(5*R*)-Δ²-isoxazoline (18). The product was synthesized according to the general method 3. Chromatography on silica gel (C_6H_{14}:EtOAc, 4:1) provided the cycloadduct **18** as a clear oil (yield 83%). R_f 0.21 (C_6H_{14}:EtOAc, 3:1); IR ($CHCl_3$, cm^{-1}) 3363, 2935, 2851, 1701, 1508, 1334, 1168, 758; ^{1}H NMR ($CDCl_3$) δ 5.47 (dd, J=6.8, 10.9 Hz, 1H), 4.63 (br, 1H), 4.54 (br, 1H), 3.89 (dd, J=5.0, 7.6 Hz, 1H), 3.50 (d, J=13.8 Hz, 1H), 3.40 (d, J=13.8 Hz, 1H), 3.21 (m, 2H), 2.12–2.0 (m, 2H), 1.91–1.75 (m, 3H), 1.66 (m, 5H), 1.52–1.37 (m, 11H), 0.95 (s, 3H), 1.24–1.10 (m, 7H), 0.94–0.86 (m, 5H); ^{13}C NMR ($CDCl_3$) δ 168.3, 159.3, 155.1, 77.2, 77.1, 65.2, 52.9, 48.0, 47.6, 44.7, 40.6, 38.1, 33.8, 33.6, 32.8, 32.6, 28.3, 26.4, 26.2, 26.0, 20.6, 19.8; MS (*m/e*) 538 (M^+), 239, 151, 126, 97; $[\alpha]_D^{30}$ −170.2 (*c* 2.08; $CHCl_3$).

3-[(1*S*)-N-(*tert*-Butyloxycarbonyl)amino-2-(4-*O*-*tert*-butyldimethylsilyl)oxyphenyl]-5-[(2*R*)-(bornane-10,2-sultamyl)-N-carbonyl]-(5*R*)-Δ²-isoxazoline (19). The product was synthesized according to the general method 3. Chromatography on silica gel (C_6H_{14}:EtOAc, 5:1) provided the cycloadduct **19** as a clear oil (yield 80%). R_f 0.32 (C_6H_{14}:EtOAc, 3:1); ^{1}H NMR ($CDCl_3$) δ 7.03 (d, J=8.4 Hz, 1H), 6.73 (d, J=8.4 Hz, 1H), 5.45 (dd, J=6.6, 11.0 Hz, 1H), 4.84 (br, 1H), 4.65 (br, 1H), 3.88 (dd, J=5.2, 7.6 Hz, 1H), 3.52–3.37 (m, 3H), 3.26 (m, 1H), 3.10–3.01 (m, 3H), 2.13–2.0 (m, 2H), 1.91–1.84 (m, 3H), 1.42–1.28 (m, 10H), 1.24–1.10 (m, 5H), 0.94–0.80 (m, 12H), 0.15 (s, 6H); $[\alpha]_D^{30}$ −151.4 (*c* 1.61; $CHCl_3$).

3-[(1*S*)-N-(*tert*-Butyloxycarbonyl)amino-2-phenylethyl]-5-[(2*S*)-(bornane-10,2-sultamyl)-N-carbonyl]-(5*S*)-Δ²-isoxazoline (20). The product was synthesized according to the general method 3. Chromatography on silica gel (C_6H_{14}:EtOAc, 5:1) provided the cycloadduct **20** as a white solid (yield 82%). Crystals of **20**, suitable for X-ray analysis, were obtained from ethyl ether–chloroform. R_f 0.34 (C_6H_{14}:EtOAc, 2:1); IR ($CHCl_3$, cm^{-1}) 3373, 2963, 1702, 1504, 1335, 1168, 757; ^{1}H NMR ($CDCl_3$) δ 7.29 (m, 5H), 5.49 (dd, J=7.4, 10.6 Hz, 1H), 4.81 (br, 1H), 4.69 (br, 1H), 3.89 (dd, J=5.1, 7.6 Hz, 1H), 3.50 (d, J=13.7 Hz, 1H), 3.40 (d, J=13.8 Hz, 1H), 3.31–3.12 (m, 3H), 3.00 (m, 1H), 2.14–2.01 (m, 2H), 1.94–1.67 (m, 3H), 1.35 (m, 12H), 1.16 (s, 3H), 0.96 (s, 3H); ^{13}C NMR ($CDCl_3$) δ 168.2, 158.6, 136.4, 129.5, 129.5, 128.5, 126.8, 65.3, 52.9, 49.0, 47.8, 44.7, 39.9, 39.1, 38.1, 32.9, 28.2, 26.4, 20.8, 19.8; MS (*m/e*) 531 (M^+), 475, 384, 340, 163, 135, 97, 91, 69; mp 184–185.5 °C; $[\alpha]_D^{30}$ +160.2 (*c* 1.00; $CHCl_3$).

3-[(2*S*,4*S*)-3-N-(*tert*-Butyloxycarbonyl)-2-(*tert*-butyl)-4-oxazolidinyl]-5-[(2*R*)-(bornane-10,2-sultamyl)-N-carbonyl]-(5*R*)-Δ²-isoxazoline (21). The product was synthesized according to the general method 2. Chromatography on silica gel (C_6H_{14}:EtOAc, 4:1) provided the cycloadduct **21** as a clear oil (yield 57%). R_f 0.43 (C_6H_{14}:EtOAc, 2:1) IR ($CHCl_3$, cm^{-1}) 2955, 1704, 1347, 1272, 1166, 1136; ^{1}H NMR ($CDCl_3$) δ 5.52 (dd, J=7.2, 11.1 Hz, 1H), 5.03 (S, 1H), 4.78 (dd, J=4.8, 7.4 Hz, 1H), 4.52 (dd, J=4.7, 8.7 Hz, 1H), 4.08 (t, J=8.2 Hz, 1H), 3.90 (dd, J=5.5, 7.1 Hz, 1H), 3.48 (d, J=13.8 Hz, 1H), 3.42 (d, J=13.8 Hz, 1H), 3.45 (m, 2H), 2.08 (m, 2H), 1.88 (m, 3H), 1.46 (S, 9H), 1.45–1.29 (m, 2H), 1.15 (s, 3H), 0.95 (s, 3H), 0.88 (S, 9H); ^{13}C NMR ($CDCl_3$) δ 168.3, 157.3, 155.5, 97.5, 81.7, 77.6, 66.2, 65.3, 55.6, 52.9, 49.0, 47.9, 44.6, 40.3, 38.0, 37.1, 32.9, 28.2, 26.4, 25.9, 20.8, 19.9; MS (*m/e*) 482 (M+-57), 466, 438, 424, 382, 135, 108, 57; $[\alpha]_D^{28}$ −185.0 (*c* 1.0; $CHCl_3$).

3-[(2*S*,4*S*)-3-N-(*tert*-Butyloxycarbonyl)-2-(*tert*-butyl)-4-oxazolidinyl]-5-[(2*S*)-(bornane-10,2-sultamyl)-N-carbonyl]-(5*S*)-Δ²-isoxazoline (22). The product was synthesized according to the general method 2. Chromatography on silica gel (C_6H_{14}:EtOAc, 4:1) provided the cycloadduct **22** as a clear oil (yield 48%). R_f 0.43 (C_6H_{14}:EtOAc, 2:1); IR ($CHCl_3$, cm^{-1}) 2958, 1703, 1314, 1273, 1165, 1136; ^{1}H NMR ($CDCl_3$) δ 5.50 (dd, J=7.1, 11.1 Hz, 1H), 5.02 (S, 1H), 4.81 (dd, J=3.9, 7.3 Hz, 1H), 4.58 (dd, J=3.9, 8.7 Hz, 1H), 4.01 (dd, J=7.4, 8.5 Hz, 1H), 3.90 (dd, J=5.0, 7.7 Hz, 1H), 3.52 (d, J=13.9 Hz, 1H), 3.42 (d, J=13.9 Hz, 1H), 3.52–3.30 (m, 2H), 2.13–2.01 (m, 2H), 1.92–1.84 (m, 3H), 1.46 (s, 9H), 1.42–1.33 (m, 2H), 1.16 (s, 3H), 0.96 (s, 3H), 0.86 (s, 9H); ^{13}C NMR ($CDCl_3$) δ 168.3, 156.9, 155.4, 97.4, 81.7, 77.5, 67.9, 65.3, 55.7, 52.9, 49.1, 47.9, 44.7, 40.4, 38.1, 36.9, 32.9, 28.2, 26.4, 25.9, 20.8, 19.8; MS (*m/e*) 482 (M^+ −57), 466, 438, 424, 382, 135, 107, 57; $[\alpha]_D^{28}$ +188.6 (*c* 1.0; $CHCl_3$).

3-[(4*S*)-3-carbobenzoxy-2,2-dimethyl-4-oxazolidinyl]-5-[(2*R*)-(bornane-10,2-sultamyl)-N-carbonyl]-(5*R*)-Δ²-isoxazoline (23). The product was synthesized according to the general method 2. Chromatography on silica gel (C_6H_{14}:EtOAc, 2:1) provided the cycloadduct **23** as a clear oil (yield 66%). The product was recrystallized from ethyl acetate–hexane to give a white solid. Crystals of **23**, suitable for X-ray analysis, were obtained from ethyl ether. R_f 0.25 (C_6H_{14}:EtOAc, 2:1); IR ($CHCl_3$, cm^{-1}) 2965, 1703, 1509, 1404, 1342, 1136, 756; ^{1}H NMR (C_6D_6, 73 °C) δ 7.99–7.81 (m, 5H), 6.36 (dd, J=5.8, 10.9 Hz, 1H), 5.82 (d, J=12.3 Hz, 1H), 5.66 (d, J=12.3 Hz, 1H), 5.36 (dd, J=2.3, 6.5 Hz, 1H), 4.56 (dd, J=2.3, 9.3 Hz, 1H), 4.36 (dd, J=6.7, 9.3 Hz, 1H), 4.29 (dd, J=4.9, 7.8 Hz, 1H), 4.07 (dd, J=5.7, 17.1 Hz, 1H), 3.63 (d, J=13.7 Hz, 1H), 3.49 (d, J=13.7 Hz, 1H), 2.71–2.62 (m, 1H), 2.47 (dd, J=7.9, 13.9 Hz, 1H), 2.33 (s, 3H), 2.10 (s, 3H), 2.08–1.96 (m, 3H), 1.71

(s, 3H), 1.50–1.46 (m, 2H), 1.19 (s, 3H); ^{13}C NMR (C_6D_6, 73 °C) δ 168.8, 157.7, 152.4, 137.1, 128.8, 128.3, 127.7, 85.2, 77.9, 67.1, 66.8, 65.3, 54.7, 52.6, 48.6, 47.7, 45.1, 38.3, 37.7, 32.7, 26.5, 26.3, 23.6, 20.7, 19.6; MS (*m/e*) 545 ($M^+ - 55$), 530, 486, 303, 245, 190, 135, 91, 55; $[\alpha]_D^{24} - 234.2$ (*c* 2.71; $CHCl_3$).

3-[(4*S*)-3-N-(*tert*-Butyloxycarbonyl)-2,2,5-trimethyl-4-oxazolidinyl]-5-[(2*R*)-(bornane-10,2-sultamyl)-N-carbonyl]-(5*R*)-Δ²-isoxazoline (24). The product was synthesized according to the general method 2. Chromatography on silica gel (C_6H_{14}:EtOAc, 5:1) provided the cycloadduct **24** as a clear oil (yield 76%). R_f 0.24 (C_6H_{14}:EtOAc, 3:1); IR ($CHCl_3$, cm^{-1}) 2954, 1697, 1380, 1132, 758; ^{1}H NMR ($CDCl_3$) δ 5.51 (dd, J=6.2, 10.3 Hz, 1H), 4.22 (m, 1H), 4.02 (m, 1H), 3.87 (dd, J=5.2, 7.8 Hz, 1H), 3.50 (d, J=13.7 Hz, 1H), 3.40 (d, J=13.8 Hz, 1H), 3.18 (m, 2H), 2.06 (m, 2H), 1.86 (m, 3H), 1.58 (s, 3H), 1.48 (s, 3H), 1.40 (s, 9H), 1.30 (d, J=5.9 Hz, 3H), 1.14 (s, 3H), 0.94 (s, 3H); MS (*m/e*) 525 (M^+), 510, 410, 227, 183, 139, 98, 57, 41; $[\alpha]_D^{24}$ −232.9 (*c* 2.22; $CHCl_3$).

3-[(1*S*)-N-(*tert*-Butyloxycarbonyl)amino-2-*O*-(*tert*-butyldimethylsilyl)oxypropyl]-5-[(2*R*)-(bornane-10,2-sultamyl)-N-carbonyl]-(5*R*)-Δ²-isoxazoline (25). The product was synthesized according to the general method 2. Chromatography on silica gel (C_6H_{14}:EtOAc, 5:1) to give the cycloadduct **25** as a clear oil (yield 44%). R_f 0.30 (C_6H_{14}:EtOAc, 3:1); IR ($CHCl_3$, cm^{-1}) 3341, 2935, 1707, 1489, 1335, 1168, 765; ^{1}H NMR ($CDCl_3$) δ 5.47 (dd, J=7.8, 10.4 Hz, 1H), 5.22 (br, 1H), 4.37 (br, 1H), 3.87 (dd, J=5.0, 7.5 Hz, 1H), 3.48 (d, J=13.7 Hz, 1H), 3.39 (d, J=13.8 Hz, 1H), 3.30 (m, 2H), 2.09 (m, 2H), 1.88 (m, 4H), 1.41 (s, 3H), 1.15 (s, 3H), 1.11 (d, J=2.7 Hz, 3H), 0.95 (s, 3H), 0.83 (s, 9H), 0.06 (s, 6H); ^{13}C NMR ($CDCl_3$) δ 168.2, 157.3, 130.6, 68.9, 65.3, 54.8, 52.9, 49.0, 47.6, 44.7, 40.6, 38.1, 32.9, 28.3, 26.4, 25.8, 20.6, 19.8, 19.3, 17.9, −4.6, −4.8; MS (*m/e*) 599 (M^+), 543, 486, 385, 159, 130, 73, 57, 41; mp 163–166 °C; $[\alpha]_D^{24} - 148.8$ (*c* 2.56; $CHCl_3$); Anal. calcd for $C_{28}H_{49}O_7N_3SiS$: C, 56.07; H, 8.23; N, 7.01. Found: C, 55.91; H, 8.32; N, 6.98.

General method 4: removal of chiral auxiliary

To a solution of cycloadduct (0.7 mmol) in 2:1, THF:H_2O (6 mL) was added LiOH·H_2O (6 mmol). After being stirred for 2–5 h, the mixture was diluted with water (5 mL) and extracted with CH_2Cl_2 to recover the chiral auxiliary. The aqueous phase was acidified with solid $KHSO_4$ (or 1 N HCl) to pH 2–3 and then extracted with ethyl acetate, dried over $MgSO_4$ and concentrated to give a carboxylic acid which was used without further purification.

General method 5: esterification of carboxylic acid using MeOH/H_2SO_4

To a solution of carboxylic acid (0.4 mmol) in MeOH (1.5 mL) was added catalytic amount of H_2SO_4. After 12 h at room temperature, the mixture was diluted with 5% $NaHCO_3$ and extracted with CH_2Cl_2, dried over $MgSO_4$ and concentrated. The product was purified by flash chromatography on silica gel.

General method 6: esterification of carboxylic acid using diazomethane

To a solution of carboxylic acid (0.1 mmol) in diethyl ether was added diazomethane in diethyl ether until a yellow color persisted. The reaction mixture was concentrated and purified by flash chromatography.

General method 7: esterification of carboxylic acid using CH_3I/$NaHCO_3$

To a solution of carboxylic acid (1.5 mmol) in DMF (10 mL) was added solid $NaHCO_3$ (4.5 mmol), CH_3I (7.5 mmol). After 12 h at room temperature, the mixture was diluted with water (15 mL) and extracted with ethyl acetate twice. The organic phase was washed with 5% sodium thiosulfate, 5% $NaHCO_3$, 10% citric acid and brine successively, dried over $MgSO_4$ and concentrated. The product was purified by flash chromatography on silica gel.

General method 8: esterification of carboxylic acid using C_2H_5I/CsF

To a solution of carboxylic acid (1.24 mmol) in DMF (5 mL) was added CsF (1.86 mmol), C_2H_5I (1.86 mmol). After 15 h, the mixture was diluted with 5% $NaHCO_3$ and extracted with ethyl acetate, dried over $MgSO_4$, and concentrated. The product was purified by flash chromatography on silica gel.

(1′*S*, 5*R*)-3-[1-N-(*tert*-Butyloxycarbonyl)aminoethyl]-5-methoxycarbonyl-Δ²-isoxazoline (26). The chiral auxiliary was removed according to the general method 4 and esterification according to the general method 5 afforded the compound. Purification by flash chromatography (C_6H_{14}:EtOAc, 4:1) gave **26** as a clear oil (yield 52%). R_f 0.20 (C_6H_{14}:EtOAc, 2:1); IR ($CHCl_3$, cm^{-1}) 3366, 2980, 1740, 1687, 1512, 1320, 1167; ^{1}H NMR ($CDCl_3$) δ 4.99 (t, J=9.0 Hz, 1H), 4.89 (br, 1H), 4.50 (br, 1H), 3.75 (s, 3H), 3.25 (d, J=8.9 Hz, 2H), 1.41 (s, 9H), 1.38 (d, J=6.9 Hz, 3H); MS (*m/e*) 273 ($M^+ + 1$), 217, 157, 113, 96, 70; $[\alpha]_D^{24} - 185.7$ (*c* 1.05; $CHCl_3$).

(1′*S*,5*R*)-3-[1-N-(*tert*-Butyloxycarbonyl)amino-2-methylpropyl]-5-ethoxycarbonyl-Δ²-isoxazoline (27). The chiral auxiliary was removed according to the general method 4, and esterification according to the general method 8 afforded the compound. Purification by flash chromatography (C_6H_{14}:EtOAc, 4:1) gave **27** as a white solid (yield 67%). R_f 0.23 (C_6H_{14}:EtOAc, 3:1); IR ($CHCl_3$, cm^{-1}) 3347, 2965, 1715, 1707, 1515, 1367, 1169; ^{1}H NMR ($CDCl_3$) δ 4.96 (t, J=8.9 Hz, 1H), 4.82 (br, 1H), 4.33 (br, 1H), 4.22 (dd, J=16.0, 7.2 Hz, 1H), 3.22 (d, J=8.9 Hz, 2H), 2.02 (br, 1H), 1.42 (s, 9H),

1.28 (t, $J=7.0$ Hz, 3H), 0.99–0.89 (m, 6H); ^{13}C NMR ($CDCl_3$) δ 170.8, 159.0, 156.2, 80.6, 77.9, 62.5, 54.6, 40.7, 31.6, 28.9, 19.9, 18.1, 14.7; MS (*m/e*) 315 ($M^+ + 1$), 259, 215, 185, 171, 141, 116, 72; $[\alpha]_D^{24} -145.9$ (*c* 1.08; $CHCl_3$).

(1′*S*,5*R*)-3-[1-N-(*tert*-Butyloxycarbonyl)amino-3-methylbutyl]-5-methoxycarbonyl-Δ²-isoxazoline (28). The chiral auxiliary was removed according to the general method 4 and esterification according to the general method 5 afforded the compound. Purification by flash chromatography (C_6H_{14}:EtOAc, 3:1) gave **28** as a clear oil (yield 76%). R_f 0.30 (C_6H_{14}:EtOAc, 3:1); IR ($CHCl_3$, cm^{-1}) 3349, 2958, 1744, 1706, 1516, 1367, 1169; ^{1}H NMR ($CDCl_3$) δ 4.95 (t, $J=8.4$ Hz, 1H), 4.69 (d, $J=8.4$ Hz, 1H), 4.49 (m, 1H), 3.74 (s, 3H), 3.22 (d, $J=7.9$ Hz, 2H), 1.72–1.49 (m, 3H), 1.40 (s, 9H), 0.90 (d, $J=6.3$ Hz, 6H); ^{13}C NMR ($CDCl_3$) δ 170.5, 159.4, 155.2, 80.0, 77.3, 52.5, 47.1, 41.6, 39.3, 28.3, 24.6, 22.8, 21.9; MS (*m/e*) 315 ($M^+ + 1$), 215, 199, 155, 138, 86, 57; HRMS (EI) calcd for $C_{15}H_{27}O_5N_2$ *m/e* 315.1921 $(MH)^+$, found 315.1909; $[\alpha]_D^{24} -163.4$ (*c* 2.36; $CHCl_3$).

(1′*S*,5*R*)-3-[1-N-(*tert*-Butyloxycarbonyl)amino-2-phenylethyl]-5-methoxycarbonyl-Δ²-isoxazoline (29). The chiral auxiliary was removed according to the general method 4 and esterification according to the general method 5 afforded the compound. Purification by flash chromatography (C_6H_{14}:EtOAc, 5:1) gave **29** as a white solid (yield 69%). R_f 0.30 (C_6H_{14}:EtOAc, 3:1); IR ($CHCl_3$, cm^{-1}) 3356, 2965, 1715, 1510, 1367, 1231, 1178, 756; ^{1}H NMR ($CDCl_3$) δ 7.33–7.16 (m, 5H), 4.99 (br, 1H), 4.49 (dd, $J=5.1$, 10.3 Hz, 2H), 3.78 (s, 3H), 3.21–3.08 (m, 2H), 2.97–2.89 (m, 2H), 1.42 (s, 9H); ^{13}C NMR ($CDCl_3$) δ 170.4, 158.8, 154.0, 136.5, 129.3, 128.6, 126.9, 80.2, 77.4, 52.6, 50.0, 40.7, 39.5, 28.3; MS (*m/e*) 349 ($M^+ + 1$), 293, 257, 201, 157, 91, 57; $[\alpha]_D^{24} -134.2$ (*c* 0.86; $CHCl_3$).

(1′*S*,5*R*)-3-[1-N-(*tert*-Butyloxycarbonyl) amino-2-cyclohexylethyl]-5-methoxycarbonyl-Δ²-isoxazoline (30). The chiral auxiliary was removed according to the general method 4 and esterification according to the general method 7 afforded the compound. The product was recrystallized from ethyl acetate–hexane to give a white needle (yield 67%). R_f 0.32 (C_6H_{14}:EtOAc, 3:1); IR ($CHCl_3$, cm^{-1}) 3349, 2925, 2851, 1720, 1514, 1366, 1170, 758; ^{1}H NMR ($CDCl_3$) δ 4.96 (dd, $J=8.4$, 9.7 Hz, 1H), 4.70 (d, $J=8.5$ Hz, 1H), 4.53 (br m, 1H), 3.74 (s, 3H), 3.21 (d, $J=8.9$ Hz, 2H), 1.77–1.73 (m, 1H), 1.65 (5, 5H), 1.53–1.43 (m, 1H), 1.40 (s, 9H), 1.36–1.09 (m, 5H), 0.93–0.81 (m, 2H); ^{13}C NMR ($CDCl_3$) δ 170.6, 159.5, 155.2, 80.0, 77.3, 52.6, 40.4, 33.8, 33.5, 32.6, 28.2, 26.3, 26.1, 25.9; $[\alpha]_D^{24} -118.9$ (*c* 2.93; $CHCl_3$).

(1′*S*,5*S*)-3-[1-N-(*tert*-Butyloxycarbonyl)amino-2-phenylethyl]-5-methoxycarbonyl-Δ²-isoxazoline (31). The chiral auxiliary was removed according to the general method 4 and esterification according to the general method 7 afforded the compound. The product was recrystallized from ethyl acetate–hexane to give a white needle (yield 94%). R_f 0.31 (C_6H_{14}:EtOAc, 2:1); IR ($CHCl_3$, cm^{-1}) 3344, 2974, 1717, 1514, 1169, 757; ^{1}H NMR ($CDCl_3$) δ 7.29–7.16 (m, 5H), 4.95 (dd, $J=6.5$, 11.5 Hz, 1H), 4.89 (br, 1H), 4.68 (br m, 1H), 3.76 (s, 3H), 3.23–2.97 (m, 4H), 1.37 (s, 9H); ^{13}C NMR ($CDCl_3$) δ 170.4, 158.7, 154.9, 136.3, 129.4, 128.6, 126.9, 52.6, 49.8, 40.3, 39.4, 28.2; MS (*m/e*) 348 (M^+), 292, 257, 201, 157, 91; $[\alpha]_D^{24} +69.2$ (*c* 1.06; $CHCl_3$). Anal. calcd for $C_{18}H_{24}O_5N_2$: C, 62.06; H, 6.94; N, 8.04. Found: C, 61.94; H, 7.02; N, 7.93.

(2′*R*,4′*S*,5*R*)-3-[3-N-(*tert*-Butyloxycarbonyl)-2-(*tert*-butyl)oxazolidinyl]-5-methoxycarbonyl-Δ²-isoxazoline (32). The chiral auxiliary was removed according to the general method 4 and esterification according to the general method 6 afforded the compound. Purification by flash chromatography (C_6H_{14}:EtOAc, 3:1) gave **32** as a white solid (yield 78%). R_f 0.38 (C_6H_{14}:EtOAc, 3:1); IR ($CHCl_3$, cm^{-1}) 2945, 1722, 1459, 1355, 1213, 1167; ^{1}H NMR ($CDCl_3$) δ 5.02 (dd, $J=7.8$, 10.0 Hz, 1H), 5.01 (s, 1H), 4.80 (dd, $J=4.1$, 7.4 Hz, 1H), 4.56 (dd, $J=4.1$, 8.6 Hz, 1H), 4.06 (br t, $J=7.6$, 8.7 Hz, 1H), 3.74 (s, 3H), 3.40–3.35 (m, 2H), 1.47 (s, 9H), 0.85 (s, 9H); ^{13}C NMR ($CDCl_3$) δ 170.8, 157.7, 155.7, 97.5, 81.8, 77.7, 68.0, 55.9, 52.6, 40.7, 36.9, 28.3, 25.9; MS (*m/e*) 356 (M^+), 292, 283, 241, 199, 149, 70, 57, 43; $[\alpha]_D^{26} -125.0$ (*c* 1.27; $CHCl_3$).

(2′*R*,4′*S*,5*S*)-3-[3-N-(*tert*-Butyloxycarbonyl)-2-(*tert*-butyl) oxazolidinyl]-5-methoxycarbonyl-Δ²-isoxazoline (33).The chiral auxiliary was removed according to the general method 4 and esterificated according to the general method 6 afforded the compound. Purification by flash chromatography (C_6H_{14}:EtOAc, 3:1) gave **33** as a clear oil (yield 83%). R_f 0.38 (C_6H_{14}:EtOAc, 3:1); IR ($CHCl_3$, cm^{-1}) 2940, 1723, 1355, 1307, 1169; ^{1}H NMR ($CDCl_3$) δ 5.02 (s, 1H), 4.98 (dd, $J=8.3$, 11.0 Hz, 1H), 4.83 (dd, $J=4.0$, 7.2 Hz, 1H), 4.57 (dd, $J=4.1$, 8.7 Hz, 1H), 4.04 (dd, $J=7.6$, 8.5 Hz, 1H), 3.77 (s, 3H), 3.40–3.30 (m, 2H), 1.47 (s, 9H), 0.87 (s, 9H); ^{13}C NMR ($CDCl_3$) δ 170.5, 157.2, 155.6, 87.4, 81.2, 77.7, 67.9, 55.8, 52.6, 40.6, 37.0, 29.7, 28.2, 25.9, 22.6; MS (*m/e*) 356 (M^+), 299, 284, 256, 241, 199, 149, 97, 70, 57; $[\alpha]_D^{26} -74.7$ (*c* 1.10; $CHCl_3$).

(1′*S*,5*R*)-3-[1-N-(*tert*-Butyloxycarbonyl)amino-2-hydroxyethyl]-5-methoxycarbonyl-Δ²-isoxazoline (34). The chiral auxiliary was removed according to the general method 4 and esterification according to the general method 5 afforded the compound. Purification by flash chromatography (C_6H_{14}:EtOAc, 3:1) gave **34** as a white solid (yield 47%). R_f 0.24 (C_6H_{14}:EtOAc, 1:1); IR ($CHCl_3$, cm^{-1}) 3405, 2968, 1717, 1511, 1367, 1168; ^{1}H NMR ($CDCl_3$) δ 5.24 (br d, $J=7.8$ Hz, 1H), 4.97 (t, $J=9.1$ Hz, 1H), 4.36–4.29 (br, 2H), 3.76 (s, 3H), 3.30 (d, $J=9.1$ Hz, 2H), 2.74 (br s, 1H), 1.42 (s, 9H), 1.20 (d, $J=6.3$ Hz, 3H); ^{13}C NMR ($CDCl_3$) δ 170.5, 158.7, 155.8, 80.3, 77.3, 67.4, 53.6, 52.7, 40.2, 28.3, 18.9; MS

(*m/e*) 303 (M^+), 247, 202, 125, 113, 74, 57; $[\alpha]_D^{24} - 170.7$ (*c* 1.07; $CHCl_3$).

(1′*S*,5*R*)-3-[1-N-(*tert*-Butyloxycarbonyl)amino-2-(4-hydroxyphenyl)ethyl]-5-methoxycarbonyl-Δ^2-isoxazoline (35). The chiral auxiliary was removed according to the general method 4 and esterification according to the general method 5 afforded the compound. Purification by flash chromatography (C_6H_{14}:EtOAc, 3:1) gave **35** as a clear oil (yield 66%). R_f 0.43 (C_6H_{14}:EtOAc, 1:1); IR ($CHCl_3$, cm^{-1}) 3353, 2925, 1707, 1515, 1229, 1166; ^1H NMR ($CDCl_3$) δ 7.03 (d, J=8.3 Hz, 2H), 6.72 (d, J=8.3 Hz, 2H), 5.52 (br, 1H), 4.93 (dd, J=6.8, 11.3 Hz, 2H), 4.65 (br, 1H), 3.76 (s, 3H), 3.13–2.98 (m, 4H), 1.39 (s, 9H); ^{13}C NMR ($CDCl_3$) δ 171.2, 159.5, 155.6, 131.1, 128.7, 116.2, 53.4, 50.7, 40.7, 39.3, 28.9; MS (*m/e*) 364 (M^+), 258, 170, 126, 107, 98, 84; $[\alpha]_D^{24} - 140.1$ (*c* 1.41; $CHCl_3$).

General method 9: reductive cleavage of Δ^2-isoxazoline

To a stirred solution of Δ^2-isoxazoline (6 mmol) in 5:1, MeOH:H_2O (70 mL) were added boric acid (12 mmol) and catalytic amount of freshly activated Raney–nickel. The mixture was stirred under H_2 (1 atm) until the reaction was judged complete by TLC analysis and then filtered through Celite and evaporated. The mixture was extracted with ethyl acetate, dried over $MgSO_4$ and concentrated. The product was purified by flash chromatography on silica gel.

Methyl (2*R*,5*S*)-5-(*tert*-butyloxycarbonyl)amino-2-hydroxy-4-oxohexanoate (36). The product was synthesized according to the general method 9. Chromatography on silica gel (C_6H_{14}:EtAOc, 1:1) gave **36** as a clear oil (yield 78%). R_f 0.32 (C_6H_{14}:EtAOc, 1:1); IR ($CHCl_3$, cm^{-1}) 3332, 2979, 1700, 1620, 1525, 1365, 1167; ^1H NMR ($CDCl_3$) δ 5.17 (br, 1H), 4.49 (dd, J=4.0, 6.2 Hz, 1H), 4.26 (br, 1H), 3.75 (s, 3H), 3.05–2.88 (m, 2H), 1.39 (s, 9H), 1.28 (d, J=7.2 Hz, 3H); MS (*m/e*) 275 (M^+), 219, 176, 144, 130, 120, 98, 73; $[\alpha]_D^{24} + 5.4$ (*c* 2.0; $CHCl_3$).

Ethyl (2*R*,5*S*)-5-(*tert*-butyloxycarbonyl) amino-2-hydroxy-6-methyl-4-oxoheptanoate (37). The product was synthesized according to the general method 9. Chromatography on silica gel (C_6H_{14}:EtAOc, 3:1) gave **37** as a clear oil (yield 91%). R_f 0.20 (C_6H_{14}:EtAOc, 3:1); IR ($CHCl_3$, cm^{-1}) 3394, 2954, 1715, 1506, 1171; ^1H NMR ($CDCl_3$) δ 5.07 (d, J=8.3 Hz, 1H), 4.42 (t, J=4.9 Hz, 1H), 4.17 (dd, J=6.9, 14.1 Hz, 2H), 3.36 (br, 1H), 3.02–2.86 (m, 2H), 2.13 (m, 1H), 1.37 (s, 9H), 1.21 (t, J=7.1 Hz, 3H), 0.94 (d, J=6.8 Hz, 3H), 0.75 (d, J=6.7 Hz, 3H); MS (*m/e*) 318 ($M^+ + 1$), 262, 218, 172, 128, 99, 83, 75; $[\alpha]_D^{24} + 30.2$ (*c* 2.92; $CHCl_3$).

Methyl (2*R*,5*S*)-5-(*tert*-butyloxycarbonyl)amino-2-hydroxy-7-methyl-4-oxooctanoate (38). The product was synthesized according to the general method 9. Chromatography on silica gel (C_6H_{14}:EtAOc, 3:1) gave **38** as a clear oil (yield 92%). R_f 0.33 (C_6H_{14}:EtAOc, 3:1); IR (neat, cm^{-1}) 3389, 2949, 1716, 1514, 1367, 1170; ^1H NMR ($CDCl_3$) δ 4.90 (br, 1H), 4.48 (dd, J=5.2, 10.1 Hz, 1H), 4.23 (br, 1H), 3.75 (s, 3H), 3.29 (br, 1H), 3.02–2.95 (m, 2H), 1.70–1.64 (m, 1H), 1.58–1.48 (m, 1H), 1.40 (s, 9H), 1.35–1.25 (m, 1H), 0.93 (d, J=4.1 Hz, 3H), 0.91 (d, J=4.1 Hz, 3H); ^{13}C NMR ($CDCl_3$) δ 207.8, 173.9, 80.1, 75.0, 67.0, 58.4, 52.5, 43.3, 39.9, 28.3, 24.8, 23.1, 21.7; MS (*m/e*) 318 ($M^+ + 1$), 262, 244, 218, 186, 130, 86, 57; $[\alpha]_D^{24} + 2.0$ (*c* 1.48; $CHCl_3$).

Methyl (2*R*,5*S*)-5-(*tert*-butyloxycarbonyl)amino-2-hydroxy-4-oxo-6-phenylhexanoate (39). The product was synthesized according to the general method 9. Chromatography on silica gel (C_6H_{14}:EtAOc, 3:1) gave **39** as a clear oil (yield 94%). R_f 0.14 (C_6H_{14}:EtAOc, 2:1); IR (neat, cm^{-1}) 3396, 2963, 1716, 1506, 1367, 1169; ^1H NMR ($CDCl_3$) δ 7.34–7.17 (m, 5H), 4.99 (br, 1H), 4.50 (dd, J=5.1, 10.3 Hz, 1H), 3.78 (s, 3H), 3.27 (br, 1H), 3.11 (dd, J=6.2, 14.1 Hz, 2H), 2.95 (br d, J=8.4 Hz, 2H), 1.41 (s, 9H); ^{13}C NMR ($CDCl_3$) δ 206.7, 173.8, 155.3, 136.2, 129.3, 128.7, 127.1, 80.3, 67.1, 60.8, 52.5, 43.9, 37.1, 28.3; MS (*m/e*) 352 ($M^+ + 1$), 296, 252, 220, 165, 120, 91, 57; $[\alpha]_D^{24} + 18.4$ (*c* 0.95; $CHCl_3$).

Methyl (2*R*,5*S*)-5-(*tert*-butyloxycarbonyl) amino-2-hydroxy-4-oxo-6-cyclohexylhexanoate (40). The product was synthesized according to the general method 9. Chromatography on silica gel (C_6H_{14}:EtAOc, 2:1) gave **40** as a clear oil (yield 82%). R_f 0.2 (C_6H_{14}:EtAOc, 2:1); IR (neat, cm^{-1}) 3387, 2924, 2851, 1717, 1512, 1171, 757; ^1H NMR ($CDCl_3$) δ 4.97 (br d, J=7.3 Hz, 1H), 4.51 (dd, J=4.8, 5.6 Hz, 1H), 4.32 (br, 1H), 3.78 (s, 3H), 3.30 (br, 1H), 3.00 (t, J=4.4 Hz, 2H), 1.87–1.83 (br, 1H), 1.71–1.56 (m, 5H), 1.49 (s, 9H), 1.43–1.12 (m, 5H), 1.01–0.86 (m, 2H); ^{13}C NMR ($CDCl_3$) δ 207.9, 173.9, 155.8, 80.1, 67.1, 57.8, 52.6, 43.3, 38.4, 34.1, 33.9, 32.5, 28.3, 26.4, 26.2, 25.9; MS (*m/e*) 358 ($M^+ + 1$), 302, 258, 226, 170, 126, 113, 97; $[\alpha]_D^{24} + 10.2$ (*c* 2.44; $CHCl_3$).

Methyl (2*S*,5*S*)-5-(*tert*-butyloxycarbonyl) amino-2-hydroxy-4-oxo-6-phenylhexanoate (41). The product was synthesized according to the general method 9. Chromatography on silica gel (C_6H_{14}:EtAOc, 2:1) gave **41** as a white needle (yield 87%). Crystals of **41**, suitable for X-ray analysis, were obtained from chloroform–hexane. R_f 0.17 (C_6H_{14}:EtAOc, 2:1); IR ($CHCl_3$, cm^{-1}) 3395, 2970, 1716, 1506, 1367, 1169, 755; ^1H NMR ($CDCl_3$) δ 7.31–7.13 (m, 5H), 5.01 (br, 1H), 4.50 (br, 2H), 3.75 (s, 3H), 3.17 (br, 1H), 3.08 (dd, J=6.3, 14.1, 2H), 3.02–2.81 (m, 2H), 1.38 (s, 9H); ^{13}C NMR ($CDCl_3$) δ 206.6, 173.9, 155.3, 135.9, 129.3, 128.6, 127.1,83.2, 80.2, 66.8, 60.5, 52.7, 44.0, 36.8, 28.2, 19.7; MS (*m/e*) 351 (M^+), 295, 252, 220, 164, 120, 84; mp 83–85 °C; $[\alpha]_D^{24} + 26.8$ (*c* 1.00; $CHCl_3$); Anal. calcd for

$C_{18}H_{25}O_6N$: C, 61.53; H, 7.17; N, 3.99. Found: C, 61.44; H, 7.06; N, 3.94.

Methyl (2*R*, 2′*S*, 4′*S*)-4-[3-N-(*tert*-butoxycarbonyl)-2-(*tert*-butyl)oxazolidinyl]-2-hydroxy-4-oxobutanoate (42). The product was synthesized according to the general method 9. Chromatography on silica gel (C_6H_{14}:EtOAc, 2:1) gave **42** as a clear oil (yield 86%). R_f 0.30 (C_6H_{14}:EtOAc, 2:1); IR (neat, cm^{-1}) 3470, 2946, 1719, 1464, 1359, 1167; ^1H NMR ($CDCl_3$) δ 5.02 (s, 1H), 4.58 (dd, J=4.2, 7.8 Hz, 1H), 4.48 (t, J=8.2 Hz, 1H), 4.42 (dd, J=4.2, 8.6 Hz, 1H), 3.92 (t, J=8.2 Hz, 1H), 3.76 (s, 3H), 3.28 (br d, J=5.7 Hz, 1H), 3.16 (d, J=4.1 Hz, 1H), 3.14 (d, J=6.3 Hz, 1H), 1.49 (s, 9H), 0.85 (s, 9H); ^{13}C NMR ($CDCl_3$) δ 205.6, 174.0, 155.9, 97.6, 82.2, 67.1, 66.3, 65.9, 52.7, 42.9, 37.3, 28.2, 25.8; MS (*m/e*) 359 (M^+), 302, 286, 258, 244, 202, 184, 142, 128, 71, 57; $[\alpha]_D^{25}$ −61.4 (*c* 1.43; $CHCl_3$).

Methyl (2*R*,5*S*)-5-(*tert*-butyloxycarbonyl) amino-2,6-dihydroxy-4-oxoheptanoate (43). The product was synthesized according to the general method 9. Chromatography on silica gel (C_6H_{14}:EtOAc, 1:1) gave **43** as a clear oil (yield 70%). R_f 0.23 (C_6H_{14}:EtOAc, 1:2); IR (neat, cm^{-1}) 3400, 2924, 2959, 1713, 1509, 1369, 1171, 757; ^1H NMR ($CDCl_3$) δ 5.38 (br d, J=7.2 Hz, 1H), 4.54 (br, 1H), 4.35 (br d, J=5.8 Hz, 1H), 4.14 (br d, J=7.2 Hz, 1H), 3.77 (s, 3H), 3.29 (br, 1H), 3.12–2.96 (m, 2H), 2.48 (br, 1H), 1.43 (s, 9H), 1.20 (d, J=6.4 Hz, 6H); ^{13}C NMR ($CDCl_3$) δ 174.0, 80.3, 67.3, 66.6, 64.9, 52.6, 43.5, 28.3, 19.5; MS (*m/e*) 306 (M^++1), 262, 250, 206, 188, 162, 118, 74, 57; $[\alpha]_D^{24}$ −13.8 (*c* 0.88; $CHCl_3$).

Methyl (2*R*,5*S*)-5-(*tert*-butyloxycarbonyl) amino-2-hydroxy-4-oxo-6-(4-hydroxyphenyl)hexanoate (44). The product was synthesized according to the general method 9. Chromatography on silica gel (C_6H_{14}:EtOAc, 1:1) gave **44** as a clear oil (yield 80%). R_f 0.16 (C_6H_{14}:EtOAc, 1:1); IR (neat, cm^{-1}) 3368, 2940, 1707, 1514, 1167; ^1H NMR ($CDCl_3$) δ 7.0 (d, J=8.2 Hz, 2H), 6.73 (d, 8.4 Hz, 2H), 5.21 (br, 1H), 5.02 (br, 1H), 4.45 (br t, 2H), 3.76 (s, 3H), 2.99 (dd, J=6.4, 14.1 Hz, 2H), 2.89 (br, 2H), 1.39 (s, 9H); ^{13}C NMR ($CDCl_3$) δ 207.9, 174.6, 155.9, 131.0, 127.9, 116.3, 81.1, 67.4, 61.4, 53.7, 44.7, 36.8, 28.9; MS (*m/e*) 368 (M^++1), 236, 180, 149, 131, 107, 97, 84; mp 123–125 °C; $[\alpha]_D^{26}$ −24.6 (*c* 1.18, CH_3OH); Anal. calcd for $C_{18}H_{25}O_7N$: C, 58.83; H, 6.86; N, 3.81. Found: C, 58.80; H, 7.09; N, 3.77.

5(*R*/*S*)-[2-(N-Carbobenzoxy-L-valyl)amino-1(*R*)-hydroxy-3-phenylpropyl]-3-(2-phenylethyl)-Δ²-isoxazoline (45). ^1H NMR ($CDCl_3$) δ 7.36–7.10 (m, 16H), 6.52 (d, J=9.4 Hz, 1H), 5.19–5.07 (m, 4H), 4.36 (br, 1H), 4.14 (dd, J=16.8, 8.1 Hz, 1H), 3.97 (br, 1H), 3.34 (d, J=8.1 Hz, 1H), 2.97 (br, 1H), 2.88 (d, J=7.5 Hz, 2H), 2.77 (t, J=8.1 Hz, 1H), 2.56 (m, 2H), 2.41 (dd, J=17.4, 6.8 Hz, 1H), 2.08 (m, 1H), 0.90 (d, J=6.8 Hz, 3H), 0.79 (d, J=6.2 Hz, 3H); mp 137–139 °C; FABMS (*m/e*) 580 (M^++Na), 557 (M^++H), 325, 275, 214, 162; Anal. calcd for $C_{33}H_{39}O_5N_3$: C, 71.06; H, 7.01; N, 7.54. Found: C, 70.41; H, 7.20; N, 7.42.

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