A Synthesis of a Versatile Intermediate Leading to Thienamycin Analogs[1)]

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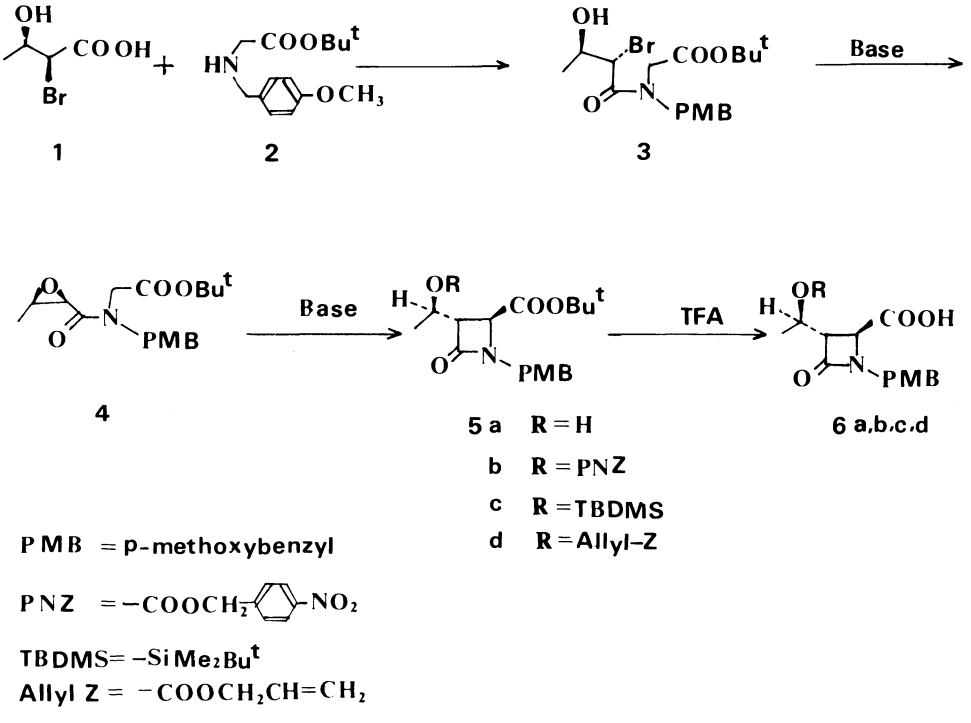
L-Threonine was converted to a versatile azetidinone derivative stereospecifically in 3 steps. This azetidinone was further transformed to (3*S*,4*R*)-3-[(*R*)-1-hydroxyethyl]-1-(4-methoxybenzyl)-4-[(phenylthio)-carbonylmethyl]-2-azetidinone (*S*-Phenyl thioester), a key intermediate for the synthesis of thienamycin and it's biologically active analogs. Since the thiol part of this *S*-phenyl thioester can be exchanged easily with other complex or useful thiols under mild conditions, important *S*-thioester precursors for the production of carbapenem analogs were obtained in high yield.

After the discovery of thienamycin,[2)] various analogs of 1-carbapenem antibiotics have been found and attracted many organic chemists to synthesize these compounds, as a result of which several synthetic methods have been reported.[3)] Recently the cyclization reaction for the formation of the carbapenem nucleus has been disclosed utilizing the trialkoxyphosphoranylidene-substituted *S*-thioester reaction,[4)] which is one of a number of versatile methods for the synthesis of carbapenem analogs. Thus the *S*-thioester of 4-carboxymethyl-2-azetidinone became an important intermediate in this route.

We have reported stereocontrolled syntheses of chiral and racemic intermediates (2-azetidinones) for thienamycin from D-*allo*-threonine,[5b)] *trans*-crotonic acid and L-threonine.[5)] This report describes the stereoselective synthesis of a precursor for thienamycin analogs (*S*-thioesters) from L-threonine by a stereocontrolled method.

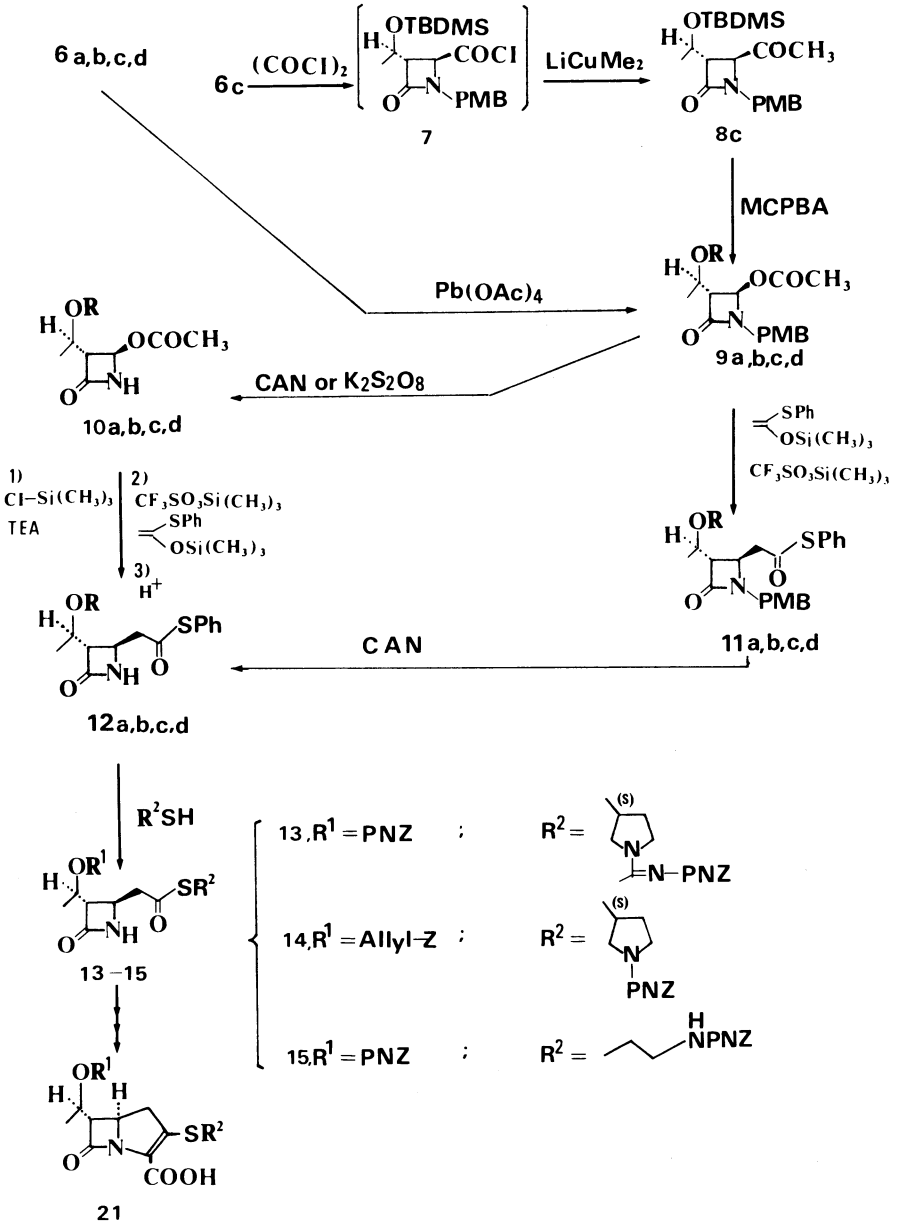
(2*S*,3*R*)-2-Bromo-3-hydroxybutyric acid (**1**) was derived in high yield from L-threonine according to a known method.[6)] The butyric acid **1** was condensed with *N*-(4-methoxybenzyl)glycine *t*-butyl ester (**2**) to give the amide **3**. The amine **2** was synthesized from *t*-butyl bromoacetate and 4-methoxybenzylamine. The compound **3** was purified by silica-gel chromatography and then converted in good yield to the *cis*-epoxy amide **4** by treating with 1.05 equiv of lithium hexamethyldisilazide in tetrahydrofuran (THF). Without isolation, this epoxy amide **4** was cyclized



Scheme 1.

with lithium hexamethyldisilazide (1.05 equiv) in THF to give *t*-Butyl (2*S*,3*S*)-3-[(*R*)-1-hydroxyethyl]-1-(4-methoxybenzyl)-4-oxo-2-azetidinecarboxylate (**5a**) in 63.9% yield from the amide **3**. If necessary, this epoxy amide can be isolated as a stable intermediate.

As mentioned in the previous paper,[5b] when cyclization reaction was carried out at −78 °C, the reaction products contained cis-isomer as a minor product. But when the same reaction was run at 20—23 °C only one product of *trans*-**5a** was obtained without containing the cis-isomer, suggesting a kinetic control is operating. Thus in the compound **5a** the stereochemistry at the 3 and 4 position of the β-lactam and the side chain is exactly correct for thienamycin. These exact configurations were only attained through the epoxide **4** by the double inversion at the compound **3**. The hydroxyl function of **5a** was protected by appropriate groups such as *p*-nitrobenzyloxycarbonyl, *t*-butyldimethylsilyl, and allyloxycarbonyl group. The de-esterification of **5a**, **b**, **d** was carried out by treating with trifluoroacetic acid (TFA) at 0 °C, to give the corresponding free acid **6a**, **b**, **d** in quantitative yield. However the *t*-butyldimethylsilyl group of **5c** was not stable to TFA due to partial desilylation, so **5c** was de-esterified with sodium hydroxide (1.0 equiv) in ethanol. These



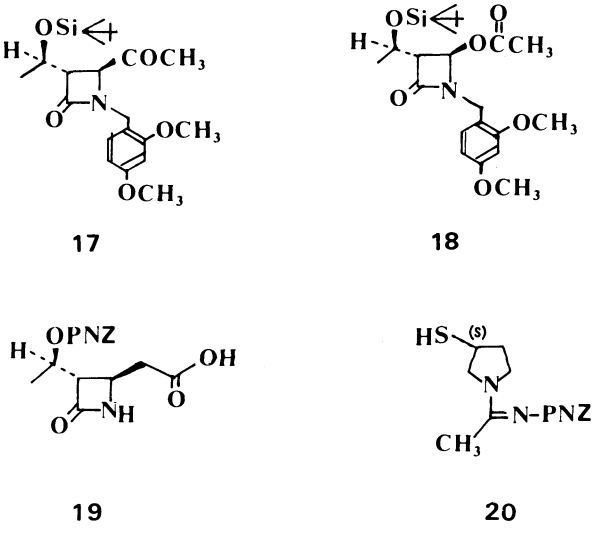
Scheme 2.

carboxylic acids were converted to 4-acetoxy-2-azetidinone derivatives by two methods: (i) The Baeyer-Villiger method[7] after conversion of the carboxylic acid to the acetyl group and (ii) the lead tetraacetate method.[8]

The carboxylic acid **6c** was converted with oxalyl di-chloride to the acid chloride **7** which was transformed into 4-acetyl derivative **8c** by reaction with lithium dimethylcuprate (I). By the Baeyer-Villiger reaction of **8c** with *m*-chloroperbenzoic acid (MCPBA), 4-acetoxy-2-azetidinone **9c** was obtained quantitatively. In this reaction the 3,4-*trans*-2-azetidinone derivative **9c** was formed selectively with retention of configuration as reported by Mislow and Brenner.[9] When this Baeyer-Villiger reaction was carried out starting from *N*-(2,4-dimethoxybenzyl) derivative **17**, no desired product **18** was obtained due to oxidation of the 2,4-dimethoxybenzene moiety. The same compound **9c** was also produced by treatment of **6c** with lead tetraacetate in *N,N*-dimethylformamide (DMF)–acetic acid.[10] Similarly, the carboxylic acids **6a**, **6b**, and **6d** gave the acetoxy derivatives **9a**, **9b**, and **9d**, respectively, by the same reaction in good yields. When starting from **6a**, a trace amount of the 3,4-cis isomer of **9a** was isolated. Removal of the *N*-protecting group of **9b,c,d** was achieved by treatment with cerium (IV) ammonium nitrate (CAN) or potassium peroxodisulfate ($K_2S_2O_8$) in good yield to afford **10b,c,d** respectively, which were identified by comparison with authentic samples. The same deprotection reaction by electrolysis seemed to be possible but tried without success (Pt or graphite as electrodes). The acetate **10b, c, d** were converted to the *S*-thioesters **12b, c, d** in quantitative yield by reaction with 1-phenylthio-1-trimethylsiloxyethylene in dichloromethane in the presence of trimethylsilyl trifluoromethanesulfonate as catalyst after trimethylsilylation of the N-atom.[11] The compound **9b—d** were also transformed to the 4-[(phenylthio)carbonylmethyl]-2-azetidinone derivatives **11b—d** in high yields by the same procedure. The *p*-methoxybenzyl group of **11b—d** was also removed with CAN in the same way to give the deprotected *S*-thioesters **12b—d**, respectively.

Generally *S*-thioesters such as **15** were synthesized by the condensation of thiol (**20**) and carboxylic acid (**19**) which was obtained, for example by reaction of the 4-acetoxy derivative **10b** with 1,1-bis(trimethylsiloxy)ethylene in the presence of a catalytic amount of trimethylsilyl trifluoromethanesulfonate. However, the yield of this condensation was unsatisfactory due to interaction of the triflate with the nitrogen part of the thiol **20**. Thus *S*-thioester exchange of **12** was tried and found to proceed under mild conditions to furnish many kind of useful *S*-thioesters, which were difficult to synthesize by the usual condensation reaction of an acid and thiol using dicyclohexylcarbodiimide. For example, in the case of the thiol **20** the reaction with **12b** proceeded smoothly in dichloromethane at room temperature in the presence of triethylamine to give the *S*-thioester **13**. This exchange reaction may be controlled by the acidity and nucleophilicity of the thiols, which is closely connected with the equilibrium constant. The compound **13** was already transformed to the carbapenem **21** by the cyclization using trialkyl phosphite.[4]

Thus we succeeded in finding a very simple method for the synthesis of the useful *S*-thioester derivatives. It seems that by this method several problems for the total synthesis of the trienamycin analogs were resolved. This *S*-thioester exchange method is useful and versatile together with an application of the previously reported cyclization by a new Wittig reaction.[4]



Scheme 3.

Experimental

All melting points were uncorrected. Optical rotation were obtained using a Perkin-Elmer 241 Polarimeter. ^{1}H NMR spectra were determined at 60 MHz with a Varian T-60 spectrometer using tetramethylsilane as internal standard. The IR absorption spectra were determined on a Jasco IR A-2 spectrophotometer. Preparative TLC was performed on silica-gel plate (Merk 60 PF254). Elemental analyses were performed by the Analytical Center of the Analytical and Metabolic Research Laboratories, Sankyo Company, Limited.

(2S,3R)-N-(4-Methoxybenzyl)-N-(t-butoxycarbonylmethyl)-2-bromo-3-hydroxybutyramide (3). To a stirred solution of (2*S*,3*R*)-2-bromo-3-hydroxybutyric acid **1** (50.96 g, 0.278 mol) were added amine **2** (70.14 g, 0.278 mol) in THF (1L), and *N,N'*-dicyclohexylcarbodiimide (57.3 g, 0.278 mol) at 20—30 °C with stirring. After 30 min, the precipitated urea

was filtered off and washed with a small amount of THF. The combined filtrate was evaporated, and chromatographed on silica-gel (900 g) with cyclohexane–EtOAc (2:1) to give amide **3** (81.9 g, 71.5%) as an oil; IR (Liquid) 1750, 1660 cm^{-1}; ^1H NMR ($CDCl_3$) δ=1.25 (3H, d, J=6.5 Hz), 1.40 (9H, s), 3.75 (3H, s), 3.90 (1H, d, J=3.5 Hz), 3.90—4.30 (1H, m), 4.20 and 4.75 (2H, ABq, J=12.5 Hz), 4.30 and 4.65 (2H, ABq, J=25.0 Hz), 6.70—7.30 (4H, m). MS m/z 336 (−79, Br).

*t-Butyl (2S,3S)-3-[(R)-1-Hydroxyethyl]-1-(4-methoxybenzyl)-4-oxo-2-azetidinecarboxylate (**5a**).* To a stirred solution of amide **3** (51.7 g, 0.124 mol) in THF (200 mL) was added lithium hexamethyldisilazide [$LiN(SiMe_3)_2$] solution [prepared by addition of n-BuLi solution (81.5 mL of 1.6 M[††] hexane solution, 0.13 mol) into a solution of hexamethyldisilazane (27 mL, 0.128 mol) in THF (75 mL) under nitrogen over a period of 15 min at 2—3 °C]. After 5 min the temperature was elevated to 20—23 °C and the same amount of [$LiN(SiMe_3)_2$] solution was further added to this solution at 20—23 °C and stirring was continued for 30 min. The reaction mixture was quenched with 10% HCl and evaporated to give an oily residue which was dissolved in ethyl acetate (EtOAc). This solution was washed with 5% $NaHCO_3$ and brine, dried ($MgSO_4$) and evaporated to give a crude oil which was chromatographed on silica-gel (1.5 Kg). Elution with cyclohexane–EtOAc (1:1) gave **5a** (26.6 g, 63.9%) as crystals; mp 75—76 °C; IR (KBr) 1760 cm^{-1}; ^1H NMR ($CDCl_3$) δ=1.25 (3H, d, J=6.5 Hz), 1.40 (9H, s), 2.50 (1H, d, J=4.0 Hz), 3.15 (1H, dd, J=3.0, 4.5 Hz), 3.75 (3H, s), 3.90 (1H, d, J=3.0 Hz), 4.00—4.40 (1H, m), 4.05 and 4.75 (2H, ABq, J=14.5 Hz), 6.80 (2H, d), 7.10 (2H, d). Found: C, 64.7; H, 7.47; N, 4.18%. Calcd for $C_{18}H_{25}NO_5$: C, 64.5; H, 7.51; N, 4.18%.

*t-Butyl (2S,3S)-3-[(R)-1-(t-Butyldimethylsiloxy)ethyl]-1-(4-methoxybenzyl)-4-oxo-2-azetidinecarboxylate (**5c**).* A mixture of **5a** (1.15 g, 3.43 mmol), t-butyldimethylsilyl chloride (1.48 g, 6.86 mmol) and 4-dimethylaminopyridine (837 mg, 6.86 mmol) in DMF (5 mL) was stirred for 16 h at room temperature. The reaction mixture was diluted with EtOAc, washed with dil HCl, water, 5% $NaHCO_3$, saturated NaCl, and dried ($MgSO_4$). After evaporation, the oily residue was chromatographed on silica-gel. Elution with cyclohexane–EtOAc (1:1) gave a crude **5c** (2.08 g) as an oil which was employed for the next reaction without further purification.

*t-Butyl (2S,3S)-1-(4-Methoxybenzyl)-3-[(R)-1-(p-nitrobenzyloxycarbonyloxy)ethyl]-4-oxo-2-azetidinecarboxylate (**5b**)* and *t-Butyl (2S,3S)-3-[(R)-1-(allyloxycarbonyloxy)ethyl]-1-(4-methoxybenzyl)-4-oxo-2-azetidinecarboxylate (**5d**).* 2-Azetidinone **5a** was converted to **5b** and **5d** by the similar reaction as in the case of **5c**.

Physical data **5b**: mp 75—76 °C; IR (KBr) 1770, 1760 cm^{-1}; ^1H NMR ($CDCl_3$) δ=1.35 (3H, d, J=6.5 Hz), 1.43 (9H, s), 3.40 (1H, dd, J=3.0, 7.0 Hz), 3.70 (3H, s), 3.85 (1H, d, J=3.0 Hz), 4.00 and 4.75 (2H, ABq, J=14.5 Hz), 4.90—5.31 (1H, m), 5.2 (2H, s), 6.50 (2H, d), 7.10 (2H, d), 7.81 (2H, d), 8.15 (2H, d). Found: C, 60.5; H, 5.82; N, 5.48%. Calcd for $C_{26}H_{30}N_2O_9$: C, 60.7; H, 5.88; N, 5.45%. **5d**: IR (Liquid) 1760 cm^{-1}; ^1H NMR ($CDCl_3$) δ=1.35 (3H, d, J=6.5 Hz), 1.40 (9H, s), 3.25 (1H, dd, J=3.0, 4.5 Hz), 3.75 (3H, s), 3.85 (1H, d, J=3.0 Hz), 4.00 and 4.75 (2H, ABq, J=14.5 Hz), 4.56 (2H, d, J=6.0 Hz), 4.92—5.20 (1H, m), 5.11—5.50 (2H, m), 5.70—6.10 (1H, m), 6.80 (2H, d), 7.15 (2H, d). MS m/z 419 (M^+).

*(2S,3S)-1-(4-Methoxybenzyl)-3-[(R)-1-(p-nitrobenzyloxycarbonyloxy)ethyl]-4-oxo-2-azetidinecarboxylic Acid (**6b**) and (2S,3S)-3-[(R)-1-(Allyloxycarbonyloxy)ethyl]-1-(4-methoxybenzyl)-4-oxo-2-azetidinecarboxylic Acid (**6d**).* 2-Azetidinone **6b** and **6d** were obtained from **5b** and **5d** with TFA as an oil in 99.2, 79.2% yield, respectively. Physical data: **6b**; IR (Liquid) 1760 cm^{-1}; ^1H NMR ($CDCl_3$) δ=1.25 (3H, d, J=6.5 Hz), 3.25 (1H, dd, J=3.0, 4.5 Hz), 3.75 (3H, s), 4.10 and 4.70 (2H, ABq, J=16 Hz), 4.11 (1H, d, J=3.0 Hz), 4.90—5.20 (1H, m), 5.10 (2H, s), 6.75 (2H, d), 7.10 (2H, d), 7.35 (2H, d), 8.15 (2H, d). MS m/z 456 (M^+). **6d**: ^1H NMR ($CDCl_3$) δ=1.40 (3H, d, J=6.5 Hz), 3.45 (1H, dd, J=3.0, 5.0 Hz), 3.79 (3H, s), 4.02 (1H, d, J=3.0 Hz), 4.00 and 4.85 (2H, ABq, J=14.0 Hz), 4.60 (2H, d, J=5.5 Hz), 5.00—5.31 (1H, m), 5.10—5.61 (2H, m), 5.70—6.20 (1H, m), 6.80 (2H, d), 7.15 (2H, d). MS m/z 363 (M^+).

*(2S,3S)-3-[(R)-1-(t-Butyldimethylsiloxy)ethyl]-1-(4-methoxybenzyl)-4-oxo-2-azetidinecarboxylic Acid (**6c**).* To a stirred solution of crude **5c** (230 mg) in EtOH (1.3 mL), was added 1 M NaOH (0.9 mL) and stirring continued at 60—70 °C for 2 h. The reaction mixture was diluted with water (10 mL) and acidified to pH 2 with dil HCl. The mixture was extracted with EtOAc and washed with water, saturated NaCl and dried ($MgSO_4$). After evaporation **6c** was obtained as crystals (201 mg, 100%): mp 107—109 °C; IR (KBr) 1758, 1720 cm^{-1}; ^1H NMR ($CDCl_3$) δ=0.30 (6H, s), 0.72 (9H, s), 1.10 (3H, d, J=6.0 Hz), 3.71 (3H, s), 3.72 (1H, t, J=2.5 Hz), 4.05 (1H, d, J=2.5 Hz), 4.07 and 4.70 (2H, ABq, J=15.0 Hz), 4.20 (1H, m), 6.81 (2H, d), 7.20 (2H, d), 7.91 (1H, s). Found: C, 60.8; H, 7.99; N, 3.51%. Calcd for $C_{20}H_{31}O_5NSi$: C, 61.1; H, 7.89; N, 3.56%.

*(2S,3S)-3-[(R)-1-(t-Butyldimethylsiloxy)ethyl]-1-(4-methoxybenzyl)-4-oxo-2-azetidinecarbonyl Chloride (**7**).* To a solution of **6c** (197 mg, 0.5 mmol) in THF (2 mL) and DMF (1 mL) was added oxalyl dichloride (0.5 mL) at 0 °C, and kept at 0 °C overnight. After evaporation, the resulted oily residue was used in the next reaction without purification.

*(3S,4S)-4-Acetyl-3-[(R)-1-(t-butyldimethylsiloxy)ethyl]-1-(4-methoxybenzyl)-2-azetidinone (**8c**).* To a stirred suspension of CuI (477 mg, 2.5 mmol) in ether (5 mL) was added a solution of MeLi (1.6 M solution in ether, 3.5 mmol) at 0 °C under nitrogen. After 5 min stirring at 0 °C, the solution was cooled to −78 °C, and a solution of acid chloride **7** (0.5 mmol) in ether (2 mL) and THF (0.5 mL) was added. After 15 min stirring at −78 °C, the reaction mixture was quenched with MeOH (1 mL), diluted with EtOAc, washed with water, saturated NaCl and dried ($MgSO_4$). After evaporation, the oily residue was chromatographed on silica gel. Elution with cyclohexane–EtOAc (3:1) gave **8c** (141 mg, 72% yield). Physical data of **8c**: IR (Liquid) 1758, 1710 cm^{-1}; ^1H NMR ($CDCl_3$) δ=0.04 (3H, s), 0.06 (3H, s), 0.85 (9H, s), 1.33 (3H, d, J=6.0 Hz), 2.00 (3H, s), 2.99 (1H, dd, J=2.5, 4.5 Hz), 3.74 (3H, s), 3.98 (1H, d, J=2.5 Hz), 4.11 and 4.59 (2H, ABq, J=14.0 Hz), 4.18 (1H, m, 6.83 (2H, d), 7.13 (2H, d). MS m/z 337 (M^+ −t-Bu).

*(3S,4S)-4-Acetoxy-3-[(R)-1-(t-butyldimethylsiloxy)ethyl]-1-(4-methoxybenzyl)-2-azetidinone (**9c**).* To a stirred solution

[††] 1 M=1 mol dm^{-3}.

of **8c** (412 mg, 1.05 mmol) in chloroform (5 mL) was added *m*-chloroperbenzoic acid (340 mg, 1.58 mmol) and the resulting solution was kept at room temperature overnight. The reaction mixture was diluted with EtOAc, washed with 5% $NaHCO_3$ (three times), saturated NaCl and dried ($MgSO_4$). After evaporation the oily residue was chromatographed on silica gel. Elution with cyclohexane–EtOAc (1:1) gave **9c** (369 mg, 86%) yield. Physical data **9c**: ^1H NMR ($CDCl_3$) δ=0.30 (3H, s), 0.80 (3H, s), 0.85 (9H, s), 1.20 (3H, d, J=6.0 Hz), 1.85 (3H, s), 3.08 (1H, dd, J=0.5, 3.0 Hz), 3.76 (3H, s), 3.90—4.20 (1H, m), 4.25 (2H, Bs), 6.01 (1H, d, J=0.5 Hz), 6.75 (2H, d), 7.15 (2H, d).

*(2S,3S)-3-[(R)-1-Hydroxyethyl]-1-(4-methoxybenzyl)-4-oxo-2-azetidinecarboxylic Acid (**6a**).* Azetidinone **5a** (20.0 g, 0.06 mol) was dissolved in trifluoroacetic acid (TFA, 50 mL) at 0 °C and stirred at the same temperature for 3 h. After evaporation of TFA, the residue was dissolved in benzene (100 mL) and evaporated again to remove the remaining TFA. The oily residue was dissolved in EtOAc (200 mL), which was washed with water, saturated $NaHCO_3$, saturated NaCl and dried ($MgSO_4$), and evaporated to give **6a** as crystals in quantitative yield; mp 100—102 °C; IR (KBr) 1740 cm^{-1}; ^1H NMR ($CDCl_3$) δ=1.30 (3H, d, J=6.5 Hz), 3.30 (1H, dd, J=3.5, 4.0 Hz), 3.75 (3H, s), 4.05 (1H, d, J=3.5 Hz), 4.00—4.40 (1H, m), 4.05 and 4.08 (2H, ABq, J=16.0 Hz), 6.45 (1H, Bs), 6.80 (2H, d), 7.15 (2H, d). Found: C, 60.2; H, 6.16; N, 4.93%. Calcd for $C_{14}H_{17}NO_5$: C, 60.2; H, 6.14; N, 5.02%.

*(3S,4R)-4-Acetoxy-3-[(R)-1-hydroxyethyl]-1-(4-methoxybenzyl)-2-azetidinone (**9a**).* To a solution of **6a** (2.80 g, 10 mmol) in DMF–AcOH (5:1, 10 mL) was added $Pb(OAc)_4$ (4.43 g, 10 mmol) with stirring under nitrogen. The mixture was stirred at 50—55 °C for 15 min, then the mixture was diluted with EtOAc (300 mL), washed with water (twice), 5% $NaHCO_3$, saturated NaCl and dried ($MgSO_4$). After evaporation of the solvent, the oily residue was chromatographed on silica gel (50 g). Elution with cyclohexane–EtOAc (1:2) gave **9a** (1.63 g, 51.3%) as crystals; mp 84—85 °C; IR (KBr) 1755 cm^{-1}; ^1H NMR ($CDCl_3$) δ=1.30 (3H, d, J=6.5 Hz), 2.5 (1H, dd, J=1.0, 4.0 Hz), 2.00 (3H, s), 3.10 (1H, Bd, J=7.0 Hz), 3.90—4.30 (1H, m), 3.80 (3H, s), 4.10 and 4.50 (2H, ABq, J=15.0 Hz), 5.75 (1H, d, J=1.0 Hz), 6.80 (2H, d), 7.15 (2H, d). Found: C, 61.32; H, 6.43; N, 4.81%. Calcd for $C_{15}H_{19}NO_5$: C, 61.4; H, 6.53; N, 4.78%.

By the lead tetraacetate method **6b** and **6d** were converted to corresponding **9b** and **9d** in 71.9 and 63% yield, respectively, as in the case of **9a**.

Physical data **9b**: IR (Liquid) 1770 cm^{-1}; ^1H NMR ($CDCl_3$) δ=1.43 (3H, d, J=6.5 Hz), 1.95 (3H, s), 3.35 (1H, dd, J=1.0, 6.5 Hz), 3.75 (3H, s), 4.10 and 4.50 (2H, ABq, J=14.5 Hz), 4.90—5.20 (1H, m), 5.23 (2H, s), 5.98 (1H, d, J=1.0 Hz), 6.78 (2H, d), 7.20 (2H, d), 7.52 (2H, d), 8.23 (2H, d). Found: C, 58.4; H, 5.31; N, 5.75%. Calcd for $C_{23}H_{24}N_2O_9$: C, 58.4; H, 5.08; N, 5.93%. MS m/z 472 (M^+). **9d**: IR (Liquid) 1765 cm^{-1}; ^1H NMR ($CDCl_3$) δ=1.40 (3H, d, J=6.5 Hz), 1.92 (3H, s), 3.28 (1H, dd, J=1.0, 6.5 Hz), 3.75 (3H, s), 4.10 and 4.50 (2H, ABq, J=15.0 Hz), 4.80—5.20 (1H, m), 4.40—4.70 (2H, m), 5.10—5.50 (2H, m), 5.70—6.20 (1H, m), 5.90 (1H, d, J=1.0 Hz), 6.75 (2H, d), 7.16 (2H, d). Found: C, 59.8; H, 6.03; N, 3.67%. Calcd for $C_{19}H_{23}NO_7$: C, 60.4; H, 6.14; N, 3.71%. MS m/z 377 (M^+).

*(3S,4R)-4-Acetoxy-3-[(R)-1-(t-butyldimethylsiloxy)ethyl]-2-azetidinone (**10c**).* To a solution of **9c** (408 mg, 1.0 mmol) in acetonitrile water (1:1, 32 mL) were added K_2HPO_4 (1.50 g) and $K_2S_2O_8$ (3.0 g). The mixture was stirred at 75 °C for 1 h under nitrogen, and concentrated *in vacuo* to half volume, and extracted with EtOAc. The extracts were washed with saturated $NaHCO_3$, saturated NaCl, dried ($MgSO_4$) and concentrated to an oily residue which was purified by preparative TLC plate on silica gel (20×20×0.2 cm). Development with cyclohexane–EtOAc (2:1) gave **10c** (115 mg, 41%) as crystals; mp 101—102 °C; IR (Nujol) 3200, 1785, 1745 cm^{-1}; ^1H NMR ($CDCl_3$) δ=0.07 (6H, s), 0.85 (9H, s), 1.24 (3H, d, J=6.5 Hz), 2.12 (3H, s), 3.20 (1H, dd, J=1.0, 3.0 Hz), 4.24 (1H, dq, J=3.0, 6.5 Hz), 5.89 (1H, d, J=1.0 Hz), 6.85 (1H, Bs); MS m/z 577 (M^+), 230, 188, 144; $[\alpha]_D^{24}$ +47.2 (c=1.0, $CHCl_3$).

*(3S,4R)-4-Acetoxy-3-[(R)-1-(p-nitrobenzyloxycarbonyloxy)ethyl]-2-azetidinone (**10b**).* To a stirred solution of **9b** (410 mg, 0.89 mmol) in acetone (3 mL) was added cerium(IV) ammonium nitrate (CAN) (910 mg, 1.75 mmol) at room temperature and stirring was continued for 1 h. The reaction mixture was diluted with EtOAc (30 mL) which was washed with water, saturated $NaHCO_3$, saturated NaCl and dried ($MgSO_4$). After evaporation an oily residue was purified by preparative TLC (20×20×0.2 cm) on silica gel with cyclohexane–EtOAc (1:1) to give deprotected **10b** (150 mg, 49% yield) as an oil; IR (Liquid) 3250, 1770 cm^{-1}; ^1H NMR ($CDCl_3$) δ=1.45 (3H, d, J=6.5 Hz), 2.10 (3H, s), 3.35 (1H, dd, J=2.5, 6.5 Hz), 4.90—5.51 (1H, m), 5.24 (2H, s), 5.81 (1H, d, J=2.5 Hz), 7.23 (1H, Bs), 7.50 (2H, d), 8.16 (2H, d).

*(3S,4R)-4-Acetoxy-3-[(R)-1-(p-nitrobenzyloxycarbonyloxy)ethyl]-1-(4-methoxybenzyl)-2-azetidinone (**9b**).* To a solution of **9a** (2.93 g, 10 mmol) in dichloromethane (20 mL) were added *p*-nitrobenzyloxycarbonyl chloride (6.45 g, 30 mmol) and 4-dimethylaminopyridine (3.66 g, 30 mmol) under ice cooling. After stirring for 1 h the reaction mixture was diluted with EtOAc and washed with dil HCl, water, saturated $NaHCO_3$, saturated NaCl and dried ($MgSO_4$). The solution was evaporated to afford an oily residue which was chromatographed on silica gel (50 g). Elution with cyclohexane–EtOAc (1:1) gave **9b** (300 mg, 74%) as an oil. The physical data was identical with that of an authentic sample obtained by the lead tetraacetate method.

*(3S,4R)-4-Acetoxy-3-[(R)-1-(t-butyldimethylsiloxy)ethyl]-1-(4-methoxybenzyl)-2-azetidinone (**9c**)* and *(3S,4R)-4-Acetoxy-3-[(R)-1-(allyloxycarbonyloxy)ethyl]-1-(4-methoxybenzyl)-2-azetidinone (**9d**).* Compound **9a** was converted to **9c** and **9d** by the similar reaction as in the case of **9b**, with *t*-butyldimethylsilyl chloride and imidazole, and allyloxycarbonyl chloride and 4-dimethylaminopyridine. The physical data were identical with that of authentic samples obtained in another route.

*(3S,4R)-1-(4-Methoxybenzyl)-4-[(phenylthiocarbonyl)methyl]-3-[(R)-1-(p-nitrobenzyloxycarbonyloxy)ethyl]-2-azetidinone (**11b**).* To a stirred solution of azetidinone **9b** (1.18 g, 2.5 mmol) in dichloromethane (10 mL) were added 1-phenylthio-1-trimethylsilyloxyethylene (2.74 g, 10 mmol) and trimethylsilyl trifluoromethanesulfonate (1.11 g, 1.25 mmol) at room temperature. The reaction mixture was kept at room temperature overnight, and diluted with EtOAc (100 mL),

washed with water, 5% $NaHCO_3$, saturated NaCl, and dried ($MgSO_4$). After evaporation, an oily residue was chromatographed on silica-gel (60 g). Elution with cyclohexane–EtOAc (1:1) gave **11b** (1.34 g, 94.9%); IR (Liquid) 1765 cm^{-1}; ^1H NMR ($CDCl_3$) δ=1.35 (3H, d, 6.5 Hz), 2.70—2.90 (2H, m), 3.15 (1H, dd, J=3.0, 7.0 Hz), 3.75 (3H, s), 3.80—4.10 (2H, m), 4.10 and 4.50 (2H, ABq, J=14.5 Hz), 4.90—5.30 (1H, m), 5.15 (2H, s), 6.75 (2H, d), 7.15 (2H, d), 7.35 (5H, s), 7.50 (2H, d), 8.15 (2H, d); MS m/z 564 (M^+).

*(3S,4R)-3-[(R)-1-(t-Butyldimethylsiloxy)ethyl-1-(4-methoxybenzyl)-4-[(phenylthiocarbonyl)methyl]-2-azetidinone (**11c**) and (3S,4R)-3-[(R)-1-(Allyloxycarbonyloxy)ethyl]-1-(4-methoxybenzyl)-4-[(phenylthiocarbonyl)methyl]-2-azetidinone (**11d**).* 2-Azetidinone **9c** and **9d** gave **11c** and **11d** respectively by the same reaction as in the case of **11b**.

Physical data **11c**: ^1H NMR ($CDCl_3$) δ=0.03 (6H, s), 0.83 (9H, s), 1.14 (3H, d, J=6.0 Hz), 2.76 (2H, d, J=6.0 Hz), 2.88 (1H, dd, J=2.0, 4.5 Hz), 3.75 (3H, s), 3.97 (1H, dt, J=2.0, 6.0 Hz), 4.16 (1H, dq, J=2.0, 6.0 Hz), 4.26 (2H, s), 6.77 (2H, d), 7.13 (2H, d), 7.35 (5H, Bs). **11d**: IR (Liquid) 1760 cm^{-1}; ^1H NMR ($CDCl_3$) δ=1.40 (3H, d, J=6.5 Hz), 2.84 (2H, d, J=5.5 Hz), 3.10 (1H, dd, J=2.0, 7.0 Hz), 3.76 (3H, s), 3.80—4.60 (1H, m), 4.10 and 4.50 (2H, ABq, J=14.0 Hz), 4.50—4.60 (2H, m), 4.80—5.20 (1H, m), 5.10—5.40 (2H, m), 5.60—6.10 (1H, m), 6.80 (2H, d), 7.12 (2H, d), 7.30—7.50 (5H, m). MS m/z 496 (M^+).

*(3S,4R)-3-[(R)-1-(p-Nitrobenzyloxycarbonyloxy)ethyl]-4-[(phenylthiocarbonyl)methyl]-2-azetidinone (**12b**).* To a stirred solution of cerium (IV) ammonium nitrate (3.0 g, 5.47 mmol) in water (2 mL) was added a solution of **11b** (203 mg, 0.36 mmol) in acetone (10 mL) and stirred for 2 h. The reaction mixture was diluted with EtOAc (200 mL), washed with water, 5% $NaHCO_3$, saturated NaCl and dried ($MgSO_4$). After evaporation an oily residue was chromatographed on silica-gel. Elution with cyclohexane–EtOAc (2:1) gave **12b** (111 mg, 69.5%) as an oil; IR (Liquid) 1770 cm^{-1}; ^1H NMR ($CDCl_3$) δ=1.44 (3H, d, J=6.5 Hz), 2.90—3.20 (3H, m), 3.86—4.10 (1H, m), 4.90—5.30 (1H, m), 5.15 (2H, s), 6.40 (1H, Bs), 7.45 (5H, s), 7.50 (2H, d), 8.15 (2H, d); MS m/z 444 (M^+).

*(3S,4R)-3-[(R)-1-(t-Butyldimethylsiloxy)ethyl]-4-[(phenylthiocarbonyl)methyl]-2-azetidinone (**12c**)* and *(3S,4R)-3-[(R)-1-Allyloxycarbonyloxy)ethyl]-4-[(phenylthiocarbonyl)methyl]-2-azetidinone (**12d**).* 2-Azetidinones **11c**, **11d** were converted to the corresponding **12c** and **12d** by the same reaction as in the case of **11b**.

Physical data **12c**: mp 95—96 °C; IR (Nujol) 1765, 1725 cm^{-1}; ^1H NMR ($CDCl_3$) δ=0.08 (6H, s), 0.87 (9H, s), 1.19 (3H, d, J=6.0 Hz), 2.55—3.25 (3H, m), 3.70—4.33 (2H, m), 6.20 (1H, Bs), 7.35 (5H, s); $[\alpha]_D^{24}$ +41.7 °C (C=1.64, $CHCl_3$). **12d**: IR (Liquid) 1770 cm^{-1}; ^1H NMR ($CDCl_3$) δ=1.40 (3H, d, J=6.5 Hz), 2.80—3.20 (3H, m), 3.80—4.20 (1H, m), 4.42—4.71 (2H, m), 4.80—5.20 (1H, m), 5.10—5.40 (2H, m), 5.60—6.10 (1H, m), 6.20 (1H, Bs), 7.32 (5H, s). Found: C, 5.81; H, 5.49; N, 3.89; S, 9.35%. Calcd for $C_{17}H_{19}NO_5S$: C, 58.4; H, 5.47; N, 4.00; S, 9.15%.

*(3S,4R)-4-[(S)-[[1-[N-(p-Nitrobenzyloxycarbonyl)acetimidoyl]-3-pyrrolidinylthio]carbonylmethyl]]-3-[(R)-1-(p-nitrobenzyloxycarbonyloxy)ethyl]-2-azetidinone (**13**).* To a stirred solution of 2-azetidinone **12b** (115 mg, 0.26 mmol) in dichloromethane (5 mL) were added 3-pyrrolidinethiol **20** (125 mg, 0.89 mmol) in dichloromethane (5 mL) and triethylamine (26 mg, 0.26 mmol) with stirring at room temperature and the resulting solution was kept at room temperature overnight. After evaporation, the oily residue was chromatographed on silica-gel. Elution with EtOAc gave **13** (168 mg, 98%) as an oil; IR (Liquid) 1770 cm^{-1}; ^1H NMR ($CDCl_3$) δ=1.22 (3H, d, J=6.0 Hz), 2.30 (3H, s), 1.60—2.60 (2H, m), 2.90 (2H, d, J=6.5 Hz), 3.04 (1H, Bd, J=7.0 Hz), 3.20—4.20 (6H, m), 4.90—5.20 (1H, m), 5.18 (2H, s), 5.13 (2H, s), 6.70 (1H, Bs), 7.25 (4H, d), 8.10—8.30 (4H, m).

*(3S,4R)-3-[(R)-1-(Allyloxycarbonyloxy)ethyl]-4-[(S)-[[1-(p-nitrobenzyloxycarbonyl)-3-pyrrolidinylthio]carbonylmethyl]]-2-azetidinone (**14**).* *S*-Phenyl thioester **12d** was converted to the corresponding exchanged *S*-thioester **14** by the same reaction as in the case of **13**; IR (Liquid) 1770 cm^{-1}; ^1H NMR ($CDCl_3$) δ=1.40 (3H, d, J=6.5 Hz), 1.60—2.70 (2H, m), 2.70—3.00 (3H, m), 3.20—4.21 (6H, m), 4.60 (2H, d, J=7.0 Hz), 4.80—5.21 (1H, m), 5.20—5.50 (2H, m), 5.20 (2H, s), 5.62—6.21 (1H, m), 6.40 (1H, Bs), 7.48 (2H, d), 8.15 (2H, d).

*(3S,4R)-4-[[2-(p-Nitrobenzyloxycarbonylamino)ethylthio]carbonylmethyl]-3-[(R)-1-(p-nitrobenzyloxycarbonyloxy)ethyl]-2-azetidinone (**15**).* To a stirred solution of 2-azetidinone **12b** (444 mg, 10 mmol) in dichloromethane (10 mL) were added 2-(*p*-nitrobenzyloxycarbonylamino)ethanethiol (512 mg, 20 mmol) and triethylamine (202 mg, 20 mmol) at room temperature and the solution was kept at the same temperature for 5 h. The mixture was diluted with EtOAc (50 mL) and washed with water, saturated $NaHCO_3$, saturated NaCl and dried ($MgSO_4$). After evaporation the oily residue was purified by column chromatography on silica-gel. Elution with cyclohexane–EtOAc gave **15** (431 mg, 73%) as an oil; IR (Liquid) 3260, 1760, 1740 cm^{-1}; ^1H NMR ($CDCl_3$) δ=1.42 (3H, d, J=6.5 Hz), 2.60—3.20 (4H, m), 3.20—3.50 (2H, m), 3.90—4.25 (2H, m), 4.80—5.30 (1H, m), 5.18 (2H, s), 5.26 (2H, s), 5.65 (1H, m), 6.90 (1H, Bs), 7.35—8.50 (8H, m).

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