# Synthetic Studies on Carbapenam Skeletons

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*Received June 15, 1996*

Syntheses of carbapenam skeletons were achieved from 1,3-propanediol through 1,3-dipolar cycloaddition. 3-(Tetrahydropyran-2-yloxy)-(**10**) and 3-(*t*-butyldimethylsilyloxy)propanal (**13**) were obtained from 1,3-propanediol. 3-Hydroxypropanals (**10, 13, 14**) were reacted with *N*-hydroxyglycine esters to give *C*-(2-hydroxyethyl)-*N*-alkoxycarbonylmethylnitrones (**15a-15d**). 1,3-Dipolar cycloaddition of the nitrones with methyl acrylate or ethyl crotonate gave 3-(2-hydroxyethyl)isoxazolidines (**16a-16b, 17a-17b, 18, 19a-19b**). 3-(2-Hydroxyethyl)isoxazolidines (**17a, 17c, 19a, 19b**) were converted to 3-(2-iodoethyl)isoxazolidines (**21a-21d**) or 3-phenylthiocarbonylmethylisoxazolidines (**25a-25d**) which were cyclized to give 2-oxa-1-azabicyclo[3.3.0]octanedicarboxylates (**22a-22d, 26a-26d**). 2-Oxa-1-azabicyclo[3.3.0]octane-4,8-dicarboxylates (**22c-22d, 26c-26d**) were transformed to 6-(1-hydroxyethyl)carbapenam-3-carboxylates (**30a-30b, 31a-31b**).

## Introduction

Thienamycin (**1**) has a unique structure and shows broad and strong antimicrobial activity.[1,2] Many synthetic studies, therefore, have been carried out to obtain structural analogs of thienamycin. A lot of synthetic strategies have been invented to give carbapenem skeletons which have the desired stereochemically defined functional groups. One of the synthetic approaches was through 1,3-dipolar cycloaddition of crotonates with nitrones to give isoxazoline derivatives, which were transformed to carbapenems.[3,4]

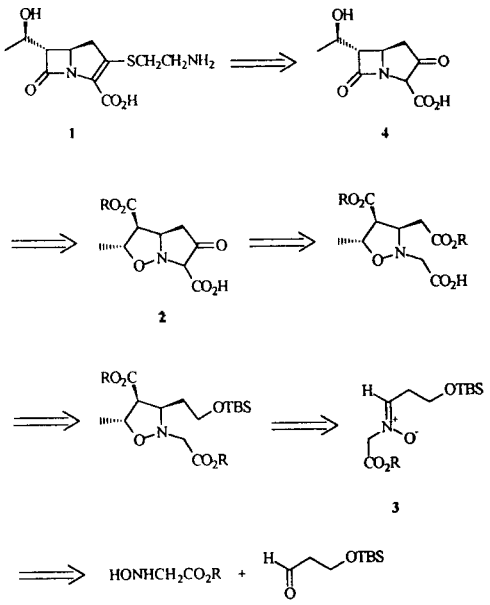
We have been involved in the development of new synthetic methods of carbapenem analogs. Retrosynthetic analysis of the thienamycin structure indicated that the carbapenem skeleton could be obtained through an important intermediate, 3-methyl-7-oxo-2-oxa-1-azabicyclo[3.3.0]ocatane-4,8-dicarboxylate (**2**). We presumed that we could obtain the compound through 1,3-dipolar cycloaddition of *C*-(2-hydroxyethyl)-*N*-alkoxycarbonylmethylnitrone (**3**) with crotonate (Scheme **1**). Thus, the present study deals with preparation of 2-oxa-1-aza-bicyclo[3.3.0]octane derivatives and conversion of these products to carbapenems (**4**).

## Results and Discussion

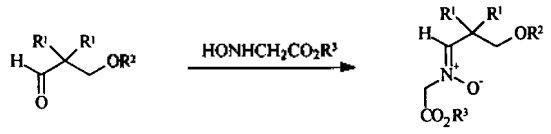
**Synthesis of C-(2-hydroxyethyl)-*N*-alkoxycarbonylmethylnitrones.** The hydroxy group of 3-hydroxypropanal was easily eliminated to give acrolein.[5] Thus, we tried to synthesize 3-hydroxypropanal derivatives in which the 3-hydroxy group was protected with benzoyl, *t*-butyldimethylsilyl or tetrahydropyran-2-yl group. 1,3-Propanediol (**5**) was treated with benzoyl chloride to give 3-benzoyloxy-1-propanol (**6**) and 1,3-dibenzoyloxypropane (**7**) in the yields of 59% and 20%, respectively. The compound **6** was reacted with 3,4-dihydro-2*H*-pyran to give 1-benzoyloxy-3-(tetrahydropyran-2-yloxy)propane (**8**) in 92% yield. The benzoyl group of **8** was removed in 96% yield by treatment of sodium methoxide. The product, **9** was oxidized with PCC to give 3-(tetrahydropyran-2-yloxy)propanal (**10**) in 62% yield. Treatment of 1,3-propanediol with *t*-butyldimethylsilyl chloride gave 3-(*t*-butyldimethylsilyloxy)propanol (**11**) and 1,3-bis(*t*-butyldimethylsilyloxy)propane (**12**) in the yields of 52% and 17%, respectively. Compound **11** was converted to 3-(*t*-butyldimethylsilyloxy)propanal (**13**) by Swern oxidation[6] in 82% yield.

In the next step these aldehydes were converted to nitrones by reaction with *N*-hydroxyamine coumpounds. Thus, we reacted the aldehydes, **10** and **13**, and 2,2-dimethyl-3-hydroxypropanal (**14**)[7] wtih *N*-hydroxyglycine ester[8] to obtain *C*-(2-hydroxyethyl)-*N*-alkoxycarbonylmethylnitrones (**15a-15d**) in 73-90% yields (Scheme 2). These nitrones showed singlets around 4.41-4.49 ppm for the protons of $NCH_2COOR$. The N=CH proton signals were observed as triplets around 6.50-6.55 ppm for compounds **15a** and **15b** and as singlets around 6.49-6.55 ppm for compounds **15c** and **15d**.

**Synthesis of isoxazolidine derivatives.** The isoxazolidine derivatives were obtained by 1,3-dipolar cycloaddition reaction of *C*-(2-hydroxyethyl)-*N*-alkoxycarbonylmethylnitrones (**15a-15d**) with methyl acrylate or ethyl crotonate by refluxing in toluene (Scheme 3). The 1,3-dipolar cycloaddition reaction gave mixtures of stereoisomers. Thus, the reaction of the nitrones with methyl acrylate gave stereoisomers of



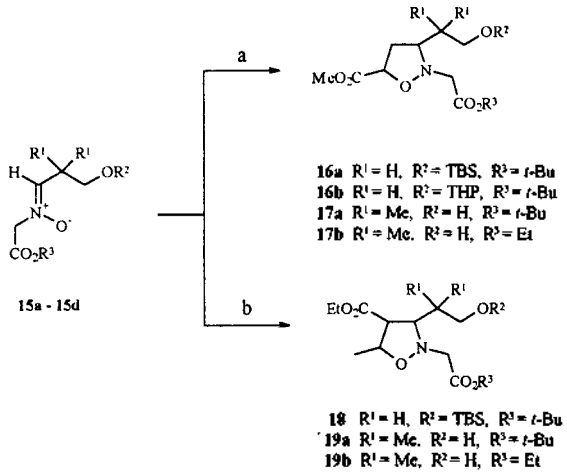

**Scheme 1.**



**10** $R^1$ = H, $R^2$ = THP
**13** $R^1$ = H, $R^2$ = TBS
**14** $R^1$ = Me, $R^2$ = H

**15a** $R^1$ = H, $R^2$ = TBS, $R^3$ = *t*-Bu
**15b** $R^1$ = H, $R^2$ = THP, $R^3$ = *t*-Bu
**15c** $R^1$ = Me, $R^2$ = H, $R^3$ = *t*-Bu
**15d** $R^1$ = Me, $R^2$ = H, $R^3$ = Et

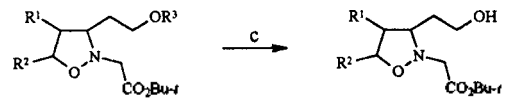
**Scheme 2.**



**16a** $R^1$ = H, $R^2$ = TBS, $R^3$ = *t*-Bu
**16b** $R^1$ = H, $R^2$ = THP, $R^3$ = *t*-Bu
**17a** $R^1$ = Me, $R^2$ = H, $R^3$ = *t*-Bu
**17b** $R^1$ = Me, $R^2$ = H, $R^3$ = Et

**18** $R^1$ = H, $R^2$ = TBS, $R^3$ = *t*-Bu
**19a** $R^1$ = Me, $R^2$ = H, $R^3$ = *t*-Bu
**19b** $R^1$ = Me, $R^2$ = H, $R^3$ = Et

a) $H_2C$=$CHCO_2Me$ b) $H_3CCH$=$CHCO_2Et$



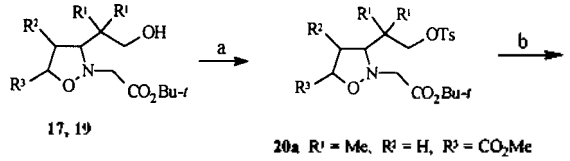
**16a** $R^1$ = H, $R^2$ = $CO_2Me$, $R^3$ = TBS
**16b** $R^1$ = H, $R^2$ = $CO_2Me$, $R^3$ = THP
**18** $R^1$ = $CO_2Et$, $R^2$ = Me, $R^3$ = TBS

**17c** $R^1$ = H, $R^2$ = $CO_2Me$
**19c** $R^1$ = $CO_2Et$, $R^2$ = Me

c) $R^3$ = TBS ; $Bu_4N^+F^-$, $R^3$ = THP ; PPTS/EtOH

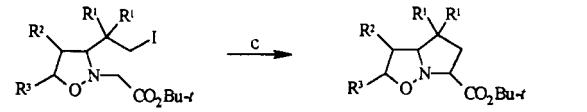
**Scheme 3.**

isoxazolidine-5-carboxylates (**16a, 16b, 17a, 17b**), whereas the reaction of those with ethyl crotonate gave stereoisomers of isoxazolidine-4-carboxylates (**18, 19a, 19b**). Compound **19a** had *cis*-configuration between the substituents at C-3 and C-4 on the isoxazolidine ring. However, the compounds **18** and **19b** were composed of two isomers having *cis* and *trans* configurations in the ratios of 4 : 1 and 2 : 3, respectively. Attempts to isolate these isomers by silica gel column chromatography were unsuccessful. But, when the isoxazolidine rings were opened and recyclized, only the compounds having *cis* configuration were known to cyclize to β-lactam rings. Thus, we proceeded to the next steps without further purification of these isomers. The silyl protecting group of compounds **16a** and **18** were removed by treatment of tetrabutylammonium fluoride to give **17c** and **19c** in 92% and 88% yields, respectively, and the tetrahydropyran-2-yl protecting group of **16b** by treatment with catalytic amounts of



**17, 19**

**20a** $R^1$ = Me, $R^2$ = H, $R^3$ = $CO_2Me$
**20b** $R^1$ = H, $R^2$ = H, $R^3$ = $CO_2Me$
**20c** $R^1$ = Me, $R^2$ = $CO_2Et$, $R^3$ = Me
**20d** $R^1$ = H, $R^2$ = $CO_2Et$, $R^3$ = Me



**21a** $R^1$ = Me, $R^2$ = H, $R^3$ = $CO_2Me$
**21b** $R^1$ = H, $R^2$ = H, $R^3$ = $CO_2Me$
**21c** $R^1$ = Me, $R^2$ = $CO_2Et$, $R^3$ = Me
**21d** $R^1$ = H, $R^2$ = $CO_2Et$, $R^3$ = Me

**22a** $R^1$ = Me, $R^2$ = H, $R^3$ = $CO_2Me$
**22b** $R^1$ = H, $R^2$ = H, $R^3$ = $CO_2Me$
**22c** $R^1$ = Me, $R^2$ = $CO_2Et$, $R^3$ = Me
**22d** $R^1$ = H, $R^2$ = $CO_2Et$, $R^3$ = Me

a) TsCl / Pyridine b) NaI / Acetone c) LiHMDS / THF, -78 ℃

**Scheme 4.**

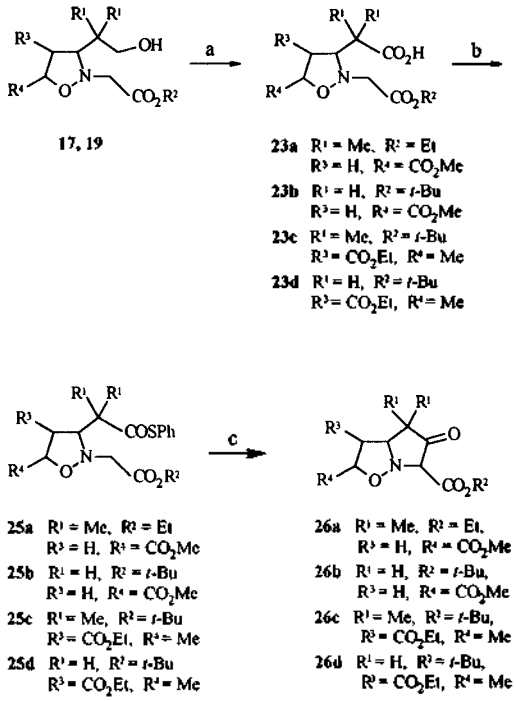
pyridinium *p*-toluenesulfonate at 55 ℃ for 4 h in ethanol to give **17c** in 86% yield.

**Synthesis of 2-Oxa-1-azabicyclo[3.3.0]octanedicarboxylates.** 3-(2-Tosyloxyethyl)isoxazolidines (**20a-20d**) were obtained in 74-79% yields by tosylation of the hydroxy groups of 3-(2-hydroxyethyl)isoxazolidines (**17a, 17c, 19a, 19c**) with *p*-toluenesulfonyl chloride in pyridine. We then obtained 3-(2-iodoethyl)isoxazolidines (**21a-21d**) in 80-95% yields by substitution of the tosyloxy groups of compounds **20a-20d** with iodide by treatment of sodium iodide in acetone. Treatment of the iodo compounds **21a-21d** with lithium hexamethyldisilazide gave the cyclized products, 2-oxa-1-azabicyclo[3.3.0]octanedicarboxylates (**22a-22d**) in 45-77% yields (Scheme 4).

The other approach for the cyclization of 3-(2-hydroxyethyl)isoxazolidines was attempted by employing the Dieckmann condensation. 3-(2-Hydroxyethyl)isoxazolidines (**17b, 17c, 19a, 19c**) were oxidized with Jones reagent to give 3-carboxyalkylisoxazolidines (**23a-23d**) in 70-82% yield. After compounds **23a** and **23c** were methylated with diazomethane attempts to cyclize the esters (**24a, 24c**) by treating with base were unsuccessful.

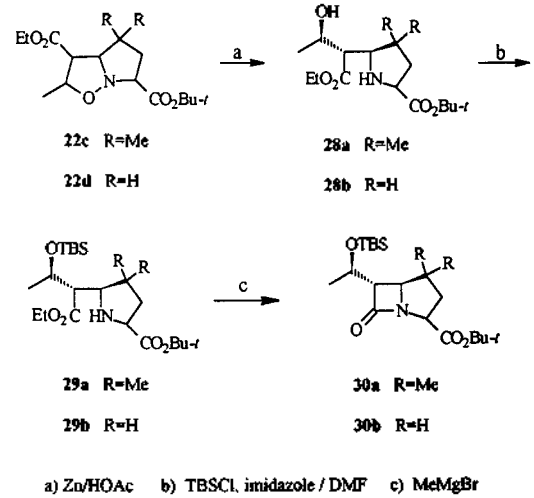
Therefore we tried to activate the ester group by converting them to phenylthioester derivatives. Compounds **23a-23d** were treated with oxalyl chloride to give acid chlorides which were converted to 3-phenylthiocarbonylmethylisoxazolidines (**25a-25d**) by treatment of thiophenol in 89-92% yields. When the compounds **25a-25d** were treated with lithium hexamethyldisilazide, the cylized products, 7-oxo-2-oxa-1-azabicyclo[3.3.0]ocatanedicarboxylates (**26a-26d**) were obtained in 56-86% yields (Scheme 5).

**Conversion of 2-oxa-1-azabicyclo[3.3.0]octane-4,8-dicarboxylates to 6-(1-hydroxyethyl)carbapenam-3-carboxylates.** The N-O bonds of 2-oxa-1-azabicyclo[3.3.0]ocatane-4,8-dicarboxylates (**22c, 22d, 26c, 26d**) were opened by reduction with zinc to obtain proline derivatives **28** and **29** (Scheme 6 & 7). The cyclization of β-amino esters to β-lactam rings was carried out by adapting the reported me-




a) $H_2CrO_4$ b) i. $(COCl)_2$ ii. PhSH, Pyridine / PhH c) LiHMDS / THF, -78℃

**Scheme 5.**

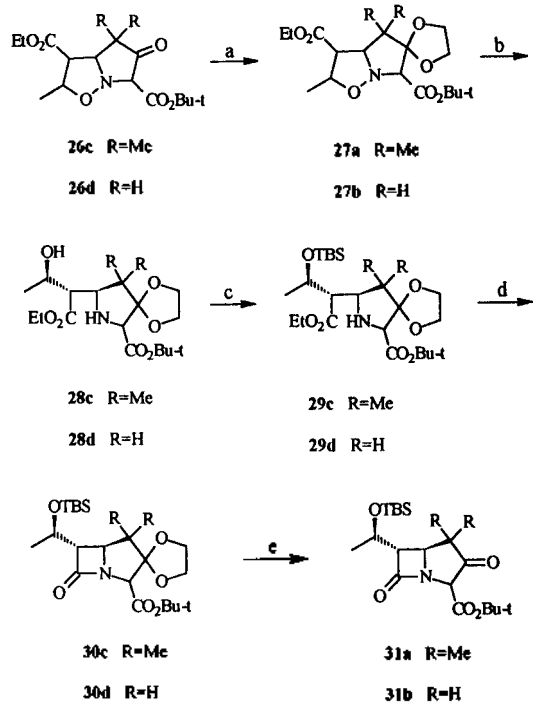



a) Zn/HOAc b) TBSCl, imidazole / DMF c) MeMgBr

**Scheme 6.**

thod. Thus, compounds **29** were treated with methylmagnesium bomide to obtain the cyclized products, 6-(1-hydroxyethyl)carbapenam-3-carboxylates (**30, 31**). For compound **26** their 7-oxo groups were to be protected. Thus, compound **26c** and **26d** were refluxed in toluene with ethylene glycol in the presence of *p*-toluenesulfonic acid to transform the 7-oxo groups to ketals. The ketal derivatives, **27a** and **27b** were obtained in 81 and 78% yields, respectively.

Reduction of the N-O bond of compounds **22** and **27** was achieved with zinc powder in glacial acetic acid and 5-(1-ethoxycarbonyl-2-hydroxypropyl)proline esters (**28a-28d**) were obtained in 72-86% yields. Compound **28** showed strong




a) $(CH_2OH)_2$, TsOH b) Zn / HOAc c) TBSCl, imidazole / DMF

d) MeMgBr e) 65% $HClO_4$

**Scheme 7.**

absorption band at 3500-3100 $cm^{-1}$ in the IR spectrum due to the hydroxy and the amino groups. The hydroxy groups of compounds **28a-28d** were protected with *t*-butyldimethylsilyl group. The *t*-butyldimethylsilyl derivatives, 5-[1-ethoxycarbonyl-2-(*t*-butyldimethylsilyloxy)propyl]proline esters (**29a-29d**) showed bands at 3300 $cm^{-1}$ in their IR spectra due to their amino groups. No hydroxy group band was observed and the Si-$CH_3$ band was shown at 1255 $cm^{-1}$. Cyclization of compounds **29a-29d** was carried out with methylmagnesium bromide and 6-[1-(*t*-butyldimethylsilyloxy)ethyl]carbapenam-3-carboxylaes (**30a-30d**) were obtained in 42-61% yields. The protecting groups of compounds **30c** and **30d** were removed with 60% perchloric acid and 6-[1-(*t*-butyldimethylsilyloxy)ethyl]-2-oxocarbapenam-3-carboxylates (**31a, 31b**) were obtained in 85% and 88% yields, respectively. Compounds **30** and **31** showed in their ir spectra a β-lactam carbonyl band at 1760-1770 $cm^{-1}$.

## Experimental

IR spectra were recorded with Perkin-Elmer 735-B IR or Jasco J-0068 FT IR spectrophotometer. $^1H$ NMR spectra were obtained with Varian EM-360 (60 MHz), Bruker AC 80 (80 MHz) or Varian VXR-200S (200 MHz) NMR spectrometer with tetramethylsilane (TMS) as an internal standard. Chemical shifts are expressed as δ (ppm). Melting points were obtained with digital melting point measurement instrument made by Electrothermal Co. without correction. THF and ethyl ether were distilled in the presence of sodium and benzophenone. Benzene was washed with concentrated sulfuric acid and distilled over sodium. DMF was dried over

KOH pellets before use. Other solvents are 1st grade and distilled before use. All the chemicals were purchased from Aldrich Chemical Co. or Merck Co.

**3-Benzoyloxy-1-propanol (6).** To the chloroform solution (150 mL) of 1,3-propanediol (7.61 g, 0.10 mol) and pyridine (8.9 mL, 0.11 mol) cooled in the 0 ℃ ice bath was added benzoyl chloride (14.1 g, 0.10 mol) slowly and the solution was stirred for 6 h at the same temperature. The reaction mixture was poured into water (150 mL). The chloroform layer was separated, washed with 5% hydrochloric acid, 10% sodium bicarbonate solution and water, dried over anhydrous magnesium sulfate, and rotary-evaporated to give a colorless residue which was chromatographed over a silica gel column with hexane-ethyl acetate (6 : 1) to give 1,3-dibenzoyloxypropane (**7**, $R_f$=0.82, hexane-ethyl acetate (4 : 1)) and the desired product (**6**, $R_f$=0.19, hexane-ethyl acetate (4 : 1)). Yield, 10.76 g (59.8%); $^1$H NMR ($CDCl_3$) δ 2.00 (m, 3H, $CH_2$, OH), 3.76 (t, 2H, $J$=6.1 Hz, $OCH_2$), 4.49 (t, 2H, $J$=6.0 Hz, $OCH_2$), 7.48 (m, 3H, Ph), 8.04 (m, 2H, Ph); IR (neat) 3400, 3100-2980, 1740, 1590, 1180 cm$^{-1}$.

**1,3-dibenzoyloxypropane (7).** Yield, 5.68 g (20%); $^1$H NMR ($CDCl_3$) δ 2.08 (m, 2H, $CH_2$), 4.49 (t, 4H, $J$=6.0 Hz, $2OCH_2$), 7.48 (m, 6H, Ph), 8.04 (m, 4H, Ph); IR (neat), 3100-2980, 1740, 1590, 1190 cm$^{-1}$.

**1-Benzoyloxy-3-(tetrahydropyran-2-yloxy)propane (8).** The solution of 3-benzoyloxy-1-propanol (9.00 g, 50 mmol), 3,4-dihydro-2*H*-pyran (4.29 g, 51 mmol) and catalytic amounts of *p*-toluenesulfonic acid (0.95 g, 5.0 mmol) in THF (150 mL) was stirred for 12 h at room temperature. After the reaction mixture was treated with sodium bicarbonate (2 g), it was rotary-evaporated to give an oily residue. The residue was dissolved in diethyl ether and the ether solution was washed with 5% sodium bicarbonate solution, dried over anhydrous magnesium sulfate, and rotary-evaporated to give a colorless liquid. Yield, 12.14 g (92%); $^1$H NMR ($CDCl_3$) δ 1.43-1.67 (m, 6H, $-(CH_2)_3-$), 2.06 (m, 2H, $J$=6.3 Hz, $CH_2$), 3.48 (m, 2H, $CH_2O$), 3.66 (m, 2H, $CH_2O$), 4.45 (t, 2H, $J$=6.1 Hz, $CH_2OCO$), 4.60 (br s, 1H, OCHO-), 7.50 (m, 3H, Ph), 8.03 (m, 2H, Ph); IR (neat) 3040-2980, 1740, 1590, 1180 cm$^{-1}$.

**3-(Tetrahydropyran-2-yloxy)-1-propanol (9).** Sodium methoxide (4.37 M, 10.3 mL, 44.7 mmol) dissolved in methanol was added to the solution of 1-benzoyloxy-3-(tetrahydropyran-2-yloxy)propane (11.88 g, 45 mmol) in methanol (100 mL) which was cooed to 0 ℃ in an ice-water bath and the mixture was stirred for 6 h at room temperature. After evaporation of the solvent, the reaction mixture was dissolved in ethyl acetate (100 mL). The ethyl acetate solution was washed with water (100 mL), dried over anhydrous magnesium sulfate, and rotary-evaporated to give a colorless liquid which was chromatographed over a silica gel column with hexane-ethyl acetate (2 : 1). Yield, 6.91 g (96%); $^1$H NMR ($CDCl_3$) δ 1.43-1.67 (m, 6H, $-(CH_2)_3-$), 2.00 (m, 3H, $CH_2$, OH), 3.50 (m, 2H, $CH_2O$), 3.55-3.90 (m 4H, 2 $CH_2O$), 4.60 (m, 1H, -OCHO-); IR (neat) 3500, 2990, 1180 cm$^{-1}$.

**3-(Tetrahydropyran-2-yloxy)propanal (10).** 3-(Tetrahydropyran-2-yloxy)-1-propanol (4.0 g, 25 mmol) dissolved in methylene chloride (20 mL) was poured into the pyridinium chlorochromate (6.47 g, 30 mmol) suspended in methylene chloride (30 mL) with vigorous stirring. The mixture was stirred for 4 h at room temperature. After dilution of the reaction mixture with diethyl ether (100 mL), the black residue was removed by passing through a short silica gel column. The colorless eluent was evaporated and the residue was chromatographed over a silica gel column with hexane-ethyl acetate (2 : 1). Yield, 2.50 g (62%); $^1$H NMR ($CDCl_3$) δ 1.43-1.67 (m, 6H, $-(CH_2)_3-$), 2.65 (dt, 2H, $J$=6.0, 2.0 Hz, $CH_2CO$), 3.50-3.90 (m, 4H, 2 $CH_2O$), 4.60 (br s, 1H, -OCHO-), 9.75 (t, 1H, $J$=2.0 Hz, CHO); IR (neat) 2990, 2840, 2720, 1725, 1125 cm$^{-1}$.

**3-(*t*-Butyldimethylsilyloxy)-1-propanol (11).** After *t*-butyldiemethylsilyl chloride (7.5 g, 0.05 mol ) was added to the solution of 1,3-propandiol (3.81 g, 0.05 mol) and imidazole (4.79 g, 0.074 mol) in DMF (70 mL), which was cooled to 0 ℃ in ice-water bath, the mixture was stirred for 6 h at the same temperature. The reaction mixture was diluted with diethyl ether (150 mL) and poured into water (100 mL). The ether layer was separated, washed with 5% hydrochloric acid solution, 10% sodium bicarbonate solution and water, dried over anhydrous magnesium sulfate, and rotary-evaporated to give a colorless liquid which was chromatographed over a silica gel column with hexane-ethyl acetate (8 : 1) to give 1,3-bis(*t*-butyldimethylsilyloxy)propane (**12**, $R_f$=0.92 hexane-ethyl acetate (**4** : 1)) and 3-(*t*-butyldiemthylsilyloxy)-1-propanol (**11**, $R_f$=0.21 hexane-ethyl acetate (4 : 1)). Yield, 4.92 g (52%); $^1$H NMR ($CDCl_3$) δ 0.02 (s, 6H, 2 $SiCH_3$), 0.87 (s, 9H, $C(CH_3)_3$), 2.00 ( m, 3H, $CH_2$, OH), 3.76 (t, 2H, $J$=6.1 Hz, $OCH_2$), 4.49 (t, 2H, $J$=6.0 Hz, $OCH_2$); IR (neat) 3400, 2980, 1255, 1180, 1100, 860 cm$^{-1}$.

**1,3-bis(*t*-Butyldimethylsilyloxy)propane (12).** Yield, 2.6 g (17%); $^1$H NMR ($CDCl_3$) δ 0.02 (s, 12H, 4 $SiCH_3$), 0.87 (s, 18H, 2 $C(CH_3)_3$), 2.00 (t, 2H, $J$=6.0 Hz, $CH_2$), 3.76 (t, 4H, $J$=6.0 Hz, 2 $OCH_2$); IR (neat) 2980, 1255, 1180, 1100, 860 cm$^{-1}$.

**3-(*t*-Butyldimethylsilyloxy)propanal (13).** After DMSO (2.55 mL, 33 mmol) was added slowly to the solution of oxalyl chloride (1.5 mL, 16.5 mmol) in methylene chloride (25 mL) in dry ice-acetone bath compound **11** (2.85 g, 15 mmol) dissolved in methylene chloride (10 mL) was dropped into this solution slowly over 5 min and the mixture was stirred for 15 min. Triethylamine (10.5 mL, 75 mmol) was added and the mixture was stirred for 1 h. The reaction mixture was warmed up to the room temperature and poured into water (75 mL).The methylene chloride layer was separated and washed with 1% hydrochlorid acid solution, 5% sodium bicarbonate solution, and water, dried over anhydrous magnesium sulfate, and rotary-evaporated to give a colorless liquid which was chromatographed over a silica gel column with hexane-ethyl acetate (8 : 1). Yield, 2.30 g (82%); $^1$H NMR ($CDCl_3$) δ 0.02 (s, 6H, 2 $SiCH_3$), 0.89 (s, 9H, $C(CH_3)_3$), 2.65 (dt, 2H, $J$=6.0, 2.0 Hz, $CH_2CO$), 3.84 (t, 2H, $J$=6.0 Hz, $CH_2O$), 9.75 (t, 1H, $J$=2.0 Hz, CHO); IR(neat) 2990, 2840, 2720, 1725, 1255, 1125, 860 cm$^{-1}$.

***N*-[3-(*t*-Butyldimethylsilyloxy)propylidene]glycine *N*-oxide *t*-butyl ester (15a).** 3-(*t*-Butyldimethylsilyloxy) propanal (1.88 g, 10.0 mmol) dissolved in diethyl ether (100 mL) was added slowly to the mixture of *N*-hydroxyglycine *t*-butyl ester (1.47 g, 10.0 mmol) and anhydrous caclium chloride (2 g) in diethyl ether (100 mL) which was cooled to 0 ℃ in an ice-water bath. The reaction mixture was stirred for 1 h at the same temperature and for 30 min at room

temperature. After the reaction mixture was filtered and the filtrate was rotary-evaporated to give a colorless liquid which was chromatographed over a silica gel column with hexane-ethyl acetate (1 : 2). Yield, 2.31 g (73%); $^1$H NMR ($CDCl_3$) δ 0.00 (s, 6H, $Si(CH_3)_2$), 0.85 (s, 9H, $SiC(CH_3)_3$), 1.43 (s, 9H, $OC(CH_3)_3$), 3.10-3.40 (m, 2H, $CH_2$), 3.63 (t, 2H, $J$=6.5 Hz, $CH_2O$), 4.43 (s, 2H, $NCH_2CO_2$), 6.55 (t, 1H, $J$=7.0 Hz, N=CH); IR (neat) 2990, 2870, 1745, 1595, 1256, 1090 cm$^{-1}$.

***N*-[3-(Tetrahydropyran-2-yloxy)propylidene]glycine *N*-oxdie *t*-butyl ester (15b).** The same procedure as described for the synthesis of comound **15a** was employed with *N*-hydroxyglycine *t*-butyl ester (1.47 g, 10.0 mmol) and 3-(tetrahydropyran-2-yloxy)propanal (1.58 g, 10.0 mmol). The product was isolated by silica gel column chromatography with hexane-ethyl acetate (1 : 4). Yield, 2.10 g (73%); $^1$H NMR ($CDCl_3$) δ 1.47 (s, 9H, $C(CH_3)_3$), 1.23-1.71(m, 6H, THP), 2.65 (m, 2H, $=CCH_2$), 3.40-3.81 (m, 4H, 2 $OCH_2$), 4.41 (s, 2H, $NCH_2CO_2$), 4.56 (m, 1H, -OCHO-), 6.50 (t, 1H, $J$=6.5 Hz, N=CH); IR (neat) 2990-2730, 1740, 1590, 1340, 1300-1150, 1040 cm$^{-1}$.

***N*-(3-Hydroxy-2,2-dimethylpropylidene)glycine *N*-oxide *t*-butyl ester (15c).** The same procedure as the synthesis of compound **15a** was employed with *N*-hydroxyglycine *t*-butyl ester (2.04 g, 13.9 mmol) and 2,2-dimethyl-3-hydroxypropanal (1.42 g, 13.9 mmol). The product was crystallized from hexane-ethyl acetate (1 : 9). Yield, 2.41 g (75%); mp 84.5 ℃; $^1$H NMR ($CDCl_3$) δ 1.25 (s, 6H, $C(CH_3)_2$), 1.48 (s, 9H, $OC(CH_3)_3$), 1.58 (br s, 1H, OH), 3.67 (s, 2H, $CH_2O$), 4.42 (s, 2H, $NCH_2CO_2$), 6.49 (s, 1H, N=CH); IR (KBr) 3500, 2990, 1740, 1580, 1340, 1180, 1040 cm$^{-1}$.

***N*-(3-Hydroxy-2,2-dimethylpropylidene)glycine *N*-oxide ethyl ester (15d).** The same procedure as described for the synthesis of compound **15a** was employed with *N*-hydroxyglycine ethyl ester (0.50 g, 4.2 mmol) and 2,2-dimethyl-3-hydroxypropanal (0.43 g, 4.2 mmol). A colorless liquid was isolated by silica gel column chromatography with ethyl acetate. Yield, 0.768 g (90%); $^1$H NMR ($CDCl_3$) δ 1.12 (br s, 1H, OH), 1.22 (s, 6H, $C(CH_3)_2$), 1.28 (t, 3H, $J$=7.0 Hz, $OCH_2C\underline{H}_3$), 3.57 (s, 2H, $CH_2O$), 4.20 (q, 2H, $J$=7.0 Hz, $OC\underline{H}_2CH_3$), 4.49 (s, 2H, $NCH_2CO_2$), 6.55 (s, 1H, N=CH); IR (neat) 3500, 1745, 1605, 1420, 1205, 1040 cm$^{-1}$.

**Ethyl 2-(*t*-butoxycarbonylmethyl)-3-[2-(*t*-butyldimethylsilyloxy)ethyl]-5-methylisoxazolidine-4-carboxylate (18).** The solution of nitrone **15a** (2.30 g, 7.25 mmol) and ethyl crotonate (1.24 g, 10.8 mmol) in toluene (40 mL) was stirred at 80-90 ℃ for 12 h under nitrogen gas. The reaction mixture was evaporated and chromatographed over a silica gel column with ethyl acetate-hexane (1 : 6) to give **18**. Yield, 2.12 g (68%); $^1$H NMR ($CDCl_3$) δ 0.00 (s, 6H, $Si(CH_3)_2$), 0.85 (s, 9H, $SiC(CH_3)_3$), 1.24 (t, 3H, $J$=7.0 Hz, $OCH_2C\underline{H}_3$), 1.33 (d, 3H, $J$=6.5 Hz, 5-$CH_3$), 1.44 (s, 9H, $C(CH_3)_3$), 1.78 (m, 2H, 3-$CH_2$), 2.78 (dd, 0.8H, $J$=8.0, 5.3 Hz, 4-H), 3.09 (dd, 0.2H, $J$=8.9, 8.7 Hz, 4-H), 3.47-3.78 (m, 5H, 3-H, $OCH_2$, N-$CH_2CO_2$), 4.12 (q, 2H, $J$=7.0 Hz, $OC\underline{H}_2CH_3$), 4.39 (m, 1H, 5-H); IR (neat) 2990, 1745, 1370, 1120, 1040 cm$^{-1}$.

**Methyl 2-(*t*-butoxycarbonylmethyl)-3-[2-(*t*-butyldimethylsilyloxy)ethyl]isoxazolidine-5-carboxylate (16a).** The same procedure as described for the synthesis of **18** was employed with nitrone **15a** (2.12 g, 6.7 mmol) and methyl acrylate (1.08 mL, 12 mmol) by stirring at 60-70 ℃ for 6 h. Yield, 2.32 g (86%); $^1$H NMR ($CDCl_3$) δ 0.00 (s, 6H, $Si(CH_3)_2$), 0.85 (s, 9H, $SiC(CH_3)_3$), 1.47 (s, 9H, $C(CH_3)_3$), 1.50-1.71 (m, 2H, 3-$CH_2$), 2.35-2.63 (m, 2H, 4-H), 3.36-3.93 (m, 3H, $CH_2O$, 3-H), 3.46 (d, 1H, $J$=16.4 Hz, $NCHCO_2$), 3.76 (s, 3H, $OCH_3$), 3.82 (d, 1H, $J$=16.4 Hz, $NCHCO_2$), 4.57 (dd, 1H, $J$=7.9, 8.2 Hz, 5-H); IR (neat) 2990, 1735, 1150, 1050 cm$^{-1}$.

**Ethyl 2-ethoxycarbonylmethyl-3-(2-hydroxy-1,1-dimethylethyl)-5-methylisoxazolidine-4-carboxylate (19b).** The same procedure as the synthesis of **18** was employed with nitrone **15d** (2.03 g, 10 mmol) and ethyl crotonate (2.28 g, 20 mmol) by stirring at 80-90 ℃ for 24 h. Yield, 1.57 g (60%); $^1$H NMR ($CDCl_3$) δ 0.91 (s, 3H, $CH_3$), 0.93 (s, 3H, $CH_3$), 1.10 (br s, 1H, OH), 1.23 (t, 6H, $J$=7.0 Hz, 2 $C\underline{H}_3CH_2O$), 1.28 (d, 3H, $J$=6.5 Hz, 5-$CH_3$), 2.82 (dd, 0.6H, $J$=8.9, 8.0 Hz, 4-H), 3.08 (dd, 0.4H, $J$=8.8, 4.9 Hz, 4-H), 3.42 (m, 1H, 3-H), 3.62 (m, 2H, $CH_2O$), 3.74 (d, 1H, $J$=18.2 Hz, $NCHCO_2$), 3.88 (d, 1H, $J$=18.2 Hz, $NCHCO_2$), 4.20 (m, 4H, $2CH_3C\underline{H}_2O$), 4.35-4.60 (m, 1H, 5H); IR (neat) 3400, 2990, 1735, 1150, 1050 cm$^{-1}$.

**Methyl 2-ethoxycarbonylmethyl-3-(2-hydroxy-1,1-dimethylethyl)isoxazolidine-5-carboxylate (17b).** The same procedure as described for the synthesis of **18** was employed with nitrone **15d** (2.03 g, 10 mmol) and methyl acrylate (1.80 mL, 20 mmol) by stirring at 60-70 ℃ for 6 h. Yield, 2.02 g (70%); $^1$H NMR ($CDCl_3$) δ 0.90 (s, 6H, 2 $CH_3$), 1.25 (t, 3H, $J$=7.1 Hz, $OCH_2C\underline{H}_3$), 2.54 (m, 2H, 4-H), 3.72 (s, 3H, $OCH_3$), 3.12-3.85 (m, 6H, $HOCH_2$-, 3-H, $NCH_2CO_2$), 4.18 (q, 2H, $J$=7.1 Hz, $OC\underline{H}_2CH_3$), 4.51 (m, 1H, 5-H); IR (neat) 3500, 2990, 1745, 1210, 1040 cm$^{-1}$.

**Ethyl 2-(*t*-butoxycarbonylmethyl)-3-(2-hydroxy-1,1-dimethylethyl)-5-methylisoxazolidine-4-carboxylate (19a).** The same procedure as described for the synthesis of **18** was employed with nitrone **15c** (2.31 g, 10 mmol) and ethyl crotonate (1.71 g, 15 mmol). Yield, 2.14 g (62%); $^1$H NMR ($CDCl_3+D_2O$) δ 1.08 (s, 3H, $CH_3$), 1.18 (s, 3H, $CH_3$), 1.20 (t, 3H, $J$=7.1 Hz, $OCH_2C\underline{H}_3$), 1.34 (d, 3H, $J$=6.5 Hz, 5-$CH_3$), 1.46 (s, 9H, $OC(CH_3)_3$), 2.81 (dd, 1H, $J$=8.9, 5.0 Hz, 4-H), 3.41-3.92 (m, 5H, $OCH_2$, 3-H, $NCH_2CO_2$), 4.19 (q, 2H, $J$=7.1 Hz, $OC\underline{H}_2CH_3$), 4.41 (m, 1H, 5-H); IR (neat) 3500, 2990, 1745, 1340, 1210, 1040 cm$^{-1}$.

**Methyl 2-(*t*-butoxycarbonylmethyl)-3-(2-hydroxy-1,1-dimethylethyl)isoxazolidine-5-carboxylate (17a).** The same procedure as described for the synthesis of **18** was employed with nitrone **15c** (2.23 g, 9.65 mmol) and methyl acrylate (1.81 mL, 20 mmol). Yield, 2.51 g (82%); $^1$H NMR ($CDCl_3$) δ 0.88 (s, 3H, $CH_3$), 0.91 (s, 3H, $CH_3$), 1.47 (s, 9H, $OC(CH_3)_3$), 2.03 (s, 1H, OH), 2.59 (m, 2H, 4-H), 3.22-3.98 (m, 5H, 3-H, $OCH_2$, $NCH_2CO_2$), 3.73 (s, 3H, $OCH_3$), 4.51 (dd, 1H, $J$=8.0, 8.3 Hz, 5-H); IR (neat) 3450, 2990, 1740, 1370, 1210, 1160, 1050 cm$^{-1}$.

**Methyl 2-(*t*-butoxycarbonylmethyl)-3-[2-(tetrahydropyran-2-yloxy)ethyl]isoxazolidine-5-carboxylate (16b).** The same procedure as described for the synthesis of **18** was employed with nitrone **15b** (1.00 g, 3.47 mmol) and methyl acrylate (0.63 mL, 7.0 mmol). Yield, 1.00 g (82%); $^1$H NMR ($CDCl_3$) δ 1.23-2.05 (m, 6H, 3-$CH_2$, THP), 1.47 (s, 9H, $OC(CH_3)_3$), 2.51 (m, 2H, 4-H), 3.39-3.84 (m, 7H, 3-H, 2 $OCH_2$, $NCH_2CO_2$), 3.76 (s, 3H, $OCH_3$), 4.48-4.67 (m, 2H, 5-H, OCHO); IR (neat) 2990, 1740, 1360, 1220, 1040 cm$^{-1}$.

**Methyl 2-(*t*-butoxycarbonylmethyl)-3-(2-hydroxyethyl)isoxazolidine-5-carboxylate (17c).** Method A. The solution of tetrabutylammonium fluoride in THF (1 M, 4.0 mL, 4.0 mmol) was added to the solution of compound **16a** (1.29 g, 3.2 mmol) in THF (5 mL) and stirred for 12 h. The reaction mixture was passed through a short silica gel column and the evaporation of the eluent gave a red colored residue. The residue was dissolved in ethyl acetate (20 mL) and the solution was washed with water, 0.1 N hydrochloric acid solution, 10% sodium bicarbonate solution, and 5% sodium chloride solution in sequences. The ethyl acetate layer was separated, dried over anhydrous sodium sulfate and rotary-evaporated to give a red colored liquid which was chromatographed over a silica gel column to give a liquid. Yield, 0.85 g (92%); $^1$H NMR ($CDCl_3$) δ 1.47 (s, 9H, $C(CH_3)_3$), 1.52-2.30 (m, 3H, OH, $CH_2$), 2.36-2.64 (m, 2H, 4-H), 3.46 (d, 1H, $J$=16.4 Hz, $NCHCO_2$), 3.82 (d, 1H, $J$=16.4 Hz, $NCHCO_2$), 3.76 (s, 3H, $OCH_3$), 3.52 (m, 1H, 3-H), 3.74-3.85 (m, 2H, $CH_2$-O), 4.57 (dd, 1H, $J$=7.9, 8.1 Hz, 5-H); IR (neat) 3400, 2990, 1740, 1340, 1190, 1040 cm$^{-1}$.

Method B. Compound **16b** (1.90 g, 5.1 mmol) in methanol (20 mL) was stirred with pyridinium *p*-toluenesulfonate (0.5 g) at 50 ℃ for 4 h. The product was isolated by following the same procedure as described in Method A to give 1.26 g (yield, 86%) of **17c**.

**Ethyl 2-(*t*-butoxycarbonylmethyl)-3-(2-hydroxyethyl)-5-methylisoxazolidine-4-carboxylate (19c).** The same procedure as described for the synthesis of compound **17c** in Method A was used to remove the silyl group of compound **18** (1.98 g, 4.6 mmol) with THF solution of tetrabutylammonium fluoride (1 M, 5.5 mL, 5.5 mmol) to give compound **19c**. Yield, 1.28 g (88%); $^1$H NMR ($CDCl_3$+$D_2O$), δ 1.24 (t, 3H, $J$=7.1 Hz, $OCH_2\underline{CH_3}$), 1.29 (d, 3H, $J$=6.1 Hz, 5-$CH_3$), 1.44 (s, 9H, $C(CH_3)_3$), 1.55-1.78 (m, 2H, -$CH_2$-), 3.14 (dd, 1H, $J$=8.9, 8.7 Hz, 4-H), 3.47-3.77 (m, 5H, 3-H, $NCH_2CO_2$, $CH_2O$), 4.14 (q, 2H, $J$=7.1 Hz, $O\underline{CH_2}CH_3$), 4.38 (m, 1H, 5-H); IR (neat) 3400, 2990, 1740, 1350, 1190, 1040 cm$^{-1}$.

**Methyl 2-(*t*-butoxycarbonylmethyl)-3-(1,1-dimethyl-2-tosyloxyethyl)isoxazolidine-5-carboxylate (20a).** To the solution of compound **17a** (0.9 g, 2.84 mmol) in pyridine (5.0 mL) which was cooled to 0 ℃ in ice-water bath was added *p*-toluenesulfonyl chloride (0.83 g, 4.3 mmol) under nitrogen gas. The mixture was stirred for 2 h and kept in refregerator for a day. The mixture was poured into crushed ice (20 g) and the aqueous solution was extracted with ethyl acetate (20 mL×2). The extract was washed with 1% hydrochloric acid solution, water, 5% sodium bicarbonate solution, and finally water, dried over anhydrous magnesium sulfate, and evaporated to give a residue which was chromatographed over a silica gel column with hexane-ethyl acetate (7 : 3). Yield, 0.99 g (74%); $^1$H NMR ($CDCl_3$) δ 0.92 (s, 6H, $C(CH_3)_2$), 1.46 (s, 9H, $C(CH_3)_3$), 2.46 (s, 3H, $PhCH_3$), 2.34-2.65 (m, 2H, 4-H), 3.15-3.37 (m, 1H, 3-H), 3.48 (d, 1H, $J$=12.3 Hz, $NCHCO_2$), 3.52 (d, $J$=12.3 Hz, $NCHCO_2$), 3.74 (s, 3H, $OCH_3$), 3.86 (d, 1H, $J$=9.3 Hz, $CH_2O$), 3.94 (d, 1H, $J$=9.3 Hz, $CH_2O$), 4.48 (dd, 1H, $J$=8.3, 8.0 Hz, 5-H), 7.32 (d, 2H, $J$=8.2 Hz, Ar), 7.68 (d, 2H, $J$=8.2 Hz, Ar); IR (neat) 3100-2990, 1740, 1600, 1360, 1180, 1040 cm$^{-1}$.

**Methyl 2-(*t*-butoxycarbonylmethyl)-3-(2-tosyloxyethyl)isoxazolidine-5-carboxylate (20b).** The same procedure as described for the synthesis of **20a** was employed with compound **17c** (1.8 g, 6.2 mmol) and p-toluenesulfonyl chloride (1.78 g, 9.4 mmol). Yield, 2.08 g (76%); $^1$H NMR ($CDCl_3$) δ 1.47 (s, 9H, $C(CH_3)_3$), 1.52-1.71 (m, 2H, 3-$CH_2$), 2.46 (s, 3H, $PhCH_3$), 2.36-2.64 (m, 2H, 4-H), 3.36-3.93 (m, 5H, $OCH_2$, $NCH_2CO_2$, 3-H), 3.76 (s, 3H, $OCH_3$), 4.57 (dd, 1H, $J$=8.1, 7.9 Hz, 5-H), 7.32 (d, 2H, $J$=8.0 Hz, Ar), 7.68 (d, 2H, $J$=8.0 Hz, Ar); IR (neat) 3100-2990, 1745, 1605, 1370, 1180, 960 cm$^{-1}$.

**Ethyl 2-(*t*-butoxycarbonylmethyl)-5-methyl-3-(1,1-dimethyl-2-tosyloxyethyl)isoxazolidine-4-carboxylate (20c).** The same procedure as described for the synthesis of **20a** was employed with compound **19a** (0.53 g, 1.52 mmol) and *p*-toluenesulfonyl chloride (0.45 g, 2.3 mmol). Yield, 0.56 g (74%); $^1$H NMR ($CDCl_3$) δ 0.99 (s, 6H, $C(CH_3)_2$), 1.20 (t, 3H, $J$=7.0 Hz, $OCH_2\underline{CH_3}$), 1.34 (d, 3H, $J$=6.5 Hz, 5-$CH_3$), 1.47 (s, 9H, $C(CH_3)_3$), 2.50 (s, 3H, $PhCH_3$), 2.81 (dd, 1H, $J$=8.8, 5.4 Hz, 4-H), 3.15-3.37 (m, 1H, 3-H), 3.64 (d, 1H, $J$=15.0 Hz, $NCHCO_2$), 3.71 (d, 1H, $J$=15.0 Hz, $NCHCO_2$), 3.80 (d, 1H, $J$=12.0 Hz, $CH_2O$), 4.00 (d, 1H, $J$=12.0 Hz, $CH_2O$), 4.22 (q, 2H, $J$=7.0 Hz, $OCH_2CH_3$), 4.45 (m, 1H, 5-H), 7.33 (d, 2H, $J$=8.0 Hz, Ar), 7.69 (d, 2H, $J$=8.0 Hz, Ar); IR (neat) 3050-2990, 1745, 1605, 1380, 1180, 1040 cm$^{-1}$.

**Ethyl 2-(*t*-butoxycarbonylmethyl)-5-methyl-3-(2-tosyloxyethyl)isoxazolidine-4-carboxylate (20d).** The same procedure as described for the synthesis of **20a** was employed with compound **19c** (0.90 g, 2.84 mmol) and *p*-toluenesulfonyl chloride (0.82 g, 4.3 mmol). Yield, 1.05 g (79%); $^1$H NMR ($CDCl_3$) δ 1.23 (t, 3H, $J$=7.0 Hz, $OCH_2\underline{CH_3}$), 1.45 (d, 3H, $J$=6.0 Hz, 5-$CH_3$), 1.47 (s, 9H, $C(CH_3)_3$), 1.66-2.00 (m, 2H, 3-$CH_2$), 2.48 (s, 3H, $PhCH_3$), 2.93 (dd, 1H, $J$=9.8, 7.9 Hz, 4-H), 3.36-3.92 (m, 5H, 3-H, $NCH_2CO_2$, $OCH_2$), 4.17 (q, 2H, $J$=7.0 Hz, $O\underline{CH_2}CH_3$), 4.58 (m, 1H, 5-H), 7.30 (d, 2H, $J$=8.2 Hz, Ar), 7.69 (d, 2H, $J$=8.2 Hz, Ar); IR (neat) 3100-2990, 1740, 1600, 1360, 1190, 1040 cm$^{-1}$.

**Methyl 2-(*t*-butoxycarbonylmethyl)-3-(2-iodo-1,1-dimethylethyl)isoxazolidine-5-carboxylate (21a).** The solution of compound **20a** (0.84 g, 1.79 mmol) and sodium iodide (1.34 g, 8.95 mmol) in acetone (5 mL) was refluxed for 3 h. After evaporation of acetone the residue was dissolved in diethyl ether (10 mL) and water (5 mL). The ether layer was separated, washed with saturated solution of sodium thiosulfate, and 5% sodium chloride solution, and dried over anhydrous magnesium sulfate. The residue obtained after evaporation of solvent was chromatographed over a silica gel column with ethyl acetate-hexane (1 : 5) to give a colorless crystal. Yield, 0.61 g (80%); mp 67.5 ℃; $^1$H NMR ($CDCl_3$) δ 1.02 (s, 3H, $CH_3$), 1.08 (s, 3H, $CH_3$), 1.48 (s, 9H, $C(CH_3)_3$), 2.48-2.68 (m, 2H, 4-H), 3.15-4.00 (m, 5H, 3-H, $CH_2I$, $NCH_2CO_2$), 3.75 (s, 3H, $OCH_3$), 4.50 (dd, 1H, $J$=7.2, 6.6 Hz, 5-H); IR (neat) 2990, 1745, 1370, 1210, 1160, 1040 cm$^{-1}$.

**Methyl 2-(*t*-butoxycarbonylmethyl)-3-(2-iodoethyl)-isoxazolidine-5-carboxylate (21b).** The same procedure as described for the synthesis of **21a** was employed with compound **20b** (0.93 g, 2.10 mmol) and sodium iodide (1.26 g, 8.40 mmol). Yield, 0.795 g (95%); $^1$H NMR ($CDCl_3$) δ 1.47 (s, 9H, $C(CH_3)_3$), 1.58-2.00 (m, 2H, 3-$CH_2$), 2.48-2.70 (m, 2H, 4-H), 3.15-4.00 (m, 5H, 3-H, $CH_2I$, $NCH_2CO_2$), 3.76 (s, 3H, $OCH_3$), 4.57 (dd, 1H, $J$=8.1, 7.9 Hz, 5-H); IR (neat) 2990, 1745, 1370, 1300-1160, 1040 cm$^{-1}$.

**Ethyl 2-(*t*-butoxycarbonylmethyl)-3-(2-iodo-1,1-dimethylethyl)-5-methylisoxazolidine-4-carboxylate (21c).** The same procedure as described for the synthesis of **21a** was employed with compound **20c** (0.32 g, 0.64 mmol) and sodium iodide (0.288 g, 1.92 mmol). Yield, 0.276 g (95%); $^1$H NMR ($CDCl_3$) δ 0.99 (s, 3H, $CH_3$), 1.20 (m, 6H, $CH_3$, $OCH_2CH_3$), 1.34 (d, 3H, $J$=6.4 Hz, 5-$CH_3$), 1.47 (s, 9H, $C(CH_3)_3$), 2.80 (dd, 1H, $J$=8.8, 5.5 Hz, 4-H), 3.21 (d, 1H, $J$=10.0 Hz, $CH_2I$), 3.51 (d, 1H, $J$=5.5 Hz, 3-H), 3.54 (d, 1H, $J$=10.0 Hz, $CH_2I$), 3.65 (d, 1H, $J$=15.0 Hz, $NCHCO_2$), 3.71 (d, 1H, $J$=15.0 Hz, $NCHCO_2$), 4.22 (q, 2H, $J$=7.0 Hz, $OCH_2CH_3$), 4.45 (m, 1H, 5-H); IR (neat) 2990, 1740, 1370, 1160, 1040 cm $^{-1}$.

**Ethyl 2-(*t*-butoxycarbonylmethyl)-3-(2-iodoethyl)-5-methylisoxazolidine-4-carboxylate (21d).** The same procedure as described for the synthesis of **21a** was employed with compound **20d** (1.00 g, 2.12 mmol) and sodium iodide (1.27 g, 8.48 mmol). Yield, 0.83 g (92%); $^1$H NMR ($CDCl_3$) δ 1.23 (t, 3H, $J$=7.0 Hz, $OCH_2CH_3$), 1.44 (d, 3H, $J$=6.0 Hz, 5-$CH_3$), 1.47 (s, 9H, $C(CH_3)_3$), 1.66-2.00 (m, 2H, 3-$CH_2$), 2.90 (dd, 1H, $J$=9.8, 7.9 Hz, 4-H), 3.15-3.54 (m, 3H, 3-H, $CH_2I$), 3.64 (d, 1H, $J$=15.0 Hz, $NCHCO_2$), 3.71 (d, 1H, $J$=15.0 Hz, $NCHCO_2$), 4.18 (q, 2H, $J$=7.0 Hz, $OCH_2CH_3$), 4.58 (m, 1H, 5-H); IR (neat) 2990, 1740, 1360, 1205, 1040 cm$^{-1}$.

**8-(*t*-Butyl) 3-methyl 6,6-dimethyl-2-oxa-1-azabicyclo[3.3.0]octane-3,8-dicarboxylate (22a).** Lithium hexamethyldisalazide (THF, 1 M, 1.5 mL, 1.5 mmol) was added to the solution of compound **21a** (0.427 g, 1.0 mmol) in THF (5 mL) which was cooled in dry ice-acetone bath. The mixture was stirred for 30 min at the same temperature and for 1 h at room temperature. After addition of 25% ammonium chloride solution, the reaction mixture was extracted with diethyl ether (5 mL). Drying of the extract over anhydrous magnesium sulfate and evaporation of the solvent gave a yellow colored residue which was chromatographed over a silica gel column with hexane-ethyl acetate (4 : 1). Yield, 0.134 g (45%); $^1$H NMR ($CDCl_3$) δ 0.96 (s, 3H, $CH_3$), 0.98 (s, 3H, $CH_3$), 1.47 (s, 9H, $C(CH_3)_3$), 2.10-2.54 (m, 4H, 4-H, 7-H), 3.70 (s, 3H, $OCH_3$), 3.15-3.80 (m, 2H, 5-H, 8-H), 4.48 (m, 1H, 3-H); IR (neat) 2990, 1745, 1340, 1190, 1040 cm $^{-1}$.

**8-(*t*-Butyl) 3-methyl 2-oxa-1-azabicyclo[3.3.0]octane-3,8-dicarboxylate (22b).** The same procedure as described for the synthesis of compound **22a** was employed with lithium hexamethyldisilazide (THF, 1 M, 1.3 mL, 1.3 mmol) and compound **21b** (0.34 g, 0.86 mmol). Yield, 0.11 g (47%); $^1$H NMR ($CDCl_3$) δ 1.47 (s, 9H, $C(CH_3)_3$), 1.50-2.38 (m, 4H, 6-H, 7-H), 2.38-2.80 (m, 2H, 4-H), 3.40-3.75 (m, 1H, 5-H), 3.76 (s, 3H, $CH_3$), 3.82 (t, 1H, $J$=8.0 Hz, 8-H), 4.57 (t, 1H, $J$=8.0 Hz, 3-H); IR (neat) 2990, 2915, 1745, 1340, 1190, 1040 cm $^{-1}$.

**8-(*t*-Butyl) 4-ethyl 3,6,6-trimethyl-2-oxa-1-azabicyclo[3.3.0]octane-4,8-dicarboxylate (22c).** The same procedure as described for the synthesis of compound **22a** was employed with lithium hexamethyldisilazide (THF, 1 M, 1.5 mL, 1.5 mmol) and compound **21c** (0.45 g, 1.0 mmol). *Yield, 0.25 g (77%); $^1$H NMR ($CDCl_3$) δ 0.98 (s, 3H, $CH_3$), 1.12 (s, 3H, $CH_3$), 1.23 (t, 3H, $J$=7.0 Hz, $OCH_2CH_3$), 1.43* (d, 3H, $J$=6.5 Hz, 5-$CH_3$), 1.47 (s, 9H, $C(CH_3)_3$), 1.90-2.30 (m, 2H, 7-H), 2.83 (dd, 1H, $J$=8.8, 5.5 Hz, 4-H), 3.50-4.00 (m, 2H, 5-H, 8-H), 4.18 (q, 2H, $J$=7.0 Hz, $OCH_2CH_3$), 4.50 (m, 1H, 3-H); IR (neat) 2990, 2915, 1745, 1340, 1190, 1040 cm $^{-1}$.

**8-(*t*-Butyl) 4-ethyl 3-methyl-2-oxa-1-azabicyclo[3.3.0]octane-4,8-dicarboxylate (22d).** The same procedure as described for the synthesis of compound **22a** was employed with lithium hexamethyldisilazide (THF, 1 M, 2.0 mL, 2.0 mmol) and compound **21c** (0.43 g, 1.0 mmol). Yield, 0.19 g (64%); $^1$H NMR ($CDCl_3$) δ 1.23 (t, 3H, $J$=7.0 Hz, $OCH_2CH_3$), 1.43-1.48 (m, 12H, 3-$CH_3$, $C(CH_3)_3$), 1.60-2.33 (m, 4H, 6-H, 7-H), 2.90 (dd, 1H, $J$=9.8, 7.9 Hz, 4-H), 3.15-3.50 (m, 1H, 5-H), 3.60-4.10 (m, 1H, 8-H), 4.20 (q, 2H, $J$=7.0 Hz, $OCH_2CH_3$), 4.60 (m, 1H, 3-H); IR (neat) 2990, 2915, 1745, 1340, 1200, 1040 cm$^{-1}$.

**Methyl 2-ethoxycabonylmethyl-3-(1-carboxy-1-methylethyl)isoxazolidine-5-carboxlate (23a).** After Jones reagent (1.6 mL, 12.8 mmol) was added to the solution of compound **17b** (0.61 g, 2.1 mmol) in acetone which was cooled at 0 ℃ in ice-water bath, the mixture was stirred at the same temperature for 3 h. After the excess amounts of Jones reagent in the reaction mixture was decomposed with 2-propanol, the reaction mixture was filterd. The filtrate was diluted with ethyl acetate (10 mL), washed with water (10 mL×2), dried over anhydrous sodium sulfate, and rotary-evaporated to give a yellow liquid. Yield, 0.45 g (70%); $^1$H NMR ($CDCl_3$) δ 0.98 (s, 3H, $CH_3$), 1.16 (s, 3H, $CH_3$), 1.30 (t, 3H, $J$=7.0 Hz, $OCH_2CH_3$), 2.45 (m, 2H, 4-H), 3.40 (m, 1H, 3-H), 3.70 (s, 3H, $OCH_3$), 3.64-4.13 (m, 2H, $NCH_2CO_2$), 4.23 (q, 2H, $J$=7.0 Hz, $OCH_2CH_3$), 4.57 (dd, 1H, $J$=8.3, 7.9 Hz, 5-H), 10.2 (br s, 1H, COOH); IR(neat) 3500-3200, 2990, 1730, 1690, 1200, 1040 cm $^{-1}$.

**Methyl 2-(*t*-butoxycarbonylmethyl)-3-carboxymethylisoxazolidine-5-carboxylate (23b).** The same procedure as described for the synthesis of compound **23a** was employed with Jones reagent (0.8 mL, 6.4 mmol) and compound **17c** (0.52 g, 1.8 mmol). Yield, 0.41 g (75%); $^1$H NMR ($CDCl_3$) δ 1.47 (s, 9H, $C(CH_3)_3$), 2.08-2.85 (m, 4H, 4-H, $CH_2CO_2$), 3.40 (m, 1H, 3-H), 3.72 (s, 3H, $OCH_3$), 3.64-4.13 (m, 2H, $NCH_2CO_2$), 4.49 (dd, 1H $J$=8.3, 7.9 Hz, 5-H); 9.63 (br s, 1H, COOH); IR (neat) 3500-3200, 2990, 1740, 1690, 1200, 1040 cm$^{-1}$.

**Ethyl 2-(*t*-butoxycarbonylmethyl)-3-(1-carboxy-1-methylethyl)-5-methylisoxazolidine-4-carboxylate (23c).** The same procedure as described for the synthesis of compound **23a** was employed with Jones reagent (0.5 mL, 4.0 mmol) and compound **19a** (0.41 g, 1.2 mmol). Yield, 0.35 g (82%); $^1$H NMR ($CDCl_3$) δ 0.99 (s, 3H, $CH_3$), 1.12 (s, 3H, $CH_3$), 1.28 (t, 3H, $J$=7.0 Hz, $OCH_2CH_3$), 1.43 (d, 3H, $J$=6.5 Hz, 5-$CH_3$), 1.47 (s, 9H, $C(CH_3)_3$), 2.93 (dd, 1H, $J$=9.8, 7.9 Hz, 4-H), 3.40 (d, 1H, $J$=7.9 Hz, 3-H), 3.61 (d, 1H, $J$=16.3 Hz, $NCHCO_2$), 4.13 (d, 1H, $J$=16.3 Hz, $NCHCO_2$), 4.23 (q, 2H, $J$=7.0 Hz, $OCH_2CH_3$), 4.53 (m, 1H, 5-H), 9.52 (br s, 1H, COOH); IR(neat) 3500-3200, 2990, 1745, 1690, 1200, 1040 cm $^{-1}$.

**Ethyl 2-(t-butoxycarbonylmethyl)-3-carboxymethyl-5-methylisoxazolidine-4-carboxylate (23d).** The same procedure as described for the synthesis of compound **23a** was employed with Jones reagent (0.5 mL, 4.0 mmol) and compound **19c** (0.32 g, 1.0 mmol). *Yield, 0.26 g (78%); $^1$H* NMR ($CDCl_3$) δ 1.28 (t, 3H, $J$=7.0 Hz, $OCH_2CH_3$), 1.44 (d, 3H, $J$=6.5 Hz, 5-$CH_3$), 1.48 (s, 9H, $C(CH_3)_3$), 2.24 (m, 2H, 3-$CH_2CO_2$), 2.89 (dd, 1H, $J$=10.0, 8.0 Hz, 4-H), 3.40 (m, 1H, 3-H), 3.63 (d, 1H, $J$=16.3 Hz, $NCHCO_2$), 4.13 (d, 1H, $J$=16.3 Hz, $NCHCO_2$), 4.20 (q, 2H, $J$=7.0 Hz, $OCH_2CH_3$), 4.57 (m,

1H, 5-H), 10.3 (br s, 1H, COOH); IR (neat) 3500-3200, 2990, 1745, 1690, 1200, 1040 cm $^{-1}$.

**Methyl 2-ethoxycarbonylmethyl-3-(1-methoxycarbonyl-1-methylethyl)isoxazolidine-5-carboxylate (24a).** Compound **23a** (0.74 g, 2.46 mmol) in diethyl ether (10 mL) was treated with an excess amount of diazomethane. After the reaction mixture was treated with acetic acid to decompose the excess amount of diazomethane, it was evaporated and chromatographed over a silica gel column. Yield, 0.72 g (92%); $^1$H NMR ($CDCl_3$) δ 1.10-1.50 (m, 9H, $3CH_3$), 2.60 (m, 2H, 4-H), 3.20-4.15 (m, 3H, 3-H, $NCH_2CO_2$), 3.70 (s, 3H, $OCH_3$), 3.75 (s, 3H, $OCH_3$), 4.18 (q, 2H, $J$=7.0 Hz, $OCH_2$), 4.52 (dd, 1H, $J$=7.9, 8.3 Hz, 5-H); IR (neat) 2990, 1745, 1340, 1200, 1040 cm $^{-1}$.

**Ethyl 2-(*t*-butoxycarbonylmethyl)-3-(1-methoxycarbonyl-1-methylethyl)-5-methylisoxazolidine-4-carboxylate (24b).** Excess diazomethane was treated to convert **23c** (0.16 g, 0.45 mmol) to **24b**. Yield, 0.12 g (72%); $^1$H NMR ($CDCl_3$) δ 0.99 (s, 3H, $CH_3$), 1.12 (s, 3H, $CH_3$), 1.28 (t, 3H, $J$=7.0 Hz, $OCH_2C\underline{H}_3$), 1.43 (d, 3H, $J$=6.5 Hz, 5-$CH_3$), 1.47 (s, 9H, $C(CH_3)_3$), 2.95 (dd, 1H, $J$=9.8, 7.9 Hz, 4-H), 3.43 (d, 1H, $J$=7.9 Hz, 3-H), 3.61 (d, 1H, $J$=16.0 Hz, $NCHCO_2$), 3.72 (s, 3H, $OCH_3$), 4.13 (d, 1H, $J$=16.0 Hz, $NCHCO_2$), 4.23 (q, 2H, $J$=7.0 Hz, $OC\underline{H}_2CH_3$), 4.53 (m, 1H, 5-H); IR (neat) 2990, 1740, 1340, 1200, 1040 cm $^{-1}$.

**Methyl 2-ethhoxycarbonylmethyl-3-(1-methyl-1-phenylthiocarbonylethyl)isoxazolidine-5-carboxylate (25a).** To the solution of compound **23a** (1.00 g, 3.3 mmol) in benzene was added oxalyl chloride (0.42 g, 3.3 mmol) and pyridine (0.27 mL) and the mixture was stirred for 1h at 0 C. After the benzene was evaporated and pyridine (2 mL) and thiophenol (0.34 ml, 3.3 mmol) was added to the residue. The mixture was stirred for 3 h at room temperature. The reaction mixture was, then, diluted with diethyl ether (10 mL), washed with water, dried over anhydrous sodium sulfate, and rotary-evaporated to give a liquid. Yield, 1.17 g (90%); $^1$H NMR ($CDCl_3$) δ 0.98 (s, 3H, $CH_3$), 1.16 (s, 3H, $CH_3$), 1.30 (t, 3H, $J$=7.0 Hz, $OCH_2C\underline{H}_3$), 2.45 (m, 2H, 4-H), 3.40 (m, 1H, 3-H), 3.64-4.13 (m, 2H, $NCH_2CO_2$), 3.70 (s, 3H, $OCH_3$), 4.23 (q, 2H, $J$=7.0 Hz, $OC\underline{H}_2CH_3$), 4.57 (dd, 1H, $J$=8.3, 7.9 Hz, 5-H), 7.40 (m, 5H, Ar); IR (neat) 3100-2980, 1745, 1720, 1600, 1360, 1200, 1040 cm $^{-1}$.

**Methyl 2-(*t*-butoxycarbonylmethyl)-3-phenylthiocarbonylmethylisoxazolidine-5-carboxylate (25b).** The same procedure as described for the synthesis of **25a** was used with compund **23b** (0.42 g, 1.4 mmol), oxalyl chloride (0.13 mL, 1.5 mmol), and thiophenol (0.16 mL, 1.5 mmol). Yield, 0.51 g (92%); $^1$H NMR ($CDCl_3$) δ 1.47 (s, 9H, $C(CH_3)_3$), 2.08-2.85 (m, 4H, 4-H, $CH_2CO$), 3.40 (m, 1H, 3-H), 3.64-4.13 (m, 2H, $NCH_2CO_2$), 3.72 (s, 3H, $OCH_3$), 4.49 (dd, 1H, $J$=8.3, 7.9 Hz, 5-H), 7.43 (m, 5H, Ar); IR (neat) 3100-2980, 1745, 1720, 1590, 1360, 1200, 1040 cm $^{-1}$.

**Ethyl 2-(*t*-butoxycarbonylmethyl)-5-methyl-3-(1-methyl-1-phenylthiocarbonylethyl)isoxazolidine-4-carboxylate (25c).** The same procedure as described for the synthesis of **25a** was used with compound **23c** (0.75 g, 2.1 mmol), oxalyl chloride (0.20 mL, 2.2 mmol), and thiophenol (0.23 mL, 2.2 mmol). Yield, 0.85 g (90%); $^1$H NMR ($CDCl_3$) δ 0.99 (s, 3H, $CH_3$), 1.12 (s, 3H, $CH_3$), 1.28 (t, 3H, $J$=7.0 Hz, $OCH_2C\underline{H}_3$), 1.43 (d, 3H, $J$=6.5 Hz, 5-$CH_3$), 1.47 (s, 9H, $C(CH_3)_3$), 2.93 (dd, 1H, $J$=9.8, 7.9 Hz, 4-H), 3.40 (m, 1H, 3-H), 3.61 (d, 1H, $J$=16.3 Hz, $NCHCO_2$), 4.13 (d, 1H, $J$=16.3 Hz, $NCHCO_2$), 4.23 (q, 2H, $J$=7.0 Hz, $OC\underline{H}_2CH_3$), 4.53 (m, 1H, 5-H), 7.43 (m, 5H, Ar); IR (neat) 3100-2980, 1745, 1720, 1590, 1360, 1200, 1040 cm $^{-1}$.

**Ethyl 2-(*t*-butoxycarbonylmethyl)-5-methyl-3-phenylthiocarbonylmethylisoxazolidine-4-carboxylate (25d).** The same procedure as described for the synthesis of **25a** was used with compund **23d** (0.50 g, 1.5 mmol), oxalyl chloride (0.14 mL, 1.6 mmol), and thiophenol (0.16 mL, 1.6 mmol). Yield, 0.56 g (89%); $^1$H NMR ($CDCl_3$) δ 1.28 (t, 3H, $J$=7.0 Hz, $OCH_2C\underline{H}_3$), 1.44 (d, 3H, $J$=6.5 Hz, 5-$CH_3$), 1.48 (s, 9H, $C(CH_3)_3$), 2.24 (m, 2H, 3-$CH_2CO$), 2.89 (dd, 1H, $J$=10.0, 8.0 Hz, 4-H), 3.40 (m, 1H, 3-H), 3.63 (d, 1H, $J$=16.3 Hz, $NCHCO_2$), 4.13 (d, 1H, $J$=16.3 Hz, $NCHCO_2$), 4.20 (q, 2H, $J$=7.0 Hz, $OC\underline{H}_2CH_3$), 4.57 (m, 1H, 5-H), 7.43 (m, 5H, Ar); IR (neat) 3100-2980, 1745, 1720, 1590, 1360, 1200, 1040 cm $^{-1}$.

**8-Ethyl 3-methyl 6,6-dimethyl-7-oxo-2-oxa-1-azabicyclo[3.3.0]octane-3,8-dicarboxylate (26a).** Under nitrogen gas environment, lithium hexamethyldisilazide (THF, 1 M, 2.0 mL, 2.0 mmol) was added to the solution of compound **25a** (0.40 g, 1.0 mmol) in THF (5.0 mL) which was cooled in dry ice-acetone bath. After the mixture was stirred at the same temperature for 30 min and at room temperature for 1 h, it was treated with 1 N ammonium chloride solution and extracted with diethyl ether (10 mL). The ether extract was dried over anhydrous sodium sulfate and rotary-evaporated to give a yellow colored liquid. Yield, 0.23 g (80%); $^1$H NMR ($CDCl_3$) δ 1.00-1.43 (m, 9H, $2CH_3$, $OCH_2C\underline{H}_3$), 2.64 (m, 2H, 4-H), 3.79 (s, 3H, $OCH_3$), 3.82 (m, 2H, 5-H), 4.23 (q, 2H, $J$=7.0 Hz, $OC\underline{H}_2CH_3$), 4.59 (m, 1H, 3-H), 4.86 (s, 1H, 8-H); IR (neat) 2990, 1745, 1700, 1370, 1180, 1040 cm $^{-1}$.

**8-(*t*-Butyl) 3-methyl 7-oxo-2-oxa-1-azabicyclo[3.3.0]octane-3,8-dicarboxylate (26b).** Compound **25b** (0.32 g, 0.80 mmol) was reacted with lithium hexamethyldisilazide (THF, 1 M, 1.6 mL, 1.6 mmol) by the same procedure as described for **26a**. Yield, 0.13 g (56%); $^1$H NMR ($CDCl_3$) δ 1.47 (s, 9H, $C(CH_3)_3$), 2.10-2.84 (m, 4H, 4-H, 6-H), 3.79 (s, 3H, $OCH_3$), 3.82 (m, 1H, 5-H), 4.62 (m, 1H, 3-H), 4.92 (s, 1H, 8-H); IR (neat) 2990, 1745, 1700, 1370, 1180, 1040 cm $^{-1}$.

**8-(*t*-Butyl) 4-ethyl 3,6,6-trimethyl-7-oxo-2-oxa-1-azabicyclo[3.3.0]octane-4,8-dicarboxylate (26c).** Compound **25c** (0.26 g, 0.58 mmol) was reacted with lithium hexamethyldisilazide (THF, 1 M, 1.2 mL, 1.2 mmol) by the same procedure as described for **26a**. Yield, 0.13 g (69%); $^1$H NMR ($CDCl_3$) δ 0.98-1.35 (m, 9H, 2 $CH_3$, $OCH_2C\underline{H}_3$), 1.44 (d, 3H, $J$=6.5 Hz, 3-$CH_3$), 1.47 (s, 9H, $C(CH_3)_3$), 3.10 (dd, 2H, $J$=9.8, 6.9 Hz, 4-H), 3.68-3.98 (m, 1H, 5-H), 4.23 (q, 2H, $J$=7.0 Hz, $OC\underline{H}_2CH_3$), 4.68 (m, 1H, 3-H), 4.90 (s, 1H, 8-H); IR (neat) 2990, 1745, 1700, 1370, 1180, 1040 cm $^{-1}$.

**8-(*t*-Butyl) 4-ethyl 3-methyl-7-oxo-2-oxa-1-azabicyclo[3.3.0]octane-4,8-dicarboxylate (26d).** Compound **25d** (0.19 g, 0.44 mmol) was reacted with lithium hexamethyldisilazide (THF, 1 M, 0.9 mL, 0.9 mmol) by the same procedure as described for **26a**. Yield, 0.10 g (74%); $^1$H NMR ($CDCl_3$) δ 1.23 (t, 3H, $J$=7.0 Hz, $OCH_2C\underline{H}_3$), 1.42 (d, 3H, $J$=6.5 Hz, 3-$CH_3$), 1.47 (s, 9H, $C(CH_3)_3$), 2.04-2.83 (m, 2H, 6-H), 3.30 (dd, 1H, $J$=8.9, 6.8 Hz, 4-H), 3.82 (m, 1H, 5-H), 4.23 (q, 2H, $J$=7.0 Hz, $OC\underline{H}_2CH_3$), 4.54 (m, 1H, 3-H), 4.89 (s, 1H,

8-H); IR (neat) 2990, 1745, 1700, 1370, 1180, 1040 $cm^{-1}$.

**8-(*t*-Butyl) 4-ethyl 7,7-ethylenedioxy-3,6,6-trimethyl-2-oxa-1-azabicyclo[3.3.0]octane-4,8-dicarboxylate (27a).** The solution of compound **26c** (0.68 g, 2.0 mmol), ethylene glycol (0.136 g, 2.2 mmol), and *p*-toluenesulfonic acid (20 mg) in toluene (50 mL) was refluxed for 12 h. After evaporaion of the solvent, the residue was dissolved in ethyl acetate (20 mL). The solution was washed with 5% sodium bicarbonate solution, dried over anhydrous magnesium sulfate, and rotary-evaporated to give a yellow colored liquid which was chromatographed over a silica gel column with hexane-ethyl acetate (4 : 1). Yield, 0.62 g (81%); $^1H$ NMR ($CDCl_3$) δ 1.18 (s, 3H, $CH_3$), 1.21 (s, 3H, $CH_3$), 1.28 (t, 3H, $J$=7.0 Hz, $OCH_2C\underline{H}_3$), 1.47 (s, 9H, $C(CH_3)_3$), 1.49 (d, 3H, $J$=6.5 Hz, 3-$CH_3$), 2.80 (dd, 1H, $J$=9.0, 8.7 Hz, 4-H), 3.57 (s, 4H, $OCH_2CH_2O$), 3.73 (d, 1H, $J$=8.7 Hz, 5-H), 4.18-4.50 (m, 4H, 3-H, 8-H, $OC\underline{H}_2CH_3$); IR (neat) 2980, 1730, 1100 $cm^{-1}$.

**8-(*t*-Butyl) 4-ethyl 7,7-ethylenedioxy-3-methyl-2-oxa-1-azabicyclo[3.3.0]octane-4,8-dicarboxylate (27b).** Compound **26d** (0.78 g, 2.49 mmol) was reacted with ethylene glycol (0.16 g, 2.6 mmol) by the same procedure as described for **27a**. Yield, 0.68 g (77%); $^1H$ NMR ($CDCl_3$) δ 1.30 (t, 3H, $J$=7.0 Hz, $OCH_2C\underline{H}_3$), 1.47 (s, 9H, $C(CH_3)_3$), 1.49 (d, 3H, $J$=6.5 Hz, 3-$CH_3$), 2.04 (dd, 1H, $J$=15.0, 6.0 Hz, 6-H), 2.24 (dd, 1H, $J$=15.0, 6.4 Hz, 6-H), 2.80 (dd, 1H, $J$=9.0, 8.7 Hz, 4-H), 3.55 (s, 4H, $OCH_2CH_2O$), 3.70 (m, 1H, 5-H), 3.98-4.52 (m, 4H, 3-H, 8-H, $OC\underline{H}_2CH_3$); IR (neat) 2980, 1730, 1100 $cm^{-1}$.

**5-(1-Ethoxycarbonyl-2-hydroxypropyl)-4,4-dimethylproline *t*-butyl ester (28a).** Zinc powder (85% purity, 0.28 g, 3.6 mgatm) was added slowly to the solution of compound **22c** (0.39 g, 1.2 mmol) in acetic acid (10 mL) which was maintained at 0 ℃. The suspension was stirred at the same temperature for 2 h and at room temperature for 1 h. The reaction mixture was filtered and the filtrate was rotary-evaporated. The residue was dissolved in ethyl acetate (20 mL) and the solution was washed with 1 M ammonia water (20 mL), dried over anhydrous magnesium sulfate, and rotrary-evaporated to give a colorless liquid. Yield, 0.34 g (86%); $^1H$ NMR ($CDCl_3$-$D_2O$) δ 1.10-1.42 (m, 6H, $OCHC\underline{H}_3$, $OCH_2C\underline{H}_3$), 1.18 (s, 3H, $CH_3$), 1.26 (s, 3H, $CH_3$), 1.47 (s, 9H, $C(CH_3)_3$), 2.04-2.58 (m, 3H, 3-H, $C\underline{H}CO_2$), 3.35 (d, 1H, $J$=7.0 Hz, 5-H), 4.15 (m, 1H, $OC\underline{H}CH_3$), 4.18-4.50 (m, 3H, 2-H, $OC\underline{H}_2CH_3$); IR (neat) 3500-3100, 2980, 1740, 1100 $cm^{-1}$.

**5-(1-Ethoxycarbonyl-2-hydroxypropyl)proline *t*-butyl ester (28b).** Compound **22d** (0.508 g, 1.7 mmol) was reduced with zinc powder (85% purity, 0.39 g, 5.1 mgatm) by the same procedure as described for **28a**. Yield, 0.42 g (82%); $^1H$ NMR ($CDCl_3$-$D_2O$) δ 1.10-1.42 (m, 6H, $OCHC\underline{H}_3$, $OCH_2C\underline{H}_3$), 1.48 (s, 9H, $C(CH_3)_3$), 2.04-2.58 (m, 5H, 3-H, 4-H, $C\underline{H}CO_2$), 3.35 (m, 1H, 5-H), 4.00-4.50 (m, 4H, $OC\underline{H}CH_3$, 2-H, $OC\underline{H}_2CH_3$); IR (neat) 3500-3100, 2980, 1740, 1100 $cm^{-1}$.

**5-(1-Ethoxycarbonyl-2-hydroxypropyl)-3,3-ethylenedioxy-4,4-dimethylproline *t*-butyl ester (28c).** Compound **27a** (0.58 g, 1.51 mmol) was reduced with zinc powder (85% purity, 0.35 g, 4.53 mgatm) by the same procedure as described for **28a**. Yield, 0.42 g (72%); $^1H$ NMR ($CDCl_3$-$D_2O$) δ 1.10-1.42 (m, 6H, $OCHC\underline{H}_3$, $OCH_2C\underline{H}_3$), 1.18 (s, 3H, $CH_3$), 1.26 (s, 3H, $CH_3$), 1.47 (s, 9H, $C(CH_3)_3$), 2.04-2.58 (m, 1H, $CHCO_2$), 3.35 (d, 1H, $J$=7.0 Hz, 5-H), 3.98 (s, 4H, $OCH_2CH_2$-O), 4.15 (m, 1H, $OC\underline{H}CH_3$) 4.18-4.50 (m, 3H, 2-H, $OC\underline{H}_2CH_3$); IR (neat) 3500-3100, 2980, 1740, 1100 $cm^{-1}$.

**5-(1-Ethoxycarbonyl-2-hydroxypropyl)-3,3-ethylenedioxyproline *t*-butyl ester (28d).** Compound **27b** (0.62 g, 1.74 mmol) was reduced with zinc powder (85% purity, 0.40 g, 5.22 mgatm) by the same procedure as described for **28a**. Yield, 0.47 g (76%); $^1H$ NMR ($CDCl_3$-$D_2O$) δ 1.10-1.42 (m, 6H, $OCHC\underline{H}_3$, $OCH_2C\underline{H}_3$), 1.48 (s, 9H, $C(CH_3)_3$), 2.04-2.58 (m, 3H, 4-H, $CHCO_2$), 3.35 (m, 1H, 5-H), 3.88 (s, 4H, $OCH_2CH_2O$), 4.00-4.50 (m, 4H, $OC\underline{H}CH_3$, 2-H, $OC\underline{H}_2CH_3$); IR (neat) 3500-3100, 2980, 1740, 1100 $cm^{-1}$.

**5-[1-Ethoxycarbonyl-2-(*t*-butyldimethylsilyloxy)propyl]-4,4-dimethylproline *t*-butyl ester (29a).** The solution of compound **28a** (0.26 g, 0.80 mmol), imidazole (55 mg, 0.81 mmol), and *t*-butyldimethylsilyl chloride (0.124 g, 0.82 mmol) in DMF (5 mL) was stirred for 12 h. The reaction mixture was diluted with diethyl ether (20 mL) and poured into water (20 mL). The ether layer was separated, washed with water (20 mL) and saturated sodium chloride solution, dried over anhydrous magnesium sulfate, and rotary-evaporated to give a colorless liquid which was chromatographed over a silica gel column with hexane-ethyl acetate (8 : 1) to give **29a**. Yield, 0.33 g (94%); $^1H$ NMR ($CDCl_3$-$D_2O$) δ 0.02 (s, 6H, $Si(CH_3)_2$), 0.87 (s, 9H, $SiC(CH_3)_3$), 1.10-1.42 (m, 6H, $OCHC\underline{H}_3$, $OCH_2C\underline{H}_3$), 1.18 (s, 3H, $CH_3$), 1.26 (s, 3H, $CH_3$), 1.47 (s, 9H, $C(CH_3)_3$), 2.04-2.58 (m, 3H, 3-H, $CHCO_2$), 3.35 (d, 1H, $J$=7.0 Hz, 5-H), 4.15 (m, 1H, $OC\underline{H}CH_3$) 4.18-4.50 (m, 3H, 2-H, $OC\underline{H}_2CH_3$); IR (neat) 3300, 2980, 1740, 1255, 1100, 835, 775 $cm^{-1}$.

**5-[1-Ethoxycarbonyl-2-(*t*-butyldimethylsilyloxy)propyl]proline *t*-butyl ester (29b).** Compound **28b** (0.32 g, 1.07 mmol) was reacted with *t*-butyldimethylsilyl chloride (0.18 g, 1.20 mmol) in the presence of imidazole (75 mg, 1.1 mmol) in DMF (5 mL) by the same procedure as described for **29a**. Yield, 0.42 g (95%); $^1H$ NMR ($CDCl_3$-$D_2O$) δ 0.06 (s, 6H, $Si(CH_3)_2$), 0.89 (s, 9H, $SiC(CH_3)_3$), 1.10-1.42 (m, 6H, $OCHC\underline{H}_3$, $OCH_2C\underline{H}_3$), 1.48 (s, 9H, $C(CH_3)_3$), 2.04-2.58 (m, 5H, 3-H, 4-H, $CHCO_2$), 3.35 (m, 1H, 5-H), 4.00-4.50 (m, 4H, $OC\underline{H}CH_3$, 2-H, $OC\underline{H}_2CH_3$); IR (neat) 3300, 2980, 1740, 1255, 1100, 835, 775 $cm^{-1}$.

**5-[(1-Ethoxycarbonyl-2-(*t*-butyldimethylsilyloxy)-propyl]-3,3-ethylenedioxy-4,4-dimethylproline *t*-butyl ester (29c).** Compound **28c** (0.31 g, 0.80 mmol) was reacted with *t*-butyldimethylsilyl chloride (0.124 g, 0.82 mmol) in the presence of imidazole (61 mg, 0.9 mmol) in DMF (5 mL) by the same procedure as described for **29a**. Yield, 0.38 g (95%); $^1H$ NMR ($CDCl_3$-$D_2O$) δ 0.02 (s, 6H, $Si(CH_3)_2$), 0.87 (s, 9H, $SiC(CH_3)_3$), 1.10-1.42 (m, 6H, $OCHC\underline{H}_3$, $OCH_2C\underline{H}_3$), 1.18 (s, 3H, $CH_3$), 1.26 (s, 3H, $CH_3$), 1.47 (s, 9H, $C(CH_3)_3$), 2.04-2.58 (m, 1H, $CHCO_2$), 3.35 (d, 1H, $J$=7.0 Hz, 5-H), 3.98 (s, 4H, $OCH_2CH_2O$), 4.15 (m, 1H, $OC\underline{H}CH_3$) 4.18-4.50 (m, 3H, 2-H, $OC\underline{H}_2CH_3$); IR (neat) 3300, 2980, 1735, 1255, 1100, 835, 775 $cm^{-1}$.

**5-[(1-Ethoxycarbonyl-2-(*t*-butyldimethylsilyloxy)-propyl]-3,3-ethylenedioxyproline *t*-butyl ester (29d).** Compound **28d** (0.34 g, 0.95 mmol) was reacted with *t*-butyldimethylsilyl chloride (0.15 g, 1.00 mmol) in the presence of imidazole (68 mg, 1.0 mmol) in DMF (5 mL) by the same procedure as described for **29a**. Yield, 0.41 g (92%); $^1H$ NMR ($CDCl_3$-$D_2O$) δ 0.04 (s, 6H, $Si(CH_3)_2$), 0.89 (s, 9H, $SiC(CH_3)_3$),

1.10-1.42 (m, 6H, $OCHC\underline{H}_3$, $OCH_2C\underline{H}_3$), 1.48 (s, 9H, $C(CH_3)_3$), 2.04-2.58 (m, 3H, 4-H, $CHCO_2$), 3.35 (m, 1H, 5-H), 3.88 (s, 4H, $OCH_2CH_2O$), 4.00-4.50 (m, 4H, 2-H, $OC\underline{H}CH_3$, $OC\underline{H}_2CH_3$); IR (neat) 3300, 2980, 1740, 1255, 1100, 835, 775 $cm^{-1}$.

***t*-Butyl 6-[1-(*t*-butyldimethylsilyloxy)ethyl]-1,1-dimethylcarbapenam-3-carboxylate (30a).** Methylmagnesium bromide (diethyl ether, 3.0 M, 0.30 ml, 0.90 mmol) was added to the solution of compound **29a** (0.30 g, 0.68 mmol) in THF (10 mL) which was maintained at −20 ℃ in dry ice-carbon tetrachloride bath. The mixture was stirred at the same temperature for 2 h and at room temperature for 12 h. After saturated ammnium chloride solution (20 mL) was added, the reaction mixture was extracted with ethyl acetate (20 mL×2). The extract was washed with 10% sodium chloride solution, dried over anhydrous sodium sulfate, and rotary-evaporated to give a colorless liquid, which was chromatographed over a silica gel column with hexane-ethyl acetate (4 : 1). Yield, 0.17 g (61%); $^1H$ NMR ($CDCl_3$) δ 0.02 (s, 6H, $Si(CH_3)_2$), 0.87 (s, 9H, $SiC(CH_3)_3$), 1.18 (s, 3H, $CH_3$), 1.23 (d, 3H, $J$=6.2 Hz, $CH_3$), 1.28 (s, 3H, $CH_3$), 1.47 (s, 9H, $C(CH_3)_3$), 2.35 (d, 2H, $J$=8.0 Hz, 2-H), 2.80 (dd, 1H, $J$=7.0, 2.1 Hz, 6-H), 3.80-3.90 (m, 1H, 5-H), 4.09 (m, 1H, 8-H), 4.31 (t, 1H, $J$=8.0 Hz, 3-H); IR (neat) 2980, 1770, 1730, 1255, 1100, 835, 775 $cm^{-1}$.

***t*-Butyl 6-[1-(*t*-butyldimethylsilyloxy)ethyl]carbapenam-3-carboxylate (30b).** Compound **29b** (0.36 g, 0.87 mmol) was reacted with methylmagnesium bromide (diethyl ether, 3.0 M, 0.38 mL, 1.14 mmol) by the same procedure as described for **30a**. Yield, 0.17 g (52%); $^1H$ NMR ($CDCl_3$) δ 0.02 (s, 6H, $Si(CH_3)_2$), 0.87 (s, 9H, $SiC(CH_3)_3$), 1.23 (d, 3H, $J$=6.2 Hz, $CH_3$), 1.47 (s, 9H, $C(CH_3)_3$), 2.04-2.58 (m, 4H, 2-H, 1-H), 2.78 (dd, 1H, $J$=7.0, 2.1 Hz, 6-H), 3.84-3.91 (m, 1H, 5-H), 4.12 (m, 1H, 8-H), 4.30 (t, 1H, $J$=8.0 Hz, 3-H); IR (neat) 2980, 1770, 1730, 1255, 1100, 835, 775 $cm^{-1}$.

***t*-Butyl 6-[1-(*t*-butyldimethylsilyloxy)ethyl]-2,2-ethylenedioxy-1,1-dimethylcarbapenam-3-carboxylate (30c).** Compound **29c** (0.36 g, 0.70 mmol) was reacted with methylmagnesium bromide (diethyl ether, 3.0 M, 0.30 mL, 0.90 mmol) by the same procedure as described for **30a**. Yield, 0.154 g (48%); $^1H$ NMR ($CDCl_3$) δ 0.04 (s, 6H, $Si(CH_3)_2$), 0.87 (s, 9H, $SiC(CH_3)_3$), 0.98 (s, 3H, $CH_3$), 1.12 (s, 3H, $CH_3$), 1.23 (d, 3H, $J$=6.5 Hz, $CH_3$), 1.47 (s, 9H, $C(CH_3)_3$), 3.18 (dd, 1H, $J$=6.8, 2.1 Hz, 6-H), 3.77-3.80 (m, 4H, $OCH_2CH_2O$), 3.88 (d, 1H, $J$=2.1 Hz, 5-H), 4.12 (m, 1H, 8-H), 4.31 (s, 1H, 3-H); IR (neat) 2980, 1760, 1740, 1255, 1100, 835, 775 $cm^{-1}$.

***t*-Butyl 6-[1-(*t*-butyldimethylsilyloxy)ethyl]-3,3-ethylenedioxycarbapenam-3-carboxylate (30d).** Compound **29d** (0.38 g, 0.80 mmol) was reacted with methylmagnesium bromide (diethyl ether, 3.0 M, 0.35 mL, 1.05 mmol) by the same procedure as described for **30a**. Yield, 0.15 g (42%); $^1H$ NMR ($CDCl_3$) δ 0.06 (s, 6H, $Si(CH_3)_2$), 0.84 (s, 9H, $SiC(CH_3)_3$), 1.22 (d, 3H, $J$=6.5 Hz, $CH_3$), 1.47 (s, 9H, $C(CH_3)_3$), 2.04 (dd, 1H, $J$=14.5, 10.0 Hz, 1-H), 2.38 (dd, 1H, $J$=14.5, 2.5 Hz, 1-H), 3.18 (dd, 1H, $J$=6.8, 2.1 Hz, 6-H), 3.78-3.91 (m, 1H, 5-H), 3.98 (s, 4H, $OCH_2CH_2O$), 4.15 (m, 1H, 8-H), 4.30 (s, 1H, 3-H); IR (neat) 2980, 1760, 1740, 1255, 1100, 835, 775 $cm^{-1}$.

***t*-Butyl 6-[1-(*t*-butyldimethylsilyloxy)ethyl]-1,1-dimethyl-2-oxocarbapenam-3-carboxylate (31a).** To the solution of compound **30c** (0.10 g, 0.22 mmol) in methylene chloride (5 mL), which was maintained at 0 ℃, was added perchloric acid (60%, 2 drops) and the mixture was stirred at the same temperature for 30 min and at room temperature for 1 h. The reaction mixture was poured into 5% ammonia water and the solution was extracted with methylene chloride (10 mL). The methylene chloride solution was dried over anhydrous sodiun sulfate and evaporated under reduced pressure to give a yellow colored liquid. The product was purified by silica gel column chromatography with hexane-ethyl acetate (4 : 1). Yield, 77 mg (85%); $^1H$ NMR ($CDCl_3$) δ 0.02 (s, 6H, $Si(CH_3)_2$), 0.87 (s, 9H, $SiC(CH_3)_3$), 1.23 (s, 3H, $CH_3$), 1.32 (s, 3H, $CH_3$), 1.35 (d, 3H, $J$=6.5 Hz, $CH_3$), 1.47 (s, 9H, $C(CH_3)_3$), 3.18 (dd, 1H, $J$=6.8, 2.1 Hz, 6-H), 3.88 (d, 1H, $J$=2.1 Hz, 5-H), 4.12 (m, 1H, 8-H), 4.67 (s, 1H, 3-H); IR (neat) 2980, 1760, 1740, 1255, 1100, 835, 775 $cm^{-1}$.

***t*-Butyl 6-[1-(*t*-butyldimethylsilyloxy)ethyl]-2-oxocarbapenam-3-carboxylate (31b).** Compound **30d** (0.11 g, 0.25 mmol) was reacted with perchloric acid (60%, 2 drops) by the same procedure as described for **31a**. Yield, 84 mg (88%); $^1H$ NMR ($CDCl_3$) δ 0.02 (s, 6H, $Si(CH_3)_2$), 0.87 (s, 9H, $SiC(CH_3)_3$), 1.35 (d, 3H, $J$=6.5 Hz, $CH_3$), 1.47 (s, 9H, $C(CH_3)_3$), 2.42 (dd, 1H, $J$=19.0, 8.0 Hz, 1-H), 2.93 (dd, 1H, $J$=19.0, 6.4 Hz, 1-H), 3.18 (dd, 1H, $J$=6.8, 2.1 Hz, 6-H), 3.84-3.91 (m, 1H, 5-H), 4.12 (m, 1H, 8-H), 4.67 (s, 1H, 3-H); IR (neat) 2980, 1760, 1740, 1255, 1100, 835, 775 $cm^{-1}$.

**Acknowledgment.** The present studies were partly supported by the Basic Sciene Research Institute program, Ministry of Education (BSRI-96-3417), and partly by New Drug Development Engineering Research Center.

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