(No. 01607001) from the Ministry of Education, Science and Culture of Japan.

Registry No. **1a**, 508-32-7; **1b**, 488-97-1; **1c**, 1137-12-8; **2a**, 54672-39-8; **2b**, 125948-46-1; **2b** (3,5-dinitrobenzoate), 125846-50-6; **2c**, 64854-50-8; **2c** (3,5-dinitrobenzoate), 125846-51-7; **3**, 83290-63-5; **4a** (isomer 1), 104462-63-7; **4a** (isomer 2), 104528-33-8; **4b** (isomer 1), 104459-12-3; **4b** (isomer 2), 104528-34-9; **5**, 97090-49-8; **6a**, 87422-04-6; **6b**, 125948-47-2; **7**, 79-92-5; **8**, 464-17-5; **9**, 99977-70-5; **10**, 466-12-6; **11**, 1925-39-9; α-pinene, 80-56-8; β-pinene, 127-91-3.

The Conversion of an Aziridine to a β-Lactam

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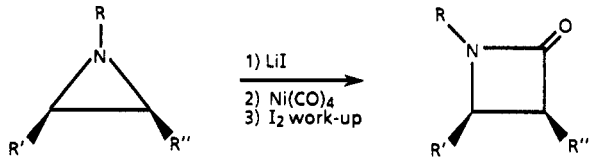
A one-pot, inert atmosphere conversion of an aziridine to a β-lactam using nickel tetracarbonyl as the carbonyl source is described. In this reaction it is the less substituted carbon–nitrogen bond which is carbonylated. The proposed mechanism for this reaction requires that a nickel acylate complex attack an alkyl iodide with inversion of configuration. Iron carbonyl complexes are unsuccessful in this carbonylation process.

Because of the ready availability of aziridines[1] and the great importance of β-lactams,[2] we have recently developed[3] a one-pot, low-pressure reaction, using nickel tetracarbonyl, for the conversion of an aziridine to a β-lactam. In this reaction, it is the *less* substituted carbon–nitrogen bond which is carbonylated. This result is complementary



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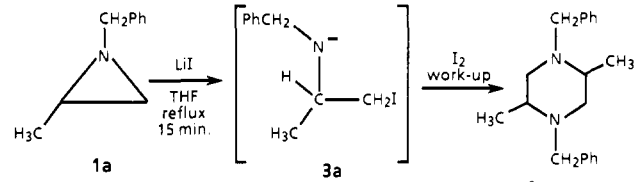
to a previously known,[4] high-pressure reaction, using rhodium, in which the *more* substituted carbon–nitrogen bond is carbonylated.

In this paper, we discuss a variety of substituents which are compatible with this chemistry (Table I) and those which are not, we report full experimental details, and we propose a mechanism of this nickel-promoted carbonylation reaction. In addition, we show that iron carbonyl complexes do not act as a carbonyl source for this transformation.

Results

Carbonylation of 1-Benzyl-2-methylaziridine (1a). Because the first step in the conversion of aziridine **1a** to β-lactam **2a** (Table I) is the S_N2 ring opening of the aziridine by lithium iodide in refluxing tetrahydrofuran (THF), the thermal stability of aziridine **1a** must be determined. Therefore, it was allowed to reflux in THF for over 3 h, and then subjected to the iodine workup conditions. 1-Benzyl-2-methylaziridine (**1a**) was recovered almost quantitatively from this sequence.

Next, **1a** was treated with lithium iodide in refluxing THF to effect a ring opening, which is complete in 15 min. To confirm this point and to observe the putative intermediate **3a**, NMR spectroscopy was attempted on the reaction mixture; however, the reaction solution is too dilute to see peaks other than those due to solvent. Upon concentration, only a mixture of stereoisomers of the six-membered ring dimer **4**[5] and the starting aziridine **1a** could



1a 3a 4

be observed. If, instead, the solution is subjected to an iodine workup, again only a mixture of the six-membered ring dimer **4** and a very small amount of the starting aziridine **1a** could be observed. When the LiI reaction is allowed to proceed for a longer period, the results are very similar to the results for the 15 min reaction.

Because lithium iodide may be contaminated by iodine, the effect of iodine on the starting material was determined. When aziridine **1a** is allowed to reflux in THF for 15 min with added iodine, only benzyl iodide and bibenzyl are isolated. Thus, the ring opening of the aziridine is due to lithium iodide and is complete in 15 min.

After ring-opening, the next step of the carbonylation sequence is the reaction of the proposed intermediate **3a** with nickel tetracarbonyl. After **1a** and lithium iodide were allowed to reflux in THF, the reaction solution was cooled to room temperature, nickel tetracarbonyl was added, and the solution was heated to reflux for an additional 3 h under an inert atmosphere. Alternatively, once the ring-opening reaction was allowed to cool to room temperature, the solution was saturated with carbon monoxide, nickel

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Table I. Substituents, Reaction Conditions, and Yields for the Carbonylation of an Aziridine

compd 1	R	R′	R″	LiI reaction time, min[a]	$Ni(CO)_4$ reaction time, h	yield, %
a	CH_2Ph	CH_3	H	15	3	50 (Ar atm) 50 (CO atm)
b	CH_2Ph	CH_3	CH_3	2 h	3	20 (Ar atm) 40 (CO atm)
c	$CH_2C_6H_4OCH_3$	CH_3	H	30	3	40 (Ar atm) 40 (CO atm)
d	C_6H_{13}	CH_3	H	15	4	40 (Ar atm) 40 (CO atm)
e	SO_2CH_3	CH_3	H	15	6	20 (Ar atm) 20 (CO atm)

[a] Except where noted.

tetracarbonyl was added, and the solution was heated to reflux for 3 h under a carbon monoxide atmosphere (using a carbon monoxide filled balloon). Both reactions give a 50% isolated yield of β-lactam **2a**, after purification. When the reaction is allowed to proceed for longer than 3 h, the yield of product decreases. If the lithium iodide step is not performed, i.e., aziridine **1a** is allowed to reflux in THF for 3 h with only nickel tetracarbonyl, or if the lithium iodide, nickel tetracarbonyl, and aziridine **1a** are combined in one step, no β-lactam **2a** is observed.

To determine which metal complex(es) is(are) involved, the reaction was performed without the oxidative workup, concentrated in vacuo, and then monitored by various spectroscopic techniques. The carbonyl stretching region of the infrared spectrum shows peaks at 2030 and 1945 cm^{-1}, which are assigned to terminal carbonyls, and at 1650 cm^{-1}, which is assigned to an acyl carbonyl, of a neutral acyl(alkyl)nickel complex.[6] The ^{13}C NMR spectrum shows only peaks due to the solvent, as was expected, because an acyl(alkyl)nickel complex is most likely paramagnetic.[6] The mass spectrum indicates the presence of a new compound, which has a fragmentation pattern different from that obtained for the starting material **1a**. Unfortunately, the data are most consistent with only an organic fragment, with no peaks for a metal complex being observed. However, no absorptions consistent with the product β-lactam **2a** are observed in the IR or ^{13}C NMR spectra until *after* the oxidative workup.

Based on ^1H and ^{13}C NMR spectroscopic data, the only regioisomer of the lactam formed is the one in which the less substituted bond of the original aziridine is carbonylated,[7] a result consistent with the initial S_N2 attack of the iodide on the aziridine.

Carbonylation of 1-Benzyl-*cis*-2,3-dimethylaziridine (1b). To determine if 2,3-disubstituted aziridines will react under these conditions, i.e., whether the iodide will induce a ring opening at a secondary center, and to determine the stereochemistry of attack of a nickel acylate complex on an alkyl halide, the reactivity of 1-benzyl-*cis*-2,3-dimethylaziridine (**1b**) was investigated next.

The dimethylaziridine **1b** was easily converted to the dimethyl β-lactam **2b** in a manner similar to that used for the monomethyl analogue; however there are two major differences. First of all, the nucleophilic ring opening of the dimethyl compound requires 2 h rather than 15 min. This is not surprising as the attack must occur at a secondary center rather than a primary center. Second, the yield of product depends strongly upon whether the reaction is run under an inert atmosphere (20% isolated yield after purification) or a carbon monoxide atmosphere (40% isolated yield after purification). Based on ^1H and ^{13}C NMR spectroscopic data, the *cis*-dimethyl aziridine generates exclusively the *cis*-dimethyl β-lactam.[7]

As with the monomethyl analogue, the nickel tetracarbonyl reaction was monitored by ^{13}C NMR and IR spectroscopies. As before, the carbonyl stretching region of the IR spectrum has three major peaks (2050, 1960, and 1670 cm^{-1}), and the ^{13}C NMR spectrum only has peaks due to solvents. Again, no peaks due to the β-lactam are observed in the IR or ^{13}C NMR spectra before the oxididative workup.

Carbonylation of 1-(*p*-Methoxybenzyl)-2-methylaziridine (1c) and 1-Hexyl-2-methylaziridine (1d). It was next decided to investigate the compatibility of other electron-donating groups with this carbonylation reaction. It was found that *N*-(*p*-methoxybenzyl)- and *N*-hexyl-substituted aziridines can be converted to the corresponding β-lactams **2c** and **2d** in 40% yield, under either an argon or CO atmosphere. As can be seen in Table I, there is some modification of the times required for the iodide ring opening reaction and for the nickel tetracarbonyl carbonylation reaction, but, in general, these reactions proceeded quite smoothly. As in the previous cases, only one regioisomer of the β-lactam is obtained from each of these reactions.

Carbonylation of 1-Methanesulfonyl-2-methylaziridine (1e). Our attention now was turned to replacing the *N*-alkyl substituent by a methyl sulfone, to determine the effect of an electron-withdrawing group (SO_2CH_3) as compared with an electron-donating group (CH_2R). 1-Methanesulfonyl-2-methylaziridine (**1e**) was subjected to the lithium iodide reaction for the standard 15 min and to the nickel tetracarbonyl reaction for over 6 h. Unfortunately, only a 20% yield of β-lactam **2e** could be obtained (after purification) using either an inert or carbon monoxide atmosphere. If the second step is allowed to proceed for a shorter period of time, no product is obtained, and, if for a longer time, the yield is even lower. As with the other starting materials, only one regioisomer of the product β-lactam is obtained.

Unsuccessful Carbonylations. Electron-withdrawing substituents are much less compatible with this carbonylation reaction than are electron-donating substituents. For example, when *N*-(*p*-nitrobenzyl)-2-methylaziridine (**5a**) is subjected to the standard reaction conditions, only unidentifiable, high molecular weight products are obtained. In addition, *N*-benzoyl-2-methylaziridine (**5b**) exclusively isomerizes to 2-phenyl-4-methyl-2-oxazoline. Control experiments show the isomerization occurs in the lithium iodide reaction, and thus, long before any nickel tetracarbonyl is added.

Another substitution pattern incompatible with this carbonylation reaction is a phenyl group at either the

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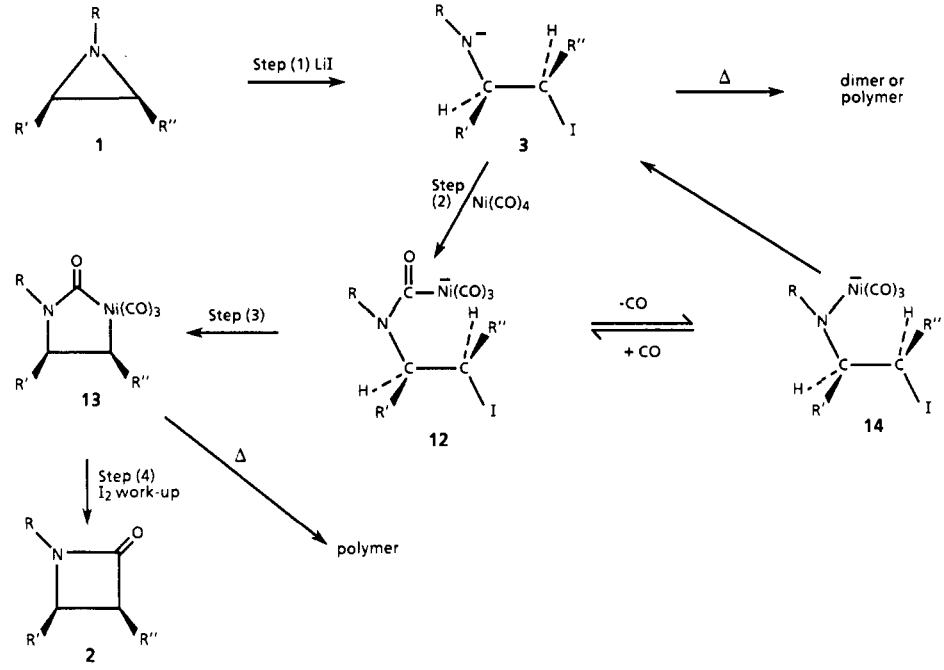
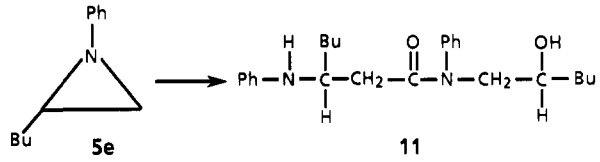


Figure 1. Proposed mechanism for the conversion of an aziridine to a β-lactam and proposed side reactions.

1-position or the 2-position of the aziridine. For the reactions of 1-propyl-2-phenylaziridine and the 1,2-diphenylaziridine (**5c** and **5d**) no β-lactam product was formed. Tentatively, the former reaction gives the dimer of the aziridine and the latter reaction generates aniline. For the reaction of 1-phenyl-2-butylaziridine (**5e**) the product (**11**) is derived from two molecules of the starting aziridine, and in addition, has incorporated carbon monoxide.



To test the viability of $Fe(CO)_5$ as the CO source, the exact same conditions as discussed previously for the conversion of **1a** to **2a** (with either an inert or carbon monoxide atmosphere) were used, except nickel tetracarbonyl was replaced by iron pentacarbonyl. When this reaction was monitored by IR spectroscopy before the workup, the spectrum shows terminal and acyl carbonyl stretches (1990, 1970, 1910, and 1730 cm^{-1}) for a neutral acyl(alkyl)iron complex which is similar to the acyl(alkyl)nickel complex. However, surprisingly, after oxidation by I_2 none of the desired β-lactam was observed; only a nearly quantitative recovery of a mixture of the aziridine **1a** and dimer **4** was obtained. The iron complexes $Fe_2(CO)_9$ and $Fe_3(CO)_{12}$ also proved unsuccessful in this carbonylation reaction.

Discussion

In this paper, we have discussed a conversion of an aziridine to a β-lactam, in moderate yield. This sequence is based on the known ability of an amide to attack nickel tetracarbonyl[8] and the known reactivity of a nickel acylate complex with an alkyl halide.[6] Unlike the previously reported conversion,[4] in our chemistry it is the less substituted carbon–nitrogen bond which is carbonylated. This is a direct result of the first step which is an S_N2 ring opening with iodide.

This chemistry works well when the nitrogen and one carbon of the aziridine are substituted with alkyl groups, less well when the nitrogen is substituted by a group which can delocalize the lone pair (such as a sulfone), and not at all when the ring is substituted with a phenyl group. Again this is complementary to the rhodium reaction[4] which requires an aryl group at the 2-position of the aziridine.

The one exception to phenyl groups being incompatible with this chemistry may be the reaction of 1-phenyl-2-butylaziridine (**5e**). In this case, product **11** appears to be the result of a reaction between the desired β-lactam (or a nickel-containing β-lactam precursor) and the starting aziridine (**5e**). All attempts to modify the workup, so the presumed β-lactam could be isolated, were unsuccessful.

A reasonable mechanism (see Figure 1) for the aziridine to β-lactam carbonylation reaction consists of four steps: (1) S_N2 ring opening of the aziridine by iodide, **1** to **3**; (2) nucleophilic attack of the nitrogen anion on the carbonyl of nickel tetracarbonyl, **3** to **12**;[9] (3) nucleophilic attack of the nickel acylate complex on the alkyl halide, **12** to **13**; and (4) an iodine-induced reductive-elimination from the metal, **13** to **2**.

The first step is an S_N2 reaction, which is slower in the conversion of **1b** to **3b** than **1a** to **3a** because of the necessity of an S_N2 reaction occurring at a secondary center. This reaction is not complete in the time period (15 min) adequate for the ring opening of **1a**; thus, the lithium iodide was allowed to react for a longer period of time (2 h). This reaction also takes a little longer for the conversion of **1c** to **3c** due to the *p*-methoxybenzyl group, the most electron-rich substituent used.

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(9) Another possibility is that dialkyl amide **3a** attacks the nickel of $Ni(CO)_3$ directly and that this complex undergoes a carbonyl insertion to give **12a**. However, the lack of a CO dependence seems to rule against this possibility.

In step 3, which also must be an S_N2 reaction to account for the observed overall retention of stereochemistry, the requirement of attack at a secondary center slows the ring closure of **12b** to **13b** as compared to all the other reactions which require attack at a primary center. This slower step allows enough time for **12b** to partially decarbonylate to give a compound such as **14b**, which then converts back to **12b** in the presence of excess carbon monoxide to account for the carbon monoxide dependence. Compound **14b** must decompose to polymeric material, possibly through **3b**, to account for the low yield of this reaction under an argon atmosphere.

When the nitrogen is substituted with a sulfone, a very low yield is obtained but no carbon monoxide dependence is observed. These data indicate that the nucleophilic attack on the nickel tetracarbonyl (**3e** to **12e**) is a slow step, probably because of the delocalization of the negative charge; however, the ring closure (**12e** to **13e**) must be independent of the nature of R, as no carbon monoxide dependence is observed.

The intermediate metal complexes **13a** and **13b**, which have been observed spectroscopically, do not undergo a spontaneous reductive elimination to give **2a** and **2b**, respectively. The reductive elimination, in step 4, only occurs upon addition of the metal complex to iodine.

Based on the proposed mechanism, a one-to-one-to-one molar ratio of aziridine to lithium iodide to nickel tetracarbonyl is required. Because the aziridine is the "most valuable" reagent, a small excess of lithium iodide was used. However, a large excess of nickel carbonyl is required for this reaction. Decreasing the amount of nickel carbonyl by half in the reaction of **1a** produces only a 23% isolated yield of β-lactam **2a**. This decrease in yield is most likely a result of the fact that nickel carbonyl boils at 43 °C, and thus large amounts of it are in the condenser and not in the flask, and that nickel carbonyl partially decomposes under the reaction conditions. The excess $Ni(CO)_4$ has caused no experimental problems and is easily and safely decomposed in the oxidative workup.

Though all isolated yields are reported for products after purification, in most cases the crude reaction mixtures are extremely clean. After the I_2 workup and subsequent water washes, the product is, conservatively, greater than 90% pure as determined by GC and ^1H NMR spectroscopy. However, the weight of the crude reaction mixture is usually about half of the theoretical amount. Thus, about half of the starting aziridine must generate intractable materials, which are removed in the workup.

Experimental Section

General. All reactions were carried out using oven-dried glassware that was cooled under an argon atmosphere or in a desiccator. All reactions were conducted under an argon or carbon monoxide atmosphere.

Tetrahydrofuran was freshly distilled from potassium benzophenone ketyl. Benzyl bromide was distilled prior to use. Acetonitrile was distilled from phosphorus pentoxide. Triethylamine was distilled from barium oxide.

Nickel tetracarbonyl was transferred from a 1-lb lecture bottle into a 10-mL sidearm flask, maintaining a strong argon flow, and stored under argon until used. Transfers were made via syringe and excess $Ni(CO)_4$ was quenched in an iodine/CCl_4 bath. (*Caution*: $Ni(CO)_4$ is toxic and extremely flammable when exposed to air. All work with this complex should be conducted in a well-ventilated hood. Maintaining an argon atmosphere during all transfers and using nonflammable solvents in the iodine bath minimizes the probability of fire.)

Instrumentation. A Varian Model 3300 gas chromatograph was used for GC analysis with a flash vaporization injector: 225 °C, flame ionization detector: 325 °C, and a 12 ft × $^1/_8$ in. 5% SP-2100 on 100/120 Supelcoport column. Temperature programming was used: initial temperature of 50 °C for 2 min; increase by 10 °C per min to 250 °C; increase by 20 °C per min to 300 °C; and held at 300 °C for 4 min.

A Kratos high-pressure liquid chromatograph was used for all final purifications with a Kratos Spectroflow 783 detector, two Spectroflow 400 pumps, a Spectroflow 591 static mixer/injector, a 250 × 7.0 mm reverse phase C_{18} column, gradient programming, and a 1-mL/min flow rate. The solvents were deaerated HPLC grade CH_3CN and H_2O filtered with the Nanopure II system.

All infrared spectra were recorded on a Perkin-Elmer Model 599 infrared spectrophotometer or 1600 series FTIR with KBr cells.

All NMR spectra were recorded on a Nicolet NT-300 NMR spectrometer or an IBM NR-80 NMR spectrometer. All chemical shifts are referenced to tetramethylsilane at 0.00 ppm.

All GC/mass spectra were recorded on a Hewlett-Packard Model 9133 spectrometer using a 0.25 mm × 15 m fused silica capillary SPB-1 column and temperature programming. High resolution mass spectra were recorded on a Kratos model mass spectrometer.

1-Benzyl-2-methylaziridine (1a). To 2.3 mL (33 mmol) of 2-methylaziridine in 250 mL of THF at −78 °C was slowly added 1.5 M *n*-butyllithium in hexane (22.0 mL, 33 mmol) over a period of 15 min, with stirring at 0 °C for an additional 0.5 h. Freshly distilled benzyl bromide (3.6 mL, 30 mmol) was slowly added over a period of 5 min at −78 °C, and the solution was left stirring at 0 °C for 1 h. After workup by the addition of saturated ammonium chloride solution (20 mL), the product was extracted into ether (250 mL) and dried with anhydrous potassium carbonate. Evaporation of the solvent gives almost pure 1-benzyl-2-methylaziridine (**1a**) which can be bulb-to-bulb distilled to give 4.06 g (92% yield): ^1H NMR ($CDCl_3$) δ 1.20 (d, J = 5.4 Hz, 3 H), 1.37 (d, J = 6.3 Hz, 1 H), 1.49–1.54 (m, 1 H), 1.57 (d, J = 3.6 Hz, 1 H), 3.39 (d, J = 13.8 Hz, 1 H), 3.46 (d, J = 13.5 Hz, 1 H), 7.24–7.36 (m, 5 H); ^{13}C NMR ($CDCl_3$) δ 18.31 (q), 34.75 (t), 34.90 (d), 64.65 (t), 126.8–139.5; IR ($CDCl_3$) 3040 (w), 2990 (m), 2960 (m), 2930 (w), 2840 (w), 2200 (w), 1490 (w), 1450 (m), 1400 (w), 1350 (w), 1245 (w), 1165 (w), 1055 (m), 910 (s), 730 (s) cm^{-1}; MS, m/e 147 (5.1%), 146 (11.7%), 132 (5.0%), 91 (29.5%), 77 (4.4%), 65 (11.8%), 56 (100%).

Control Experiments for the Ring Opening of 1a. A mixture of 0.15 g (1.0 mmol) of 1-benzyl-2-methylaziridine (**1a**) and 0.20 g (1.5 mmol) of lithium iodide in 30 mL of THF was heated at reflux for 15 min under an argon atmosphere. The reaction mixture was then cooled to room temperature and added to 1.00 g (3.90 mmol) of solid iodine; ether was added and the solution was allowed to stir for 15 min. The solution was washed with saturated sodium bisulfite and 10% potassium carbonate, and dried with anhydrous potassium carbonate. Dimer: ^1H NMR ($CDCl_3$) δ 1.01 (d, J = 6.3 Hz, 3 H), 1.06 (d, J = 6.3 Hz, 3 H), 1.86–1.96 (m, 3 H), 2.61–2.73 (m, 3 H), 3.07 (d, J = 13.2 Hz, 1 H), 3.44 (s, 1 H), 3.82 (s, 1 H), 4.06 (d, J = 13.2 Hz, 1 H), 7.25–7.34 (m, 10 H); MS, m/e 294 (9.3%), 203 (16.8%), 160 (17.9%), 148 (17.8%), 134 (25.5%), 133 (31.3%), 132 (8.9%), 120 (9.0%), 92 (11.8%), 91 (100%), 65 (8.9%).

Secondly, a mixture of 0.15 g (1.0 mmol) of **1a** and 1.5 mL (11 mmol) of nickel tetracarbonyl in 30 mL of THF was heated at reflux for 3 h under an argon atmosphere. This reaction was worked up as above to give aziridine **1a** (41%), bibenzyl (12%), and dimers (34%).

1-Benzyl-4-methyl-2-azetidinone (2a). A mixture of 0.15 g (1.0 mmol) of 1-benzyl-2-methylaziridine and 0.20 g (1.5 mmol) of lithium iodide in 30 mL of THF was heated at reflux for 15 min under an argon atmosphere. It was then cooled to room temperature, 1.5 mL (11 mmol) of nickel tetracarbonyl was added, and the solution was heated to reflux under an argon atmosphere for 3 h. After this period, the reaction mixture was added to 1.00 g (3.90 mmol) of solid iodine. Additional iodine was added to the solution until there was no more bubbling; ether was added and the solution was allowed to stir for 15 min. The solution was washed with saturated sodium bisulfite, washed with 10% potassium carbonate, dried with potassium carbonate, concentrated, and then purified (0.09 g, 0.5 mmol, 50% yield). If the second step was under a carbon monoxide atmosphere, the first step was run as above. After the solution was cooled, CO gas was bubbled into it for 15 min, nickel carbonyl was added, the flask was

Table II

LiI reaction time, min	$Ni(CO)_4$ reaction time, h	isolated yield of **2a**, g (%)
15	1	0.03 (20)
15	2	0.05 (30)
15	3	0.09 (50)
15	4	0.03 (20)
15	5	0.02 (10)
15	10	0.01 (6)
15	20	0.01 (6)
30	3	0.07 (40[a])
60	3	0.05 (30[a])

[a] Crude yield.

connected to a balloon filled with carbon monoxide, and then the reaction mixture was allowed to reflux for 3 h (0.09 g, 0.5 mmol, 50% yield): ^1H NMR ($CDCl_3$) δ 1.22 (d, J = 6.6 Hz, 3 H), 2.54 (dd, J = 2.1, 14.4 Hz, 1 H), 3.07 (dd, J = 5.1, 14.4 Hz, 1 H), 3.57–3.60 (m, 1 H), 4.10 (d, J = 15.3 Hz, 1 H), 4.59 (d, J = 15.3 Hz, 1 H), 7.25–7.38 (m, 5 H); ^{13}C NMR ($CDCl_3$) δ 18.51 (q), 44.07 (t), 44.33 (t), 47.04 (d), 127.6–136.0, 166.89 (s); IR ($CDCl_3$) 2960 (w), 2920 (w), 1730 (s), 1460 (m), 1450 (m), 1375 (m) cm^{-1}; MS, m/e 176 (2.9%), 175 (24.9%), 133 (55.0%), 132 (33.6%), 105 (47.1%), 104 (27.6%), 92 (10.8%), 91 (100%), 89 (6.0%), 78 (7.7%), 77 (11.8%), 65 (23.0%).[7]

Reaction Time Variation. These reactions were performed as in the previous section except the times of the ring opening and of the nickel tetracarbonyl reactions were varied (see Table II).

Monitoring Reaction by ^{13}C NMR, IR, and Mass Spectroscopies. This reaction was run under the same condition as above except after it was refluxed with nickel tetracarbonyl for 3 h; the reaction mixture was cooled to room temperature and concentrated to obtain about 3 mL of reaction mixture. The vacuum was broken under an argon atmosphere and the reaction mixture was added to an argon-filled NMR tube or IR solution cell. IR and NMR data are given in the text. MS, m/e 148 (1.6%), 147 (13.0%), 146 (8.7%), 132 (4.3%), 92 (8.1%), 91 (100%), 89 (7.1%), 77 (3.6%), 69 (4.3%), 65 (17.9%), 63 (6.5%), 56 (6.5%).

***threo*-2-Azido-3-iodobutane.** To a stirred slurry of 15.0 g (0.230 mol) of sodium azide in 100 mL of acetonitrile in a methanol–ice cold bath was slowly added 18.3 g (0.113 mol) of iodine monochloride over a period of 20 min. The reaction mixture was stirred for an additional 10 min, 9.0 mL (0.10 mol) of *cis*-2-butene was added, and the mixture was allowed to warm to room temperature and stirred for 20 h. The red-brown slurry was poured into 250 mL of water, and the mixture was extracted with 250 mL of ether in three portions. These extracts were combined and washed with 150 mL of 5% sodium thiosulfate, leaving a colorless, ethereal solution. This solution was washed with 900 mL of water in four portions and dried over magnesium sulfate. Removal of the ether in vacuo at room temperature gives the iodo azide product (18.0 g, 80% yield). This compound was used without further purification: IR (ether) 2100 (s, N_3).[10a]

***cis*-2,3-Dimethylaziridine.** A mixture of 90 mL of anhydrous ether and 5.0 g of $LiAlH_4$ in a 250-mL, three-necked flask fitted with a reflux condenser, a magnetic bar, and an addition funnel, was cooled with an ice bath. To the vigorously stirred slurry was slowly added through the addition funnel a solution of 18.0 g (0.080 mol) of β-iodo azide in 15 mL of ether over a period of 20 min. Once the addition was completed, the mixture was allowed to warm to room temperature and stirred for 12 h. The workup was accomplished by the slow addition of 20 mL of 20% sodium hydroxide, followed by 45 min of vigorous stirring. The white granular salts were filtered through a medium-porosity sintered-glass funnel and washed well with ether. The ethereal solution was dried with magnesium sulfate and concentrated in vacuo at room temperature to give 7.2 g of a 1:2 mixture of ether and *cis*-2,3-dimethylaziridine (4.8 g of the aziridine, 84% yield): ^1H NMR (80 MHz, ether + $CDCl_3$) δ 1.1–1.3 (m, 7 H for the aziridine, 6 H for ether), 1.9–2.2 (m, 2 H for the aziridine), 3.48 (q, 4 H for ether).[10b]

1-Benzyl-*cis*-2,3-dimethylaziridine (1b). To 2.8 g of the ether/*cis*-2,3-dimethylaziridine mixture (1.9 g, 0.026 mol of the aziridine) in 250 mL of THF at −78 °C was slowly added 1.5 M of *n*-butyllithium in hexane (22.0 mL, 33.0 mmol) over a period of 15 min with stirring at 0 °C for an additional 1 h. Freshly distilled benzyl bromide (3.6 mL, 30 mmol) was slowly added over a period of 5 min at −78 °C; the solution mixture was left stirring at 0 °C for 1 h. After workup by the addition of a saturated ammonium chloride solution (20 mL), the product was extracted into ether (250 mL) and dried with anhydrous potassium carbonate. Evaporation of the extract gives a crude weight of 2.8 g. After bulb-to-bulb distillation, 1-benzyl-*cis*-2,3-dimethylaziridine (**1b**) (2.4 g, 57% yield) was obtained: ^1H NMR ($CDCl_3$) δ 1.13–1.18 (m, 6 H), 1.50–1.59 (m, 2 H), 3.49 (s, 2 H), 7.22–7.35 (m, 5 H); ^{13}C NMR ($CDCl_3$) δ 12.95, 38.86, 64.59, 126.6–139.7; IR (neat) 3020 (w), 2960 (s), 2920 (s), 2880 (m), 1490 (w), 1450 (m), 1440 (m), 1420 (m) cm^{-1}; MS, m/e 161 (1.2%), 92 (1.7%), 91 (17.7%), 89 (2.9%), 77 (2.5%), 70 (100%), 68 (1.7%), 65 (8.3%), 63 (2.2%).

1-Benzyl-*cis*-3,4-dimethyl-2-azetidinone (2b). This reaction uses the same conditions as the monomethyl analogue (**1a** to **2a**) except that 0.16 g (1.0 mmol) of 1-benzyl-*cis*-2,3-dimethylaziridine (**1b**) was used and the iodide ring opening was allowed to proceed for 2 h rather than 15 min (Ar atm: 0.03 g, 0.2 mmol, 20% yield; CO atm: 0.07 g, 0.4 mmol, 40% yield): ^1H NMR ($CDCl_3$) δ 1.09 (d, J = 6.3 Hz, 3 H), 1.18 (d, J = 7.5 Hz, 3 H), 3.24 (dq, J = 5.4, 7.5 Hz, 1 H), 3.64 (dq, J = 5.7, 6.0 Hz, 1 H), 4.08 (d, J = 15.3 Hz, 1 H), 4.58 (d, J = 15.3 Hz, 1 H), 7.24–7.37 (m, 5 H); ^{13}C NMR ($CDCl_3$) δ 8.80, 13.54, 43.87, 46.98, 50.47, 127.5–136.2, 170.96; IR ($CDCl_3$) 2960 (s), 2920 (m), 2860 (s), 1730 (s), 1440 (m), 1375 (s), 1345 (m) cm^{-1}; MS, m/e 189 (23.8%), 133 (43.6%), 132 (28.1%), 105 (35.3%), 104 (24.7%), 92 (22.0%), 91 (100%).[7] This reaction was monitored by IR and ^{13}C NMR spectroscopy in the same manner as the conversion of **1a** to **2a**. The data are given in the text.

1-(*p*-Methoxybenzyl)-2-methylaziridine (1c). This reaction uses the same conditions as the preparation of **1a** except that 1.9 mL (28 mmol) of 2-methylaziridine, 1.5 M *n*-butyllithium (18.3 mL, 27.5 mmol), and 3.4 mL (25 mmoles) of *p*-methoxybenzyl chloride were used, and the solution was left stirring at 0 °C for 2 h. The crude aziridine **1c**, which is 96% pure by GC, can be bulb-to-bulb distilled to give 3.96 g (90% yield): ^1H NMR ($CDCl_3$) δ 1.18 (d, J = 5.4 Hz, 3 H), 1.34 (d, J = 6.3 Hz, 1 H), 1.42–1.51 (m, 1 H), 1.53 (d, J = 3.3 Hz, 1 H), 3.34 (s, 2 H), 3.77 (s, 3 H), 6.86 (d, J = 8.7 Hz, 2 H), 7.25 (d, J = 8.7 Hz, 2 H); ^{13}C NMR ($CDCl_3$) δ 18.38 (q), 34.68 (t), 34.81 (d), 55.20 (q), 64.11 (t), 113.75 (d), 129.03 (d), 131.75 (s), 158.67 (s); IR (neat) 3038 (w), 2978 (m), 2956 (m), 2926 (m), 2906 (m), 2833 (m), 1612 (s), 1586 (m), 1512 (s), 1464 (s), 1442 (m), 1401 (m), 1354 (m), 1301 (s), 1250 (s), 1174 (s), 1107 (w), 1059 (m), 1036 (s), 884 (w), 849 (m), 822 (s), 798 (m), 767 (m) cm^{-1}; MS, m/e 177 (7.0%), 162 (3.2%), 122 (8.8%), 121 (100%), 91 (7.1%), 89 (3.3%), 78 (14.3%), 77 (13.1%), 65 (4.6%), 63 (4.4%), 56 (35.4%).

1-(*p*-Methoxybenzyl)-4-methyl-2-azetidinone (2c). This reaction was run in the same manner as the analogous reaction of **1a** to **2a**, except that 0.18 g (1.0 mmol) of 1-(*p*-methoxybenzyl)-2-methylaziridine (**1c**) was used and the iodide ring opening was allowed to proceed for 30 min rather than 15 min (Ar atm: 0.08 g, 0.4 mmol, 40% yield; CO atm: 0.08 g, 0.4 mmol, 40% yield): ^1H NMR ($CDCl_3$) δ 1.21 (d, J = 6.0 Hz, 3 H), 2.52 (dd, J = 2.1, 14.7 Hz, 1 H), 3.04 (dd, J = 5.1, 14.6 Hz, 1 H), 3.53–3.58 (m, 1 H), 3.80 (s, 3 H), 4.05 (d, J = 15.0 Hz, 1 H), 4.53 (d, J = 15.0 Hz, 1 H), 6.87 (d, J = 8.4 Hz, 2 H), 7.19 (d, J = 8.4 Hz, 2 H); ^{13}C NMR ($CDCl_3$) δ 18.58 (q), 43.80 (t), 44.08 (t), 46.86 (d), 55.29 (q), 114.15 (d), 128.1–159.2, 166.79 (s); IR ($CDCl_3$) 3048 (w), 3029 (w), 3008 (w), 1735 (s), 1613 (m), 1513 (m), 1465 (w), 1441 (w), 1401 (w), 1382 (m), 1248 (m), 1096 (w), 1036 (w) cm^{-1}; MS, m/e 205 (21.5%), 163 (8.9%), 122 (8.6%), 121 (100%), 84 (9.2%), 78 (15.6%), 77 (13.2%).

1-Hexyl-2-methylaziridine (1d). This reaction was run in the same manner as the preparation of **1c** except that 3.5 mL (25 mmol) of 1-bromohexane was used and the solution was left stirring at 0 °C for 3 h instead of 1 h. The yield of crude **1d** was 3.31 g (94%). After bulb-to-bulb distillation aziridine **1d** (3.17

(10) (a) Fowler, F. W.; Hassner, A.; Levy, L. A. *J. Am. Chem. Soc.* **1967**, *89*, 2077. (b) Hassner, A.; Matthews, G. J.; Fowler, F. W. *Ibid.* **1969**, *91*, 5046.

g, 90% yield) was obtained: ^{1}H NMR ($CDCl_3$) δ 0.89 (t, J = 6.9 Hz, 3 H), 1.16 (d, J = 5.4 Hz, 3 H), 1.24–1.59 (m, 12 H), 2.15–2.25 (m, 1 H); ^{13}C NMR ($CDCl_3$) δ 14.09, 18.48, 22.65, 27.24, 30.03, 31.97, 34.43, 34.68, 61.61; IR (neat) 3038 (w), 2956 (s), 2928 (s), 2857 (s), 2808 (m), 1468 (m), 1456 (m), 1401 (m), 1378 (w), 1357 (w), 1243 (w), 1170 (w), 1069 (w) cm^{-1}; MS, m/e 141 (4.2%), 140 (4.2%), 127 (8.3%), 126 (95.5%), 112 (17.3%), 98 (25.6%), 85 (9.6%), 84 (29.2%), 72 (19.7%), 71 (96.5%), 70 (67.3%), 69 (7.3%), 68 (5.7%), 58 (22.3%), 57 (66.8%), 56 (100%).

1-Hexyl-4-methyl-2-azetidinone (2d). This reaction was run as described in the conversion of aziridine **1a** to lactam **2a**, except that 0.14 g (1.0 mmol) of 1-hexyl-2-methylaziridine (**1d**) was used and the nickel carbonyl reaction was allowed to proceed for 4 h (Ar atm: 0.06 g, 0.4 mmol, 40% yield; CO atm: 0.06 g, 0.4 mmol, 40% yield): ^{1}H NMR ($CDCl_3$) δ 0.89 (t, J = 6.9 Hz, 3 H), 1.26–1.60 (m, 11 H), 2.48 (dd, J = 2.0, 14.3 Hz, 1 H), 2.94–3.13 (m, 1 H), 3.04 (dd, J = 5.1, 14.4 Hz, 1 H), 3.18–3.39 (m, 1 H), 3.60–3.70 (m, 1 H); ^{13}C NMR ($CDCl_3$) δ 13.98 (q), 18.70 (t), 22.52 (t), 26.76 (t), 28.08 (t), 31.41 (t), 40.28 (t), 43.81 (t), 47.14 (d), 166.82 (s); IR ($CDCl_3$) 3054 (w), 3021 (w), 2958 (m), 2928 (m), 2863 (w), 1734 (s), 1616 (w), 1466 (m), 1425 (m), 1408 (m), 1381 (m), 1264 (m), 1248 (m), 1098 (m) cm^{-1}; MS, m/e 169 (3.8%), 141 (4.9%), 128 (5.1%), 127 (4.0%), 126 (5.3%), 112 (11.3%), 99 (15.0%), 98 (29.7%), 85 (17.3%), 84 (7.5%), 71 (4.5%), 70 (7.5%), 69 (5.3%), 58 (4.5%), 57 (14.8%), 56 (100%).

1-Methanesulfonyl-2-methylaziridine (1e). To a mixture of 3.6 mL (50 mmol) of 2-methylaziridine and 10.4 mL (75.0 mmol) of triethylamine in 13 mL of methylene chloride at 0° to −10 °C (MeOH–ice bath) was slowly added 7.8 mL (55 mmol) of methanesulfonyl chloride over a period of 10 min, with stirring for an additional 30 min.[11] To the mixture was added 100 mL of methylene chloride; the product was washed with 50 mL of ice water, followed by 25 mL of cold 10% HCl, 25 mL of saturated sodium bicarbonate, and 25 mL of saturated sodium chloride, and finally dried with anhydrous magnesium sulfate. Removal of solvent yielded pure 1-methanesulfonyl-2-methylaziridine (6.59 g, 98% yield): ^{1}H NMR ($CDCl_3$) δ 1.34 (d, J = 5.4 Hz, 3 H), 2.09 (d, J = 4.5 Hz, 1 H), 2.59 (d, J = 7.2 Hz, 1 H), 2.74–2.84 (m, 1 H), 3.05 (s, 3 H); ^{13}C NMR ($CDCl_3$) δ 16.87, 34.25, 35.22, 39.60; IR ($CDCl_3$) 2970 (m), 2930 (m), 2250 (m), 1300 (s), 1230 (s), 1140 (s), 1030 (s) cm^{-1}; MS, m/e 84 (2.4%), 80 (1.5%), 79 (8.8%), 64 (3.0%), 63 (3.5%), 57 (4.0%), 56 (100%).

1-Methanesulfonyl-4-methylazetidinone (2e). This reaction was run under the same conditions as for the benzyl analogue (**1a** to **2a**) except that 0.14 g (1.0 mmol) of 1-methanesulfonyl-2-methylaziridine (**1e**) was used; the nickel carbonyl reaction was allowed to proceed for 6 h; and methylene chloride, rather than ether, was added to help with the extraction (Ar atm: 0.03 g, 0.2 mmol, 20% yield; CO atm: 0.03 g, 0.2 mmol, 20% yield): ^{1}H NMR ($CDCl_3$) δ 1.61 (d, J = 6.3 Hz, 3 H), 2.74 (dd, J = 3.7, 15.9 Hz, 1 H), 3.19 (s, 3 H), 3.29 (dd, J = 6.0, 15.6 Hz, 1 H), 4.29–4.38 (m, 1 H); ^{13}C NMR ($CDCl_3$) δ 19.94 (q), 42.40 (q), 44.25 (t), 51.52 (d), 163.97 (s); IR ($CDCl_3$) 2980 (w), 2930 (w), 1780 (s), 1345 (s), 1270 (m), 1200 (w), 1160 (s), 1140 (s), 950 (m), 770 (m) cm^{-1}; MS, m/e 124 (5.1%), 123 (3.6%), 122 (100%), 106 (5.1%), 79 (42.4%), 56 (8.9%).

Reaction Time Variation. These reactions were performed as in the previous section except the time of the nickel tetracarbonyl reaction was varied.

$Ni(CO)_4$ reaction time, h	isolated yield of **2e**, g (%)
1	0 (0)
3	0 (0)
6	0.03 (20)
9	0.02 (10)

1-(*p*-Nitrobenzyl)-2-methylaziridine (5a). A mixture of 0.57 g (10 mmol) of 2-methylaziridine, 2.17 g (10.0 mmol) of *p*-nitrobenzyl bromide, and 1.0 g (10 mmol) of triethylamine in 100 mL of THF was heated at 40 °C for 16 h. Triethylamine hydrobromide was filtered off and 50 mL of ether was added to the solution. The solution then was washed with 25 mL of water and dried with anhydrous magnesium sulfate. The crude aziridine **5a** (1.83 g, 95% yield) was pure by GC: ^{1}H NMR ($CDCl_3$) δ 1.24 (d, J = 5.1 Hz, 3 H), 1.41 (d, J = 6.3 Hz, 1 H), 1.51–1.60 (m, 1 H), 1.65 (d, J = 3.3 Hz, 1 H), 3.54 (ab quartet, J = 15.0, 19.2 Hz, 2 H), 7.53 (d, J = 8.7 Hz, 2 H), 8.19 (d, J = 9.0 Hz, 2 H); ^{13}C NMR ($CDCl_3$) δ 18.23, 35.01, 35.27, 63.77, 123.57, 128.26, 147.02, 147.28; IR (neat) 2968 (w), 2929 (w), 2819 (w), 1605 (m), 1519 (s), 1492 (w), 1454 (w), 1345 (s), 1172 (w), 1151 (w), 1109 (m), 1067 (w), 911 (s), 858 (m), 734 (s) cm^{-1}; MS, m/e 192 (5.5%), 191 (6.0%), 177 (3.0%), 90 (5.7%), 89 (12.4%), 77 (3.7%), 63 (7.9%), 57 (4.2%), 56 (100%).

Attempted Synthesis of 1-(*p*-Nitrobenzyl)-4-methyl-2-azetidinone. This reaction was run in the same manner as the analogous reaction of **1a** to **2a**, except that 0.19 g (1.0 mmol) of 1-(*p*-nitrobenzyl)-2-methylaziridine (**5a**) was used. The crude product weight is only 0.03 g and shows no evidence of a β-lactam as determined by IR spectroscopy; i.e., the characteristic peak in the 1730- to 1780-cm^{-1} region is not present.

1-Benzoyl-2-methylaziridine (5b). To a solution of 1.15 g (20.0 mmol) of 2-methylaziridine and 2.03 g (20.0 mmol) of triethylamine in 30 mL of anhydrous benzene was added, drop by drop, a solution of 2.81 g (20.0 mmol) of benzoyl chloride in 25 mL of benzene.[12] The reaction mixture was kept at room temperature for 3 h and then the triethylamine hydrochloride was filtered off and the benzene was evaporated. The yield of crude **5b** was 3.09 g (96%). Bulb-to-bulb distillation of the crude product gave 2.74 g (85%) of aziridine **5b**: ^{1}H NMR ($CDCl_3$) δ 1.35 (d, J = 5.4 Hz, 3 H), 2.11 (d, J = 3.3 Hz, 1 H), 2.49–2.57 (m, 2 H), 7.40–7.54 (m, 3 H), 8.01 (d, J = 7.2 Hz, 2 H); ^{13}C NMR ($CDCl_3$) δ 18.12 (q), 32.50 (t), 34.92 (d), 128.8–133.9, 179.54 (s); IR ($CDCl_3$) 3014 (w), 2999 (w), 2470 (w), 1669 (s), 1602 (m), 1581 (m), 1467 (m), 1450 (m), 1407 (s), 1370 (m), 1320 (s), 1301 (s), 1230 (m), 1176 (w), 1158 (w), 1093 (w), 1071 (w) cm^{-1}; MS, m/e 161 (5.1%), 160 (7.1%), 120 (6.5%), 117 (11.4%), 106 (7.3%), 105 (100%), 77 (59.6%), 76 (5.7%), 56 (29.5%).

Reaction of 1-Benzoyl-2-methylaziridine (5b). This reaction was run in the same manner as the analogous reaction of **1a** to **2a**, except that 0.16 g (1.0 mmol) of 1-benzoyl-2-methylaziridine (**5b**) was used. The crude product (0.16 g, 100%) showed two compounds by preparative thin-layer chromatography (20% ethyl acetate in hexane as eluent): 0.10 g (63% yield) of 2-phenyl-4-methyl-2-oxazoline (**6**) and 0.03 g (20% yield) of 2-phenyl-5-methyl-2-oxazoline, (**7**).[13] **2-Phenyl-4-methyl-2-oxazoline (6):** ^{1}H NMR ($CDCl_3$) δ 1.37 (d, J = 6.3 Hz, 3 H), 3.90 (t, J = 7.8 Hz, 1 H), 4.32–4.45 (m, 1 H), 4.53 (dd, J = 8.3, 9.6 Hz, 1 H), 7.37–7.50 (m, 3 H), 7.93–7.96 (m, 2 H); ^{13}C NMR ($CDCl_3$) δ 21.47 (q), 61.97 (d), 74.07 (t) 127.8–131.3, 163.51 (s); IR (neat) 3061 (w), 2966 (m), 2924 (w), 2894 (w), 1646 (s), 1603 (m), 1580 (m), 1494 (m), 1450 (m), 1375 (m), 1357 (m), 1341 (m), 1304 (m), 1259 (m), 1111 (m), 1057 (s), 1026 (m), 971 (m), 781 (m) cm^{-1}; MS, m/e 161 (40.4%), 146 (100%), 131 (36.0%), 130 (34.0%), 118 (25.5%), 117 (18.6%), 105 (14.4%), 104 (35.9%), 103 (48.1%), 91 (47.6%), 77 (52.8%), 76 (23.0%). **2-Phenyl-5-methyl-2-oxazoline (7):** ^{1}H NMR ($CDCl_3$) δ 1.59 (d, J = 6.9 Hz, 3 H), 3.82 (dd, J = 5.3, 10.9 Hz, 1 H), 4.41 (t, J = 10.7 Hz, 1 H), 5.09–5.17 (m, 1 H), 7.11–7.26 (m, 3 H), 7.41–7.44 (m, 2 H); ^{13}C NMR ($CDCl_3$) δ 16.56, 46.98, 55.84, 128.2–137.5, 174.44; IR ($CDCl_3$) 3062 (w), 2961 (w), 2925 (w), 2868 (w), 1697 (m), 1654 (s), 1450 (m), 1377 (w), 1337 (m), 1262 (m), 1074 (w), 1020 (w), 908 (s), 732 (s) cm^{-1}; MS, m/e 161 (40.5%), 146 (100%), 131 (37.8%), 130 (42.3%), 118 (34.2%), 104 (33.3%), 103 (56.8%), 91 (42.3%), 77 (50.5%).

1-Propyl-2-phenylaziridine (5c). (a) Conversion of Styrene Oxide to 1-Phenyl-2-propylamino-1-ethanol. A mixture of 2.40 g (20.0 mmol) of styrene oxide and 1.18 g (20.0 mmol) of propylamine was heated at 100 °C for 44 h. The crude product (3.56 g, 99%) is a pure mixture of 1-phenyl-2-propylamino-1-ethanol (**8**, major) and 2-phenyl-2-propylamino-1-ethanol (**9**, trace).[4c] The crude product was used in the next step without further purification: ^{1}H NMR ($CDCl_3$) (mixture of **8** and **9**) δ 0.85–0.94 (m, 3 H), 1.48 (q, J = 7.2 Hz, 2 H), 2.53–2.86 (m, 5 H), 4.66–4.77 (m, 1 H), 7.25–7.36 (m, 5 H); ^{13}C NMR ($CDCl_3$) (**8**) δ 11.70, 23.16, 51.35, 57.14, 71.75, 125.9–142.9; (**9**) δ 11.70, 20.31, 49.40, 63.07, 70.83, 125.9–142.7; IR ($CDCl_3$) (mixture of **8** and **9**)

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3364 (br m), 3063 (w), 3028 (w), 2959 (m), 2932 (m), 2874 (m), 2832 (m), 1493 (m), 1453 (m), 1340 (w), 1201 (w), 1115 (w), 1086 (m), 1062 (m), 1027 (w) cm^{-1}; MS, *m/e* 148 (8.3%), 79 (13.1%), 77 (19.9%), 72 (100%).

(b) Cyclization of a Mixture of 8 and 9. To an ice-cold solution of 2.63 g (10.0 mmol) of triphenylphosphine in 15 mL of acetonitrile was added, drop by drop, an ice-cold solution of 1.60 g (10.0 mmol) of bromine in 6 mL of acetonitrile. To the mixture was slowly added 1.79 g (10.0 mmol) of the crude amino alcohol, followed by drop by drop addition of 3.03 g (30.0 mmol) of triethylamine in 6 mL of acetonitrile at 0 °C. The reaction mixture was then stirred at room temperature for 30 min, triethylamine hydrobromide was filtered off, and the solution was concentrated by rotary evaporation.[4c,14] The residue was treated with hexane (2 × 20 mL), concentrated to 10 mL, and filtered to remove triphenylphosphine oxide; then the solution was evaporated to give 1.04 g (65% yield): ^1H NMR ($CDCl_3$) δ 0.96 (t, *J* = 7.4 Hz, 3 H), 1.57–1.70 (m, 3 H), 1.88 (d, *J* = 3.0 Hz, 1 H), 2.24–2.33 (m, 2 H), 2.46–2.51 (m, 1 H); ^{13}C NMR ($CDCl_3$) δ 11.97 (q), 23.04 (t), 37.74 (t), 41.22 (d), 63.61 (t), 126.2–140.5; IR ($CDCl_3$) 3036 (w), 2962 (s), 2934 (s), 2875 (m), 2821 (m), 1606 (w), 1496 (m), 1456 (m), 1381 (m), 1205 (m), 1177 (w), 1086 (m) cm^{-1}; MS, *m/e* 161 (11.5%), 160 (79.7%), 132 (19.8%), 118 (49.6%), 117 (12.1%), 91 (100%), 89 (12.3%), 84 (17.3%), 78 (11.7%), 77 (17.7%), 65 (21.7%).

Attempted Synthesis of 1-Propyl-4-phenyl-2-azetidinone. This reaction was run under the same condition as the analogous reaction of **1a** to **2a**, except that 0.16 g (1.0 mmol) of 1-propyl-2-phenylaziridine (**5c**) was used. The reaction gives no β-lactam as determined by IR spectroscopy (the characteristic peak in the 1730–1780-cm^{-1} region is not present) and ^{13}C NMR spectroscopy (there is no peak downfield of the phenyl resonances). The major product has been tentatively assigned as the dimer by mass spectroscopy: *m/e* 322 (39.1%), 293 (39.1%), 251 (42.0%), 250 (50.7%), 148 (46.4%), 146 (66.7%), 119 (49.3%), 118 (88.4%), 104 (95.7%), 91 (100%).

1,2-Diphenylaziridine (5d). Aziridine **5d** was prepared in a manner analogous to the preparation of **5c** by treatment of styrene oxide (2.40 g, 20.0 mmol) with aniline (1.86 g, 20.0 mmol) at 100 °C for 24 h to give a crude mixture, which can be purified by column chromatography (20% ethyl acetate in hexane as eluent) to give a 2:1 ratio of 2-phenyl-2-phenylamino-1-ethanol (**10a**) and 1-phenyl-2-phenylamino-1-ethanol (**10b**) (2.64 g, 62% yield). This was followed by reaction of the amino alcohol mixture (2.13 g, 10.0 mmol) with triphenylphosphine and bromine to give aziridine **5d** (1.05 g, 54% yield).[4c,14]

Amino alcohol **10b** could be isolated in pure form: ^1H NMR ($CDCl_3$) δ 3.30 (dd, *J* = 8.6, 13.1 Hz, 1 H), 3.43 (dd, *J* = 3.9, 12.9 Hz, 1 H), 4.92 (dd, *J* = 4.2, 8.7 Hz, 1 H), 6.66–6.77 (m, 3 H), 7.17–7.25 (m, 2 H), 7.32–7.43 (m, 5 H); ^{13}C NMR ($CDCl_3$) δ 51.78 (t), 72.48 (d), 113.45 (d), 118.09 (d), 125.9–129.3, 141.7 (s), 147.86 (s); MS, *m/e* 213 (15.3%), 183 (15.3%), 182 (100%), 106 (99.8%), 104 (31.2%), 79 (17.4%), 77 (84.0%).

Amino alcohol **10a** could not be obtained pure, and thus, the reported data are for a mixture of **10a** and **10b**: ^1H NMR ($CDCl_3$) δ 2.19 (br s), 2.79 (br, s), 3.19–3.39 (m), 3.62 (m), 3.83–3.85 (m), 4.40–4.44 (m), 4.84 (dd, *J* = 3.6, 8.4 Hz) 6.51–6.73 (m), 7.04–7.39 (m); ^{13}C NMR ($CDCl_3$) δ 51.6 (t), 59.74 (d), 67.17 (t), 72.28 (d), 113.36, 113.76, 118.03, 127.5–129.2, 140.09 (d), 147.14 (s); IR (neat) 3402 (br, s), 3086 (w), 3056 (m), 3028 (m), 2879 (w), 1605 (s), 1506 (s), 1453 (m), 1432 (m), 1318 (m), 1261 (m), 1196 (m), 1180 (m), 1062 (m), 1028 (m), 993 (w), 914 (w), 871 (w), 750 (s), 700 (s) cm^{-1}; MS, *m/e* 213 (11.3%), 182 (8.5%), 107 (10.6%), 106 (100%), 79 (12.9%), 77 (24.5%).

1,2-Diphenylaziridine (5d): ^1H NMR ($CDCl_3$) δ 2.38–2.39 (m, 1 H), 2.44 (d, *J* = 6.6 Hz, 1 H), 3.08 (dd, *J* = 3.3, 6.3 Hz, 1 H), 6.95–7.39 (m, 10 H); ^{13}C NMR ($CDCl_3$) δ 37.49 (dd), 41.51 (d), 120.5–128.9, 139.80 (s), 154.94 (s); IR (neat) 3058 (w), 3030 (w), 2981 (w), 1601 (s), 1490 (s), 1464 (m), 1452 (m), 1394 (m), 1315 (m), 1276 (m), 1224 (w), 1154 (m), 1078 (w), 1025 (w), 1001 (w), 986 (w) cm^{-1}; MS, *m/e* 195 (35.4%), 194 (100%), 104 (17.3%), 91 (13.2%), 77 (13.8%).[15]

Attempted Synthesis of 1,4-Diphenyl-2-azetidinone. This reaction was run under the same conditions as the conversion of **1a** to **2a**, except that 0.20 g (1.0 mmol) of 1,2-diphenylaziridine (**5d**) was used. The reaction only gives 0.06 g of product and no β-lactam is formed as determined by IR and ^{13}C NMR spectroscopy. The major product is tentatively identified as aniline.

1-Phenyl-2-butylaziridine (5e). Aziridine **5e** was prepared in a manner analogous to the preparation of **5c** by treatment of a mixture of 2.00 g (20.0 mmol) of 1,2-epoxyhexane and 1.86 g (10.0 mmol) of aniline at 100 °C for 36 h to give 2.30 g (60% yield after recrystallization from hexane) of 1-phenylamino-2-hexanol: ^1H NMR ($CDCl_3$) δ 0.93 (t, *J* = 7.1 Hz, 3 H), 1.37–1.58 (m, 6 H), 1.95 (br s, 1 H), 3.00 (dd, *J* = 8.6, 12.8 Hz, 1 H), 3.27 (dd, *J* = 3.2, 12.8 Hz, 1 H), 3.83–3.85 (m, 1 H), 3.90–4.05 (m, 1 H), 6.64–6.76 (m, 3 H), 7.15–7.26 (m, 2 H); ^{13}C NMR ($CDCl_3$) δ 13.98, 22.71, 27.81, 34.81, 50.34, 70.40, 113.33, 117.89, 129.30, 148.32; IR ($CDCl_3$) 3401 (br, s), 2958 (m), 2932 (m), 2860 (m), 1604 (s), 1506 (s), 1466 (m), 1432 (w), 1380 (w), 1319 (m), 1256 (m), 1180 (w), 1060 (w) cm^{-1}; MS, *m/e* 193 (15.2%), 107 (10.8%), 106 (100%), 77 (16.1%).

This was followed by reaction of 1.93 g (10.0 mmol) of the amino alcohol with triphenylphosphine and bromine[4c,14] to give 1.21 g (69% yield) of aziridine **5e**: ^1H NMR ($CDCl_3$) δ 0.96 (t, *J* = 7.2 Hz, 3 H), 1.27–1.65 (m, 7 H), 2.06–2.09 (m, 2 H), 6.91–6.99 (m, 3 H), 7.20–7.26 (m, 2 H); ^{13}C NMR ($CDCl_3$) δ 14.11, 22.65, 29.91, 32.95, 34.04, 40.18, 120.8–128.9, 155.10; IR ($CDCl_3$) 3077 (w), 3062 (w), 3035 (w), 2956 (m), 2930 (m), 2859 (w), 1598 (m), 1491 (s), 1466 (m), 1407 (w), 1293 (w), 1282 (w), 913 (s), 765 (s), 740 (s); MS, *m/e* 175 (34.8%), 146 (72.8%), 133 (24.3%), 132 (65.9%), 118 (24.6%), 106 (27.0%), 105 (24.8%), 104 (69.6%), 91 (49.6%), 77 (100%).

Attempted Synthesis of 1-Phenyl-4-butyl-2-azetidinone. This reaction was run under the same conditions as the conversion of **1a** to **2a**, except 0.18 g (1.0 mmol) of 1-phenyl-2-butylaziridine (**5e**) was used. The reaction gives 0.05 g (30% yield) of *N*-phenyl-*N*-(2-hydroxyhexyl)-3-(*N*-phenylamino)heptamide (**11**): ^1H NMR ($CDCl_3$) δ 0.85–0.98 (m, 6 H), 1.20–1.40 (m, 8 H), 1.48–1.67 (m, 4 H), 2.50–2.53 (m, 2 H), 3.21–3.23 (m, 2 H), 3.65–3.82 (m, 3 H), 5.08 (hex., *J* = 5.7 Hz, 1 H), 6.45–6.70 (m, 6 H), 7.07–7.18 (m, 4 H); ^{13}C NMR ($CDCl_3$) δ 13.94 (q), 14.02 (q), 22.63 (t), 27.50 (t), 28.32 (t), 31.89 (t), 34.75 (t), 39.67 (t), 47.47 (t), 50.48, 50.67, 73.38 (d), 112.79, 113.50, 117.58, 129.23, 129.42, 147.15 (s), 147.86 (s), 172.00 (s); IR (neat) 3408 (w), 3054 (w), 3023 (w), 2957 (s), 2931 (s), 2860 (m), 1723 (s), 1602 (s), 1506 (s), 1465 (m), 1436 (m), 1378 (w), 1318 (m), 1258 (m), 1181 (m), 909 (s) cm^{-1}. High resolution MS: calc for $C_{25}H_{36}N_2O_2$ 396.2748; found 396.2720.

Reaction of Aziridine 1a with $Fe(CO)_5$. This reaction was performed in a manner similar to that used for the conversion of **1a** to **2a** except 1.5 mL (11 mmol) of $Fe(CO)_5$ was used. After the usual iodine workup, the reaction gives a nearly quantitative yield (as determined by weight) of an 85% **1a** to 15% **4** ratio (as determined by gas chromatography).

Reaction of Aziridine 1a with $Fe_2(CO)_9$. This reaction has performed in a manner similar to the conversion of **1a** to **2a** except 0.39 g (1.0 mmol) of solid $Fe_2(CO)_9$ was added to the cooled reaction solution and then it was allowed to stir at room temperature for 23 h. After this time period, the usual I_2 workup was used. This reaction gives a nearly quantitative yield (as determined by weight) of a 90% **1a** to 10% **4** ratio (as determined by gas chromatography).

Reaction of Aziridine 1a with $Fe_3(CO)_{12}$. This reaction was performed in a manner similar to the above except 0.50 g (1.0 mmol) of $Fe_3(CO)_{12}$ was allowed to stir in THF for 1 h at room temperature. This solution (which contains 3 mmol of the $Fe(CO)_4$/THF complex) was added at room temperature to the previously refluxed aziridine **1a**/LiI reaction mixture. This combined solution was allowed to reflux for 3 h and then worked up in the usual manner. This reaction gives a nearly quantitative yield (as determined by weight) of a 53% **1a** to 47% **4** ratio (as determined by gas chromatography).

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Registry No. **1a**, 24417-03-6; **1b**, 24432-51-7; **1c**, 56338-34-2; **1d**, 125972-91-0; **1e**, 119005-31-1; **2a**, 4391-83-7; **2b**, 62965-01-9; **2c**, 125972-92-1; **2d**, 78159-36-1; **2e**, 119005-32-2; **4**, 125641-47-6; **5a**, 56338-28-4; **5b**, 21384-41-8; **5c**, 54280-88-5; **5d**, 2952-05-8; **5e**, 125972-93-2; **6**, 25393-66-2; **7**, 23437-02-7; **8**, 942-94-9; **10a**, 13891-02-6; **10b**, 31121-09-2; **11**, 125972-94-3; 2-methylaziridine, 75-55-8; *threo*-2-azido-3-iodobutane, 4098-12-8; *cis*-2-butene, 590-18-1; *cis*-2,3-dimethylaziridine, 930-19-8; styrene oxide, 96-09-3; 1-propyl-4-phenyl-2-azetidinone, 103776-26-7; 1,2-epoxyhexane, 1436-34-6; 1-(phenylamino)-2-hexanol, 97206-75-2.

Notes

A Reinvestigation and Improvement in the Synthesis of *meso*-2,5-Dibromoadipates by Application of Le Chatelier's Principle

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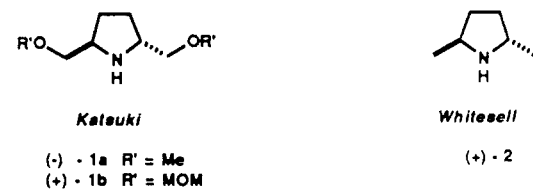
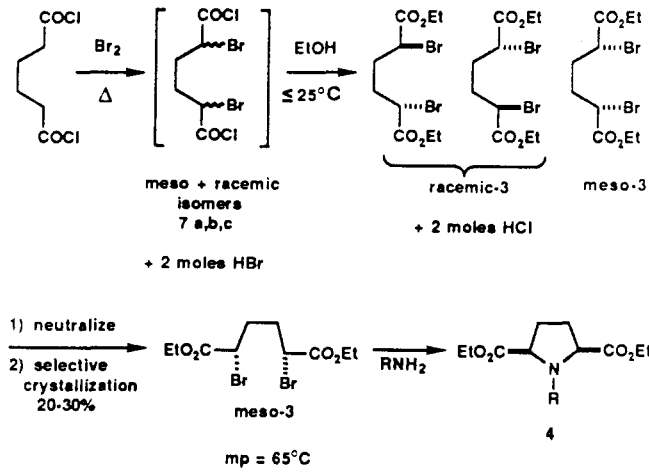
The preparation of 2,5-disubstituted pyrrolidines as intermediates for organic synthesis has continued to be an area of active study.[1] Recently, several C_2-symmetric chiral auxiliaries have been fashioned from 2,5-disubstituted pyrrolidines by Katsuki[2] and also by Whitesell.[3] After incorporation within a substrate, these ancillary reagents direct selective nucleophilic addition of enolates or enamines with electrophiles, often with high diastereoselectivity.[4]

In the case of compounds **1a** and **1b** (Chart I), pyrrolidine ring formation begins with ethyl 2,5-dibromoadipate commonly obtained as a mixture of three stereoisomers (as shown in Scheme I). The favored protocol uses only meso isomer **3** even though this results in formation of the incorrect *cis*-2,5-pyrrolidine dicarboxylate **4** which must be epimerized.[5] Fortunately, this epimerization is an efficient process.[6]

Chart I. C_2-Symmetric Secondary Amines



Scheme I



meso-2,5-Dibromoadipic esters have been generally more useful in heterocyclic synthesis than the *racemic* stereoisomers because they are nicely crystalline and efficiently separated from the lower melting racemic mixture.[7] The reaction of *meso*-**3** with primary amines affords only a single cis 2,5-disubstituted pyrrolidine isomer.[8] The racemic isomer is reported to form polymeric material and a mixture of cis and trans isomers upon direct nucleophilic addition of amines; however, the exact reasons for these differences in selectivity have not been determined.[8c] As a result of this precedent, we became interested in the application of *meso*-**3** to the synthesis of pyrrolidines and in elaborating the resulting product **4** into other bicyclic

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