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Headline Articles

Asymmetric Synthesis of β-Amino Acids by Addition of Chiral Enolates to Nitrones via *N*-Acyloxyiminium Ions

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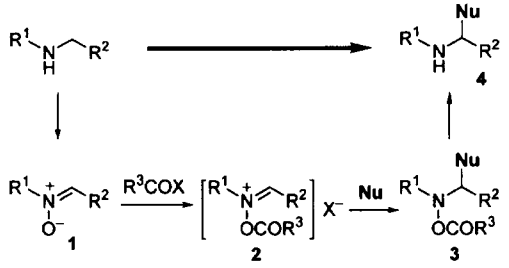
N-Acyloxyiminium ions, generated by the reaction of nitrones with acyl halides, are highly reactive species and undergo facile reaction with a wide range of nucleophiles, such as ketene silyl acetals, titanium(IV) and boron enolates, hydrido- and allyltin(IV) reagents, and alkynyltitanium(IV) reagents, to give α-substituted amine derivatives. Optically active β-amino acids can be prepared by the reaction of *N*-acyloxyiminium ions with both boron and titanium(IV) enolates bearing chiral auxiliaries. Reversal of diastereoselectivity was observed by the reactions of the boron and titanium(IV) enolates. Using these reactions, all of the four stereoisomers of α-methyl-β-phenylalanines, for example, can be prepared highly diastereoselectively. Cyclic *N*-acyloxyiminium ions are useful for the asymmetric synthesis of pyrrolidine and piperidine alkaloids; (5*R*,8*R*,8a*S*)-5-cyano-8-methylindolizidine, which is a common key intermediate for synthesis of 5-substituted 8-methylindolizidines, was prepared selectively.

Asymmetric synthesis of β-amino acids[1] is of importance in view of pharmacological activity,[2,3] structural property,[4] and useful precursors for synthesis of nitrogen-containing biologically active compounds such as β-lactam antibiotics.[5] Therefore various methods for synthesis of optically active β-amino acids, which include homologation of α-amino acids,[6] stereoselective addition of enolates to the C=N double bonds of imines,[7] and stereoselective addition of amines to α,β-unsaturated carboxylic acid derivatives,[8] have been explored.

We have reported convenient methods for asymmetric synthesis of β-amino acids by diastereoselective addition of chiral ketene silyl acetals to nitrones[9] and 1,3-dipole cycloaddition of nitrones to alkenes bearing chiral auxiliaries.[10]

Nitrones are valuable intermediates for synthesis of nitrogen compounds, because various substituents can be introduced at the carbon α to the nitrogen.[11] Hard carbon nucleophiles such as Grignard reagents and organolithium reagents undergo reaction with nitrones readily,[12,13] and cyanide ion can also be introduced to give α-cyano hydroxylamine derivatives, which are useful precursors of α-amino acids.[14] However, soft nucleophiles such as enolates do not undergo reaction with nitrones directly; therefore, Lewis acids such as zinc iodide have been used to promote these reactions.[15] The addition of enolates to nitrones would provide an attractive method for synthesis of β-amino acids. Actually we succeeded in diastereoselective addition of chiral ketene silyl acetals to nitrones.[9] By using this reaction, syntheses of chiral precursors of pyrrolidine alkaloids[16] and β-lactam antibiotics[9] have been carried out. The latter is a rare example of diastereoselective addition of chiral nucleophiles to achiral nitrones,[17] although many methods for diastereoselective addition of achiral nucleophiles to chiral nitrones have been reported.[18]

In order to raise the reactivity of nitrones, we generated *N*-acyloxyiminium species upon treatment of nitrones with



Scheme 1.

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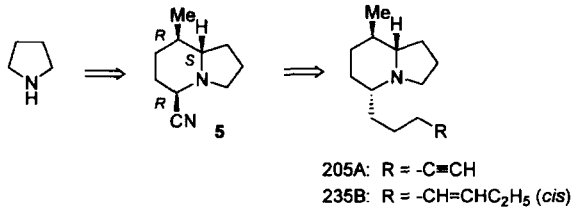


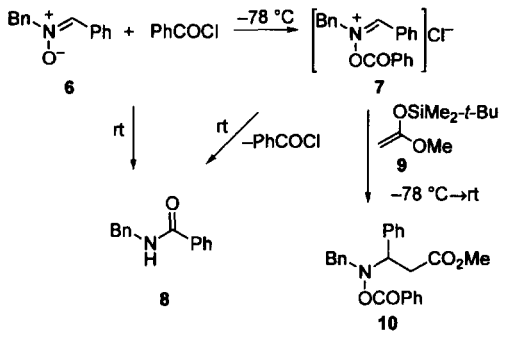
Scheme 2.

acyl halides.[19] It is known that the reaction of nitrones **1** with acyl halides gives *N*-acyloxyiminium ions **2**, which undergo rearrangement to give amides[20] or imines.[21] We tried to trap *N*-acyloxyiminium ions **2** with nucleophiles before the rearrangement, as shown in Scheme 1. Fortunately, we found that *N*-acyloxyiminium ions **2** are highly reactive species and undergo reaction with a variety of nucleophiles and even soft nucleophiles to give α-substituted *O*-acylhydroxylamines **3**, which are the precursors of α-substituted amines **4**. In 1984 we discovered the catalytic methods for direct synthesis of nitrones from secondary amines upon treatment with hydrogen peroxide in the presence of catalysts such as sodium tungstate[13,22] and selenium(IV) oxide.[23] Thereafter, similar methods for synthesis of nitrones have also been reported.[24,25] Furthermore, regioselective synthesis of nitrones can be carried out by decarboxylative oxidation of *N*-alkyl-α-amino acids.[16,26] Therefore, oxidation of secondary amines to nitrones and their treatments with enolates via *N*-acyloxyiminium ions would provide a convenient and useful method for synthesis of β-amino acid derivatives.

In this paper, we wish to report generation of *N*-acyloxyiminium ions and asymmetric synthesis of β-amino acids by addition of chiral enolates to the *N*-acyloxyiminium ions. Usefulness of this method is demonstrated by asymmetric synthesis of (5*R*,8*R*,8a*S*)-5-cyano-8-methylindolizidine (**5**), which is a common key synthetic intermediate of a series of 8-methylindolizidines such as 205A and 235B (Scheme 2).[27]

Results and Discussion

Generation and Reaction of *N*-Acyloxyiminium Species. Generation of *N*-acyloxyiminium species was examined upon treatment of nitrones with acylating reagents at low temperature. When *N*-benzylidenebenzylamine *N*-oxide (**6**) was allowed to react with benzoyl chloride in dichloromethane at −78 °C, the reaction reached completion within 30 min to give *N*-benzoyloxyiminium species **7** (Scheme 3). A solution of **7** was warmed up to room temperature to give *N*-benzylbenzamide (**8**) in 84% yield via a well-known rearrangement.[20] In order to trap the *N*-benzoyloxyiminium intermediate **7**, ketene *t*-butyldimethylsilyl methyl acetal (**9**) was added to the above solution at −78 °C. Methyl 3-(*N*-benzoyloxy-*N*-benzylamino)-3-phenylpropionate (**10**) was obtained in 99% yield. The amide **8** could not be detected. It is noteworthy that the reaction of the nitrone **6** with the ketene silyl acetal **9** does not proceed in the absence of benzoyl chloride. These results clearly indicate that the *N*-acyloxyiminium species **7** shows higher reactivity toward ketene silyl acetals than nitrone **6** itself.

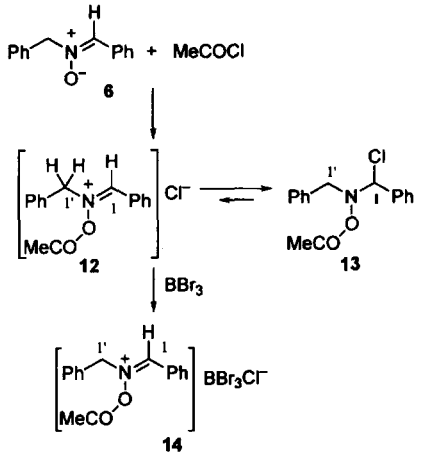


Scheme 3.

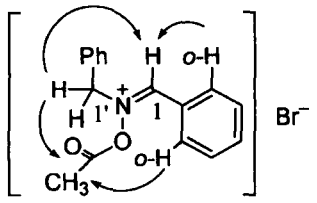
Other reagents such as acetic anhydride, methyl chloroformate, and methanesulfonyl chloride did not react with nitrone **6** at low temperature. When a mixture of nitrone **6** and an excess amount of acetic anhydride was heated at 55 °C, *N*-acetyl-*N*-benzylbenzamide (**11**) (83%) and amide **8** (17%) were obtained. These results indicate that acyl halides such as benzoyl chloride are excellent reagents for activation of nitrones.

Next, the NMR study was carried out in order to characterize the *N*-acyloxyiminium intermediate. Acetyl chloride was used as an acylating reagent, because the complex signals were observed due to signal overlapping when benzoyl chloride was used. The ^{1}H NMR spectrum of the *N*-acyloxyiminium intermediate, which was prepared from nitrone **6** and acetyl chloride in chloroform-*d* in situ, showed two sets of signals of *N*-acetyloxyiminium ion **12** and α-chloro amine **13** in the ratio of 1 : 11 (Scheme 4). When boron tribromide was added to the solution of the intermediate in order to trap the chloride, the intermediate **14** was detected as a single species. This result indicates that the intermediate bearing a better counter anion than chloride should form *N*-acyloxyiminium ions predominantly. Actually, when acetyl bromide was employed, *N*-acetyloxyiminium ion **15** was detected clearly as almost a single species (Fig. 1).

The geometry of *N*-acyloxyiminium ion **15** was determined by NOE experiments (Fig. 1). When the H-1′ of **15** (5.8 ppm) was irradiated, signal enhancement was observed at the signals of H-1, acetyl, and aromatic protons. When



Scheme 4.



(Z)-15

Fig. 1. NOEs of *N*-acetyloxyiminium ion **15**.

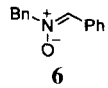
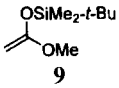
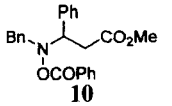
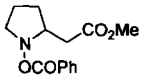
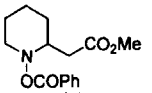
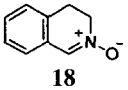
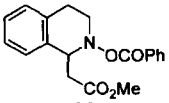
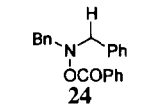
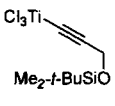
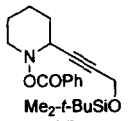
the *o*-H of **15** (8.2 ppm) was irradiated, the signals of H-1, acetyl, and aromatic protons were enhanced. These results indicate that **15** has *Z* geometry of the C=N bond. When the minor signals at 6.0 and 8.4 ppm were irradiated, no significant enhancement was observed, and the presence of the *E* isomer of **15** could not be proved.

The signals of H-1 and C-1 of **15** appeared at 11.5 and 159 ppm, respectively; these values were shifted to down-field in comparison with those of nitrone **6** (7.3 ppm for H-1 and 134 ppm for C-1). The remarkable down-field shift of the C-1 signal of the *N*-acyloxyiminium ions compared with the signal of nitrone **6** indicates that, as the electron density at the C-1 position decreases, it causes enhancement of the reactivity toward nucleophiles.

Synthesis of α-Substituted Amine Derivatives. The introduction of nucleophiles to nitrones via the corresponding *N*-acyloxyiminium ions can be applied to the synthesis of various α-substituted amine derivatives, because nitrones can be prepared readily by catalytic oxidation of secondary amines.[13,22,23] The results of the reactions of nitrones with various nucleophiles via their *N*-benzoyloxyiminium ions are summarized in Table 1. The reaction of the nitrone **6** with ketene silyl acetal **9** via *N*-benzoyloxyiminium ion **7** gave the adduct **10** in 99% yield (Entry 1). The β-amino acid derivative **10** was converted to the corresponding β-amino acid ester, methyl 3-(benzylamino)-3-phenylpropionate (**27**), upon treatment with zinc/acetic acid in 78% yield. 1-Pyrroline *N*-oxide (**16**) underwent smooth reaction with benzoyl chloride at low temperature to give the corresponding *N*-benzoyloxyiminium ion **26**, and addition of ketene silyl acetal **9** gave methyl (1-benzoyloxypyrrolidin-2-yl)acetate (**20**) in 92% yield (Entry 2). The reactions of cyclic nitrones **17** and **18**, derived from piperidine and 1,2,3,4-tetrahydroisoquinoline, respectively, with ketene silyl acetal **9** gave adducts **21** (68%) and **22** (87%), respectively (Entries 3 and 4). These products can be easily transformed to the corresponding β-amino acid esters by reduction with zinc/acetic acid as well as by catalytic hydrogenation. Thus, methyl pyrrolidin-2-ylacetate (**28**) and methyl piperidin-2-ylacetate (**29**) were obtained from the adducts **20** and **21** by catalytic hydrogenation in 66% and 86% yields, respectively. The β-amino acid derivatives thus obtained are important as potent synthetic intermediates for pyrrolidine, piperidine, and isoquinoline alkaloids.

Various less reactive nucleophiles also react with nitrones via *N*-acyloxyiminium intermediates to give α-substituted hydroxylamine derivatives. Allylation of nitrones have been accomplished by using allylmagnesium and allylzinc reagents.[12,13] Allylsilanes[28] and allyltins(IV)[29] have been also used in the presence of a stoichiometric amount of trimethylsilyl triflate. However, allylation of *N*-benzoyloxyiminium ion **7** with allyltributyltin occurred smoothly in the absence of Lewis acids to give *O*-benzoyl-*N*-benzyl-*N*-(1-phenyl-3-buten-1-yl)hydroxylamine (**23**) in 89% yield (Entry 5).

Table 1. Reaction of Nitrones with Nucleophiles via *N*-Benzoyloxyiminium Ions[a)]

Entry	Nitrone	Nucleophile	Product	Yield/%
1	 **6**	 **9**	 **10**	99
2	 **16**	**9**	 **20**	92
3	 **17**	**9**	 **21**	68
4	 **18**	**9**	 **22**	87
5	**6**		 **23**	89
6	**6**	Bu_3SnH	 **24**	83
7	**17**	 **19**	 **25**	61

a) After treatment of nitrones with benzoyl chloride, the reactions with nucleophiles were carried out. See text and experimental section.

Introduction of a hydride can be performed upon treatment of *N*-benzoyloxyiminium ion **7** with tributyltin hydride to afford *O*-benzoyl-*N*,*N*-dibenzylhydroxylamine (**24**) in 83% yield (Entry 6). Reduction of nitrones with lithium aluminum hydride (lithium tetrahydridoaluminate) or sodium borohydride (sodium tetrahydroborate) gives free hydroxylamines;[30] however, the reduction via *N*-acyloxyiminium ions with tributyltin hydride gives *O*-protected hydroxylamines, which are more stable and more easily handled than free hydroxylamines.

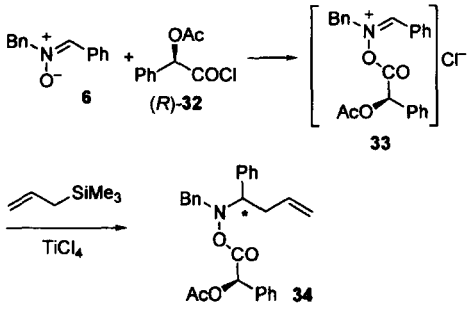
Alkynylation of *N*-acyloxyiminium ions can be performed by using titanium(IV) acetylides. The *N*-benzoyloxyiminium ion, derived from nitrone **17**, reacted with the titanium(IV) acetylide **19**, which was prepared from lithium (*t*-butyldi-

methylsiloxymethyl)acetylide and titanium(IV) chloride, to give *N*-benzoyloxy-2-(3-*t*-butyldimethylsiloxy-1-propyn-1-yl)piperidine (**25**) (61%) (Entry 7). The α-substituted piperidine **25** is a useful precursor for piperidine alkaloids[31] and is also converted to the corresponding *N*-hydroxy-α-amino acids by oxidation of the acetylene group.[32] Chemoselective N–O bond cleavage of **25** was performed upon treatment with zinc/acetic acid to give 2-(3-*t*-butyldimethylsiloxy-1-propyn-1-yl)piperidine (**30**) in 65% yield, while 2-(3-*t*-butyldimethylsiloxy-1-propyl)piperidine (**31**) was obtained by the catalytic hydrogenation in 63% yield.

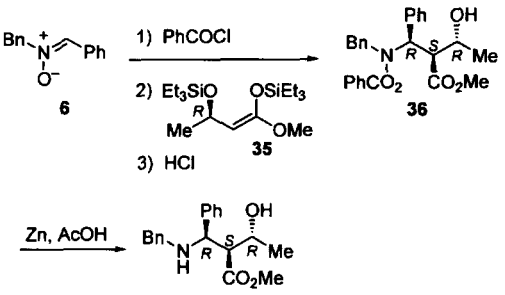
Chiral *N*-Acyloxyiminium Ions. If optically active *N*-acyloxyiminium ions can be generated upon treatment of nitrones with chiral acyl halides, their reactions with achiral nucleophiles would occur diastereoselectively, to give optically active *O*-acylhydroxylamine derivatives. Then, removal of the chiral acyl auxiliary would give the corresponding optically active hydroxylamines and amines, respectively.

Chiral *N*-acyloxyiminium ion **33**, which was derived from nitrone **6** and (*R*)-*O*-acetylmandelyl chloride ((*R*)-**32**), was allowed to react with allyltributyltin in the presence of titanium(IV) chloride in dichloromethane at −78 °C to give homoallylamine derivative **34** (99%) in 36% de. In the absence of titanium(IV) chloride, diastereoselection of *N*-acyloxyiminium ion **33** was not observed. When allyltrimethylsilane was allowed to react with **33** in the presence of titanium(IV) chloride, the adduct **34** was obtained in 71% yield, and the diastereomeric excess was improved to 64% de (Scheme 5). The homoallylamine derivatives can be converted into β-amino acids by oxidative cleavage of olefin,[33] indicating that the present reaction can be used as a method for asymmetric synthesis of β-amino acids. Although the diastereoselectivity is not so high at this stage, this method has the high potential to the asymmetric synthesis of α-substituted amine derivatives.

Addition of Chiral Ketene Silyl Acetals. The reaction of *N*-acyloxyiminium ions with chiral ketene silyl acetals provides a convenient method for synthesis of optically active β-amino acid derivatives, which are key intermediates of nitrogen-containing biologically active compounds such as β-lactam antibiotics, peptides, and alkaloids. We have reported that the zinc iodide-catalyzed addition of (*Z*)-(*R*)-1-methoxy-1,3-bis(triethylsiloxy)-1-butene (**35**) to nitrones proceeds with high diastereoselectivity, and that this method can be used for synthesis of β-lactam antibiotics.[9] The reaction of *N*-benzoyloxyiminium ion **7** with chiral ketene silyl acetal **35** was found to proceed at −78 °C to give methyl (2*S*,3*R*,1′*R*)-2-[α-(*N*-benzoyloxy-*N*-benzylamino)-benzyl]-3-hydroxybutanoate (**36**) in 72% yield as a single diastereomer (> 99% de) (Scheme 6), which was reduced to methyl (2*S*,3*R*,1′*R*)-2-[α-(benzylamino)benzyl]-3-hydroxybutanoate (**37**) upon treatment with zinc/acetic acid.

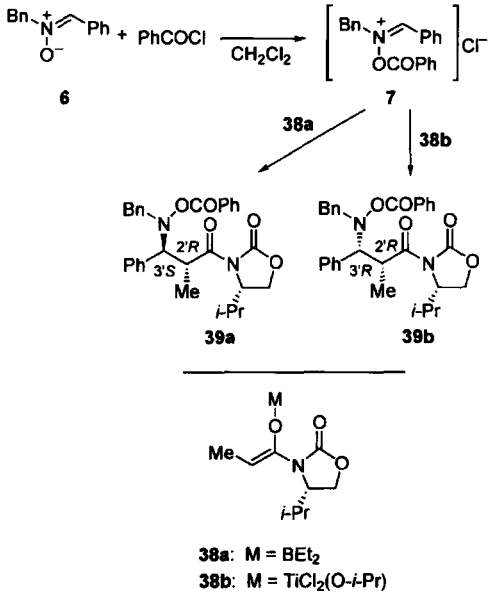


Scheme 5.



Scheme 6.

Additions of Boron and Titanium(IV) Enolates Bearing Chiral Auxiliaries. In order to establish a general method for asymmetric synthesis of β-amino acids using *N*-acyloxyiminium ions, diastereoselective addition of chiral boron and titanium(IV) enolates to *N*-acyloxyiminium was examined. The reaction of enolate **38** derived from (*S*)-4-(1-methylethyl)-3-propionyl-2-oxazolidinone[34] with *N*-benzoyloxyiminium ion **7** was carried out in dichloromethane at −78 °C (Scheme 7). The boron and titanium(IV) enolates **38** were prepared in situ by using diethylboryl triflate and titanium(IV) trichloride isopropoxide in the presence of *N*,*N*-diisopropylethylamine, respectively.[34,35] The *N*-benzoyloxyiminium ion **7** was allowed to react with enolates **38** to give a mixture of two diastereomers of β-amino acid derivatives **39**. The diastereomeric ratios were determined by ^{1}H NMR. The reversal of diastereoselectivity was observed with the reactions of boron and titanium(IV) enolates. That is, the reaction



Scheme 7.

of **7** with the chiral boron enolate **38a** gave *anti* (2′*R*,3′*S*)-isomer **39a** as a major isomer (82%, *anti*/*syn* = 80 : 20), while the reaction with titanium(IV) enolate **38b** afforded *syn* (2′*R*, 3′*R*)-isomer **39b** predominantly (69%, *anti*/*syn* = 16 : 84). When benzoyl bromide was employed as an activator of nitrone **6**, a similar result was obtained; the reaction with the boron enolate **38a** gave the adduct **39a** in 70% yield with the ratio of *anti*/*syn* = 83 : 17. In each case, only two diastereomers were obtained among possible four isomers, and each diastereomer can be separated simply by column chromatography on silica gel. These adducts can be converted to the corresponding β-amino acids (vide infra).

The stereochemistry of the present reaction can be rationalized by assuming the models shown in Fig. 2. Complete stereocontrol at the C-2′ position of **39** comes from diastereofacial selection of chelated (*Z*)-enolates **38**,[34,35] which is induced by bulky *i*-Pr group. The *N*-acyloxyiminium ion **7** approaches to the *si* face of the enolates, giving 2′*R*-configuration.

The stereochemistry at the C-3′ position of **39** reflects the enantiofacial selection of (*Z*)-*N*-benzoyloxyiminium ion **7**, which is affected by the coordination number of the metal of the chelated enolates **38**. It is also important that *N*-acyloxyiminium ions are electrophilic enough to react with enolates in the absence of Lewis acids. The intermediate **7** would react with the boron enolate **38a** without coordination to the boron, as shown in the open transition model **I**, to give the 3′*S*-isomer, because there is no coordination site in the chelated enolate **38a**. In contrast, the benzoyl group of the *N*-acyloxyiminium ion **7** coordinates to the titanium of enolate **38b** as shown in the closed transition model **II**, to give the 3′*R*-isomer predominantly. In these models, the phenyl group attaching to the C=N moiety of the intermediate **7** would orient to the opposite site to the oxazolidinone ring of

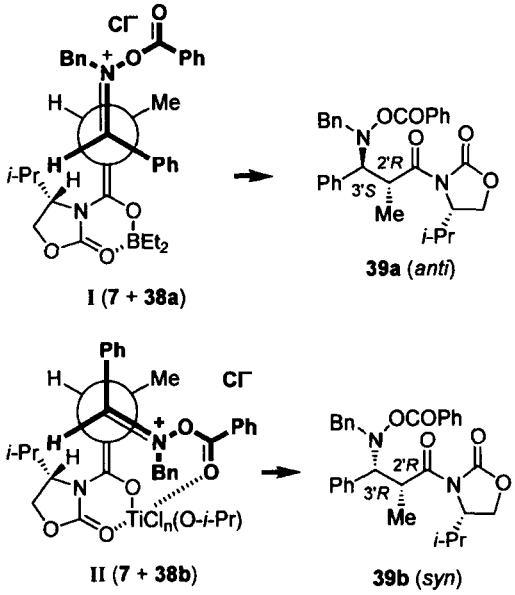
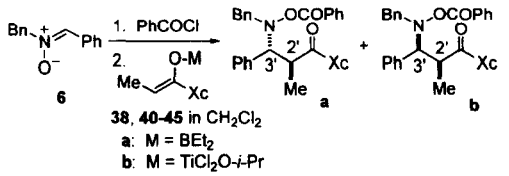
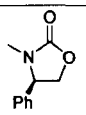
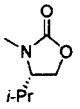
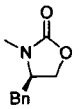
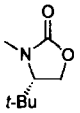
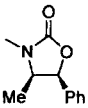
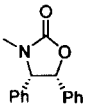
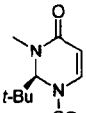


Fig. 2. Proposed open (**I**) and closed (**II**) transition state models for addition of enolates **38a** or **38b** to *N*-benzoyloxyiminium ion **7**.

Table 2. Reaction of Nitrone **6** with Chiral Enolates via *N*-Benzoyloxyiminium Ion **7**[a)]



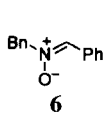
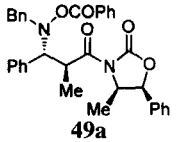
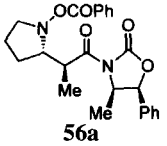
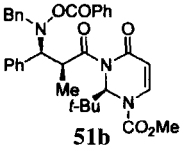
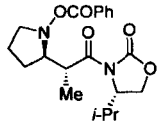
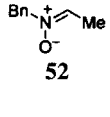
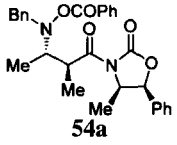
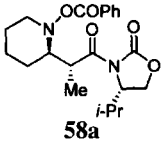
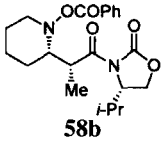
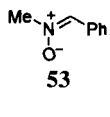
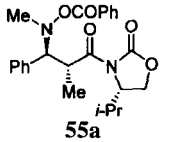
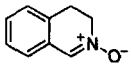
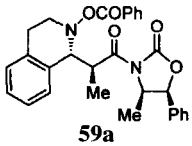
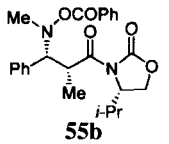
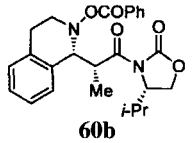
Entry	Enolate : Xc	Major Product[a)]	Yield/%[b)]	Ratio of **a** : **b**[b)]
1	**40a**: 	(2′*S*,3′*R*)-**46a**	70	86 : 14
2	**40b**:	(2′*S*,3′*S*)-**46b**	45	8 : 92
3	**38a**: 	(2′*R*,3′*S*)-**39a**	82[c)]	80 : 20
4	**38b**:	(2′*R*,3′*R*)-**39b**	69[c)]	14 : 86
5	**41a**: 	(2′*S*,3′*R*)-**47a**	83	71 : 29
6	**41b**:	(2′*S*,3′*S*)-**47b**	49	11 : 89
7	**42a**: 	(2′*R*,3′*S*)-**48a**	91	95 : 5
8	**42b**:	(2′*R*,3′*R*)-**48b**	85	16 : 84
9	**43a**: 	(2′*S*,3′*R*)-**49a**	81 (92)[d)]	93 : 7 (98 : 2)[d)]
10	**43b**:	(2′*S*,3′*S*)-**49b**	65	15 : 85
11	**44a**: 	(2′*R*,3′*S*)-**50a**	70	87 : 13
12	**44b**:	(2′*R*,3′*R*)-**50b**	46	13 : 87
13	**45a**: 	(2′*S*,3′*R*)-**51a**	98	80 : 20
14	**45b**:	(2′*S*,3′*S*)-**51b**	79	2 : 98

a) See experimental section. b) Determined by ^{1}H NMR analysis. c) Isolated yield as a diastereomeric mixture. d) Toluene was used as a solvent.

38 because of the steric repulsion, giving the corresponding diastereoselectivity.

As mentioned above, the bulkiness of a chiral auxiliary is an important factor to the diastereoselectivity. Therefore, various kinds of chiral oxazolidinones[34,35] and pyrimidinone[36] were examined as chiral auxiliaries for the addition of the enolates to *N*-benzoyloxyiminium ion **7**. The results are summarized in Table 2. In all cases, reversal of diastereochemistry was observed with boron and titanium(IV) enolates. The boron enolates having more bulky substituents on the oxazolidinones induced higher diastereoselectivity. As a result, the reaction of nitrone **6** with the boron enolate **43a** bearing (4*R*,5*S*)-4-methyl-5-phenyl-2-oxazolidinone auxiliary via the *N*-benzoyloxyiminium ion **7** in toluene gave *anti* isomer **49a** in 92% yield with 96% de (Entry 9). On the other hand, the addition of the titanium(IV) enolate **45b** bearing (*S*)-2-*t*-butyl-2,3-dihydro-4(1*H*)-

Table 3. Reaction of Nitrones with Chiral Enolates via *N*-Benzoyloxyiminium Ions[a)]

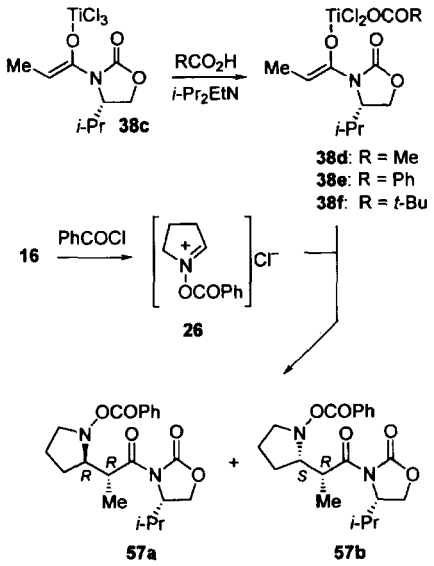
Entry	Nitrone	Enolate	Major Product	Yield/% (**a** : **b**)[b)]	Entry	Nitrone	Enolate	Major Product	Yield/% (**a** : **b**)[b)]
1	 **6**	**43a**	 **49a**	81 (93 : 7)	7	 **16**	**43a**	 **56a**	85 (88 : 12)
2	**6**	**45b**	 **51b**	79 (2 : 98)	8	**16**	**38b**	 **57a**	16 (72 : 28)
3	 **52**	**43a**	 **54a**	79 (95 : 5)	9	 **17**	**38a**	 **58a**	78 (89 : 11)
4	**52**	**43b**	**54a**	68 (84 : 16)	10	**17**	**38b**	 **58b**	76 (42 : 58)
5	 **53**	**38a**	 **55a**	84 (83 : 17)	11	 **18**	**43a**	 **59a**	83 (92 : 8)
6	**53**	**38b**	 **55b**	76 (13 : 87)	12	**18**	**38b**	 **60b**	72 (20 : 80)

a) See experimental section. b) Determined by ^{1}H NMR analysis.

pyrimidinone auxiliary gave higher diastereoselectivity than those of the titanium(IV) enolates bearing oxazolidinone auxiliaries. Thus, *syn* isomer **51b** was obtained in 79% yield with 96% de (Entry 14). These adducts could be easily isolated by column chromatography as single diastereomers.

Acyclic and cyclic nitrones **6**, **16**—**18**, **52**, and **53** have been subjected to the reaction with chiral enolates via *N*-benzoyloxyiminium ions at −78 °C in dichloromethane. Some representative results are summarized in Table 3. In most cases, the adducts were obtained in good yields with high diastereoselectivities, although the conditions have not been optimized. In the reactions of nitrones **6**, **53**, **17**, and **18**, reversal of diastereoselectivity was observed by changing the metal of the enolates from boron to titanium(IV) (Entries 1 vs. 2, 5 vs. 6, 9 vs. 10, and 11 vs. 12), whereas in the reactions of nitrones **52** and **16**, *anti*-isomers **54a**, **56a**, and **57a** were obtained, respectively, by the reactions with both of boron and titanium(IV) enolates (Entries 3 vs. 4 and 7 vs. 8). It is considered that the diastereoselectivity is dependent on the bulkiness of the substituents at the carbon of nitrones; when the substituent is large enough, reversal of the diastereoselectivity is observed between boron and titanium(IV) enolates. In the reaction of six-membered nitrone **17**, the diastereoselectivity was reversed. Although the reaction with boron enolate **38a** gave the adduct **58a** in 78% de (Entry 9), poor diastereoselectivity was observed in the reaction with titanium(IV) enolate **38b** (Entry 10). This is why the substituent of **17** is not large enough to afford high diastereoselectivity with both boron and titanium(IV) enolates.

The cyclic *N*-benzoyloxyiminium ions, derived from six-membered nitrones **17** and **18**, underwent smooth reaction with both the boron and titanium(IV) enolates to give the corresponding adducts in good yields. However, the reaction of cyclic *N*-benzoyloxyiminium ion **26**, derived from five-membered nitrone **16**, with the titanium(IV) enolate **38b** gave adduct **57** in only 16% yield, whereas the similar reaction with boron enolate **43a** gave adduct **56** in 85% yield with 76% de (Entries 7 and 8). It is considered that the five-membered *N*-benzoyloxyiminium intermediate **26** is less stable toward the titanium of enolate **38b** as a Lewis acid than the other *N*-acyloxyiminium intermediates. Therefore modification of the titanium(IV) enolate was investigated by replacing



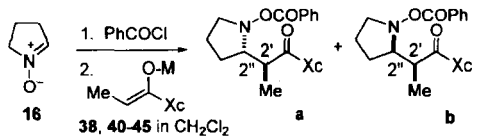
Scheme 8.

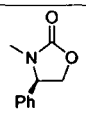
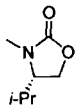
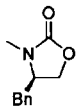
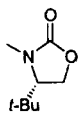
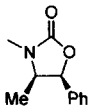
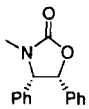
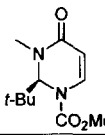
ligands (Scheme 8).

The titanium(IV) enolate **38c**, derived from (*S*)-4-(1-methylethyl)-3-propionyl-2-oxazolidinone, upon treatment with titanium(IV) chloride and *N*,*N*-diisopropylethylamine,[35] would react with acetic acid in the presence of *N*,*N*-diisopropylethylamine to replace one of the chloro ligands on the titanium with the acetato ligand, giving enolate **38d**. To estimate the ligand exchange reactions of the titanium(IV) enolate **38c**, the reactions of **38c** with acetic acid were carried out at −78 and 0 °C. Then *N*-benzoyloxyiminium ion **26** was added to allow to react with the titanium(IV) enolates obtained. When the ligand exchange reaction and addition reaction to the intermediate **26** were performed at −78 °C, the adduct **57** was not obtained. In contrast, the yield of the adduct **57** increased to 40% when the addition reaction was carried out after enolate **38c** was treated with acetic acid at 0 °C. Thus, ligand exchange of the titanium(IV) enolate **38c** by treatment with acetic acid and *N*,*N*-diisopropylethylamine occurs at 0 °C, but not at −78 °C. Now we are in a position to be able to control the reactivity of the titanium(IV) enolate by replacing the ligand, and the reaction of *N*-benzoyloxyiminium ion **26** can be performed smoothly. The addition of enolate **38d** to the *N*-benzoyloxyiminium ion **26** at 0 °C gave the adduct **57** in 59% yield. The diastereomeric ratio was determined to be 84 : 16 by ^{1}H NMR analysis. Other carboxylic acids such as benzoic acid and pivalic acid were employed as ligands, and the reaction of **26** with enolates **38e** having benzoato ligand and **38f** having pivalato ligand afforded the adduct **57** in 55 and 35% yields with similar diastereomeric ratios (86 : 14 and 88 : 12), respectively. In the reactions of *N*-benzoyloxyiminium ion **26**, the isomer **57a** was obtained predominantly by using either boron or titanium(IV) enolate. The configuration of the isomer **57a** was determined to be 2′*R*,2″*R* (*anti*) by derivation to the known alkaloid (vide infra). The configuration of the diastereomer **57b** was estimated to be 2′*R*,2″*S* (*syn*) based on the model in Fig. 2.

Next, in order to improve the diastereoselectivity, enolates having different chiral auxiliaries were examined. The results of the reactions of *N*-benzoyloxyiminium ion **26** with the modified titanium(IV) enolates **38e** and **40e—45e** having a benzoato ligand at 0 °C in dichloromethane are summarized in Table 4. Only two diastereomers among four possible isomers were obtained in satisfactory yields with good diastereomeric ratios. The best result was obtained when the enolate **43e** was used, affording the adduct **56** in 75% yield with 82% de (Entry 5).

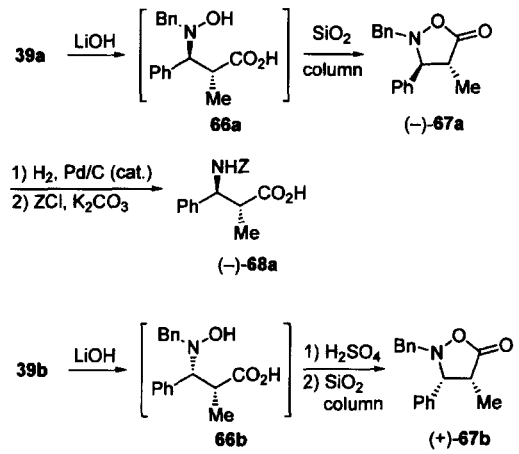
Table 4. Reaction of Nitrone **16** with Chiral Titanium(IV) Enolates via *N*-Benzoyloxyiminium Ion **26**[a]



Entry	Enolate : Xc	Major Product[a]	Yield/%[b]	Ratio of **a** : **b**[b]
1	**40e**: 	(2′*S*,2″*S*)-**61a**	48	86 : 14
2	**38e**: 	(2′*R*,2″*R*)-**57a**	55[c]	86 : 14
3	**41e**: 	(2′*S*,2″*S*)-**62a**	75[c]	83 : 17
4	**42e**: 	(2′*R*,2″*R*)-**63a**	49	80 : 20
5	**43e**: 	(2′*S*,2″*S*)-**56a**	75	91 : 9
6	**44e**: 	(2′*R*,2″*R*)-**64a**	67	69 : 31
7	**45e**: 	(2′*S*,2″*S*)-**65a**	81	69 : 31

a) See experimental section. b) Determined by 1H NMR analysis. c) Isolated yield as a diastereomeric mixture.

Synthesis of All the Four Stereoisomers of α-Methyl-β-phenylalanine. Asymmetric synthesis of α-methyl-β-phenylalanine has been reported by Davies et al. where the chiral amide reacts with double bonds of cinnamic acid derivatives diastereoselectively.[8a] In the present reaction of *N*-acyloxyiminium ions with chiral enolates, enantiomerically pure α-methyl-β-phenylalanines can be obtained conveniently as well as *N*-hydroxy-α-methyl-β-phenylalanine derivatives. Hydrolysis of **39a**, followed by column chromatography on silica gel, gave 2-benzyl-4-methyl-3-phenyl-

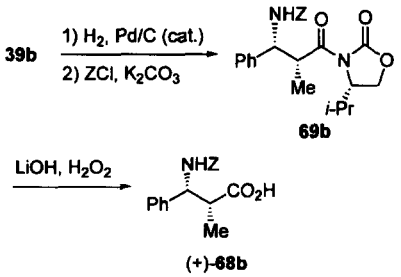


Scheme 9.

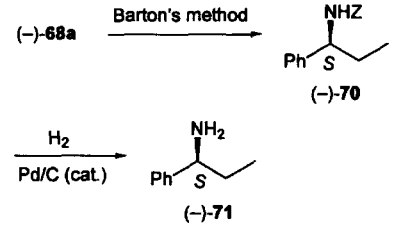
5-isoxazolidinone ((−)-**67a**) (58%), which was formed by cyclization of *N*-hydroxy-*β*-amino acid **66a** on silica gel. In contrast, (+)-**67b** was obtained after cyclization of **66b** by using sulfuric acid (Scheme 9). The relative configurations of **67a** and **67b** were confirmed to be *trans* and *cis*, respectively, by NOE experiments.

N-Benzyloxycarbonyl-*α*-methyl-*β*-phenylalanine ((−)-**68a**) was obtained from (−)-**67a** by catalytic hydrogenation, followed by protection of the amino group with benzyloxycarbonyl (*Z*) group. Alternatively, (+)-**68b** was obtained from **39b** by a modified pathway because of the low yield of (+)-**67b**. Thus, cleavage of the N–O bond of **39b** by catalytic hydrogenation, followed by protection of the amino group, gave the *N*-protected *β*-amino acid derivative **69b**. Then, hydrolysis of **69b** gave (+)-**68b** in 95% yield with recovery of the chiral auxiliary (Scheme 10).

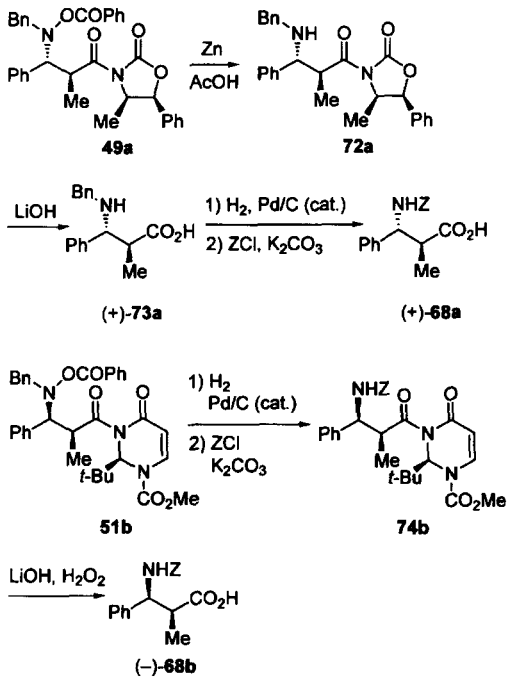
β-Amino acid (−)-**68a** was decarboxylated by means of Barton's method[37] to give *N*-benzyloxycarbonyl-1-phenyl-1-propylamine ((−)-**70**) to confirm the absolute configuration (Scheme 11). Thus, (−)-**70** was determined to have *S*-configuration after deprotection by catalytic hydrogenation to the



Scheme 10.



Scheme 11.

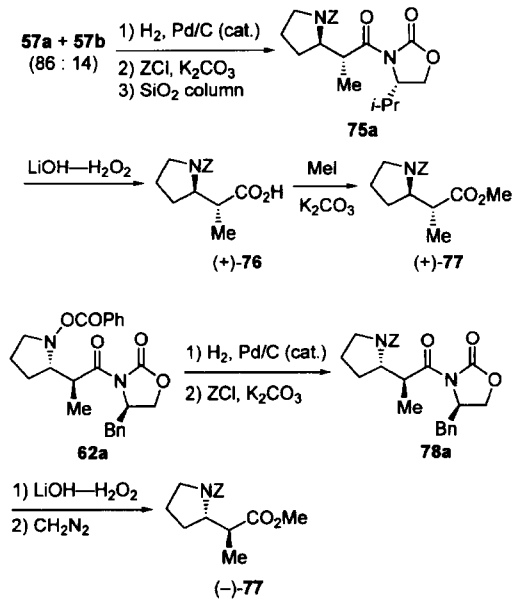


Scheme 12.

known (*S*)-1-phenyl-1-propylamine ((−)-**71**).[38] Therefore, the absolute configuration of the *β*-amino acid derivative **39a** was determined to be 2′*R*,3′*S*. Similarly the configuration of **39b** was determined to be 2′*R*,3′*R* after converting to (+)-**70**.

The antipodes (+)-**68a** and (−)-**68b** of α-methyl-β-phenylalanine could be obtained from the adducts **49a** and **51b**, respectively, as shown in Scheme 12. To avoid decomposition of the chiral auxiliary, the N–O bond of **49a** was cleaved by treatment with zinc/acetic acid, giving (4*R*,5*S*)-3-[(2*S*,3*R*)-3-benzylamino-2-methyl-3-phenylpropionyl]-4-methyl-5-phenyl-2-oxazolidinone ((+)-**72a**). Hydrolysis of (+)-**72a** gave *N*-benzyl-*α*-methyl-*β*-phenylalanine ((+)-**73**). Hydrogenolysis of (+)-**73**, followed by protection with benzyloxycarbonyl group, gave (+)-**68a**. The stereoisomer (−)-**68b** was obtained by a similar pathway through **74b**. Thus, all the four isomers of *α*-methyl-*β*-phenylalanine could be synthesized based on the reactions of *N*-benzoyloxyiminium ion with chiral enolates.

The adducts **57a** and **62a**, which have a pyrrolidine skeleton, can be also converted into the corresponding *β*-amino acid esters (Scheme 13). Although **57a** could not be obtained as a single diastereomer, catalytic hydrogenation of the diastereomeric mixture of **57**, followed by protection of the amino group with benzyloxycarbonyl group, gave *β*-amino acid derivative **75a** as a single diastereomer after column chromatography on silica gel. Then, hydrolysis of **75a** with lithium hydroxide and hydrogen peroxide gave *N*-benzyloxycarbonyl-*β*-amino acid (+)-**76** with recovery of the chiral auxiliary. The protected *β*-amino acid (+)-**76** could be converted to the corresponding *β*-amino acid ester (+)-**77** upon treatment with methyl iodide and potassium carbonate. On the other hand, the adduct **62a** was isolated as a single

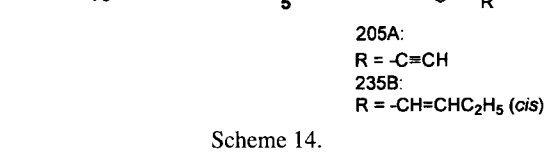


Scheme 13.

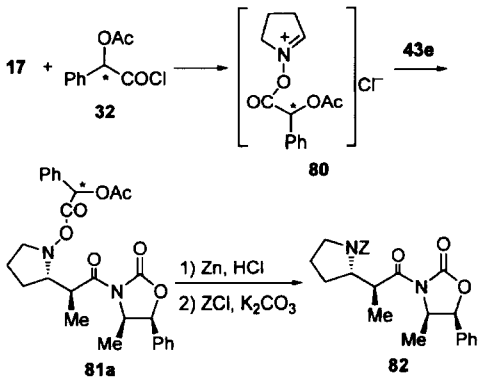
diastereomer easily by crystallization from ethyl acetate and hexane. Then, **62a** was converted into the *N*-protected β-amino acid ester (−)-**77** by a similar method via **78a**.

Asymmetric Synthesis of 5-Cyano-8-methylindolizidines. The present reaction can be applied to the asymmetric synthesis of indolizidine alkaloids. 5-Substituted-8-methylindolizidine is one of the major subclasses of indolizidine alkaloids. Indolizidine alkaloids constitute a family of natural products that have been detected in extracts from the skins of neotropical frogs and show biological activity as noncompetitive inhibitors of the acetylcholine receptor complex. (−)-5-Cyano-8-methylindolizidine (**5**) is a common key intermediate for the synthesis of these 8-methylindolizidines.[27] The β-amino acid derivative **79** has a suitable configuration for the synthesis of these alkaloids (Scheme 14).

For further improvement in our efforts to obtain **79** highly diastereoselectively, the acyl moiety of *N*-acyloxyiminium ions was examined because the reactions with titanium(IV) enolates would proceed via coordination of the carbonyl oxygen of the *N*-acyloxyiminium ions to the titanium as proposed in Fig. 2. The reaction of the *N*-acyloxyiminium ion **80**, which was derived from nitrone **16** and chiral acyl chloride **32**, with chiral titanium(IV) enolate **43e** was examined (Scheme 15). When (*R*)-**32** was employed, the adduct **81a** was obtained in 56% yield as a mixture of two diastereomers. The diastereomeric excess was 94%. Almost the same selectivity was obtained (96% de), when (*S*)-**32** was used. Therefore, the reaction using racemic *O*-acetylmandelyl chloride (±)-**32** was carried out. The adduct was obtained in 84% yield, and the diastereomeric excess, at 2′ and 2″ positions, was 96%. Reduction of the mixture of **81** with zinc/hydrochloric acid, followed by protection of the amino group with benzyloxycarbonyl group, gave **82** in 88% yield as a single diastereomer after silica-gel column chromatography.

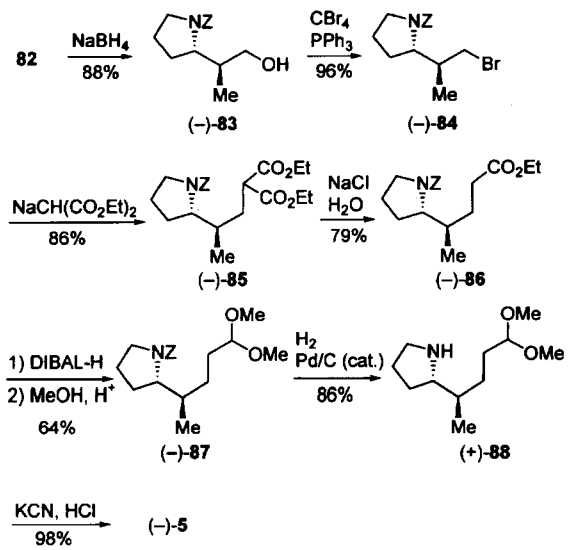


Scheme 14.



Scheme 15.

The strategy for synthesis of indolizidine **5** from enantiomerically pure β-amino acid derivative **82** is shown in Scheme 16. The amino alcohol (−)-**83** was obtained by reductive cleavage of chiral auxiliary of **82** with sodium borohydride in 88% yield as a single diastereomer, along with recovery of the chiral auxiliary. Carbon chain elongation was accomplished by addition of diethyl malonate as follows: Bromination of alcohol (−)-**83** with carbon tetrabromide and triphenylphosphine gave the bromide (−)-**84** (96%), followed by substitution with diethyl sodiomalonate gave diester (−)-**85** (86%). Then, δ-amino acid ester (−)-**86** was obtained by decarboxylation of (−)-**85** in 79% yield. Reduction of the ester (−)-**86** to the corresponding aldehyde upon treatment with diisobutylaluminum hydride (DIBAL-H), followed by acetalization with methanol in the presence of *p*-toluenesulfonic acid, gave acetal (−)-**87** in 64% yield.



Scheme 16.

Deprotection of (−)-**87** by catalytic hydrogenation afforded amino acetal (+)-**88** in 86% yield. The ^{1}H and ^{13}C NMR spectra, the IR spectrum, and the optical rotation of (+)-**88** are in good agreement with the reported data.[27] No epimerization was observed by NMR analysis in this stage. Treatment of (+)-**88** with potassium cyanide and hydrochloric acid in dichloromethane, according to the reported procedure,[27] gave (−)-**5** in 98% (93 : 7) along with its epimer at the C-5 position. The α-amino nitrile (−)-**5** can be converted into various 5-substituted 8-methylindolizidines, such as 205A and 235B, by the reported procedure.[27]

In conclusion, *N*-acyloxyiminium ions are generated by the reaction of nitrones with acyl halides, which are stable at low temperature and readily react with soft nucleophiles such as enolates. By using this new methodology, α-substituted amine derivatives can be synthesized conveniently, because nitrones can be prepared directly from secondary amines by our catalytic method. Optically active β-amino acid derivatives can be also synthesized highly diastereoselectively by employing chiral enolates. The diastereoselectivity of the reaction of *N*-acyloxyiminium ions is strongly dependent on the metal of enolates, and reversal of diastereoselectivity was observed with boron and titanium(IV) enolates. Selective synthesis of all the four isomers of α-methyl-β-phenylalanine has been accomplished by choosing an appropriate chiral auxiliary and a metal of enolates. Furthermore, the present reaction can be applied to the asymmetric synthesis of biologically active nitrogen-containing compounds. The synthesis of (−)-5-cyano-8-methylindolizidine, which is a common intermediate for 5-substituted 8-methylindolizidine alkaloids, is a typical example.

Experimental

General. All melting points were determined on a Yanagimoto micro melting point apparatus and are uncorrected. Optical rotations were measured on a JASCO DIP-370 polarimeter. IR spectra were recorded on a Shimadzu FTIR 4100 spectrometer. NMR spectra were obtained on a JEOL JNM-GSX-270 (^{1}H, 270 MHz, ^{13}C, 68 MHz) spectrometer; chemical shifts (δ) were expressed in parts per million relative to tetramethylsilane. Splitting patterns are designated as s, singlet; d, doublet; t, triplet; q, quartet; m, multiplet; br, broad. Unless otherwise noted, they were measured in $CDCl_3$ at 35 °C. Elemental analyses were carried out on a Yanagimoto Model MT-3 CHN corder. High resolution mass spectra (HRMS) were recorded on a JEOL JMS-DX303 mass spectrometer. Other mass spectra were recorded on a Hitachi M1000H mass spectrometer with a Hitachi LC-APCI interface. Ionization methods (APCI: atmospheric pressure chemical ionization; EI: electron impact; FAB: fast atom bombardment) are indicated in parentheses. Analytical TLC was performed on E. Merck silica gel 60 F254 (Art. 5714). Silica-gel column chromatography was carried out on E. Merck silica gel 60 (230—400 mesh).

Molecular sieves 4-Å is commercially available and dried over P_2O_5 at 120 °C in vacuo before use. Ketene t-butyldimethylsilyl methyl acetal (**9**),[39] *O*-acetylmandelyl chloride (**32**),[40] (*Z*)-(*R*)-1-methoxy-1,3-bis(triethylsiloxy)-1-butene (**35**),[41] and diethylboryl triflate (Et_2BOTf)[42] were prepared by reported procedures.

Preparation of Nitrones. *N*-Benzylidenebenzylamine *N*-oxide (**6**), 1-pyrroline *N*-oxide (**16**), 2,3,4,5-tetrahydropyridine *N*-oxide (**17**), and 3,4-dihydroisoquinoline *N*-oxide (**18**) were prepared by the catalytic oxidation of the corresponding secondary amines with a 30% H_2O_2 solution in the presence of $Na_2WO_4 \cdot 2H_2O$ (4 mol%) according to the reported procedure.[13,22] Cyclic nitrones **16** and **17** were used immediately after preparation, but a solution in CH_2Cl_2 can be stored at −20 °C under argon for a week. *N*-Ethylidenebenzylamine *N*-oxide (**52**) and *N*-benzylidenemethylamine *N*-oxide (**53**) were prepared by condensation of the corresponding hydroxylamines and aldehydes, as shown below.

Preparation of *N*-Benzylhydroxylamine.[43] A mixture of nitrone **6** (32.4 g, 153 mmol) in 1.7 M H_2SO_4 (100 mL, 1 M = 1 mol dm^{-3}) was steam-distilled until no benzaldehyde was observed in the distillate (4 h). To the resultant aqueous solution was added 4 M NaOH (80 mL) to pH 9, and the mixture was extracted with EtOAc. The combined extracts were dried over Na_2SO_4, filtered, and evaporated. The residue was crystallized from *i*-Pr_2O to give a colorless crystal (13.3 g, 71%): mp 58.0—58.5 °C; IR (KBr) 3620, 3275, 2910, 2855, 1512, 1499, 1454, 1427, 1350, 1065, 1035, 853, 748, 700, 608 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ = 3.95 (s, 2 H, CH_2), 7.23—7.37 (m, 5 H, Ph); ^{13}C NMR ($CDCl_3$) δ = 58.2, 127.6, 128.4, 129.1, 137.0.

Preparation of *N*-Benzylidenemethylamine *N*-Oxide (53). A mixture of *N*-methylhydroxylamine hydrochloride (1.01 g, 12.0 mmol), benzaldehyde (1.82 mL, 18.0 mmol), K_2CO_3 (1.65 g, 12 mmol), H_2O (5 mL), and CH_2Cl_2 (10 mL) was stirred under argon at room temperature for 30 h. The organic layer was separated, washed with sat. $NaHCO_3$ solution and brine, and dried over $MgSO_4$. Removal of the solvent and purification by column chromatography (SiO_2, 0—5% MeOH in CH_2Cl_2) gave **53** (76%): IR (Nujol®) 1650, 1412, 1158, 940 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ = 3.87 (s, 3 H, CH_3), 7.36 (s, 1 H, NCH), 7.38—7.45 (m, 3 H, Ph), 8.16—8.25 (m, 2 H, Ph); ^{13}C NMR ($CDCl_3$) δ = 54.4, 128.4, 128.5, 130.4, 130.5, 135.1. Found: C, 71.07; H, 6.71; N, 10.29%. Calcd for C_8H_9NO: C, 71.09; H, 6.71; N; 10.36%.

***N*-Ethylidenebenzylamine *N*-Oxide (52):** IR (Nujol®) 1609, 1170, 1097, 706 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ = 2.00 (d, *J* = 5.9 Hz, 3 H, CH_3), 4.90 (s, 2 H, CH_2), 6.72 (q, *J* = 5.9 Hz, 1 H, CH), 7.35—7.44 (m, 5 H, Ph); ^{13}C NMR ($CDCl_3$) δ = 12.7, 69.0, 128.9, 129.3, 132.7, 134.6.

Preparation of Propionic Acid Derivatives Bearing Chiral Auxiliaries. Propionic acid derivatives were prepared by the reaction of lithium salt of the corresponding chiral auxiliaries with propionyl chloride according to the literature procedures: (*S*)-4-(1-methylethyl)-3-propionyl-2-oxazolidinone,[34a] (*R*)-4-phenyl-3-propionyl-2-oxazolidinone,[35b] (*R*)-4-benzyl-3-propionyl-2-oxazolidinone,[35a] (*S*)-4-*t*-butyl-3-propionyl-2-oxazolidinone,[35b] (4*R*,5*S*)-4-methyl-5-phenyl-3-propionyl-2-oxazolidinone,[34a] (4*S*,5*R*)-4,5-diphenyl-3-propionyl-2-oxazolidinone,[35a] and (*S*)-2-*t*-butyl-1-methoxycarbonyl-3-propionyl-2,3-dihydro-4(1*H*)pyrimidinone.[36]

General Procedure for the Formation of *N*-Acyloxyiminium Ions from Nitrones and Acyl Chlorides. To a mixture of nitrone (2.0 mmol) and 4 Å molecular sieves (300 mg) in CH_2Cl_2 (6.0 mL) was added acyl chloride (2.0 mmol) dropwise at −78 °C under argon. Then, the solution was stirred below −70 °C for 0.5 h.

NMR Studies of *N*-Acyloxyiminium Ions. To a solution of *N*-benzylidenebenzylamine *N*-oxide (**6**) (32 mg, 0.15 mmol) in $CDCl_3$ (0.60 mL) in a NMR tube was added acyl halide (0.15 mmol) at −78 °C under argon. After the reaction was checked by TLC analysis, ^{1}H and ^{13}C NMR spectra were measured at −25 °C.

Signals of *N*-acetyloxyiminium ion **12** and α-chloro amine **13** were observed in the ratio of 1 : 11 (Scheme 4). The signals corresponding to the protons H-1 and H-1′ of **13** are observed at 6.6 and

4.2 ppm, respectively. In the ^{13}C NMR spectrum, the signals of C-1 and C-1′ of **13** appear at 89 and 57 ppm, respectively. Signals at 8.6 and 5.6 ppm seem to correspond to H-1 and H-1′ of **12**, respectively, and a signal at 169 ppm corresponds to C-1 of **12**.

Boron tribromide (0.060 mmol) was added to the solution prepared from nitrone **6** and acetyl chloride at −78 °C, and ^1H and ^{13}C NMR spectra were measured. The signal of H-1 of **14** was observed at 9.6 ppm, and the ^{13}C NMR spectrum showed the C-1 signal at 164 ppm. The difference NOE spectra of the sample prepared from nitrone **6** and acetyl bromide were also measured (Fig. 1). When the H-1′ of **15** (5.8 ppm) was irradiated, signal enhancement was observed at the signals of H-1, acetyl, and aromatic protons. When the *o*-H of **15** (8.2 ppm) was irradiated, the signals of H-1, acetyl, and aromatic protons were enhanced. These results indicate that **15** has *Z* geometry for the C=N bond. When the minor signals at 6.0 and 8.4 ppm were irradiated, no significant enhancement was observed. The signals of H-1 and C-1 of **15** appeared at 11.5 and 159 ppm, respectively.

Reaction of Nitrone 6 with Benzoyl Chloride. To a solution of nitrone **6** (423 mg, 2.0 mmol) and 4-Å molecular sieves (200 mg) in CH_2Cl_2 (4 mL) was added benzoyl chloride (0.255 mL, 2.2 mmol) at −70 °C. The solution was stirred at −70 °C for 30 min. The temperature was gradually raised to room temperature, and the mixture was stirred for 12 h. Purification by chromatography (SiO_2, 2.5—20% EtOAc in hexane) gave *N*-benzylbenzamide (**8**) (355 mg, 84%) and *N*,*O*-dibenzoyl-*N*-benzylhydroxylamine (129 mg, 16%). **8**: mp 105.0—106.0 °C; IR (Nujol®) 1640, 1549, 727, 696 cm^{-1}; ^1H NMR ($CDCl_3$) δ = 4.47 (d, *J* = 5.4 Hz, 2 H, $PhCH_2$), 7.14—7.48 (m, 9 H, Ph and NH), 7.70 (d, *J* = 7.0 Hz, 2 H, Ph); ^{13}C NMR ($CDCl_3$) δ = 43.8, 127.0, 127.3, 127.6, 128.3, 129.8, 131.3, 134.1, 138.2, 167.5. HRMS (FAB) Found: *m/z* 212.1082. Calcd for $C_{14}H_{14}NO$: M+H$^+$, 212.1075. *N*,*O*-Dibenzoyl-*N*-benzylhydroxylamine: mp 98.0—99.0 °C; IR (Nujol®) 1763, 1671,1451, 1346, 1017, 704 cm^{-1}; ^1H NMR ($CDCl_3$) δ = 5.10 (s, 2 H, $PhCH_2$), 7.28—7.44 (m, 11 H, Ph), 7.65—7.70 (m, 2 H, Ph), 7.79—7.86 (m, 2 H, Ph); ^{13}C NMR ($CDCl_3$) δ = 53.4, 126.7, 127.8, 127.9, 128.1, 128.2, 128.4, 128.5, 128.6, 129.7, 130.1, 131.0, 133.2, 133.5, 134.1, 135.1, 164.2, 170.7. HRMS (FAB) Found: *m/z* 332.1306. Calcd for $C_{21}H_{18}NO_3$: M+H$^+$, 332.1287.

Reaction of Nitrone 6 with Acetic Anhydride. A solution of **6** (3.04 g, 14.4 mmol) in acetic anhydride (30 mL) was heated at 55 °C for 3 h. The reaction mixture was concentrated, and the residue was purified by column chromatography (SiO_2, 10% EtOAc in hexane) to give *N*-acetyl-*N*-benzylbenzamide (**11**) (3.19 g, 83%) and **8** (0.543 mg, 17%). **11**: IR (Nujol®) 1700, 1663, 1449, 1372, 1346, 980, 700 cm^{-1}; ^1H NMR ($CDCl_3$) δ = 2.15 (s, 3 H, CH_3CO), 5.02 (s, 2 H, $PhCH_2$), 7.18—7.32 (m, 5 H, Ph), 7.38—7.46 (m, 2 H, Ph), 7.49—7.58 (m, 3 H, Ph). HRMS (FAB) Found: *m/z* 254.1186. Calcd for $C_{16}H_{16}NO_2$: M+H$^+$, 254.1181.

Typical Procedure for Reaction of *N*-Benzoyloxyiminium Ion with Ketene Silyl Acetal. The reaction of *N*-benzoyloxyiminium ion **7**, generated from nitrone **6** with benzoyl chloride, with ketene *t*-butyldimethylsilyl methyl acetal (**9**) can be described. To a solution of **6** (422 mg, 2.00 mmol) in CH_2Cl_2 (6.0 mL) was added benzoyl chloride (0.24 mL, 2.10 mmol) under argon atmosphere at −78 °C. After stirring at −70 °C, to the mixture was added **9** (0.53 mL, 2.4 mmol) at −78 °C. The reaction mixture was gradually warmed up to room temperature, followed by stirring at room temperature for 12 h. The solution was diluted with EtOAc and hexane, and the organic layer was washed successively with water, sat. $NaHCO_3$, and brine and dried over $MgSO_4$. The filtrate was concentrated under reduced pressure. Purification of the oil residue by column chromatography (SiO_2, 5—10% EtOAc in hexane) gave methyl 3-(*N*-benzoyloxy-*N*-benzylamino)-3-phenylpropionate (**10**) (776 mg, 99%) as an oil: IR (neat) 1745, 1452, 1176, 1082, 1059, 1024, 756, 708 cm^{-1}; ^1H NMR ($CDCl_3$) δ = 2.78 (dd, *J* = 6.8 and 15.4 Hz, 1 H, C<u>H</u>HCO$_2$), 3.14 (dd, *J* = 7.1 and 15.4 Hz, 1 H, C<u>H</u>HCO$_2$), 3.36 (s, 3 H, CH_3), 3.88 (d, *J* = 13.7 Hz, 1 H, C<u>H</u>HPh), 4.08 (d, *J* = 13.7 Hz, 1 H, C<u>H</u>HPh), 4.65 (dd, *J* = 6.8 and 7.1 Hz, 1 H, CHPh), 7.14—7.58 (m, 13 H, Ph), 7.85—7.92 (m, 2 H, Ph); ^{13}C NMR ($CDCl_3$) δ = 39.4, 51.4, 60.3, 67.3, 127.5, 128.1, 128.2, 128.3, 128.6, 128.7, 128.9, 129.2, 129.3, 132.9, 135.9, 165.0, 171.5. HRMS (FAB) Found: *m/z* 390.1718. Calcd for $C_{24}H_{24}NO_4$: M+H$^+$, 390.1706.

Methyl (1-Benzoyloxypyrrolidin-2-yl)acetate (20). The reaction of 1-pyrroline *N*-oxide (**16**) (425 mg, 5.00 mmol) with **9** via *N*-benzoyloxyiminium ion **26** gave **20** (1.21 g, 92%) as an oil: IR (neat) 2953,1738, 1314, 1258, 1206, 1086, 1064, 1026, 712 cm^{-1}; ^1H NMR ($CDCl_3$) δ = 1.53—1.73 (m, 1 H, C<u>H</u>HCH$_2$), 1.85—2.05 (m, 2 H, CH_2CH_2), 2.15—2.32 (m, 1 H, C<u>H</u>HCH$_2$), 2.53 (dd, *J* = 8.1 and 15.6 Hz, 1 H, C<u>H</u>HCO$_2$), 2.84 (dd, *J* = 5.6 and 15.6 Hz, 1 H, C<u>H</u>HCO$_2$), 3.03 (dd, *J* = 9.3 and 19.0 Hz, 1 H, CHHN), 3.60 (s, 3 H, CH_3), 3.52—3.75 (m, 2 H, C<u>H</u>HN and NCH), 7.38—7.50 (m, 2 H, Ph), 7.52—7.63 (m, 1 H, Ph), 7.96—8.04 (m, 2 H, Ph); ^{13}C NMR ($CDCl_3$) δ = 20.3, 27.1, 37.8, 51.6, 56.0, 64.2, 128.3, 129.3, 133.0, 165.1, 171.9. HRMS (FAB) Found: *m/z* 264.1260. Calcd for $C_{14}H_{18}NO_4$: M+H$^+$, 264.1236.

Methyl (1-Benzoyloxypiperidin-2-yl)acetate (21): 68% yield; IR (neat) 2948,1742, 1316, 1271, 1248, 1167, 1082, 1059, 1024 cm^{-1}; ^1H NMR ($CDCl_3$) δ = 1.20—2.00 (m, 6 H, $(CH_2)_3$), 2.38 (dd, *J* = 5.9 and 15.6 Hz, 1 H, C<u>H</u>HCO$_2$), 2.75 (dd, *J* = 5.9 and 15.6 Hz, 1 H, C<u>H</u>HCO$_2$), 2.70—2.85 (m, 1 H, C<u>H</u>HN), 3.30—3.50 (m, 2 H, NCH and C<u>H</u>HN), 3.40 (s, 3 H, CH_3), 7.39—7.65 (m, 3 H, Ph), 7.98—8.04 (m, 2 H, Ph); ^{13}C NMR ($CDCl_3$) δ = 23.4, 25.2, 31.9, 39.4, 51.3, 57.8, 63.5, 128.3, 129.4, 130.0, 133.0, 164.7, 172.4. HRMS (FAB) Found: *m/z* 278.1398. Calcd for $C_{15}H_{20}NO_4$: M+H$^+$, 278.1392.

Methyl (2-Benzoyloxy-1,2,3,4-tetrahydroisoquinolin-1-yl)acetate (22): 87% yield; IR (neat) 1740, 1451, 1262, 1248, 1177, 1086, 1059, 1024, 754, 710 cm^{-1}; ^1H NMR ($CDCl_3$) δ = 2.85 (dd, *J* = 5.3 and 15.6 Hz, 1 H, C<u>H</u>HCO$_2$), 2.96 (dd, *J* = 7.7 and 15.6 Hz, 1 H, C<u>H</u>HCO$_2$), 3.07 (br t, *J* = 6.1 Hz, 2 H, CH_2Ph), 3.50 (dt, *J* = 6.1 and 12.2 Hz, 1 H, C<u>H</u>HN), 3.60 (s, 3 H, CH_3), 3.65 (dt, *J* = 6.1 and 12.2 Hz, 1 H, C<u>H</u>HN), 4.98 (dd, *J* = 5.3 and 7.7 Hz, 1 H, CHN), 7.11—7.26 (m, 4 H, Ph), 7.36—7.63 (m, 3 H, Ph), 7.93—7.99 (m, 2 H, Ph); ^{13}C NMR ($CDCl_3$) δ = 26.0, 40.1, 49.8, 51.8, 62.1, 126.4, 126.9, 128.3, 128.6, 128.9, 129.4, 130.0, 133.1, 133.5, 135.2, 164.6, 171.9. HRMS (FAB) Found: *m/z* 326.1409. Calcd for $C_{19}H_{20}NO_4$: M+H$^+$, 326.1393.

Typical Procedure for Reduction of *O*-Benzoylhydroxylamines with Zn/AcOH. Methyl 3-(Benzylamino)-3-phenylpropionate (27). A mixture of **10** (150 mg, 0.385 mmol) and zinc powder (252 mg, 3.85 mmol) in AcOH (1.5 mL) was stirred at 60 °C for 1 h. The reaction mixture was filtered, and the filtrate was concentrated in vacuo. The oil residue was treated with concd aq NH_3 and diluted with EtOAc and water. The organic layer was separated, washed with brine, and dried over $MgSO_4$. Removal of the solvent and purification by chromatography (SiO_2, 10% EtOAc in hexane) gave **27** (81 mg, 78%) as an oil: IR (neat) 1736, 1454, 1198, 1167, 737, 700 cm^{-1}; ^1H NMR ($CDCl_3$) δ = 2.22 (br s, 1 H, NH), 2.63 (dd, *J* = 5.4 and 15.6 Hz, 1 H, C<u>H</u>HCO$_2$), 2.74 (dd, *J* = 8.8 and 15.6 Hz, 1 H, C<u>H</u>HCO$_2$), 3.54 (d, *J* = 13.2 Hz, 1 H, C<u>H</u>HPh), 3.62 (s, 3 H, CH_3), 3.65 (d, *J* = 13.2 Hz, 1 H, C<u>H</u>HPh), 4.12 (dd, *J* = 5.4 and 8.8 Hz, 1 H, NCH), 7.18—7.38 (m, 10 H, Ph); ^{13}C NMR ($CDCl_3$) δ = 42.8, 51.2, 51.6, 58.7, 126.9, 127.0, 127.5,

128.1, 128.3, 128.6, 140.0, 142.3, 172.1. HRMS (FAB) Found: *m/z* 270.1491. Calcd for $C_{17}H_{20}NO_2$: M+H$^+$, 270.1494.

Typical Procedure for Reduction of *O*-Benzoylhydroxylamines by Catalytic Hydrogenation. Methyl Pyrrolidin-2-ylacetate (28). A mixture of **20** (1.20 g, 4.55 mmol) and 10% Pd/C (473 mg) in MeOH (4 mL) was stirred under atmospheric pressure of H_2 at 0 °C for 1 h. The catalyst was filtered off, and the solvent was evaporated in vacuo. The residue was purified by SiO_2 column chromatography to afford **28** (429 mg, 66%): IR (CH_2Cl_2) 2975, 1733, 1630 cm^{-1}; ^{1}H NMR ($CDCl_3$, 270 MHz) δ = 1.25—1.44 (m, 1 H, CHHCH$_2$), 1.66—2.02 (m, 3 H, CH$_2$CHH), 2.23 (s, 1 H, NH), 2.44 (dd, J = 8.2 and 15.6 Hz, 1 H, CHHCO$_2$), 2.50 (dd, J = 5.6 and 15.6 Hz, 1 H, CHHCO$_2$), 2.82—3.07 (m, 2 H, CH$_2$N), 3.30—3.50 (m, 1 H, NCH), 3.68 (s, 3 H, CH$_3$). MS (APCI) *m/z* 144 (M+H$^+$).

Methyl Piperidin-2-ylacetate (29): 86% yield; IR (CH_2Cl_2) 2950, 2870, 1733, 1443, 1173 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ = 1.06—1.85 (m, 6 H, (CH$_2$)$_3$), 1.97 (s, 1 H, NH), 2.33 (dd, J = 1.6 and 10.2 Hz, 1 H, CHHCO$_2$), 2.39 (d, J = 10.2 Hz, 1 H, CHHCO$_2$), 2.66 (dt, J = 3.1 and 11.7 Hz, 1 H, CHHN), 2.84—3.08 (m, 2 H, CHHN and NH), 3.68 (s, 3 H, CH$_3$). MS (APCI) *m/z* 158 (M+H$^+$).

Reaction of *N*-Benzoyloxyiminium Ion 7 with Allyltributyltin. To a mixture of **6** (423 mg, 2.00 mmol) and 4 Å molecular sieves (300 mg) in CH_2Cl_2 (6 mL) was added benzoyl chloride (0.244 mL, 2.10 mmol) at −78 °C. The reaction mixture was stirred at −40 °C for 30 min. To the solution at −78 °C was added allyltributyltin (0.744 mL, 2.40 mmol) dropwise, and the reaction mixture was stirred at −40 °C for 30 min. Column chromatography of the reaction mixture (SiO_2, 0—5% EtOAc in hexane) gave *O*-benzoyl-*N*-benzyl-*N*-(1-phenyl-3-buten-1-yl)hydroxylamine (**23**) (637 mg, 89%) as an oil: IR (neat) 1748, 1453, 1242, 1082, 1061, 1026, 752, 706 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ = 2.58—2.90 (m, 2 H, CH$_2$CH=), 3.90 (d, J = 13.9 Hz, 1 H, CHHPh), 4.08 (d, J = 13.9 Hz, 1 H, CHHPh), 4.08 (dd, J = 5.6 and 9.3 Hz, 1 H, NCH), 4.85—5.00 (m, 2 H, CH=CH$_2$), 5.56—5.74 (m, 1 H, CH=CH$_2$), 7.14—7.56 (m, 13 H, Ph), 7.85—7.94 (m, 2 H, Ph); ^{13}C NMR ($CDCl_3$) δ = 38.0, 60.1, 70.8, 116.9, 127.4, 127.9, 128.0, 128.3, 129.1, 129.2, 129.3, 132.8, 134.8, 136.2, 165.0. HRMS (FAB) Found: *m/z* 358.1800. Calcd for $C_{24}H_{24}NO_2$: M+H$^+$, 358.1807.

Reaction of *N*-Benzoyloxyiminium Ion 7 with Tributyltin Hydride. To a solution of **6** (221 mg, 1.00 mmol) and tributyltin hydride (0.322 mL, 1.20 mmol) in CH_2Cl_2 (3 mL) was added benzoyl chloride (0.12 mL, 1.05 mmol) at −78 °C. The reaction mixture was gradually warmed up to room temperature, followed by being stirred at room temperature for 12 h. The reaction mixture was chromatographed (SiO_2, 0—5% EtOAc in hexane) to give crude crystalline *O*-benzoyl-*N*,*N*-dibenzylhydroxylamine (**24**). Trituration of crude **24** with 10% EtOAc in hexane gave pure **24** (263 mg, 83%) as white crystals: mp 99.0—100.0 °C; IR (Nujol®) 1726, 1254, 1096, 1069, 1026, 750, 708 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ = 4.20 (s, 4 H, CH$_2$Ph and CH$_2$Ph), 7.20—7.52 (m, 13 H, Ph), 7.78—7.86 (m, 2 H, Ph); ^{13}C NMR ($CDCl_3$) δ = 62.1, 127.6, 128.26, 128.31, 129.2, 129.3, 129.4, 132.8, 135.9, 165.0. HRMS (FAB) Found: *m/z* 318.1504. Calcd for $C_{21}H_{20}NO_2$: M+H$^+$, 318.1494. Found C, 79.03; H, 6.09; N, 4.46%. Calcd for $C_{21}H_{19}NO_2$: C, 79.47; H, 6.03; N, 4.41%.

Reaction of *N*-Benzoyloxyiminium Ion with Titanium(IV) Acetylide 19. To a solution of 4 Å molecular sieves (250 mg) and nitrone **17** (198 mg, 2.00 mmol) in CH_2Cl_2 (2 mL) was added benzoyl chloride (0.255 mL, 2.20 mmol) at −78 °C, and the solution was stirred at −50 °C for 30 min. To the stirred solution were successively added $TiCl_4$ (0.219 mL, 2.00 mmol) and lithium acetylide, prepared from 3-(*t*-butyldimethylsiloxy)-1-propyne (0.450 mL, 2.40 mmol) and butyllithium (1.6 M, 2.40 mmol) at 0 °C for 30 min, at −78 °C, then the reaction mixture was warmed up to −50 °C (1 M = 1 mol dm^{-3}). The reaction mixture was diluted with hexane. The organic phase was washed with sat. $NaHCO_3$ and brine, and dried over $MgSO_4$. Evaporation of the solvent and purification of the crude oil by column chromatography (SiO_2, 5—7.5% EtOAc in hexane) gave 1-benzoyloxy-2-(3-*t*-butyldimethylsiloxy-1-propyn-1-yl)piperidine (**25**) (457 mg, 61%): IR (neat) 2951, 2930, 2886, 2859, 1744, 1453, 1246, 1136, 1088, 1067, 1026, 1006, 837, 779, 710 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ = 0.08 (br s, 6 H, Si(CH$_3$)$_2$), 0.87 (br s, 9 H, SiC(CH$_3$)$_3$), 1.3—2.6 (m, 6 H, (CH$_2$)$_3$), 2.8—3.6 (m, 3 H), 4.2—4.5 (m, 2 H), 7.35—7.44 (m, 2 H, Ph), 7.48—7.56 (m, 1 H, Ph), 7.98—8.04 (m, 2 H, Ph). HRMS (FAB) Found: *m/z* 374.2159. Calcd for $C_{21}H_{32}NO_3Si$: M+H$^+$, 374.2151.

2-(3-*t*-Butyldimethylsiloxy-1-propyn-1-yl)piperidine (30). A mixture of **25** (373 mg, 1.00 mmol) and zinc powder (327 mg) in a solvent mixture of CH_2Cl_2 (2 mL) and AcOH (1 mL) was stirred at room temperature for 3 h. The precipitate was filtered off and the solvent was evaporated in vacuo. The residue was diluted with EtOAc, and the organic layer was washed with sat. $NaHCO_3$ and brine. After the layer was dried over $MgSO_4$, evaporation of the solvent and purification by SiO_2 column chromatography gave **30** (164 mg, 65%): IR (CH_2Cl_2) 2952, 2880, 1080, 835 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ = 0.10 (br s, 6 H, Si(CH$_3$)$_2$), 0.87 (br s, 9 H, SiC(CH$_3$)$_3$), 1.30—1.90 (m, 6 H, (CH$_2$)$_3$), 1.95 (s, 1 H, NH), 2.60—2.75 (m, 1 H, HCHN), 3.00—3.20 (m, 1 H, CHHN), 3.60—3.72 (m, 1 H, NCH), 3.34 (d, J = 1.8 Hz, 2 H, CH$_2$O). MS (APCI) *m/z* 254 (M+H$^+$).

2-(3-*t*-Butyldimethylsiloxy-1-propyl)piperidine (31). Piperidine **31** (186 mg, 63%) was obtained as an oil from **25** (431 mg, 1.15 mmol) by catalytic hydrogenation: IR (CH_2Cl_2) 2952, 2880, 1090 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ = 0.01 (s, 6 H, Si(CH$_3$)$_2$), 0.91 (s, 9 H, SiC(CH$_3$)$_3$), 0.95—1.82 (m, 10 H), 1.75 (s, 1 H, NH), 2.34—2.50 (m, 1 H, CHHN), 2.58 (dt, J = 3.1 and 11.6 Hz, 1 H, CHHN), 2.90—3.10 (m, 1 H, NCH), 3.56 (t, J = 6.2 Hz, 2 H, CH$_2$O). MS (APCI) *m/z* 258 (M+H$^+$).

Reactions of Chiral *N*-Acyloxyiminium Species Prepared from Nitrones with (*R*)-*O*-Acetylmandelyl Chloride (32). Preparation of *O*-[(2*R*)-2-Acetoxyphenylacetyl]-*N*-benzyl-1-phenyl-3-buten-1-ylhydroxylamine (34). To a solution of *N*-acyloxyiminium ion **33** (0.50 mmol), which was prepared from nitrone **6** (106 mg, 0.50 mmol) and (*R*)-**32** (0.091 mL, 0.50 mmol) in situ, and 4-Å molecular sieves (100 mg) in CH_2Cl_2 (1.5 mL) was added $TiCl_4$ (0.06 mL, 0.55 mmol) at −78 °C, and the mixture was stirred at 0 °C for 0.5 h. After cooling at −78 °C again, to the mixture was added allyltrimethylsilane (0.119 mL, 0.75 mmol), then the mixture was stirred at 0 °C for 1 h. To the mixture were added hexane (5 mL), sat. $NaHCO_3$ (5 mL), and 10 M KF (5 mL), and the mixture was stirred at room temperature for 0.5 h. The mixture was filtered through Celite®, and the cake was washed with EtOAc. The organic layer was separated, washed with sat. $NaHCO_3$ and brine, and dried over $MgSO_4$. After filtration and removal of the solvent, the yield and the diastereomeric ratio were determined by ^{1}H NMR analysis. The product was purified by column chromatography (SiO_2, EtOAc in hexane) to give **34** (71% yield, 64% de) as a diastereomeric mixture: IR (neat) 1773, 1750, 1497, 1454, 1373, 1235, 1142, 1050, 750, 698 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ = 2.13 (s, 3 H, CH$_3$), 2.33—2.72 (m, 2 H, CH$_2$CH=CH$_2$), 3.58—3.96 (m, 3 H, PhCH$_2$, PhCH), 4.79—4.93 (m, 2 H, CH$_2$=CH), 5.46—5.64 (m, 1 H, CH=CH$_2$), 5.81 (s, 1 H, CHOAc of major isomer), 5.82 (s, 1 H, CHOAc of minor isomer), 7.08—7.38 (m, 15 H, Ph); ^{13}C NMR

($CDCl_3$) δ = 20.6, 37.7, 59.8, 70.9, 73.6, 116.8, 127—129 (Ph), 133.5, 134.8, 135.7, 137.9, 167.2, 170.0. HRMS (FAB) Found: *m/z* 430.2006. Calcd for $C_{27}H_{28}NO_4$: M+H$^+$, 430.2019.

Diastereoselective Addition of Chiral Ketene Silyl Acetal 35 to *N*-Benzoyloxyiminium Ion 7. To a mixture of nitrone **6** (211 mg, 1.00 mmol) and 4 Å molecular sieves (150 mg) in CH_2Cl_2 (3.0 mL) was added benzoyl chloride (0.122 mL, 1.05 mmol) at −78 °C. The reaction mixture was stirred at −40 °C for 30 min. To the solution was added (*Z*)-(*R*)-1-methoxy-1,3-bis(triethylsiloxy)-1-butene (**35**) (0.447 mL, 1.20 mmol) dropwise at −78 °C, and the reaction temperature was gradually raised to room temperature during 1 h. The reaction mixture diluted with MeOH (3 mL) was treated with 6 M HCl (0.2 mL) at 0 °C for 30 min and neutralized with sat. $NaHCO_3$. The solution was extracted with hexane. The organic layer was washed with brine, dried over $MgSO_4$, and evaporated. Column chromatography (SiO_2, 2.5—15% EtOAc in hexane) of the crude oil gave methyl (2*S*,3*R*,1′*R*)-2-[α-(*N*-benzoyloxy-*N*-benzylamino)benzyl]-3-hydroxybutanoate (**36**) (242 mg, 72%) as an oil: $[\alpha]_D^{24}$ −33.0° (*c* 2.21, MeOH); IR (neat) 3428, 1738, 1453, 1314, 1258, 1082, 1061, 1026, 704 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ = 1.00—1.40 (m, 3 H, CHC<u>H</u>$_3$), 3.24 (dd, *J* = 8.1 and 11.8 Hz, 1 H, C<u>H</u>CO$_2$), 3.26 (s, 3 H, CH_3), 3.60—4.65 (m, 3 H, C<u>H</u>CH$_3$ and NC<u>H</u>$_2$Ph), 4.21 (d, *J* = 11.8 Hz, 1 H, NCHPh), 7.25—7.65 (m, 13 H, Ph), 7.90—8.03 (m, 2 H, Ph). HRMS (FAB) Found: *m/z* 434.1971. Calcd for $C_{26}H_{28}NO_5$: M+H$^+$, 434.1968.

Methyl (2*S*,3*R*,1′*R*)-2-[α-(Benzylamino)benzyl]-3-hydroxybutanoate (37).[9] A solution of **36** (226 mg, 0.521 mmol) and Zn (510 mg, 7.81 mmol) in AcOH (4.0 mL) was stirred at 55 °C for 30 min. The reaction mixture was filtered and the filtrate was evaporated in vacuo. The residue was treated with EtOAc (20 mL) and concd aq NH_3 (1 mL). The organic layer was separated, washed with brine, and dried over $MgSO_4$. Removal of the solvent and purification by column chromatography (SiO_2, 10—20% EtOAc in hexane) gave **37** in 73% yield: $[\alpha]_D^{24}$ +59.5° (*c* 1.11, MeOH); IR (Nujol®) 3378, 1728, 1466, 1437, 1379, 1327, 1198 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ = 1.16 (d, *J* = 6.1 Hz, 3 H, CHC<u>H</u>$_3$), 2.69 (dd, *J* = 9.0 and 11.0 Hz, 1 H, C<u>H</u>CO$_2$), 3.28 (s, 3 H, OCH_3), 3.55 (d, *J* = 12.4 Hz, 1 H, C<u>H</u>HPh), 3.64 (d, *J* = 12.4 Hz, 1 H, C<u>H</u>HPh), 4.00 (d, *J* = 11.0 Hz, 1 H, CHPh), 4.21 (dq, *J* = 9.0 and 6.1 Hz, 1 H, C<u>H</u>CH$_3$), 7.15—7.42 (m, 10 H, Ph); ^{13}C NMR ($CDCl_3$) δ = 21.6, 50.7, 51.2, 59.1, 65.2, 70.7, 127.1, 127.5, 128.0, 128.3, 128.6, 128.7, 138.1, 139.6, 171.6. HRMS (FAB) Found: *m/z* 314.1761. Calcd for $C_{19}H_{24}NO_3$: M+H$^+$, 314.1756. Found: C, 72.56; H, 7.29; N, 4.62%. Calcd for $C_{19}H_{23}NO_3$: C, 72.82; H, 7.40; N, 4.47%.

Diastereoselective Addition of Chiral Enolates to *N*-Acyloxyiminium Ions. General Procedure for the Preparation of Boron Enolates (M: BEt_2).[34] To a mixture of propionic acid derivative (2.0 mmol) and 4-Å molecular sieves in CH_2Cl_2 (6.0 mL) were added successively Et_2BOTf (0.395 mL, 2.3 mmol) and *i*-Pr_2EtN (0.401 mL, 2.4 mmol) at −78 °C under argon, and the mixture was stirred at 0 °C for 0.5 h.

General Procedure for the Preparation of Titanium(IV) Enolates (M: $TiCl_2$(O-*i*-Pr)).[35] To a mixture of Ti(O-*i*-Pr)$_4$ (0.17 mL, 0.60 mmol) and 4-Å molecular sieves in CH_2Cl_2 (4.0 mL) was added $TiCl_4$ (0.19 mL, 1.7 mmol) under argon, and the mixture was stirred at room temperature until it became a clear solution. After cooling at −78 °C, to the solution were added a solution of propionic acid derivative (2.0 mmol) in CH_2Cl_2 (2.0 mL) followed by *i*-Pr_2EtN (0.418 mL, 2.4 mmol). Then, the mixture was stirred at 0 °C for 0.5 h.

General Procedure for the Preparation of Titanium(IV) Enolates Bearing Carboxylato Ligand (M: $TiCl_2$(OCOR)). To a mixture of propionic acid derivatives (2.0 mmol) and 4-Å molecular sieves (300 mg) in CH_2Cl_2 (4 mL) were added $TiCl_4$ (2.2 mmol) followed by *i*-Pr_2EtN (2.4 mmol) at −78 °C under argon. The mixture was stirred at 0 °C for 0.5 h. After cooling to −78 °C again, a mixture of carboxylic acid (2.4 mmol), *i*-Pr_2EtN (2.6 mmol), and 4-Å molecular sieves (200 mg) in CH_2Cl_2 (2.0 mL) was added to the mixture. Then, the mixture was stirred at 0 °C for 0.5 h.

General Procedure for the Reaction of *N*-Acyloxyiminium Ions with Boron Enolates. To a solution of enolate (2.0 mmol) was added a solution of *N*-acyloxyiminium ion (3.0 mmol), which was prepared from nitrone (3.0 mmol) and acyl chloride (3.0 mmol), dropwise at −78 °C under argon, and the reaction mixture was stirred at the same temperature for 1 h. To the mixture were added hexane, sat. $NaHCO_3$, and EtOAc. The organic layer was separated, washed with sat. $NaHCO_3$ and brine, and dried over $MgSO_4$. After filtration and removal of the solvent, $CHCl_2CHCl_2$ was added as an internal standard, and the yield and diastereomeric ratio were determined by ^{1}H NMR analysis; these results are summarized in Tables 2 and 3. The product was purified by column chromatography (SiO_2, 5—25% EtOAc in hexane), and the spectral data are described below.

General Procedure for the Reaction of *N*-Acyloxyiminium Ions with Titanium(IV) Enolates. To a solution of enolate (2.0 mmol) was added a solution of *N*-acyloxyiminium ion (3.0 mmol), which was prepared from nitrone (3.0 mmol) and acyl chloride (3.0 mmol), dropwise at −78 °C under argon, and the mixture was stirred at the same temperature for 1 h. When the carboxylate-modified titanium(IV) enolate was used, the reactions were carried out at 0 °C. To the mixture were added hexane, sat. $NaHCO_3$, and 10 M KF, and the mixture was stirred at room temperature for 0.5 h. The mixture was filtered through Celite®, and the cake was washed with EtOAc. The organic layer was separated, washed with sat. $NaHCO_3$ and brine, and dried over $MgSO_4$. After filtration and removal of the solvent, $CHCl_2CHCl_2$ was added as an internal standard, and the yield and diastereomeric ratio were determined by ^{1}H NMR analysis. The results are summarized in Tables 2, 3, and 4. The product was purified by column chromatography (SiO_2, 5—25% EtOAc in hexane), and the spectral data are described below.

(4*S*)-3-[(2*R*,3*S*)-3-(*N*-Benzoyloxy-*N*-benzylamino)-2-methyl-3-phenylpropionyl]-4-(1-methylethyl)-2-oxazolidinone (39a): mp 153.5—154 °C, $[\alpha]_D^{29}$ +103.9° (*c* 1.02, $CHCl_3$); IR (Nujol®) 1777, 1752, 1703, 1202, 1059, 710 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ = 0.84 (d, *J* = 7.1 Hz, 3 H, CH_3), 1.05 (d, *J* = 7.1 Hz, 3 H, CH_3), 1.14 (d, *J* = 6.8 Hz, 3 H, CH_3), 2.52—2.70 (m, 1 H), 3.87 (d, *J* = 12.9 Hz, 1 H, C<u>H</u>HPh), 4.07 (d, *J* = 12.9 Hz, 1 H, C<u>H</u>HPh), 4.18—4.28 (m, 2 H), 4.42—4.52 (m, 1 H), 4.50 (d, *J* = 11.0 Hz, 1 H, CHPh), 4.78 (dq, *J* = 11.0 and 7.1 Hz, 1 H, C<u>H</u>CH$_3$), 7.20—7.90 (m, 15 H, Ph); ^{13}C NMR ($CDCl_3$) δ = 15.0, 16.1, 17.7, 29.1, 39.0, 59.3, 60.3, 63.2, 70.9, 127.5—135.9, 153.8, 164.8, 175.5. HRMS (FAB) Found: *m/z* 501.2361. Calcd for $C_{30}H_{33}N_2O_5$ M+H$^+$, 501.2390.

(4*S*)-3-[(2*R*,3*R*)-3-(*N*-Benzoyloxy-*N*-benzylamino)-2-methyl-3-phenylpropionyl]-4-(1-methylethyl)-2-oxazolidinone (39b): mp 158—159 °C, $[\alpha]_D^{20}$ −41.4° (*c* 0.99, $CHCl_3$); IR (Nujol®) 1773, 1745, 1701, 1453, 1383, 1213, 700 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ = 0.23 (d, *J* = 6.8 Hz, 3 H, CH_3), 0.57 (d, *J* = 7.1 Hz, 3 H, CH_3), 1.53 (d, *J* = 6.4 Hz, 3 H, CH_3), 1.51—1.59 (m, 1 H), 3.87 (d, *J* = 12.7 Hz, 1 H, C<u>H</u>HPh), 4.00 (dd, *J* = 2.7 and 8.8 Hz, 1 H), 4.10 (dd, *J* = 8.8 and 6.5 Hz, 1 H), 4.19 (d, *J* = 12.7 Hz, 1 H, C<u>H</u>HPh), 4.22 (d, *J* = 11.0 Hz, 1 H, CHPh), 4.18—4.26 (m, 1 H), 4.90 (dq, *J* = 11.0 and 6.6 Hz, 1 H), 7.20—8.20 (m, 15 H, Ph); ^{13}C NMR ($CDCl_3$) δ = 14.2, 16.3, 17.6, 28.2, 39.8, 58.2, 59.4, 62.8, 70.1,

127.6—136.0, 153.5, 165.1, 175.2. Found: C, 71.87; H, 6.48; N, 5.64%. Calcd for $C_{30}H_{32}N_2O_5$: C, 71.98; H, 6.44; N, 5.60%.

(4*R*)-3-[(2*S*,3*R*)-3-(*N*-Benzoyloxy-*N*-benzylamino)-2-methyl-3-phenylpropionyl]-4-phenyl-2-oxazolidinone (46a): ^{1}H NMR ($CDCl_3$) δ = 0.84 (d, J = 6.8 Hz, 3 H, CH_3), 3.71 (d, J = 12.7 Hz, 1 H, CHHPh), 3.96 (d, J = 12.7 Hz, 1 H, CHHPh), 4.27 (dd, J = 6.0 and 9.0 Hz, 1 H), 4.31 (d, J = 10.5 Hz, 1 H, CHPh), 4.65 (dd, J = 9.0 and 9.0 Hz, 1 H), 4.86 (dq, J = 10.5 and 6.8 Hz, 1 H, CH_3CH), 5.41 (dd, J = 6.0 and 9.0 Hz, 1 H), 6.88—7.59 (m, 15 H, Ph), 7.53—7.81 (m, 3 H, Ph), 7.90—7.96 (m, 2 H, Ph); ^{13}C NMR ($CDCl_3$) δ = 15.7, 57.5, 59.0, 60.5, 69.7, 71.3, 125.9—139.1 (Ph), 153.5, 165.0, 175.7.

(4*R*)-3-[(2*S*,3*S*)-3-(*N*-Benzoyloxy-*N*-benzylamino)-2-methyl-3-phenylpropionyl]-4-phenyl-2-oxazolidinone (46b): $[\alpha]_D^{26}$ −7.13° (*c* 1.01, $CHCl_3$); IR (Nujol®) 1781, 1742, 1701, 1256, 698 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ = 1.54 (d, J = 6.6 Hz, 3 H, CH_3), 3.72 (d, J = 12.5 Hz, 1 H, CHHPh), 3.96 (dd, J = 4.4 and 8.8 Hz, 1 H), 4.10 (d, J = 11.0 Hz, 1 H, PhCHCH), 4.14 (d, J = 12.5 Hz, 1 H, CHHPh), 4.50 (dd, J = 8.8 and 8.8 Hz, 1 H), 4.97 (dq, J = 11.0 and 6.6 Hz, 1 H, CH_3CH), 5.18 (dd, J = 4.4 and 8.8 Hz, 1 H), 6.45—6.48 (m, 2 H, Ph), 6.97—7.59 (m, 16 H, Ph), 7.98—8.01 (m, 2 H, Ph); ^{13}C NMR ($CDCl_3$) δ = 16.4, 39.9, 57.7, 59.4, 69.4, 69.8, 124.7, 127.6, 127.7, 128.1, 128.4, 128.5, 128.8, 129.3, 129.4, 130.6, 133.0, 135.4, 136.0, 138.1, 153.2, 165.1, 174.9. Found: C, 74.40; H, 5.81; N, 5.31%. Calcd for $C_{28}H_{30}N_2O_5$: C, 74.13; H, 5.66; N, 5.24%.

(4*R*)-3-[(2*S*,3*R*)-3-(*N*-Benzoyloxy-*N*-benzylamino)-2-methyl-3-phenylpropionyl]-4-benzyl-2-oxazolidinone (47a): mp 99—102 °C; $[\alpha]_D^{26}$ +33.1° (*c* 0.737, $CHCl_3$); IR (KBr) 1788, 1769, 1738, 1686, 1287, 1248, 1223, 1053, 721, 706, 694 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ = 0.89 (d, J = 6.8 Hz, 3 H, CH_3CHCO), 3.00 (dd, J = 11.7 and 13.7 Hz, 1 H, CHCHHPh), 3.89 (d, J = 13.0 Hz, 1 H, NHCHPh), 3.92 (dd, J = 3.4 and 13.7 Hz, 1 H, CHCHHPh), 3.99 (d, J = 13.0 Hz, 1 H, NHCHPh), 4.11 (dd, J = 7.8 and 8.9 Hz, 1 H, CHHO), 4.16 (dd, J = 3.7 and 8.9 Hz, 1 H, CHHO), 4.49 (d, J = 11.2 Hz, 1 H, NCHPh), 4.71 (dddd, J = 3.4, 3.7, 7.8, and 11.5 Hz, 1 H, $NCHCH_2O$), 4.84 (dq, J = 11.2 and 6.8 Hz, 1 H, $COCHCH_3$), 7.12—7.68 (m, 18 H, Ph), 7.79—8.00 (m, 2 H, Ph); ^{13}C NMR ($CDCl_3$) δ = 15.7, 37.6, 38.9, 56.2, 60.7, 66.3, 72.3, 126.9-137.0, 153.4, 165.1, 176.2. Found: C, 74.18; H, 5.89; N, 5.14%. Calcd for $C_{34}H_{32}N_2O_5$: C, 74.43; H, 5.88; N, 5.11%.

(4*R*)-3-[(2*S*,3*S*)-3-(*N*-Benzoyloxy-*N*-benzylamino)-2-methyl-3-phenylpropionyl]-4-benzyl-2-oxazolidinone (47b): mp 101—104 °C; $[\alpha]_D^{24}$ +36.3° (*c* 0.985, $CHCl_3$); IR (KBr) 1788, 1769, 1738, 1688, 1287, 1248, 1223, 1053, 721, 708, 694 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ = 1.56 (d, J = 6.6 Hz, 3 H, CH_3CHCO), 1.79 (dd, J = 10.0 and 13.4 Hz, 1 H, CHCHHPh), 2.33 (dd, J = 3.2 and 13.4 Hz, 1 H, CHCHHPh), 3.82 (d, J = 12.7 Hz, 1 H, CHHPh), 3.89 (dd, J = 2.9 and 9.0 Hz, 1 H, CHHO), 3.98 (dd, J = 7.8 and 9.0 Hz, 1 H, CHHO), 4.21 (d, J = 12.7 Hz, 1 H, NCHHPh), 4.23 (d, J = 11.0 Hz, 1 H, NCHPh), 4.34—4.43 (m, 1 H, $NCHCH_2O$), 4.90 (dq, J = 11.0 and 6.6 Hz, 1 H, $COCHCH_3$), 6.83—6.93 (m, 2 H, Ph), 7.14—7.62 (m, 16 H, Ph), 7.97—8.04 (m, 2 H, Ph); ^{13}C NMR ($CDCl_3$) δ = 16.1, 36.7, 40.0, 54.9, 59.5, 65.5, 70.5, 127.0, 127.7, 128.1, 128.3, 128.4, 128.5, 128.8, 129.1, 129.3, 129.4, 129.4, 130.7, 133.0, 135.4, 135.8, 136.0, 152.8, 165.1, 175.4. Found: C, 74.28; H, 5.90; N, 5.12%. Calcd for $C_{34}H_{32}N_2O_5$: C, 74.43; H, 5.88; N, 5.11%.

(4*S*)-3-[(2*R*,3*S*)-3-(*N*-Benzoyloxy-*N*-benzylamino)-2-methyl-3-phenylpropionyl]-4-*t*-butyl-2-oxazolidinone (48a): $[\alpha]_D^{26}$ +119.8° (*c* 0.97, $CHCl_3$); IR (Nujol®) 1774, 1752, 1705, 1183, 1103, 976, 710 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ = 0.79 (d, J = 7.8 Hz, 3 H, $COCHCH_3$), 1.17 (s, 9 H, $C(CH_3)_3$), 3.85 (d, J = 12.8 Hz, 1 H, CHHPh), 4.04 (d, J = 12.8 Hz, 1 H, CHHPh), 4.17 (dd, J = 7.6 and 9.3 Hz, 1 H), 4.28 (dd, J = 1.6 and 9.3 Hz, 1 H), 4.47 (dd, J = 1.6 and 7.6 Hz, 1 H) 4.52 (d, J = 11.2 Hz, 1 H, NCH), 4.70—4.91 (m, 1 H, NCHCH), 7.12—7.57 (m, 13 H, Ph), 7.81—7.92 (m, 2 H, Ph); ^{13}C NMR ($CDCl_3$) δ = 16.4, 25.7, 36.1, 38.9, 60.7, 62.0, 65.1, 71.1, 127.5, 128.0, 128.1, 128.2, 128.3, 129.4, 129.6, 131.1, 132.6, 134.3, 135.8, 154.1, 164.8, 175.6. Found: C, 72.24; H, 6.64; N, 5.41%. Calcd for $C_{31}H_{34}N_2O_5$: C, 72.35; H, 6.66; N, 5.44%.

(4*S*)-3-[(2*R*,3*R*)-3-(*N*-Benzoyloxy-*N*-benzylamino)-2-methyl-3-phenylpropionyl]-4-*t*-butyl-2-oxazolidinone (48b): $[\alpha]_D^{27}$ −24.4° (*c* 1.02, $CHCl_3$); IR (Nujol®) 1779, 1748, 1701, 1319, 1184, 959, 760, 705 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ = 0.37 (s, 9 H, $(CH_3)_3$), 1.51 (d, J = 6.6 Hz, 3 H, CH_3CHCO), 3.81 (d, J = 13.0 Hz, 1 H, CHHPh), 4.01—4.18 (m, 4 H, CH_2O, $CHCH_2O$, and CHHPh), 4.21 (d, J = 11.0 Hz, 1 H, NCH), 4.96 (dq, J = 11.0 and 6.6 Hz, 1 H, NCHCH), 7.19—7.60 (m, 13 H, Ph), 7.92—8.02 (m, 2 H, Ph); ^{13}C NMR ($CDCl_3$) δ = 16.5, 24.9, 35.2, 39.4, 59.4, 61.0, 64.7, 70.3, 127.6, 128.2, 128.4, 128.5, 129.3, 129.4, 129.5, 130.8, 132.9, 135.4, 136.1, 154.2, 165.1, 175.2. Found: C, 72.08; H, 6.67; N, 5.41%. Calcd for $C_{31}H_{34}N_2O_5$: C, 72.35; H, 6.66; N, 5.44%.

(4*R*, 5*S*)- 3- [(2*S*, 3*R*)- 3- (*N*- Benzoyloxy- *N*- benzylamino)- 2-methyl-3-phenylpropionyl]-4-methyl-5-phenyl-2-oxazolidinone (49a): mp 140.5—142.0 °C; $[\alpha]_D^{24}$ +20.2° (*c* 1.02, $CHCl_3$); IR (KBr) 1778, 1750, 1698, 1454, 1387, 1370, 1346, 1260, 1234, 1196, 1057, 1024, 700 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ = 0.90 (d, J = 7.1 Hz, 3 H, CH_3CHCO), 1.20 (d, J = 6.6 Hz, 3 H, CH_3CHN), 3.84 (d, J = 13.0 Hz, 1 H, CHHPh), 4.00 (d, J = 13.0 Hz, 1 H, CHHPh), 4.46 (d, J = 11.2 Hz, 1 H, NCHPh), 4.78—4.94 (m, 2 H, NCHCH and $CHCH_3$), 5.63 (d, J = 7.8 Hz, 1 H, CHPh), 7.16—7.58 (m, 18 H, Ph), 7.88—7.93 (m, 2 H, Ph); ^{13}C NMR ($CDCl_3$) δ = 14.4, 15.9, 39.0, 55.2, 60.4, 71.8, 78.7, 126.1, 127.5, 128.0, 128.2, 128.3, 128.6, 128.6, 129.3, 129.4, 129.7, 130.9, 132.7, 133.9, 134.2, 135.9, 153.0, 165.0, 175.8. Found: C, 74.60; H, 5.95; N, 5.07%. Calcd for $C_{34}H_{32}N_2O_5$: C, 74.42; H, 5.88; N, 5.11%.

(4*R*, 5*S*)- 3- [(2*S*, 3*S*)- 3- (*N*- Benzoyloxy- *N*- benzylamino)- 2-methyl-3-phenylpropionyl]-4-methyl-5-phenyl-2-oxazolidinone (49b): $[\alpha]_D^{24}$ +73.4° (*c* 1.02, $CHCl_3$); IR (KBr) 1780, 1744, 1699, 1454, 1383, 1368, 1342, 1256, 1240, 1196, 1055, 1024, 701 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ = 0.08 (d, J = 6.6 Hz, 3 H, CH_3CHN), 1.58 (d, J = 6.6 Hz, 3 H, CH_3CHCO), 3.82 (d, J = 12.7 Hz, 1 H, CHHPh), 4.18 (d, J = 11.2 Hz, 1 H, CHPh), 4.20 (d, J = 12.7 Hz, 1 H, CHHPh), 4.50 (dq, J = 7.3 and 6.6 Hz, 1 H, $NCHCH_3$), 4.94 (dq, J = 11.2 and 6.6 Hz, 1 H, $COCHCH_3$), 5.48 (d, J = 7.3 Hz, 1 H, OCH), 7.13—7.60 (m, 18 H, Ph), 8.00—8.04 (m, 2 H, Ph); ^{13}C NMR ($CDCl_3$) δ = 13.2, 16.2, 39.9, 54.2, 59.5, 70.3, 78.3, 125.6, 127.7, 128.0, 128.1, 128.4, 128.5, 128.6, 128.6, 129.3, 129.4, 129.5, 130.6, 133.0, 133.3, 135.8, 136.0, 152.5, 165.1, 175.2. Found: C, 74.70; H, 6.09; N, 5.09%. Calcd for $C_{34}H_{32}N_2O_5$: C, 74.42; H, 5.88 N, 5.11%.

(4*S*, 5*R*)- 3- [(2*R*, 3*S*)- 3- (*N*- Benzoyloxy- *N*- benzylamino)- 2-methyl-3-phenylpropionyl]-4,5-diphenyl-2-oxazolidinone (50a): $[\alpha]_D^{24.5}$ −27.9° (*c* 0.756, $CHCl_3$); IR (KBr) 3063, 3032, 2934, 1782, 1748, 1703, 1454, 1349, 1260, 1240, 1184, 1061, 700 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ = 0.90 (d, J = 6.8 Hz, 3 H, $CHCH_3$), 3.74 (d, J = 12.9 Hz, 1 H, CHHPh), 4.03 (d, J = 12.9 Hz, 1 H, CHHPh), 4.38 (d, J = 11.0 Hz, 1 H, NCHPh), 4.98 (br, 1 H, $CHCH_3$), 5.69 (d, J = 8.1 Hz, 1 H, CHPh), 5.86 (d, J = 8.1 Hz, 1 H, CHPh), 6.83—7.58 (m, 23 H, Ph), 7.95—8.05 (m, 2 H, Ph); ^{13}C NMR ($CDCl_3$) δ = 16.1, 60.4, 63.8, 70.7, 77.2, 79.9, 126.5, 126.6, 126.6, 127.3, 127.7, 127.8, 127.9, 128.0, 128.2, 128.3, 128.3, 129.4, 129.4, 130.0, 131.1, 132.6, 133.4, 133.8, 134.6, 135.4, 153.3, 165.0 175.4.

HRMS (FAB) Found: *m/z* 611.2546. Calcd for $C_{39}H_{35}N_2O_5$: M+H$^+$, 611.2546. Found: C, 76.33; H, 5.92; N, 4.50%. Calcd for $C_{39}H_{34}N_2O_5$: C, 76.70; H, 5.61; N, 4.59%.

(4*S*, 5*R*)- 3- [(2*R*, 3*R*)- 3- (*N*- Benzoyloxy- *N*- benzylamino)- 2-methyl-3-phenylpropionyl]-4,5-diphenyl-2-oxazolidinone (50b): mp 76.5—80.0 °C; $[\alpha]_D^{26}$ −65.8° (*c* 0.814, $CHCl_3$); IR (KBr) 3065, 2930, 1780, 1744, 1701, 1454, 1341, 1256, 1238, 1184, 1055, 698 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ = 1.62 (d, *J* = 6.6 Hz, 3 H, CHC<u>H</u>$_3$), 3.74 (d, *J* = 12.4 Hz, 1 H, C<u>H</u>HPh), 4.14 (d, *J* = 11.0 Hz, 1 H, NCHPh), 4.18 (d, *J* = 12.4 Hz, 1 H, C<u>H</u>HPh), 5.12 (dq, *J* = 11.0 and 6.6 Hz, 1 H, C<u>H</u>CH$_3$), 5.41 (d, *J* = 7.8 Hz, 1 H, CHPh), 5.72 (d, *J* = 7.8 Hz, 1 H, CHPh), 6.07 (d, J = 8.3 Hz, 2 H, Ph), 6.66—7.63 (m, 21 H, Ph), 7.98—8.10 (m, 2 H, Ph); ^{13}C NMR ($CDCl_3$) δ = 16.8, 40.1, 59.4, 62.9, 69.7, 79.8, 125.7, 126.2, 126.9, 127.2, 127.6, 127.9, 128.1, 128.2, 128.3, 128.4, 128.6, 129.3, 129.4, 129.5, 130.8, 132.7, 133.0, 133.5, 135.5, 136.0, 153.2, 165.2, 174.8. HRMS (FAB) Found: *m/z* 611.2534. Calcd for $C_{39}H_{35}N_2O_5$: M+H$^+$, 611.2546.

(2*S*)-3-[(2*S*,3*R*)-3-(*N*-Benzoyloxy-*N*-benzylamino)-2-methyl-3-phenylpropionyl]-2-*t*-butyl-2,3-dihydro-1-methoxycarbonyl-4(1*H*)pyrimidinone (51a): $[\alpha]_D^{26}$ +5.1° (*c* 1.05, $CHCl_3$); IR (Nujol®) 1742, 1689, 1626, 1313, 1171, 806 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ = 0.72 (d, *J* = 7.1 Hz, 3 H, C<u>H</u>$_3$CHCO), 1.15 (s, 9 H, (C<u>H</u>$_3$)$_3$), 3.82 (d, *J* = 12.9 Hz, 1 H, C<u>H</u>HPh), 3.85 (s, 3 H, CO_2CH_3), 4.11 (d, *J* = 12.9 Hz, C<u>H</u>HPh), 4.52 (d, *J* = 11.9 Hz, 1 H, CHPh), 4.88 (dq, *J* = 11.0 and 7.1 Hz, 1 H, CH$_3$C<u>H</u>CO), 5.23 (d, *J* = 7.8 Hz, 1 H, COC<u>H</u>=CH), 6.90 (s, 1 H, C<u>H</u>C$_4$H$_9$), 7.20—7.55 (m, 13 H, Ph), 7.60 (br d, *J* = 7.8 Hz, 1 H, COCH=C<u>H</u>), 7.90—7.96 (m, 2 H, Ph); ^{13}C NMR ($CDCl_3$) δ = 16.5, 27.0, 40.6, 40.7, 54.1, 60.4, 69.6, 70.9, 105.2, 127.5, 128.0, 128.1, 128.2, 129.3, 129.6, 130.3, 131.1, 132.4, 134.7, 136.0, 138.9, 139.0, 152.8, 164.0, 164.8, 176.3. Found: C, 70.01; H, 6.50; N, 7.16%. Calcd for $C_{34}H_{37}N_3O_6$: C, 69.97; H, 6.39; N, 7.20%.

(2*S*)-3-[(2*S*,3*S*)-3-(*N*-Benzoyloxy-*N*-benzylamino)-2-methyl-3-phenylpropionyl]-2-*t*-butyl-2,3-dihydro-1-methoxycarbonyl-4(1*H*)pyrimidinone (51b): $[\alpha]_D^{27}$ +98.2° (*c* 0.97, $CHCl_3$); IR (Nujol®) 1741, 1684, 1624, 1215, 1177, 806, 706 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ = 0.49 (s, 9 H, (CH$_3$)$_3$) 1.44 (d, *J* = 6.8 Hz, 3 H, C<u>H</u>$_3$CHCO), 3.79 (s, 3 H, CH$_3$CO$_2$), 3.84 (d, *J* = 12.9 Hz, 1 H, C<u>H</u>HPh), 4.17 (d, *J* = 12.9 Hz, 1 H, C<u>H</u>HPh), 4,28 (d, *J* = 11.0 Hz, 1 H, CHPh), 4.98 (dq, *J* = 11.0 and 6.8 Hz, 1 H, CH$_3$C<u>H</u>CO) 5.23 (d, *J* = 7.8 Hz, 1 H, COC<u>H</u>=CH), 6.58 (s, 1 H, C<u>H</u>C$_4$H$_9$), 7.20—7.65 (m, 14 H, COCH=C<u>H</u> and Ph), 7.95—8.03 (m, 2 H, Ph); ^{13}C NMR ($CDCl_3$) δ = 16.8, 26.2, 39.7, 41.9, 54.1, 59.5, 68.5, 70.1, 104.7, 127.6, 127.8, 127.9, 128.3, 128.5, 128.6, 129.3, 129.5, 131.0, 132.9, 136.1, 136.3, 139.3, 152.5, 164.1, 165.0, 175.7. Found: C, 69.86; H, 6.49; N, 7.15%. Calcd for $C_{34}H_{37}N_3O_6$: C, 69.97; H, 6.39; N, 7.20%.

(4*R*,5*S*)-3-[(2*S*,3*S*)-3-(*N*-Benzoyloxy-*N*-benzylamino)-2-methylbutanoyl]-4-methyl-5-phenyl-2-oxazolidinone (54a): IR (KBr) 2942, 1785, 1743, 1696, 1603, 1453, 1368, 1198, 1059, 959, 703 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ = 1.11 (d, *J* = 6.7 Hz, 3 H, CH$_3$), 1.15 (d, *J* = 7.0 Hz, 3 H, CH$_3$), 1.31 (d, *J* = 6.7 Hz, 3 H, CH$_3$), 3.59 (dq, *J* = 10.3 and 6.7 Hz, 1 H, CHNO), 4.06 (d, *J* = 13.2 Hz, 1 H, C<u>H</u>HPh), 4.20 (dq, *J* = 10.3 and 7.0 Hz, 1 H, CH$_3$C<u>H</u>CO), 4.28 (d, *J* = 13.2 Hz, 1 H, C<u>H</u>HPh), 4.81 (dq, *J* = 6.7 and 7.6 Hz, 1 H, CH$_3$C<u>H</u>N), 5.61 (d, *J* = 7.6 Hz, 1 H, CHPh), 7.05—7.55 (m, 13 H), 7.88 (s, 1 H), 7.90 (s, 1 H); ^{13}C NMR ($CDCl_3$) δ = 9.6, 14.4, 14.9, 41.1, 55.0, 59.7, 62.6, 78.6, 126.0, 127.5, 128.0, 128.3, 128.6, 128.7, 129.3, 129.4, 129.9, 132.6, 133.9, 136.1, 152.8, 164.9, 176.0. HRMS (FAB) Found: *m/z* 487.2158. Calcd for $C_{29}H_{31}N_2O_5$: M+H$^+$, 487.2233.

(4*S*)-3-[(2*R*,3*S*)-3-(*N*-Benzoyloxy-*N*-methylamino)-2-methyl-3-phenylpropionyl]-4-(1-methylethyl)-2-oxazolidinone (55a): mp 131.5—132.0 °C; $[\alpha]_D^{33}$ +78.12° (*c* 1.18, MeOH); IR (Nujol®) 1770, 1736 (OCO), 1711, 1265, 1201 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ = 0.95 (d, *J* = 7.1 Hz, 3 H, C<u>H</u>$_3$CHCO), 0.98 (d, *J* = 7.3 Hz, 3 H C<u>H</u>$_3$CH), 1.01 (d, *J* = 6.8 Hz, 3 H, C<u>H</u>$_3$CH), 2.54 (dqq, *J* = 3.7, 7.1, and 7.3 Hz, 1 H, (CH$_3$)$_2$C<u>H</u>), 2.68 (s, 3 H, CH$_3$N), 4.19—4.26 (m, 2 H, CH$_2$O), 4.43 (d, *J* = 10.7 Hz, 1 H, CHPh), 4.47 (ddd, *J* = 3.7, 3.9, and 5.7 Hz, 1 H, CHC<u>H</u>N), 4.80 (dq, *J* = 6.8, and 10.7 Hz, 1 H, CH$_3$C<u>H</u>CO), 7.34—7.48 (m, 1 H, Ph), 7.50—7.57 (m, 1 H, Ph), 7.92—7.98 (m, 2 H, Ph); ^{13}C NMR ($CDCl_3$) δ = 14.8, 15.6, 18.4, 28.7, 38.8, 43.5, 59.0, 63.2, 74.3, 128.1, 128.2, 128.32, 128.33, 129.5, 130.5, 132.8, 134.1, 153.8, 164.5, 175.5. HRMS (FAB) Found: *m/z* 425.2090. Calcd for $C_{24}H_{29}N_2O_5$: M+H$^+$, 425.2076.

(4*S*)-3-[(2*R*,3*R*)-3-(*N*-Benzoyloxy-*N*-methylamino)-2-methyl-3-phenylpropionyl]-4-(1-methylethyl)-2-oxazolidinone (55b): mp 151.0—152.0 °C; $[\alpha]_D^{30}$ −69.0° (*c* 1.17, MeOH); IR (Nujol®) 1773, 1732, 1707, 1255, 1066, 704 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ = 0.25 (d, *J* = 6.9 Hz, 3 H, C<u>H</u>$_3$CHCH), 0.62 (d, *J* = 6.8 Hz, 3 H, C<u>H</u>$_3$CHCH), 1.49 (d, *J* = 6.6 Hz, 3 H, C<u>H</u>$_3$CHCO), 1.63 (dqq, *J* = 3.0, 6.8, and 6.9 Hz, 1 H, (CH$_3$)$_2$C<u>H</u>), 2.72 (s, 3 H, CH$_3$N), 4.05 (dd, *J* = 2.7 and 8.8 Hz, 1 H, C<u>H</u>HO), 4.14 (dd, *J* = 8.3 and 8.8 Hz, 1 H, C<u>H</u>HO), 4.20 (d, *J* = 11.5 Hz, 1 H, PhCH), 4.25 (ddd, *J* = 2.7, 3.0, and 8.3 Hz, 1 H, (CH$_3$)$_2$CHC<u>H</u>), 4.96 (dq, *J* = 11.5 and 6.6 Hz, 1 H, CH$_3$C<u>H</u>CO), 7.27—7.63 (m, 8 H, Ph), 8.02—8.10 (m, 2 H, Ph); ^{13}C NMR ($CDCl_3$) δ = 14.0, 16.1, 17.6, 28.1, 40.0, 43.6, 58.2, 62.8, 74.0, 128.2, 128.6, 129.3, 129.4, 130.3, 133.1, 135.7, 153.5, 165.2, 175.1. HRMS (FAB) Found: *m/z* 425.2067. Calcd for $C_{24}H_{29}N_2O_5$: M+H$^+$, 425.2076.

(4*R*, 5*S*)- 3- [(2*S*)- 2- {[(2*S*)- 1- Benzoyloxypyrrolidin- 2- yl]-propionyl}]-4-methyl-5-phenyl-2-oxazolidinone (56a): IR (KBr) 2980, 1782, 1738, 1699, 1453, 1385, 1370, 1346, 1256, 1196, 1123, 1088, 1065, 1026 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ = 0.87 (d, *J* = 6.6 Hz, 3 H, C<u>H</u>$_3$CHN), 1.25 (d, *J* = 6.8 Hz, 3 H, NCOCHC<u>H</u>$_3$), 1.7—1.84 (m, 4 H, (CH$_2$)$_2$), 3.16 (ddd, *J* = 7.0, 7.6, and 12.3 Hz, 1 H, NC<u>H</u>H), 3.58 (ddd, *J* = 5.8, 6.4 and 12.3 Hz, 1 H, NC<u>H</u>H), 3.78 (dd, *J* = 7.8 and 8.3 Hz, 1 H, NC<u>H</u>CH$_2$), 4.15 (dq, *J* = 8.3 and 6.6 Hz, 1 H, NCOC<u>H</u>CH$_3$), 4.75 (dq, *J* = 7.3 and 6.8 Hz, 1 H, NC<u>H</u>CHPh), 5.60 (d, *J* = 7.3 Hz, 1 H, CHO), 7.22—7.58 (m, 8 H, Ph), 7.95—8.01 (m, 2 H, Ph); ^{13}C NMR ($CDCl_3$) δ = 14.0, 14.5, 21.8, 25.2, 39.8, 54.9, 57.4, 69.9, 78.7, 125.7, 128.3, 128.6, 128.6, 129.4, 129.6, 132.8, 133.5, 152.6, 165.0, 175.1. Found: C, 68.23; H, 6.28; N, 6.49%. Calcd for $C_{24}H_{26}N_2O_5$: C, 68.23; H, 6.20; N, 6.63%.

(4*S*)-3-[(2*R*)-2-{[(2*R*)-1-Benzoyloxypyrrolidin-2-yl]propionyl}]-4-(1-methylethyl)-2-oxazolidinone (57a): ^{1}H NMR ($CDCl_3$) δ = 0.82 (d, *J* = 6.8 Hz, 3 H, C<u>H</u>$_3$CHCH$_3$), 0.86 (d, *J* = 6.8 Hz, 3 H, C<u>H</u>$_3$CHCH$_3$), 1.22 (d, *J* = 7.0 Hz, 3 H, NCOCHC<u>H</u>$_3$), 1.88—2.04 (m, 4 H, (CH$_2$)$_2$), 2.24—2.43 (m, 1 H, C<u>H</u>(CH$_3$)$_2$), 3.05—3.22 (m, 1 H, NC<u>H</u>H), 3.50—3.66 (m, 1 H, NC<u>H</u>H), 3.73—3.85 (m, 1 H, NC<u>H</u>CH$_2$), 4.07—4.19 (m, 1 H, NCOC<u>H</u>CH$_3$), 4.19 (dd, *J* = 8.0 and 12.0 Hz, 1 H), 4.22 (dd, *J* = 8.0 and 12.0 Hz, 1 H), 4.38—4.49 (m, 1 H), 7.38—8.05 (m, 5 H, Ph); ^{13}C NMR ($CDCl_3$) δ = 14.4, 14.6, 18.0, 21.3, 28.2, 39.4, 57.0 58.5, 62.9, 69.3, 153.6, 165.0, 174.9. HRMS (FAB) Found: *m/z* 375.1914. Calcd for $C_{20}H_{27}N_2O_5$: M+H$^+$, 375.1920.

(4*S*)-3-{(2*R*)-2-[(2*R*)-1-Benzoyloxypiperidin-2-yl]propionyl}-4-(1-methylethyl)-2-oxazolidinone (58a): IR (neat) 1777, 1736, 1701, 1452, 1300, 1248, 1207, 1180, 1121, 1090, 1067, 1026, 1005, 754, 712 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ = 0.89 (d, *J* = 6.8 Hz, 3 H, C<u>H</u>$_3$CHCH$_3$), 0.93 (d, *J* = 6.8 Hz, 3 H, C<u>H</u>$_3$CHCH$_3$), 1.16 (d, *J* = 6.8 Hz, 3 H, COCHC<u>H</u>$_3$), 1.20—1.96 (m, 6 H, (CH$_2$)$_3$), 2.23—

2.42 (m, 1 H, C<u>H</u>(CH$_3$)$_2$), 2.74—2.93 (m, 1 H, NC<u>H</u>HCH$_2$), 3.39 (ddd, J = 3.2, 4.9, and 8.1 Hz, 1 H, NC<u>H</u>CH$_2$), 3.62—3.69 (m, 1 H, NC<u>H</u>HCH$_2$), 4.21 (dd, J = 3.7 and 9.0 Hz, 1 H, NCHC<u>H</u>HO), 4.26 (dd, J = 9.0 and 9.0 Hz, 1 H, NCHC<u>H</u>HO), 4.36 (dq, J = 4.9 and 6.8 Hz, 1 H, CH$_3$C<u>H</u>), 4.51 (ddd, J = 3.7, 9.0 and 9.0 Hz, 1 H, NC<u>H</u>CH$_2$O), 7.26—7.59 (m, 3 H, Ph), 8.08—8.26 (m, 2 H, Ph); ^{13}C NMR ($CDCl_3$) δ = 14.3, 17.9, 23.4, 28.2, 39.7, 58.2, 62.9, 66.0, 126.7, 128.3, 129.3, 129.3, 129.7, 132.8, 153.3, 164.7, 175.9. HRMS (FAB) Found: m/z 389.2050. Calcd for $C_{21}H_{29}N_2O_5$: M+H$^+$, 389.2076.

(4*S*)-3-{(2*R*)-2-[(2*S*)-1-Benzoyloxypiperidin-2-yl]propionyl}-4-(1-methylethyl)-2-oxazolidinone (58b): IR (neat) 1777, 1740, 1701, 1451, 1387, 1373, 1304, 1265, 756, 709 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ = 0.84 (d, J = 6.4 Hz, 3 H, C<u>H</u>$_3$CHCH$_3$), 0.72 (d, J = 6.2 Hz, 3 H, CH$_3$CHC<u>H</u>$_3$), 1.26 (d, J = 6.4 Hz, 3 H, CHC<u>H</u>$_3$), 1.38—1.97 (m, 7 H, CH$_2$(C<u>H</u>$_2$)$_3$CH and C<u>H</u>(CH$_3$)$_2$), 2.82—3.04 (m, 1 H, NC<u>H</u>H), 3.22 (ddd, J = 3.4, 6.4, and 10.4 Hz, 1 H, NC<u>H</u>CHCH$_3$), 3.63—3.73 (m, 1 H, NC<u>H</u>H), 3.98—4.14 (m, 1 H, NCHC<u>H</u>CH$_3$), 4.12—4.24 (m, 2 H, NCHC<u>H</u>$_2$O), 4.34—4.42 (m, 1 H, NC<u>H</u>CH$_2$O), 7.36—7.58 (m, 3 H, Ph), 7.93—8.05 (m, 2 H, Ph); ^{13}C NMR ($CDCl_3$) δ = 14.5, 18.0, 23.8, 24.5, 28.2, 41.1, 56.6, 58.7, 62.8, 76.5, 77.0, 77.5, 128.0, 128.1, 128.4, 129.4, 129.5, 132.6, 153.8, 264.9, 175.4. HRMS (FAB) Found: m/z 389.2094. Calcd for $C_{21}H_{29}N_2O_5$: M+H$^+$, 389.2076.

(4*R*, 5*S*)-3-[(2*S*)-2-{[(1*S*)-2-Benzoyloxy-1, 2, 3, 4-tetrahydroisoquinolin-1-yl]propionyl}]-4-methyl-5-phenyl-2-oxazolidinone (59a): mp 75—78 °C; $[\alpha]_D^{22}$ −14.7° (c 0.791, $CHCl_3$); IR (KBr) 2969, 1775, 1742, 1699, 1452, 1368, 1344, 1258, 1240, 1223, 1198, 1063, 1024, 708 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ = 1.02 (d, J = 6.6 Hz, 3 H, C<u>H</u>$_3$CHN), 1.25 (d, J = 6.8 Hz, 3 H, NCOCHC<u>H</u>$_3$), 2.28 (ddd, J = 2.2, 5.9, and 17.1 Hz, 1 H, C<u>H</u>H), 3.13 (ddd, J = 6.3, 11.0, and 17.1 Hz, 1 H, C<u>H</u>H), 3.62 (ddd, J = 2.2, 6.3, and 14.6 Hz, 1 H, C<u>H</u>H), 3.91 (ddd, J = 5.9, 11.0, and 14.6 Hz, 1 H, C<u>H</u>H), 4.35 (dq, J = 10.5 and 6.8 Hz, 1 H, C<u>H</u>CH$_3$), 4.74 (d, J = 10.5 Hz, 1 H, NCHPh), 4.89 (dq, J = 7.3 and 6.6 Hz, 1 H, C<u>H</u>CHPh), 5.67 (d, J = 7.3 Hz, 1 H, CHO), 7.15—7.85 (m, 12 H, Ph), 7.75—7.85 (m, 2 H, Ph); ^{13}C NMR ($CDCl_3$) δ = 14.4, 16.1, 23.6, 41.7, 47.2, 55.2, 67.4, 78.9, 125.3, 125.8, 127.2, 128.2, 128.4, 128.6, 128.7, 128.9, 129.2, 129.3, 129.6, 132.6, 132.7, 133.5, 134.0, 153.2, 164.0, 175.3. Found: C, 71.88; H, 5.90; N, 5.92%. Calcd for $C_{29}H_{28}N_2O_5$: C, 71.88; H, 5.82 N, 5.78%.

(4*S*)-3-{(2*R*)-2-[(1*S*)-2-Benzoyloxy-1, 2, 3, 4,-tetrahydroisoqunolin-1-yl]propionyl}-4-(1-methylethyl)-2-oxazolidinone (60b): $[\alpha]_D^{28}$ +52.7° (c 1.10, $CHCl_3$); IR (neat) 2969, 1771, 1744, 1703, 1453, 1258, 1242, 1208, 1086, 1063, 1024, 754, 710 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ = 0.95 (d, J = 7.1 Hz, 3 H, CH(C<u>H</u>$_3$)$_2$), 0.99 (d, J = 6.8 Hz, 3 H, CH(C<u>H</u>$_3$)$_2$), 1.22 (d, J = 6.8 Hz, 3 H, CHC<u>H</u>$_3$), 2.68 (dqq, J = 3.4, 6.8, and 7.1 Hz, 1 H, C<u>H</u>(CH$_3$)$_2$), 2.77 (dd, J = 6.1 and 17.1 Hz, 1 H, C<u>H</u>HPh), 3.15 (ddd, J = 6.8, 11.0, and 17.1 Hz, 1 H, C<u>H</u>HPh), 3.68 (dd, J = 6.8 and 14.9 Hz, C<u>H</u>H), 3.88 (ddd, J = 6.1, 11.0, and 14.9 Hz, 1 H, C<u>H</u>H), 4.20—4.33 (m, 2 H), 4.38 (dq, J = 10.7 and 6.8 Hz, 1 H, C<u>H</u>CH$_3$), 4.58 (ddd, J = 3.4, 7.8, and 7.8 Hz, 1 H), 4.67 (d, J = 10.7 Hz, 1 H, CHN), 7.12—7.51 (m, 7 H, Ph), 7.75—7.83 (m, 2 H, Ph); ^{13}C NMR ($CDCl_3$) δ = 14.4, 16.0, 18.1, 23.1, 27.7, 41.2, 46.6, 58.7, 62.8, 67.5, 125.2, 127.1, 128.2, 128.9, 129.3, 129.5, 132.5, 132.6, 133.6, 154.2, 163.8, 175.1. HRMS Found: m/z 437.2076. Calcd for $C_{25}H_{29}N_2O_5$: M+H$^+$, 437.2076.

(4*R*)-3-[(2*S*)-2-{[(2*S*)-1-Benzoyloxypyrrolidin-2-yl]propionyl}]-4-phenyl-2-oxazolidinone (61a): IR (Nujol®) 1784, 1750, 1713, 1340, 1325, 770, 695 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ = 1.19 (d, J = 6.8 Hz, 3 H, CH$_3$), 1.53—1.65 (m, 2 H, CH$_2$), 1.77—1.89 (m, 2 H, CH$_2$), 3.03 (dt, J = 8.0 and 11.0 Hz, 1 H, CH$_2$C<u>H</u>N), 3.56—3.72 (m, 2 H, CH$_3$C<u>H</u> and NC<u>H</u>H), 4.13—4.25 (m, 2 H, C<u>H</u>HO and NC<u>H</u>H), 4.64 (dd, J = 8.8 and 9.0 Hz, 1 H, PhCH), 5.42 (dd J = 4.4 and 8.8 Hz, 1 H, C<u>H</u>HO), 7.18—7.61 (m, 8 H, Ph), 7.92—8.04 (m, 2 H, Ph); ^{13}C NMR ($CDCl_3$) δ = 11.9, 20.8, 23.2, 39.3, 56.5, 58.0, 68.4, 69.7, 125.8, 128.3, 128.4, 128.5, 129.0, 129.5, 132.8, 138.8, 153.2, 165.1, 174.7. Found: C, 67.45; H, 5.94; N, 6.83%. Calcd for $C_{23}H_{24}N_2O_5$: C, 67.63; H, 5.92; N, 6.86%.

(4*R*)-3-[(2*S*)-2-{[(2*S*)-1-Benzoyloxypyrrolidin-2-yl]propionyl}]-4-benzyl-2-oxazolidinone (62a): mp 143.5—146.0 °C; $[\alpha]_D^{27}$ +3.9° (c 1.04, $CHCl_3$); IR (KBr) 2957, 2924, 2855, 1784, 1736, 1701, 1453, 1387 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ = 1.24 (d, J = 7.1 Hz, 3 H, CHC<u>H</u>$_3$), 1.70—2.17 (m, 4 H, C<u>H</u>$_2$C<u>H</u>$_2$), 2.67 (dd, J = 11.4 and 13.5 Hz, 1 H, CHC<u>H</u>HPh), 3.22 (dt, J = 12.5 and 7.3 Hz, 1 H, NC<u>H</u>H), 3.43 (d, J = 13.5 Hz, 1 H, CHC<u>H</u>HPh), 3.55 (dt, J = 12.5 and 6.3 Hz, 1 H, NC<u>H</u>H), 3.82 (dd, J = 8.3 and 8.3 Hz, 1 H, NC<u>H</u>CH$_2$), 4.05—4.17 (m, 3 H, NCOC<u>H</u>CH$_3$ and CH$_2$O), 4.64 (ddd, J = 3.1, 11.1, and 13.2 Hz, 1 H, NC<u>H</u>CH$_2$Ph) 7.19—7.56 (m, 8 H, Ph), 7.96—8.01 (m, 2 H, Ph); ^{13}C NMR ($CDCl_3$) δ = 22.1, 25.5, 37.7, 39.7, 39.7, 55.5, 66.0, 70.4, 127.0, 128.3, 128.8, 129.4, 132.8, 135.9, 153.1, 165.0, 175.3. Found: C, 68.00; H, 6.20; N, 6.63%. Calcd for $C_{24}H_{26}N_2O_5$: C, 68.23; H, 6.20; N, 6.63%.

(4*S*)-3-[(2*R*)-2-{[(2*R*)-1-Benzoyloxypyrrolidin-2-yl]propionyl}]-4-*t*-butyl-2-oxazolidinone (63a): IR (neat) 1777, 1740, 1700, 1453, 1387, 1217, 711 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ = 0.92 (s, 9 H, (CH$_3$)$_3$), 1.21 (d, J = 7.0 Hz, 3 H, CHC<u>H</u>$_3$), 1.72—2.02 (m, 4 H, (CH$_2$)$_2$), 3.06—3.24 (m, 1 H, CHNO), 3.53—3.70 (m, 1 H, C<u>H</u>HN), 3.74—3.85 (m, 1 H, C<u>H</u>CH$_3$), 4.15—4.30 (m, 3 H, C<u>H</u>HNO and CH$_2$), 4.44 (dd, J = 2.9 and 7.0 Hz, 1 H, CH-*t*-Bu), 7.35—7.64 (m, 3 H, Ph), 7.95—8.16 (m, 2 H, Ph); ^{13}C NMR ($CDCl_3$) δ = 12.2, 21.2, 23.9, 25.6, 35.7, 38.9, 56.8, 61.2, 65.0, 69.2, 128.3, 129.4, 129.6, 132.7, 154.2, 165.1, 175.1. HRMS (FAB) Found: m/z 389.2063. Calcd for $C_{21}H_{29}N_2O_5$: M+H$^+$, 389.2076.

(4*S*, 5*R*)-3-{(2*R*)-2-[(2*R*)-1-Benzoyloxypyrrolidin-2-yl)-propionyl]}-4,5-diphenyl-2-oxazolidinone (64a): IR (KBr) 3069, 3000, 2965, 2938, 1773, 1734, 1692, 1339, 1269, 1258, 1088, 1067, 1024, 698 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ = 1.24 (d, J = 7.1 Hz, 3 H, C<u>H</u>$_3$CHN), 1.58—1.71 (m, 2 H, 2 x C<u>H</u>H), 1.79—1.92 (m, 2 H, 2 x C<u>H</u>H), 3.04 (dt, J = 11.8 and 8.5 Hz, 1 H, C<u>H</u>HN), 3.70 (dt, J = 11.8 and 6.1 Hz, 1 H, C<u>H</u>HN), 3.76 (dt, J = 6.8 and 8.8 Hz, 1 H, NC<u>H</u>CH$_2$), 4.18 (br, 1 H, C<u>H</u>CH$_3$), 5.68 (d J = 7.9 Hz, 1 H, CHPh), 5.83 (d J = 7.9 Hz, 1 H, CHPh), 6.83—7.15 (m, 9 H, Ph), 7.38—7.58 (m, 4 H, Ph), 8.15—8.19 (m, 2 H, Ph); ^{13}C NMR ($CDCl_3$) δ = 12.3, 20.5, 23.1, 39.7, 56.4, 63.0, 68.0, 80.1, 126.2, 126.6, 128.0, 128.0, 128.0, 128.2, 128.4, 129.4, 129.5, 132.8, 132.9, 134.4, 153.1, 165.2, 174.4. HRMS (FAB) Found: m/z 485.2083. Calcd for $C_{29}H_{29}N_2O_5$: M+H$^+$, 485.2076.

(2*S*)-3-[(2*S*)-2-{[(2*S*)-1-Benzoyloxypyrrolidin-2-yl]propionyl}]-2-*t*-butyl-2,3-dihydro-1-methoxycarbonyl-4(1*H*)pyrimidinone (65a): IR (neat) 2971, 1748, 1686, 1624, 1443, 1425, 1372, 1333, 1294, 1215, 1111, 761, 709 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ = 0.93 (s, 9 H, (CH$_3$)$_3$), 1.16 (d, J = 6.9 Hz, 3 H, CH$_3$), 1.76—2.04 (m, 4 H, C<u>H</u>$_2$C<u>H</u>$_2$), 3.01—3.14 (m, 1 H, CHNO), 3.62—3.75 (m, 1 H, C<u>H</u>H), 3.87 (s, 3 H, CH$_3$), 3.85—3.97 (m, 1 H, C<u>H</u>H), 4.03 (dq, J = 6.9 and 6.9 Hz, C<u>H</u>CH$_3$), 5.30 (d, J = 7.2 Hz, 1 H, C<u>H</u>=CH), 6.83 (s, 1 H, CH-*t*-Bu), 7.39—7.71 (m, 4 H, Ph and C<u>H</u>=CH), 8.09—8.13 (m, 2 H, Ph); ^{13}C NMR ($CDCl_3$) δ = 12.4, 20.8, 22.8, 26.9, 40.2, 40.8, 54.2, 56.4, 68.2, 69.1, 104.9, 128.3, 129.4, 129.7, 132.7, 132.8, 139.2, 163.8, 164.2, 165.3, 175.9. HRMS (FAB) Found: m/z 458.2307. Calcd for $C_{24}H_{32}N_3O_6$: M+H$^+$, 458.2291.

(4*R*,5*S*)-3-[(2*S*)-2-{(2*S*)-1-[(2*R*)-2-Acetoxyphenylacetoxy]-pyrrolidin-2-yl}propionyl]-4-methyl-5-phenyl-2-oxazolidinone

(81a): IR (KBr) 2976, 1784, 1761, 1703, 1456, 1346, 1228, 1149, 766, 704 cm^{-1}; ^1H NMR ($CDCl_3$) δ = 0.85 (d, J = 6.7 Hz, 3 H, $C\underline{H}_3CHN$), 1.15 (d, J = 6.8 Hz, 3 H, $C\underline{H}_3CHCO$), 1.44—2.21 (m, 4 H, $C\underline{H}_2C\underline{H}_2$), 2.18 (s, 3 H, CH_3CO), 3.06 (ddd, J = 7.3, 7.5, and 13.0 Hz, 1 H, $C\underline{H}HN$), 3.14—3.30 (m, 1 H, $CH\underline{H}N$), 3.54 (dd, J = 8.4 and 8.4 Hz, 1 H, $NC\underline{H}CH_2$), 4.01 (br, 1 H, $CH_3C\underline{H}CO$), 4.73 (dq, J = 7.6 and 6.7 Hz, 1 H, $C\underline{H}CHPh$), 5.62 (d, J = 7.6 Hz, 1 H, $PhC\underline{H}CH$), 5.93 (s, 1 H, $C\underline{H}O_2CCH_3$), 7.02—7.54 (m, 10 H, Ph); ^{13}C NMR ($CDCl_3$) δ = 14.3, 20.7, 22.2, 25.8, 39.2, 54.9, 57.7, 70.8, 73.6, 78.8, 125.9, 127.5, 128.5, 128.6, 128.7, 129.0, 133.6, 133.8, 152.7, 166.9, 170.0, 174.9. HRMS (FAB) Found: m/z 495.2136. Calcd for $C_{27}H_{31}N_2O_7$: M+H$^+$, 495.2131.

(4*R*,5*S*)-3-[(2*S*)-2-{(2*S*)-1-[(2*S*)-2-Acetoxyphenylacetoxy]-pyrrolidin-2-yl}propionyl]-4-methyl-5-phenyl-2-oxazolidinone (81a′): IR (Nujol®) 1780, 1745, 1701, 1350, 1237, 1042, 763, 728, 700 cm^{-1}; ^1H NMR ($CDCl_3$) δ = 0.84 (d, J = 6.6 Hz, 3 H, $C\underline{H}_3CHN$), 1.19 (d, J = 6.8 Hz, 3 H, $C\underline{H}_3CHCO$), 1.48—2.04 (m, 4 H, $C\underline{H}_2C\underline{H}_2$), 2.15 (s, 3 H, CH_3CO), 2.89 (ddd, J = 6.6, 6.8, and 12.7 Hz, 1 H, $C\underline{H}HN$), 3.28 (ddd, J = 6.4, 7.0 and 12.7 Hz, 1 H, $CH\underline{H}N$), 3.67 (q, J = 8.2 Hz, 1 H, $NC\underline{H}CH_2$), 3.96 (dq, J = 8.2 and 6.8 Hz, 1 H, $CH_3C\underline{H}CO$), 4.75 (dq, J = 6.8 and 6.6 Hz, 1 H, $C\underline{H}CHPh$), 5.61 (d, J = 6.8 Hz, 1 H, $PhC\underline{H}CH$), 5.91 (s, 1 H, $C\underline{H}O_2CCH_3$), 7.20—7.54 (m, 10 H, Ph); ^{13}C NMR ($CDCl_3$) δ = 14.3, 20.6, 22.1, 25.3, 39.7, 54.9, 57.1, 70.4, 73.8, 78.8, 125.8, 127.7, 128.5, 128.6, 128.7, 129.1, 133.6, 133.9, 152.6, 166.8, 170.0, 174.8. HRMS (FAB) Found: m/z 495.2119. Calcd for $C_{27}H_{31}N_2O_7$: M+H$^+$, 495.2131.

Preparation of (4*R*,5*S*)-2-Benzyl-4-methyl-3-phenyl-5-isoxazolidinone ((−)-67a). To a solution of **39a** (100 mg, 0.22 mmol) in CH_2Cl_2/EtOH/H_2O (1 : 2 : 1, 1 mL) was added 2 M LiOH in H_2O (0.66 mL, 1.32 mmol), and the mixture was stirred at room temperature for 6 h. The reaction mixture was neutralized with 2 M HCl and concentrated in vacuo. Column chromatography (SiO_2, 5—50% EtOAc in hexane) gave (−)-**67a** (34 mg, 58%): mp 129—131 °C; $[\alpha]_D^{29}$ −157.6° (c 1.02, MeOH): IR (KBr) 1777, 1497, 1455, 1331, 1310, 1248, 1179, 1105, 1051, 878, 764, 696 cm^{-1}; ^1H NMR ($CDCl_3$) δ = 1.18 (d, J = 7.1 Hz, 3 H, CH_3), 2.96 (dq, J = 12.2 and 7.1 Hz, 1 H, $C\underline{H}CH_3$), 3.83 (d, J = 12.2 Hz, 1 H, CHPh), 3.87 (d, J = 14.7 Hz, 1 H, $C\underline{H}HPh$), 4.15 (d, J = 14.7 Hz, 1 H, $C\underline{H}HPh$), 7.26—7.49 (m, 10 H, Ph); ^{13}C NMR ($CDCl_3$) δ = 11.1, 45.9, 60.9, 77.8, 127.7, 127.7, 128.3, 129.1, 129.2, 135.4, 135.8, 174.9.

Preparation of (4*R*,5*R*)-2-Benzyl-4-methyl-3-phenyl-5-isoxazolidinone ((+)-67b). To a solution of **39b** (108 mg, 0.22 mmol) in CH_2Cl_2/EtOH (1 : 2, 1 mL) was added 2 M LiOH in H_2O (0.66 mL, 1.32 mmol), and the mixture were stirred at room temperature for 6 h. To the reaction mixture was added MeOH (2 mL) and H_2SO_4 (0.004 mL), then the mixture was stirred at 60 °C for 6 h. After concentration in vacuo, column chromatography (SiO_2, 5—50% EtOAc in hexane) gave (+)-**67b** (18 mg, 31%): $[\alpha]_D^{25}$ +202.3° (c 0.51, MeOH); IR (neat) 1778, 1454, 1196, 754, 700 cm^{-1}; ^1H NMR ($CDCl_3$) δ = 1.04 (d, J = 7.6 Hz, 3 H, CH_3), 2.96—3.04 (m, 1 H, $C\underline{H}CH_3$), 3.95 (d, J = 14.7 Hz, 1 H, $C\underline{H}HPh$), 4.24 (d, J = 14.7 Hz, 1 H, $C\underline{H}HPh$), 4.51 (d, J = 7.3 Hz, 1 H, CHPh), 7.23—7.49 (m, 10 H, Ph); ^{13}C NMR ($CDCl_3$) δ = 11.4, 42.4, 61.1, 72.5, 127.7—135.4 (Ph), 176.3.

Preparation of (2*R*,3*S*)-3-(Benzyloxycarbonylamino)-2-methyl-3-phenylpropionic Acid ((−)-68a). Isoxazolidinone (−)-**67a** (439 mg, 1.64 mmol) was hydrogenated in AcOH/MeOH (5 : 1, 12 mL) in the presence of 20% $Pd(OH)_2$/C (400 mg, 0.32 mmol) under atmospheric pressure of H_2 at room temperature for 3 h. After filtration of the catalyst and removal of the solvent, to the residue were added THF (10 mL), H_2O (10 mL), K_2CO_3 (453 mg, 3.28 mmol), and benzyl chloroformate (0.351 mL, 2.46 mmol). After the mixture was stirred for 30 min, EtOAc (30 mL) and 6 M HCl (3 mL) were added. The organic layer was separated, washed with brine, and dried over $MgSO_4$. Evaporation and purification of the oil residue by column chromatography (SiO_2, 5—10% MeOH in CH_2Cl_2) gave (−)-**68a** (465 mg, 90%) as a white solid: mp 135.0—137.5 °C; $[\alpha]_D^{28}$ −21.6° (c 1.02, $CHCl_3$); IR (Nujol®) 3349, 1692, 1530, 1464, 1291, 1250, 758, 700 cm^{-1}; ^1H NMR ($CDCl_3$, 55 °C) δ = 1.02—1.30 (m, 3 H, CH_3), 2.84—3.02 (m, 1 H, $C\underline{H}CH_3$), 4.81—4.98 (m, 1 H, CHPh), 5.06 (s, 2 H, CH_2Ph), 6.30 (br s, 1 H, NH), 7.17—7.36 (m, 10 H, Ph), 9.60 (br s, 1 H, CO_2H); ^{13}C NMR ($CDCl_3$, 55 °C) δ = 15.5, 44.8, 57.0, 67.0, 126.3, 127.5, 128.1, 128.4, 128.5, 128.7, 136.2, 140.2, 156.2, 179.7. HRMS (FAB) Found: m/z 314.1369. Calcd for $C_{18}H_{20}NO_4$: M+H$^+$, 314.1392.

Preparation of (2*R*,3*R*)-3-(Benzyloxycarbonylamino)-2-methyl-3-phenylpropionic Acid ((+)-68b). Oxazolidinone **39b** (651 mg, 1.30 mmol) was hydrogenated in AcOH (6.5 mL) in the presence of 10% Pd/C (400 mg) under atmospheric pressure of H_2 at room temperature for 12 h. After filtration of the catalyst and removal of the solvent, to the residue were added THF (5 mL), sat. $NaHCO_3$ (2.0 mL), and benzyl chloroformate (0.204 mL, 1.43 mmol). After the mixture was stirred for 30 min, EtOAc was added and organic layer was washed with brine. After drying over $MgSO_4$, the solution was concentrated under reduced pressure. Purification of the oil residue by column chromatography (SiO_2, 5—10% MeOH in CH_2Cl_2) gave (4*S*)-3-[(2*R*,3*R*)-3-(benzyloxycarbonylamino)-2-methyl-3-phenylpropionyl]-4-(1-methylethyl)-2-oxazolidinone (**69b**) (414 mg, 75%) as a solid. The solid was dissolved in THF—H_2O (3 : 1, 16 mL), and to the solution were added successively 30% H_2O_2 (0.38 mL, 3.8 mmol) and $LiOH\cdot H_2O$ (64 mg, 1.5 mmol) with ice-cooling. The mixture was stirred at room temperature for 1 h, then $NaHSO_3$ was added. After evaporation and addition of EtOAc (15 mL), H_2O (10 mL), and 1 M NaOH (3 mL), the organic layer was separated and aqueous layer was extracted with EtOAc. Combined extracts were dried over $MgSO_4$ and evaporated to give recovered chiral auxiliary (91 mg, 92%). To the aqueous layer was added 6 M HCl (1 mL) and the mixture was extracted with EtOAc. The organic layer was washed with brine and dried over $MgSO_4$. Removal of the solvent gave (+)-**68b** (228 mg, 95%) as a solid. Analytical sample was obtained by washing the solid with i-Pr_2O (190 mg, 79%). **69b**: $[\alpha]_D^{34}$ +53.1° (c 1.15, MeOH); IR (Nujol®) 3369, 1765, 1730, 1680, 1526, 1395, 1375, 1238, 1211 cm^{-1}; ^1H NMR ($CDCl_3$) δ = 0.44 (d, J = 6.8 Hz, 3 H, $C\underline{H}_3CHCH_3$), 0.72 (d, J = 7.1 Hz, 3 H, $C\underline{H}_3CHCH_3$), 1.17 (d, J = 6.8 Hz, 3 H, $C\underline{H}_3CHCO$), 1.79—1.95 (m, 1 H, $C\underline{H}(CH_3)_2$), 4.10 (dd, J = 3.5 and 9.3 Hz, 1 H, $C\underline{H}HO$), 4.18 (dd, J = 8.3 and 9.3 Hz, 1 H, $C\underline{H}HO$), 4.36 (dt, J = 8.3 and 3.5 Hz, 1 H, $NC\underline{H}CH_2O$), 4.39 (dq, J = 6.8 and 6.8 Hz, 1 H, CHCON), 5.00 (d, J = 12.5 Hz, 1 H, $C\underline{H}HPh$), 5.11 (d, J = 12.5 Hz, 1 H, $C\underline{H}HPh$), 5.21—5.40 (m, 2 H, CHPh and NH), 7.18—7.41 (m, 10 H, Ph); ^{13}C NMR ($CDCl_3$) δ = 12.7, 14.1, 17.7, 28.2, 43.0, 56.7, 58.2, 63.1, 66.8, 126.8, 127.5, 128.0, 128.4, 128.5, 136.3, 140.4, 153.7, 155.7, 173.9. HRMS (FAB) Found: m/z 425.2088. Calcd for $C_{24}H_{29}N_2O_5$: M+H$^+$, 425.2076. (+)-**68b**: mp 167.0—169.0 °C; $[\alpha]_D^{31}$ +36.1° (c 0.97, MeOH); IR (Nujol®) 3358, 1692, 1532, 1287, 1258, 1019 cm^{-1}; ^1H NMR ($CDCl_3$, 55 °C) δ = 1.16 (d, J = 7.1 Hz, 3 H, $C\underline{H}_3CHCO$), 2.96 (quint, J = 7.1 Hz, 1 H, CHCO), 5.01—5.13 (m, 3 H, CHPh and CH_2Ph), 5.67 (br s, 2 H, CO_2H and NH), 7.20—7.36 (m, 10 H, Ph); ^{13}C NMR ($CDCl_3$) δ = 13.1, 44.8, 57.2, 67.1, 126.9, 127.8, 128.0, 128.1, 128.5, 128.6, 136.4, 139.6, 156.1, 178.0. Found: C, 68.69; H, 6.09; N, 4.45%. Calcd for $C_{18}H_{19}NO_4$: C, 69.00; H, 6.11; N, 4.47%.

Decarboxylation of β-Amino Acid 68a to *N*-Benzyloxycarbonyl-1-phenylpropylamine (70). To a solution of (−)-**68a** (445 mg, 1.42 mmol) in CH_2Cl_2 (10 mL) were added 4-methylmorpholine (0.171 mL, 1.56 mmol) and isobutyl chloroformate (0.184 mL, 1.42 mmol) at −20 °C under argon, and the mixture was stirred at −10 °C. After 10 min, triethylamine (0.396 mL, 2.84 mmol) and a solution of 2-mercaptopyridine *N*-oxide (180 mg, 1.42 mmol) in CH_2Cl_2 (3 mL) were added, and the mixture was stirred at −20 °C for 10 min. After addition of *t*-BuSH (1.60 mL, 14.2 mmol), the solution was irradiated with a 150 W tungsten lamp for 10 min. After evaporation and addition of EtOAc, the organic layer was washed with H_2O and brine, and dried over $MgSO_4$. After removal of the solvent, the residue was purified by column chromatography (SiO_2, 2.5—7.5% EtOAc in hexane) to give (−)-**70** (233 mg, 61%): $[\alpha]_D^{24}$ −46.2° (*c* 1.01, MeOH); IR (Nujol®) 3345, 1688, 1528, 1285, 1262, 1235 cm^{-1}; ^1H NMR ($CDCl_3$) δ = 0.87 (t, *J* = 7.6 Hz, 3 H, CH_3CH_2), 1.65—1.86 (m, 2 H, CH_2CH_3), 4.50—4.66 (m, 1 H, CHPh), 5.03 (d, *J* = 12.0 Hz, 1 H, CHHPh), 5.09 (d, *J* = 12.0 Hz, 1 H, CHHPh), 5.10 (d, *J* = 8.4 Hz, 1 H, NH), 7.19—7.38 (m, 10 H, Ph); ^{13}C NMR ($CDCl_3$) δ = 10.6, 29.6, 56.8, 66.6, 126.3, 127.2, 128.0, 128.4, 128.5, 136.4, 142.3, 155.7. HRMS (FAB) Found: *m/z* 270.1493. Calcd for $C_{17}H_{20}NO_2$: M+H$^+$, 270.1494. (+)-**70**: $[\alpha]_D^{29}$ +45.1° (*c* 0.99, MeOH).

Preparation of (*S*)-1-Phenyl-1-propylamine ((−)-71).[38] Carbamate (−)-**70** (99 mg, 0.367 mmol) was hydrogenated in MeOH (1.0 mL) in the presence of 10% Pd/C (99 mg) and AcOH (0.063 mL, 1.1 mmol) at atmospheric pressure of H_2 at room temperature for 10 min. After filtration of the catalyst and removal of the solvent, the residue was diluted with CH_2Cl_2 and washed with sat. $NaHCO_3$. After drying over $MgSO_4$, the solvent was removed to give (−)-**71** (49 mg, 98%) as an oil: $[\alpha]_D^{22}$ −16.1° (*c* 2.43, benzene); IR (neat) 2963, 2928, 1491, 1455, 700 cm^{-1}; ^1H NMR ($CDCl_3$) δ = 0.86 (t, *J* = 7.3 Hz, 3 H, CH_3CH_2), 1.63 (s, 2 H, NH_2), 1.69 (dq, *J* = 6.8 and 7.3 Hz, 2 H, CH_2CH_3), 3.79 (t, *J* = 6.8 Hz, 1 H, CHPh), 7.19—7.37 (m, 5 H, Ph); ^{13}C NMR ($CDCl_3$) δ = 10.9, 32.4, 57.8, 126.3, 126.8, 128.3, 146.4.

Preparation of (4*R*,5*S*)-3-[(2*S*,3*R*)-3-Benzylamino-2-methyl-3-phenylpropionyl]-4-methyl-5-phenyl-2-oxazolidinone (72a). To a solution of **49a** (1.02 g, 1.85 mmol) in AcOH (20 mL) was added zinc powder (3.1 g), and the mixture was stirred at 60 °C for 8 h. The mixture was filtered through Celite®, and the cake was washed with MeOH. The filtrate was evaporated, and to the residue, sat. $NaHCO_3$ and EtOAc were added. The suspension was filtered again through Celite®, and the cake was washed with EtOAc. The organic layer was separated and dried over Na_2SO_4. Evaporation followed by column chromatography (SiO_2, 5—40% EtOAc in hexane) gave **72a** as a foam (344 mg, 43%) and (5*S*,6*R*)-1-benzyl-5,6-dihydro-5-methyl-6-phenyluracil (**89**) as a colorless solid (240 mg, 44%). **72a:** IR (Nujol®) 2930, 1780, 1700, 1458, 1377 cm^{-1}; ^1H NMR ($CDCl_3$) δ = 0.93 (d, *J* = 6.6 Hz, 3 H, CH_3), 1.00 (d, *J* = 6.6 Hz, 3 H, CH_3), 2.17 (br, 1 H, NH), 3.37 (d, *J* = 13.2 Hz, 1 H, CHHPh), 3.14 (d, *J* = 13.2 Hz, 1 H, CHHPh), 3.69 (d, *J* = 10.5 Hz, 1 H, NCHPh), 4.28 (dq, *J* = 10.5 and 6.6 Hz, 1 H, $COCHCH_3$), 4.82 (dq, *J* = 6.1 and 6.6 Hz, 1 H, $NCHCH_3$), 5.66 (d, *J* = 6.1 Hz, 1 H, OCHPh), 7.10—7.46 (m, 15 H, Ph); ^{13}C NMR ($CDCl_3$) δ = 14.3, 15.3, 43.2, 50.8, 55.5, 67.1, 78.9, 125.7, 126.6, 127.5, 127.7, 128.0, 128.2, 128.5, 128.6, 128.7, 133.4, 140.3, 141.7, 153.8, 176.4. HRMS (EI) Found: *m/z* 429.2144. Calcd for $C_{27}H_{29}N_2O_3$: M$^+$, 429.2178. **89:** mp 182—188 °C; $[\alpha]_D^{24}$ −2.87° (*c* 1.18, $CHCl_3$); IR (KBr) 3200, 3050, 1700, 1471, 1270, 1230 cm^{-1}; ^1H NMR ($CDCl_3$) δ = 1.16 (d, *J* = 7.1 Hz, 3 H, CH_3), 2.76 (dq, *J* = 3.2 and 7.1 Hz, 1 H, $CHCH_3$), 3.65 (d, *J* = 14.9 Hz, 1 H, CHHPh), 4.14 (d, *J* = 3.2 Hz, 1 H, CHPh), 5.47 (d, *J* = 14.6 Hz, 1 H, CHHPh), 7.30—7.40 (m, 10 H, Ph), 8.61 (br, 1 H, NH); ^{13}C NMR ($CDCl_3$) δ = 16.3, 43.3, 48.6, 61.8, 126.2, 127.9, 128.5, 128.6, 128.8, 129.2, 136.2, 137.9, 152.8, 172.1; HRMS (EI) Found: *m/z* 294.1351. Calcd for $C_{18}H_{18}N_2O_2$: M$^+$, 294.1368.

Preparation of (2*S*,3*R*)-3-Benzylamino-2-methyl-3-phenylpropionic Acid ((+)-73a). Oxazolidinone **72a** (380 mg, 0.887 mmol) was dissolved in THF—H_2O (3 : 1, 12 mL), and to the solution was added $LiOH·H_2O$ (186 mg, 4.43 mmol) with ice cooling. The mixture was stirred at room temperature for 7 days and extracted with Et_2O. The organic layer was dried over Na_2SO_4 and evaporated. Chromatography (SiO_2, 10—60% EtOAc in hexane) gave recovered oxazolidinone (132 mg, 84%). The aqueous phase was acidified with AcOH (0.45 mL) and extracted with EtOAc. Drying over Na_2SO_4 and removal of the solvent gave (+)-**73a** (170 mg, 59%) as a colorless solid. The analytical sample was obtained by the trituration of the solid with Et2O: mp 146.0—147.0 °C; $[\alpha]_D^{24}$ +55.9° (*c* 1.09, MeOH); IR (KBr) 3450, 1645, 1612, 1601, 1458, 1394, 700 cm^{-1}; ^1H NMR ($CDCl_3$) δ = 0.95 (d, *J* = 7.3 Hz, 3 H, CH_3), 2.91 (dq, *J* = 11.0 and 7.3 Hz, 1 H, $CHCH_3$), 3.51 (d, *J* = 13.5 Hz, 1 H, CHHPh), 3.77 (d, *J* = 11.0 Hz, 1 H, CHPh), 4.19 (d, *J* = 13.5 Hz, 1 H, CHHPh), 7.26—7.46 (m, 10 H, Ph), 9.78 (br, 2 H, NH and CO_2H); ^{13}C NMR (CD_3OD) δ = 15.3, 43.9, 48.2, 64.0, 128.4, 128.5, 128.7, 128.8, 129.2, 133.3, 135.8, 178.8. HRMS (CI) Found: *m/z* 270.1467. Calcd for $C_{17}H_{20}NO_2$: M+H$^+$, 270.1494.

(2*S*,3*R*)-3-(Benzyloxycarbonylamino)-2-methyl-3-phenylpropionic Acid ((+)-68a). Amino acid (+)-**73a** (118 mg, 0.438 mmol) was hydrogenated in MeOH (4 mL) in the presence of 10% Pd/C (50% wet, 120 mg) and AcOH (0.05 mL) at atmospheric pressure of H_2 at room temperature for 1 h. After filtration of the catalyst and removal of the solvent, to the residue were added THF (2 mL), H_2O (2 mL), K_2CO_3 (194 mg, 1.4 mmol), and benzyl chloroformate (0.075 mL, 0.53 mmol), and the mixture was stirred for 1 h. After evaporation, H_2O was added, and the mixture was extracted with Et_2O. Dried over $MgSO_4$, the solution was concentrated under reduced pressure. Purification of the oil residue by column chromatography (SiO_2, 20—30% EtOAc in hexane) gave (+)-**68a** (118 mg, 86%) as a colorless solid. The analytical sample was obtained by the trituration with *i*-Pr_2O: mp 135.0—137.5 °C; $[\alpha]_D^{23}$ +22.2 ° (*c* 1.03, $CHCl_3$).

(2*S*)-3-[(2*S*,3*S*)-3-(*N*-Benzyloxycarbonylamino)-2-methyl-3-phenylpropionyl]-2-*t*-butyl-2,3-dihydro-1-methoxycarbonyl-4(1*H*)pyrimidinone (74b). β-Amino acid derivative **51b** (400 mg, 0.685 mmol) was dissolved in MeOH (5 mL) and 2 M HCl (1.0 mL). After addition of 10% Pd/C (50% wet, 146 mg), hydrogenation was carried out at room temperature under atmospheric pressure of H_2 for 4 h. The reaction mixture was filtered, and the solvent was removed in vacuo, then the oil residue was dissolved in EtOAc–H_2O (3 : 1, 4.0 mL). To the solution were added $NaHCO_3$ (800 mg) and benzyl chloroformate (0.147 mL, 1.03 mmol), and the reaction mixture was stirred at room temperature for 1.5 h. The reaction mixture was extracted with EtOAc, washed with brine, and dried over $MgSO_4$. The solvent was removed under reduced pressure, and the oil residue was purified by column chromatography (SiO_2, EtOAc in hexane) to afford **74b** (311 mg, 89%) as a waxy solid: $[\alpha]_D^{24}$ +94.9° (*c* 1.16, $CHCl_3$); IR (KBr) 3350, 1728, 1694, 1132, 1314, 1294, 1223, 1177, 698 cm^{-1}; ^1H NMR ($CDCl_3$) δ = 0.73 (s, 9 H, *t*-Bu), 1.06 (d, *J* = 6.8 Hz, 3 H, CH_3), 3.85 (s, 3 H, CH_3), 4.23 (dq, *J* = 6.4 and 6.4 Hz, 1 H, $CHCH_3$), 5.01 (d, *J* = 12.2 Hz, 1 H, CHHPh), 5.07 (d, *J* = 12.2 Hz, 1 H, CHHPh), 5.35 (br d, *J* = 6.8 Hz, 1 H, CHPh), 5.45 (br, 1 H, CH-*t*-Bu), 6.80 (br, 1 H), 7.17—7.37 (m, 9 H), 7.43—7.50 (m, 2 H), 7.62 (br d,

J = 7.0 Hz, 1 H); ^{13}C NMR ($CDCl_3$) δ = 12.7, 26.4, 40.1, 45.2, 54.2, 66.7, 68.7, 104.7, 126.9, 127.2, 128.0, 128.1, 128.4, 136.5, 139.6, 141.0, 152.5, 155.8, 164.0, 174.6.

(2*S*,3*S*)-3-(Benzyloxycarbonylamino)-2-methyl-3-phenylpropionic Acid ((−)-68b). To a solution of **74b** (351 mg, 0.692 mmol) in THF–H_2O (3.0 mL : 1.0 mL) were added 30% H_2O_2 (0.565 mL, 5.54 mmol) and LiOH·H_2O (58 mg, 1.38 mmol) at 0 °C. After stirring at room temperature for 0.5 h, $NaHSO_3$ (633 mg) was added. The mixture was extracted with EtOAc, and the combined organic extracts were dried over $MgSO_4$. Removal of the solvent and purification by column chromatography (SiO_2, EtOAc) gave 2-*t*-butyl-1-methoxycarbonyl-2,3-dihydro-4(1*H*)pyrimidinone (132 mg, 90%) as a colorless solid and (−)-**68b** (204 mg, 94%) as a colorless solid. Further, (−)-**68b** was recrystallized from $CHCl_3$ to give a colorless crystal (67 mg): mp 169.0—171.0 °C; $[\alpha]_D^{31}$ −36.7° (*c* 1.10, MeOH).

Preparation of (4*S*)-3-{(2*R*)-2-[(2*R*)-1-Benzyloxycarbonylpyrrolidin-2-yl]propionyl}-4-(1-methylethyl)-2-oxazolidinone (75a): To a solution of a diastereomeric mixture of **57a** and **57b** (1.80 g, 4.82 mmol) in MeOH (16 mL) and AcOH (1.4 mL) was added 10% Pd/C (1.80 g), then hydrogenation was carried out at room temperature under atmospheric pressure of H_2 for 12 h. The reaction mixture was filtered, and the solvent was removed by evaporation, then the oil residue was dissolved in THF—H_2O (1 : 1, 50 mL). To the solution were added K_2CO_3 (2.00 g, 14.5 mmol) and benzyl chloroformate (1.03 mL, 7.23 mmol), and the mixture was stirred at room temperature for 0.5 h. The reaction mixture was extracted with EtOAc, washed with brine, and dried over $MgSO_4$, and the solvent was removed under reduced pressure. The oil residue was purified by column chromatography (SiO_2, 10% EtOAc in hexane) to afford a single diastereomer of **75a** (1.46 g, 82%) as a colorless oil: $[\alpha]_D^{25}$ +43.0° (*c* 1.32, MeOH); IR (neat) 2967, 1781, 1699, 1455, 1410, 1385, 1364, 1302, 1231, 1206, 1103, 754 cm^{-1}; ^{1}H NMR ($CDCl_3$, 55 °C) δ = 0.81 (d, J = 7.1 Hz, 3 H, C$\underline{H}_3$CHCH$_3$), 0.87 (d, J = 7.1 Hz, 3 H, C$\underline{H}_3$CHCH$_3$), 1.08 (d, J = 6.6 Hz, 3 H, NCOCHC$\underline{H}_3$), 1.70—2.05 (m, 4 H, C$\underline{H}_2$C$\underline{H}_2$), 2.20—2.40 (m, 1 H, C$\underline{H}$(CH$_3$)$_2$), 3.28—3.42 (m, 1 H, NC$\underline{H}$H), 3.50—3.66 (m, 1 H, NC$\underline{H}$H), 4.14 (dd, J = 3.7 and 9.0 Hz, 1 H, C$\underline{H}$HO), 4.19 (dd, J = 9.0 and 9.0 Hz, 1 H, C$\underline{H}$HO), 4.25—4.46 (m, 3 H, NC$\underline{H}$CH$_2$, NCOC$\underline{H}$CH$_3$, C$\underline{H}$CH$_2$O), 5.10 (s, 2 H, CH$_2$Ph), 7.22—7.42 (m, 5 H, Ph); ^{13}C NMR ($CDCl_3$, 55 °C) δ = 12.5, 14.4, 17.9, 23.7, 27.8, 28.2, 40.2, 47.1, 58.6, 59.2, 62.9, 66.7, 127.7, 128.3, 136.9, 153.5, 155.1, 174.9. HRMS (FAB) Found: *m/z* 389.2058. Calcd for $C_{20}H_{27}N_2O_5$: M+H$^+$, 389.2076.

Preparation of (2*R*)-2-[(2*R*)-1-Benzyloxycarbonylpyrrolidin-2-yl]propionic Acid ((+)-76) and Methyl (2*R*)-2-[(2*R*)-1-Benzyloxycarbonylpyrrolidin-2-yl]propionate ((+)-77). To a solution of **75a** (5.20 g, 13.4 mmol) in THF–H_2O (160 mL : 53 mL) were added 30% H_2O_2 (6.61 mL, 67.1 mmol) and LiOH·H_2O (1.13 g, 26.8 mmol) at 0 °C. After stirring at room temperature for 1 h, the solvent was removed, and water (60 mL) was added. The reaction mixture was washed with CH_2Cl_2, and the organic phase was dried over $MgSO_4$ and evaporated to give recovered oxazolidinone. The aqueous layer was acidified with 6 M HCl at pH 1 and extracted with CH_2Cl_2. The combined extracts were dried over $MgSO_4$, and the solvent was evaporated. The resulting colorless oil of (+)-**76** was dissolved in DMF (7.5 mL). To the solution were added CH_3I (1.29 mL, 20.7 mmol) and K_2CO_3 (2.20 g, 15.9 mmol), and the mixture was stirred at room temperature for 18 h. To the mixture was added hexane–EtOAc (1 : 1), and this was washed with H_2O and brine. The organic layer was dried over $MgSO_4$. Removal of the solvent and purification by column chromatography (SiO_2, 10—40% EtOAc in hexane) gave (+)-**77** (3.17 g, 81%) as a colorless oil. (+)-**76:** $[\alpha]_D^{25}$ +26.3° (*c* 1.45, MeOH); IR (neat) 3400, 1730, 1703, 1420, 1360, 1111 cm^{-1}; ^{1}H NMR ($CDCl_3$, 55 °C) δ = 1.04 (d, J = 7.2 Hz, 3 H, CHC$\underline{H}_3$), 1.70—2.10 (m, 4 H, (CH$_2$)$_2$), 3.20—3.42 (m, 2 H), 3.50—3.66 (m, 1 H), 4.28—4.38 (m, 1 H), 5.13 (s, 2 H, CH$_2$Ph), 7.22—7.38 (m, 5 H, Ph), 9.17 (br, 1 H, CO$_2$H); ^{13}C NMR ($CDCl_3$, 55 °C) δ = 9.9, 23.8, 27.0, 41.3, 47.3, 58.4, 66.8, 127.6, 127.7, 128.3, 136.7, 154.9, 179.0. HRMS (FAB) Found: *m/z* 278.1401. Calcd for $C_{15}H_{20}NO_4$: M+H$^+$, 278.1392. (+)-**77:** $[\alpha]_D^{22}$ +11.6° (*c* 0.92, MeOH); IR (neat) 2978, 2951, 1734, 1703, 1414, 1360, 1339, 1206, 1103, 754, 698 cm^{-1}; ^{1}H NMR ($CDCl_3$, 55 °C) δ = 1.04 (d, 3 H, J = 7.2 Hz, CHC$\underline{H}_3$), 1.72—2.04 (m, 4 H, (CH$_2$)$_2$), 3.10—3.40 (m, 1 H, C$\underline{H}$CH$_3$), 3.26—3.42 (m, 1 H), 3.52—3.66 (m, 1 H), 3.62 (s, 3 H, CO$_2$CH$_3$), 4.22—4.32 (m, 1 H), 5.13 (s, 2 H, CH$_2$Ph), 7.26—7.40 (m, 5 H, Ph); ^{13}C NMR ($CDCl_3$, 55 °C) δ = 10.5, 24.0, 27.2, 41.0, 47.4, 51.5, 58.8, 66.8, 127.8, 127.9, 128.4, 137.0, 154.9, 175.0. HRMS (FAB) Found: *m/z* 292.1535. Calcd for $C_{16}H_{22}NO_4$: M+H$^+$, 292.1549.

Preparation of (4*R*)-3-{(2*S*)-2-[(2*S*)-1-Benzyloxycarbonylpyrrolidin-2-yl]propionyl}-4-benzyl-2-oxazolidinone (78a). Catalytic hydrogenation of **62a** (7.42 g, 17.6 mmol) in the presence of 10% Pd/C (4.7 g), followed by protection with benzyl chloroformate, gave **78a** (6.70 g, 87%) as a colorless crystal: mp 86.0—87.0 °C; $[\alpha]_D^{24}$ −7.4° (*c* 1.04, $CHCl_3$); IR (neat) 2974, 1773, 1701, 1411, 1096, 919, 698 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ = 1.13 (d, J = 7.0 Hz, 3 H, CH$_3$), 1.76—2.09 (m, 4 H, C$\underline{H}_2$C$\underline{H}_2$), 2.42 (br, 1 H, C$\underline{H}$HPh), 3.19—3.71 (m, 3 H, CH$_2$N and C$\underline{H}$HPh), 4.03 (dd, J = 3.4 and 9.0 Hz, 1 H, OC$\underline{H}$HCH), 4.09 (dd, J = 8.0 and 9.0 Hz, 1 H, OC$\underline{H}$HCH), 4.28 (m, 2 H, C$\underline{H}$CH$_3$ and CHN), 4.61 (ddd, J = 3.4, 3.4, 8.0, and 14.0 Hz, 1 H, C$\underline{H}$CH$_2$Ph), 5.08 (d, J = 12.0 Hz, 1 H, C$\underline{H}$HPh), 5.15 (d, J = 12.0 Hz, 1 H, C$\underline{H}$HPh), 7.11—7.52 (m, 10 H, Ph); ^{13}C NMR ($CDCl_3$) δ = 13.0, 23.8, 28.3, 38.0, 40.5, 47.1, 55.6, 59.7, 66.1, 66.7, 127.1, 127.6, 127.8, 128.4, 128.8, 129.4, 135.9, 137.2, 153.1, 155.1, 175.1. HRMS (FAB) Found: *m/z* 437.2086. Calcd for $C_{25}H_{29}N_2O_5$: M+H$^+$, 437.2076. Found: C, 68.65; H, 6.51; N, 6.50%. Calcd for $C_{25}H_{28}N_2O_5$: C, 68.79; H, 6.47; N, 6.42%.

Preparation of Methyl (2*S*)-2-[(2*S*)-1-Benzyloxycarbonylpyrrolidin-2-yl]propionate ((−)-77). Hydrolysis of **78a** (6.69 g, 15.3 mmol) by LiOH–30% H_2O_2, followed by treatment with diazomethane in ether, gave (−)-**77** (4.50 g, 99%) as a colorless oil: $[\alpha]_D^{24}$ −14.3° (*c* 0.98, MeOH).

Preparation of (4*R*,5*S*)-3-{(2*S*)-2-[(2*S*)-1-Benzyloxycarbonylpyrrolidin-2-yl]propionyl}-4-methyl-5-phenyl-2-oxazolidinone (82). β-Amino acid derivative **81a** (4.35 g, 8.8 mmol) was dissolved in MeOH (30 mL) and 4 M HCl (20 mL). Zinc powder (11.68 g, 176 mmol) was added to the solution, and the mixture was stirred at 60 °C for 0.5 h. The mixture was cooled to room temperature and filtered. After removal of the solvent, the oil residue was dissolved in THF–H_2O (1 : 1, 45 mL). To the solution were added K_2CO_3 (2.00 g, 14.5 mmol) to adjust pH to 8 and benzyl chloroformate (2.51 mL, 17.6 mmol), and the mixture was stirred at room temperature for 2 h. After extraction with EtOAc, washing with brine, and drying over $MgSO_4$, the solvent was removed under reduced pressure, and the oil residue was purified by column chromatography (SiO_2, 15—20% EtOAc in hexane) to afford **82** (3.40 g, 7.78 mmol, 88%) as a colorless oil: $[\alpha]_D^{24}$ +21.1° (*c* 1.01, CH_2Cl_2); IR (neat) 1779, 1705, 1499, 1456, 1410, 1200, 1148, 1030, 988, 959, 767, 736, 699 cm^{-1}; ^{1}H NMR ($CDCl_3$, 50 °C) δ = 0.81 (d, J = 6.6 Hz, 3 H, CH$_3$), 1.15 (br s, 3 H, CH$_3$), 1.74—2.08 (m, 4 H, C$\underline{H}_2$C$\underline{H}_2$), 3.28—3.70 (m, 2 H), 4.20—4.39 (m, 2 H), 4.77 (ddq, J = 7.4, 6.6, and 6.6 Hz, 1 H, CH$_3$C$\underline{H}$CO), 5.08 (br,

2 H, CH_2Ph), 5.61 (d, J = 7.4 Hz, 1 H, PhCHO) 7.12—7.54 (m, 10 H, Ph); ^{13}C NMR ($CDCl_3$, 50 °C) δ = 14.4, 23.8, 28.2, 40.5, 47.2, 47.3, 54.9, 66.7, 77.2, 78.8, 125.8, 127.8, 127.9, 128.4, 128.6, 128.7, 133.7, 137.1, 152.2, 155.1, 174.9. HRMS (FAB) Found: *m/z* 437.2075. Calcd for $C_{25}H_{29}N_2O_5$: M+H$^+$, 437.2076.

Asymmetric Synthesis of 5-Substituted 8-Methylindolizidine Alkaloids. Preparation of (2*S*)-2-[(2*S*)-1-Benzyloxycarbonylpyrrolidin-2-yl]-1-propanol ((−)-83). β-Amino acid derivative **82** (273 mg, 0.63 mmol) was dissolved in THF–H_2O (2 : 1, 10.5 mL) and cooled at 0 °C. To the solution, $NaBH_4$ (95 mg, 2.5 mmol) was added, and the mixture was stirred at 5 °C for 15 h. To the mixture was added 1.6 M aq NaH_2PO_4 dropwise. After removal of THF, the mixture was extracted with EtOAc, washed with brine, and dried over $MgSO_4$. After filtration and removal of the solvent, the oil residue was purified by column chromatography (SiO_2, 30—50% EtOAc in hexane) to afford (−)-**83** (146 mg, 88%) as a colorless oil along with 97 mg (82%) of the recovered chiral auxiliary. (−)-**83**: $[\alpha]_D^{23}$ −37.3° (*c* 1.43, MeOH); IR (neat) 3424, 2969, 2880, 1678, 1455, 1416, 1358, 1339, 1101, 769 cm^{-1}; ^1H NMR ($CDCl_3$, 50 °C) δ = 1.03 (d, J = 7.0 Hz, 3 H, CH_3), 1.49 (br, 1 H, C<u>H</u>CH_3), 1.75—1.98 (m, 4 H, $(CH_2)_2$), 3.24—3.47 (m, 2 H), 3.47—3.71 (m, 2 H), 3.72—3.95 (m, 2 H), 5.14 (d, J = 12.0 Hz, 1 H, C<u>H</u>HPh), 5.17 (d, J = 12.0 Hz, 1 H, C<u>H</u>HPh), 7.28—7.38 (m, 5 H, Ph); ^{13}C NMR ($CDCl_3$, 50 °C) δ = 14.7, 23.6, 28.6, 39.0, 46.3, 59.6, 64.0, 67.2, 127.8, 128.0, 128.5, 136.7, 157.0. HRMS (EI) Found: *m/z* 263.1494. Calcd for $C_{15}H_{21}NO_3$: M$^+$, 263.1521.

Preparation of (2*S*)-1-Benzyloxycarbonyl-[(1*S*)-2-bromo-1-methylethyl]pyrrolidine ((−)-84). Amino alcohol (−)-**83** (397 mg, 1.50 mmol) was dissolved in THF (8 mL) under argon and cooled to 0 °C. To the solution, PPh_3 (590 mg, 2.25 mmol) and CBr_4 (746 mg, 2.25 mmol) were added, and the reaction mixture was warmed up to room temperature. The solution was stirred for 10 min, then sat. $NaHCO_3$ was added. The mixture was extracted with EtOAc, washed with brine, and dried over $MgSO_4$. After filtration and removal of the solvent, the oil residue was purified by column chromatography (SiO_2, 15% EtOAc in hexane) to afford (−)-**84** (471 mg, 96%) as a colorless oil: $[\alpha]_D^{25}$ −39.4° (*c* 1.26, $CHCl_3$); IR (neat) 2970, 1699, 1499, 1456, 1410, 1356, 1103, 770, 698 cm^{-1}; ^1H NMR ($CDCl_3$, 55 °C) δ = 0.97 (d, J = 6.6 Hz, 3 H, CH_3), 1.73—1.98 (m, 4 H, $(CH_2)_2$), 2.38 (septet, J = 6.6 Hz, 1 H, CH_3C<u>H</u>), 3.12—3.45 (m, 3 H), 3.53—3.70 (m, 1 H), 3.93—4.04 (m, 1 H), 5.11 (d, J = 12.5 Hz, 1 H, C<u>H</u>HPh), 5.15 (d, J = 12.5 Hz, 1 H, C<u>H</u>HPh), 7.15—7.42 (m, 5 H, Ph); ^{13}C NMR ($CDCl_3$, 55 °C) δ = 14.4, 24.0, 26.9, 37.3, 38.8, 46.9, 60.8, 66.9, 127.8, 127.9, 128.5, 137.0, 155.4. HRMS (FAB) Found: *m/z* 325.0707. Calcd for $C_{15}H_{21}BrNO_2$: M+H$^+$, 325.0756.

Preparation of Diethyl (2*R*)-2-[(2*S*)-1-Benzyloxycarbonylpyrrolidin-2-yl]propylmalonate ((−)-85). A solution of diethyl malonate (8.95 mL, 58.9 mmol) in 1,2-dimethoxyethane (DME) (20 mL) was added to the suspension of NaH (53.6 mmol, secured from 2.14 g of 60% mineral oil dispersion through hexane washing) in DME (20 mL). A solution of (−)-**84** (1.75 g, 5.36 mmol) in DME (20 mL) was added to the above solution dropwise over 20 min, and the mixture was stirred at 60 °C for 20 h. Ethereal AcOH was added to neutralize the excess sodiomalonate, and the mixture was extracted with EtOAc and washed with brine. After drying over $MgSO_4$, the solvent was removed. The oil residue was purified by column chromatography (SiO_2, 10—20% EtOAc in hexane) to afford (−)-**85** (1.87 g, 86%) as a colorless oil: $[\alpha]_D^{23}$ −13.6° (*c* 1.71, $CHCl_3$); IR (neat) 2995, 1751, 1732, 1701, 1410, 1030, 769, 698 cm^{-1}; ^1H NMR ($CDCl_3$, 50 °C) δ = 0.81 (d, J = 6.8 Hz, 3 H, CH_3), 1.16—1.29 (m, 6 H, CH_2C<u>H</u>$_3$), 1.62—2.29 (m, 7 H), 3.23—3.34 (m, 1 H), 3.39 (br t, J = 6.4 Hz, 1 H, $CH(CO_2)_2$), 3.61 (br, 1 H), 3.86 (br q, J = 5.0 Hz, 1 H, CHN), 4.02—4.27 (m, 4 H, C<u>H</u>$_2CH_3$), 5.12 (s, 2 H, CH_2Ph), 7.26—7.37 (m, 5 H, Ph); ^{13}C NMR ($CDCl_3$, 50 °C) δ = 13.8, 14.0, 24.1, 26.2, 32.7, 33.5, 39.9, 47.3, 50.5, 61.2, 61.3, 62.7, 66.6, 127.7, 128.4, 137.2, 155.2, 169.3, 169.6. HRMS (FAB) Found: *m/z* 406.2196. Calcd for $C_{22}H_{32}NO_6$: M+H$^+$, 406.2230.

Preparation of Ethyl (4*R*)-4-[(2*S*)-1-Benzyloxycarbonylpyrrolidin-2-yl]pentanoate ((−)-86). Diester (−)-**85** (1.85 g, 4.6 mmol) was dissolved in DMSO (25 mL), and NaCl (539 mg, 9.22 mmol) and water (0.33 mL, 18.44 mmol) were added to the solution. The mixture was stirred under argon at 170 °C for 10 h. To the mixture was added H_2O, and the mixture was extracted with EtOAc—Et_2O (3 : 1), washed with brine, and dried over $MgSO_4$. After filtration and removal of the solvent, the oil residue was purified by column chromatography (SiO_2, 15% EtOAc in hexane) to afford (−)-**86** (1.22 g, 3.65 mmol, 80%) as a pale yellow oil: $[\alpha]_D^{25}$ −26.9° (*c* 1.05, $CHCl_3$); IR (neat) 2973, 1732, 1703, 1456, 1412, 1183, 1100, 1028, 770, 700 cm^{-1}; ^1H NMR ($CDCl_3$, 50 °C) δ = 0.79 (d, J = 6.8 Hz, 3 H, CH_3), 1.23 (t, J = 7.1 Hz, 3 H, CH_2C<u>H</u>$_3$), 1.34—1.52 (m, 1 H), 1.57—1.93 (m, 5 H), 1.93—2.49 (m, 3 H), 3.23—3.36 (m, 1 H), 3.62 (br, 1 H), 3.79—3.91 (m, 1 H), 4.10 (q, J = 7.1 Hz, 2 H, C<u>H</u>$_2CH_3$), 5.10 (d, J = 12.5 Hz, 1 H, C<u>H</u>HPh), 5.15 (d, J = 12.5 Hz, 1 H, C<u>H</u>HPh), 7.24—7.39 (m, 5 H, Ph); ^{13}C NMR ($CDCl_3$, 50 °C) δ = 13.7, 14.2, 24.2, 25.9, 29.0, 32.6, 34.7, 47.2, 60.2, 61.5, 66.7, 127.7, 127.8, 128.4, 137.2, 155.2, 173.6. HRMS (FAB) Found: *m/z* 334.2000. Calcd for $C_{19}H_{28}NO_4$: M+H$^+$, 334.2019.

Preparation of (2*S*)-1-Benzyloxycarbonyl-2-[(2*R*)-5,5-dimethoxypent-2-yl]pyrrolidine ((−)-87). Ester (−)-**86** (157 mg, 0.47 mmol) was dissolved in CH_2Cl_2 (15 mL) and cooled to −78 °C under argon. To the solution was added dropwise DIBAL-H (1.0 M in hexane, 0.54 mmol). The mixture was stirred at the same temperature for 30 min. The reaction was quenched with $Na_2SO_4 \cdot 10H_2O$ and diluted with hexane. The mixture was filtered and evaporated. The oil residue was dissolved in MeOH (12 mL), and $TsOH \cdot H_2O$ (catalytic amount) was added, then the mixture was refluxed for 3 h. After addition of sat. $NaHCO_3$, the mixture was extracted with Et_2O, and the combined extracts were washed with brine and dried over $MgSO_4$. After filtration and removal of the solvent, the oil residue was purified by column chromatography (SiO_2, 20% EtOAc in hexane) to afford (−)-**87** (101 mg, 0.30 mmol, 64%) as a colorless oil: $[\alpha]_D^{22}$ −26.7° (*c* 1.39, $CHCl_3$); IR (neat) 2955, 1699, 1408, 1190, 1100, 698 cm^{-1}; ^1H NMR ($CDCl_3$, 50 °C) δ = 0.78 (d, J = 6.8 Hz, 3 H, CH_3), 1.05—2.30 (m, 9 H), 3.29 (s, 6 H, OCH_3), 3.15—3.38 (m, 1 H), 3.62 (br, 1 H), 3.86 (m, 1 H), 4.30 (br, 1 H), 5.10 (d, J = 12.5 Hz, 1 H, C<u>H</u>HPh), 5.15 (d, J = 12.5 Hz, 1 H, C<u>H</u>HPh), 7.26—7.38 (m, 5 H, Ph); ^{13}C NMR ($CDCl_3$, 50 °C) δ = 13.8, 24.2, 25.7, 28.7, 30.7, 34.5, 47.3, 52.7, 61.8, 66.5, 104.8, 127.7, 128.0, 128.4, 137.2, 155.2.

Preparation of (2*S*)-2-[(2*R*)-5,5-Dimethoxypent-2-yl]-pyrrolidine ((+)-88).[27] Acetal (−)-**87** (490 mg, 1.46 mmol) was hydrogenated in MeOH (8 mL) in the presence of 10% Pd/C (160 mg) at room temperature under atmospheric pressure of H_2 for 1.5 h. Filtration, followed by removal of the solvent, gave (+)-**88** (253 mg, 1.25 mmol, 86%): $[\alpha]_D^{23}$ +7.8° (*c* 1.12, CH_2Cl_2) (Ref. 27 $[\alpha]_D$ +7.4° (*c* 1.1, CH_2Cl_2)); IR (neat) 3347, 2957, 1460, 1383, 1192, 1127, 1059 cm^{-1}; ^1H NMR ($CDCl_3$) δ = 0.88 (d, J = 6.8 Hz, 3 H, CH_3), 1.08—1.88 (m, 10 H), 2.74 (m, 1 H), 2.82 (m, 1 H), 2.99 (m, 1 H), 3.31 (s, 6 H, OCH_3), 4.33 (t, J = 5.5 Hz, 1 H, C<u>H</u>$(OCH_3)_2$); ^{13}C NMR ($CDCl_3$, 50 °C) δ = 16.2, 25.5, 29.3, 29.4, 30.1, 38.5, 46.8, 52.7, 64.4, 105.1. HRMS (EI) Found: *m/z* 201.1735. Calcd for $C_{11}H_{23}NO_2$: M$^+$, 201.1729.

Preparation of (5*R*, 8*R*, 8a*S*)- (−)- 5- Cyano- 8- methylindolizidine ((−)-5).[27] Amino acetal (+)-**88** (240 mg, 1.19 mmol) was dissolved in CH_2Cl_2–H_2O (1 : 1, 30 mL), and KCN (932 mg, 14.3 mmol) was added, then the pH was adjusted to 3 with concd HCl. The mixture was stirred for 10 h. After basification with 2 M NaOH, the mixture was extracted with CH_2Cl_2, and the combined extracts were dried over $MgSO_4$, filtered, and evaporated to afford (−)-**5** as a colorless oil (191 mg, containing another diastereomer in 7%, 98% yield): $[\alpha]_D^{24}$ −25.8° (*c* 1.64, CH_2Cl_2) (Ref. 27 $[\alpha]_D$ −18.8° (*c* 1, CH_2Cl_2)); IR (neat) 2953, 2224, 1460, 1167 cm^{-1}; ^1H NMR ($CDCl_3$, 50 °C) δ = 0.92 (d, *J* = 6.5 Hz, 3 H, CH_3), 1.20—1.47 (m, 3 H), 1.61—2.06 (m, 7 H), 2.49 (q, *J* = 8.8 Hz, 1 H, C_3-H), 2.95 (dt, *J* = 3.0 and 8.5 Hz, 1 H, C_{8a}-H), 4.03 (t, *J* = 3.4 Hz, 1 H, C_5-H); ^{13}C NMR ($CDCl_3$, 50 °C) δ = 18.3, 20.3, 28.7, 28.9, 29.4, 36.7, 51.3, 51.4, 64.8, 116.6. HRMS (EI) Found: *m/z* 164.1288. Calcd for $C_{10}H_{16}N_2$: M^+, 164.1313.

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