An Approach to 3,4,7,8-Tetrahydroazocine -

Synthesis of 4-Methanesulfonyloxy-octahydrocyclopenta[b]pyrrole

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To my family
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ABSTRACT

A synthetic route to 4-methanesulfonyloxy-octahydrocyclopenta[b]pyrrole (34) is described. Compound (34), a possible precursor for the synthesis of a potentially novel ligand, 3,4,7,8-tetrahydroazocine (9), was achieved from cyclopentenone (35) in five steps.

Photochemical cycloaddition of cyclopentenone (35) with 1,1-diethoxyethene (36a) gave cis-6,6-diethoxybicyclo[3.2.0]heptan-6-one (28a), which upon lithium aluminum hydride reduction and acid hydrolysis gave 2-hydroxybicyclo[3.2.0]heptan-6-one (27a). 2-Acetoxy (27b), 2-tetrahydropyranyl (27c) and 2-methanesulfonyloxy (27d) derivatives of (27a) were synthesized.

Conventional Beckmann and Schmidt rearrangements of (27) to give the 4-substituted-2-oxo-octahydrocyclopenta[b]pyrrole skeleton (33) were unsuccessful. Utilization of the reactive O-mesitylenesulfonylhydroxylamine (53), however, gave excellent results. The regioselectivity of the Beckmann rearrangement was shown to be temperature dependent; as observed for (27a) and (27b), the selectivity increased as the temperature decreased.

The lactam analogue of (34), 4-methanesulfonyloxy-2-oxo-octahydrocyclopenta[b]pyrrole (33d) was obtained by selective methanesulfonation of 4-hydroxy-2-oxo-octahydrocyclopenta[b]pyrrole (33a). Reduction of (33d) with diborane yielded the desired molecule (34).
Solvolytic reactions of (23d) and (34) were studied in 95% ethanol, and attempts to trap the possible fragmentation product by diphenylisobenzofuran or as transition metal complexes by dibenzonitrile palladous chloride and 1,5-cyclooctadiene rhodium (I) chloride dimer failed to yield fruitful result so far.
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Chemistry of unsaturated eight-membered N-heterocyclic rings, unlike their five, six or seven-membered ring homologs, has not been thoroughly explored. The fully unsaturated member of this family, azocine (1), was accidentally characterized in 1971, during an attempt to the synthesis of cubane from the flash vacuum pyrolysis of diazabasketene\(^1\).

\[
\text{HCN} \quad \begin{array}{c}
\text{N} \\
\text{N}
\end{array} 
\quad + \quad \text{N}_2 
\]

\[
\begin{array}{c}
\text{N} \\
\text{N}
\end{array} 
\quad \rightarrow 
\begin{array}{c}
\text{N}
\end{array} 
\quad + \quad \text{HCN}
\]

The azocine molecule is a highly reactive, acid sensitive species and readily decomposes above -50\(^\circ\)C. Several 2-alkoxyazocines\(^2\) (2) have been synthesized as stable compounds and exist in the puckered "rub" conformation\(^3\) (3) similar to that of the cyclooctatetraene\(^4\) (4).
2-Alkoxyazocines readily undergo two-electron reduction\(^5\) to give planar aromatic dianions (5). Interestingly, no intermediate radical anion has been detected. The striking similarity of the electrochemical properties of the azocinyl and cyclooctatetraenyl dianions\(^6\) suggests that the replacement of a carbon by a nitrogen atom does not change the \(n\)-electron conjugative properties. It is also noted that no organometallic chemistry has ever been explored for azocine and its derivatives.
Recently, 1,2,3,4,7,8-hexahydroazocine (6) was obtained from 4-cycloheptenone and had been shown to undergo transannular cyclizations to afford 1-substituted pyrrolizidines (7). A palladium complex (8) of the hexahydroazocine (6) was proposed to exist as a yellow-brown precipitate in tetrahydrofuran but the structure had not been characterized.
To our surprise, dihydro- and tetrahydroazocines, which have ten and eleven isomers respectively, are not known. Only a few derivatives of dihydro- and tetrahydroazocines, however, have been reported in the literature (Fig I). In most cases these derivatives were prepared by partial reduction of substituted azocines.

Fig I. Selected dihydroazocine and tetrahydroazocine derivatives
In this thesis, we propose to synthesize 3,4,7,8-tetrahydroazocine (9). This compound, possesses a nonconjugated imine function, is structurally related to the highly interesting hydrocarbon, 1,5-cyclooctadiene (COD) (10). This project is aimed to study the structural and chemical effects which might arise from the replacing one of the C=C bond in (10) by a more reactive C=N function.

The chemistry of transition metal complexes with (10) is well documented. The complex (11)₉ is a useful synthon in organic chemistry.
To illustrate, Pd(COD)Cl₂ reacted with carbanion of malonic ester to afford the bicyclo[3.3.0]octane derivative. Bicyclo[3.3.1]2-nonen-9-one was obtained from COD via a palladium complex (Scheme I). In addition,
insertion of perfluoroacetone\textsuperscript{12} to the platinum complex (12) gave the 5-substituted cyclooctene (13). Furthermore, photochemical cycloaddition of COD in the presence of CuCl yielded the tricyclooctane\textsuperscript{13} (14) (Scheme II).

An organocopper complex was proposed as an intermediate.
Heteroatoms such as N, O, S etc. can readily form \( \sigma \)-complexes with transition metals and play a significant role in various aspects of inorganic, analytical as well as biological chemistry. When an unsaturated ligand bearing a heteroatom, such as imine or carbonyl functions, two types of metal complexes may be formed. One is \( \sigma \)-donation through the lone pairs on the heteroatom (15); the other is formation of a \( \pi \)-complex (16).

\[
\begin{align*}
\text{C=X} & \quad M \\
\text{X = O, N-R, S} & \quad M
\end{align*}
\]

(15) (16)

In general, nonconjugated imines favor \( \sigma \)-complexes formation\(^{14}\). On the other hand, \( \pi_{C=N} \)-complexes are only found in conjugated imine systems. Thus, the structure of \( \phi \text{CH=CH-CH=CH} \phi \text{Fe(CO)}_3 \) (17), was confirmed by X-ray analysis\(^{15}\). Moreover, several 1-azabutadiene and 1,4-diazabutadiene derivatives were found to form \( \pi_{C=N} \) complexes with ruthenium\(^{16}\) and iron\(^{17}\).
Presumably, this can be rationalized that the conjugated imine ligand should have low lying π* orbital which might allow back donation from metal to be more favorable than that in the isolated imine. To the best of our knowledge, an isolated C=N bond with π\textsubscript{C=N}-donation to transition metals has not been encountered.

Whether 3,4,7,8-tetrahydroazocine (9) could form a π-complex with transition metals like cyclooctadiene remained an interesting question. However, the conformation of (9) would be expected similar to COD. Consequently, the lone pair electrons on the nitrogen would not be directed toward the metal if the metal ion would occupy a similar position as it does in COD metal complexes (18). In other words, the formation of a σ-complex would be unlikely in this case.
SYNTHETIC STRATEGY

Our target molecule (9) contains a cis carbon-carbon double bond and an imine moiety. An obvious way to this molecule seems to be a one-step cyclization of an α,ω-aminoaldehyde (19). However, to our knowledge, no successful intramolecular eight-membered ring imine formation has been reported.

The present method suggests that a solvolytic fragmentation of an octahydrocyclopenta[b]pyrrole with a good leaving group at C-4 position will lead to the simultaneous formation of C=C and C=N bonds.
There are numerous examples of heterolytic fragmentations of \(\gamma\)-aminoalcohol derivatives\(^{18}\). Thus, the stereoisomeric N-methyldecahydroquinol-5-yl toluenesulfonates (20), (21) and (22) underwent different courses of fragmentation\(^{19}\) under solvolytic conditions (Scheme III).

**Scheme III**
The mechanism for synchronous fragmentation is stereoelectronically controlled, which operates only if both the $C_\alpha$-$L$ bond and the orbital of the lone pair of electrons on the nitrogen are anti, and parallel anti-periplanar to the $C_\beta$-$C_\gamma$ bond.\(^{29}\)

Compounds (20) and (21), satisfied the necessary antiparallelism of the electron pairs involved and underwent through an exclusive fragmentation giving (23) and (24) respectively. Compound (22), on the other hand, did not have the "correct" stereochemistry, afforded substitution and $\beta$-elimination products.

In view of the structural similarity between (21) and the bicyclic octahydrocyclopenta[b]pyrrole derivative (25), we should expect the solvolytic product of (25) to be the desired eight-membered iminium ion (26) (Scheme IV).
The stereochemistry of (25) should therefore be critical. It is apparent that the two five-membered rings should be cis-fused and the leaving group be in the endo position. The orientation of the lone pair electrons on nitrogen is not so important because of the rapid inversion of the amine.

Although the $C_\alpha-L$ bond, lone pair of electrons on the nitrogen and $C_\beta-C_\gamma$ bond are not exactly parallel by inspecting the model\textsuperscript{21}, the deviation would be small and the fragmentation reaction might occur for compound (25).
By far the substrate, γ-aminoalcohol derivatives, which were found in the literature to proceed fragmentations were exclusively tertiary amines. However, their secondary amine counterparts were apparently not known.

The present problem is then the synthesis of (25). No satisfactory synthesis of 4-substituted octahydrocyclopenta[b]pyrroles has been reported in the literature. Our approach focuses on a stereospecific generation of a cis-fused azabicyclo[3.3.0]octane skeleton and simultaneously introduction of a good leaving group at the C-4 position with an endo stereochemistry.

The azabicyclo[3.3.0]skeleton could be synthesized by a Beckmann type rearrangement of a bicyclo[3.2.0] derivative (27a). The hydroxyl function could be converted to the corresponding methanesulfonate and the cyclic amine might be produced by reduction of the lactam (Scheme V). Compound (27a) could be

\[ L = \text{-OSO}_2\text{CH}_3 \]
available from a stereoselective reduction of a bicyclic ketone (28a) and subsequent acid hydrolysis of the ketal (29) (Scheme VI). In the reduction of (28a), lithium aluminum hydride should preferentially attack from the less hindered exo site to give the hydroxyl derivative (27a) with the desired stereochemistry.

![Scheme VI](image)

The regioselectivity of the Beckmann rearrangement of (27) is vital to the overall synthetic plan. Sometimes, unsymmetrical cyclobutanone could yield two isomeric lactams. The relative ratio depends on the nature of the substrate and the choice of the reagent. From the point of migratory aptitude, the shifting of the methine carbon (C-5) via route a to give the desired lactam should be more favorable than the migration of the methylene carbon (C-7) via route b to afford the other isomer.
On the other hand, the choice of reagent is also important. The bicyclic ketone (30), for example, underwent Beckmann rearrangement with hydroxylamine to give exclusive methylene migration product \( 22 \) (31). When N-methylhydroxylamine \( 23 \) was employed, the other isomer was formed as the sole product.
Recently, O-mesitylenesulfonylhydroxylamine\textsuperscript{24} was used to effect a regioselective ring expansion of an unsymmetrical cyclobutanone (32).

\[
\begin{align*}
\text{O} & \quad \text{SO}_3\text{NH}_2 \quad \text{(MSH)} \\
\text{Al}_2\text{O}_3, \text{CH}_2\text{Cl}_2, 0^\circ\text{C} & \\
\end{align*}
\]

The preferential migration of the more substituted carbon and the retention of configuration of the migrating center, suggested that the use of this reagent possessed an advantage over other methods. In addition, it is noteworthy that the hydroxyl group in (32) could survive under the reaction conditions without racemization.

In the beginning of this work, we were worried about the stability of the hydroxyl group in (27a) and the nitrogen function in the hydroxylactam (33a).
during further transformations. Various protective groups had been used in this study and they are summarized in Scheme VII.

Scheme VII
A much simplified route was later discovered to achieve our goal. The methanesulfonate function could be efficiently introduced into the hydroxy-lactam (33a) without difficulty. The resulting lactam-methanesulfonate (33d) might then be reduced to the corresponding amino-methanesulfonate (34) by the use of diborane \(^{25}\) without affecting the leaving group (Scheme VIII).
RESULTS AND DISCUSSIONS

Upon irradiation, cyclopentenone (35) and 1,1-diethoxyethene (36a) were smoothly transformed to the bicyclic adduct (28a) in 53% yield. No isomeric product (37a) was obtained at all. It was noted that a ten fold excess of (36a) should be used to depress self-dimerization\textsuperscript{26} of cyclopentenone. The reaction was carefully followed by ir and was shown to be completed in 2.75 h per gram of cyclopentenone. Large scale synthesis or prolonged irradiation led to decreased yield of (28a). The optimal yield was obtained on a 2 gram-scale of (35).

\[
\begin{align*}
\text{(35)} & \quad \text{(36)} \\
\text{(28a)} & \quad \text{a) } R = \text{Et} \\
\text{(37a)} & \quad \text{b) } R = \text{Me}
\end{align*}
\]

Compound (28a) exhibits a carbonyl absorption at 1743 cm\textsuperscript{-1} and shows two triplets at \( \delta 1.18 \) and 1.15 with two quartets at \( \delta 3.45 \) and 3.42 in the nmr spectrum, indicating two nonequivalent ethoxy groups. The mass spectrum of (28a) reveals a molecular ion at m/e 198. The fragmentation patterns are summarized in Scheme IX. The presence of the cyclobutane ring is confirmed
by the presence of peaks at m/e 83 and m/e 116, probably formed by a \([\pi_2 + \pi_2]\) cycloreversion process. The base peak at m/e 43, a protonated ketene \(H_2C=CH=OH\), may be produced from successive fragmentations of ethoxy radical and ethylene moiety from the species with m/e 116, or from the loss of \(C_3H_4\) from the protonated cyclopentenone (m/e 83).

\[\text{Scheme IX}\]
The photocycloaddition of α,β-unsaturated ketones with ketene acetals has received considerable attention. Corey and his coworkers were able to demonstrate cis-6,6-dimethoxybicyclo[3.2.0]heptan-2-one (28b) was formed as the only product from 2-cyclopentenone (35) and 1,1-dimethoxyethene (36b). The mechanism of the cycloaddition was suggested to be influenced by the electronic distribution of the excited cyclopentenone and the ground state ethylene ketal, the regiospecificity could be rationalized by means of frontier molecular orbital theory.

The hydroxy-ketal (29), obtained via lithium aluminum hydride reduction of (28a), was hydrolyzed to the hydroxy-ketone (27a) in 89% yield. Compound (29) was characterized by the presence of a hydroxyl function and the absence of carbonyl absorption in the ir spectrum. The ethoxy groups remained intact during the course of reduction.

The stereochemistry of C-2 in (27a) is of great concern to us. In general, the hydride will attack from the less hindered site during lithium aluminum hydride reduction of a carbonyl function. A close examination
of the 3-dimensional structure of (28a) shows the exo site is much less sterically hindered than the endo one; and therefore the resulting hydroxyl group should be in an endo configuration (Fig II). The stereochemistry at C-2 is exactly what we desire for the synthesis described in early section.

The hydroxy-ketone (27a) had been similarly obtained\textsuperscript{36} in 67% yield by sodium borohydride reduction of (28b) and subsequent acid hydrolysis of the corresponding dimethoxy-ketal. The stereochemistry of the hydroxyl group was unambiguously assigned to be endo by an nmr study\textsuperscript{37}.

![Fig II. Stereoselective reduction of (28a)](image)

The ir spectrum of (27a) exhibits a sharp peak at 1780 cm\textsuperscript{-1}, which corresponds to the carbonyl stretching frequency of a cyclobutanone moiety. This was further supported by the appearance of a signal at δ 214.0 in the \textsuperscript{13}C-nmr spectrum\textsuperscript{*}.

The mass spectrum of (27a) shows a molecular ion at m/e 126, with other prominent peaks at m/e 108, m/e 84, m/e 83 and m/e 67. Elimination of water

\textsuperscript{*} Chemical shift of the carbonyl-carbon in cyclobutanone is 208.2 (See J.B. Stothers, Carbon-13 NMR Spectroscopy, 289, Academic Press, 1972).
and ketene moieties would account for the ions m/e 108 and m/e 84. The base peak (m/e 67) is formed by a heterolytic cleavage of the C-O bond from the cyclopentenol (m/e 84) (Scheme X).

Having the hydroxy-ketone (27a) at hand, we planned to synthesize the bicyclic-lactam (33a). Both classical Beckmann and Schmidt rearrangements were used in this transformation. In general, the migration of the more substituted C-5 should be more favorable than that of the less substituted C-7 in (27), and therefore, lactam (33a) would be the major product.
To our dismay, the Schmidt rearrangement of (27a) was unsuccessful. Three different conditions had been studied (Table I). In all cases the reaction mixture turned to dark brown within 5 minutes, and only starting material (presence of 1780 cm⁻¹ in the IR spectrum of the product) was isolated in low yield (ca. 20%).

Table I. Schmidt rearrangements of (27a)

<table>
<thead>
<tr>
<th>Conditions</th>
<th>Time</th>
<th>Temp</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. 3 eq. of hydrazoic acid + excess</td>
<td>20 min</td>
<td>0°C</td>
</tr>
<tr>
<td>concentrated sulfuric acid in CHCl₃</td>
<td></td>
<td></td>
</tr>
<tr>
<td>2. Same as those in 1</td>
<td>2 h</td>
<td>0°C</td>
</tr>
<tr>
<td>3. 15 fold excess of polyphosphoric acid²⁹ + 2 eq. of NaN₃</td>
<td>10 min</td>
<td>160°C</td>
</tr>
</tbody>
</table>

The attention was then directed to the hydroxy-oxime (39a), a highly viscous liquid, which was readily available in 77% yield from (27a) and hydroxylamine. The oxime (39a) exhibits a broad absorption around 3600-3100 cm⁻¹ in the IR spectrum and at δ 10.2 in its NMR spectrum. Fourteen carbon signals, instead of seven appear in the ¹³C-NMR spectrum suggests that the

![Diagram](27) -> (NH₂OH·HCl) -> (29)

a) R = H  
b) R = -COCH₃
oxime (39a) exists as a mixture of the anti and syn isomers. The exact ratio of the two isomers had not been determined.

Unfortunately, the Beckmann rearrangement of (39a) under various conditions summarized in Table II received the same fate as the Schmidt reaction. The characteristic carbonyl absorption (1780 cm⁻¹) of the cyclobutanone reappeared in all cases.

Table II. Beckmann rearrangements of (39a)

<table>
<thead>
<tr>
<th>Conditions</th>
<th>Time</th>
<th>Temp</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. 1.1 eq. of sodium hydroxide + 1.1 eq. p-TsCl in water</td>
<td>12 h</td>
<td>25°C</td>
</tr>
<tr>
<td>2. Excess conc. H₂SO₄</td>
<td>12 h</td>
<td>25°C</td>
</tr>
<tr>
<td>3. Excess conc. H₂SO₄</td>
<td>15 min</td>
<td>120°C</td>
</tr>
<tr>
<td>4. 1.1 eq. of p-TsCl + excess pyridine in CH₂Cl₂</td>
<td>30 h</td>
<td>25°C</td>
</tr>
<tr>
<td>5. Trifluoroacetic acid</td>
<td>12 h</td>
<td>25°C</td>
</tr>
</tbody>
</table>

In a controlled experiment, (27a) was shown to be unstable and decomposed to black oil on mixing with concentrated acids (e.g. HCl, H₂SO₄, polyphosphoric acid). The instability of the hydroxy-ketone (27a) under acidic conditions and the readily cleavage of the oxime (39a) toward acids or bases are the major drawback of the rearrangements, even the ring enlargement would be thermodynamically unfavorable. Thus, we first felt a protected hydroxyl group may survive under the rearrangement conditions. It was with this idea in mind
that (27b), (27c) and (27d) were synthesized.

\[
\text{(27) }
\]

\begin{align*}
\text{a) } & R = \text{H} \\
\text{b) } & R = \text{COCH}_3 \\
\text{c) } & R = 2'-\text{tetrahydropyranyl} \\
\text{d) } & R = \text{SO}_2\text{CH}_3
\end{align*}

By careful addition of (27a) into a mixture of pyridine and acetyl chloride, (27b) was isolated in 94% yield. The ir spectrum (1789 and 1742 cm\(^{-1}\)) of (27b) suggested the presence of two carbonyl functions, and the absence of absorption higher than 3000 cm\(^{-1}\) indicated that the hydroxyl function was reacted.

The oxime formation of (27b) was straightforward. The acetate-oxime (39b) also exists as a mixture of syn and anti isomers, has characteristic ir absorptions of acetate (1743 cm\(^{-1}\)) and hydroxyl functions (3600-3200 cm\(^{-1}\)) but no peaks around 1780 cm\(^{-1}\). The nmr spectrum of (39b) exhibits signals for the acidic hydrogen (C=\text{N}-\text{OH}, \delta 9.6) and the methyl protons (\delta 2.0) in addition to other unresolved signals.

Various conditions were attempted to effect the Schmidt rearrangement of (27b) (Table III). Again only small amount of the starting material was recovered. Presumably (27b) is still unstable in these media.

In a similar manner, Beckmann rearrangements of (39b) were employed with various reagents as outlined in Table IV. Again, the oxime (39b) was cleaved to
regenerate the corresponding ketone (27b).

**Table III. Schmidt rearrangements of (27b)**

<table>
<thead>
<tr>
<th>Conditions</th>
<th>Time</th>
<th>Temp</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. Hydrazoic acid in chloroform + excess trifluoroacetic acid</td>
<td>1 h</td>
<td>0°C</td>
</tr>
<tr>
<td>2. Excess polyphosphoric acid + 1.1 eq. of NaN₃</td>
<td>10 h</td>
<td>25°C</td>
</tr>
<tr>
<td>3. Hydrazoic acid in CHCl₃ + conc. HCl</td>
<td>6 h</td>
<td>100°C</td>
</tr>
</tbody>
</table>

**Table IV. Beckmann rearrangements of (39b)**

<table>
<thead>
<tr>
<th>Conditions</th>
<th>Time</th>
<th>Temp</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. Conc. sulfuric acid</td>
<td>15 min</td>
<td>140°C</td>
</tr>
<tr>
<td>2. Excess PCl₅ in ether</td>
<td>7 h</td>
<td>25°C</td>
</tr>
<tr>
<td>3. 1.1 eq. of p-TsCl + excess pyridine in CH₂Cl₂</td>
<td>12 h</td>
<td>25°C</td>
</tr>
<tr>
<td>4. Excess PCl₅ in ether</td>
<td>8 h</td>
<td>50°C</td>
</tr>
<tr>
<td>5. Excess polyphosphoric acid</td>
<td>12 h</td>
<td>180°C</td>
</tr>
<tr>
<td>6. Mesitylenesulfonyl chloride + pyridine</td>
<td>12 h</td>
<td>25°C</td>
</tr>
</tbody>
</table>
Compound (27c) was prepared by mixing dihydropyran and (27a) in chloroform with one drop of concentrated hydrochloric acid in 78% yield. It was noted that an excess of dihydropyran was not desirable because (38) was formed as a side product by self-condensation and was difficult to separate. It should be mentioned that (27c) exists as a diastereoisomeric mixture, (27c) and (27c').

![Chemical structures](image)

The IR spectrum of (27c) is characterized by the absence of hydroxyl group in the region of 3600-3200 cm\(^{-1}\). The carbonyl group of the cyclobutanone appears at 1786 cm\(^{-1}\) and its \(^{13}\)C-nmr spectrum having a total of 24 signals (12 pairs).

Reaction of p-toluenesulfonyl chloride with (27a) in the presence of pyridine did not give the corresponding p-toluenesulfonate (41), probably due to the sterically hindered endo-hydroxyl environment. On the other hand,
under similar conditions, excellent yield (82%) of (27d) was obtained when methanesulfonyl chloride was used. Compound (27d) was somewhat thermally unstable and slightly decomposed upon distillation.

Compound (27d) was then purified by chromatography. Its ir spectrum contains, in addition to 1785 cm⁻¹, two strong absorptions at 1359 cm⁻¹ and 1180 cm⁻¹, which are the characteristics of the methanesulfonate group. The methyl group appears as a sharp singlet at δ 3.2 in the nmr spectrum.

The mass spectra of all the 2-substituted bicyclo[3.2.0]heptan-6-ones (27) are summarized in Scheme XI. The relative intensities of the fragments are outlined in Table V.

Table V. Relative intensities (%) of mass fragments of (27a-d)

<table>
<thead>
<tr>
<th>m/e</th>
<th>%</th>
<th>109</th>
<th>108</th>
<th>67</th>
<th>66</th>
<th>M-42</th>
<th>M-125</th>
</tr>
</thead>
<tbody>
<tr>
<td>(27a)</td>
<td>5</td>
<td>2</td>
<td>15</td>
<td>100</td>
<td>31</td>
<td>9</td>
<td>-</td>
</tr>
<tr>
<td>(27b)</td>
<td>0</td>
<td>2</td>
<td>16</td>
<td>100</td>
<td>34</td>
<td>23</td>
<td>24</td>
</tr>
<tr>
<td>(27c)</td>
<td>0</td>
<td>2</td>
<td>4</td>
<td>54</td>
<td>3</td>
<td>0</td>
<td>100</td>
</tr>
<tr>
<td>(27d)</td>
<td>4</td>
<td>1</td>
<td>10</td>
<td>100</td>
<td>38</td>
<td>0</td>
<td>17</td>
</tr>
</tbody>
</table>

* Presumably, a thermal elimination might occur. This reaction was supported by the presence of olefinic signals in the nmr spectra of the distillate.
The general features of the fragmentation patterns for the bicyclic ketones are the elimination of ketene and subsequent C₂-O bond cleavage, which are reflected by the high abundance of peaks at m/e 66 and m/e 67. Typical McLafferty rearrangements are found in (27b) and (27d) to extrude acetic acid and methanesulfonic acid, respectively.
Since the Beckmann and Schmidt rearrangements to the bicyclic lactam were demonstrated to be unsuccessful, we realized that these reaction conditions may be too drastic for our substrates. Efforts had therefore been made to see if it was possible to carry out the transformation under milder conditions.

It has been known that oxime tosylates or sulfonates are excellent precursors for Beckmann rearrangement of ketones. We therefore chose the highly reactive O-mesitylenesulfonylhydroxylamine as the reagent for the lactam formation. Thus, (27) was treated with O-mesitylenesulfonylhydroxylamine (MSH) to give the oxime mesitylenesulfonate (43) which was converted to a mixture of (33) and (40) in excellent yield upon treatment with basic alumina.

The reaction of (27a) with excess MSH at room temperature gave a highly viscous liquid (33a) and (40a) (2:1) in 84% yield. The IR spectrum of the
mixture reveals the presence of a γ-lactam (1683 cm\(^{-1}\)). The hydroxy-lactams (33a) and (40a) are highly polar molecules, insoluble in most organic solvents (e.g. chloroform, dichloromethane) but readily soluble in alcohols and water. On refrigeration, (33a) and (40a) slowly solidified. Compound (33a) was first enriched by recrystallization of the solid from ethyl acetate, and then selectively crystallized from methanol.

The lactam (33a) was unambiguously proved by its \(^{13}\)C-nmr spectrum. The assignments of the \(^{13}\)C-signals of (33a) with the isomer (40a) and 2-pyrrolidinone \(^{42}\) are shown in Fig III.

The separation procedure at this stage was very tedious. Fortunately, we later found that the desired lactam-methanesulfonate (33d) could be easily separated from the other isomer (40d). Therefore, in the following transformations, no attempts were made to purify individual isomers.

![Fig III. \(^{13}\)C-Chemical shifts of 2-pyrrolidinone, (33a) and (40a)](image-url)
In a similar manner, the keto-acetate (27b) was converted to lactam-acetates (33b) and (40b) (3:1) in 92% yield by the reaction with excess MSH at room temperature. The lactam-acetates are soluble in chloroform but decompose above 100°C. Presumably, a syn-elimination might occur as suggested from the nmr and 13C-nmr spectra of the distillate.

The regioselectivity of the lactam formation was shown to be temperature dependent (Table VI).

<table>
<thead>
<tr>
<th>Table VI. Isomer ratios (33)/(40) at various temperature</th>
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<tbody>
<tr>
<td></td>
</tr>
<tr>
<td>(27a)</td>
</tr>
<tr>
<td>(27b)</td>
</tr>
</tbody>
</table>
As shown in the table, the regioselectivity improves as the reaction temperature decreases. Substituents on C-2 position of the bicyclic ketone (27) might also influence the product distribution. However, more experimental work might be needed to clarify this point.

The reduction of the hydroxy-lactams utilizing lithium aluminum hydride at room temperature was proved to be unsuccessful. The product shows a carbonyl absorption at 1730 cm\(^{-1}\), cleavage of the lactams during reduction might account for this observation. Similar examples have been reported in the literature\(^4\).\(^4\)

0-Tetrahydropyranyl ethers are known to be stable in basic media and to lithium aluminum hydride. Thus, 0-tetrahydropyranyl ketone (27c) was mixed with MSH and stirred with basic alumina to afford hydroxy-lactams (33a) and (40a). Surprisingly, the protective tetrahydropyranyl group was cleaved, which might be the first example concerning the instability of 0-tetrahydropyranyl ether in basic medium! The hydroxyl group, however, could again be protected with tetrahydropyranyl moiety in 92% yield by mixing hydroxy-lactams (33a) and (40a) with dihydropyran. Interestingly, (33c) and (40c) were inert toward lithium aluminum hydride reduction.

Secondary amide, containing an acidic proton, is known to react slower than tertiary amide with lithium aluminum hydride. Precipitation of amide-metal salt might account for the retardation of reaction. In order to avoid this salt formation, protection of the amidic proton in (33b) and (40b) with
a benzyl group might be helpful. However, N-benzylation of lactam-acetates (33b) and (40b) under various conditions were in vain.

\[
\begin{align*}
\text{RCNHR}' & \xrightarrow{\text{LiAlH}_4} \text{RCNR} \\
& \xrightarrow{\text{Li}^+} \text{further reduction}
\end{align*}
\]

The problems we now encountered were the reduction of the amide and the introduction of the leaving group, methanesulfonate. The sequence of these two reactions was vital to a successful synthesis of amino-methanesulfonate (34). Reduction of the amide first would give the corresponding amine, which would be more nucleophilic and reactive than the hydroxyl group. Protection of the amine and subsequent removal of the protecting group would therefore be inevitable for a selective introduction of methanesulfonate (Scheme XII). Obviously this synthetic plan would involve more steps and therefore the overall yield would be decreased.

\[
\text{Scheme XII}
\]
On the other hand, introduction of the leaving group first would give the lactam-sulfonate. Then the reduction should be conducted under much milder conditions to ensure that the C4-O bond in the lactam-sulfonate would remain intact (Scheme XIII).

![Scheme XIII](image.png)

It is noted that borane-tetrahydrofuranate is a facile reagent for the reduction of amides while the sulfonate group has been found to be unreactive under this condition. Consequently, we chose the latter approach and synthesized the lactam-sulfonate (33d) first.

2-Methanesulfonyloxybicyclo[3.2.0]heptan-6-one (27d) was reacted with excess MSH at -10 °C. As might be expected, the leaving group was solvolyzed under basic conditions to yield hydroxy-lactams (33a) and (40a).

Since the amide-nitrogen was less nucleophilic than the hydroxyl function, the methanesulfonyl chloride could be selectively introduced. The transformation was firstly attempted by mixing hydroxy-lactams, pyridine and methanesulfonyl chloride in DMF at room temperature. To our surprise, no reaction occurred at all. The lactim-sulfonate (33d) was later prepared by employing sodium hydride as a base to abstract the hydroxyl proton.
The hydroxy-lactams (33a) and (40a) were dissolved in hot tetrahydrofuran and were carefully added into a stoichiometric amount of sodium hydride in tetrahydrofuran at room temperature. The hydrogen evolution was very slow and this process ceased after one day or more. Methanesulfonyl chloride was then added to yield the lactam-sulfonates (33d) and (40d). The desired isomer (33d) was separated from (40d) by chromatography to give needle-like crystals (mp 97-99°C) after recrystallization from chloroform. The nmr signal at δ 3.1 is attributed to the methyl protons. The broad absorption from δ 7.5 to 7.2 is due to the acidic hydrogen of the lactam moiety. The IR spectrum of (33d) shows a broad N-H absorption around 3600-3200 cm⁻¹ and a strong peak at 1180 cm⁻¹, a characteristic of methanesulfonate.

The fragmentation patterns of the bicyclic 4-substituted lactams (33) are summarized in Scheme XIV. The relative abundances of the ions are tabulated in Table VII.

The existence of a γ-lactam is revealed by the high abundance of ions at
Scheme XIV
Table VII. Relative abundance (%) of mass fragments of (33a-d)

<table>
<thead>
<tr>
<th>m/e</th>
<th>M</th>
<th>M-140</th>
<th>141</th>
<th>140</th>
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<tbody>
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<td>(33a)</td>
<td>30</td>
<td>-</td>
<td>30</td>
<td>3</td>
</tr>
<tr>
<td>(33b)</td>
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<tr>
<td>(33d)</td>
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<td>1</td>
<td>12</td>
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</table>

<table>
<thead>
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<th>123</th>
<th>113</th>
<th>112</th>
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<td>(33a)</td>
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<td>12</td>
<td>46</td>
<td>48</td>
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<td>(33b)</td>
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<td>19</td>
</tr>
<tr>
<td>(33c)</td>
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<td>6</td>
<td>19</td>
<td>2</td>
</tr>
<tr>
<td>(33d)</td>
<td>26</td>
<td>100</td>
<td>1</td>
<td>14</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>m/e</th>
<th>94</th>
<th>83</th>
<th>67</th>
<th>66</th>
</tr>
</thead>
<tbody>
<tr>
<td>(33a)</td>
<td>100</td>
<td>52</td>
<td>37</td>
<td>9</td>
</tr>
<tr>
<td>(33b)</td>
<td>72</td>
<td>16</td>
<td>11</td>
<td>3</td>
</tr>
<tr>
<td>(33c)</td>
<td>24</td>
<td>6</td>
<td>17</td>
<td>2</td>
</tr>
<tr>
<td>(33d)</td>
<td>13</td>
<td>10</td>
<td>21</td>
<td>4</td>
</tr>
</tbody>
</table>
m/e 84 and m/e 83* in all of the four compounds concerned. Elimination of ROH for (33b) and (33d) is one of the most important fragmentation pathways through a McLafferty rearrangement.

Since there is only one hydrogen cis to the methanesulfonate group (H₅), the syn-elimination of (33d) would give (44). Cleavage of the C₄-O bond of (33d) to reject an alkoxy radical to give m/e 124 is another fragmentation pathway. The structure of this ion is unknown. Whether it retains the bicyclic structure or rearranges into a keto-azacyclooctadiene cation (42) remains unresolved. Theoretically speaking, one should expect the bicyclic ion (45) would be less stable than (42) because the former contains a sextet carbon, in contrast to the complete octet structure of (42).

* High resolution mass spectral analysis indicated their structural formulae were C₄H₆NO and C₄H₅NO respectively.
Excess borane-tetrahydrofuranate, obtained by adding freshly distilled boron trifluoride etherate into a suspension of sodium borohydride in dry tetrahydrofuran, was refluxed with lactam-methanesulfonate (33d) under nitrogen atmosphere for 8 h. The resulting borane-amine-complex and excess diborane were hydrolyzed by adding 6 N hydrochloric acid followed by standard work-up procedure to give the amino-methanesulfonate in 64% yield. The product was air sensitive and quickly turned into a brownish oil after exposure to atmosphere for 1 h, and was also unstable toward silica gel. Attempts to chromatograph (34) led to decomposition.

The crude (34) slowly solidified at room temperature. The disappearance of the carbonyl absorption (1850-1600 cm⁻¹) indicated that the lactam was reduced; the methanesulfonate remained intact on the basis of the presence of the absorptions at 1360 and 1183 cm⁻¹. This was further supported by a broad multiplet around δ 5.1-4.7 (H₄) and a singlet methyl signal at δ 3.0 in its nmr spectrum.

The assignments of the major fragments for the mass spectrum of (34) are summarized in Scheme XV. Contrary to the lactam-methanesulfonate (33d), amino-methanesulfonate (34) favors C₄-O-OS₂CH₃ bond cleavage to give m/e 110, which may similarly have a bicyclic structure (55) or have a rearranged skeleton (26). A common feature of (34) and (33d) they share is the absence of their molecular ions. This reflects that the parent ions (m/e 205,
Scheme XV

(26) \[ \text{C}_6\text{H}_9\text{SO}_2\text{CH}_3^+ \quad \text{m/e 176 (10%)} \]

or

\[ \textbf{C}_7\text{H}_{11}\text{N}^+ \quad \text{m/e 110 (100%)} \]

\(- \text{H}^+ \)

\(- \text{CH}_3\text{SO}_2\text{O} \quad \text{T}^+ \)

\[ \text{C}_7\text{H}_{10}\text{N}^+ \quad \text{m/e 108 (19%)} \]

\(- \text{H}^+ \)

\[ \text{C}_7\text{H}_9\text{N}^+ \quad \text{m/e 107 (3%)} \]

\(- \text{H}^+ \)

\[ \text{C}_7\text{H}_8\text{N}^+ \quad \text{m/e 106 (4%)} \]

\[ \text{m/e 126 (3%)} \quad \text{m/e 109 (20%)} \]
m/e 219 respectively) have a high tendency to undergo further fragmentations.

Solvolysis of lactam-methanesulfonate (33d) in aqueous ethanol in the presence of diphenylisobenzofuran was conducted as a preliminary test whether a fragmentation reaction would be possible for our system.

Diphenylisobenzofuran is a well known diene to trap reactive double bonds. In theory, the solvolysis of lactam-methanesulfonate (33d) could have three different pathways (Scheme XVI). The formation of double bond via routes b and c could be trapped by the diphenylisobenzofuran to give Diels-Alder adducts (46) and (47) respectively. On the other hand, solvolytic displacement of the methanesulfonyl group via route a would not give any C=C bond.

After refluxing the above mixture for 72 h, excess diphenylisobenzofuran was separated by chromatography. The second component, a white solid (mp 146-148°C) exhibits a carbonyl absorption around 1685 cm⁻¹. ¹H-nmr, ¹³C-nmr and mass spectral analyses (M⁺, 285) indicated that it was α-dibenzoylbenzene, probably formed from an oxidation of diphenylisobenzofuran.
Scheme XVI

(46)  (47)
Further flushing with acetone-chloroform (1:1) afforded a yellowish residue which was shown to contain no aromatic or olefinic hydrogens. The structure of this material was still unknown. The failure of the isolation of fragmentation product may attribute to the low basicity of the amidic nitrogen.

The solvolysis of (34) was similarly tested in ethanolic solution. Iminium ion is known to be highly unstable in acidic media, readily hydrolyzed in aqueous solution to give an aldehyde or ketone plus the amino function. For this reason, excess base (e.g. sodium hydride or 2,2,6,6-tetramethyl-4-piperidinol) was added to neutralize the methanesulfonic acid formed during solvolysis.

Two transition metal complexes, Pd(φCN)₂Cl₂ and Rh₂Cl₂(COD)₂ were used
with a hope to trap the possible tetrahydroazocine (9) or related products. Solvolysis of amino-methanesulfonate (34) in the presence of Pd(φCN)₂Cl₂ was conducted at 80°C for 18 h in nitrogen atmosphere. It was noted that the red mixture turned into palladium black after 1 h. The product contains olefinic protons corresponded to δ 6.0-4.5 in the nmr spectrum, and at δ 148 and 133 in ¹³C-nmr spectrum. The methanesulfonate group was cleaved as shown by the disappearance of the methyl absorption at δ 3.0 in the proton nmr spectrum.

In contrast, the solvolysis of (34) in the presence of Rh₂(COD)₂Cl₂ and sodium hydride in tetrahydrofuran produced different results. The methanesulfonate group remained unsolvolyzed. No olefinic proton was observed in nmr and neither did olefinic carbon in ¹³C-nmr. The reaction product was a yellow solid, exhibiting complex absorption patterns from δ 2.6-1.2 and a multiplet around δ 5.3 in nmr spectrum. The structure was yet unidentified.
EXPERIMENTAL

Nuclear magnetic resonance (nmr) spectra were measured using a JEOL 60-HL spectrometer (60 MHz) unless otherwise specified. $^{13}$C-nmr spectra were measured on a JEOL FX-90Q spectrometer (90 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. Gas chromatographic analyses were performed on a Hewlett Packard 700 laboratory chromatograph equipped with a 6 ft x 0.5 in stainless steel column packed with 10% silicon gum rubber SE-30 on chromosorb W (80-100). Melting points (mp) and boiling points (bp) are uncorrected. Elemental analyses were performed by Australian Microanalytical Service, Melbourne, Australia. Reagents and solvents were commercial grades, and were purified by standard procedures 30.

2-Cyclopentenone (35)

2-Cyclopentenone (35) was prepared according to a modified procedure of Alder and Flock 49. Freshly distilled cyclopentadiene (70 g, 1.06 mol) was placed in a 500 mL flask and stirred vigorously and kept at 20-25°C by external cooling with a dry ice-acetone bath. Anhydrous hydrogen chloride (38.7 g, 1.06 mol) was bubbled into the nmr liquid until a deep purple color
developed, which was crude cyclopentenyl chloride (108.7 g, 1.06 mol) and was used immediately. Without further purification, the cyclopentenyl chloride was added dropwise to a solution of sodium dichromate dihydrate (88 g, 0.30 mol) in water (300 mL) in a 1 L flask that was immersed in an acetone-ice bath. The reaction mixture was stirred efficiently and kept at 0-10°C. Aqueous sulfuric acid (150 mL, 50% by volume) was then added slowly to the brownish mixture. The temperature of the reaction was maintained carefully below 10°C throughout the addition. The green mixture was diluted with water (400 mL) and extracted with chloroform (6x150 mL). Combined organic layers were washed with water (3x150 mL) followed by saturated sodium carbonate solution (3x150 mL) and dried over sodium sulfate. The solvent was then removed in vacuo. The residue was distilled through a short Vigreux column. Pure 2-cyclopentenone (35) (40 g, 46%) was obtained by fractional distillation under reduced pressure: bp 42-44°C/10 mm (lit. 50: bp 63-69°C/23 mm).

Bromoacetaldehyde Diethylacetal (48)

Bromoacetaldehyde diethylacetal (48) was synthesized according to known procedure 51. Vinyl acetate (86 g, 1.00 mol) was transformed into (48) (130 g, 66%) and was freshly distilled before use: bp 67-68°C/18 mm (lit. 51: bp 64-65°C/18 mm); νmax (CDCl₃) 3 4.6 (1 H, t, H₁), 3.6 (4 H, q, OCH₂), 3.3 (2 H, d, ᵃ₂) and 1.2 (6 H, t, CH₃); ir (neat) 1150 and 1090 cm⁻¹ (ketal).
Ketene Diethylacetal (1,1-diethoxyethene) (36a)

Ketene diethylacetal (36a) was prepared according to the procedure given by McElvain and Kundiger. Bromoacetaldehyde diethylacetal (48) (50 g, 0.25 mol) was transformed into 1,1-diethoxyethene (17.7 g, 61%): bp 118-121 °C/760 mm (lit. bp 83-86 °C/200 mm).

6,6-Diethoxybicyclo[3.2.0]heptan-2-one (28a)

A solution of cyclopentenone (35) (2.0 g, 24.4 mmol) and freshly distilled ketene diethylacetal (36a) (20.0 g, 172 mmol) in pentane (400 mL) under nitrogen atmosphere was placed in a pyrex photochemical reactor and irradiated (400W, medium pressure mercury arc, Applied Photophysics 400LQ) at 0 °C for 7.5 h. The pentane and excess ketene diethylacetal (16.0 g, 138 mmol) were removed in vacuo. Distillation of the residue gave 6,6-diethoxybicyclo[3.2.0]heptan-2-one (28a) (2.5 g, 53%): bp 54-56 °C/0.05 mm; nmr (CDCl₃) δ 3.45 (4 H, q, OCH₂), 3.42 (4 H, q, OCH₂), 3.1-1.6 (8 H, m, H₁, H₃, H₄, H₅, H₇), 1.18 (3 H, t, CH₃) and 1.15 (3 H, t, CH₃); ir (neat) 1743 (carbonyl), 1142 and 1057 cm⁻¹ (ketal); ms (m/e) 198 (2%), 153 (15%), 142 (11%), 116 (38%), 83 (39%), 55 (20%) and 43 (100%).

6,6-Diethoxybicyclo[3.2.0]heptan-2-ol (29)

To a 250 mL round-bottomed flask fitted with a drying tube was placed a suspension of lithium aluminum hydride (0.9 g, 23.7 mmol) in dry tetra-
hydrofuran (50 mL). 6,6-Diethoxybicyclo[3.2.0]heptan-2-one (28a) (4.8 g, 24.4 mmol) in freshly distilled tetrahydrofuran (75 mL) was added dropwise at 0°C. After the addition was completed, the mixture was stirred for 4 h. Excess lithium aluminum hydride was decomposed by the addition of ethyl acetate. The mixture was poured into ice-water (100 mL) and extracted with dichloromethane (4x100 mL). Combined organic extracts were washed with brine solution and dried over magnesium sulfate, filtered and evaporated in vacuo to give 6,6-diethoxybicyclo[3.2.0]heptan-2-ol (29) in nearly quantitative yield, which was used in next step without further purification: ir (neat) 3600-3200 (hydroxyl), 1150 and 1050 cm⁻¹ (ketal).

endo-2-Hydroxybicyclo[3.2.0]heptan-6-one (27a)

A mixture of 6,6-diethoxybicyclo[3.2.0]heptan-2-ol (29) (4.8 g, 24.0 mmol), dichloromethane (100 mL), water (10 mL) and 2 drops of concentrated hydrochloric acid was stirred for 4 h at room temperature. The mixture was then neutralized with dilute sodium hydroxide solution and was extracted with dichloromethane (2x50 mL). Combined organic extracts were washed with saturated sodium carbonate solution (50 mL), dried over magnesium sulfate, filtered and evaporated in vacuo to give crude 2-hydroxybicyclo[3.2.0]-heptan-6-one (27a), which was purified by vacuum distillation (2.7 g, 89%): bp 69-70°C/0.05 mm; nmr (CDCl₃) δ 4.6-4.2 (1 H, m, H₃), 3.8 (1 H, bs, OH),

* The nmr spectrum was measured on a 270 MHz spectrometer by Dr. K. T. Mak, University of Chicago, to whom thanks are due.
3.6-3.4 (1 H, m, $H_3$), 3.1-2.9 (3 H, m, $H_1$ and $H_2$) and 2.1-1.5 (4 H, m, $H_3$ and $H_4$); $^{13}$C-nmr (CDCl$_3$) $\delta$ 214.0 (C-6), 73.9 (C-2), 63.2 (C-5), 45.3 (C-7), 32.3 (C-1), 31.4 (C-3) and 24.6 (C-4); ir (neat) 3600-3200 (hydroxyl), 1780 (C=O) and 1079 cm$^{-1}$ (C-O); ms (m/e) 126 (5%), 108 (15%), 83 (49%), 67 (100%), 66 (31%) and 55 (22%); ms (exact mass) C$_7$H$_{10}$O$_2$, found 126.0666 (calcd 126.0679).

Anal. Calcd for C$_7$H$_{10}$O$_2$: C, 66.64; H, 7.99

Found: C, 66.38; H, 8.08

2-Hydroxybicyclo[3.2.0]heptan-6-one oxime (39a)

A mixture of 2-hydroxybicyclo[3.2.0]heptan-6-one (27a) (1.4 g, 11.1 mmol), hydroxylamine hydrochloride (2.7 g, 38.9 mmol) and sodium bicarbonate (3.4 g, 40.5 mmol) in methanol (100 mL) was refluxed for 3 h. The mixture was cooled to room temperature. Water (20 mL) was then added and the mixture was extracted with chloroform (2x50 mL). Combined organic extracts were dried over magnesium sulfate, filtered and evaporated in vacuo to give a pale yellow oil, which was chromatographed on silica gel (70-230 mesh) using chloroform as eluent to give small amount of 6,6-dimethoxybicyclo[3.2.0]-heptan-2-ol $. Further elution with chloroform afforded the desired product (39a) (1.2 g, 77%) as a colorless oil. Attempts to distill led to decomposition: nmr (DMSO-d$_6$) $\delta$ 10.2 (1 H, bs, C=N-OH), 4.7 (1 H, m, $H_2$), 4.0 (1 H, m, $H_3$), 3.5 (1 H, bs, OH), 2.3 (1 H, m, $H_1$), 2.6 (2 H, m, $H_7$) and 1.8-1.4 (4 H, m, $H_3$ and $H_4$); $^{13}$C-nmr (CD$_3$OD) $\delta$ 162.0, 161.0, 75.0, 74.6, 43.5,

* Identified by $^{13}$C-nmr spectrum. $^+$ Two isomers.
2-Acetoxybicyclo[3.2.0]heptan-6-one (27b)

In a 150 mL round-bottomed flask was placed a solution of acetyl chloride (10 mL) in dry diethyl ether (15 mL). The mixture was cooled in an ice-water bath. Pyridine (10 mL) in dry ether (25 mL) was added dropwise into the flask. Precipitation of the pyridinium salt was noted immediately. After the addition was completed, 2-hydroxybicyclo[3.2.0]heptan-6-one (27a) (2.0 g, 15.9 mmol) in diethyl ether (25 mL) was added dropwise and the mixture was stirred for 9 h. Hydrochloric acid (20 mL, 10%) was added to dissolve the salt and the solution was extracted with dichloromethane (2x250 mL). Combined organic extracts were washed firstly with dilute hydrochloric acid (2x100 mL, 10%) and then with sodium hydroxide solution (3x100 mL, 10%). It was dried over magnesium sulfate, filtered and evaporated in vacuo to give 2-acetoxybicyclo[3.2.0]heptan-6-one (27b) (2.5 g, 94%). An analytical sample was obtained by distillation: bp 52-54°C/0.05 mm; nmr (CDCl₃) δ 5.2 (1 H, m, H₂), 3.6 (1 H, m, H₃), 3.3-3.1 (1 H, m, H₁), 3.0 (2 H, m, H₇), 2.0 (3H, s, CH₃) and 2.3-1.5 (4 H, m, H₃ and H₄); ¹³C-nmr (CDCl₃) δ 211.2 (C-6), 170.5 (ester-C), 76.3 (C-2), 63.1 (C-5), 46.3 (C-7), 30.3 (C-1), 28.7 (C-3), 24.3 (C-4) and 21.0 (CH₃); ir (neat) 1789 (ketone carbonyl), 1742 (ester carbonyl) and 1251 cm⁻¹ (C-O); ms (m/e) 168 (not observed), 126 (25%), 108 (11%), 67(57%), 65
(21%) and 43(100%).

Anal. Calcd for C_{9}H_{12}O_{3}: C, 64.27; H, 7.19

Found: C, 64.20; H, 7.55

2-Acetoxybicyclo[3.2.0]heptan-6-one oxime (39b)

A mixture of 2-acetoxybicyclo[3.2.0]heptan-6-one (27b) (150 mg, 0.89 mmol), hydroxylamine hydrochloride (350 mg, 5.04 mmol) and sodium bicarbonate (450 mg, 5.35 mmol) in methanol (10 mL) was refluxed for 5 h. The mixture was then poured into water (5 mL) and extracted with chloroform (2x25 mL). Combined organic extracts were dried over magnesium sulfate, filtered and evaporated in vacuo to give a colorless oil. The ir spectrum exhibited no absorption around 1780 cm\(^{-1}\). The residue was chromatographed on silica gel and eluted with chloroform to give small amount of 2-acetoxy-5,6-dimethoxybicyclo[3.2.0]heptane*. Further elution yielded 2-acetoxybicyclo[3.2.0]heptan-6-one oxime (39b), which was purified by vacuum distillation (130 mg, 80%): bp 80°C/0.01 mm; nmr (CDCl\(_3\)) \(\delta\) 9.6 (1 H, bs, C=NO-H), 5.1 (1 H, m, H\(_2\)), 3.5 (1 H, m, H\(_3\)), 3.0 (1 H, m, H\(_4\)), 2.8 (2 H, m, H\(_7\)), 2.0 (3 H, s, CH\(_3\)) and 2.1-1.6 (4 H, m, H\(_3\) and H\(_4\)); \(^{13}\)C-nmr (CDCl\(_3\)) \(\delta\) 170.9, 170.9, 160.1, 159.1, 76.6, 76.3, 47.3, 47.0, 33.9, 33.4, 28.9, 28.4, 26.9, 26.9, 24.5, 24.5, 20.9 and 20.9; ir (neat) 3500-3200 (CNO-H), 1743 (C=O) and 1255 cm\(^{-1}\) (C-0); ms (m/e) 183 (24%), 141 (30%), 124 (32%), 123 (38%), 122 (34%), 106 (39%), 105 (31%), 104 (15%), 67 (42%) and 43 (100%); ms (exact mass) C\(_9\)H\(_{13}\)NO\(_3\), found

* Identified by \(^{13}\)C-nmr spectrum. + Two isomers.
Schmidt rearrangement of (27a)

To a chloroform solution (5 mL) of 2-hydroxybicyclo[3.2.0]heptan-6-one (27a) (200 mg, 1.59 mmol), hydrazoic acid* (100 mg, 2.33 mmol) and concentrated sulfuric acid (2 mL) were added in one portion. The mixture was stirred for 2 h at 0 °C and then poured into ice-water (5 mL). The black mixture was extracted with dichloromethane (3×25 mL). Combined organic extracts were dried over magnesium sulfate, filtered and evaporated in vacuo to give a black oil (ca. 100 mg) which was mainly the starting material (27a) as suggested by its ir spectrum.

Beckmann rearrangement of (39a)

A mixture of 2-hydroxybicyclo[3.2.0]heptan-6-one oxime (39a) (150 mg, 1.06 mmol) and concentrated sulfuric acid (0.8 mL) was stirred at room temperature for 12 h. The mixture was neutralized with potassium hydroxide solution and extracted with chloroform (3×50 mL). Combined organic extracts were dried over magnesium sulfate, filtered and evaporated in vacuo to give a black oil (ca. 50 mg), which was shown to be 2-hydroxybicyclo[3.2.0]heptan-6-one (27a) by ir analysis.

* Hydrazoic acid was obtained either in situ by reaction of concentrated H_2SO_4 with sodium azide or from chloroform solution of hydrazoic acid.
Schmidt rearrangement of (27b) by polyphosphoric acid

Phosphorous pentoxide (2 g) was mixed with phosphoric acid (2.4 mL, 25%) and refluxed for 2 h and cooled to room temperature. 2-Acetoxybicyclo[3.2.0]heptan-6-one (27b) (200 mg, 1.19 mmol) and sodium azide (82 mg, 1.26 mmol) were added in sequence. The mixture was stirred for 10 h, and poured into ice-water (10 mL), neutralized with sodium hydroxide solution, and extracted with chloroform (2x50 mL). Combined organic extracts were dried over magnesium sulfate, filtered and evaporated in vacuo to give a black oil (ca. 100 mg), which contained mainly unreacted starting material (27b).

Beckmann rearrangement of (39b)

2-Acetoxybicyclo[3.2.0]heptan-6-one oxime (39b) (200 mg, 1.09 mmol) in ether (2 mL) was added dropwise into a suspension of phosphorous pentachloride (400 mg, 1.92 mmol) in ether (2 mL) in a round-bottomed flask fitted with a drying tube. The flask was refluxed for 8 h and then cooled to room temperature. The solution was made alkaline by the addition of sodium hydroxide solution and extracted with chloroform (2x100 mL). Combined organic layers were dried over magnesium sulfate, filtered and evaporated in vacuo to give a brownish liquid (ca. 50 mg), which was mainly 2-acetoxybicyclo[3.2.0]heptan-6-one (27b).
Mesitylene Sulfonyl Chloride (50)

Mesitylene sulfonyl chloride (50) was synthesized according to the procedure of Wang and Cohen\(^\text{53}\). (50) (47 g, 86\%) was obtained from freshly distilled mesitylene (30 g, 0.25 mol); mp 57°C (lit.\(^\text{53}\): 57°C), which was recrystallized in petroleum ether (60-80°C) before use.

Ethyl Acetimidate Hydrochloride (51)

Ethyl acetimidate hydrochloride (51) was synthesized according to the procedure given by Sandler and Karo\(^\text{54}\). Acetonitrile (135 g, 3.29 mol), ethanol (151 g, 3.28 mol) and dry hydrogen chloride (120 g, 3.29 mol) were reacted to form (51) (345 g, 85\%).

Ethyl Acetohydroxamate (52)

Ethyl acetohydroxamate was synthesized from (51) in two steps by the procedure given by E. Schmidt\(^\text{55}\). (51) (30 g, 0.24 mol) was allowed to react with potassium carbonate (69 g, 0.5 mol) and then with hydroxylamine hydrochloride (21.3 g, 0.30 mol) to give (52) (11 g, 44\%); bp 83°C/20 mm (lit.\(^\text{55}\): 59-60°C/13 mm).

O-Mesitylenesulfonylhydroxylamine (53)

O-Mesitylenesulfonylhydroxylamine (53) was synthesized in two steps from
ethyl acetohydroxamate (52) and mesitylenesulfonyl chloride (50). (53)\textsuperscript{56} (12 g, 40%) was obtained from ethyl acetohydroxamate (52) (14 g, 0.14 mol) and mesitylenesulfonyl chloride (50) (30 g, 0.14 mol): mp 52-53°C (lit.\textsuperscript{56}: mp 54-55°C); nmr (CDCl\textsubscript{3}) 6 7.0 (2 H, m, H\textsubscript{3} and H\textsubscript{5}), 5.6-5.3 (2 H, bs, NH\textsubscript{2}), 2.6 (6 H, s, o-CH\textsubscript{3}) and 2.4 (3 H, s, p-CH\textsubscript{3}).

4-Hydroxy-2-oxo-octahydrocyclopenta[b]pyrrole (33a) and 4-hydroxy-1-oxo-octahydrocyclopenta[c]pyrrole (40a)

To a stirred solution of (27a) (2.0 g, 15.9 mmol) in dichloromethane (20 mL) was added a solution of 0-mesitylenesulfonylhydroxylamine\textsuperscript{56} (53) (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 (43a), 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 by suction. 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 (70-230 mesh) using chloroform as eluent. The first component was methyl mesitylenesulfonate. Hydroxy-lactams (33a) and (40a) 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 \textsuperscript{13}C-nmr showed the ratio of (33a) to (40a) was approximately 3:1. The desired isomer (33a) was isolated as white needle by successive recrystallization
from ethyl acetate and then from methanol: mp 164-168°C; nmr (CD$_3$OD) $\delta$ for (33a) 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$_6$); nmr (CD$_3$CD) $\delta$ for (40a) 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 (CD$_3$OD) $\delta$ for (33a) 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); $^{13}$C-nmr (CD$_3$OD) $\delta$ for (40a) 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); ir (KBr, disc) (33a) 3500-3150 (O-H and N-H) and 1683 cm$^{-1}$ (C=O); ms (m/e) (33a) 141 (30%), 124 (10%), 123 (13%), 113 (46%), 112 (48%), 85 (26%), 84 (100%), 83 (52%), 67 (37%), 57 (37%) and 56 (42%); ms (exact mass) (33a) C$_7$H$_{11}$NO$_2$, found 141.0769 (calcd 141.0790).

Anal. (33a) Calcd for C$_7$H$_{11}$NO$_2$: C, 59.56; H, 7.85; N, 9.92

Found C, 59.78; H, 7.48; N, 9.63

**4-Acetoxy-2-oxo-octahydrocyclopenta[b]pyrrole (33b) and 4-acetoxy-1-oxo-octahydrocyclopenta[c]pyrrole (40b)**

To a stirred solution of 2-acetoxybicyclo[3.3.0]heptan-6-one (27b) (3.0 g, 17.9 mmol) in dichloromethane (4.5 mL) was added a solution of 0-mesitylensulfonylhydroxylamine (7.0 g, 32.6 mmol) in dichloromethane (2.5 mL) at $-10^\circ$C and the reaction mixture was allowed to stand for 10 min. The solvent was removed under reduced pressure to yield crystalline oxime sulfonate (43b), which was suspended in benzene (2 mL) and was added into a stirred slurry of basic alumina (100 g) in methanol (150 mL) at $-10^\circ$C. The
mixture was stirred for 4 h and filtered by suction. 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 (33b) and (40b) (3.0 g, 92%) were distilled with moderate decomposition to yield a colorless liquid, which on refrigeration gave a white solid. $^{13}$C-nmr spectrum indicated the ratio of (33b) to (40b) was approximately 5:1. Attempts to separate (33b) from (40b) were unsuccessful:

bp 136°C/0.02 mm; nmr (CDCl$_3$) $\delta$ 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$_6$); $^{13}$C-nmr (CDCl$_3$) $\delta$ for (33b) 178.1 (C-2), 170.3 (ester carbonyl), 75.4 (C-4), 57.8 (C-6), 39.3 (C-3), 30.5 (C-5), 30.1 (C-5), 28.7 (C-6) and 20.9 (CH$_3$); $^{13}$C-nmr (CDCl$_3$) $\delta$ for (40b) 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$_3$); ir (neat) (33b) & (40b) 3400-3200 (N-H), 1742 (ester carbonyl), 1699 (lactam carbonyl) and 1249 cm$^{-1}$ (C-0); ms (m/e) 183 (19%), 141 (13%), 140 (8%), 124 (17%), 123 (100%), 113 (25%), 84 (72%), 80 (38%), 67 (11%) and 43 (95%); ms (exact mass) C$_9$H$_{13}$NO$_2$, found 183.0879 (calcd 183.0895).

Attempted N-benzylation of lactam-acetates (33b) & (40b)

A mixture of (33b) and (40b) (314 mg, 1.72 mmol, 5:1) in dry xylene (10 mL) was added dropwise to a suspension of sodium hydride (44 mg, 1.83 mmol) in dry xylene (5 mL) under nitrogen atmosphere. The solution turned
into light brown in color and was heated to 180°C for 1 h, benzyl bromide (350 mg, 2.05 mmol) was then added with stirring. When the addition was completed, the mixture was refluxed for additional 3 h, and cooled to room temperature. Water (20 mL) was added and the solution was extracted by dichloromethane (3x75 mL). Combined organic extracts were washed with sodium hydroxide solution (3x20 mL, 5%), dried over magnesium sulfate, filtered and evaporated in vacuo to give a brownish oil (ca. 300 mg). Analysis by nmr and ir showed it contained solely unreacted (33b) and (40b).

2-Tetrahydropyranyloxybicyclo[3.2.0]heptan-6-one (27c)

2-Hydroxybicyclo[3.2.0]heptan-6-one (27a) (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 (27c) was obtained as a diastereoisomeric mixture by distillation (1.3 g, 78%): bp 74°C/0.02 mm; nmr (CDCl₃) δ 4.6 (1 H, m, H₂₁), 4.4 (1 H, m, H₂), 3.8 (1 H, m, H₂₂), 3.6 (2 H, m, H₂, and H₃), 3.0 (3 H, m, H₁ and H₇) and 2.0-1.4 (10 H, m, H₃, H₄, H₅, H₆, H₇, and H₈). ¹³C-nmr (CDCl₃) δ 213.0, 212.5, 208.8, 207.5, 195.0, 194.0, 192.9, 192.6, 192.6, 192.4, 196.5, 194.7, 191.6, 191.5, 190.9, 190.9, 189.5, 187.7, 185.5, 185.5, 182.5, 182.5, 182.5, 181.0, 181.0, 179.7, 179.7; ir (neat) 1786 cm⁻¹ (C=O); ms (m/e) 210 (not observed), 126 (6%), 125 (21%), 108 (6%), 85 (100%), 83 (39%) and 67 (78%).
Reaction of (27c) with 0-mesitylenesulfonylhydroxylamine (53)

The procedure was the same as described in the reaction of (27a) with (53). 2-Tetrahydropyranoylxybicyclo[3.2.0]heptan-6-one (27c) (1.2 g, 5.7 mmol) was transformed into hydrolyzed products, hydroxy-lactams (33a) and (40a) (0.64 g, 80%) instead of (33c) and (40c).

2-Oxo-4-tetrahydropyranoyl-octahydrocyclopenta[b]pyrrole (33c) and 1-exo-4-tetrahydropyranoyl-octahydrocyclopenta[c]pyrrole (40c)

Hydroxy-lactams (33a) and (40a) (1.0 g, 7.1 mmol) were dissolved in hot tetrahydrofuran (5 mL). Freshly distilled dihydropyran (0.6 g, 7.1 mmol) and one drop of concentrated hydrochloric acid were added and the mixture was stirred for 3 h at room temperature. Powdered anhydrous sodium carbonate was added to neutralize the solution. The solid was filtered and washed with chloroform (2 x 50 mL). The combined organic solution was evaporated in vacuo to give (33c) and (40c) (1.4 g, 92%) as a colorless liquid:

\[ \text{nmr (CDCl}_3) \delta (33c) \& (40c) 7.8-7.6 (bs, NH), 4.7-4.5 (m, H}_2, \text{ and H}_6, 4.2-3.2 (m, H}_4, \text{ and H}_9, 3.0-2.0 (m, H}_3, \text{ and H}_3, 1.9-1.5 (m, H}_5, H}_6, H}_7, H}_4, \text{ and H}_5); \text{ ir (neat) 3400-3200 (N-H) and 1690 cm}^{-1} (C=O); \text{ ms (m/e) 225 (not observed), 141 (30%), 125 (23%), 124 (35%), 85 (100%) and 67 (17%).} \]

Attempted reduction of a mixture of (33c) and (40c) by lithium aluminum hydride

A mixture of (33c) and (40c) (0.5 g, 2.2 mmol) in dry tetrahydrofuran
(25 mL) was added dropwise to a stirred mixture of lithium aluminum hydride (0.1 g, 2.6 mmol) in tetrahydrofuran (20 mL). The mixture was stirred overnight, excess lithium aluminum hydride was decomposed by the addition of ethyl acetate. Water (50 mL) was added and the mixture was extracted with dichloromethane (2x50 mL). Combined organic layers were dried over magnesium sulfate, filtered and evaporated in vacuo to give colorless oil (ca. 400 mg), which was unreacted starting material.

2-Methanesulfonyloxybicyclo[3.2.0]heptan-6-one (27d)

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 (27a) (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 (27d) (0.4 g, 82%). Pure (27d) was obtained by distillation with slightly decomposition or chromatographed on silica gel (70-230 mesh) using benzene as eluent; bp 70°C/0.2 mm; nmr (CDCl₃) δ 5.2 (1 H, m, H₂), 3.5 (1 H, m, H₅), 3.20 (3 H, s, CH₃), 3.15 (2 H, m, H₇), 2.8 (1 H, m, H₁) and 2.5-1.6 (4 H, m, H₃ and H₄); ¹³C-nmr (CDCl₃) δ 210.1 (C-6), 82.3 (C-2), 62.8 (C-5), 46.6 (C-7), 38.2 (CH₃), 31.0 (C-1), 29.4 (C-3) and 23.9 (C-4); ir (neat) 1785 (C=O), 1359 and 1180 cm⁻¹ (CH₃SO₂O⁻); ms (m/e)
204 (0.4%), 108 (5%) and 67 (100%); ms (exact mass) C_{12}H_{12}SO_{4}, found 204.0449 (calcd 204.0456).

Reaction of (27d) with 0-mesitylenesulfonylhydroxylamine (53)

The procedure was essentially the same as described previously for (27a). 2-Methanesulfonyloxybicycle[3.2.0]heptan-6-one (27d) (0.5 g, 2.5 mmol) in dichloromethane (2 mL) was added into a dichloromethane solution (5 mL) of (53) (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 suction 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. The first component was methyl mesitylenesulfonate. Hydroxy-lactams (33a) and (40a) (0.28 g, 81%) were obtained when eluted by acetone-chloroform (1:1) mixture.

4-Methanesulfonyloxy-2-oxo-octahydrocyclopenta[b]pyrrole (33d)

Hydroxy-lactams (33a) and (40a) (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, 50% 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 (40d) (150 mg, 0.68 mmol) was eluted with acetone-chloroform (1:3). The desired isomer (33d) (300 mg, 1.37 mmol) was obtained from the fraction using acetone-chloroform (2:1) as eluent. Unreacted hydroxylactams (33a) and (40a) (200 mg, 1.42 mmol) were isolated by flushing the column with acetone. The overall yield for (33d) and (40d) was 48% and 24% respectively (based on unrecovered hydroxy-lactams). Compound (33d) slowly crystallized on refrigeration. An analytical sample of (33d) was obtained as colorless needles by recrystallization from chloroform: mp 97-99°C; nmr (CDCl₃) δ 7.5-7.2 (1 H, bs, NH), 5.0 (1 H, m, H₄), 4.2 (1 H, m, H₆a), 3.5-3.2 (1 H, m, H₃a), 3.1 (3 H, s, CH₃), 2.5 (2 H, m, H₃) and 2.1-1.7 (4 H, m, H₅ and H₆); ¹³C-nmr (CDCl₃) δ 177.4 (C-2), 81.2 (C-4), 57.1 (C-6a), 40.7 (C-3a), 38.5 (CH₃), 30.7, 30.3 and 30.1 (C-3, C-5 and C-6); IR (KBr, disc) 3600-3200 (N-H), 1683 (C=O), 1360 and 1180 cm⁻¹ (CH₃S=O); ms (m/e) 219 (not observed), 140 (12%), 124 (26%), 123 (100%) and 67 (21%); ms (exact mass for m/e 123) C₇H₉NO, found 123.0675 (calcd 123.0684).

Anal. Calcd for C₈H₁₃SO₄N: C, 43.92; H, 5.98; N, 6.39; S, 14.62

Found C, 44.05; H, 6.19; N, 6.26; S, 14.30
Solvolytic study of (33d) in 95% ethanol

A mixture of (33d) (50 mg, 0.23 mmol) and 1,2-diphenylisobenzofuran (130 mg, 0.48 mmol) were dissolved in 95% ethanol (20 mL), to which potassium hydroxide (100 mg) was added. The mixture was refluxed for 72 h, cooled to room temperature and then poured into chloroform (50 mL). The solution was dried over sodium carbonate, filtered and evaporated in vacuo to give a yellowish liquid, which was chromatographed on silica gel (70-230 mesh) and eluted with benzene-petroleum ether (60-75°C) (1:1) to recover unreacted diphenylisobenzofuran (18 mg). o-Dibenzoylbenzene (53 mg, mp 146-148°C, lit.57: mp 148°C) was obtained when eluted with benzene-chloroform (1:1). Further flushing with acetone gave a colorless liquid (11 mg) which showed no aromatic protons (δ 9.0-6.5) in the nmr spectrum. The olefinic region (δ 6.0-4.0) did not exhibit any proton absorption either. Attempts to determine the structure were not successful.

Boron tetrahydrofuranate (54)

The complex was prepared by a modification of known procedure48. To a stirred suspension of sodium borohydride (4.1 g, 0.11 mol) in freshly distilled tetrahydrofuran (150 mL) was added dropwise a solution of distilled boron trifluoride etherate (21.4 g, 0.15 mol) in tetrahydrofuran (30 mL). The solution was stirred at room temperature for 10 h under nitrogen atmosphere. The mixture was then transferred into a dry box and the solid sodium tetrafluoroborate was filtered, the filtrate (110 mL) had a concentration of
approximately 1.1 M in borane (0.12 mol 81%), as determined by measuring the hydrogen evolved on hydrolysis, which was stored under nitrogen in a refrigerator.

4-Methanesulfonyloxy-octahydrocyclopenta[b]pyrrole (34)

4-Methanesulfonyloxy-2-oxo-octahydrocyclopenta[b]pyrrole (33d) (160 mg, 0.73 mmol) was mixed with borane tetrahydrofuranate (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 (34) 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 (34) (96 mg, 64%). Attempts to purify it by chromatography led to decomposition: nmr (CDCl₃) δ 5.1-4.7 (1 H, m, H₄), 3.8-3.1 (2 H, m, H₃a and H₆a), 3.0 (3 H, s, CH₃), 2.9-2.7 (2 H, m, H₂) and 2.1-1.5 (7 H, m, H₃, H₅, H₆ and NH); ¹³C-nmr (CDCl₃) δ 83.5 (C-4), 62.4 (C-6a), 48.1 (C-2), 46.1 (C-3a), 38.3 (CH₃), 31.1 (C-5), 29.8 (C-6) and 28.1 (C-3); ir (neat) 3600-3200 (N-H), 1360 and 1183 cm⁻¹ (CH₃SO₂O); ms (m/e) 205 (not observed), 176 (10%), 110 (100%), 109 (20%), 108 (19%), 82 (11%), 81 (13%), 80 (21%), 79 (11%), 68 (29%) and 67 (12%); ms (exact mass
for m/e 110) C_{7}H_{12}N, found 110.0958 (calcd 110.0969).

**Reaction of (34) with dibenzonitrile palladous chloride**

A mixture of (34) (40 mg, 0.20 mmol), 2,2,6,6-tetramethyl-4-piperidinol (20 mg, 0.13 mmol) and dibenzonitrile palladous chloride\(^{58}\) (30 mg, 0.21 mmol) in 95% ethanol (4 mL) was refluxed under nitrogen atmosphere for 18 h. The solution was poured into boiled absolute ethanol (10 mL) and filtered when hot, the red filtrate was evaporated in vacuo to afford a reddish oil. Acetone (2 mL) was added to precipitate the 2,2,6,6-tetramethyl-4-piperidinol and the solution was filtered. The filtrate was concentrated in vacuo to yield a brownish oil. The nmr spectrum of this crude oil showed a broad multiplet at ~6 5.6-4.5 and complex absorption patterns from ~6 3.4-0.8. Its \(^{13}\)C-nmr spectrum exhibited peaks at ~6 143, 133, 82, 73, 46, 39 and 30. The structure of this oil was yet unidentified.

**Reaction of (34) with 1,5-cyclooctadiene rhodium (I) chloride dimer**

A mixture of (34) (18 mg, 0.09 mmol), sodium hydride (8 mg, 80% dispersion in oil, 0.27 mmol) and Rh\(_2\)Cl\(_2\)(COD)\(_2\)\(^{59}\) (50 mg, 0.10 mmol) in tetrahydrofuran (3 mL) was heated to 70°C for 1 h under nitrogen atmosphere. The resulting solution was stirred at room temperature for 12 h. The residue was filtered and washed with chloroform (2x10 mL). The organic layer was evaporated in vacuo to give a pale yellow solid. The structure was not yet identified: nmr (CDCl\(_3\)) ~6 5.2-4.8, 4.1, 3.3, 3.0, 2.6-1.2 and 1.0;
$^{13}$C-nmr (CDCl$_3$) $\delta$ 79.6, 38.7, 30.9, 29.7 and 26.5.
REFERENCES AND NOTES


8. R.M. Coates and E.F. Johnson, J. Amer. Chem. Soc., 93, 4016 (1971);


21. Examination of the model indicates the maximum deviation from antiparallelism is 20°.
25. For a review see C.F. Lane, Chem. Rev., 76, 773 (1976).


