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# NEW SYNTHESIS OF 4-ACETOXY-2-AZETIDINONES BY USE OF ELECTROCHEMICAL OXIDATION

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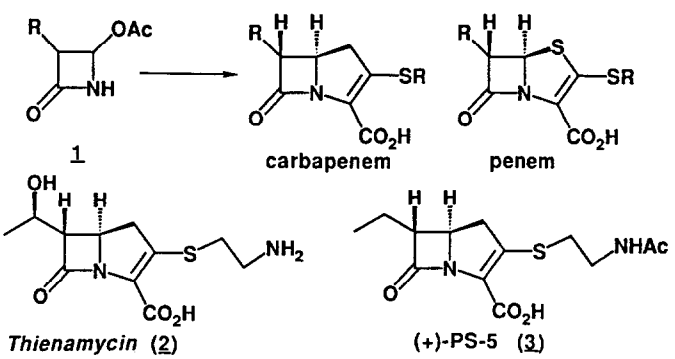
Abstract----4-Acetoxy-2-azetidinone was synthesized from 4-carboxy-2-azetidinone by Kolbe-type electrolysis. Optically pure 4-acetoxy-3-[1-(t-butyldimethylsiloxy)ethyl]-2-azetidinone, which is an important intermediate for the synthesis of thienamycin, and (+)-PS-5 were synthesized by use of this method.

In order to synthesize new bicyclic β-lactams, 4-acetoxy-2-azetidinone is a highly versatile intermediate because the acetoxy moiety is readily displaced by various nucleophiles. Especially, 4-acetoxy-2-azetidinones **1** having a substituent at C-3 position are important for the synthesis of thienamycin(**2**), (+)-PS-5(**3**) and other biologically active β-lactams. 4-Acetoxy-2-azetidinone is prepared by condensation of vinyl acetate and chlorosulfonyl isocyanate,[1] showing that it is quite difficult to introduce the acyloxy group directly into C-4 position of β-lactam. Recently, Easton and Love reported that a benzyloxy group could be introduced directly at C-4 position of β-lactam by radical reaction.[2] Though the result is quite interesting, the reaction requires high substrate specificity. On the other hand, there are two excellent methods for conversion of functional groups at C-4 position into acetoxy group. One of them is the conversion of carboxy group at C-4 position into acetyl group by $Pb(OAc)_4$ oxidation[3] and the other is the conversion of acetyl group at C-4 position into acetoxy group by treatment with mCPBA.[4] The yields of these reactions are high, but the reagents such as lead or per-acid have remained problematic for industrial production. On the other hand, very interestingly, condensation of silyl enolether with chlorosulfonyl isocyanate was reported to afford optically active β-lactams.[5]

**Scheme 1**



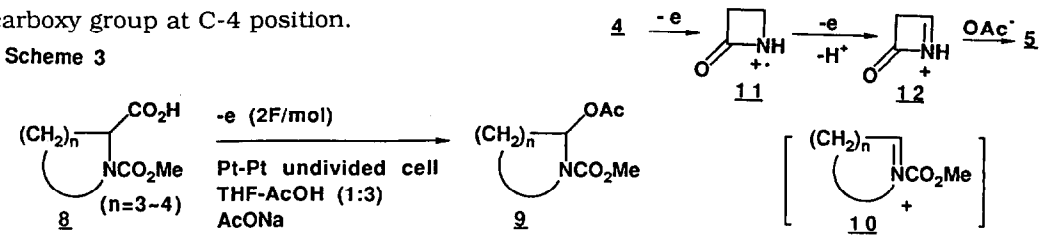
We have already reported the new synthesis of 4-acetoxy-β-lactams by use of electrochemical oxidation.[6,7] Namely, β-lactam **4** was electrolyzed in an undivided cell in AcOH-$CH_3CN$(1:9) in the presence of n-$Bu_4NBF_4$ under constant current to give desired 4-acetoxy-2-azetidinone **5** in 49 % yield. In a similar manner, 3-methylene-2-azetidinone **6** gave 4-acetoxy-3-methylene-2-azetidinone **7**(39 % yield). However, since no oxidation peak of β-lactam was shown below 2.2 V by cyclic voltammetry in $CH_3CN$,[8] it was predicted that the direct electrolysis of β-lactam could not be applied to β-lactams having oxidation-labile functions. Now we want to report a new synthetic method of optically active 4-acetoxy-2-azetidinones **1** having substituent at C-3 position by use of electrochemical oxidation and to describe a formal total synthesis of (+)-PS-5 by use of this method.

Scheme 2


**New Synthesis of 4-Acetoxy-β-lactams from 4-Carboxy-β-lactams by Kolbe-type Electrolysis**

Recent studies of Kolbe-type electrolysis suggested that the decarboxylation of carboxylic acid having heteroatoms at the α-position easily occurred under the lower oxidation potential to generate the cations because they were stabilized by adjacent nitrogen[9] or oxygen[10], which could smoothly react with nucleophiles. Iwasaki et al. reported the quite interesting result of the Kolbe-type electrolysis. When N-carbomethoxy-α-amino acids **8** were electrolyzed in an undivided cell in the presence of AcONa in THF-AcOH, α-acetoxylated compounds **9** were obtained in high yields. The intermediate of this reaction was considered to be iminium cation **10**. On the other hand, it was assumed that the direct acetoxylation into β-lactams in AcOH proceeded through one electron abstraction from amide nitrogen of **4**. Then elimination of proton from carbon α to nitrogen was followed by further one electron abstraction to give acyl-imminium cation **12**, which was attacked by acetate anion to produce 4-acetoxy-2-azetidinone **5**. Thus, the acyl-iminium cation **12** generated by the direct acetoxylation into β-lactam should be also provided by the Kolbe-type electrolysis of β-lactam having carboxy group at C-4 position.

Scheme 3




Thus, 4-carboxy-2-azetidinone **13**[11] was electrolyzed using platinum plates as electrode in the presence of NaOAc as electrolyte in an undivided cell in $CH_3CN$-AcOH(3:1). After

2.7 F/mol of electricity was passed through the solution under constant current, 4-acetoxy-2-azetidinone **5** was obtained in 33 % yield. The yield was improved with the increase of the electricity(Table 1, Run 1-3) and $CH_3CN$-AcOH(3:1) as the solvent gave a good result. In this reaction, NaOAc must be electrolyzed under these reaction conditions. Therefore, the decrease of the amount of NaOAc made to decrease the electricity(Table 1, Run 6-8). These results indicate that Kolbe-type electrolysis to 4-carboxy-2-azetidinone is an excellent method for the synthesis of 4-acetoxy-2-azetidinone.

Scheme 4

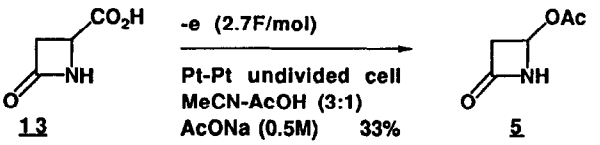
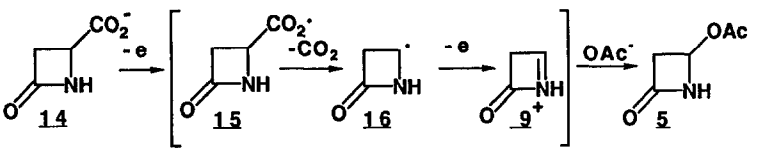



Table 1 Electrochemical oxidation of 13 in the presence of AcONa-AcOH

| Run | Solvent | F / mol | AcONa (eq) | Yield (%) |
|---|---|---|---|---|
| 1 | MeCN-AcOH (3:1) | 2.7 | 0.5M (4.5eq) | 33 |
| 2 | MeCN-AcOH (3:1) | 4.0 | 0.5M (4.5eq) | 62 |
| 3 | MeCN-AcOH (3:1) | 5.0 | 0.5M (4.5eq) | 76 |
| 4 | MeCN-AcOH (3:1) | 6.5 | 0.5M (4.5eq) | 64 |
| 5 | THF-AcOH (1:3) | 5.0 | 0.5M (4.5eq) | 67 |
| 6 | MeCN-AcOH (3:1) | 2.7 | 1.42eq | 58 |
| 7 | MeCN-AcOH (3:1) | 2.7 | 0.25eq | 76 |
| 8 | MeCN-AcOH (3:1) | 2.1 | 0.25eq | 58 |




**Synthesis of Optically Pure 4-Acetoxy-3-hydroxyethyl-2-azetidinone**

This method was applied to the synthesis of 4-acetoxy-3-hydroxyethyl-2-azetidinone. The key carboxylic acid **24** was first prepared by cycloaddition of diketene with imine.[12] Condensation of diketene **17** with imine **18** gave β-lactam **19**. Reduction of ketone with K-Selectride followed by deprotection of DAM(dianisylmethyl) group and silyl group afforded β-lactam **22**, and then hydroxy group was protected with silyl group. In order to convert the ethynyl group of **23** to the carboxy group, compound **23** was treated with $KMnO_4$ in the presence of Adogen 464 and AcOH in $CH_2Cl_2$-$H_2O$[13] to give the desired carboxylic acid **24** in 63 % yield. The β-lactam **24** was electrolyzed in an undivided cell using platinum plates in the presence of AcONa in AcOH-$CH_3CN$(1:4) under constant current and we could obtain the desired 4-acetoxy-3-[1-(*t*-butyldimethylsiloxy)ethyl]-2-azetidinone **25** in 62 % yield(Table 2, Run 1). The reaction was carried out under various conditions and the results are shown in Table 2. The best result was obtained when 11.0 F/mol of electricity was passed through the solution. These results indicate that this Kolbe-type electrolysis smoothly proceeds to

afford 4-acetoxy-2-azetidinone from 4-carboxy-2-azetidinone having oxidation labile function.

Scheme 5

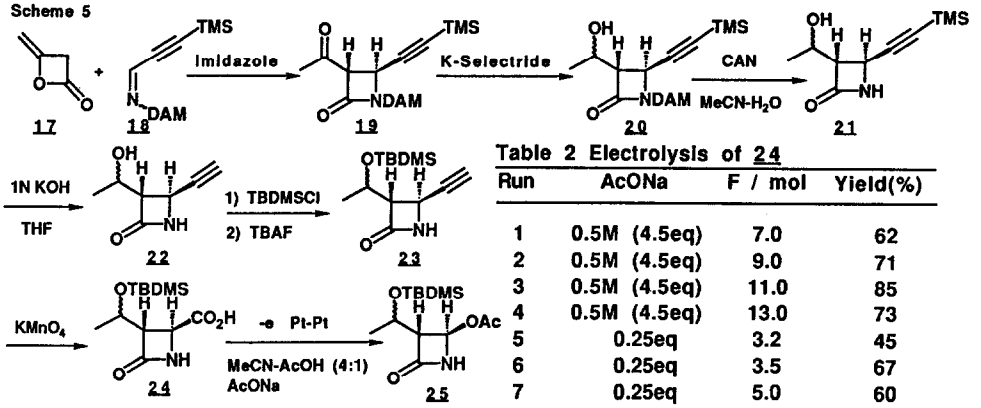
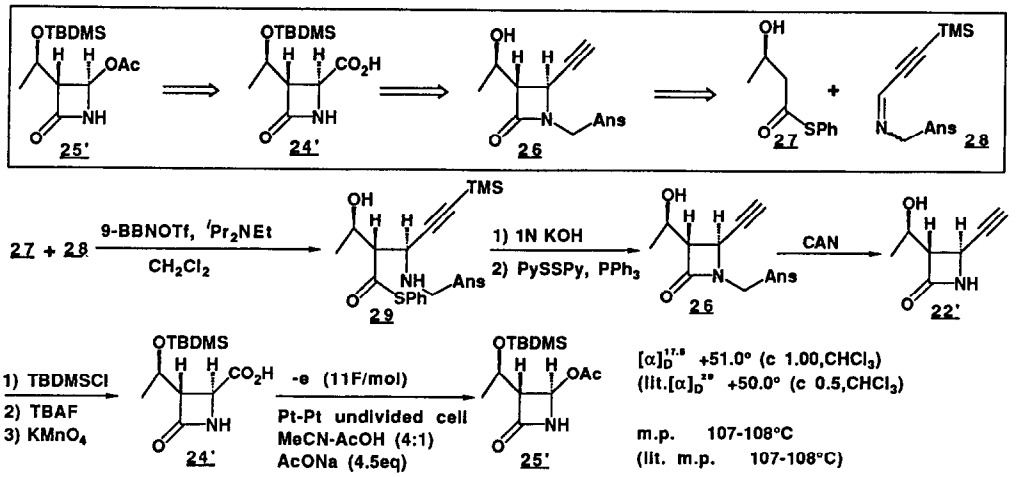



Table 2 Electrolysis of 24

| Run | AcONa | F / mol | Yield(%) |
|---|---|---|---|
| 1 | 0.5M (4.5eq) | 7.0 | 62 |
| 2 | 0.5M (4.5eq) | 9.0 | 71 |
| 3 | 0.5M (4.5eq) | 11.0 | 85 |
| 4 | 0.5M (4.5eq) | 13.0 | 73 |
| 5 | 0.25eq | 3.2 | 45 |
| 6 | 0.25eq | 3.5 | 67 |
| 7 | 0.25eq | 5.0 | 60 |

Subsequently, the synthesis of optically pure 4-acetoxy-3-hydroxyethyl-2-azetidinone was tried, which was a versatile intermediate for the synthesis of thienamycin and its derivatives. The optically pure carboxylic acid **24'** was prepared from readily available 3(*R*)-hydroxybutylic acid by use of our method[14] as shown in Scheme 6. Condensation of the boron enolate generated from the thiol ester **27** with imine **28** followed by cyclization afforded β-lactam **26** in high stereoselectivity, which was treated with ceric ammonium nitrate(CAN) to provide **22'**. Conversion of **22'** into carboxylic acid **24'** smoothly proceeded in a similar manner as mentioned above. The β-lactam **24'** was electrolyzed in a similar manner to give the desired 4-acetoxy-β-lactam **25'** in 84 % yield as optically pure form[$[\alpha]^{17.5}$ +51.0°(c, 1.00, $CHCl_3$), mp 107.0-108.0 °C).[15]

Scheme 6

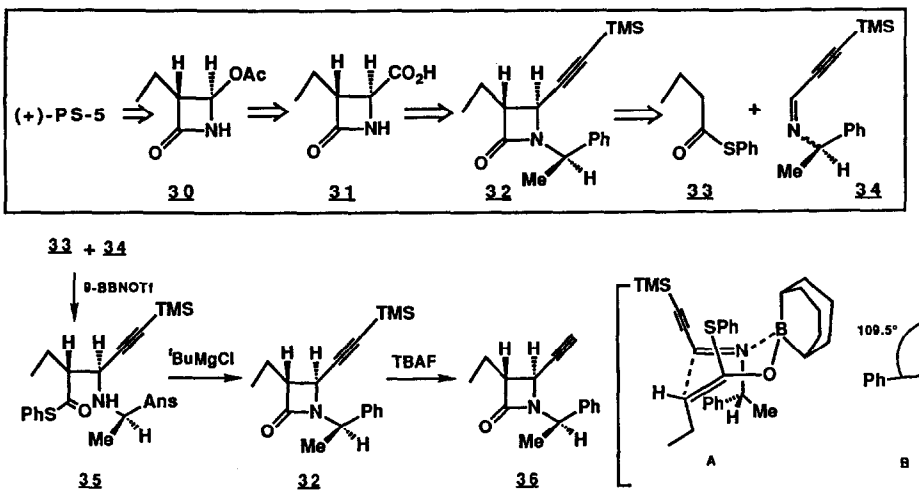



**An Efficient Formal Total Synthesis of (+)-PS-5**

The carbapenem, (+)-PS-5(**3**), is an antibiotic which is active against Gram-positive and Gram-negative bacteria including β-lactamase-producing organisms.[16] Our previous

work[17] and the results described above prompted us to synthesize (+)-PS-5.[18] The key carboxylic acid **31** was prepared from (*S*)-phenyl butanethioate (**33**) and imine **34** derived from (*R*)-α-methylphenethylamine and 3-(trimethylsilyl)-2-propynal by our method.[17] That is, condensation of boron enolate prepared from **33** and 9-BBNOTf in the presence of diisopropylethylamine with imine **34** afforded compound **35**, which was followed by treatment with t-BuMgCl and then TBAF to produce β-lactam **36** in a highly stereoselective manner.[19] On the basis of MM2 calculation of imine, the most stable conformation of imine derived from (*R*)-α-methylphenethylamine is depicted as **B**. (The caluculation was performed replacing the acetylenic moiety of imine **34** into methyl group.) Thus, this highly stereoselective synthesis of amine **35** should be achieved via the cyclic transition state depicted as **A**.

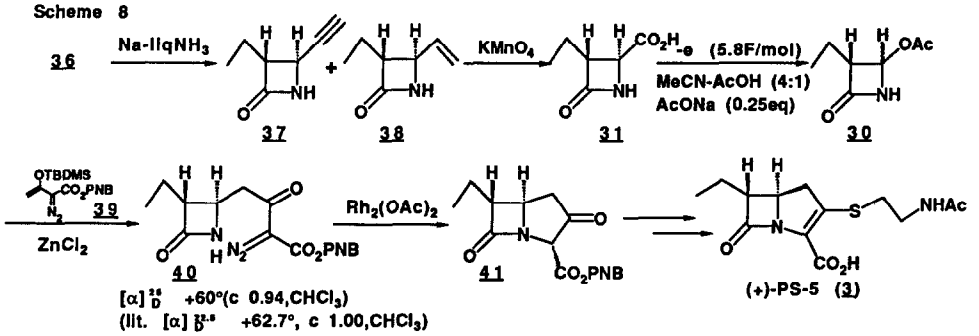
**Scheme 7**




Deprotection of phenethyl group on the lactam nitrogen of **36** with Na-liq.$NH_3$ gave β-lactam **37** and **38** in 81 % yield(**37**/**38**=1/2). A mixture of **37** and **38** was oxidized with $KMnO_4$ in the presence of Adogen 464[13] to afford 4-carboxy-3-ethyl-β-lactam **31** in 66 % yield. The electrochemical oxidation of β-lactam **31** was carried out in an undivided cell using platinum plates as electrode in the presence of NaOAc(0.25 eq.) in AcOH-$CH_3CN$(1:4). After 5.8 F/mol of electricity was passed through the solution, 4-acetoxy-3-ethyl-2-azetidinone(**30**) was obtained in 84 % yield (cis/trans=1/2).[20] Treatment of a mixture of β-lactam **30** with **39** in the presence of $ZnCl_2$ afforded compound **40** in 59 % yield as an optically pure single isomer{[ α ]$^{25}$ +60° (c, 0.94, $CHCl_3$)}, whose spectral data were fully identical with the data reported.[21] Treatment of compound **40** with $Rh_2(OAc)_4$ provided carbapenem **41** in quantitative yield. The results indicated that a formal total synthesis of (+)-PS-5(**3**) was achieved by very short steps.

In conclusion, Kolbe-type electrolysis is quite effective for the synthesis of 4-acetoxy-2-azetidinones, especially 4-acetoxy-2-azetidinones having oxidation-labile substituents at C-3 position, from 4-carboxy-2-azetidinone.

Scheme 8




**Experimental Section**

Solvents were purified when necessary by standard procedure. NMR spectra were recorded on either a JEOL JNM-FX100 or JEOL JNM-GX270. IR spectra were recorded on a JASCO A-300 spectrophotometer. Mass spectra were obtained from JEOL JMS-DX303 or JEOL JMS-HX110. Melting points were determined by Isii Melting point Apparatus and were not corrected. Electrolysis was carried out by YANACO VE-8 controlled potential electrolyser and optical rotation was determined by JASCO DIO-370, Digital Polarimeter. Merk silica gel 60(70-325 mesh and 230-400 mesh) was used for column chromatography. *S*-Phenyl (3*R*)-hydroxybutanethioate(**27**) was prepared from methyl (3R)-hydroxybutylate.

***S*-Phenyl (2*S*, 3*S*)-2[(1*R*)-Hydroxyethyl]-3-N-*p*-methoxybenzylamino-5-trimethylsilyl-4-pentynethioate(29).** A solution of *p*-methoxybenzylamine(263 mg, 1.9 mmol), 3-trimethylsilylpropynal(242 mg, 1.9 mmol) and $MgSO_4$ in $Et_2O$(5 mL) was stirred for 30 min at room temperature. After filtration, solvent was removed and the residual imine **28** was used without purification. To a solution of thiol ester **27**(290 mg, 1.5mmol) and diisopropylethylamine(0.6 mL, 3.4 mmol) in $CH_2Cl_2$(6 mL) was added 9-BBNOTf(0.92 g, 3.4 mmol) at -78 °C and the solution was stirred at the same temperature for 10 min and at -30 °C for 2 hr. To the solution was slowly added imine **28** in $CH_2Cl_2$(8 mL) at -50° C. The temperature was gradually raised to -30 °C and the solution was stirred for 2hr. To the solution was added a mixed solution of phosphate buffer(pH 7.0, 10 mL), MeOH(10 mL) and 31% $H_2O_2$(5 mL) at -78 °C and the solution was stirred at room temperature for 10 min. The aqueous layer was extracted with ethyl acetate and the organic layer was dried over $Na_2SO_4$ and concentrated. The residue was purified by chromatography($Et_2O$-n-hexane=1:3) to give colorless oil of **29**(449 mg, 69 %): IR ν(neat) 3350, 2180, 1700 $cm^{-1}$; NMR δ($CDCl_3$) 0.22(s, 9 H), 2.24(d, J=6 Hz, 3 H), 2.90(m, 1 H), 3.6-4.1(m, 3 H), 3.8(s, 3 H), 4.1-4.5(m, 1 H), 6.84(d, J=9 Hz, 2 H), 7.24(d, J=9 Hz, 2 H), 7.42(s, 5H); MS, m/z 441($M^+$), 247(bp); HRMS Calcd for $C_{24}H_{31}O_3NSiS$ 441.1784, Found 441.1818.

**(3*S*, 4*S*)-4 Ethynyl-3-[(1*R*)-hydroxyetyl]-N-*p*-methoxybenzyl-2-azetidi -none(26).** To a solution of **29**(383 mg, 0.87 mmol) in THF(5 mL) was added 1N KOH solution(5 mL) and the solution was stirred at room temperature for 3 hr. The solution was neutralyzed with 1N HCl and the aqueous layer was extracted with ethyl acetate. The organic layer was dried over $Na_2SO_4$ and concentrated. To the refluxing solution of the residue containing 2,2'-dipyridyldisulfide(287 mg, 1.3 mmol) in $CH_3CN$(70 mL) was added a solution of $PPh_3$(342 mg, 1.3 mmol) in $CH_3CN$(14 mL) and the whole solution was refluxed for 3 hr. Solvent was removed and the residue was purified by chromatography($Et_2O$) to give colorless crystals of **26**(155 mg, 69 %): mp 92-93 °C(from $Et_2O$-hexane); IR ν(neat) 3350, 3250, 1745, 1610, 1520 $cm^{-1}$; NMR δ($CDCl_3$) 1.26(d, J=6.6 Hz, 3 H), 2.15(brs, 1 H), 2.44(d, J=2.2 Hz, 1 H), 3.29(dd, J=2.2, 2.4 Hz, 1 H), 3.79(s, 3 H), 3.98(d, J=15 Hz, 1 H), 4.08(dd, J=2.2, 2.2 Hz, 1 H), 4.2(dq, J=4.4, 6.6

Hz, 1 H), 4.70(d, J=15 Hz, 1 H), 6.86(d, J=8.4 Hz, 2 H), 7.21(d, J=8.4 Hz, 2 H); MS, m/z 259($M^+$), 214, 163, 121(bp); HRMS Calcd for $C_{15}H_{17}O_3N$ 259.1208 Found 259.1202. Anal Calcd for $C_{15}H_{17}O_3N$ C, 69.48; H, 6.61; N, 5.40. Found C, 69.57; H, 6.61; N, 5.33. $[\alpha]^{13.5}$-24.2°(c, 1.00, $CHCl_3$).

**(3*S*, 4*S*)-4-Ethynyl-3-[(1*R*)-hydroxyethyl]-2-azetidinone(22').** To a solution of **26**(210.9 mg, 0.814 mmol) in $CH_3CN$(7.5 mL) was added ceric ammonium nitrate(CAN)(982.4 mg, 1.79 mmol) in $H_2O$(12.5 mL) at 0 °C and the solution was stirred at 0 °C for 7 hr and at room temperature for 17 hr . Water(25 mL) was added and the aqueous layer was extracted with ethyl acetate. The organic layer was washed with sat. $NaHCO_3$ solution and brine, dried over $Na_2SO_4$ and concentrated. The residue was purified by chromatography(ethyl acetate-n-hexane=1:1) to give **22'**(82.2 mg, 73 %): mp 103.0-103.5 °C(from ethyl acetate-hexane); IR ν(neat) 1765 $cm^{-1}$; NMR δ($CDCl_3$) 1.32(d, J=6.2 Hz, 3 H), 1.78(brs, 1 H), 2.46(d, J=2.2 Hz, 1 H), 3.38(ddd, J=0.8, 2.2, 4.5 Hz, 1 H), 4.26(dq, J=4.5, 6.2 Hz, 1 H), 4.34(dd, J=2.2, 2.2 Hz, 1 H), 6.07(brs, 1 H); MS, m/z 135, 95, 81, 53, 43(bp); Anal Calcd for $C_7H_9O_2N$ C, 60.42; H, 6.52; N, 10.07. Found C, 60.26; H, 6.41; N, 9.91. $[\alpha]^{14.5}$+30.18°(c, 1.08, MeOH).

**(3*S*, 4*S*)-4-Ethynyl-3-[(1*R*)-*tert*-butyldimethylsiloxyethyl]-azetidinone (23')** To a solution of **22'**(13.9 mg, 0.1 mmol) and $Et_3N$(63 mL, 0.45 mmol) in DMF(0.04 mL) was added t-$BuMe_2SiCl$(60.3 mg, 0.4 mmol) at 0 °C and the solution was stirred for 11 hr at room temperature. After usual work up, the residue was dissolved in THF(0.16 mL). To the solution was added AcOH(14 μL, 0.24 mmol) and *n*-$Bu_4NF$(0.12 mL, 0.12 mmol) at 0 °C and the solution was stirred for 10 min. Ethyl acetate was added and the organic layer was washed with sat.$NaHCO_3$ and brine, dried over $Na_2SO_4$ and concentrated. The residue was purified by chromatography ($Et_2O$-n-hexane=1:3-1:1) to give colorless crystals of **23'**(22.5 mg, 89 %). mp 68-70 °C(from hexane); IR ν(neat) 3250, 1770$cm^{-1}$; NMR δ($CDCl_3$) 0.07(s, 6 H), 0.87(s, 9 H), 1.23(d, J=6.2 Hz, 3 H), 2.42(d, J=2.2 Hz, 1 H), 3.31(ddd, J=0.8, 2.6, 3.0 Hz, 1 H), 4.24(dq, J=3.0, 6.2 Hz, 1 H), 4.34(dd, J=2.2, 2.6 Hz, 5.91(brs, 1 H); MS, m/z 238, 196, 152(bp), 109, 75; Anal Calcd for $C_{13}H_{23}O_2NSiI$ C, 61.62; H, 9.15; N, 5.53. Found C, 61.51; H, 9.20; N, 5.45. $[\alpha]^{13.5}$-2.69°(c, 0.52, $CHCl_3$).

**(3*S*, 4*S*)-3-[(1*R*)-*tert*-Butyldimethylsiloxyethyl]-4-carboxy-2-azetidinone (24').** To a solution of **23'**(81.5 mg, 0.322 mmol) and Adogen 464(24.9 mg) in $CH_2Cl_2$ was added $KMnO_4$(108.0 mg, 0.68 mmol) in AcOH(0.42 mL) and $H_2O$(1.7 mL) and the solution was refluxed for 40 min. To the solution was added $NaHSO_4$(96.0 mg, 0.8 mmol) and the solution was stirred at room temperature for 30 min. The solution was made acid by 50 % $H_2SO_4$ and the aqueous layer was extracted with $CH_2Cl_2$. The organic layer was dried over $MgSO_4$ and concentrated to give **24'**(55.0 mg, 63 %). From the neutral fraction the starting material **23'**(23.4 mg, 27 %) was recovered. **24'**: mp 137-138 °C(from n-hexane-$CH_2Cl_2$); IR ν(neat) 3450, 3300, 1775, 1745 $cm^{-1}$; NMR δ($CDCl_3$) 0.08(s, 6H), 0.88(s, 9 H), 1.26(d, J=6.0 Hz, 3 H), 3.3-3.4(m, 1 H), 4.1-4.5(m, 2 H), 6.0-6.2(brs, 1 H); MS, m/z 274($M^+$+1), 258, 216(bp), 130, 75, 69; $[\alpha]^{14}$-30°(c, 0.19, MeOH).

**(3*R*, 4*R*)-4-Acetoxy-3-[(1*R*)-*tert*-butyldimethylsiloxyethyl]-2-azetidinone (25').** A crude product which was prepared from **24'**(23.7 mg, 0.087 mmol) and AcONa(90.3 mg, 1.1 mmol) in $CH_3CN$-AcOH(4:1, 2.5 mL) in a similar procedure for the the synthesis of **5** was purified by chromatography(ethyl acetate-n-hexane=1:3) to give colorless crystals of **25'**(20.9 mg, 84 %). mp 107.0-108.0 °C(from $Et_2O$-n-hexane, lit.[15] 107-108 °C); $[\alpha]^{17.5}$ 51°(c, 1.00, $CHCl_3$)[lit.[15] $[\alpha]^{20}$ 53.4°(c, 1.00, $CHCl_3$)]

**N-Dianisylmethyl-3-acetyl-4-trimethylsilylethynyl-2-azetidinone(19).** To a benzene solution of 3-trimethylsilyl-2-propyn-1-al(1.26 g, 10.0 mmol) was added dianisylmethylamine (2.43 g, 10.0 mmol) at 0 °C and the solution was stirred for 10 min. After solvent was removed and the residual dianysilmethyl-2-trimethylsilyl ethynylimine was dissolved in THF(40 mL) containing imidazole(0.68 g, 10.0 mmol).

To the solution was added diketene(**17**, 1.68 g, 20.0 mmol) in THF(20 mL) at 0 °C for 5 hr under argon and the solution was stirred for 2 hr at 0 °C. To the reaction mixture was added 1N HCl solution(120 mL) and the aqueous layer was extracted with ethyl acetate. The organic layer was dried over $Na_2SO_4$ and evaporated. The residue was purified by chromatography($Et_2O$-n-hexane=1:1) to give colorless oil of **19**(3.96 g, 91 %): IR ν(neat) 2200, 1765, 1720 $cm^{-1}$; NMR δ($CDCl_3$) 0.13(s, 9 H), 2.30(s, 3 H), 3.80(s, 6 H), 4.23(d, J=2.7 Hz, 1 H), 4.47(d, J=2.7 Hz, 1 H), 5.85(s, 1 H), 6.93-7.27(m, 8 H); MS, m/z 435($M^+$), 392, 268, 242, 228, 227, 151, 97, 43.

**N-Dianisylmethyl-3-(1-hydroxyethyl)-4-trimethylsilylethynyl-2-azetidinone(20).** To the solution of K-selectride(0.5 M THF solution, 2.2 mL, 1.10 mmol) was added a solution of β-lactam **19**(200 mg, 0.46 mmol) in 5 mL $Et_2O$ and the solution was stirred for 45 min. The reaction mixture was poured into sat. $NH_4Cl$ solution and the aqueous layer was extracted with ethyl acetate. The organic layer was dried over $Na_2SO_4$ and concentrated. The residue was purified by chromatography ($Et_2O$-n-hexane=1:1-1:0) to give colorless oil of **20**(128 mg, 64 %) and **19**(70 mg, 35 %). **20** : IR ν(neat) 3450, 2200, 1745 $cm^{-1}$; NMR δ($CDCl_3$) 0.17(s, 9 H), 1.23(d, J=6.6 Hz, 3 H), 2.62(brs, 1 H), 3.17-3.33(m, 1 H), 3.77(s, 3 H), 4.03(d, J=2.4 Hz, 1 H), 5.91(s, 1 H), 6.70-6.93(m, 4 H), 7.08-7.37(m, 4 H); MS, m/z 437($M^+$), 227.

**3-(1-Hydoxyethyl)-4-trimethylsilylethynyl-2-azetidinone(21).** To a solution of alcohol **56**(1.10 g, 2.5 mmol) in 35 mL $CH_3CN$-$H_2O$(9:1) was added CAN(2.73 g, 4.98 mmol) at room temperature and the solution was stirred for 30 min. Water was added and the aqueous layer was extracted with ethyl acetate. The organic layer was dried over $Na_2SO_4$ and concentrated. The residue was purified by chromatography ($Et_2O$) to give colorless oil of **21**(448 mg, 85 %): IR ν(neat) 3350, 2200, 1755 $cm^{-1}$; NMR δ($CDCl_3$) 0.18(s, 9 H), 1.30 and 1.38(d, J=6.6 Hz, 3 H), 3.20-3.42(m, 1 H), 4.20 and 4.28(d, J=2.4 Hz, 1 H), 6.52(brs, 1 H); MS, 153, 75, 73.

**4-Ethynyl-3-(1-hydroxyethyl)-2-azetidinone(22).** A solution of **21**(448.3 mg, 2.12 mmol) in THF(4.2 mL) and aq. 1 N-NaOH(4.2 mL) was stirred for 2 hr at room temperature. After THF was evaporated under reduced pressure, the aqueous layer was extracted with ethyl acetate by salting-out technique and dried over $Na_2SO_4$. The residue was purified by chromatography(ethyl acetate-n-hexane=1:1) to give colorless oil of **22**(245.5 ng, 83 %). The spectral data was identical with those of **22'**.

**S-Phenyl (2*R*, 3*S*) 2-ethyl-3-N-(*R*)-α-benzylmethylamino-5-trimethylsilyl-4-pentynethiate(35).** To a solution of thiol ester(1.8 g, 10 mmol) and *i*-$Pr_2NEt$(2.1 mL, 12 mmol) in $CH_2Cl_2$(20 mL) was added 9-BBNOTf(2.2 mL, 12 mmol) at -78 °C and the solution was stirred at 0 °C for 1 hr. To the solution was added imine **34** in $CH_2Cl_2$(20 mL), which was prepared from 3-trimethylsilylpropynal(1.51 g, 12 mmol), (*R*)-α-benzylmethylamine(1.55 g, 12 mmol) and $MgSO_4$ in benzene, was added. The solution was gradually warmed to room temperature and the solution was stirred at 25 °C for 20 hr. Phosphate buffer(pH 7, 50 mL) was added to the reaction mixture at -78 °C and the solution was stirred at 25 °C for 30 min. The aqueous layer was extracted with $CH_2Cl_2$ and the organic layer was dried over $Na_2SO_4$ and concentrated. The residue was purified by short chromatography($Et_2O$-n-hexane=1:4). To the residue in $Et_2O$-MeOH(2:1, 40 mL) was added c-$H_2SO_4$(5 mL) and the solution was stirred at room temperature for 5 hr. The solution was neutralyzed by $K_2CO_3$ and the aqueous layer was extracted with ethyl acetate. The organic layer was dried over $Na_2SO_4$ and concentrated. The residue was purified by chromatography($Et_2O$-n-hexane=1:20) to give pale yellow oil of **35**(2.8 g, 69 %). IR ν(neat) 2150, 1700 $cm^{-1}$; NMR δ($CDCl_3$) 0.17(s, 9 H), 1.00(t, J=8.0 Hz, 3 H), 1.24(d, J=6.5 Hz, 3 H), 1.6-2.1(m, 2 H0, 2.7(ddd, J=6.0, 8.0, 16.0 Hz, 1 H), 3.75(d, J=8.0 Hz, 1 H), 4.05(q, J=6.5 Hz, 1 H), 7.15-7.50(m, 5 H); MS, m/z 409($M^+$), 304, 230, 126, 105(bp); HRMS Calcd for $C_{24}H_{31}ONSiS$, 409.1895 Found 409.1885.

**(3*R*, 4*S*)-3-Ethyl-4-trimethylsilylethyl-N-(*R*)-α-benzylmethylamino-2-azetidinone(32).** To the solution of **35**(102.0 mg, 0.249 mmol) in $Et_2O$(10 mL) was added t-BuMgCl(1.1 M THF solution, 0.5 mL, 0.5 mmol) and the solution was stirred at 0 °C for 3 hr. The solution was neutralyzed with 1N HCl solution and the aqueous layer was extracted with ethyl acetate. The organic layer was dried over $Na_2SO_4$ and concentrated. The residue was purified by chromatography($Et_2O$-n-hexane=1:4) to give pale yellow oil of **32**(46.0 mg, 62 %): IR ν(neat) 2175, 1755 $cm^{-1}$; NMR δ($CDCl_3$) 0.80((t, J=8.0 Hz, 3 H), 1.30-1.85(m, 2 H), 1.60(d, J=6.0 Hz, 1 H), 3.00(ddd, J=2.2, 6.0, 7.0 Hz, 1 H), 3.45(d, J=2.2 Hz, 1 H), 4.95(q, J=6.0 Hz, 1 H); MS, m/z 299($M^+$), 152, 137(bp), 105; HRMS Calcd for $C_{18}H_{25}ONSi$, 299.1705 Found 299.1677.

**(3*R*, 4*S*),-3-Ethyl-4-ethynyl-N-(*R*)-α-benzylmethylamino-2-azetidinone (36).** To the solution of **32**(1.20 g, 4.0 mmol) in THF(4 mL) was added *n*-$Bu_4NF$(1 M solution, 6 mL, 6.0 mmol) at 0 °C and the solution was stirred at 0 °C for 30 min. Water was added and the aqueous layer was extracted with $Et_2O$. The organic layer was dried over $Na_2SO_4$ and concentrated. The residue was purified by chromatography ($Et_2O$) to give colorless oil of **36**(915 mg, 100 %). IR ν(neat) 1765 $cm^{-1}$; NMR δ($CDCl_3$) 0.90(t, J=7.4 Hz, 3 H), 1.40-1.90(m, 2 H), 1.68(d, J=7.0 Hz, 3 H), 2.44(d, J=2.0 Hz, 1 H), 3.10(ddd, J=2.1, 5.8, 8.0 Hz, 1 H), 3.50(t, J=2.1 Hz, 1 H), 5.06(q, J=7.0 Hz, 1 H), 7.33(s, 5 H). MS, m/z 132, 105, 79.

**(3*R*, 4*S*)-3-Ethyl-4-ethynyl-2-azetidinone(37) and (3*R*, 4*R*)-3-Ethyl-4-vinyl-2-azetidinone(38).** To a solution of liq.$NH_3$(4 mL) containing Na(85 mg, 3.69 mmol) was added **36**(141.0 mg, 0.621 mmol) in $Et_2O$(4 mL) at -78 °C and the solution was stirred for 30 min. To the solution was added sat. NaCl solution(0.5 mL) and the liq.$NH_3$ was evaporated at room temperature. The residue was dissolved in $Et_2O$ and the organic layer was dried over $Na_2SO_4$ and concentrated. The residue was purified by chromatography($Et_2O$) to give colorless oil of **37** and **38**(44 mg, 57 %). **37**: IR ν(neat) 2125, 1750 $cm^{-1}$; NMR δ($CDCl_3$) 1.10(t, J=7.2 Hz, 3 H), 1.50-2.00(m, 2 H), 2.45(d, J=2.0 Hz, 1 H), 3.20-3.42(m, 1 H), 3.90(t, J=2.5 Hz, 1 H), 3.90(t, J=2.5 Hz, 1 H), 5.80-6.10(brs, 1 H); MS, m/z 105, 79(bp), 65, 52, 41. **38**: IR ν(neat) 1750, 1640 $cm^{-1}$; NMR δ($CDCl_3$) 1.20(t, J=7.2 Hz, 3 H), 1.60-2.00(m, 2 H), 2.70-2.90(m, 1 H), 3.80(dd, J=2.2, 6.8 Hz, 1 H), 5.10-5.40(m, 2 H), 5.80-6.10(m, 1 H), 6.20-6.60(brs, 1 H); MS, m/z 84, 67, 55, 41.

**(3*R*, 4*S*)-3-Ethyl-4-carboxy-2-azetidinone(31).** From a mixture of **37** and **38**(18.0 mg, 0.146 mmol), **31**(19.0 mg, 67 %) was obtained in a similar manner for the synthesis of **24'**. IR ν(neat) 3450, 3300, 1740 $cm^{-1}$; NMR δ($CDCl_3$) 1.10(t, J=7.3 Hz, 3 H), 1.60-2.10(m, 2 H), 3.30(brt, J=4.6 Hz, 3 H), 3.93(d, J=2.4 Hz, 1 H), 6.30(brs, 1 H), 6.90(brs, 1 H); MS, m/z 144($M^+$+1), 100(bp), 82, 73, 55, 41; HRMS Calcd for $C_6H_{10}O_3N$($M^+$1), 144.0653 Found 144.0647.

**(3*R*)-4-Acetoxy-3-ethyl-2-azetidinone(30).** A crude product which was prepared from **31**(16.0 mg, 0.112 mmol) and AcONa(2.2 mg, 0.027 mmol) in $CH_3CN$-AcOH(4:1) in a similar manner for the synthesis of **5** was purified by chromatography(ethyl acetate) to give **30**(14.7 mg, 84 %) after 5.8 F/mol of electricity was passed through the solution. IR ν(neat) 3500, 1780, 1750 $cm^{-1}$; NMR δ($CDCl_3$) 1.06(t, J=2.7 Hz, 3 H), 1.60-2.00(m, 2 H), 2.12 and 2.13(s, 1 H), 3.16(t, J=5.0 Hz, 3.20-3.35(m), 5.55(s), 5.86(d, J=3.0 Hz); MS, m/z 158($M^+$+1), 114(bp), 97; HRMS Calcd for $C_7H_{12}O_3N$($M^+$1), 158.0817. Found 158.0824.

**(3*R*,4*R*)-3-Ethyl-4-[3-diazo-2-oxo-3-(*p*-nitrobenzyloxycarbonyl)propyl]-2-azetidinone(40).** A solution of 4-acetoxy-β-lactam **30**(13.8 mg, 0.088 mmol), diazo-compound **39**(66.0 mg, 0.176 mmol) and $ZnCl_2$(6.0 mg, 0.044 mmol) in $CH_2Cl_2$(1.5 mL) was stirred at room temperature for 1.5 hr. The organic layer was washed with brine, dried over $Na_2SO_4$ and concentrated. The residue was purified by chromato-

graphy(ethyl acetate-n-hexane=1:4) to give colorless oil of **40**(18.7 mg, 59 %). The spectral data were identical with those of the literature.[21] $[\alpha]^{27}+60°$(c, 0.94, $CHCl_3$) [lit.[21] $[\alpha]^{27}+62°$(c, 1.00, $CHCl_3$)]

**p-Nitrobenzyl (2R, 5R, 6 R)-6-Ethyl-3,7-dioxo-1-azabicyclo[3,2,0] heptane-2-carboxylate(41).** A solution of **40**(4.5 mg, 0.013 mmol) and $Rh_2(OAc)_4$ in benzene(0.5 mL) was refluxed for 30 min. The solution was filtered through celite and the solvent was removed to give **41**(4.2 mg, 100 %). The spectral data were fully agreed with those of the literature.[21]

**References and Notes**

1. Szabo, W. A. *Aldchimica Acta*, 1977, *10*, 23.Hanser, F. M.; Ellenberger, S. R. *Synthesis*, 1987, 324.
2 Easton, C. J.; Love, S. G. *Tetrahedron Lett.*, 1986, *27*, 2315. Easton, C. J.; Love, S. G.; Wang, P. *J. Chem. Soc., Perkin trans. I*, 1990, 277.
3. Reider, P. J.; Grabowski, E. J. J. *Tetrahedron Lett.*, 1982, *23*, 2293.
4. Shiozaki, M.; Ishida, N.; Maruyama, H.; Hiraoka, T. *Tetrahedron*, 1983, *39*, 2399.
5. Ohashi, T.; Suga, K.; Sada, I.; Miyama, T.; Watanabe, K. Eur. Pat. Appl. Ep 167, 155(Cl. Co7F7/10), 08 Jan. 1986. Japan Kokai Tokkyo, Koho 1986, JP61-18791.
6. Electrochemical oxidation of lactams: Okita, M.; Wakamatsu, T.; Ban, Y. J. *Chem. Soc. Chem. Comm.*, 1979, 749. Okita, M.; Wakamatsu, T.; Mori, M.; Ban, Y. *Heterocycles*, 1980, *14*, 1089.
7. Preliminary reports: Mori, M.; Kagechika, K.; Tohjima, K.; Shibasaki, M. *Tetrahedron Lett.*, 1988, *29*, 1409.
8. M. Okita; Mori, M.; Wakamatsu, T.; Ban, Y. *Heterocycles*, 1985, *23*, 247. Mori, M.; Ban, Y. *ibid.*, 1985, *23*, 317. Mori, M. "Recent Advances in Electroorganic Synthesis" edited by Torii, S. Elsevier, 1987, p 89.
9. Iwasaki, T.; Horikawa, H.; Matsumoto, K.; Miyoshi, M. *J. Org. Chem.*, 1977, *42*, 2419. idem. *ibid.*, 1979, *44*, 1552.
10. Thomas, H. G.; Katzer, E. *Tetrahedron Lett.*, 1974, 887.
11. Salzmann, T. N.; Ratcliffe, R. W.; Christensen, B. G.; Bouffard, F. A. *J. Am. Chem. Soc.*, 1980, *102*, 6161.
12. Sugasawa, J.; Aida, K.; Enomoto, M.; Sasaki, A. *Japan Kokai tokkyo Koho* 1984, JP59-70663.
13. Lee, D. G.; Chang, V. S. *Synthesis*, 1978, 462.
14. Iimori, T.; Shibasaki, M., *Tetrahedron Lett.*, 1986, *27*, 2149. Iimori, T, Ishida, Y.; Shibasaki, M. *ibid.*, 1986, *27*, 2153.
15. DiNinno, F; Beattie, T. R.; Christensen, B. G. *J. Org Chem.*, 1977, *42*, 2960. Girijavallabhan, V. M.; Ganguly, A. K.; McCombie, S. W.; Pinto, P.; Rizvi, R. *Tetrahedron Lett.*, 1981, *22*, 3485. Hirai, K.; Iwano, Y.; Fujimoto, K. *Heterocycles*, 1982, *17*, 201. Allmendinger, T.; Rihs, G.; Wetter, H. *Helv. Chim. Acta*, 1988, *71*, 395.
16. Yamamoto, K.; Yoshioka, T.; Kato, Y.; Shibamoto, N.; Okamura, K.; Shimauchi, Y.; Ishikura, T. *J. Antibiotic*, 1980, *33*, 796.
17. Shibasaki, M., Ishida, Y., Iwasaki, G.; Iimori, T. *J. Org. Chem.*, 1987, *52*, 3488.
18. Recent formal total synthesis of (+)-PS-5: Odrizola, J. M.; Cossio, F. P.; Palomo, C. *J. Chem. Soc., Chem. Commun.*, 1988, 809.
19. Preliminary report: Mori, M.; Kagechika, K.; Sasai, H.; Shibasaki, M. *Chem. Express*, 1989, *4*, 89.
20. Georg, G. I.; Kant, J. *J. Org. Chem.*, 1988, *53*, 692.
21. Favara, D.; Omodei-Sale, A.; Consonni, P.; Depaoli, A. *Tetrahedron Lett.*, 1982, *23*, 3105.