Tetrahedron Vol. 49, No. 9, pp. 1841-1852, 1993
Printed in Great Britain

0040-4020/93 $6.00+.00

Chiral Synthons for 2-Amino Alcohols. Facile Preparation of Optically Active Amino Hydroxy Acids of Biological Interest.

Tadao Ishizuka, Seigo Ishibuchi and Takehisa Kunieda*

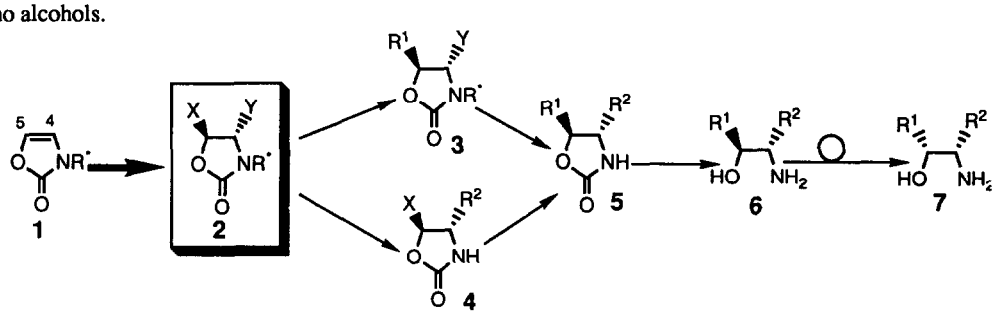
Faculty of Pharmaceutical Sciences, Kumamoto University
Oe-honmachi, Kumamoto 862, Japan

(*Received in Japan* 4 *November* 1992)

Abstract: A promising method for the versatile synthesis of chiral 2-amino alcohols is provided by the enantioselective fuctionalization of the olefinic moiety of the simple heterocycle, 2-oxazolone, involving a stereodefined introduction of easily replaceable groups followed by stepwise substitution. Versatility of this method is shown in chiral synthesis of unusual hydroxy amino acids such as statine and hydroxyglutamic acid, which are the key components of bioactive peptides

The 2-amino alcohol skeleton is a structural unit found in a substantial number of bioactive natural compounds such as peptidic enzyme inhibitors,[1] amino sugar antibiotics,[2] alkaloids and sympathomimetic amines.[3] A number of papers have dealt with the stereochemically controlled construction of such functional skeletons,[4] most of which are *ad-hoc* for each target structure and appear of limited use in terms of synthetic versatility.

In this paper, we describe a promising methodology for the versatile synthesis of 2-amino alcohols to utilize the simple heterocycle, 2-oxazolone (**1**),[5] as a building block. Scheme 1 outlines our synthetic strategy, in which the enantioselective functionalization of the olefinic moiety of the 2-oxazolone ring is provided by *regio*- and *stereo*-defined introduction of easily replaceable groups (X and Y) (**1**→**2**), followed by stereospecific and stepwise substitutions with appropriate groups (R^1 and R^2)(**2**→**3**→**5** or **2**→**4**→**5**). This method would result in the predominant formation of *threo*-configurational products (**6**), which, if needed, are readily convertible to *erythro*-compounds (**7**) by well-established procedures for the inversion of hydroxy groups.[6] The versatile chiral synthons (**2**), thus formed, would permit individual construction of the four possible stereoisomers of the 2-amino alcohols.



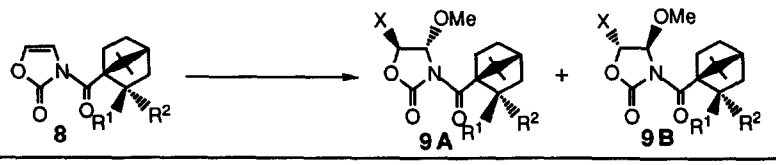
Scheme 1.

The 3-acyl-2-oxazolones smoothly underwent electrophilic reactions with *N*-bromosuccinimide (NBS) and phenylselenenyl chloride (PhSeCl) in methanol to give *trans*-5-bromo-4-methoxy- and *trans*-4-methoxy-5-phenylseleno-adducts, respectively, with full *regio*- and *trans*-stereoselectivity. Both functional groups, thus introduced, were reactive enough to be stepwise replaced by the 5-substitution prior to the conversion of the 4-

* Dedicated to Professor Syun-ichi Yamada on the occasion of his 77 th birthday.

methoxy group,[7] which is suggestive of the good potential of the 2-amino alcohol synthons *via* compound **3**. The chiral *N*-acylated 2-oxazolones (**8**) derived from diphenyl phosphoryloxazolone[8] (DPPOx) and (1*S*)-2-oxo- or (1*S*)-2-*exo*-alkoxyapocamphane-1-carboxylic acids[9] smoothly reacted with NBS or Br_2 in methanol to yield a diastereomeric mixture of *trans*-5-bromo-4-methoxy derivatives with only moderate diastereoselectivity in favor of the (4*S*, 5*S*)-isomer (**9A**, X=Br). The diastereoselectivity was greatly improved when trimethyl orthoesters were used in place of methanol as the methoxy-donating agent.[10] Thus, the 2-*exo*-ethoxymethoxy-derivative gave the highest diastereoselectivity of 96% d.e. on treatment with Br_2 in trimethyl orthoacetate (Table 1, Entry 10).

Table 1. Diastereotopic Functionalizations of Chiral 3-Acyl-2-oxazolones (**8**).



Entry	R^1(*exo*)	R^2(*endo*)	Conditions	X	Yield (%)	A : B[a]
1	=O		NBS, MeOH, r.t.	Br	68	1.7 : 1
2	=O		Br_2, MeOH, -78°C	Br	75	4.3 : 1
3	=O		Br_2, $MeC(OMe)_3$,TMSOTf, -100°C	Br	78	19 : 1
4	=O		PhSeCl, MeOH, 0°C, 24h	PhSe	52	1 : 6.1
5	OMe	H	Br_2, $MeC(OMe)_3$, -78°C	Br	89	12.5 : 1
6	OMe	H	PhSeCl, MeOH, 0°C, 24h	PhSe	83	1 : 4
7	OCH_2CH_2OMe	H	Br_2, $MeC(OMe)_3$, -78°C	Br	79	17 : 1
8	OCH_2CH_2OMe	H	PhSeCl, MeOH, 0°C, 24h	PhSe	94	1 : 19
9	OCH_2CH_2OMe	H	PhSeCl, MeOH, -20°C, 24h	PhSe	82	1 : 45
10	OCH_2OEt	H	Br_2, $MeC(OMe)_3$, -78°C	Br	79	46 : 1
11	OCH_2OEt	H	PhSeCl, MeOH, -20°C, 24h	PhSe	53	1 : 10

a) Determined by ^{1}H-NMR (400MHz).

On the other hand, reactions with PhSeCl in methanol resulted in a preferential formation of (4*R*,5*R*)-4-methoxy-5-phenylseleno-2-oxazolidinones (**9B**, X=PhSe) which surprisingly had the *opposite* configuration to those of the major methoxybromination products.[11] When the (1*S*)-2-*exo*-methoxyethoxy-1-apocamphancarbonyl moiety was used as a chiral auxiliary, the diastereo-face discrimination was most effectively enhanced to 96%d.e.(Table 1, Entry 9). The absolute configuration of the adducts (**9A** and **9B**) were confirmed by transformation to enantiomeric 5-allyl-4-methoxy-2-oxazolidinones (**13** and **16**) followed by the chemical correlation with γ-amino-β-hydroxybutyric acid (GABOB) of known configuration.[12]

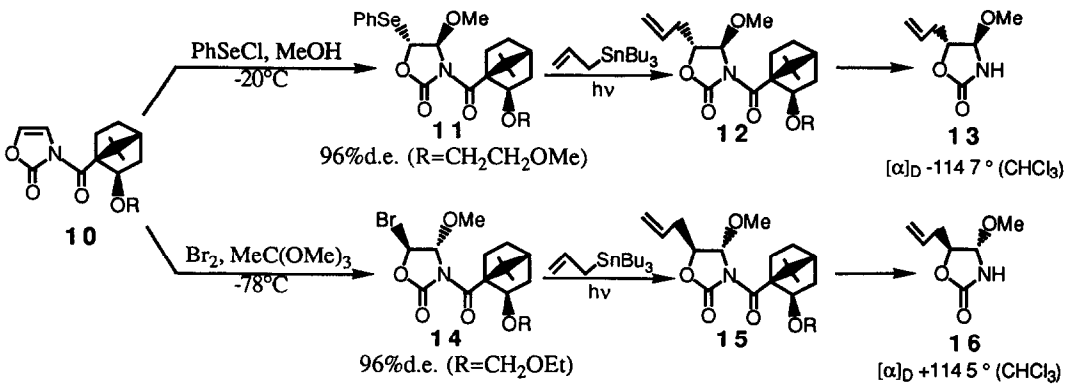
The selective substitution at the 5-position was readily performed with the 4-methoxy group unaffected under radical conditions. Thus, upon the UV-irradiation in the presence of allyltributylstannane, both 5-phenylseleno- and 5-bromo-adducts (**11** and **14**) yielded the 5-allyl-4-methoxy derivatives (**12** and **15**) with full retention of configuration due to the steric repulsion by the 4-substituents (Scheme 2).[13]

Contrary to our expectation on the facile acid-catalyzed 4-substitution of 4-methoxy-2-oxazolidinones in the *N*,*O*-acetal forms *via* iminium cations, the attempts were unsuccessful under a wide variety of substitution conditions. The *N*-deacylation, which greatly contributes to the stabilization of iminium cation intermediates, was essential for the smooth substitution at the 4-position.

The reductive ($NaBH_4$-MeOH, $LiBH_4$-MeOH) or strongly nucleophilic ($PhCH_2SLi$, Bu_2CuLi) reagents were required for smooth removal of the sterically congested acyl groups such as 2-oxo- (ketopinyl) and 2-

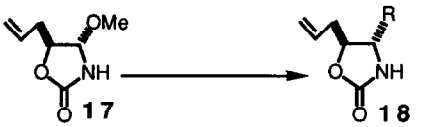
alkoxy-1-apocamphanecarbonyls. Lithium benzylmercaptide[14] is the reagent of choice for the reuse of the chiral auxiliaries recovered.

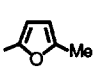
Thus, both enantiomers of (4*R*,5*R*)-and (4*S*,5*S*)-5-allyl-4-methoxy-2-oxazolidinones (**13** and **16**) were selectively obtained from 3-[(1*S*)-2-*exo*-alkoxy-1-apocamphanecarbonyl]-2-oxazolones (**10**) by alteration of the electrophilic reagents[15] as outlined in Scheme 2.



Scheme 2.

Table 2. Substitution at 4-Position of 4-Methoxy-2-oxazolidinone (**17**).



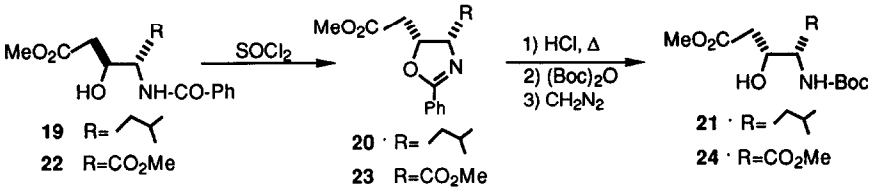
Entry	Conditions	R	Yield (%)
1	BuCuCNLi, BF_3•OEt_2, -30°C	Bu	91
2	*i*-Pr CuCNMgBr, BF_3•OEt_2, -30°C	*i*-Pr	94
3	*t*-BuCuCNMgBr, BF_3•OEt_2, -30°C	*t*-Bu	67
4	PhCuCNMgBr, BF_3•OEt_2, -30°C	Ph	85
5	$(vinyl)_2CuCN(MgBr)_2$, BF_3•OEt_2, -30°C	vinyl	69
6	 , HCO_2H, r.t.		92
7	 $SiMe_3$, $TiCl_4$, 0°C		95

The *N*-deacylated 4-methoxy-2-oxazolidinones (**13** and **16**) smoothly reacted with several kinds of nucleophilic reagents in the presence of acid catalysts to yield the 4-substituted-2-oxazolidinones with high retention of configurations (Table 2). Cuprate reagents in combination with BF_3•OEt_2 were particularly useful for introduction of a wide variety of groups such as *prim*- to *tert*-alkyls, aryls, alkenyls and alkynyls.[16] This direct replacement of 4-methoxy groups under mild conditions greatly extends the versatility of the type 2 chiral synthons.

Hydrolytic ring-cleavage of 2-oxazolidinones under drastic conditions unavoidably formed complex side-products. An alternative method involving treatment of *N*-Boc cyclic carbamates with catalytic amount of cesium carbonate was successfully employed for mild ring-opening of *N*-Boc-2-oxazolidinones to open-chained *N*-Boc-

2-aminoalcohols.[17] This method was mild enough to cleave smoothly methyl *trans*-(4*S*,5*R*)- and *cis*-(4*S*,5*S*)-5-methyl-3-*tert*-butoxycarbonyl-2-oxazolidinone-4-carboxylates into *N*-Boc-L-threonine methyl ester and *N*-Boc-L-*allo*-threonine methyl ester, respectively, without any detectable amounts of epimerized and β-eliminated products.

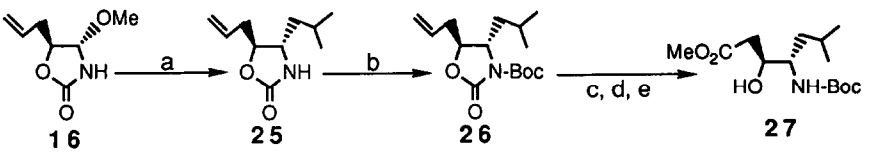
Interconversion between *threo*- and *erythro*-2-amino alcohols could be readily attained by facile inversion of the hydroxy groups. Among the methods,[6] the configurational inversion *via* oxazoline formation[6c] may be the most reliable and convenient route in which serious side reactions such as β-elimination and epimerization could be completely avoided as evidenced by the transformations between (±)-statine (**19**) and (±)-epistatine (**21**) and between (±)-*threo*-β-hydroxyglutamic acid (**22**) and its (±)-*erythro*-derivative (**24**) (Scheme 3).



Scheme 3.

Based on the above promising findings on the key steps, we describe here the improved synthesis from the (4*S*,5*S*)-compound (**16**) of (3*S*, 4*S*)-statine,[18] a key component of protease inhibitor, pepstatin[1a], and from (4*R*, 5*R*)-compound (**13**) of (2*S*,3*R*)-β-hydroxyglutamic acid[3b,19] which is a component of the peptide antibiotic S-520.

On treatment of (4*S*, 5*S*)-5-allyl-4-methoxy-2-oxazolidinone (**16**) with the cuprate-BF_3•OEt_2 reagent system, *iso*-butyl group was directly introduced to give high yield of **25** with complete stereoselectivity in good yield. Oxidative cleavage of the C=C bond followed by opening the 2-oxazolidinone ring with catalytic amount of Cs_2CO_3 yielded (3*S*,4*S*)-*N*-Boc-statine methyl ester (**27**) in optically pure form as outlined in Scheme 4. An alternative route for the somewhat lengthy conversion was previously reported.[10]

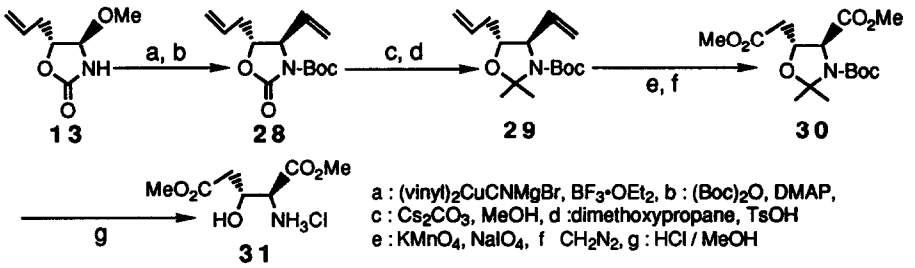


Scheme 4

No contamination with the *erythro*-isomer was unequivocally shown by direct comparison of the ^{1}H-NMR spectrum with that of epistatine (**21**). The analogs including cyclohexylstatine were similarly synthesized.[16]

Starting from the versatile intermediate, (4*R*, 5*R*)-5-allyl-4-methoxy-2-oxazolidinone (**13**), we readily synthesized optically pure dimethyl (2*S*, 3*R*)-3-hydroxyglutamate hydrochloride (**31**) by its ready conversion to the key intermediate (4*R*, 5*R*)-**28** followed by simultaneous cleavage of both the double bonds with $KMnO_4$-$NaIO_4$ as outlined in Scheme 5. Compound **31**, thus obtained, was proved configurationally pure as well.

The enantiomer **13** was also employed for the facile synthesis of a series of (2*S*, 3*R*)-3-amino-2-hydroxy-carboxylic acids, which were the key components of enzyme inhibitors, amastatin and bestatin.[20]



Scheme 5.

In conclusion, the present methodology apparently has wide applications for the facile construction of chiral 2-amino alcohol skeletons which are involved in a variety of biologically active natural products.

EXPERIMENTAL

Melting points were determined on a Yanaco micro melting point apparatus and are uncorrected. ^{1}H-NMR spectra were recorded in $CDCl_3$ at 400MHz and 60MHz on a JEOL GSX400 and Hitachi R-24B instruments respectively, with tetramethylsilane as an internal standard. Optical rotations were measured with a JASCO DIP-370 polarimeter. Column chromatography was performed using silica gel 60 (70-230 mesh, Merck). All the solvents were distilled before use ; THF over Na / benzophenone , Et_2O over $LiAlH_4$, CH_2Cl_2 over CaH_2 and MeOH over MeONa.

General procedure for 3-[(1S)-2-substituted-1-apocamphanecarbonyl]-2-oxazolones (8).

To a solution of lithium salt of 2-oxo- and 2-*exo*-alkoxy-1-apocamphanecarboxylic acids (1 mmol) in THF (5 mL) was added DPPOx (1 mmol, dissolved in 5 mL of THF) at 0 °C under argon atmosphere. The mixture was stirred at 0°C for 1h and then passed through a silica gel pad with AcOEt as eluent. Removal of the AcOEt *in vacuo* followed by chromatographic purification on silica gel (CH_2Cl_2) gave the 2-oxazolone derivatives.

3-[(1*S*)-2-Oxo-1-apocamphanecarbonyl]-2-oxazolone : Colorless crystals (90 %). mp. 129-130 °C (from EtOH) ; $[\alpha]_D^{25}$ -49.2 ° (c 1.00, $CHCl_3$) ; IR (KBr / cm^{-1}) 1692, 1736, 1789 ; ^{1}H-NMR (400MHz) δ 1.179 (s, 3H), 1.251 (s, 3H), 1.54-1.61 (m, 1H), 2.01-2.18 (m, 4H), 2.99-3.07 (m, 1H), 6.81 (d, 1H, J=2.2 Hz), 7.25 (d, 1H, J=2.2 Hz) ; Anal. Calcd for $C_{13}H_{15}NO_4$: C, 62.64 ; H, 6.07 ; N, 5.62. Found : C, 62.45 ; H, 6.09 ; N, 5.35.

3-[(1*S*)-2-*exo*-Methoxy-1-apocamphanecarbonyl]-2-oxazolone : Colorless crystals (91 %). mp. 77.5-78.0 °C (from hexane) ; $[\alpha]_D^{30}$ -58.0 ° (c 1.00, $CHCl_3$) ; ^{1}H-NMR (400MHz) δ 1.14 (s, 3H), 1.17-1.21 (m, 1H), 1.32 (s, 3H), 1.61-1.93 (m, 5H), 2.39-2.43 (m, 1H), 3.18 (s, 3H), 4.61 (dd, 1H, J=3.7 Hz, 7.7 Hz), 6.78 (d, 1H, J=2.2 Hz), 7.29 (d, 1H, J=2.2 Hz) ; Anal. Calcd for $C_{14}H_{19}NO_4$: C, 63.38 ; H, 7.22 ; N, 5.28. Found : C, 63.32 ; H, 7.18 ; N, 5.39.

3-[(1*S*)-2-*exo*-Methoxyethoxy-1-apocamphanecarbonyl]-2-oxazolone : Colorless crystals (91 %). mp. 61-62 °C (from hexane) ; $[\alpha]_D^{30}$ -51.1 ° (c 1.00, $CHCl_3$) ; ^{1}H-NMR (400MHz) δ 1.15 (s,3H), 1.17-1.26 (m, 1H), 1.33 (s, 3H), 1.69-1.92 (m, 5H), 2.41-2.46 (m, 1H), 3.26 (s, 3H), 3 34-3.42 (m, 3H), 3.54-3.59 (m, 1H), 4.70 (dd, 1H, J=3.7 Hz, 7.7 Hz), 6 79 (d, 1H, J=2.2 Hz), 7.29 (d, 1H, J=2.2 Hz) ; Anal. Calcd for $C_{16}H_{23}NO_5$: C, 62.12 ; H, 7.49 ; N, 4.53 Found : C, 62.03 ; H, 7.40 ; N, 4.52.

3-[(1*S*)-2-*exo*-Ethoxymethoxy-1-apocamphanecarbonyl]-2-oxazolone : Colorless crystals (93 %). mp. 41.0-42.5 °C (from hexane) ; $[\alpha]_D^{28}$ -58.7 ° (c 1.00, $CHCl_3$) ; ^{1}H-NMR (400MHz) δ 1.13 (t, 3H, J=7.0 Hz), 1.13 (s, 3H), 1.11-1.25 (m, 1H), 1.37 (s, 3H), 1.68-1.70 (m, 1H), 1.74-1.87 (m, 3H), 1.93-2.00 (m, 1H), 2.45-2.50 (m, 1H), 3.36-3.50 (m, 2H), 4.58 (d, 1H, J=2.2 Hz), 7.29 (d, 1H, J=2.2 Hz) ; Anal. Calcd for $C_{16}H_{23}NO_5$: C, 62.12 ; H, 7.49 ; N, 4.53 Found : C, 61.88 , H, 7.52 ; N, 4.47.

Methoxybrominations: General procedure.

A solution of bromine (1.4 mmol) in CH_2Cl_2 (5 mL) was added dropwise over 30 min to 3-acyl-2-oxazolone (1 mmol) in trimethyl orthoacetate (5 mL) at specified temperature under argon atmosphere. The mixture was quickly passed through a short column of silica gel with CH_2Cl_2 as the eluent and the eluate was evaporated *in vacuo*. Chromatography on silica gel with CH_2Cl_2 readily gave the diastereomers **9A** and **9B** (X=Br) in optically pure form. The following singlet peaks due to the H_5-proton in the ^{1}H-NMR (400 MHz) spectra of the crude products were used for determination of the ratios of **9A** to **9B**.

5-Bromo-4-methoxy-3-acyl-2-oxazolidinones		Chemical shift (δ)	
R^1	R^2	**9A** (4*S*, 5*S*)	**9B** (4*R*, 5*R*)
=O		5.77 (s)	5.86 (s)
OMe	H	5.77 (s)	5.86 (s)
OCH_2CH_2OMe	H	5.84 (s)	5.89 (s)
OCH_2OEt	H	5.85 (s)	5.83 (s)

A typical example is given as follows. Under the standard conditions, 3-[(1*S*)-2-*exo*-methoxyethoxy-1-apocamphanecarbonyl]-2-oxazolone gave 79 % yield of (4*S*, 5*S*)- and (4*R*, 5*R*)-5-bromo-4-methoxy-derivatives in a diastereomeric ratio of 17 : 1.

(4*S*, 5*S*)-5-Bromo-4-methoxy-3-[(1*S*)-2-*exo*-methoxyethoxy-1-apocamphanecarbonyl]-2-oxazolidinone : Colorless crystals. mp. 28-29 °C (from hexane) ; $[\alpha]_D^{29}$ -137.2 ° (c 0.40, $CHCl_3$) ; ^{1}H-NMR (400MHz) δ 1.15 (s, 3H), 1.18-1.22 (m, 1H), 1.33 (s, 3H), 1.68-1.73 (m, 2H), 1.77-1.97 (m, 3H), 2.34-2.40 (m, 1H), 3.32 (s, 3H), 3.41-3.56 (m, 7H), 4.49 (dd, 1H, J=3.7 Hz, 7.7 Hz), 5.84 (s, 1H), 6.18 (s, 1H) ; Anal. Calcd for $C_{17}H_{26}BrNO_6$: C, 48.58 ; H, 6.24 ; N, 3.33. Found : C, 48.46 ; H, 6.23 ; N, 3.48.

(4*R*, 5*R*)-5-Bromo-4-methoxy-3-[(1*S*)-2-*exo*-methoxyethoxy-1-apocamphane-carbonyl]-2-oxazolidinone : Clorless crystals. mp. 68 °C (dec.) (from hexane) ; $[\alpha]_D^{29}$ +115.6 ° (c 0.50, $CHCl_3$) ; ^{1}H-NMR (400MHz) δ 1.13 (s, 3H), 1.15-1.20 (m, 1H), 1.35 (s, 3H), 1.66-1.87 (m, 4H), 1.92-2.00 (m, 1H), 2.18-2.22 (m, 1H), 3.30 (s, 3H), 3.40-3.46 (m, 3H), 3.51 (s, 3H), 3.54-3.62 (m, 1H), 4.65 (dd, 1H, J=3.7 Hz, 7.7 Hz), 5.89 (s, 1H), 6.16 (s, 1H) ; Anal. Calcd for $C_{17}H_{26}BrNO_6$: C, 48.58 ; H, 6.24 ; N, 3.33. Found : C, 48.72 ; H, 6.34 ; N, 3.41.

Methoxyselenylation: General procedure.

Phenylselenenyl chloride (2 mmol, dissolved in 1 mL of CH_2Cl_2) was added to the mixture of 3-acyl-2-oxazolone (1 mmol), MeOH (1.8 mL) and CH_2Cl_2 (2 mL) at 0°C under argon atmosphere and the solution was stirred for 24 h. The mixture was passed through a short column of silica gel with CH_2Cl_2 as the eluent and the eluate was concentrated *in vacuo*. Chromatography on silica gel with CH_2Cl_2 gave **9A** and **9B** (X=PhSe) derivatives whose ratios were determined based on the following doublet peaks due to the H_5-proton in the ^{1}H-NMR (400 MHz) spectra.

4-Methoxy-5-phenylseleno-3-acyl-2-oxazolidinones		Chemical shifts (δ)	
R^1	R^2	**9A** (4*S*, 5*S*)	**9B** (4*R*, 5*R*)
=O		5.62 (d, J=1.5 Hz)	5.73 (d, J=1.1 Hz)
OMe	H	5.75 (d, J=1 1 Hz)	5.88 (d, J=0.7 Hz)
OCH_2CH_2OMe	H	5.76 (d, J=1.1 Hz)	5.89 (d, J=0.7 Hz)
OCH_2OEt	H	5.75 (d, J=1.1 Hz)	5.84 (d, J=0.7 Hz)

A typical example is as follows. Under the conditions as above, 3-[(1*S*)-2-*exo*-methoxyethoxy-1-apocamphanecarbonyl]-2-oxazolone gave 82 % yield of (4*S*, 5*S*)- and (4*R*, 5*R*)-4-methoxy-5-phenylseleno-derivatives in a ratio of 1 : 45.

(4*R*, 5*R*)-4-methoxy-3-[(1*S*)-2-*exo*-methoxyethoxy-1-apocamphanecarbonyl]-5-phenylselenyl-2-oxazolidinone : Colorless crystals. mp. 64 °C (from hexane) ; $[\alpha]_D^{29}$ +176.5 ° (c 1.00, $CHCl_3$) : ^{1}H-NMR (400MHz) δ 0.99 (s, 3H), 1.24 (s, 3H), 1.00-1.30 (m, 1H), 1.55-1.71 (m, 4H), 1.82-1.89 (m, 1H), 1.90-1.98 (m, 1H), 3.28 (s, 3H), 3.33-3.41 (m, 3H), 3.42 (s, 3H), 3.49-3.54 (m, 1H), 4.50 (dd, 1H, J=3.7 Hz, 7.7 Hz), 5.67 (d, 1H, J=0.7 Hz), 5.89 (d, 1H, J=0.7 Hz) 7.26-7.41 (m, 3H), 7.66-7.69 (m, 2H) ; Anal. Calcd for $C_{23}H_{31}NO_6Se$: C, 55.64 ; H, 6.29 ; N, 2.82. Found : C, 55.90 ; H, 6.26 ; N, 2.86.

(4*S*, 5*S*)-4-Methoxy-3-[(1*S*)-2-*exo*-methoxyethoxy-1-apocamphanecarbonyl]-5-phenylselenyl-2-oxazolidinone : Colorless crystals. mp. 78-79 °C (from hexane) ; ^{1}H-NMR (400MHz) δ 1.13 (s, 3H), 1.34 (s, 3H), 1.10-1.20 (m, 1H), 1.65-1.98 (m, 5H), 2.37 (ddd, J=1H, 3.7 Hz, 8.8 Hz, 12.1 Hz), 3.34 (s, 3H), 3.44 (s, 3H), 3.46-3.60(m, 4H), 4.54 (dd, 1H, J=3.7 Hz, 7.7 Hz), 5.68 (d, 1H, J=1.1 Hz), 5.76 (d, 1H, J=1.1 Hz), 7.33 -7.40 (m, 3H), 7.64-7.67 (m, 2H) ; high resolution MS Calcd for $C_{23}H_{31}NO_6Se$: m / z 497.1317, Found: m / z 497.1313.

3-[(1*S*)-2-*exo*-methoxy-1-apocamphancarbonyl]-5-allyl-4-methoxy-2-oxazolidinones (12 and 15 ; R=Me).

a) A solution of (4*S*, 5*S*)-5-bromo-3-[(1*S*)-2-*exo*-methoxy-1-apocamphanecarbonyl]-4-methoxy-2-oxazolidinone (**14**, R=Me) (295 mg, 0.78 mmol) and allyltributylstannane (518 mg, 2 eq.) in Et_2O (3.8 mL) was UV-irradiated (100W, Hg-high pressure) for 2 h in a quartz flask under argon atmosphere. Removal of the solvent *in vacuo* and column chromatography on silica gel (CH_2Cl_2) gave (4*S*, 5*S*)-5-allyl-3-[(1*S*)-2-*exo*-methoxy-1-apocamphanecarbonyl]-4-methoxy-2-oxazolidinone (**15**, R=Me) (204 mg, 71 %) as colorless crystals : mp. 65-67 °C ; $[\alpha]_D^{27}$ -52.4° (c 0.89, $CHCl_3$) ; ^{1}H-NMR (400MHz) δ 1.15 (s, 3H), 1.27 (s, 3H), 1.13-1.21 (m, 1H), 1.63-1.68 (m, 2H), 1.75-1.95 (m, 3H), 2 29-2.51 (m, 3H), 3.16 (s, 3H), 3.44 (s, 3H), 4.32-4.39 (m, 2H), 5.17-5.24 (m, 2H), 5.38 (d, 1H, J=0.7 Hz), 5.70-5.82 (m, 1H) ; high resolution MS Calcd for $C_{18}H_{27}NO_5$: m / z 337.1889, Found: m / z 337.1861 ; Anal. Calcd for $C_{18}H_{27}NO_5$: C, 64.07 ; H, 8.07 ; N, 4.15. Found : C, 64.20 ; H, 8.38 ; N, 4.08.

b) Similar treatment of (4*R*, 5*R*)-3-[(1*S*)-2-*exo*-methoxy-1-apocamphanecarbonyl]-4-methoxy-5-phenyl-seleno-2-oxazolidinone (**11**, R=Me) gave (4*R*, 5*R*)-5-allyl-3-[(1*S*)-2-*exo*-methoxy-1-apocamphanecarbonyl]-4-methoxy-2-oxazolidinone (**12**, R=Me) in 71 % yield as clorless oil : $[\alpha]_D^{27}$ +31.2 ° (c 1.01, $CHCl_3$) ; ^{1}H-NMR (400MHz) δ 1.11 (s, 3H), 1.06-1.20 (m, 1H), 1.31 (s, 3H), 1.64-1.81 (m, 4H), 1.86-1.93 (m, 1H), 2.22-2.48 (m, 3H), 3.22 (s, 3H), 3.42 (s, 3H), 4.38 (dt, 1H, J=1.1 Hz, 7.0 Hz), 4.56 (dd, 1H, J=3.7 Hz, 7.7 Hz), 5.18-5.26 (m, 2H), 5.51 (d, 1H, J=1.1 Hz), 5.66-5.78 (m, 1H) ; high resolution MS Calcd for $C_{18}H_{27}NO_5$: m / z 337.1889, Found : m / z 337.1957.

(4*S*, 5*S*)- and (4*R*, 5*R*)-5-Allyl-4-metoxy-2-oxazolidinones (13 and 16).

To a solution of $PhCH_2SLi$ prepared from $PhCH_2SH$ (2 mmol) and n-BuLi (1.5 mmol) in THF (2 mL) was added 3-acyl-5-allyl-4-methoxy-2-oxazolidinone (1 mmol) in THF (4 mL) at 0 °C under argon atmosphere. After complete deacylation (at 0 °C to reflux) monitored by TLC, saturated NH_4Cl solution (2 mL) and AcOEt (150 mL) were successively added and the organic layer was washed (brine) and dried (Na_2SO_4). Evaporation *in vacuo* and purification by silica gel column chromatography yielded 5-allyl-4-methoxy-2-oxazolidinone(80~90 %) in addition to thiobenzyl ester (almost quantitative).

(4*R*, 5*R*)-5-Allyl-4-metoxy-2-oxazolidinone (13) : Colorless crystals. mp. 49.5-50.5°C ; $[\alpha]_D^{22}$ -114.6° (c 1.10, $CHCl_3$) ; Anal. Calcd for $C_7H_{11}NO_3$: C, 53.49 ; H, 7.15 ; N, 8.91. Found : C, 53.74 ; H, 7.13 ; N, 8.71. ^{1}H-NMR (400 MHz) was identical with that of (4*S*, 5*S*)-isomer (**14**).

(4*S*, 5*S*)-5-Allyl-4-metoxy-2-oxazolidinone (16) : Colorless crystals. mp. 49.5-50.5°C ; $[\alpha]_D^{22}$ +114.5° (c 1.00, $CHCl_3$) ; IR (nujol / cm^{-1}) 3292, 1758 ; ^{1}H-NMR (400MHz) δ 2.38-2.58 (m, 2H), 3.33 (s, 3H), 4.45 (dt, 1H, J=2Hz, 6Hz), 4.7 (d, 1H,J=2Hz), 5.18-5.25 (m, 2H), 5.70-5.84 (m, 1H), 7.55(br.s, 1H) ; Anal. Calcd for $C_7H_{11}NO_3$: C, 53.49 ; H, 7.15 ; N, 8.91. Found : C, 53.69 ; H, 7.00 ; N, 8.65.

Substitutions at the 4-position of (±)-trans-5-allyl-4-methoxy-2-oxazolidinone (17).

(±)-5-Allyl-4-(5-methyl-2-furanyl)-2-oxazolidinone.

To a solution of (±)-*trans*-5-allyl-4-methoxy-2-oxazolidinone (387 mg, 2.7 mmol) and 2-methylfuran (2.165 g, 27 mmol) in CH_2Cl_2 (5.3 mL) was added formic acid (2.7 mL) at 0°C and the mixture was stirred at room temperature overnight. The solvent was removed *in vacuo* and the residue was purified by silica gel column chromatography to yield 5-allyl-4-(5-methyl-2-furanyl)-2-oxazolidinone (512 mg, 92%) as colorless oil : ^{1}H-NMR (60 MHz) δ 2.20 (s, 3H), 2.4-2.7 (m, 2H), 4.4-4.6 (m, 2H), 4.9-5.3 (m, 2H), 5.4-6.0 (m, 2H), 6.1 (d, 1H, J=3 Hz), 7.0 (br.s, 1H).

(±)-*trans*-4,5-Diallyl-2-oxazolidinone.

To a solution of (±)-*trans*-5-allyl-4-methoxy-2-oxazolidinone (97 mg, 0.62 mmol) and allyltrimethylsilane (142 mg, 1.2 mmol) in CH_2Cl_2 (2 mL) was added titanium tetrachloride (0.02 mL, 0.3 eq.) at -30°C under argon atmosphere. The mixture was stirred at -30°C for 15 min and then at 0°C for 1 h. After addition of MeOH (1 mL), the solvent was removed *in vacuo*. Column chromatography on silica gel yielded *trans*-4,5-diallyl-2-oxazolidinone (96.8 mg, 94%) as colorless oil : ^{1}H-NMR (60 MHz) δ 2.30 (t, 2H, J=6.6 Hz), 2.45 (t, 2H, J=6.6 Hz), 3.55 (dt, 1H, J=6Hz, 6Hz), 4.25 (dt, 1H, J=6 Hz, 6Hz), 4.95-6.15 (m, 6H), 6.83 (br.s, 1H).

(±)-*trans*-4-Allyl-5-butyl-2-oxazolidinone.

To a solution of LiCl (373 mg, 8.8 mmol, dried at 150°C for 1 h under reduced pressure) and CuCN (394 mg, 4.4 mmol) in THF (5 mL) was added *n*-BuLi (2 5 mL, 4 mmol, 1.59M in hexane) at -30°C under argon atmosphere and the whole was stirred for 1 h. (±)-*trans*-5-Allyl-4-methoxy-2-oxazolidinone (157 mg, 1mmol, dissolved in 2.5 mL of THF) and BF_3•OEt_2 (0.25 mL, 2 mmol) were added successively and the mixture was stirred at -30°C for 1 h. The reaction was quenched by addition of saturated NH_4Cl solution (1 mL) and the mixture was filtered through short column of silica gel with AcOEt as eluent. Concentration of the eluant *in vacuo* followed by column chromatography on silica gel (CH_2Cl_2 : AcOEt = 8 : 2) gave *trans*-4-allyl-5-butyl-2-oxazolidinone (167 mg, 91 %) as colorless oil : ^{1}H-NMR (400 MHz) δ 0.89-0.93 (m, 3H), 1.23-1.40 (m, 4H), 1.50-1.56 (m, 2H), 2.39-2.53 (m, 2H), 3.48 (dt, 1H, J= 5 86 Hz, 12.28 Hz), 4.23 (dt, 1H, J= 5.86 Hz, 11.54 Hz), 5.16-5.22 (m, 2H), 5.74-5.84 (m, 1H), 6.33 (br, 1H).

Stereochemical inversion of OH group.

***cis*-5-(Methoxycarbonylmethyl)-2-phenyl-4-*iso*-butyl-2-oxazoline (20).**

To a solution of methyl *threo*-2-benzamido-3-hydroxy-6-methylheptanoate (**19**) (30 mg, 0.1 mmol) in Et_2O (0.1 mL) was added thionyl chloride (0.06 mL, 8 eq.) at 0°C and the mixture was stirred for 3 h at 0°C. The reaction mixture was poured into the stirred mixture of Na_2CO_3 (340 mg) in H_2O (2.7 mL) and AcOEt (2.7 mL) at 0°C, and the whole was extracted with AcOEt (50 mL x 3). After concentration of the extract *in vacuo*, silica gel column chromatography (CH_2Cl_2 : AcOEt = 9 · 1) yielded **20** as colorless oil (20 mg, 71 %) : ^{1}H-NMR (60 MHz) δ 1.05 (d, 5H,J=3 Hz), 1.20-2.20 (m, 3H), 2.60-2.70 (m, 2H), 3 65 (s, 3H), 4.05-4.50 (m, 1H), 4.85-5.70 (m, 1H), 7.1-7.4 (m, 3H), 7.6-7.9 (m, 2H).

Methyl *erythro*-4-[(*tert*-butoxycarbonyl)amino]-3-hydroxy-6-methylheptanoate (21).

A solution of **20** (20 mg) in 6M HCl (5 mL) was stirred at 80°C overnight. The mixture was washed with AcOEt (20 mL) and then aqueous layer was evaporated *in vacuo*. The residue was dissolved in H_2O (1.4 mL) and NEt_3 (0.04 mL, dissolved in 1.4 mL of dioxane) and di-*tert*-butyl dicarbonate (31 mg, dissolved in 1.4 mL of dioxane) were added to the solution. After stirring overnight, usual work-up yielded crude acid which was treated with CH_2N_2 to yield, after purification by silica gel column chromatography (CH_2Cl_2 : AcOEt = 9 : 1), methyl ester **21** (15.2 mg, 74 %) as colorless oil ^{1}H-NMR (400 MHz) δ 0.91-0 95 (m, 6H), 1.32-1.34 (m, 3H), 1.44 (s, 9H), 2.69 (dd, 1H, J=16.1 Hz, 6.6 Hz), 2.82 (dd, 1H, J=6.59 Hz, 16.12 Hz), 3.725 (s, 3H), 4.00 (br.s, 1H), 4.55 (m, 2H), 6.1 (br.s, 1H).

***cis*-4-Methoxycarbonyl-5-(methoxycarbonylmethyl)-2-phenyl-2-oxazoline (23).**

Analogously to **20**, this was obtained from **22** as colorless oil (70 %) : ^{1}H-NMR (60 MHz) δ 2.79 (d, 2H, J=6 Hz), 3 70 (s, 3H), 3.71(s, 3H), 4 9-5 5(m, 2H), 7.2-7 6(m, 3H), 7 8-8.1(m, 2H).

Dimethyl *erythro*-2-[(*tert*-butoxycarbonyl)amino]-β-hydroxyglutamate (24).

Analogously to **21**, this was obtained from **23** as colorless oil (46 %) : ^{1}H-NMR (60 MHz) δ 2.62 (dd, 1H, J=3.7 Hz, 16.5 Hz), 2.69 (dd, 1H, J=8.8 Hz, 16.5 Hz), 3.71 (s, 3H), 3.78 (s, 3H), 4.26-4.44 (m, 2H), 5.3 (br, 1H).

Synthesis of Statine.

(4*S*, 5*S*)-5-Allyl-4-*iso*-butyl-2-oxazolidinone (25).

To a mixture of LiCl (373 mg, 8.8 mmol, dried at 150 °C for 1 h under reduced pressure) and CuCN (394 mg, 4.4 mmol) in THF (5 mL) was added *iso*-butylmagnesium bromide (10 mL, 0.4 M in THF, 4 mmol) at -30 °C under argon atmosphere and the mixture was stirred for 1 h. (4*S*, 5*S*)-5-Allyl-4-methoxy-2-oxazolidinone (**16**) (157 mg, 1 mmol) and BF_3•OEt_2 (0.25 mL, 2 mmol) in THF (2.5 mL) were successively added and it was stirred at -30 °C for 24 h. Usual work-up followed by column chromatography on silica gel (CH_2Cl_2) gave **25** (166 mg, 92 %) as colorless oil : $[\alpha]_D^{27}$ -72.4° (c 0.95, $CHCl_3$) ; ^{1}H-NMR (400 MHz) δ 0.92 (d, 3H, J=7.0 Hz), 0.94 (d, 3H, J=7.0 Hz), 1.25-1.90 (m, 5H), 2.40-2.55 (m, 2H), 3.57 (dt, 1H, J=5.5 Hz, 8.8 Hz), 4.20 (dd, 1H, J=5.5 Hz, 11.7 Hz), 5.17-5.22 (m, 2H), 5.74-5.85 (m, 1H), 6.37 (br, 1H) ; high resolution MS : Calcd for $C_{10}H_{17}NO_2$: m / z 183.1255. Found : m / z 183.1259.

(4*S*, 5*S*)-5-Allyl-3-(*tert*-butoxycarbonyl)-4-*iso*-butyl-2-oxazolidinone (26).

To a solution of **25** (475 mg, 2.59 mmol) in THF (16 mL) was added di-*tert*-butyl dicarbonate (1.132 g, 5.18 mmol) and 4-*N*,*N*-dimethyaminopyridine (158 mg, 1.3 mmol) and the whole was stirred at room temperature overnight. The reaction mixture was concentated *in vacuo* and purification by column chromatography on silica gel (hexane : AcOEt = 9 : 1) gave **26** (704 mg, 96 %) as colorless oil : $[\alpha]_D^{29}$ +8.2° (c 0.95, $CHCl_3$) ; ^{1}H-NMR (400 MHz) δ 0.95 (d, 3H, J=6.4 Hz), 0.97 (d, 3H, J=6.4 Hz), 1.46-1.70 (m, 3H), 1.55 (s, 9H), 2.36-2.50 (m, 2H), 3.95 (ddd, 1H, J=2.4 Hz, 2.4 Hz, 9.8 Hz), 4.18 (ddd, 1H, J=2.4 Hz, 6.3 Hz, 6.3 Hz), 5.20-5.26 (m, 2H), 5.69-5.81 (m, 1H) ; MS (FAB) : m / z 284 (MH^+).

(4*S*, 5*S*)-3-(*tert*-butoxycarbonyl)-5-carboxymethyl-4-*iso*-butyl-2-oxazolidinone.

To a solution of **26** (425 mg, 1.5 mmol) and $NaIO_4$ (4.812 g, 22.5 mmol) in MeCN (3 mL)-CCl_4 (3 mL)-H_2O (4.5 mL) was added $RuCl_3$•xH_2O (6.8 mg, 0.033 mmol) and the whole was stirred at room temperature for 48 h. The reaction mixture was extracted with CH_2Cl_2 (50 mL x 3) and the extract was washed (brine), dried (Na_2SO_4) and concentrated *in vacuo*. The residue was purified by silica gel column chromatography (hexane : AcOEt = 1 : 1 → AcOEt) to yield (4*S*, 5*S*)-5-allyl-3-(*tert*-butoxycarbonyl)-5-carboxymethyl-4-*iso*-butyl-2-oxazolidinone (437 mg, 96 %) as colorless oil : $[\alpha]_D^{29}$ +21.2 ° (c 1.00, $CHCl_3$) ; ^{1}H-NMR (400 MHz) δ 0.96 (d, 3H, J=5.9 Hz), 0.99 (d, 3H, J=5.9 Hz), 1.49-1.70 (m, 3H), 1.55 (s, 9H), 2 75 (dd, 1H, J=6.6 Hz, 16.9 Hz), 2.84 (dd, 1H, J=6.6 Hz, 16.9 Hz), 4.00-4.06 (m, 1H), 4 54 (dt, 1H, J=2.2 Hz, 6.6 Hz).

Methyl (3*S*, 4*S*)-4-[(*tert*-butoxycarbonyl)amino]-3-hydroxy-6-methylheptanoate (27).

To a solution of (4*S*, 5*S*)-5-allyl-3-(*tert*-butoxycarbonyl)-5-carboxymethyl-4-*iso*-butyl-2-oxazolidinone (288 mg, 0.94 mmol) in MeOH (9.3 mL) was added Cs_2CO_3 (610 mg, 1.87 mmol) and the whole was stirred at room temperature overnight. After acidification with citric acid in AcOEt (100 mL), the whole was washed (brine), dried (Na_2SO_4) and concentrated *in vacuo*. The residue was treated with diazomethane and column chromatography of the product on silica gel (CH_2Cl_2 : AcOEt = 9 . 1) yielded **27** (135 mg, 50 %) as colorless crystals : mp. 59-60 °C (from hexane) ; $[\alpha]_D^{27}$ -35.7 ° (c 1.20, EtOH) ; ^{1}H-NMR (400 MHz) δ 0.93 (d, 6H, J=6.6 Hz), 1.30-1.40 (m, 1H), 2.50-2.57 (m, 2H), 3.28 (br.d, 1H, J=2.9 Hz), 3.57-3.66 (m, 1H), 3.71 (s, 3H), 3.99-4.06 (m, 1H), 4.73 (d, 1H, J=9.5 Hz) ; Anal. Calcd for $C_{14}H_{27}NO_5$: C, 58.11 ; H, 9.41 ; N, 4.84. Found : C, 57.77 ; H, 9.10 ; N, 4.84.

Synthesis of β-hydroxy-L-glutamic acid.

(4*R*, 5*R*)-5-Allyl-4-vinyl-2-oxazolidinone.

To a suspension of CuCN (1.946 g, 22 mmol) in THF (27 mL) was added a solution of vinylmagnesium bromide (44.3 mL, 43 mmol, 0.98 M in THF) at -30 °C under argon atmosphere and the whole was stirred for 1

h. A solution of (4*R*, 5*R*)-5-allyl-4-methoxy-2-oxazolidinone (**13**) (854 mg, 5.43 mmol) in THF (14 mL) and BF_3•OEt_2 (1.3 mL, 2 eq.) were successively added and the mixture was stirred at -30 °C for 15 h. Usual work-up followed by column chromatography on silica gel (CH_2Cl_2) yielded (4*R*, 5*R*)-5-allyl-4-vinyl-2-oxazolidinone (572 mg, 69 %) as colorless oil : $[\alpha]_D^{29}$ +103.3° (c 1.10, MeOH) ; ^{1}H-NMR (400 MHz) δ 2.51 (t, 2H, J=6.2 Hz), 4.03 (ddd, 1H, J=1.1 Hz, 6.2 Hz, 7.3 Hz), 4.28 (dd, 1H, J=6.2 Hz, 12.5 Hz), 5.17-5.33 (m, 4H), 5.74-5.86 (m, 2H), 6.22 (br, 1H) ; high resolution MS : Calcd for $C_8H_{11}NO_2$: m/z 153.0788. Found: m/z 153.0790.

(4*R*, 5*R*)-5-Allyl-3-(*tert*-butoxycarbonyl)-4-vinyl-2-oxazolidinone (28).

To a solution of (4*R*, 5*R*)-5-allyl-4-vinyl-2-oxazolidinone (125 mg, 0.81 mmol) in THF (4 mL) were added di-*tert*-butyl dicarbonate (355 mg, 1.6 mmol, dissolved in 3 mL of THF) and 4-*N*, *N*-dimethylaminopyridine (50 mg, 0.4 mmol) and the mixture was stirred at room temperature overnight. Evaporation under reduced pressure followed by column chromatography on silica gel (CH_2Cl_2) gave **28** (197 mg, 96 %) as colorless oil : $[\alpha]_D^{28}$ +46.7° (c 1.03, $CHCl_3$) ; ^{1}H-NMR (400 MHz) δ 1.51 (s, 9H), 2.47-2.51 (m, 2H), 4.20 (dt, 1H, J=4.4 Hz, 5.9 Hz), 4.34 (dd, 1H, J=4.4 Hz, 7.7 Hz), 5.20-5.35 (m,4H), 5.70-5.87 (m, 2H) ; MS (FAB) : m / z 254 (MH^+).

(3*R*, 4*R*)-3-[(*tert*-Butoxycarbonyl)amino]-1,6-heptadien-4-ol.

To a solution of **28** (161 mg, 0.64 mmol) in MeOH (6.4 mL) was added Cs_2CO_3 (104 mg, 0.32 mmol) and the whole was stirred at room temperature for 24 h. The reaction mixture was passed through silica gel short column with AcOEt as eluent. Concentration of the eluant *in vacuo* and column chromatography on silica gel (CH_2Cl_2 : AcOEt = 9 : 1) gave (3*R*, 4*R*)-3-[(*tert*-butoxycarbonyl)amino]-1,6-heptadien-4-ol (139 mg, 96 %) as colorless crystals : mp. 36-37 °C (from hexane) ; $[\alpha]_D^{26}$ +47.2° (c 0.61, $CHCl_3$) ; ^{1}H-NMR (400 MHz) δ 1.45 (s, 9H), 2.20-2.38 (m, 2H), 3.73 (ddd, 1H, J=3.3 Hz, 4.8 Hz, 8.1 Hz), 4.17 (br, 1H), 4.94 (br, 1H), 5.13-5.33 (m, 4H), 5.79-5.90 (m, 2H) ; Anal. Calcd for $C_{12}H_{21}NO_3$. C, 63.41 ; H, 9.31 ; N, 6.16. Found : C, 63.19 ; H, 9.40 ; N, 6.25.

(4*R*, 5*R*)-5-Allyl-3-(*tert*-butoxycarbonyl)-2,2-dimethyl-4-vinyloxazolidine (29).

A solution of (3*R*, 4*R*)-3-[(*tert*-butoxycarbonyl)amino]-1,6-heptadien-4-ol (131 mg, 0.58 mmol), 2,2-dimethoxypropane (0.15 mL, 1.2 mmol) and *p*-toluensulfonic acid hydrate (0.006 mmol) in benzene (2.2 mL) was stirred at 80 °C for 1 h. Et_2O (90 mL) was added and the mixture was washed (brine), dried (Na_2SO_4) and concentrated *in vacuo*. Purification by column chromatography on silica gel (CH_2Cl_2) yielded **29** (132 mg, 86 %) as colorless oil : $[\alpha]_D^{27}$ +33.1° (c 1.10, $CHCl_3$) ; ^{1}H-NMR (400 MHz) δ 1.44 (s, 9H), 1.51 (s, 3H), 1.60 (s, 3H), 2.28-2.47 (m, 2H), 3.81 (dt, 1H, J=4.8 Hz, 7.0 Hz), 3.89 (br, 1H), 5.10-5.27 (m, 4H), 5.60-5.77(m, 1H), 5.79-5.91 (m, 1H).

(4*S*, 5*R*)-3-(*tert*-Butoxycarbonyl)-2,2-dimethyl-4-methoxycarbonyl-5-(methoxycarbonyl-methyl)-oxazolidine (30).

To a solution of **29** (96 mg, 0.36 mmol) and $NaIO_4$ (460 mg, 2.15 mmol) in H_2O (2.8 mL) and acetone (5.6 mL) was added $KMnO_4$ (57 mg, 0.36 mmol) in H_2O (2.8 mL) and the mixture was stirred at room temperature for 5 h. Formaldehyde (5 mL, 37 % solution in H_2O) was added and the whole was filtered through sintered glass filter. The filtrate was acidified with citric acid and extracted with AcOEt (50 mL x 3). The extract was washed (brine), dried (Na_2SO_4) and concentrated *in vacuo*. Treatment with diazomethane followed by column chromatography on silica gel (CH_2Cl_2 : AcOEt = 19 : 1) gave **30** (59 mg, 50 %) as colorless oil : $[\alpha]_D^{27}$ -14.6° (c 1.00, $CHCl_3$) ; ^{1}H-NMR (400 MHz) δ 1.40 (s, 6H), 1.48 (s, 3H), 1.57-1.65 (m, 6H), 2.74 (d, 2H, J=6.2 Hz), 3.76 (s, 3H), 3.77 (s, 3H), 4.09 (d, 0 64H, J=7.3 Hz), 4.17 (d, 0.36H, J=7.3 Hz), 4.45-4.56 (m, 1H) ; MS (FAB) : m / z 332 (MH^+).

Dimethyl (2*S*, 3*R*)-3-hydroxyglutamate hydrochloride (31).

The oxazolidin **30** (37 mg, 0.11 mmol) was dissolved in MeOH (3 mL) saturated with HCl gas and stirred at 0 °C for 1 h. Evaporation *in vacuo* gave **31** (18 mg, 71 %) as colorless crystals : mp. 141-142 °C (from AcOEt-MeOH) ; $[\alpha]_D^{28}$ +11.0 ° (c 1.20, MeOH) ; ^{1}H-NMR(400 MHz, CD_3OD) δ 2.68 (dd, 1H, J=7.7 Hz, 16.5 Hz), 2.75 (dd, 1H, J=5.5 Hz, 16.5 Hz), 3.72 (s, 3H), 3.86 (s, 3H), 4.13 (d, 1H, J=3.7 Hz), 4.53-4.61 (m, 1H) ; Anal. Calcd for $C_7H_{14}Cl\ NO_5$: C, 36.93 ; H, 6.20 ; N, 6.15 Found : C, 36.67 ; H, 6.23 ; N, 6.09.

REFERENCES AND NOTES

1. a) *Pepstatin*: Umezawa, H.; Aoyagi, T.; Morishima, H.; Matsuzaki, M.; Hamada, M.; Takeuchi, T. *J.Antibiot.*, **1970**, *23*, 259.
   b) *Amastatin*: Aoyagi, T.; Tobe, H.; Kojima, F.; Hamada, M.; Takeuchi, T.; Umezawa, H. *J Antibiot.*, **1978**, *31*, 636.
   c) *Bestatin*: Umezawa, H.; Aoyagi, T.; Suda, H.; Hamada, M.; Takeuchi, T. *J.Antibiot.*, **1976**, *29*, 97.
2. *Daunomycin*: a) Grein, A.; Spella, C.; Di Marco, A.; Canevazzi, G. *Giorn Microbiol.*, **1963**, *11*, 109 : b) Di Marco, A.; Gaetani, P.; Orezzi, P.; Scarpinato, B ; Silverstrini, R.; Soldati, M.; Dasdia, T.; Valentini, L. *Nature*, **1964**, *201*, 706 : c) Arcamone, F.; Cassinelli, G.; Orezzi, P.; Franceschi, G.; Mondelli, R. *J.Amer.Chem.Soc.*, **1964**, *86*, 5334 ; e) Iwamoto, R.H.; Lim, P.; Bhacca, N.S. *Tetrahedron Lett.*, **1968**, *36*, 3891.
3. a) Otsuka, M.; Miyata, Y. *J. Neurochem.*, **1971**, *18*, 287 : b) Shoji, J.; Sakazaki, R. *J. Antibio.*, **1970**, *23*, 418.
4. a) Yamashita, H. *Chem Lett.*, **1987**, 525 : b) Trost, B.M.; Sudhaker, A.R.S. *J.Amer.Chem.Soc.*, **1987**, *109*, 3792 : c) Imi, K.; Yanagihara, N.; Utimoto, K. *J Org Chem.*, **1983**, *52*, 1013 : d) Kretchmer, R.A.; Daly, P.J. *J.Org.Chem.*, **1976**,*41*, 192 : e) Sharpless, K.B.; Chong, A.O.; Oshima, K. *ibid.*, **1976**,*41*, 177 : f) Kamimura, A.; Ono, N. *Tetrahedron Lett.*, **1989**, *30*, 731 : g) Claremon, D.A.; Lumma, P.K.; Philips, B.T. *J.Amer.Chem.Soc.*, **1986**, *108*, 8265 : h) Seebach, D.; Stuky, G. *Angew.Chem.Int.Ed. Engl.*, **1988**, *27*, 1351 : i) Kobayashi, S.; Isobe, T.; Ohno, M. *Tetrahedron Lett.*, **1984**, *25*, 5079 : j) Hirama, M.; Shigemoto, T.; Yamazaki, Y.; Ito, S. *ibid.*, **1985**, *26*, 4133 : k) Ito, Y.; Sawamura, M.; Hayashi, T. *J.Amer.Chem.Soc.*, **1986**, *108*, 6405 : l) *idem, Tetrahedron Lett.*, **1987**, *28*, 6215 : m) Ito, Y.; Sawamura, M.; Shirakawa, E.; Hashizaki, K.; Hayashi, T. *Tetrahedron*, **1988**, *44*, 5253 : n) Herold, P. *Helv Chim.Acta*, **1988**, *71*, 354 · o) Reetz, M.T.; Drewes, M.W.; Schimtz, A. *Angew.Chem.Int.Ed. Engl* , **1987**, *26*, 1141 : p) Dellaria Jr., J.F.; Maki, R.G *Tetrahedron Lett.*, **1986**, *27*, 1337 : q) Kitamura, M.; Okuma, T.; Takaya, H.; Noyori, R. *Tetrahedron Lett.*, **1988**, *29*, 1555 : r) Harris, B.D.; Joullie, M.N. *Tetrahedron*, **1988**, *44*, 3489 : s) Maibaum, J.; Rich, D. *J.Org.Chem.*, **1988**, *53*, 869.
5. a) Scholz, K.H.; Heine, H.G.; Hartmann, W. *Liebigs Ann.Chem* , **1976**, 1319 : b) Matsuura, T.; Kunieda, T.; Takizawa, T. *Chem Pharm.Bull.*, **1977**, *25*, 239 : c) Wang, P-C. *Heterocycles*, **1985**, *9*, 2237.
6. a) Mitsunobu, O. *Synthesis*, **1981**, 1 : b) Corey, E.J.; Nicolaou, K.C.; Shibasaki, M.; Machida, Y.; Shiner, C.S. *Tetrahedron Lett* , **1975**, 3183 : c) Elliot, D.F. *J.Chem.Soc* , **1950**, 62.
7. Another type of synthon potential for the reaction sequence **2**→**4**→**5** was recently introduced. Matsunaga, H.; Ishizuka, T.; Marubayashi, N.; Kunieda, T. *Chem. Pharm. Bull.*, **1992**, *40*, 1077.
8. a) Kunieda, T.; Hirobe, M. *J.Syn.Org.Chem.Jpn.*, **1983**, *41*, 77 : b) Kunieda, T.; Abe, Y.; Higuchi, T.; Hirobe, M. *Tetrahedron Lett* , **1980**, *21*, 3065 : c) *idem, ibid* , **1981**, *22*, 1257 : d) *idem, ibid.*, **1982**, *23*, 1159 : e) *idem, Chem.Pharm.Bull.*, **1984**, *32*, 2174 : f) Kunieda, T.; Higuchi, T.; Abe, Y.; Hirobe, M. *Tetrahedron*, **1983**, *39*, 3253 : g) Kunieda, T.; Abe, Y., Hirobe, M. *Chem.Lett.*, **1984**, 1427.
9. Ishizuka, T.; Kimura, K.; Ishibuchi, S., Kunieda, T. *Chem.Pharm.Bull.*, **1990**, *38*, 1717.
10. Kunieda, T.; Ishizuka, T.; Higuchi, T.; Hirobe, M. *J.Org.Chem.*, **1988**, *53*, 3381.
11. Ishizuka, T.; Ishibuchi, S.; Kunieda, T. *Tetrahedron Lett.*, **1989**, *30*, 3449.
12. *N*-Benzoyl-γ-amino-β-hydroxybutyric acid (GABOB), which was synthesized from **13**, showed a specific rotation of -9.8 ° (c 1 3, H_2O), indicative of 3*R*-isomer, based on the literature values of $[\alpha]_D$ -11.84 ° (H_2O) for *R*-form and $[\alpha]_D$ +10.0 ° (H_2O) for *S*-form.
    Tomita, M.; Sendju, Y. *Hoppe-Seyler's Z. Physiol. Chem.*, **1927**, *169*, 263.
13. Functional groups such as cyanoethyl, carboxymethyl and vinyl other than allyl and methallyl functions could be introduced at the 5-position, but in much lower yields.
14. Damon, R.E.; Coppola, G.M. *Tetrahedron Lett.*, **1990**, *31*, 2849.

15. Mechanism of the reversed π-facial selection in methoxybromination and methoxyselenylation of 3-[(1*S*)-2-*exo*-alkoxy-1-apocamphanecarbonyl]-2-oxazolones (**10**) has been briefly discussed in ref. 11 and the following article. Kunieda, T.; Ishizuka, T. Synthetic Methodology for 2-Amino Alcohols of Biological Interest. In *Studies in Natural Products Chemistry* ; Atta-ur-Rahman ed.; Elsevier Science Publishers ; Amsterdam, 1992; *in press*.
16. Ishibuchi, S.; Ikematsu, Y.; Ishizuka, T.; Kunieda, T. *Tetrahedron Lett.*, **1991**, *32*, 3523.
17. Ishizuka, T.; Kunieda, T. *Tetrahedron Lett.*, **1987**, *28*, 4185.
18. a) Kogen, H.; Nishi, T. *J. Chem. Soc. Chem. Comn.*, **1987**, 311 : b) Sakaitani, M.; Ohfune, Y. *Tetrahedron Lett.*, **1987**, *28*, 3987 : c) Kano, S.; Yokomatsu, T.; Iwasawa, H.; Shibuya, S. *Tetrahedron Lett.*, **1987**, *28*, 6331 : d) Reetz, M.T.; Drewes, M.W.; Schmitz, A. *Angew. Chem. Int. Ed. Engl.*, **1987**, *26*,1141 : e) Harris, B.D.; Bhat, K.L.; Joullie, M.M. *Tetrahedron Lett.*, **1987**, *28*, 2837 : f) Kano, S.; Yuasa, Y.; Yokomatsu, T., Shibuya, S. *J. Org Chem* , **1988**, *53*, 3865 : g) Nishi,T.; Kitamura, M.; Ohkuma, T.; Noyori, R. *Tetrahedron Lett* , **1988**, *29*, 6327 : h) Midland, M.M.; Afonso, M.M. *J. Am. Chem. Soc.*, **1989**, *111*, 4368 : i) Takahata, H.; Yamazaki, K.; Takamatsu, T.; Yamazaki, T.; Momose, T. *J. Org. Chem.*, **1990**, *55*, 3947 : j) Woo, P.W.K. *Tetrahedron Lett.*, **1985**, *26*, 2973 : k) Dufour, M.N.; Juoin, P.; Poncet, J.; Pontaroni, A ; Castro, B. *J. Chem. Soc. Perkin Trans. I*, **1986**, 1895 : l) Mulzer, J.; Büttelmann, B.; Münch, W. *Liebigs Ann. Chem.*, **1988**, 445 : m) Rittle, K.E.; Homnick, C.f.; Ponticello, G.S.; Evans, B.E. *J. Org. Chem.*, **1982**, *47*, 3016 : n) Hollaway, M.W.; Salituro, F.G.; Rich, D.H. *J. Med. Chem.*, **1987**, *30*, 374 : o) Danishefsky, S.; Kobayashi, S.; Keerwin, Jr., J.F. *J. Org. Chem.*, **1982**, *47*, 1981 : p) Schostarez, H.J. *J Org. Chem* , **1988**, *53*, 3628 : q) Steulemann, R.; Klostermeyer, H. *Liebigs Ann. Chem.*, **1975**, 2445 : r) Kinoshita, M.; Hagiwara, A.; Aburaki, S. *Bull. Chem. Soc. Jpn.*, **1975**, *48*, 570 : s) Liu, W.S.; Glover, G.I. *J. Org. Chem.*, **1978**, *43*, 754 : t) Takemoto, Y.; Matsumoto, T.; Ito, Y.; Terashima, S. *Tetrahedron Lett.*, **1990**, *31*, 217 : u) Misiti, D.; Zappia, G. *ibid.*, **1990**, *31*, 7359 : v) Ohta, T.; Shiokawa, S.; Sakamoto, T.; Nozoe,S. *ibid.*, **1990**, *31*, 7329 : w) Koot, W-J.; Ginkel, R.; Kranenburg, M.; Hiemstra, H.; Louwrier, S.; Moolenaar, M.J.; Speckamp, W.M. *ibid.*, **1991**, *32*, 401.
19. a) Garner, P. *Tetrahedron Lett* , **1984**, *25*, 5855 : b) Kamiya, T. *Chem.Pharm.Bull.*, **1966**, *14*, 1307 : c) Akabori, S.; Kaneko, T.; Sakurai, S.; Izumi, Y. *Nippon Kagaku Zasshi*, **1954**, *75*, 942 : d) Kaneko, T.; Yoshida, R.; Kakuta, H. *ibid.*, **1959**, *80*, 316 · e) Takahata, H.; Takamatsu, T.; Yamazaki, T. *J.Org. Chem.*, **1989**, *54*, 4812 . f) Takeuchi, H., Watanabe, K.; Nomoto, K.; Ofune, Y.; Takeuchi, T. *European J.Pharmacology*, **1984**, *102*, 325.
20. Ishibuchi, S.; Nagatani, T.; Ishizuka, T., Kunieda, T. *Natural Product Letters*, **1992**, *1*, 21.