Tetrahedron Vol. 41, No. 3, pp. 519 to 525, 1985
Printed in Great Britain.

0040–4020/85 $3.00 + .00

ON THE REGIOSELECTIVITY OF THE BECKMANN REARRANGEMENT OF CYCLOBUTANONES WITH O-MESITYLENE-SULFONYLHYDROXYLAMINE. A CONVENIENT SYNTHESIS OF SUBSTITUTED OCTAHYDROCYCLOPENTA[b]PYRROLES

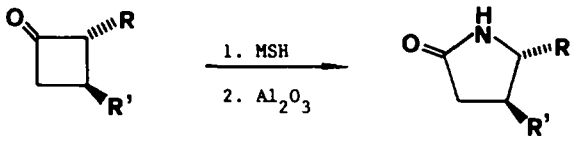
Tien-Yau Luh*, Hak-Fun Chow, Wai Yee Leung and Shang Wai Tam*

Department of Chemistry,
The Chinese University of Hong Kong,
Shatin, N.T., Hong Kong

(*Received in Japan* 29 *October* 1984)

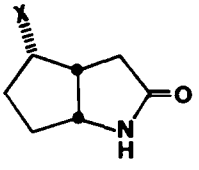
Abstract. Cyclobutanones were smoothly transformed into γ-lactams by Tamura reagent. The stereoelectronic effects on the modified Beckmann rearrangement were discussed. The extension to the synthesis of substituted octahydrocyclopenta[b]pyrroles was described.

The synthesis of pyrrolidine derivatives can usually be achieved by various kinds of cyclization reactions.[1] Relatively little attention was paid to the nitrogen insertion reaction[2,3] of cyclobutanones to give the corresponding pyrrolidones. To illustrate, Tamura reagent, O-mesitylenesulfonylhydroxylamine (MSH)[3] was recently used to effect a regio- and stereo-selective ring expansion of an unsymmetrical cyclobutanone (eq. 1).[4] On the other hand, dif-

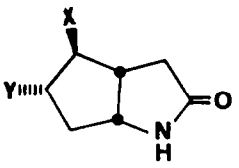


(1)

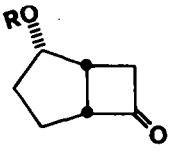
ferent regioselectivity was obtained when hydroxylamine was employed.[5] We recently need significant quantities of substituted octahydrocyclopenta[b]pyrroles 1, 2 and 3 for various purposes. Since



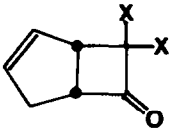
1 a X = OH
b X = OAc
c X = OMs



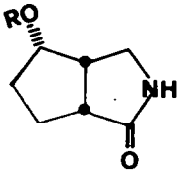
2 a X = Y = Br
b X = Br, Y = OMe



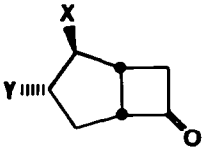
3 a R = H
b R = Ac
c R = Ms
d R = THP



4 a X = Cl
b X = H



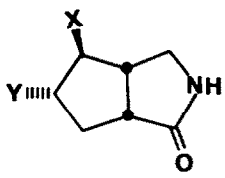
5 a R = H
b R = Ac



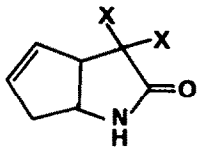
6 a X = Y = Br
b X = Br, Y = OMe

cyclobutanones can very smoothly undergo ring expansion to give γ-lactams, (eq. 1)[4] and the corresponding four-membered ring systems 3[6] and 4[7] or their derivatives can easily be synthesized, we felt that 1 and 2 might be readily obtained by using Tamura reagent.[3,8] We now wish to report a convenient synthesis of 1 and 2, and the stereoelectronic effects on the nitrogen insertion reaction in cyclobutanone by means of Tamura reagent.

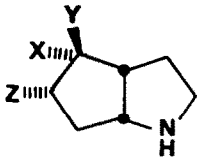
Treatment of 3a with MSH at room temperature followed by basic alumina, afforded a mixture of 1a and 5a in a ratio of 2 to 1, respectively. Similarly, 3b was transformed into 1b and 5b (2:1). These results were in contrast to a previous report[4,5] which suggested a regiospecific rearrangement under these conditions. In a similar manner, 6a afforded 2a and 7a (3:1), and 6b yielded 2b



7 a X = Y = Br
b X = Br, Y = OMe



8 a X = Cl
b X = H



9 a X = OMs, Y = Z = H
b X = H, Y = Z = Br
c X = H, Y = Br, Z = OMe

and 7b (3:1). Consequently, the nature of the substituent and the stereochemistry (exo or endo) of the substituent at positions 2 and 3 in bicyclo[3.2.0]heptanones 3 and 6 hardly affect the regioselectivity of the Beckmann rearrangement promoted by Tamura reagent. However, the selectivity improved when the reaction was operated at lower temperature. Thus, at -10°C a mixture of 1b and 5b in a ratio of 5 to 1 was obtained from 3b. It is interesting to note that both methanesulfonyl and tetrahydropyranyl groups are unstable under the reaction conditions. Thus both 3c and 3d afforded the same mixture of 1a and 5a. Presumably, the hydrolysis may proceed before rearrangement.

Although 1 and 2 were conveniently synthesized as described above, there is a drawback in these preparations. In all of these reactions, separations from their respective isomers were necessary. It is generally believed that the leaving group in oxime derivatives should be anti to the migratory group.[2d] Therefore, we felt that substituent with an electronegative group at C-7 position in 4 might affect the stereochemistry of the oxime which, in turn, might lead to some degree of regioselectivity.[10] We have tested this idea by reacting of 4a with Tamura reagent. Interestingly, only one isomer 8a was obtained in 68% yield. This observation clearly demonstrates the electronic effect on the migratory aptitude in the modified Beckmann rearrangement. Since 4a can readily be synthesized[7] such reactions would provide a convenient route for the synthesis of cyclopenta[b]pyrrole skeleton. The removal of the two chlorine atoms should be straightforward. Thus, treatment of 8a with zinc in glacial acetic acid afforded 8b in 89% yield. Addition of bromine to 8b yielded a single isomer 2a. On treatment with N-bromosuccinimide in methanol, 8b was smoothly transformed into 2b. The stereochemistry of these two products is identical to those obtained from the reactions of 6a and 6b whose stereochemistry was previously assigned.[9] The lactams, 1c, 2a and 2b were reduced with BH_3.THF to give 9a, 9b and 9c respectively.

In summary, we have depicted that cyclobutanones could readily be transformed into γ-lactam by Tamura reagent. The migratory aptitude strongly depends on the nature of the α-substituent(s) to the ketone function. By carefully choosing the appropriate substrate(s), substituted octahydrocyclopenta[b]pyrroles were conveniently prepared.

EXPERIMENTAL

Melting points (mp) and boiling points (bp) are uncorrected. ^{1}H-nuclear magnetic resonance (nmr) spectra were measured using a JEOL 60-HL spectrometer (60 MHz). ^{13}C-nmr spectra were measured on a JEOL FX-90Q spectrometer (22.5 MHz). Chemical shifts are reported in parts per million (ppm) downfield with respect to internal tetramethylsilane standard. Infrared (ir) spectra were determined on a Perkin-Elmer 283 spectrometer, and only peaks of significant maxima are reported. Mass spectra (ms) were obtained on a VG 7070F high resolution mass spectrometer. Elementary analyses were performed by Australian Microanalytical Service, Melbourne, Australia. Reagents and solvents were purified by standard procedures. MSH,[3a] 3a[6], 3b[6], 4a[7], 4b[7], 6a[9] and 6b[9] were prepared according to literature procedures.

4-Hydroxy-2-oxo-octahydrocyclopenta[b]pyrrole 1a and 4-hydroxy-1-oxo-octahydrocyclopenta[c]-pyrrole 5a. To a stirred solution of 3a (2.0 g, 15.9 mmol) in dichloromethane (20 mL) was added a solution of MSH (3.5 g, 16.3 mmol) in dichloromethane (20 mL) at -10°C. The reaction mixture was allowed to stand for 0.5 h. The solvent was removed in vacuo at room temperature to yield the crystalline oxime mesitylenesulfonate, which was then dissolved in benzene-methanol (3:1, 20 mL) and added dropwise to a stirred suspension of basic alumina (Merck, activity I; 100 g) in methanol (100 mL). The mixture was stirred for 4 h and filtered. The basic alumina was washed with anhydrous methanol (2x150 mL). The combined methanolic solution was concentrated in vacuo and the residue was chromatographed on silica gel. Hydroxy-lactams 1a and 5a were eluted by acetone-chloroform (2:1). The eluate was concentrated in vacuo, which on standing gave a white solid (1.9 g, 84%). Analysis by ^{13}C-nmr showed the ratio of 1a to 5a was approximately 3:1. The desired isomer 1a was isolated as white needle by successive recrystallization from ethyl acetate and then from methanol: mp 164-168°C; nmr δ(CD_3OD): 7.7-7.3 (1 H, bs, NH), 4.2-3.8 (3 H, m, H_4, H_{6a} and OH), 3.5-2.4 (2 H, m, H_3), 2.4-2.0 (1 H, m, H_{3a}) and 1.8-1.4 (4 H, m, H_5 and H_6); ^{13}C-nmr δ(CD_3OD): 180.8 (C-2), 73.7 (C-4), 59.8 (C-6a), 42.3 (C-3a), 33,9 (C-3), 31.2 (C-5) and 30.9 (C-6); ir (KBr, disc): 3500-3150 and 1683 cm^{-1}; ms (m/e): 141.0769 (calcd. for $C_7H_{11}NO_2$ 141.0790). Anal. Calcd for $C_7H_{11}NO_2$: C, 59.56; H, 7.85; N, 9.92 Found C, 59.78; H, 7.48; N, 9.63.

For the minor isomer, 5a nmr δ(CD_3OD): 7.7-7.3 (1 H, bs, NH), 4.2-3.8 (2 H, m, H_4 and OH), 3.5-2.4 (3 H, m, H_3 and H_{6a}), 2.4-2.0 (1 H, m, H_{3a}) and 1.8-1.4 (4 H, m, H_5 and H_6); ^{13}C-nmr δ(CD_3OD) : 183.0 (C-1), 75.0 (C-4), 46.5 (C-6a), 42.7 (C-3a), 41.6 (C-3), 32.2 (C-5) and 26.9 (C-6).

4-Acetoxy-2-oxo-octahydrocyclopenta[b]pyrrole 1b and 4-acetoxy-1-oxo-octahydrocyclopenta[c]-pyrrole 5b. To a stirred solution of 2-acetoxybicyclo[3.2.0]heptan-6-one 3b (3.0 g, 17.9 mmol) in dichloromethane (4.5 mL) was added a solution of MSH (7.0 g, 32.6 mmol) in dichloromethane (2.5 mL) at -10°C and the reaction mixture was allowed to stand for 10 min. The solvent was removed in vacuo to yield crystalline oxime sulfonate, which was suspended in benzene (2 mL) and was added into a stirred slurry of basic alumina (100 g) in methanol (150 mL) at -10°C. The mixture was stirred for 4 h and filtered. The basic alumina was washed with methanol (2x150 mL) and the combined methanolic solution was concentrated in vacuo. The residue was dissolved in chloroform (30 mL) and the insoluble material was removed by filtration. After evaporation of the solvent, the crude lactam-acetates 1b and 5b (3.0 g, 92%) were distilled with moderate decomposition to yield a colorless liquid, which on refrigeration gave a white solid (bp 136°C/0.02 mm). ^{13}C-nmr spectrum indicated the ratio of 1b to 5b was approximately 5:1. Attempts to seperate 1b from 5b were unsuccessful; nmr δ($CDCl_3$):7.3-6.9 (1 H, bs, NH), 5.2-4.8 (1 H, m, H_4), 4.2-3.9 (1 H, m, H_{6a}), 3.3-2.8 (1 H, m, H_{3a}), 2.4-2.1 (2 H, m, H_3), 2.0 (3 H, s, CH_3) and 2.1-1.7 (4 H, m, H_5 and H_6); ir(NaCl): 3400-3200, 1742, 1699 cm^{-1}; ms (m/e): 183.0879 (Calcd. for $C_9H_{13}NO_2$ 183.0895); ^{13}C-nmr: for 1b δ ($CDCl_3$): 178.1 (C-2), 170.3 (ester carbonyl), 75.4 (C-4), 57.8 (C-6a), 39.3 (C-3a), 30.5 (C-3), 30.1 (C-5), 28.7 (C-6) and 20.9 (CH_3); ^{13}C-nmr for 5b δ ($CDCl_3$): 180.4 (C-1), 170.4 (ester

carbonyl), 76.7 (C-4), 45.0 (C-6a), 40.8 (C-3), 39.7 (C-3a), 30.5 (C-5), 25.6 (C-6) and 21.0 (CH_3).

2-Tetrahydropyranyloxybicyclo[3.2.0]heptan-6-one 3d. 2-Hydroxybicyclo[3.2.0]heptan-6-one 3a (1.0 g, 7.9 mmol) in chloroform (2 mL) was mixed with dihydropyran (0.7 g, 8.3 mmol, freshly distilled from KOH pellets), followed by the addition of 3 drops of concentrated hydrochloric acid. The mixture was stirred overnight under nitrogen. Powdered anhydrous sodium carbonate (1 g) was added to neutralize the solution. The solid was filtered and washed with chloroform (2x50 mL). The organic solvent was removed *in vacuo*. Pure 3d was obtained as a diastereoisomeric mixture by distillation (1.3 g, 78%): bp 74°C/0.02 mm; nmr δ ($CDCl_3$): 4.6 (1 H, m, H_2), 4.4 (1 H, m, H_2), 3.8 (1 H, m, H_5), 3.6 (2 H, m, H_6), 3.0 (3 H, m, H_1 and H_7) and 2.0-1.4 (10 H, m, H_3, H_4, $H_{3'}$, H_4, and $H_{5'}$); ^{13}C-nmr δ ($CDCl_3$): 213.0, 212.5, 98.8, 97.5 79.0, 78.0, 62.9, 62.6, 62.6, 62.4, 46.5, 45.7, 31.6, 31.5, 30.9, 30.9, 29.5, 28.7, 25.5, 25.5, 24.5, 24.2, 19.7 and 19.5; ir (NaCl) 1786 cm^{-1}.

2-Methanesulfonyloxybicyclo[3.2.0]heptan-6-one 3c . To a solution of pyridine (1.02 g, 12.9 mmol) in ether (2 mL) was added dropwise a solution of methanesulfonyl chloride (1.48 g, 12.9 mmol). The mixture was stirred at 0°C for 15 min. 2-Hydroxybicyclo[3.2.0]heptan-6-one 3a (0.3 g, 2.4 mmol) was added dropwise and the mixture was stirred overnight. The solution was poured into dilute hydrochloric acid (10 mL, 10%) and was extracted with dichloromethane (2x100 mL). The combined organic solution was washed with dilute hydrochloric acid solution (3x20 mL), dilute potassium hydroxide solution (3x20 mL), and dried over magnesium sulfate, filtered and evaporated *in vacuo* to give 3c (0.4 g, 82%). Pure 3c was obtained by distillation with slight decomposition or by chromatography on silica gel (70-230 mesh) using benzene as eluent: bp 70°C/0.2 mm; nmr δ ($CDCl_3$): 5.2 (1 H, m, H_2), 3.5 (1 H, m, H_5), 3.20 (3 H, s, CH_3), 3.15 (2 H, m, H_7), 2.8 (1 H, m, H_1) and 2.5-1.6 (4 H, m, H_3 and H_4); ^{13}C-nmr δ ($CDCl_3$): 210.1 (C-6), 82.3 (C-2), 62.8 (C-5), 46.6 (C-7), 38.2 (CH_3), 31.0 (C-1), 29.4 (C-3) and 23.9 (C-4); ir(NaCl): 1785, 1359 and 1180 cm^{-1} ms (m/e): 204.0449 (Calcd. for $C_8H_{12}SO_4$ 204.0456).

Reaction of 3c with MSH. The procedure was essentially the same as described previously for 3a. 2-Methanesulfonyloxybicyclo[3.2.0]heptan-6-one 3c (0.5 g, 2.5 mmol) in dichloromethane (2 mL) was added into a dichloromethane solution (5 mL) of MSH (0.6 g, 2.8 mmol) at -10°C. The mixture was stirred for 15 min and the solvent was evaporated *in vacuo*, the residue was redissolved in benzene (15 mL) and added dropwise to a slurry of basic alumina in methanol (100 mL) and stirred for 4 h. The solution was filtered and washed with methanol (2x50 mL). Combined organic layers were removed *in vacuo* to give a viscous oil, which was chromatographed on silica gel using chloroform as eluent. Hydroxy-lactams 1a and 5a (0.28 g, 81%) were obtained when eluted by acetone-chloroform (1:1) mixture.

Reaction of 3d with MSH. The procedure was the same as described in the reaction of 3a. 2-Tetrahydropyranyloxybicyclo[3.2.0]heptan-6-one 3d (1.2 g, 5.7 mmol) was transformed into hydrolyzed products, hydroxy-lactams 1a and 5a (0.64 g, 80%).

4-Methanesulfonyloxy-2-oxo-octahydrocyclopenta[b]pyrrole 1c. Hydroxy-lactams 1a and 5a (600 mg, 4.26 mmol, 3:1) were dissolved in dry tetrahydrofuran (70 mL) and were added dropwise into a suspension of sodium hydride (130 mg, 80% dispersion in oil, 4.3 mmol) in tetrahydrofuran (5 mL) under nitrogen atmosphere. The solution was stirred at room temperature for 16 h until the hydrogen evolution subsided. Methanesulfonyl chloride (800 mg, 6.98 mmol) was added dropwise to the above mixture and was stirred for another 8 h at room temperature. The solution was then poured into a chloroform-tetrahydrofuran mixture (2:1, 150 mL), boiled and filtered when the solution was still hot. Evaporation of the filtrate *in vacuo* gave a colorless oil, which was chromatographed on silica gel (70-230 mesh). The first fraction eluted with benzene was methanesulfonyl chloride. The lactam-methanesulfonate 5c (150 mg, 0.68 mmol) was eluted with acetone-chloroform (1:3). The desired isomer 1c (300 mg, 1.37 mmol) was obtained from the fraction using acetone-chloroform (2:1) as eluent. Unreacted hydroxylactams 1a and 5a (200 mg, 1.42 mmol)

were isolated by flushing the column with acetone. The overall yield for 1c was 48% based on unrecovered hydroxy-lactams. Compound 1c slowly crystallized on refrigeration. An analytical sample of 1c was obtained as colorless needles by recrystallization from chloroform: mp 97-99°C; nmr δ ($CDCl_3$): 7.5-7.2 (1 H, bs, NH), 5.0 (1 H, m, H_4), 4.2 (1 H, m, H_{6a}), 3.5-3.2 (1 H, m, H_{3a}), 3.1 (3 H, s, CH_3), 2.5 (2 H, m, H_3) and 2.1-1.7 (4 H, m, H_5 and H_6); ^{13}C-nmr δ ($CDCl_3$): 177.4 (C-2), 81.2 (C-4), 57.1 (C-6a), 40.7 (C-3a), 38.5 (CH_3), 30.7, 30.3 and 30.1 (C-3, C-5 and C-6); ir (KBr) 3600-3200, 1683, 1360 and 1180 cm^{-1}; Anal. Calcd for $C_8H_{13}SO_4N$: C, 43.82; H, 5.98; N, 6.39; S, 14.62 Found C, 44.06; H, 6.19; N, 6.26; S, 14.30

4-exo-Brome-5-endo-methoxy-2-oxo-octahydrocyclopenta[b]pyrrole 2b and 4-exo-bromo-5-endo-methoxy-2-oxo-octahydrocyclopenta[c]pyrrole 7b . To a stirred solution of 2-exo-bromo-3-endo-methoxy-bicyclo[3.2.0]heptan-6-one 6b (2.0 g, 9.14 mmol) in dichloromethane (10 mL) was added dropwise a solution of MSH (2.6 g, 12.0 mmol) in dichloromethane (10 mL) at -10°C and the reaction mixture was allowed to stand for 15 min. The solvent was removed under reduced pressure to give crystalline oxime-sulfonate which was dissolved in benzene:methanol (3:1, 8 mL) and was added into a stirred slurry of basic alumina (80 g) in anhydrous methanol (150 mL). The mixture was stirred for 4 h and filtered. The basic alumina was washed with anhydrous methanol (2 x 70 mL) and the combined methanolic solution was concentrated in vacuo. The residue was dissolved in chloroform (70 mL) and the insoluble material was removed by filtration. After evaporation of the solvent, the residue was chromatographed on silica gel. Products 2b and 7b (1.6 g, 75%, ratio 3:1) were eluted by acetone-chloroform (1:2) as inseparable isomeric mixture: nmr δ ($CDCl_3$): 8.0-7.7 (1H, bs NH), 4.4-3.8 (3H, m, H_4, H_5 and H_{6a}), 3.4 (3H, s, CH_3), 3.2-3.0 (1H, m, H_{3a}), 2.8-1.8 (4H, m, H_3 and H_6); ir(KBr): 3500-3200, 1662 cm^{-1}; ^{13}C-nmr for 2b δ ($CDCl_3$): 176.7, 88.9 57.3, 56.9, 56.1, 46.3, 43.1 and 36.5; ^{13}C-nmr for 7b δ($CDCl_3$): 179.7, 88.5, 57.3, 57.1, 56.3, 47.5, 47.2, 31.4.

3,3-Dichloro-2-oxo-hexahydrocyclopenta-4-en[b]pyrrole 8a. To a stirred solution of 7,7-dichlorobicyclo[3.2.0]hept-2-en-6-one 4a (3.0 g, 16.9 mmol) in dichloromethane (20 mL) was added dropwise a solution of MSH (4.3 g, 20.0 mmol) in dichloromethane (20 mL) at room temperature. The reaction mixture was then stirred for an additional 1 h. The solvent was removed in vacuo to yield a colorless oil which was then dissolved in benzene-methanol (3:1, 20 mL) and added dropwise to a stirred suspension of basic alumina (110 g) in anhydrous methanol (110 mL). The mixture was stirred for 4 h and filtered. The alumina was washed with methanol (2 x 100 mL). The combined methanolic solution was concentrated in vacuo. The residue was dissolved in chloroform (30 mL) and the insoluble material was removed. After evaporation of the solvent, the residue was chromatographed on silica gel (70-230 mesh). The first fraction was a mixture of methyl mesitylenesulfonate and 4a. The lactam product, 3,3-dichloro-2-oxo-hexahydrocyclopenta-4-en[b]pyrrole 8a was eluted by acetone-chloroform (1:2). The eluate was concentrated in vacuo to give a white solid (2.2 g, 68%). An analytical sample of 8a was obtained as colorless crystals by recrystallization from dichloromethane-petroleum ether: mp 138-140°C; nmr δ ($CDCl_3$): 8.5-8.0 (1H, bs, NH), 6.0-5.7 (2h,m, H_4 and H_5), 4.6-4.4 (1H, m, H_{3a}), 4.3-4.1 (1H, m, H_{6a}) and 2.8-2.5 (2H, m, H_6); ^{13}C-nmr δ ($CDCl_3$): 168.9 (C-2), 131.9, 128.2 (C-4 and C-5), 84.1 (C-3), 63.4 (C-3a), 54.3 (C-6a) and 39.4 (C-6); ir (KBr): 3500-3200 and 1726 cm^{-1}; ms (m/e): 195, 193, 191; Anal. Calcd for $C_7H_7Cl_2NO$: C, 43.77; H, 3.67; Cl, 36.92 Found: C, 43.83; H, 3.87; Cl, 37.30.

2-oxo-Hexahydrocyclopenta-4-en[b]pyrrole 8b. To a vigorously stirred suspension of zinc dust (0.4 g, 6.1 mmol) in glacial acetic acid (2 mL) at room temperature was added dropwise a solution of 8a (2.0 g, 10.4 mmol) in glacial acetic acid (4 mL). After addition was completed, the temperature was raised and maintained at 70°C for 20 min. The reaction mixture was cooled and treated with chloroform, and the zinc residue was filtered. The organic layer was washed with a saturated sodium carbonate solution to remove acetic acid and dried over magnesium sulfate and filtered. The solvent was removed in vacuo to give a white solid (1.1 g, 89%) which was recrystallized from dichloromethane-petroleum ether: mp 114-116°C; nmr δ ($CDCl_3$): 8.0-7.5 (1H, bs, NH), 5.9-5.6 (2H, m, H_4 and H_5), 4.5-4.3 (1H, m, H_{6a}), 3.6-3.4 (1H, m, H_{3a}), 2.7-2.2 (4H, m, H_3 and H_6); ^{13}C-nmr δ

($CDCl_3$): 178.2 (C-2), 131.7, 128.7 (C-4 and C-5), 56.4 (C-6a), 46.1 (C-3), 35.8 (C-3a) and 34.9 (C-6); ir (KBr): 3500-3200 and 1683 cm^{-1}; ms (m/e) 123; Anal. Calcd for C_7H_9NO: C, 68.27; H, 7.37; N, 11.37 Found: C, 68.53; H, 7.32; N, 11.46.

4-exo-5-endo-Dibromo-2-oxo-octahydrocyclopenta[b]pyrrole 2a. Method 1. From 2-oxo-3-endo-dibromobicyclo[3.2.0]heptan-6-one 6a. To a stirred solution of 6a (3.0 g, 11.2 mmol) in dichloromethane (20 mL) was added a solution of MSH (3.2 g, 15 mmol) in dichloromethane (20 mL) at -10°C. The reaction mixture was allowed to stand for 0.5 h. The solvent was removed in vacuo at room temperature to yield the crystalline oxime mesitylene-sulfonate which was dissolved in benzene:methanol (3:1, 20 mL) and added dropwise to a stirred suspension of basic alumina (100 g) in anhydrous methanol (100 mL). The mixture was stirred for 4 h and filtered by suction. The alumina was washed with methanol (2 x 100 mL). The combined methanolic solution was concentrated in vacuo. The residue was dissolved in chloroform (80 mL) and the insoluble material was removed by filtration. After evaporation of the solvent, the residue were chromatographed on silica gel. The lactam-dibromide, 7a (0.6 g, 18.9%) was eluted with acetone-chloroform (1:2). The desired isomer, 2a (1.6 g, 52.1%) was obtained from further flushing the column as colorless crystals (from benzene): mp 150-152°C; nmr δ (DMSO-d_6): 8.0-7.7 (1H, bs, NH), 4.8-4.2 (3H, m, H_4, H_5 and H_{6a}), 3.3-3.2 (1H, m, H_{3a}) and 2.6-2.2 (4H, m, H_3 and H_5); ir (KBr): 3500-3150 and 1684 cm^{-1}.

Method 2. From 2-oxo-hexahydrocyclopenta-4-en[b]pyrrole 8b. To a solution containing 8b (1.0 g, 8.13 mmol) in dichloromethane (60 mL) was added dropwise a solution of bromine (4.3 g, 26.4 mmol) in dichloromethane (60 mL) over 1 h. The resulting red solution was stirred overnight at room temperature and poured into water (300 mL). The organic layer was washed with saturated sodium hydrogen carbonate solution (100 mL) and then water (100 mL) and dried over magnesium sulfate. Evaporation of the solvent in vacuo gave a yellow solid which was chromatographed on silica gel using acetone-chloroform (1:1) as eluent. The eluate was concentrated in vacuo to give a white solid (1.4 g, 61%) which upon recrystallization from benzene gave 2a as colorless crystals: mp 150-151°C; nmr (DMSO) δ(DMSO-d_6) 8.0-7.7 (1H, bs, NH), 4.7-4.2 (3H, m, H_4, H_5, H_{6a}), 3.3-3.2 (1H, m, H_{3a}) and 2.6-2.2 (4H, m, H_3 and H_6); ^{13}C-nmr δ(DMSO-d_6) 176.3 (C-2), 59.8 (C-6a), 48.3, 46.0 (C-4 and C-5), 43.9 (C-3a), 37.1 and 36.7 (C-3 and C-6); ir (KBr): 3500-3200 and 1683 cm^{-1}; Anal. Calcd for $C_7H_9Br_2NO$: C, 29.72; H, 3.21; N, 4.95; Br, 56.48 Found: C, 29.90; H, 3.31; N, 4.91; Br, 55.90.

4-exo-Bromo-5-endo-methoxy-2-oxo-octahydrocyclopenta[b]pyrrole 2b. 2-Oxo-hexahydrocyclopenta-4-en[b]pyrrole 8b (1.5 g, 12.2 mmol) was dissolved in dry methanol (30 mL) to which NBS (2.2 g, 12.5 mmol) was added. After stirring for 18 h at room temperature, the solution was diluted with chloroform (30 mL) and extracted with water (6 x 15 mL). The aqueous extracts were washed with chloroform (2 x 20 mL). The combined organic layers were dried over magnesium sulfate and filtered. The solvent was removed in vacuo to give a white solid (2.4 g, 84%) which on crystallization from benzene gave 2b as colorless crystals: mp 127-128°C; nmr δ ($CDCl_3$): 8.0-7.7 (1H, bs, NH), 4.5-3.9 (3H, m, H_4, H_5 and H_{6a}), 3.4 (3H, s, CH_3), 3.3-3.1 (1H, m, H_{3a}) and 2.7-2.3 (4H, m, H_3 and H_6); ir (KBr): 3500-3200 and 1680 cm^{-1}; Anal. Calcd for $C_8H_{12}BrNO_2$: C, 41.05; H, 5.17; N, 5.98 Found: C, 41.13; H, 5.23; N, 5.76.

4-Methanesulfonyloxy-octahydrocyclopenta[b]pyrrole 9a. The lactam 1c (160 mg, 0.73 mmol) was mixed with BH_3.THF (15 mL, 1.1 M, 17 mmol) and refluxed under nitrogen for 7 h. The reaction mixture was set aside at room temperature for 2 h. Concentrated hydrochloric acid (6 mL, 32%) was carefully added and the mixture was stirred for 5 h. It was poured into chloroform (75 mL) and solid potassium hydroxide was added to adjust the pH to 10. The organic layer was washed with brine solution (10 mL) and dried over magnesium sulfate, filtered and evaporated in vacuo to give a colorless liquid, which was a mixture of the desired product 9a and significant amount of 1,4-butanediol formed from the decomposition of tetrahydrofuran during work-up. 1,4-Butanediol was removed by high vacuum distillation, the residue being crude 9a (96 mg, 64%). Attempts to purify

it by chromatography led to decomposition: nmr δ ($CDCl_3$): 5.1-4.7 (1 H, m, H_4), 3.8-3.1 (2 H, m, H_{3a} and H_{6a}), 3.0 (3 H, s, CH_3), 2.9-2.7 (2 H, m, H_2) and 2.1-1.5 (7 H, m, H_3, H_5, H_6 and NH); ^{13}C-nmr δ ($CDCl_3$): 83.5 (C-4), 62.4 (C-6a), 48.1 (C-2), 46.1 (C-3a), 38.3 (CH_3), 31.1 (C-5), 29.8 (C-6) and 28.1 (C-3); ir (NaCl): 3600-3200, 1360 and 1183 cm^{-1}; ms (m/e): 110.0961(Calcd for $C_7H_{12}N$ 110.0969).

4-exo-5-endo-Dibromo-octahydrocyclopenta[b]pyrrole 9b. The procedure was the same as described in the preparation of . The lactam 2a (1.0 g, 3.6 mmol) was transformed into 9b (0.6 g, 62%):nmr δ ($CDCl_3$) 4.6-3.3 (4H, m, H_4, H_5, H_{6a} and H_{3a}), 3.0-2.6 (2H, m, H_2), 2.4-2.2 (2H, m, H_6) and 2.0-1.6 (3H, m, H_3 and NH); ir (NaCl) 3500-3200 cm^{-1}; ms (m/e) 188.0050 (calcd for $C_7H_{11}BrN$ 188.0050).

4-exo-Bromo-5-endo-methoxyoctahydrocyclopenta[b]pyrrole 9c. The procedure was the same as described in the reaction of 1a. Compound 2b (1 g, 4.3 mmol) was transformed into 9c (0.6 g, 65%): nmr δ ($CDCl_3$) 4.2-3.6 (3H, m, H_4, H_5 and H_{6a}), 3.45 (3H, s, CH_3), 3.3-3.1 (1H, m, H_{3a}), 3.0-2.2 (4H, m, H_2 and H_5) and 2.0-1.4 (3H, m, H_3 and NH); ir (NaCl) 3600-3200 cm^{-1}; ms (m/e) 140.1061 (calcd for $C_8H_{14}NO$ 140.1075).

Acknowledgement. The authors thank W.C. Ho and T.K. Fung for laboratory assistance and to C.P. Yuen of the University of Hong Kong for measuring ^{13}C-nmr spectra.

REFERENCES AND NOTES

1. (a) R. Livingstone in "Rodd's Chemistry of Carbon Compounds", S. Coffey, ed., Elsevier, Amsterdam, 2nd ed., 1973, Vol. 1Va, p. 379. (b) C.W. Bird and G.W.H. Cheesman in "Comprehensive Heterocyclic Chemistry" A.R. Katritzky and C.W. Rees, eds.,Pergamon, Oxford, 1984, vol.4, p.89.
2. For review see: (a) L.G. Donaruma and W.Z. Heldt, Org. Reactions., 11, 1 (1960); (b) H. Wolff, Org. Reactions, 3, 307 (1946); (c) G. Koldobskii, G.F. Teveschchenko, E.S. Gerasimova, and L.I. Bagal, Russ. Chem. Rev., 40, 835 (1971); (d) G.R. Krow, Tetrahedron, 37, 1283 (1981).
3. (a) Y. Tamura, H. Fujiwara, K. Sumoto, M. Ikeda, and Y. Kita, Synthesis, 215 (1973). (b) For review see: Y. Tamura, J. Minamikawa, and M. Ikeda, Synthesis, 1 (1977).
4. A.E. Greene, J.P. Deprés, H. Nagano, and P. Crabbé, Tetrahedron Lett., 2365 (1977).
5. (a) P.W. Jeffs and G. Molina, Chem. Commun., 3 (1973). (b) J.P. Deprés, Ph.D. Dissertation Université Scientifique et Medicale, Grenoble, France; (c) P. Crabbé, private communication.
6. E.J. Corey, J.D. Bass, R. LeMahien and R.B. Mitra, J. Am. Chem. Soc., 86, 5570 (1964); D. Termont, D. De Kenkeleire and M. Vandewalle, J.C.S. Perkin I, 2349 (1977); A. DeBruyn, D. Termont, D. DeKeukeleire and M.J.O. Anteunis, Bull. Soc. Chim. Belg., 87, 201, (1978).
7. P.A. Grieco, J. Org. Chem., 37, 2363 (1972).
8. Various conditions (HN_3 and CF_3CO_2H, 0°C, 1h; NaN_3 and polyphosphoric acid, 25°C, 10h; HN_3 and HCl, 100°C, 6h) were attempted to effect Schmidt rearrangement of 3a and 3b. In all cases, the reaction mixture turned to dark brown within 5 min, and only small amount of starting material was recovered. Similarly, Beckmann rearrangements of the oximes of 3a and 3b were employed with various reagents (H_2SO_4, 140°C, 15 min; PCl_5, 60°C, 8h; PCl_5, 25°C, 7h; TsCl and pyridine, 25°C, 12h; polyphosphoric acid, 180°C, 12h; $Me_3C_6H_2SO_2Cl$ and pyridine, 25°C, 12h; CF_3CO_2H, 25°C, 12h). Starting ketones were regenerated.
9. Z. Grudzinski and S.M. Roberts, J. Chem. Soc. Perkin I, 1767 (1975).
10. The similar electronic effect of the α-chlorine substituent has also been used to advantage in the synthesis of γ-lactone. See: S.M. Ali and S.M. Roberts, J.C.S.Chem.Commun. 887 (1975); B.-W. Au-yeung and I. Fleming, J.C.S.Chem.Commun. 79 (1977); A. Hassner, H.W. Pinnick and J.M. Ansell, J.Org.Chem., 43, 1774 (1978).