A FORMAL SYNTHESIS OF (+)-α-ALLOKAINIC ACID *VIA* SULFANYL RADICAL ADDITION-CYCLIZATION REACTION

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Abstract — Sulfanyl radical addition-cyclization of the diallylamines in the presence of thiophenol and AIBN gave the 2,3,4-trisubstituted pyrrolidines which were effectively converted into the known key intermediate for the synthesis of (+)-α-allokainic acid *via* conversion of the phenylsulfanylmethyl group into the isopropenyl group at the 4-position.

INTRODUCTION

The kainoids, a family involving α-kainic acid and its 4-epimer, α-allokainic acid, domoic acids, and acromelic acids, possess a pyrrolidine dicarboxylic acids nucleus as a common structural feature (Figure 1). Since they have been found to exhibit powerful biological activities, principally neuroexcitatory, total syntheses of such kainoids have been achieved by several groups during the last decade.[1]

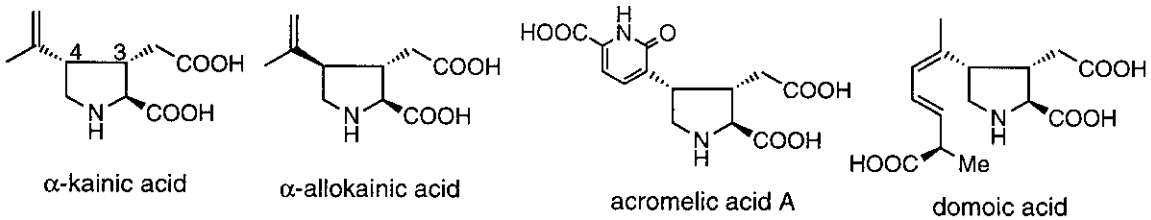
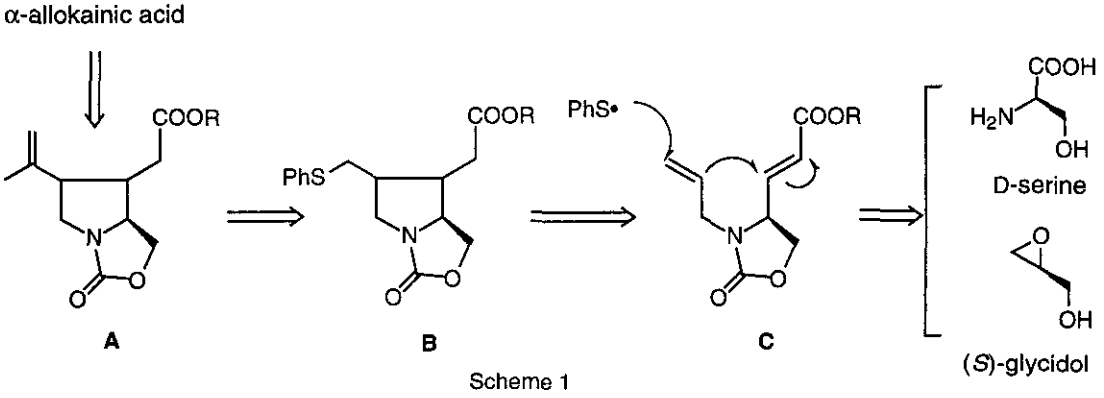


Figure 1 Kainoids

Recently, we have reported a concise synthesis of the 3,4-disubstituted pyrrolidin-2-ones *via* the sulfanyl radical addition-cyclization of the dienylamide.[2-4] This finding appeared to be suited for the synthesis of the kainoids. We now report a novel synthesis of (+)-α-allokainic acid *via* the sulfanyl radical addition-cyclization of the diallylamines. As a disconnective analysis is shown in Scheme 1, our synthetic strategy

consists of two key steps: [1] construction of 2,3,4-trisubstituted pyrrolidine ring by sulfanyl radical addition-cyclization (**C**→**B**) and [2] conversion of phenylsulfanylmethyl group into isopropenyl group (**B**→**A**).

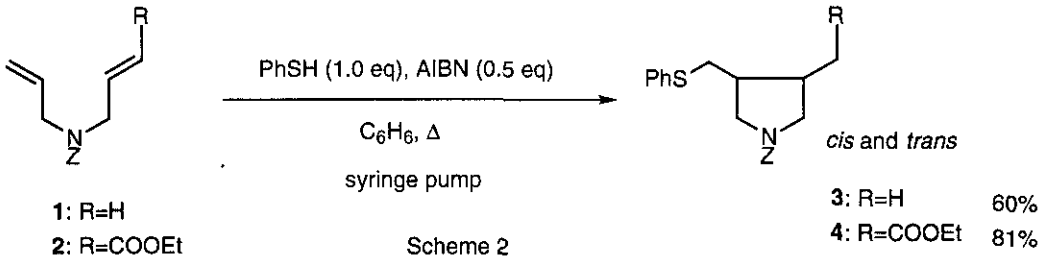


Scheme 1

RESULTS AND DISCUSSION

Preparation of Substituted Pyrrolidines

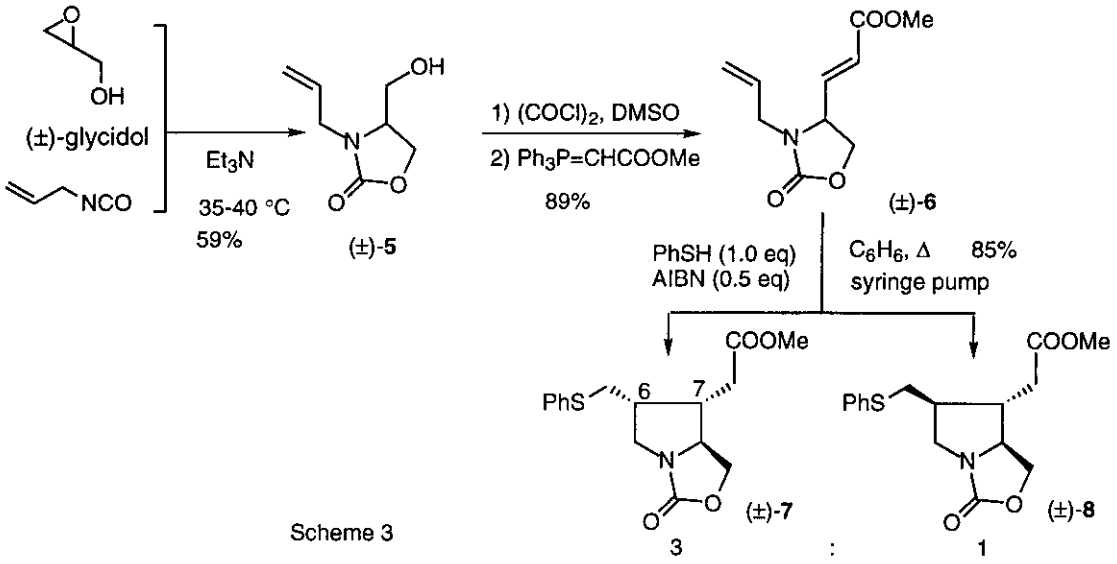
We first investigated the sulfanyl radical addition-cyclization reaction of model compounds (**1**) and (**2**) (Scheme 2). A solution containing thiophenol (1 eq) and AIBN (0.5 eq) in benzene was added dropwise by a syringe pump over 2 h to a solution of the carbamate (**1**) in boiling benzene while stirring under nitrogen. The solution was then refluxed for further 2 h and the solvent was removed *in vacuo*. The resulting residue was purified by medium-pressure column chromatography (MPCC) to give a mixture of the *cis*- and *trans*-pyrrolidines (**3**) in 60% combined yield as an inseparable mixture. The product (**3**) exhibited a molecular ion peak at *m/z* 341 in ms spectrum and showed ^{1}H-NMR signals due to methyl and aromatic protons at δ 0.98 (3H, br d, *J*=7 Hz) and 7.15-7.40 (10H, m), respectively. The ratio of the *cis*- and *trans*-products was not deduced from ^{1}H-NMR spectrum. The substrate (**2**) carrying a conjugated ester underwent the sulfanyl radical addition-cyclization to give a 1 : 1 mixture of the *cis*- and *trans*-pyrrolidines (**4**) in 81% combined yield as an inseparable mixture. These results suggest that the radical cyclization is suited for the synthesis of kainic acids.



Scheme 2

Before approaching to chiral synthesis of kainic acids, we examined the sulfanyl radical addition-cyclization

of the racemic substrate ((±)-**6**) having oxazolidinone ring as a preliminary investigation (Scheme 3). (±)-**6** was prepared from (±)-glycidol according to the known procedures.[5] According to Katsumura's method,[5] treatment of (±)-glycidol with allyl isocyanate in the presence of triethylamine afforded the *N*-allyloxazolidinone ((±)-**5**) in 59% yield. Swern oxidation of (±)-**5** followed by Wittig reaction of the resulting unstable aldehyde with methyl (triphenylphosphoranylidene)acetate gave the desired oxazolidinone ((±)-**6**) in 89% yield.



Scheme 3

The radical cyclization of (±)-**6** also proceeded smoothly to give a 3 : 1 mixture of the cyclized products ((±)-6,7-*cis*-**7**) and ((±)-6,7-*trans*-**8**) in combined 85% yield which was separated by MPCC. The structures of **7** and **8** were deduced from ^{1}H-NMR spectra and established unambiguously by single-crystal X-ray analysis of (±)-6,7-*trans*-isomer (**8**) (Figure 2). The preferential formation of the *cis*-**7** in radical cyclization can be explained *via* more favorable transition state **A** than **B** due to the orbital correlation between the radical and olefin (Scheme 4). Beckwith[6] has explained that the preferential formation of the *cis*-product from the 1-substituted hexenyl radical is ascribed to the effects of orbital symmetry. Thus, we have developed a new and simple synthetic method for kainoids using the sulfanyl radical addition-cyclization reaction.

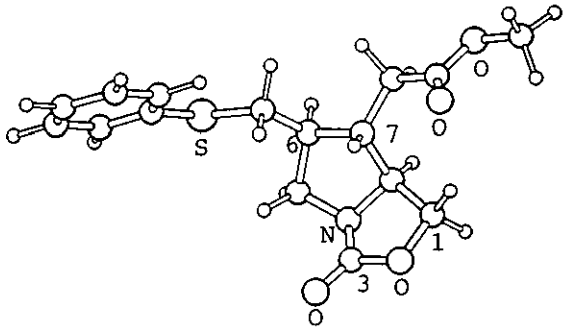
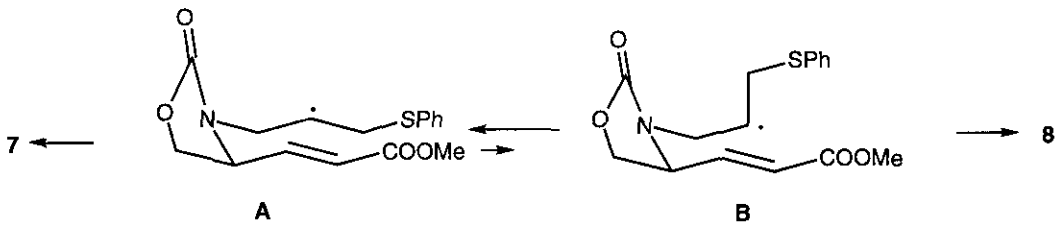


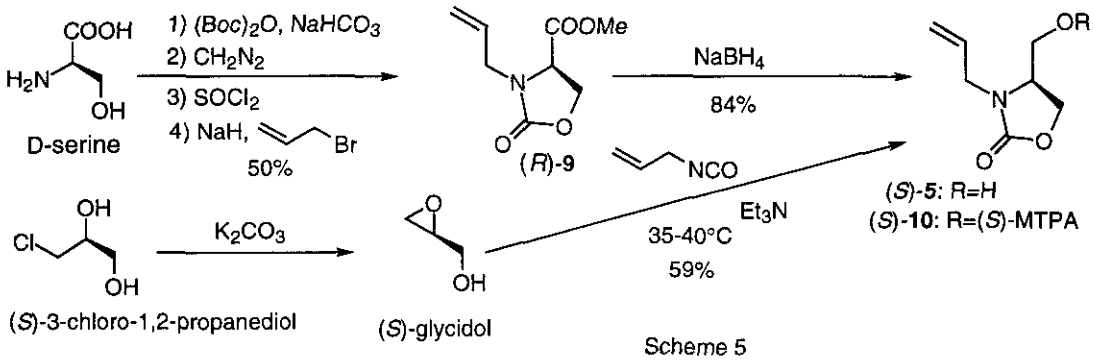
Figure 2 The Crystal Strucutre of (±)-6,7-*trans*-**8**



Scheme 4

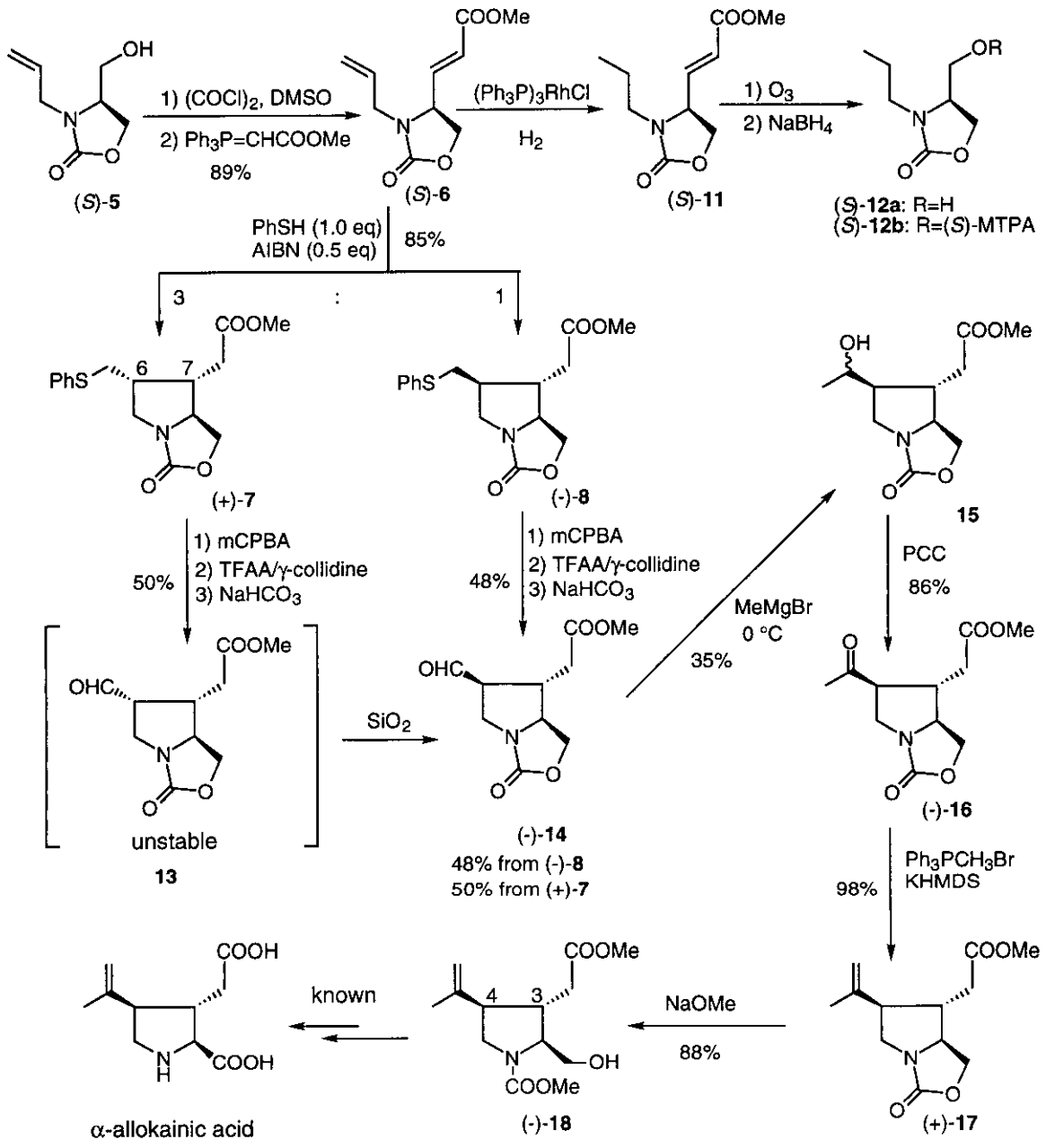
Formal Total Synthesis of (+)-α-Allokainic Acid

According to the results obtained in the racemic compounds as shown in the previous chapter, we started to synthesize (+)-α-allokainic acid by applying radical cyclization of the chiral substrate ((*S*)-**6**). (*S*)-**6** was prepared from (*S*)-**5** by the same reaction sequence used for the synthesis of (±)-**6**. (*S*)-**5** was prepared from either D-serine or (*S*)-glycidol by two different routes as follows (Scheme 5).



Scheme 5

According to Shirahama's procedure,[7] (*S*)-**5** was prepared from D-serine *via* a route involving *t*-butoxycarbonylation, esterification, construction of oxazolidinone ring, allylation, and reduction in 42% yield with five steps. According to the established procedure,[8] (*S*)-3-chloro-1,2-propanediol was converted into (*S*)-glycidol. (*S*)-**5** also was prepared from (*S*)-glycidol in 59% yield with one step by the same reaction sequence used for the synthesis of (±)-**5**. Optical purity of (*S*)-**5** was determined to be 100% enantiomeric excess (*e. e.*) by ^{1}H-NMR (500 MHz) spectroscopic analysis of the corresponding (*S*)-MTPA ester ((*S*)-**10**) which was derived from (*S*)-**5** by esterification using (*R*)-α-methoxy-α-(trifluoromethyl)phenylacetyl chloride. Swern oxidation of (*S*)-**5** followed by Wittig reaction of the resulting unstable aldehyde gave the desired oxazolidinone ((*S*)-**6**) in 89% yield. Optical purity of (*S*)-**6** was determined as follows. (*S*)-**6** was catalytically hydrogenated in the presence of chlorotris(triphenylphosphine)rhodium (I) to give the *N*-*n*-propyloxazolidinone ((*S*)-**11**). Ozonolysis of (*S*)-**11** followed by reduction of the resulting ozonide with sodium borohydride gave the alcohol ((*S*)-**12a**). Optical purity of (*S*)-**12a** was determined to be formed in 70% *e.e.* by ^{1}H-NMR (500 MHz) spectroscopic analysis of the corresponding (*S*)-MTPA ester ((*S*)-**12b**) (Scheme 6).



Scheme 6

The fact suggests that the racemization would occur partially during Swern oxidation of the alcohol ((*S*)-**5**) and/or the following Wittig reaction of the resulting unstable aldehyde. Though there have been reported two examples of the synthesis of kainoids *via* the analogous aldehyde,[7,9] authors have not given any comments on the racemization in their synthesis.

Radical cyclization of (*S*)-**6** also proceeded smoothly to give a 3 : 1 mixture of the cyclized products ((+)-

6,7-*cis*-**7**) and ((-)-6,7-*trans*-**8**) in combined 85% yield. Oxidation of the *trans*-sulfide ((-)-**8**) with *m*-chloroperbenzoic acid (mCPBA) at 0 ℃ gave the corresponding sulfoxide which was subjected to Pummerer reaction to give the desired *trans*-aldehyde ((-)-**14**) in 48% yield with three steps from the starting sulfide. Oxidation of the *cis*-sulfide ((+)-**7**) followed by Pummerer reaction gave the unstable *cis*-aldehyde (**13**) which was found to be readily isomerized into the *trans*-isomer ((-)-**14**) during the course of purification by silica gel chromatography. Treatment of the *trans*-aldehyde ((-)-**14**) with methylmagnesium bromide at 0 ℃ gave the alcohol (**15**) as an inseparable mixture of the diastereomers in 35 % yield. Attempted addition reaction of less basic and more oxophilic methylcerium chloride[10] to (-)-**14** was unsuccessful. Oxidation of the alcohol (**15**) with PCC followed by Wittig-Horner reaction of the resulting ketone ((-)-**16**)[11] afforded the olefin ((+)-**17**)[11] in 84% yield. Ring cleavage of the oxazolidinone ((+)-**17**) was effected with sodium methoxide to give the alcohol ((-)-**18**), $[\alpha]_D^{25}$ -20.8° (*c*=0.24, $CHCl_3$) (lit., $[\alpha]_D^{29}$ -31.7°(*c*=0.71, $CHCl_3$)). (-)-**18** exhibited superimposable IR and ^{1}H-NMR spectra with those of the authentic sample[12] kindly provided by Professor Ogasawara. Since (-)-**18** had previously been transformed into (+)-α-allokainic acid, the present method provides a new asymmetric synthesis of (+)-α-allokainic acid (Scheme 6).

In conclusion, the sulfanyl radical addition-cyclization reaction provides a new entry to kainoids including kainic acids.

ACKNOWLEDGEMENTS

We wish to thank the Ministry of Education, Science, Sports and Culture of Japan and the Science Research Promotion Fund of the Japan Private School Promotion Foundation for research grants. Thanks are also extended to Professor K. Ogasawara, Tohoku University, for sending us the precious spectral data of the alcohol ((-)-**18**) and Dr. K. Nagao, Daiso, Co. Ltd. for a generous gift of (*S*)-3-chloro-1,2-propanediol.

EXPERIMANTAL

^{1}H-NMR spectra were measured using Varian Gemini-200 (200 MHz), Varian Gemini-300 (300 MHz), and VXR-500 (500 MHz) instruments for solutions in deuteriochloroform, unless otherwise stated (tetramethylsilane was used as the internal reference); *J* values are given in Hz. IR spectra were measured with a Perkin Elmer 1600 FTIR machine for solutions in chloroform, unless otherwise stated and mass spectra were taken Hitachi M-4100 spectrometer. Mps were determined with a Kofler-type hot-stage apparatus and are uncorrected. All reactions were performed under nitrogen and extracts from the reaction mixtures were washed with water, dried ($MgSO_4$), and concentrated under reduced pressure. TLC was performed on precoated silica gel $60F_{254}$ (0.25 mm thick, Merck) with UV detection at 254 and 300 nm. Medium-pressure column chromatography (MPCC) was undertaken on a 530-4-10V apparatus (Yamazen) with Lobar größe B (310-25, Lichroprep Si60, Merck) as column absorbent. For flash column chromatography (FCC), Merck Kieselgel 60 (230-400 mesh) was used. All products described in this

paper were found to be homogeneous by TLC, MPCC and ^{1}H-NMR spectra.

Phenylmethyl *N,N*-Diallylcarbamate (1) A solution of benzyloxycarbonyl chloride (2.0 g, 12 mmol) in benzene (107 mL) was added at 0°C to a stirred solution of diallylamine (970 mg, 10 mmol) and triethylamine (2 mL, 15 mmol) in benzene (20 mL). The mixture was stirred at 0°C for 30 min and then filtered to remove triethylamine hydrochloride. The filtrate was condensed under reduced pressure and the residue was purified by MPCC (*n*-hexane-ethyl acetate = 1 : 1) to give the title carbamate (**1**) (2.2 g, 96%) as colorless oil. IR : 1670 (NCOO) cm^{-1}. ^{1}H-NMR (300 MHz) δ : 3.88 (4H, m, $NCH_2\times2$), 5.05-5.20 (4H, m, $=CH_2\times2$), 5.14 (2H, s, OCH_2Ph), 5.75 (2H, m, $CH=CH_2\times2$), 7.33 (5H, m, Ph). HRMS *m/z* : Calcd for $C_{14}H_{17}NO_2$ (M^+) 231.1258. Found : 231.1250.

Sulfanyl Radical Addition-Cyclization of the Carbamate (1) A solution of thiophenol (0.1 mL, 1.0 mmol) and AIBN (82 mg, 0.5 mmol) in benzene (20 mL) was added dropwise over 4 h (*via* a syringe pump) with stirring to a solution of the carbamate (**1**) (230 mg, 1.0 mmol) in boiling benzene (10 mL). The solution was then refluxed for further 2 h and the solvent was evaporated at rt under reduced pressure to give a residue which was purified by MPCC (*n*-hexane-ethyl acetate = 2 : 1) to give a mixture of phenylmethyl *cis/trans*-3-methyl-4-(phenylsulfanyl)methyl-1-pyrrolidinecarboxylate (**3**) (205 mg, 60%) as an inseparable mixture. IR : 1692 (NCOO) cm^{-1}. ^{1}H-NMR (300 MHz) δ : 0.98 (3H, very br d, *J*=7 Hz, Me), 1.85-3.80 (8H, m, 2-H_2+3-H+4-H+5-H_2+4-CH_2), 5.12 (2H, very br s, OCH_2Ph), 7.15-7.40 (10H, m, Ph×2). HRMS *m/z* : Calcd for $C_{20}H_{23}NO_2S$ (M^+) 341.1449. Found : 341.1451.

Ethyl (*E*)-4-[[(Phenylmethoxy)carbonyl](2-propenyl)amino]-2-butenoate (2) A solution of allylamine (2.28 g, 40 mmol) and ethyl 4-bromocrotonate (3.86 g, 20 mmol) in methylene dichloride (50 mL) was stirred at rt for 4 h. After addition of water (100 mL), the reaction mixture was extracted with methylene dichloride. The extract was dried and concentrated to give a residue which was purified by FCC (ethyl acetate) to give ethyl 4-(2-propenylamino)-2-butenoate (1.9 g, 55%) as pale yellow oil. According to the procedure given for the carbamate (**1**), treatment of ethyl (*E*)-4-(2-propenylamino)-2-butenoate (1.26 g, 7.4 mmol) with benzyloxycarbonyl chloride (1.5 g, 8.9 mmol) and triethylamine (1.48 mL, 11.1 mmol) gave the carbamate (**2**) (1.48 g, 68%) as pale yellow oil. IR : 1700 (COO + NCOO) cm^{-1}. ^{1}H-NMR (300 MHz) δ : 1.29 (3H, t, *J*=7 Hz, Me), 3.89 (2H, m, NCH_2), 4.02 (2H, m, NCH_2), 4.19 (2H, q, *J*=7 Hz, OCH_2), 5.15 (2H, s, OCH_2Ph), 5.04-5.23 (2H, m, $CH=CH_2$), 5.64-5.95 (2H, m, $CH=CH_2$ + $=CH$-COOEt), 6.84 (1H, br d, *J*=17 Hz, CH=CH-COOEt), 7.34 (5H, m, Ph). HRMS *m/z* : Calcd for $C_{17}H_{21}NO_4$ (M^+) 303.1470. Found : 303.1440.

Sulfanyl Radical Addition-Cyclization of the Carbamate (2) According to the procedure given for sulfanyl radical addition-cyclization of the carbamate (**1**), a solution of thiophenol (0.1 mL, 1.0 mmol) and AIBN (82 mg, 0.5 mmol) in benzene (20 mL) was added with stirring dropwise over 4 h (*via* a syringe

pump) to a solution of the carbamate (**2**) (303 mg, 1.0 mmol) in boiling benzene (10 mL). The solution was then refluxed for further 3 h and the solvent was evaporated at rt under reduced pressure to give a residue which was purified by MPCC (*n*-hexane-ethyl acetate = 2 : 1) to give a 1 : 1 mixture of ethyl *cis/trans*-1-(phenylmethoxy)carbonyl-4-(phenylsulfanyl)methyl-3-pyrrolidineacetate (**4**) (334 mg, 81%) as an inseparable mixture. IR : 1728 (COO), 1694 (NCOO) cm^{-1}. ^{1}H-NMR (300 MHz) δ : 1.24 (3/2H, t, *J*=7 Hz, Me), 1.25 (3/2H, t, *J*=7 Hz, Me), 2.26-3.62 (10H, m, 2-H_2+3-H+4-H+5-H_2+4-CH_2+3-CH_2), 4.11 (1H, q, *J*=7 Hz, OCH_2Me), 4.13 (1H, q, *J*=7 Hz, OCH_2Me), 5.11 (1H, s, OCH_2Ph), 5.10 and 5.13 (1H, ABq, *J*=13 Hz, OCH_2Ph), 7.15-7.45 (10H, m, Ph×2). HRMS *m/z* : Calcd for $C_{23}H_{27}NO_4S$ (M^+) 413.1659. Found : 413.1671.

(±)-4-(Hydroxymethyl)-3-(2-propenyl)-2-oxazolidinone (5) According to Katsumura's method,[5] a solution of (±)-glycidol (682 mg, 9.2 mmol), allyl isocyanate (0.82 mL, 9.2 mmol), and triethylamine (2.31 mL, 16.6 mmol) in methylene dichloride (6 mL) was stirred at 35-40°C for 18 h. The reaction mixture was then concentrated at rt under reduced pressure to give a residue which was purified by MPCC (*n*-hexane-ethyl acetate = 5 : 1) to give the (±)-alcohol (**5**) (844 mg, 59%) as pale yellow oil. IR : 3418 (OH), 1740 (NCOO) cm^{-1}. ^{1}H-NMR (500 Hz) δ : 3.64 (1H, dd, *J*=12, 3 Hz, C*H*OH), 3.76 (1H, br dd, *J*=16, 8 Hz, NCH), 3.80 (1H, dd, *J*=12, 4 Hz, C*H*OH), 3.88 (1H, m, 4-H), 4.09 (1H, ddt, *J*=16, 5, 1.5 Hz, NCH), 4.27 (1H, dd, *J*=9, 6 Hz, 5-H), 4.37 (1H, t, *J*=9 Hz, 5-H), 5.26 (1H, dm, *J*=10 Hz, 3'-H), 5.28 (1H, dm, *J*=17 Hz, 3'-H), 5.82 (1H, dddd, *J*=17, 10, 8, 5 Hz, 2'-H). HRMS *m/z* : Calcd for $C_7H_{11}NO_3$ (M^+) 157.0738. Found : 157.0748.

Methyl (±)-(*E*)-3-(2-Oxo-3-(2-propenyl)oxazolidin-4-yl)-2-propenoate (6) A solution of freshly distilled dimethyl sulfoxide (1.08 mL, 15.3 mmol) in methylene dichloride (4.8 mL) was added to a solution of oxalyl chloride (0.64 mL, 7.3 mmol) in methylene dichloride (19 mL) at -78°C and the reaction mixture was stirred for 5 more min at the same temperature. A solution of the (±)-alcohol (**5**) (1.0 g, 6.37 mmol) was added to the reaction mixture over 5 min and stirring was continued for another 20 min after which triethylamine (3.55 mL, 25.5 mmol) was added and the solution brought to -15°C over 1.5 h. A solution of methyl (triphenylphosphoranylidene)acetate (2.98 g, 8.92 mmol) in methylene dichloride (4.8 mL) was added to the reaction mixture and the temperature was allowed to reach at 25°C over 1.5 h. The reaction mixture was poured into brine and the solution was extracted with methylene dichloride. The extract was dried and concentrated to give a residue which was purified by MPCC (*n*-hexane-ethyl acetate = 6 : 1) to give the (±)-ester (**6**) (1.20 g, 89%) as pale yellow oil. IR : 1740 (COO + NCOO) cm^{-1}. ^{1}H-NMR (300 MHz) δ : 3.50 (1H, dd, *J*=16, 8 Hz, NCH), 3.78 (3H, s, OMe), 4.04 (1H, dd, *J*=8, 6 Hz, 5-H), 4.17 (1H, dm, *J*=16 Hz, NCH), 4.39 (1H, td, *J*=8, 6 Hz, 4-H), 4.78 (1H, t, *J*=8 Hz, 5-H), 5.20 (1H, br d, *J*=18 Hz, CH=CH_2), 5.25 (1H, br d, *J*=11 Hz, CH=CH_2), 5.73 (1H, m, C*H*=CH_2), 6.03 (1H, d,

J=16 Hz, CH=C*H*-COOMe), 6.74 (1H, dd, *J*=16, 8 Hz, C*H*=CH-COOMe). HRMS *m/z* : Calcd for $C_{10}H_{13}NO_4$ (M^+) 211.0843. Found : 211.0854.

Sulfanyl Radical Addition-Cyclization of the (±)-Ester (6) A solution of thiophenol (0.11 mL, 1.12 mmol) and AIBN (92 mg, 0.56 mmol) in benzene (22 mL) was added dropwise over 4 h (*via* a syringe pump) with stirring to a solution of the (±)-ester (**6**) (240 mg, 1.12 mmol) in boiling benzene (6 mL). The solution was then refluxed for further 3 h and the solvent was evaporated at rt under reduced pressure to give a residue which was purified by MPCC (*n*-hexane-diethyl ether = 1 : 5) to give methyl (6α,7α,7aα)-(±)-tetrahydro-3-oxo-6-(phenylsulfanyl)methyl-1*H*,3*H*-pyrrolo[1,2-*c*]oxazole-7-acetate (**7**) (232 mg, 64%) as pale yellow oil and methyl (6α,7β,7aβ)-(±)-tetrahydro-3-oxo-6-(phenylsulfanyl)methyl-1*H*,3*H*-pyrrolo[1,2-*c*]oxazole-7-acetate (**8**) (78 mg, 21%) as colorless crystals mp 121-122°C (C_6H_6).

(±)-**7**: IR : 1753 (NCOO + COO) cm^{-1}. ^{1}H-NMR (500 MHz) δ : 2.39 (2H, m, 7-CH + 7-H), 2.63 (1H, dd, *J*=15, 5 Hz, 7-CH) 2.64 (1H, m, 6-H), 2.75 (1H, dd, *J*=13, 9 Hz, 6-CH), 3.04 (1H, dd, *J*=13, 5 Hz, 6-CH), 3.19 (1H, dd, *J*=12, 6 Hz, 5-H), 3.69 (3H, s, OMe), 3.78 (1H, td, *J*=8, 4 Hz, 7a-H), 3.89 (1H, dd, *J*=12, 8 Hz, 5-H), 4.22 (1H, dd, *J*=9.5, 4 Hz, 1-H), 4.53 (1H, dd, *J*=9.5, 8 Hz, 1-H), 7.22-7.36 (5H, m, Ph). HRMS *m/z* : Calcd for $C_{16}H_{19}NO_4S$ (M^+) 321.1034. Found : 321.1039.

(±)-**8**: IR : 1745 (NCOO + COO) cm^{-1}. ^{1}H-NMR (500 MHz) δ : 2.03 (1H, dq, *J*=10, 4 Hz, 7-H), 2.28 (1H, m, 6-H), 2.29 (1H, dd, *J*=16, 10 Hz, 7-CH), 2.69 (1H, dd, *J*=16, 4 Hz, 7-CH), 2.93 (1H, dd, *J*=13, 8 Hz, 6-CH), 3.10 (1H, dd, *J*=13, 6 Hz, 6-CH), 3.45 (1H, dd, *J*=12, 9 Hz, 5-H), 3.53 (1H, dd, *J*=12, 9 Hz, 5-H), 3.67 (3H, s, OMe), 3.76 (1H, td, *J*=8, 4 Hz, 7a-H), 4.35 (1H, dd, *J*=9, 4 Hz, 1-H), 4.50 (1H, dd, *J*=9, 8 Hz, 1-H), 7.21-7.37 (5H, m, Ph). HRMS *m/z* : Calcd for $C_{16}H_{19}NO_4S$ (M^+) 321.1034. *Found : 321.1052.* X-ray crystallographic data: $C_{16}H_{19}NO_4S$, *Mr*=321.10, orthorhombic; *a*=19.926(2), *b*=12.326(2), *c*=12.316(2)Å, Z=8, U=3024.8(5)Å^3, *Dx*=1.412 g/cm^3, *R* value 0.064 for 2577 reflections, space group Pbca.

(*S*)-4-(Hydroxymethyl)-3-(2-propenyl)-2-oxazolidinone ((*S*)-(5))

Method A-----According to the Shirahama's method,[7] the ester ((*R*)-**9**) was prepared from D-serine.

Sodium borohydride (378 mg, 0.01 mol) was added in small portions with stirring at 0°C to a solution of the ester ((*R*)-**9**) (1.9 g, 0.01 mol) in methanol (40 mL). The reaction mixture was stirred at rt for 2 h. After addition of water (10 mL), the reaction mixture was extracted with methylene dichloride. The extract was dried and concentrated to give a residue which was purified by MPCC (*n*-hexane-ethyl acetate = 2 : 1) to give the (*S*)-alcohol (**5**) (1.36 g, 84%) ($[\alpha]_D^{23}$ -36.5° (*c*=1.85, $CHCl_3$)) as pale yellow oil, which was identical with the racemic (±)-alcohol (**5**) by comparison of their spectral data.

Method B-----According to the procedure given for the racemic (±)-alcohol (**5**), treatment of (*S*)-glycidol

with allyl isocyanate gave the (*S*)-alcohol (**5**) ($[\alpha]_D^{23}$ -38.5°(*c*=1.85, $CHCl_3$)).

Methyl [*S*-(*E*)]-3-[2-Oxo-3-(2-propenyl)oxazolidin-4-yl]-2-propenoate ((*S*)-(6)) According to the procedure given for the racemic (±)-ester (**6**), Swern oxidation of (*S*)-alcohol (**5**) followed by Wittig reaction of the resulting aldehyde gave (*S*)-ester (**6**) ($[\alpha]_D^{26}$ -3.2° (*c*=0.94, $CHCl_3$)), which was identical with the racemic (±)-ester (**6**) by comparison of their spectral data.

(*S*)-4-Hydroxymethyl-3-propyl-2-oxazolidinone ((*S*)-(12a)) A solution of *S*-**6** (100 mg, 0.47 mmol) in benzene (5 mL) was catalytically hydrogenated over chlorotris(triphenylphosphine)rhodium (I) (60 mg, 0.06 mmol) under hydrogen atmosphere at rt for 3 h. The reaction mixture was filtered through a pad of Florisil and the solvent was evaporated. A residue was purified by MPCC (*n*-hexane-ethyl acetate = 6 : 1) to give the (*S*)-*n*-propyl compound (**11**) (33 mg, 32%) as pale yellow oil. Ozone was passed through the solution of (*S*)-**11** (33 mg, 0.21 mmol) in methylene dichloride (9 mL) at -78 ℃ for 30 min. The reaction mixture was treated with a large amount of sodium borohydride. The reaction mixture was kept at rt for 12 h. Usual workup followed by purification using MPCC (ethyl acetate) gave the (*S*)-alcohol (**12a**) (18 mg, 73%) as pale yellow oil. IR : 3413 (OH), 1741 (NCOO) cm^{-1}. ^{1}H-NMR 300 MHz) δ : 0.94 (3H, t, *J*=7 Hz, Me), 1.49-1.70 (2H, m, 2'-H_2), 3.10 (1H, ddd, *J*=14, 9, 6 Hz, NCH), 3.43 (1H, br dt, *J*=14, 7 Hz, NCH), 3.68 (1H, br dd, *J*=12, 3 Hz, C*H*OH), 3.80 (1H, dd, *J*=12, 4 Hz, C*H*OH), 3.88 (1H, m, 4-H), 4.24 (1H, br dd, *J*=9, 6 Hz, 5-H), 4.36 (1H, t, *J*=9 Hz, 5-H). HRMS *m/z* : Calcd for $C_7H_{13}NO_3$ (M^+) 159.0895. Found : 159.0879. $[\alpha]_D^{25}$ +9.4°(*c*=0.85, $CHCl_3$).

Sulfanyl Radical Addition-Cyclization of the (*S*)-Ester (6) According to the procedure given for sulfanyl radical addition-cyclization of the racemic (±)-ester (**6**), sulfanyl radical addition-cyclization of the (*S*)-ester (**6**) gave methyl [6*R*-(6α,7α,7aα)]-tetrahydro-3-oxo-6-(phenylsulfanyl)methyl-1*H*,3*H*-pyrrolo[1,2-*c*]oxazole-7-acetate (**7**) ($[\alpha]_D^{20}$ +20.0° (*c*=1.00, $CHCl_3$)) and methyl [6*S*-(6α,7β,7aβ)]-tetrahydro-3-oxo-6-(phenylsulfanyl)methyl-1*H*,3*H*-pyrrolo[1,2-*c*]oxazole-7-acetate (**8**) ($[\alpha]_D^{22}$ -18.8° (*c*=1.54, $CHCl_3$)), which were identical with the racemic products ((±)-**7**) and ((±)-**8**), respectively, by comparison of their spectral data.

Methyl [6*S*-(6α,7β,7aβ)]-6-Formyl-tetrahydro-3-oxo-1*H*,3*H*-pyrrolo[1,2-*c*]oxazole-7-acetate (14) A solution of *m*-chloroperbenzoic acid (mCPBA) (635 mg (70% assay), 2.6 mmol) in methylene dichloride (120 mL) was added dropwise over 3 h at 0°C to a stirred solution of [6*S*-(6α,7β,7aβ)]-**8** (827 mg, 2.6 mmol) in methylene dichloride (36 mL). After addition of water, the reaction mixture was extracted with methylene dichloride. The extract was washed with saturated aqueous sodium

bicarbonate, dried and concentrated to give a residue which was purified by MPCC (*n*-hexane-ethyl acetate = 1 : 1) to give the [6*S*-(6α,7β,7aβ)]-sulfoxide (717 mg, 82%) as pale yellow oil. A solution of trifluoroacetic anhydride (0.22 mL, 1.60 mmol) in acetonitrile (4 mL) was added dropwise with stirring at 0°C to a solution of the [6*S*-(6α,7β,7aβ)]-sulfoxide (269 mg, 0.80 mmol) and γ-collidine (0.32 mL, 2.40 mmol) in acetonitrile (13 mL). After the reaction mixture was stirred at 0° C for 1 h, γ-collidine (0.32 mL, 2.40 mmol) and a solution of trifluoroacetic anhydride (0.22 mL, 1.60 mmol) in acetonitrile (4 mL) were added successively to the reaction mixture and the reaction mixture was stirred at 0℃ for 1 h. An aqueous solution (17 mL) of sodium bicarbonate (813 mg, 9.68 mmol) was added to the reaction mixture which was stirred at rt for 3 h and concentrated under reduced pressure. The resulting mixture was diluted with water and extracted with methylene dichloride. The extract was dried and concentrated to give a residue which was purified by MPCC (*n*-hexane-ethyl acetate = 1 : 1) to give the [6*S*-(6α,7β,7aβ)]-aldehyde (**14**) (106 mg, 59%) as pale yellow oil. IR : 1740 (NCOO + COO + CHO) cm^{-1}. ^{1}H-NMR (200 MHz) δ : 2.42-2.75 (3H, m, 7-H, 7-CH_2), 2.94 (1H, m, 6-H), 3.50 (1H, dd, *J*=12, 10 Hz, 5-H), 3.70 (3H, s, OMe), 3.83 (1H, br td, *J*=8, 4 Hz, 7a-H), 3.96 (1H, dd, *J*=12, 6 Hz, 5-H), 4.42 (1H, dd, *J*=8, 4 Hz, 1-H), 4.56 (1H, t, *J*=8 Hz, 1-H), 9.64 (1H, d, *J*=3 Hz, CHO). HRMS *m/z* : Calcd for $C_{10}H_{13}NO_5$ (M^+) 227.0793. Found : 227.0814. $[\alpha]_D^{23}$ -20.9°(*c*=1.24, $CHCl_3$).

Oxidation of [6*R*-(6α,7α,7aα)]-7 and Subsequent Pummerer Rearrangement According to the procedure given for the [6*S*-(6α,7β,7aβ)]-sulfoxide, oxidation of the [6*R*-(6α,7α,7aα)]-**7** (314 mg, 0.98 mmol) with mCPBA (241 mg (70% assay), 0.98 mmol) gave the [6*R*-(6α,7α,7aα)]-sulfoxide (257 mg, 78%) as pale yellow oil. According to the procedure given for the [6*S*-(6α,7β,7aβ)]-aldehyde (**14**), Pummerer rearrangement of the [6*R*-(6α,7α,7aα)]-sulfoxide (160 mg, 0.47 mmol) with trifluoroacetic anhydride (0.26 mL, 1.88 mmol) and γ-collidine (0.4 mL, 2.82 mmol) followed by treatment of the resulting acetal with sodium bicarbonate (484 mg, 5.76 mmol) at 0 ℃ gave the crude [6*R*-(6α,7α,7aα)]-aldehyde (**13**). ^{1}H-NMR (200 MHz) δ : 2.42-2.75 (4H, m, 6-H, 7-H, 7-CH_2), 3.56 (1H, dd, *J*=12, 4 Hz, 5-H), 3.70 (1H, m, 7a-H), 3.72 (3H, s, OMe), 3.86 (1H, dd, *J*=12, 8 Hz, 5-H), 4.25 (1H, dd, *J*=8, 4 Hz, 1-H), 4.50 (1H, dd, *J*=8, 6 Hz, 1-H), 9.83 (1H, d, *J*=1 Hz, CHO). On purification of the crude aldehyde (**13**) by MPCC (*n*-hexane-ethyl acetate = 1 : 1), the [6*S*-(6α,7β,7aβ)]-aldehyde (**14**) (69 mg, 64%) was obtained as a result of isomerization at the 6-position in **13**. The [6*S*-(6α,7β,7aβ)]-aldehyde (**14**) was identical with the authentic sample, prepared from (-)-**8**, by comparison of their spectral data.

Methyl [6*S*-(6α,7β,7aβ)]-Tetrahydro-6-(1-hydroxyethyl)-3-oxo-1*H*,3*H*-pyrrolo[1,2-*c*]-oxazole-7-acetate (15) A 1.2 M solution of MeMgBr in THF (0.25 mL, 0.3 mmol) was slowly added with stirring at 0°C to a solution of the aldehyde (**14**) (35 mg, 0.15 mmol) in THF (6 mL). After the reaction mixture was stirred at 0°C for 3 h, a saturated aqueous solution of ammonium chloride was added and the mixture was extracted with methylene dichloride. The organic phase was dried and

concentrated to give a residue which was purified by MPCC (*n*-hexane-ethyl acetate = 2 : 1) to give a 1 : 2 diastereomeric mixture of the alcohol (**15**) (13 mg, 35%) as pale yellow oil. IR : 3437 (OH), 1740 (NCOO + COO) cm^{-1}. ^{1}H-NMR (300 MHz) δ : 1.21 (1H, d, *J*=7 Hz, Me), 1.22 (2H, d, *J*=7 Hz, Me), 3.68 (1H, s, OMe), 3.69 (2H, s, OMe). HRMS *m/z* : Calcd for $C_{11}H_{17}NO_5$ (M^+) 243.1106. Found : 243.1125.

Methyl [6*S*-(6α,7β,7aβ)]-6-Acetyltetrahydro-3-oxo-1*H*,3*H*-pyrrolo[1,2-*c*]oxazole-7-acetate (16) Pyridinium chlorochromate (PCC) (53 mg, 0.24 mmol) was added with stirring at rt to a solution of the alcohol (**15**) (30 mg, 0.12 mmol) in methylene dichloride (12 mL). The reaction mixture was stirred for 2 h and and the solvent was evaporated at rt under reduced pressure to give a residue. A suspension of the residue in Et_2O was filtered through a pad of Florisil and the solvent was evaporated to give a residue which was purified by MPCC (*n*-hexane-ethyl acetate = 2 : 1) to give the ketone (**16**) (26 mg, 86%) as pale yellow oil. IR : 1751 (NCOO + COO + CO) cm^{-1}. ^{1}H-NMR (200 MHz) δ : 2.23 (3H, s, COMe), 2.37 (1H, dd, *J*=17, 10 Hz, C*H*-COOMe), 2.53-2.63 (2H, m, C*H*-COOMe, 7-H), 3.06 (1H, m, 6-H), 3.56 (1H, dd, *J*=12, 10 Hz, 5-H), 3.68 (3H, s, OMe), 3.75 (1H, dd, *J*=12, 6 Hz, 5-H), 3.81 (1H, td, *J*=8, 4 Hz, 7a-H), 4.44 (1H, dd, *J*=9, 4 Hz, 1-H), 4.55 (1H, dd, *J*=9, 8 Hz, 1-H). HRMS *m/z* : Calcd for $C_{11}H_{15}NO_5$ (M^+) 241.0936. Found : 241.0950. $[\alpha]_D^{20}$ -10.6° (*c*=1.88, $CHCl_3$). [lit.,[9] $[\alpha]_D$ -17.9° (*c*=1.1, $CHCl_3$)].

Methyl [6*R*-(6α,7β,7aβ)]-Tetrahydro-6-(1-methylethenyl)-3-oxo-1*H*,3*H*-pyrrolo[1,2-*c*]-oxazole-7-acetate (17) A 0.5 M solution of potassium bis(trimethylsilyl)amide in toluene (0.5 mL, 0.25 mmol) was added at 0°C to a stirring suspension of methyltriphenylphosphonium bromide (100 mg, 0.28 mmol) in toluene (2 mL). After the reaction mixture was stirred at 0°C for 30 min, a solution of the ketone (**16**) (26 mg, 0.11 mmol) in toluene (2 mL) was added to the reaction mixture. The reaction mixture was kept at 0°C for 40 min. After addition of a saturated aqueous solution of ammonium chloride, the reaction mixture was extracted with methylene dichloride. The organic phase was washed with water, dried and concentrated to give a residue which was purified by MPCC (*n*-hexane-ethyl acetate= 3 : 1) to give the isopropenyl compound (**17**) (25 mg, 98%) as pale yellow oil. IR : 1740 (NCOO + COO) cm^{-1}. ^{1}H-NMR (300 MHz) δ : 1.71 (3H,br s, Me), 2.04-2.26 (2H, m, 7-H + 7-CH), 2.57 (1H, dd, *J*=15, 3 Hz, 7-CH), 2.72 (1H, br q, *J*=10 Hz, 6-H), 3.41 (1H, dd, *J*=11, 10 Hz, 5-H), 3.44 (1H, dd, *J*=11, 9 Hz, 5-H), 3.67 (3H, s, OMe), 3.78 (1H, td, *J*=8, 4 Hz, 7a-H), 4.40 (1H, dd, *J*=9, 4 Hz, 1-H), 4.52 (1H, dd, *J*=9, 8 Hz, 1-H), 4.85 (1H, br s, C=CH), 4.88 (1H, br s, C=CH). HRMS *m/z* : Calcd for $C_{12}H_{17}NO_4$ (M^+) 239.1138. Found : 239.1157. $[\alpha]_D^{20}$ +2.0°(*c*=0.99, $CHCl_3$). [lit.,[9] $[\alpha]_D$ +4.0°(*c*=1.0, $CHCl_3$)].

Methyl [2*S*-(2α,3β,4α)]-2-Hydroxymethyl-1-methoxycarbonyl-4-(1-methylethenyl)-3-pyrrolidineacetate (18) Sodium (46 mg, 2 mmol) was dissolved in anhydrous methanol (2 mL).

To the solution was added with stirring at rt a solution of the oxazolidinone (**17**) (6 mg, 0.026 mmol) in anhydrous methanol (1 mL). The resulting solution was stirred at rt for 2.5 h and then diluted with saturated aqueous ammonium chloride and extracted with methylene dichloride. The extract was washed, dried, and concentrated to give a residue which was purified by MPCC (*n*-hexane-ethyl acetate = 1 : 1) to give the carbamate (**18**) (6 mg, 88%) as pale yellow oil. IR : 3445 (OH), 1733 (COO), 1678 (NCOO) cm^{-1}. ^{1}H-NMR (300 MHz) δ : 1.70 (3H, br s, Me), 2.26 (1H, m, 3-H), 2.38-2.48 (3H, m, 3-CH_2, 4-H), 3.16 (1H, t, *J*=11 Hz, 5-H), 3.65 (3H, s, OMe), 3.72 (3H, s, OMe), 3.58-3.88 (4H, m, 2-H, 5-H, 2-CH_2), 4.85 (1H, br s, C=CH), 4.88 (1H, br s, C=CH). HRMS *m/z* : Calcd for $C_{13}H_{21}NO_5$ (M^+) 271.1414. Found : 271.1418. $[\alpha]_D^{25}$ -20.8°(*c*=0.24, $CHCl_3$) (lit.,[12] $[\alpha]_D^{29}$ -31.7°(*c*=0.71, $CHCl_3$)).

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