SYNTHETIC STUDIES ON CARBAPENEM ANTIBIOTICS FROM PENICILLINS. VI[1]. SYNTHESES OF OPTICALLY ACTIVE *O*-METHYLCARPETIMYCIN AND *O*-METHYL-6-EPICARPETIMYCIN

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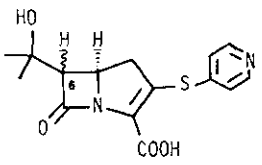
Abstract——The syntheses of the optically active *O*-methylcarpetimycin 2a and *O*-methyl-6-epicarpetimycin 2b were achieved by a route involving one-pot syntheses of 5a and 5b from 3.

The potent and broad antibacterial activity of the carbapenem family of antibiotics represented by thienamycins[2] and carpetimycins[3] has attracted considerable attentions in recent years. In these carbapenem antibiotics the existence of the hydroxyalkyl side chains at C-6 is of great interest from the viewpoint of structure-activity relationships, because these side-chains might be considered to function in the direct binding of the antibiotics to the receptor sites of the bacterial cell-wall enzymes[4]. In the previous papers,[5,6] we reported the syntheses



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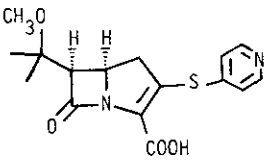
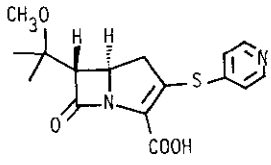
a: 6R, b: 6S



2a (6R)

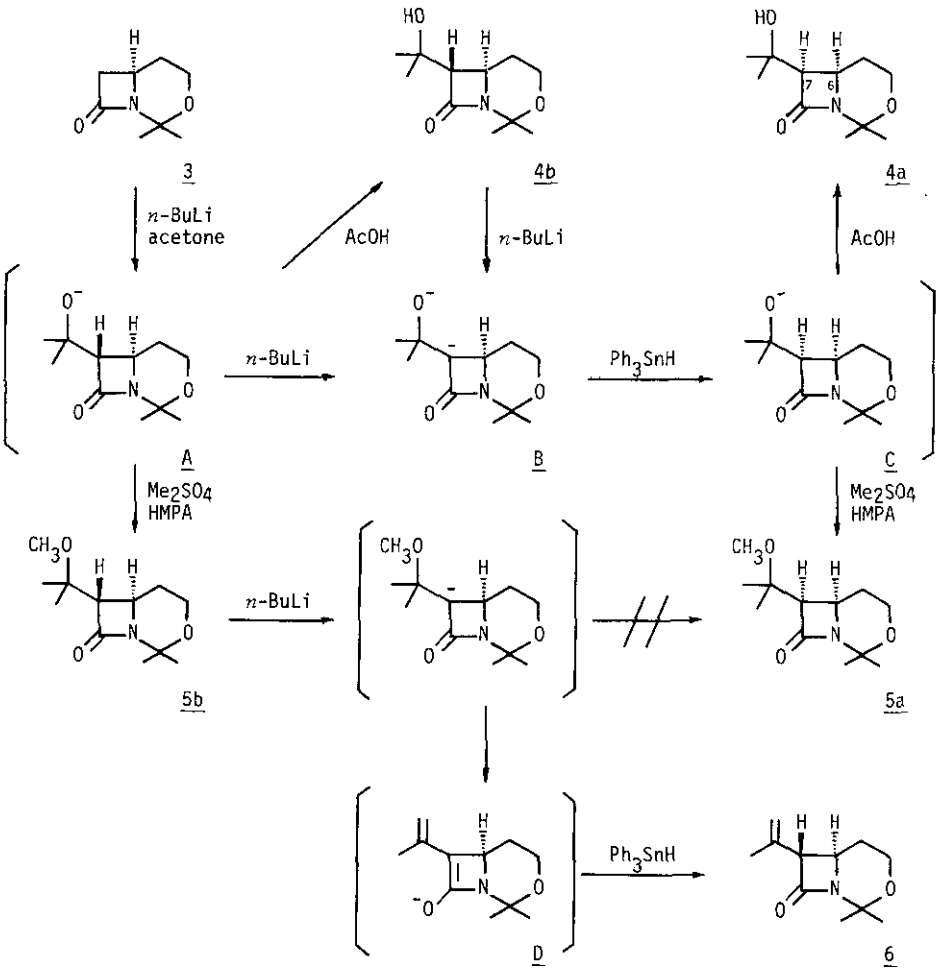


2b (6S)

of a carpetimycin 1a and a 6-epicarpetimycin 1b. As part of our continuing program on the synthesis of carbapenem antibiotics, we have now been interested in preparing the *O*-alkylcarpetimycins in order to clarify the role of the hydroxy

group of carpetimycins in exertion of the antibacterial activity. Herein we report the syntheses of *O*-methylcarpetimycin 2a and the corresponding *O*-methyl-6-epi-carpetimycin 2b and their antibacterial activities.

In the preceding paper,[7] we reported a method for the stereoselective synthesis of 6,7-cis-azetidinone 4a from 3 by a kinetic protonation of the dianion B derived from the aldol reaction intermediate A. This method was extended to the synthesis of *O*-methyl-6,7-cis-azetidinone 5a, a key intermediate for *O*-methylcarpetimycin 2a. Although 5a could be obtained from 3 by three-step reactions involving aldol reaction of 3 with acetone to 4b,[7] conversion of 4b to 4a via kinetic protonation,[7] and methylation of 4a to 5a, we sought a more direct method for preparation of 5a from 3. Thus, we initially attempted methylation of the intermediate A to 5b and



subsequent conversion of 5b to 5a by kinetic protonation. Compound 5b, the intermediary product in this sequence of reactions, would serve simultaneously as a key intermediate for *O*-methyl-6-epicarpetimycin 2b.

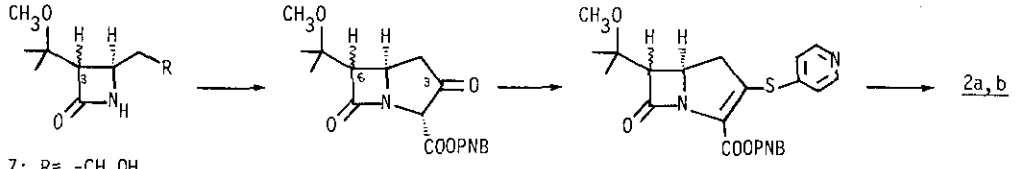
For the preparation of the intermediate A, 3 was treated with *n*-BuLi (1.05 equiv) at -78°C and followed by addition of acetone (1.05 equiv) at the same temperature. The intermediate thus formed in situ was then treated with Me_2SO_4 (2 equiv) in the presence of HMPA (1.05 equiv) at r. t. overnight to give, after quenching with AcOH and workup in the usual manner, 5b in 59% isolation yield. It was found that in the latter *O*-alkylation reaction the addition of HMPA was an indispensable requirement, because treatment of the intermediate A with Me_2SO_4 in the absence of HMPA did not give the desired product 5b.

With a view to converting 5b to 5a by kinetic protonation, we treated 5b with *n*-BuLi (2 equiv) and then with Ph_3SnH (4 equiv) in a manner similar to that used for conversion of 4b to 4a[7], resulting, after quenching with AcOH, in the formation of isopropenylazetidinone 6 in 87% yield by elimination of the methoxy group probably via the conjugated enolate D. It is probable that the protonation occurred at the oxygen of D probably upon quenching with AcOH and the resulting enol was transformed to the thermodynamically stable trans product 6. Therefore, we turned to conversion of A to C at first and methylation of C subsequently. After treatment of 3 with *n*-BuLi and acetone as described above, the reaction mixture was treated with an additional *n*-BuLi (3 equiv) at -78°C giving the intermediate B, which was successively treated with Ph_3SnH (8 equiv) at -78°C∿r. t. to give the intermediate C. After cooling again to -78°C, Me_2SO_4 and NMPA were added and the reaction mixture was kept at r. t. overnight. Workup in the usual manner and column chromatography on silica gel gave 5a in 26% yield along with 41% yield of 5b. When 4a was isolated after treatment of C with AcOH (37% yield)[7] and then subjected to alkylation with Me_2SO_4 in a similar conditions, the yield of 5a was 52% (22% total yield from 3). The one-pot preparation of 5a from 3 is thus advantageous because of the simpler operation and the somewhat better yield of 5a.

For the synthesis of *O*-methylcarpetimycin 2a, the acetonide protecting group in 5a was removed by treatment with aqueous AcOH to give alcohol 7a, which, on Jones oxidation, gave rise to carboxylic acid 8a. After conversion of 8a to β-keto ester 9a according to the Masamune's method[8], 9a was transformed to the protected *O*-methylcarpetimycin 12a by employing the Merck method[9] as follows. Diazotization of 9a to 10a was followed by cyclization via a carbene insertion reaction by

treatment with $Rh_2(OAc)_4$ to give 11a, whose 3-carbonyl group was activated by treatment with $(CF_3SO_2)_2O$ and then allowed to react with 4-mercaptopyridine to give 12a. Deprotection of 12a by hydrogenation yielded the optically active *O*-methylcarpetimycin 2a.

A similar sequence of reactions from 5b provided *O*-methyl-6-epicarpetimycin 2b. Thus, deprotection of 5b by treatment with aqueous AcOH, followed by Jones oxidation, gave carboxylic acid 8b, which was converted to ß-keto ester 9b and then transformed to 2b via 10b, 11b, and 12b, in a similar manner as described above.



7: R= $-CH_2OH$
8: R= -COOH
9: R= $-COCH_2COOPNB$
10: R= $-COC(N_2)COOPNB$

a: 3R, b: 3S

11

a: 6R, b: 6S

12

a: 6R, b: 6S

The antibacterial activities of 2a and 2b were found to be appreciably less than those of the corresponding parent compounds 1a and 1b (MIC against *S. aureus* : 1a, 0.2; 1b, 1.3; 2a, 1.3; 2b, 25 µg/mL. MIC against *E. coli*: 1a, 0.3; 1b, 21; 2a, 35; 2b, 100 µg/mL). These results indicated that the existence of the hydroxy group on the C-6 side chains is desirable for the activity in the carpetimycin series of compounds.

EXPERIMENTAL

IR spectra were recorded on a Shimazu IR-420 spectrometer. ^1H NMR spectra were taken on a JNM-PS-100 or a JNM-MH-100 spectrometer at 100MHz using $SiMe_4$ as an internal standard. UV spectra were measured with a Hitachi 320 spectrophotometer. For thin layer chromatography (TLC), Merck Kieselgel 60 F-254 was used. For column chromatography, Merck kieselgel 60 (70-230 mesh ASTM) was used.

(6R,7R)-2,2-Dimethyl-7-(1-methoxy-1-methylethyl)-1-aza-3-oxabicyclo[4.2.0.]octan-8-one (5a) from 3: To a solution of azetidinone 3 (143 mg, 0.92 mmol) in THF (7.15 mL) was added dropwise a solution of *n*-BuLi (0.65 mL, 1.5M solution, 0.97

mmol) in hexane at -78°C. After stirring for 10 min, a solution of acetone (0.071 mL, 0.97 mmol) in THF (0.71 mL) was added and the mixture was stirred for 20 min at the same temperature. To this mixture was added an additional solution of *n*-BuLi (1.84 mL, 2.76 mmol) in hexane and, after stirring for 1.5 h, a solution of Ph_3SnH (1.88 mL, 7.36 mmol) in THF (18.8 mL) was added. The resulting mixture was allowed to warm to room temperature over a period of 1 h and stirred at room temperature for 40 min. After cooling to -78°C, HMPA (176 μL, 1.01 mmol) and Me_2SO_4 (696 μL, 1.84 mmol) were added and the mixture was allowed to warm to room temperature and stirred at room temperature overnight. After quenching with AcOH (421 μL, 7.36 mmol), the solvent was removed by evaporation and the residue was dissolved in $CHCl_3$ (100 mL) and washed with a mixture of 10% aq $NaHCO_3$ (8 mL) and brine (20 mL). The washings were extracted with $CHCl_3$ and the combined $CHCl_3$ extracts were washed with brine, dried over $MgSO_4$, and evaporated. The residue was chromatographed on silica gel (60 g) eluting with a mixture of acetone and CH_2Cl_2 (1:100 to 1:9) to give 5a (54.4 mg, 26% yield) and 5b (85.7 mg, 41% yield). 5a: IR(CH_2Cl_2) 2930, 1740, 1370, 1075 cm^{-1}; NMR($CDCl_3$) δ1.21(s, 3H), 1.37(s, 3H), 1.39(s, 3H), 1.5-1.8 (m, 1H), 1.74(s, 3H), 2.3-3.0(m, 1H), 3.16(d, 1H, J=5Hz), 3.25(s, 3H), 3.5-4.0(m, 1H), 3.87(dd, 2H, J=3, 10Hz). 5b: IR(CH_2Cl_2) 1745, 1370, 1350, 1070, 1060 cm^{-1}; NMR($CDCl_3$) δ1.26(s, 6H), 1.40(s, 3H), 1.6-2.0(m, 2H), 1.77(s, 3H), 2.89(d, 1H, J=3Hz), 3.20(s, 3H), 3.58(ddd, 1H, J=3, 6, 9Hz), 3.86(dd, 2H, J=3, 7Hz).

Preparation of 5a from 4a: To a solution of 4a[7] (43.0 mg, 0.202 mmol) in THF (1.29 mL) was added dropwise a solution of *n*-BuLi (0.128 mL of 1.74 M solution, 0.222 mmol) in hexane at -78°C and the mixture was stirred for 10 min at the same temperature. To this mixture was added HMPA (38.6 μL, 0.222 mmol) and the stirring was continued for 10 min. Then, a solution of Me_2SO_4 (38.2 μL, 0.404 mmol) in THF (0.344 mL) was added and the resulting mixture was allowed to warm to room temperature over a period of 1 h and stirred at room temperature overnight. After quenching with AcOH (12.7 μL, 0.222 mmol), the solvent was removed by evaporation and the residue was dissolved in EtOAc (10 mL) and washed with a mixture of 10% aq $NaHCO_3$ (0.3 mL) and brine (3 mL). The washings were extracted with EtOAc and the combined EtOAc extracts were washed with brine, dried over $MgSO_4$, and evaporated. The residue was chromatographed on silica gel (2.2 g) eluting with a mixture of EtOAc and CH_2Cl_2 (1:100 to 1:1) to give 5a (24.0 mg, 52% yield).

(6R,7S)-2,2-Dimethyl-7-(1-methoxy-1-methylethyl)-1-aza-3-oxabicyclo[4.2.0]octan-8-one (5b) from 3: To a solution of 3 (150 mg, 0.966 mmol) in THF (7.5 mL) was

added dropwise a solution of *n*-BuLi (0.677 mL, 1.5M solution, 1.01 mmol) in hexane at -78°C and the mixture was stirred for 10 min at the same temperature. Then, a solution of acetone (74.2 μL, 1.01 mmol) in THF (0.74 mL) was added and the mixture was stirred for 20 min. To this mixture were added HMPA (176 μL, 1.01 mmol) and Me_2SO_4 (183 μL, 1.932 mmol) and the mixture was allowed to warm to room temperature and stirred at room temperature overnight. After quenching with AcOH (111 μL, 1.932 mmol), the solvent was removed by evaporation and the residue was dissolved in $CHCl_3$ and washed with a mixture of 10% aq $NaHCO_3$ (2 mL) and brine (15 mL). The washings were extracted with $CHCl_3$ and the combined extracts were washed with brine, dried over $MgSO_4$, and evaporated. The residue was chromatographed on silica gel (20 g) eluting with a mixture of acetone and CH_2Cl_2 (1:100 to 1:9) to give 5b (130 mg, 59% yield).

(6R,7S)-2,2-Dimethyl-7-(1-methyleth-2-enyl)-1-aza-3-oxabicyclo[4.2.0]octan-8-one (6): To a solution of 5b (165 mg, 0.726 mmol) in THF (4.95 mL) was added dropwise a solution of *n*-BuLi (0.51 mL of 1.5 M solution, 0.762 mmol) in hexane at -78°C and the mixture was stirred for 30 min at the same temperature. To this mixture was added a solution of Ph_3SnH (0.2 mL, 0.799 mmol) in THF (2 mL) and the resulting mixture was allowed to warm to room temperature over a period of 1 h and stirred at room temperature for 1 h. After quenching with AcOH (60 μL, 1.09 mmol), the solvent was removed by evaporation and the residue was dissolved in EtOAc (40 mL) and washed with a mixture of 10% aq $NaHCO_3$ (2 mL) and brine (10 mL). The washings were extracted with EtOAc and the combined EtOAc extracts were washed with brine, dried over $MgSO_4$, and evaporated. The residue was chromatographed on silica gel (33 g) eluting with a mixture of acetone and CH_2Cl_2 (1:100 to 1:9) to give 6 (123 mg, 87% yield) as a white solid: IR(CH_2Cl_2) 1750, 1370, 1350, 1060 cm^{-1}; NMR($CDCl_3$) δ1.45(s, 3H), 1.50-2.20(m, 2H), 1.78(s, 3H), 1.80(s, 3H), 3.42(d, J=3Hz, 1H), 3.90(ddd, 1H, J=3, 6, 9Hz),4.95(m, 1H), 5.03(m, 1H).

(3R, 4R)-4-(2-Hydroxyethyl)-3-(1-methoxy-1-methylethyl)azetidin-2-one (7a): A solution of 5a (345 mg, 1.52 mmol) in a mixture of AcOH (5.52 mL) and H_2O (1.38 mL) was heated at 65°C for 30 min. The reaction mixture was cooled to room temperature and evaporated. Xylene was added to the residue and the resulting suspension was evaporated. The crystalline residue was dissolved in a mixture of MeOH and xylene and the solution was evaporated. This operation was repeated again and the resultant crystalline residue was washed with hexane to give 7a (275 mg, 97% yield): IR(CH_2Cl_2) 3600, 2900, 1750 cm^{-1}; NMR($CDCl_3$) δ1.31(s, 3H), 1.43(s,

3H), 2.0-2.2(m, 2H), 1.60(broad s, 1H), 3.26(s, 3H), 3.35(d, 1H, J=6Hz), 3.6-4.0(m, 3H), 6.66(broad s, 1H).

(3R, 4S)-4-(2-Hydroxyethyl)-3-(1-methoxy-1-methylethyl)azetidin-2-one (7b) was obtained in 95% yield from 5b in a manner similar to that used for the preparation of 7a: IR(CH_2Cl_2) 3400, 2930, 1750, 1370, 1060 cm^{-1}; NMR($CDCl_3$) δ1.26(s, 3H), 1.32(s, 3H), 1.7-2.0(m, 2H), 3.06(d, 1H, J=3Hz), 3.24(s, 3H), 3.6-3.9(m, 3H), 6.5(broad s, 1H).

(2R, 3R)-2-[3-(1-Methoxy-1-methylethyl)-4-oxoazetidin-2-yl]acetic acid (8a): A solution of 7a (250 mg, 1.33 mmol) in acetone (26.7 mL) was added to a 2N solution of Jones reagent (2.67 mL, 5.34 mmol) in acetone (24.03 mL) at room temperature over a period of 40 min and the mixture was stirred for 40 min. After addition of an excess of isopropyl alcohol, the solvent was removed by evaporation and the residue was dissolved in $CHCl_3$ and washed with brine. The aqueous layer was extracted with $CHCl_3$ and the extracts were combined, dried over $MgSO_4$, and evaporated. The resultant crystalline residue was washed with hexane to give 8a (211 mg, 79% yield): IR(Nujol) 3280, 3200, 1730, 1710 cm^{-1}; NMR(D_2O) δ1.25(s, 3H), 1.36(s, 3H), 2.98(d, 2H, J=7Hz), 3.22(s, 3H), 3.54(d, 1H, J=5Hz), 4.19(dt, 1H, J=5, 7Hz).

(2R, 3S)-2-[3-(1-Methoxy-1-methylethyl)-4-oxoazetidin-2-yl]acetic acid (8b) was obtained in 46% yield from 7b in a manner similar to that used for the preparation of 8a: IR(CH_2Cl_2) 3400, 2940, 1760, 1735, 1385, 1370, 1070 cm^{-1}; NMR(D_2O) δ 1.27(s, 6H), 2.70(d, 1H, J=6Hz), 2.75(d, 1H, J=2Hz), 3.21(s, 3H), 3.90(dt, 1H, J=2, 6Hz).

4-Nitrobenzyl (2R, 3R)-4-[3-(1-methoxy-1-methylethyl)-4-oxoazetidin-2-yl]3-oxo-butanoate (9a): N,N'-Carbonyldiimidazole (487.4 mg, 3.01 mmol) was added to a solution of 8a (550 mg, 2.73 mmol) in THF (22 mL) at room temperature. After stirring for 5 h, the magnesium salt of mono-*p*-nitrobenzyl malonate (1.505 g, 13.01 mmol) was added and the mixture was stirred overnight at room temperature. The solvent was removed by evaporation and the residue was dissolved in EtOAc and washed successively with 0.1N HCl, H_2O, 10% aq $NaHCO_3$, H_2O, 5% aq citric acid, H_2O, and brine. Drying over $MgSO_4$ and evaporation gave an oil, which was chromatographed on silica gel (25 g) eluting with a mixture of EtOAc (0-50%) in CH_2Cl_2 to give 9a (775 mg, 75% yield): IR(CH_2Cl_2) 3400, 3020, 1760, 1720, 1610, 1520, 1350 cm^{-1}; NMR($CDCl_3$) δ1.24(s, 3H), 1.44(s, 3H), 3.23(s, 3H), 3.2-3.4(m,

3H), 3.62(s, 2H), 4.0-4.2(m, 1H), 5.32(s, 2H), 6.20(broad s, 1H), 7.60(d, 2H, J=8Hz), 8.30(d, 2H, J=8Hz).

4-Nitrobenzyl (2R, 3S)-4-[3-(1-methoxy-1-methylethyl)-4-oxoazetidin-2-yl]-3-oxobutanoate (9b) was obtained in 63% yield from 8b in a manner similar to that used for the preparation of 9a: an amorphous solid; IR(CH_2Cl_2) 1755, 1715, 1600, 1520, 1345 cm^{-1}; NMR($CDCl_3$) δ1.26(s, 3H), 1.29(s, 3H), 2.5-3.4(m, 2H), 2.87(d, 1H, J=3Hz), 3.2(s, 3H), 3.59(s, 2H), 3.91(dt, 1H, J=3, 7Hz), 5.29(s, 2H), 6.16(broad s, 1H), 7.56(d, 2H, J=9Hz), 8.26(d, 2H, J=9Hz).

4-Nitrobenzyl (2R, 3R)-2-diazo-4-[3-(1-methoxy-1-methylethyl)-4-oxoazetidin-2-yl]-3-oxobutanoate (10a): A solution of *p*-toluenesulfonyl azide (470 mg, 2.38 mmol) in MeCN (4.23 mL) was added to a solution of 9a (752 mg, 1.99 mmol) in MeCN (15.04 mL) at 0°C. After stirring for 10 min, a solution of Et_3N (0.997 mL, 7.15 mmol) in MeCN (8.973 mL) was added and the stirring was continued for 50 min at the same temperature. The reaction mixture was evaporated and the residue was chromatographed on silica gel eluting with EtOAc (0.5%) in CH_2Cl_2 to give 10a (733 mg, 91% yield): IR(CH_2Cl_2) 3400, 2930, 2150, 1760, 1720, 1650, 1610, 1530, 1350 cm^{-1}; NMR($CDCl_3$) δ1.27(s, 3H), 1.44(s, 3H), 3.26(s, 3H), 3.35(d, 1H, J=7Hz), 3.58(m, 2H), 4.16(m, 1H), 5.42(s, 2H), 6.23(broad s, 1H), 7.62(d, 2H, J=9Hz), 8.33(d, 2H, J=9Hz).

4-Nitrobenzyl (2R, 3S)-2-diazo-4-[3-(1-methoxy-1-methylethyl)-4-oxoazetidin-2-yl]-3-oxobutanoate (10b) was obtained in 86% yield from 9b in a manner similar to that used for the preparation of 10a: an amorphous solid; IR(CH_2Cl_2) 3400, 2150, 1760, 1720, 1650, 1610, 1530, 1350 cm^{-1}; NMR($CDCl_3$) δ1.26(s, 3H), 1.30(s, 3H), 2.6-3.5(m, 2H), 2.95(d, 1H, J=3Hz), 3.2(s, 3H), 3.97(dt, 1H, J=3, 7Hz), 5.37(s, 2H), 6.15(broad s, 1H), 7.55(d, 2H, J=8Hz), 8.25(d, 2H, J=8Hz).

4-Nitrobenzyl (2R, 5R, 6R)-3,7-dioxo-6-(1-methoxy-1-methylethyl)-1-azabicyclo-[3.2.0]heptane-2-carboxylate (11a): A mixture of 10a (707 mg, 1.75 mmol) and $Rh_2(OAc)_4$ (ca. 5 mg) in benzene (20 mL) was refluxed for 30 min. After cooling to room temperature, the mixture was filtered by the aid of cellulose powder. The filtrate was evaporated to give 11a (690 mg, 100% yield): IR(CH_2Cl_2) 1770, 1750, 1610, 1520, 1350 cm^{-1}; NMR($CDCl_3$) δ1.25(s, 3H), 1.46(s, 3H), 2.60(dd, 1H, J=7, 19Hz), 3.18(s, 3H), 3.64(d, 1H, J=5Hz), 3.96(dd, 1H, J=7, 19Hz), 4.18(dt, 1H, J=5, 7Hz), 4.68(s, 1H), 5.30(ABq, 2H, J=16Hz), 7.60(d, 2H, J=8Hz), 8.26(d, 2H, J=8Hz).

4-Nitrobenzyl (2R, 5R, 6S)-3,7-dioxo-6-(1-methoxy-1-methylethyl)-1-azabicyclo-[3.2.0]heptane-2-carboxylate (11b) was obtained in 95% yield from 10b in a manner similar to that used for the preparation of 11a: an amorphous solid; IR(CH_2Cl_2) 1770, 1750, 1605, 1525, 1350 cm^{-1}; NMR($CDCl_3$) δ1.33(s, 3H), 1.37(s, 3H), 2.4(dd, 1H, J=8, 18Hz), 2.93(dd, 1H, J=8, 18Hz), 3.2(d, 1H, J=3Hz), 3.25(s, 3H), 4.1(dt, 1H, J=3, 8Hz), 4.72(s, 1H), 5.34(s, 2H), 7.45(d, 2H, J=9Hz), 8.14(d, 2H, J=9Hz).

4-Nitrobenzyl (5R, 6R)-6-(1-methoxy-1-methylethyl)-7-oxo-3-(4-pyridylthio)-1-azabicyclo[3.2.0]hept-2-ene-2-carboxylate (12a): A mixture of 11a (450 mg, 1.20 mmol), 4-(N,N-dimethylamino)pyridine (17.5 mg, 0.144 mmol), and N,N-diisopropyl-N-ethylamine (0.3 mL) in CH_2Cl_2 (22.5 mL) was cooled to -30°C and a solution of $(CF_3SO_2)_2O$ (0.253 mL, 1.5 mmol) in CH_2Cl_2 (1.899 mL) was added and the resulting mixture was stirred for 30 min at the same temperature. Then, the reaction mixture was cooled to -30°C and a solution of N,N-diisopropyl-N-ehtylamine (0.833 mL, 4.78 mmol) in CH_2Cl_2 (7.497 mL) and a solution of pyridine-4-thiol (159.5 mg, 1.43 mmol) in DMF (5.63 mL) were added. After stirring for 30 min at the same temperature and for 30 min at 0°C, the solvent was removed by evaporation and the residue was dissolved in EtOAc and washed with H_2O and brine. Drying over $MgSO_4$ and evaporation gave an oil, which was chromatographed on silica gel (13.5 g) deactivated with 10% H_2O, eluting with a mixture of benzene and acetone (100:1 to 6:1), to give 12a (379 mg, 71% yield) as a pale yellow solid: IR(CH_2Cl_2) 1780, 1710 cm^{-1}; NMR($CDCl_3$) δ1.14(s, 3H), 1.43(s, 3H), 2.57(dd, 1H, J=10, 18Hz), 3.22(s, 3H), 3.58(d, 1H, J=8Hz), 3.83(dd, 1H, J=10, 18Hz), 4.22(ddd, 1H, J=8, 10, 20Hz), 5.42(ABq, 2H, J=13Hz), 7.2-7.5(m, 2H), 7.6-7.8(m, 2H), 8.1-8.4(m, 2H), 8.5-8.7(m, 2H).

4-Nitrobenzyl (5R, 6S)-6-(1-methoxy-1-methylethyl)-7-oxo-3-(4-pyridylthio)-1-azabicyclo[3.2.0]hept-2-ene-2-carboxylate (12b) was obtained in 83% yield from 11b in a manner similar to that used for the preparation of 12a: an amorphous solid; IR(CH_2Cl_2) 1780, 1720, 1705, 1520, 1350 cm^{-1}.

Potassium (5R, 6R)-6-(1-methoxy-1-methylethyl)-7-oxo-3-(4-pyridylthio)-1-azabicyclo[3.2.0]hept-2-ene-2-carboxylate (2a): A mixture of 12a (520 mg, 1.11 mmol) and PtO_2 (173 mg) in a mixture of dioxane (62.4 mL), 0.1M aq K_2HPO_4 (33.23 mL), H_2O (8.39 mL) and EtOH (5.2 mL) was shaken for 1 h under hydrogen atmosphere (50 psi) at room temperature. After removal of the catalyst by filtration, the filtrate was washed with Et_2O at 0°C and concentrated. The residue was dissolved in H_2O (260

mL) containing KCl (13 g). The aqueous solution was chromatographed on non-ionic absorption resin, Diaion HP-20AG, eluting with H_2O (3 L) and 5% aq isopropyl alcohol (2 L). The fractions, which showed UVmax at 303 nm, were combined, concentrated, and lyophilized to give 2a (305 mg, 74% yield) as a white powder: IR(Nujol) 1750, 1600, 1570 cm^{-1}; NMR(D_2O) δ1.22(s, 3H), 1.38(s, 3H), 2.77(dd, 1H, J=10, 17Hz), 3.24(s, 3H), 3.52(dd, 1H, J=10, 17Hz), 3.86(d, 1H, J=7Hz), 4.33(ddd, 1H, J=7, 9, 10Hz), 7.3-7.7(m, 2H), 8.3-8.7(m, 2H); UV(H_2O) λmax 303 nm (ε, 9000).

Potassium (5R, 6S)-6-(1-methoxy-1-methylethyl)-7-oxo-3-(4-pyridylthio)-1-aza-bicyclo[3.2.0]hept-2-ene-2-carboxylate (2b) was obtained in 71% yield from 12b in a manner similar to that used for the preparation of 2a: a white powder; IR(Nujol) 3350, 1750, 1615, 1570, 1380 cm^{-1}; NMR(D_2O) δ1.3(s, 3H), 1.33(s, 3H), 2.89(d, 2H, J=10Hz), 3.24(s, 3H), 3.58(d, 1H, J=3Hz), 4.2(dt, 1H, J=3, 10Hz), 7.47(d, 2H, J=6Hz), 8.43(m, 2H); UV(H_2O) λmax 303 nm (ε, 10600).

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Received, 30th April, 1985