Trials for the Synthesis of *(R)*-4-Mercapto-pyrrolidin-2-one (*(R)*-MPD)

Satoshi Kobayashi, Katsuhiro Kobayashi, Koichi Hirai*

Process Development Laboratories, Sankyo Co., Ltd. No.173, Nakahara-Kamijuku, Hiratsuka-shi, Kanagawa 254-0071, Japan

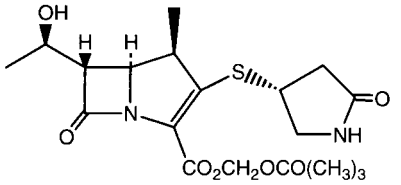
Fax +81(463)316525; E-mail: khirai@hira.sankyo.co.jp

Received 9 February 1999

Abstract: Several trials were made for the syntheses of *(S)*-4-hydroxy-pyrrolidin-2-one (*(S)*-HPD) and *(R)*-4-mercapto-pyrrolidin-2-one (*(R)*-MPD), a substituent at the 2-position of the orally active carbapenem antibiotic CS-834. The latter was synthesized from prochiral dimethyl or diethyl 3-*p*-methoxybenzylthioglutarate using pig liver esterase technology to give monoester with an optical purity of 51-71% *e.e.* as a key intermediate.

Key words: γ-lactam formation, 4-mercapto-pyrrolidone, pig liver esterase, intramolecular Schmidt reaction, Curtius rearrangement, 4-hydroxy-pyrrolidone, CS-834

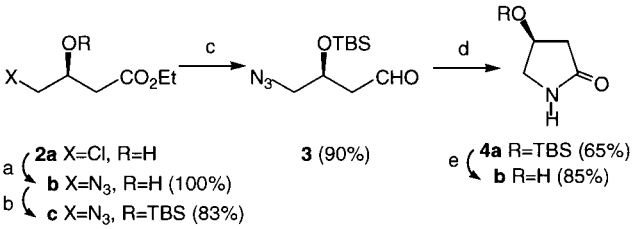
The considerable amount of research in the field of carbapenem antibiotics has led to the serial launch of Thienam®, Carbenin® and Meropenem® in the market as highly effective injections. On the other hand, current interest in the research and development of the 1-ß-methylcarbapenem derivative for oral administration has encouraged medicinal chemists to find a couple of promising candidates[1] including the original Sankyo compound, CS-834(**1**).[2]



CS-834 (1)

In this paper we would like to report our efforts to synthesize the optically active *(R)*-4-mercapto-pyrrolidin-2-one (*(R)*-MPD)(**14**) and *(S)*-4-hydroxy-pyrrolidin-2-one (*(S)*-HPD)(**4b**) which is a direct precursor of *(R)*-MPD, the substituent at the 2-position of CS-834 (**1**). Presently *(S)*-HPD is commercially available and a method applicable for its large scale production has been patented already from our laboratories.[3] During the synthetic study of these two molecules many other trials have been made from different aspects, and here we would like to report some of our results.

At the bench scale *(S)*-HPD (**4b**) was made from *(S)*-hydroxy-GABA.[4] The patent method from our laboratories starts from ethyl *(S)*-4-chloro-3-hydroxybutyrate (**2a**) as follows: NaN_3 treatment in DMF to give azide derivative **2b** was followed by hydrogenation on Pd/C to afford the corresponding 4-amino derivative, which was heated in methanol to lactonize into the desired *(S)*-HPD (**4b**). Along these lines we focused our attention on the intramolecular Schmidt reaction to form the lactam ring.[5] Therefore we reduced the azide derivative (**2c**) to aldehyde **3** in 90% yield with DIBAL in *n*-hexane at -78 °C, and then treated this aldehyde **3** with 1.1 *eq.* of $TiCl_4$ to afford *(S)*-TBS-HPD (**4a**) in 65% isolated yield. Removal of the TBS protecting group was performed under acidic conditions to give the expected *(S)*-HPD (**4b**), mp 157 °C, satisfactorily (Scheme 1).

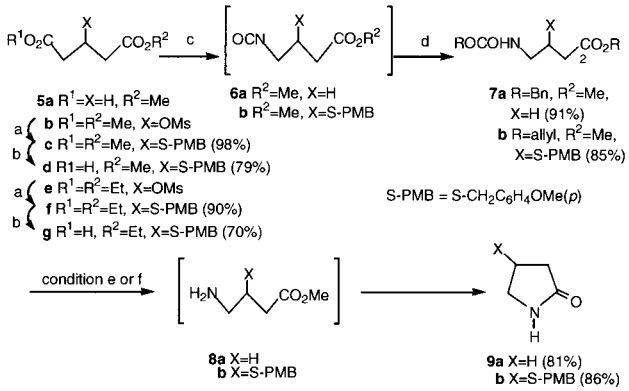


Scheme 1 Conditions: a) NaN_3, DMF, 100 °C, 3 h. b)TBS-Cl, imidazole, DMF, 25 °C, 14 h. c) DIBAL, *n*-hexane, -78 °C, 15 min. d) $TiCl_4$, CH_2Cl_2, -20 °C, 1 h. e) H^+

Another approach used a chemoenzymatic methodology. At the beginning of the work we checked a route to prepare γ-lactam (**9a**) from glutaric acid as a simple model. Monomethyl glutarate **5a** was converted to the urethane derivative **7a** in 91% yield via isocyanate intermediate **6a** (Curtius rearrangement reaction)[6] by treating **5a** with DPPA (diphenylphosphoryl azide) in toluene and benzyl alcohol successively. The benzylic protective group was easily removed under hydrogenolytic conditions to amine **8a**, and then to γ-lactam **9a** smooth heating the methanol solution to 60 °C.

Next, our trial was commenced with dimethyl 3-*p*-methoxybenzylthio (3-PMB-S)-glutarate **5c**. Firstly, commercially available dimethyl 3-hydroxyglutarate was mesylated with methanesulfonyl chloride (1.05 *eq.*) in pyridine to give the mesylate **5b** in 93% isolated yield. The *O*-mesyl part was substituted by *p*-methoxybenzyl mercaptan (PMB-SH) in the presence of NaH in THF to the desired PMB-S dimethyl ester **5c** in 98% yield. Then, dimethyl ester **5c** was carefully hydrolyzed with 1 *eq.* KOH in $MeOH/H_2O$ to the monomethyl ester **5d**. Compound **5d** was treated with DPPA under the same conditions as the above described methyl glutarate **5a** case to give isocyanate **6b**, which was smoothly reacted with benzyl alcohol to the benzyloxycarbonyl (Z-) protected com-

pound. In the Curtius rearrangement reaction some unknown byproduct was detected at the same R_f position on TLC in about 20% yield. Furthermore deprotection under hydrogenolytic conditions using Pd/C or PtO_2 was unsuccessful with the starting *Z*-protected material being recovered. Therefore, we took advantage of the conventional method to access the target amine **8b**. Under ice-cooling, half ester **5d** was treated with Et_3N (1.2 *eq.*) and $ClCO_2Et$ in acetone (x 20vol) for 30 min to give the mixed anhydride which was then reacted with *aq.* NaN_3 (1.5 *eq.*) for 1 h at the same temperature. The acylazide thus formed was extracted with dichloromethane three times. After usual work-up the next Curtius rearrangement was performed in toluene solution at 105 °C for 1.5 h, then reacted with allyl alcohol to the allyl urethane derivative **7b**. Under the mild deprotection conditions using palladium acetate (condition f)[7] the allyl protective group in **7b** was smoothly removed to amine **8** and then to the γ-lactam **9b** successfully (Scheme 2).



Scheme 2 Conditions: a) *p*-Methoxybenzyl mercaptan, NaH, THF, room temperature, 2.5 h. b) KOH, MeOH (**5c**) or KOH, EtOH (**5f**), 75 °C, 1 h. c) Diphenylphosphoryl azide, Et_3N, Toluene, 100 °C, 1 h. or $ClCO_2Et$, Et_3N, acetone, 0 °C, 30 min then NaN_3, H_2O, 0 °C, 1 h: Toluene, 110 °C, 2 h. d) benzyl alcohol or allyl alcohol 110 °C, 5h. e) H_2, 10% Pd-C, MeOH, room temperature, 3 h then 60 °C, 4 h. f) $Pd(OAc)_2$, PPh_3, HCO_2H, Et_3N, THF, 80 °C, 30 min.

With this seemingly minor, but actually serious problem solved in the *dl* form we could direct our attention to the investigation of the enzymatic conversion methodology.[8] The PMB-S dimethyl ester **5c** was hydrolyzed with pig liver esterase (PLE) in phosphate buffer to yield the optically active half ester **10a** *albeit* in moderate *e.e.* The results of the conversion and enantiomeric excess (*e.e.*) of this reaction are summarized in Table 1. The best result was 81% conversion with 71% *e.e.* (entry 10) using diethyl ester **5f**. The direct determination of the *e.e.* of the product was unsuccessful by the chiral HPLC method. Therefore, every product was subjected to the amido-formation reaction with *(S)*-(-)-1-phenylethylamine followed by HPLC analysis (CHIRALPAK AD column).

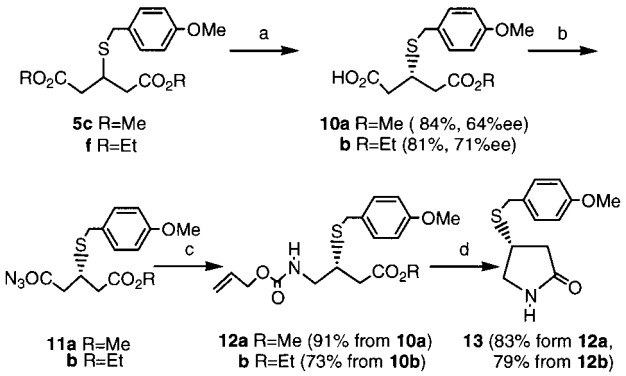
The absolute configuration was proved to be *S*. This was also proved to be correct by converting **10a** or **10b** to compound **13** by the allyl deprotection method (condition f**)** depicted in Scheme 2 (Scheme 3). In this case the standard sample was prepared by benzylation of authentic *(R)*-4-mercapto-pyrrolidin-2-one (**14**) with PMB-Cl.

Table 1 Results of Enantioselective Hydrolysis of Diesters of **5** by PLE [a]

Entry	R	Solvent [b]	pH	Temp (°C)	Time (hr)	Conversion Yield (%)	Absolute Config. [d]	*e.e.* [e] (%)
1	Me	P. B. (100vol.)	7	25	6	98	*S*	54
2	Me	P. B. (100vol.)	7	21	6	97	*S*	57
3	Me	P. B. (100vol.)	7	30	6	97	*S*	52
4	Me	P. B. (200vol.)	7	25	6	96	*S*	56
5	Me	P. B. (100vol.)	6	25	6	55	*S*	60
6	Me	P. B. (100vol.)	8	25	6	89	*S*	51
7	Me	P. B. (100vol.)	7	5	9.5	84	*S*	64
8	Me	P. B. (100vol.)	6	5	6	85	*S*	65
9	Me	P. B. (100vol.) [c]	7	25	6	70	*S*	53
10	Et	P. B. (100vol.)	6	5	52	81	*S*	71
11	Et	P. B. (100vol.)	7	5	48	61	*S*	71

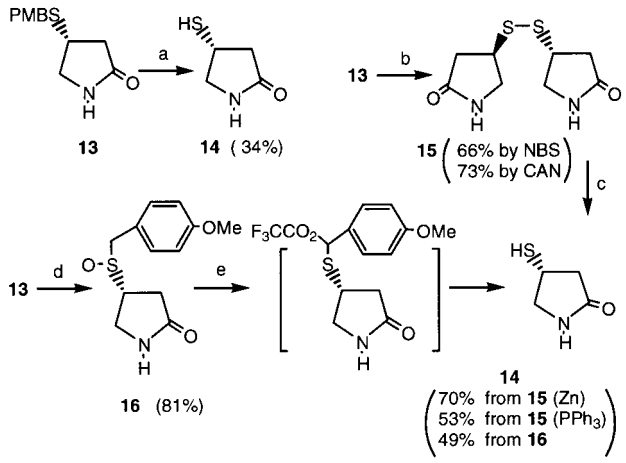
[a]PLE: Pig Liver Esterase (EC 3.1.1.1) from Fluka; Suspension in 3.2 M ammonium sulfate solution; ~103 U/mg (10mg/ml). [b]All experiments were run in the phosphate buffer (P.B.) and followed by titration with 1*N* NaOH, using a pH-stat apparatus. [c]0.3% MeOH was added. [d]Absolute configuration was determined by HPLC analysis (CHIRALPAK AD by Daicel) of the 4-*p*-methoxybenzylthio-pyrrolidin-2-one derivative (**13**). [e]Determined by HPLC analysis after conversion of the mixture of the enantiomeric half esters into the mixture of the diastereomeric amides with *(S)*-(-)-1-phenylethylamine.

Removal of the *p*-methoxybenzyl protective group was successfully achieved by a CF_3CO_2H and CF_3SO_3H combination in the presence of anisole to give the optically active target molecule in 34% yield (Scheme 4). Other methods of oxidative removal of this protective group were also assessed. Oxidation to sulfoxide **16** by *m*CPBA was performed without any problems in 81% yield. Next, Pummerer reaction of **16** with trifluoroacetic anhydride and collidine for 1 h in THF and work up with 3% *aq.* $NaHCO_3$ gave the desired *(R)*-4-mercapto-pyrrolidin-2-one(**14**) in 49% yield.



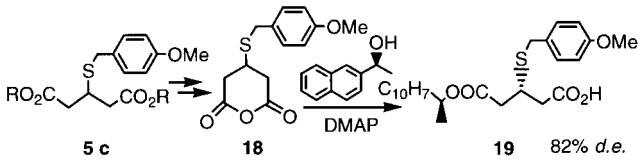
Scheme 3 Conditions: a) Pig Liver Esterase, 0.1M Phospate buffer. b) $ClCO_2Et$, Et_3N, acetone, 0 °C, 30 min then NaN_3, H_2O, 0 °C, 1 h. c) allyl alcohol, Toluene, 110 °C, 7h. d) $Pd(OAc)_2$, PPh_3, HCO_2H, Et_3N, THF, 80 °C, 30 min.

On the other hand, both oxidative deprotections using NBS in dichloro methane /H_2O or CAN in acetonitrile/ H_2O gave the disulfide **15** in 66 and 73% isolated yield respectively. The S-S bond could be cleaved efficiently to the target mercaptan **14** by Zn dust in acetic acid or triphenylphosphine treatment in dioxane.



Scheme 4 Conditions: a) CF_3CO_2H, CF_3SO_3H, anisole, room temperature, 2 h. b) NBS, CH_2Cl_2, H_2O, room temperature, 2 h. or CAN, MeCN, H_2O, room temperature, 5 h. c) Zn dust, Toluene, AcOH, 110 °C, 3.5 h. or PPh_3, dioxane, H_2O, 100 °C, 12 h. d) *m*-CPBA, CH_2Cl_2, 0 °C, 30 min. e) $(CF_3CO)_2O$, collidine, THF, 0 °C, 1.5 h.

At this stage our interest was turned to the diastereoselective differentiation of the anhydride **18** by *(S)*-2-naphthylethanol as a comparison with the above PLE hydrolysis methodology. Evans and Black[9] traced the work of the Heathcock group,[10] in which symmetry-breaking enantioselective transesterification of 3-(*t*-butyldimethyl silyloxy)-pentanedioic anhydride with *(S)*-2-naphthylethanol was reported to provide a 34:1 diastereomeric mixture after 6 days at -60 °C. Using the reported procedure by Heathcock,[10] we prepared the requisite anhydride **18** from dimethyl ester **5c**. Enantioselective ring opening of this anhydride **18** in dichloromethane afforded the *(S)*-PMB-S derivative **19** with 82% *d.e.* after 10 days (Scheme 5). Determination of the *d.e.* of product **19** was unsuccessful by direct separation using HPLC. Derivatization to the methyl ester was found to be suitable for satisfactory separation using CHIRALPAK AD. From these results it is clear that no substantial difference was observed between the enzymatic and chemical reaction towards 3-PMB-S glutarate derivatives.



Scheme 5

Acknowledgement

The authors are grateful to Dr. T. Takebayashi for the fruitful discussion and to Miss S. Endo for her technical assistance.

References and Notes

(1) **Tribactams**:. Rossi, T.; Biondi, S.; Contini, S.; Thomas, R. J.; Marchioro, C. *J. Am. Chem. Soc*., **1995**, *117*, 9604. Ghiron, C.; Rossi, T. *Targets in Heterocyclic Systems* (Italian Society of Chemistry), **1997**, *1*, 161. G. Gaviraghi, *Eur. J. Med. Chem*., **1995**, 30 (Supplement), 467. **DZ-2640**: Nishi, T.; Ishida, Y.; Sugita, K.; Ohtsuka, M.; Takemura, M.; Hayakawa, I., Hayano, T. *35th Intersci. Conf. Antimicrob. Agents Chemother*. (Sept 17-20, San Francisco), **1995**, Abst. F-133. **L-084**: Abe, T.; Hayashi, K.; Mihira, A.; Satoh, C.; Tamai, S.; Yamamoto, S.; Hikida, M.; Kumagai, T.; Kitamura, M. *38th Intersci. Conf. Antimicrob. Agents Chemother*., (Sept 24-27, San Diego), **1998**, Abst. F-64. **TA-949**: Seki, M.; Kondo, K.; Iwasaki, T. *13th French-Japanese Symposium on Medicinal and Fine Chemistry* (May 25-28, Hayama), **1998**, Abst. *P*-12.

(2) Kawamoto, I.; Miyauchi, M.; Endo, R.; Hisaoka, M.; Yasuda, H.; Kuwahara, S. *36th Intersci. Conf. Antimicrob. Agents Chemother*., (New Orleans), **1996**, Abst. F-105. Miyauchi, M.; Endo, R.; Hisaoka, M.; Yasuda, H.; Kawamoto, I. *J. Antibiot*., **1997**, *50*, 429.

(3) Kobayashi, K.; Fukuhara, H.; Takebayashi, T.; Kawamoto, I. *Japan Kokai Tokkyo Koho* JP 96-119935, May 14, **1996** (Priority Claim, Aug. 31, **1994**).

(4) *(S)*-hydroxy-GABA is now commercially available from DAISO Co., Ltd. (Japan). Pellegata, R.; Pinza, M.; Pifferi, G. *Synthesis*, **1978**, 614.

(5) Norris, P.; Horton, D.; Levine, B. R. *Tetrahedron Lett*., **1995**, *36*, 7811.

(6) Ninomiya, K.; Shioiri, T.; Yamada, S. *Tetrahedron*, **1984**, *30*, 2151. Ninomiya, K.; Shioiri, T.; Yamada, S. *Chem. Pharm. Bull*., **1974**, *22*, 1398.

(7) Donnelly, D. M. X.; Finet, J.-P.; Rattigan, B. A. *J. Chem. Soc*., *Perkin Trans. I*, **1993**, 1729.

(8) Nakada, M.; Kobayashi, S.; Ohno, M. *Tetrahedron Lett*., **1988**, *32*, 3951. Nakada, M.; Kobayashi, S.; Iwasaki, S.; Ohno, M. *Tetrahedron Lett*., **1993**, *34*, 1035 and references cited therein.

(9) Evans, D. A.; Black, W. C. *J. Am. Chem. Soc*., **1993**, *115*, 4497

(10) Theisen, P. D.; Heathcock, C. H. *J. Org. Chem*., **1993**, *58*, 142; *J. Org. Chem*., **1988**, *53*, 2374.

(11) Ethyl *(S)*-3-azido-2-hydroxybutyrate (**2b**): IR (film):3436, 2102, 1725 cm^{-1}. ^1H NMR ($CDCl_3$) δ: 1.28 (3H, t, *J* = 7.2 Hz), 2.54 (2H, d, *J* = 6.1 Hz), 3.30 (1H, bs), 3.35 (2H, d, *J* = 5.3Hz), 4.00-4.38 (1H, m), 4.19 (2H, q, *J* = 7.2 Hz). TLC: R_f = 0.45 (AcOEt:*n*-Hexane = 1:3). Ethyl *(S)*-3-azido-2-*t*-butyldimethylsilyloxy-butyrate (**2c**): IR (film): 2092, 1736 cm^{-1}. ^1H NMR ($CDCl_3$) δ:0.09 (3H, s), 0.13 (3H, s), 0.89 (9H, s), 1.26 (3H, t, *J* = 7.0 Hz), 2.54 (2H, d, *J* = 6.2 Hz), 3.21 (1H, dd, *J* = 12.6, 3.5 Hz), 3.40 (1H, dd, *J* = 12.6, 4.4 Hz), 4.02-4.37 (1H, m), 4.13 (2H, q, *J* = 7.0 Hz). TLC: R_f = 0.45 (AcOEt:*n*-Hexane = 1:10). *(S)*-3-Azido-2-*t*-butyldimethylsilyloxybutanal (**3**): IR (film): 2098, 1724 cm^{-1}. ^1H NMR ($CDCl_3$) δ: 0.05 (3H, s), 0.10 (3H, s), 0.89 (9H, s), 2.68 (2H, dd, *J* = 6.0, 1.8 Hz), 3.20 (1H, dd, *J* = 12.9, 5.0 Hz), 3.41 (1H, dd, *J* = 12.9, 4.4 Hz), 4.29-4.41 (1H, m), 9.80 (1H, t, *J* = 1.8 Hz). TLC: R_f = 0.40 (AcOEt:*n*-Hexane = 1:10). *(S)*-4-*t*-Butyldimethyl-silyloxypyrrolidin-2-one (**4a**): ^1H NMR ($CDCl_3$) δ: 0.07 (6H, s), 0.88 (9H, s), 2.23 (1H, dd, *J* = 17.0, 4.4 Hz), 2.57 (1H, dd, *J* = 17.0, 6.7), 3.23

(1H, dd, *J* = 9.5, 3.5 Hz), 3.59 (1H, dd, *J* = 9.5, 5.4 Hz), 4.44-4.68 (1H, m), 6.84 (1H, br). TLC: R_f = 0.40 (AcOEt).

(12) Dimethyl 3-methansulfonyloxyglutarate (**5b**): 12.03 g (0.105 mmol) of methanesulfonyl chloride was added dropwise to a solution of commercially available 17.62 g (0.100 mmol) of dimethyl 3-hydroxyglutarate in 176 ml of pyridine under ice-cooling, and stirring further 2 h at room temperature. After concentration of the solution under reduced pressure 100 ml of water were added and the product was extracted with 150 ml of CH_2Cl_2 several times. The combined CH_2Cl_2 layer was dried over $MgSO_4$. After usual work-up the residue was chromatographed on silica gel to afford 23.54 g (93%) of the compound **5b** (eluent hexane:AcOEt (6:1)). HRMS calcd for $C_{14}H_{19}O_5S$ [M^++1]: 255.0538, found: 255.0522. IR ($CHCl_3$): 2957, 1739, 1440, 1361, 1310, 1175 cm^{-1}. ^1H NMR ($CDCl_3$) δ: 2.81-2.97 (4H, m), 3.09 (3H, s), 3.72 (6H, s), 5.27-5.34 (1H, m). Dimethyl 3-*p*-methoxybenzylthioglutarate (**5c**): To a suspension of 1.728 g (72 mmol) of NaH in THF was added a solution of 10.18 g (60 mmol) of *p*-methoxybenzylmercaptan in 60 ml of THF under ice-cooling. After stirring at the same temperature for 30 min, 15.26 g (60 mmol) of dimethyl mesylate **5b** in 60 ml of THF was added. Stirring was continued for 2.5 h at room temperature and the solvent was distilled under reduced pressure. Water (200 ml) was added and the product was extracted with CH_2Cl_2 several times and the combined CH_2Cl_2 solution was dried over $MgSO_4$. After evaporation of the solvent the residue was chromatographed on silica gel to give 17.62 g (94%) of compound **5c** (eluent hexane:AcOEt (8:1)). HRMS calcd for $C_{15}H_{20}O_5S$ [M^+]: 312.1031, found:312.1054. IR ($CHCl_3$): 2955, 1736, 1611, 1586, 1512, 1438 cm^{-1}. ^1H NMR ($CDCl_3$) δ:2.59-2.70 (4H, m), 3.36-3.43 (1H, m), 3.68 (3H, s), 3.77 (2H, s), 3.79 (3H, s), 6.84 (2H, d, *J* = 8.8 Hz), 7.25 (2H, d, *J* = 8.8 Hz).

(13) Monomethyl *(S)*-3-*p*-methoxybenzylthioglutarate (**10a**): To a suspension of 3.12 g (10 mmol) of diester (**5c**) in 312 ml of 0.1 M phosphate buffer solution (500 v/w) was added 1.0 ml [103 u/mg protein (10 mg/ml)] of PLE solution, and the whole solution was stirred at 25 °C for 6 hours. During the reaction time the pH of the solution was kept at 7.0 ± 0.02 by the addition of 1 M aqueous solution of NaOH. After 6 hr the pH was adjusted at 10 and the unreacted diester was extracted with diethyl ether. The aqueous layer was fixed at pH 2.0 by 1N HCl solution and the generated monoester was extracted with diethyl ether several times. The combined organic layer was dried over $MgSO_4$ and evaporated to give the desired 2.6 g of monoester **10a**. HRMS calcd for $C_{14}H_{18}O_5S$ [M^+]: 298.0875, found: 298.0885. IR ($CHCl_3$): 3513, 2955, 1736, 1713, 1611, 1586, 1512, 1439 cm^{-1}. ^1H NMR ($CDCl_3$) δ:2.60-2.75 (4H, m), 3.34-3.41 (1H, m), 3.68 (3H, s), 3.78 (2H, s), 3.79 (3H, s), 6.84 (2H, d, *J* = 8.7 Hz), 7.24 (2H, d, *J* = 8.7 Hz).

(14) Methyl *(R)*-4-allyloxycarbonylamino-3-*p*-methoxybenzyl-thioglutarate (**12a**): To a solution of 1.194 g (4 mmol) of monomethyl *(S)*-3-*p*-methoxybenzylthioglutarate (**10a**) in 24 ml of acetone was added triethylamine (486 mg, 4.8 mmol) and ethyl chlorocarbonate (651 mg, 6.0 mmol) under ice-cooling. After stirring at the same temperature for 30 min, aqueous sodium azide (390 mg (6.0 mmol) in 4.8 ml water) was added. After 60 min the reaction mixture was poured into 200 ml of ice water and the product was extracted several times with CH_2Cl_2. The combined organic layer was dried over $MgSO_4$ and evaporated. The residue was dissolved in 24 ml of toluene and the solution was refluxed for 2 h and then 580 mg (10 mmol) of allyl alcohol were added every 30 min for 5 h under reflux. After evaporation the residue was chromatographed on silica gel (eluent hexane:AcOEt (10:1)) giving 1.291 g (91%) of compound **12a**. HRMS calcd for $C_{17}H_{23}NO_5S$ [M^+]: 353.1297, found: 353.1311. IR ($CHCl_3$): 3450, 2955, 1726, 1649, 1610, 1585, 1512, 1465, 1439 cm^{-1}. ^1H NMR ($CDCl_3$) δ: 2.50-2.62 (2H, m), 3.09-3.16 (1H, m), 3.30-3.33 (2H, m), 3.68 (3H, s), 3.74 (2H, s), 3.79 (3H, s), 4.54 (2H, d, *J* = 5.4 Hz), 5.05 (1H, br), 5.22 (1H, dd, *J* = 11.1, 1.3 Hz), 5.30 (1H, dd, *J* = 17.5, 1.3 Hz), 5.91 (1H, ddt, *J* = 17.5, 11.1, 5.4 Hz), 6.85 (2H, d, *J* = 8.7 Hz), 7.24 (2H, d, *J* = 8.7 Hz).

(15) *(R)*-4-*p*-Methoxybenzylthio-pyrrolidin-2-one (**13**): To a mixture of **12a**, palladium acetate (11 mg, 0.05 mmol), triphenylphosphine (26 mg, 0.1 mmol) in 14 ml of THF was added triethylamine (303 mg, 3.0 mmol) and formic acid (92 mg, 2.0 mmol) and the solution was refluxed for 30 min. CH_2Cl_2 (140 ml) was poured and the organic layer was washed with 100 ml of water. After drying over $MgSO_4$ and evaporation of the solvent the residue was chromatographed on silica gel to give 198 mg (83%) of the compound **13** (eluent hexane:AcOEt (1:5)). HRMS calcd for $C_{12}H_{15}NO_2S$ [M^+]: 237.0823, found: 237.0837. IR ($CHCl_3$): 3441, 2958, 1745, 1702, 1611, 1586, 1512, 1486, 1465 cm^{-1}. ^1H NMR ($CDCl_3$) δ: 2.27 (1H, dd, *J* = 17.0, 7.2 Hz), 2.59 (1H, dd, *J* = 17.0, 8.6 Hz), 3.22 (1H, dd, *J* = 10.1, 6.0 Hz), 3.35-3.42 (1H, m), 3.56 (1H, dd, *J* = 10.1, 7.2 Hz), 3.73 (2H, s), 3.80 (3H, s), 6.38 (1H, br), 6.85 (2H, d, *J* = 8.7 Hz), 7.22 (2H, d, *J* = 8.7 Hz).

(16) *(R)*-4-Mercapto-pyrrolidin-2-one (**14**): To a solution of 1.187 g (5 mmol) of *(R)*-4-*p*-methoxybenzylthio-pyrrolidin-2-one (**13**) in 5.5 ml (50 mmol) of anisole were added 12 ml of trifluoroacetic acid and 1.50 g (10 mmol) of trifluoromethanesulfonic acid successively at room temperature for 2 h. The volatiles were removed in vacuo and the residue (almost only anisole) was removed by washing with hexane. The remaining insoluble part was chromatographed on silica gel and 119 mg (34%) of compound **14** was obtained (eluent hexane:AcOEt (1:5)). IR (KBr): 3232, 2534, 1677, 1478, 1445, 1414, 1251 cm^{-1}. ^1H NMR ($CDCl_3$) δ: 1.96 (1H, d, *J* = 7.0 Hz), 2.26 (1H, dd, *J* = 17.1, 6.6 Hz), 2.75 (1H, dd, *J* = 17.1, 7.1 Hz), 3.27 (1H, dd, *J* = 9.9, 5.2 Hz), 3.55-3.70 (1H, m), 3.76 (1H, ddd, *J* = 9.9, 7.3, 0.7 Hz), 7.00 (1H, br s). $[\alpha]_D$+36.5° (c = 1.179, MeOH). mp. 69.5-70 °C.

(17) Sulfoxide (**16**): ^1H NMR ($CDCl_3$) δ: 2.30-2.90 (2H, m), 3.30 (3H, m), 3.80 (3H, s), 4.42 (2H, s), 6.90 (2H, d, *J* = 9.1 Hz), 7.22 (2H, d, *J* = 9.1 Hz). Naphtyl ester (**19**): ^1H NMR ($CDCl_3$) δ:1.60 (3H, d, *J* = 5.5 Hz), 2.62 (2H, d, *J* = 6.5 Hz), 2.67 (2H, d, *J* = 7.5 Hz), 3.2-3.6(1H, m), 3.71 (3H, s), 6.08 (1H, q, *J* = 6.0 Hz), 6.69 (2H, d, *J* = 9.1 Hz), 7.10 (2H, d, *J* = 9.1 Hz), 7.30-7.95 (7H, m), 8.20 (1H, br).

Article Identifier:
1437-2096,E;1999,0,S1,0909,0912,ftx,en;W07099ST.pdf