than Ala because of the orbital overlap stability of the carboxylate anion.

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Registry No. Ser, 56-45-1; Ser(*t*-Bu), 18822-58-7; Thr, 72-19-5; Thr(*t*-Bu), 4378-13-6; Met, 63-68-3; Phe, 63-91-2; Ala, 56-41-7; Asp(OMe), 2177-62-0; Asp, 56-84-8; Glu(OMe), 1499-55-4; Glu, 56-86-0; α-Aaa, 1118-90-7; Pga, 98-79-3.

Reaction of Novel Imide Reducing Reagents with Pyrrolizidinediones

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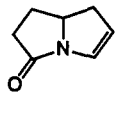
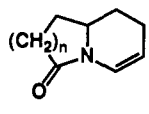
The reduction of pyrrolizidinediones **4a** and **4b** with $(i\text{-Bu})_2AlH$ and $LiBHEt_3$ affords the corresponding hexahydro-5-hydroxy-3*H*-pyrrolizin-3-ones **8a** and **8b** in good yield. $LiBHEt_3$ also reduces *N*-methylglutarimide (**18**) in 53% yield. The combination of $NaBH_4/MeOH/Ac_2O/CH_2Cl_2$ selectivity reduces an imide in the presence of an ester. Hexahydro-5-(methylthio)-3*H*-pyrrolizin-3-ones are products of the $NaBH_4$ reduction of pyrrolizidinediones in $MeSH/CH_2Cl_2/Ac_2O$. The reduction products, thioethers (**5a–c**) and lactamols (**8a–c**), are intermediates in the synthesis of pyrrolizinones **1a–c**.

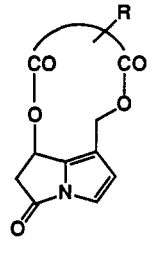
The pyrrolizidine alkaloids comprise a large class of natural products which have drawn synthetic interest due to their interesting structures and biological properties.[1,2] Although the pharmacologic properties of these compounds have ranged from antitumor activity[3] to hepatotoxicity,[4] no report has appeared describing their lipid altering or antiatherosclerotic activity. In conjunction with our search for lipid lowering and antiatherosclerotic medicinal agents,[5] we desired to synthesize **1a**. Similar 5–6 and 6–6 membered ring systems containing enamides of type **2** have been synthesized, and by virtue of their methods of synthesis the olefin is confined to the 6-membered ring.[6] Naturally occurring pyrrolizidine alkaloids are known which also contain the enamide group,[1] for example **3**.[7] However, the synthetic routes to these compounds were not directly applicable to **1**.[8] Recently, a [3 + 2] annulation approach to nitrogen heterocycles has afforded compounds similar to **1**, which contained tetrasubstituted olefins.[9]



1a



2, n = 1 or 2



3

Imide **4a** seemed a logical precursor to the desired target **1a**, via a reduction–elimination sequence. One attraction for this moiety is its ease of synthesis.[10,11] Another feature of the imide group is its ready conversion by reduction to hydroxy lactams, which are direct precursors to acyl imminium ions.[12] The reactive acyl imminium ions add diastereoselectively to olefins, affording complex molecular arrays.[13] The first reproducible and high-yielding method for the reduction of succinimides and glutarimides was introduced by Speckamp and consists of $NaBH_4$ in acidic EtOH.[14] Another reagent for the reduction of succinimides was introduced by Chamberlain and consists of $NaBH_4$ in MeOH at −5 °C.[15] A third method employs

† Deceased June 29, 1981.

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(13) (a) Hart, D. J. *J. Am. Chem. Soc.* **1980**, *102*, 397–398. (b) Wijnberg, B. P.; Speckamp, W. N. *Tetrahedron Lett.* **1980**, *21*, 1987–1990. (c) Nossin, P. M. M.; Speckamp, W. N. *Tetrahedron Lett.* **1980**, *21*, 1991–1994. (d) Harding, K. E.; Davis, C. S. *Tetrahedron Lett.* **1988**, *29*, 1891–1894, and references therein.

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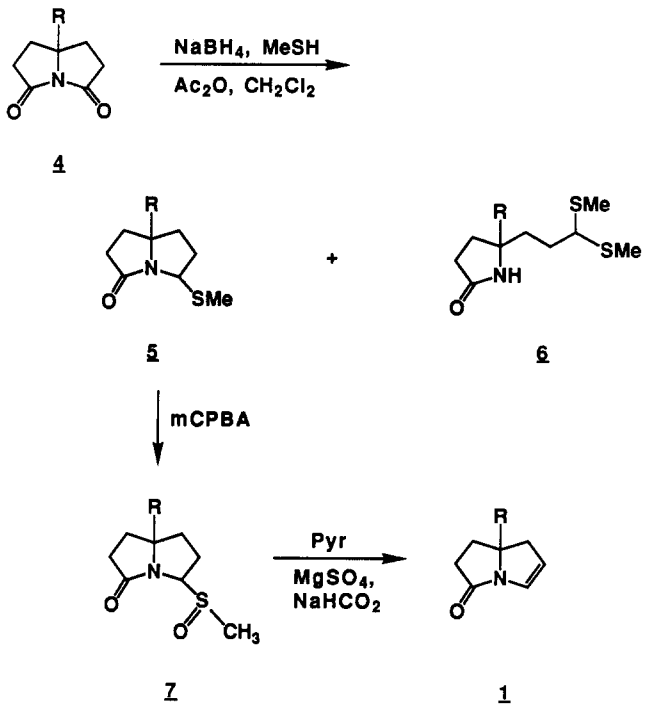
0022-3263/89/1954-4535$01.50/0

Scheme I[a]



[a] a, R = H; b, R = CH_3; c, R = $CH_2CH_2CO_2CH_3$; d, R = $CH_2CH_2CO_2H$.

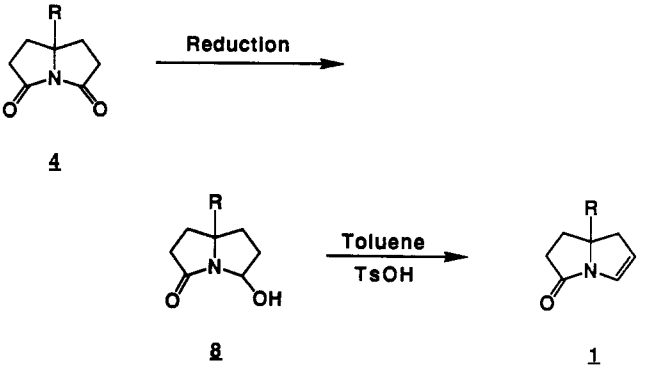
DIBAL in aprotic solvent.[16] To date the imides reduced have been mainly succinimides and a few examples of glutarimides. There have been only limited reports of reductions of pyrrolizidinediones, 4.[17]

Since the yields reported were low, we decided to study in more detail the reduction of these imides and the related chemistry of the reaction products. This led to the discovery of reaction conditions ($NaBH_4$/MeSH/Ac_2O/CH_2Cl_2) for the direct conversion of imides to lactam thioethers, the use of $LiBHEt_3$ (Super Hydride) as a reagent for imide reduction, and the fine tuning of conditions ($NaBH_4$/Ac_2O/MeOH/CH_2Cl_2) for the chemoselective reduction of a strained imide in the presence of an ester. Further, we have transformed the thioethers and lactamols into enamides. Of these, **1a** and **1b** are of interest due to their antiatherosclerotic activity.[5]

Results and Discussion

The reported reduction of **4a** to **8a** in low yield and to overreduced compound by currently employed imide reduction methods[17a] prompted us to reexamine older reports of reduction of phthalimides with sodium borohydride. In the first of these, reduction of phthalimide in methanol gave a mixture of lactamol, plus two additional products of successively lower oxidation state.[18] In the second article, reduction of the imide employing an alkyl thiol as a solvent afforded predominately the lactamol, accompanied by a minor amount of the corresponding thioether.[19]

Scheme II[a]



[a] a, R = H; b, R = CH_3; c, R = $CH_2CH_2CO_2CH_3$.

We hoped that use of these conditions, with some modification, would lead to desired lactamol **8a**, which could be converted readily to enamide **1a**.

Reduction of imide **4a** with sodium borohydride in methanethiol at ice-bath temperature gave, after acid quench, a mixture of the thioether **5a** and the open chain dithioacetal **6a** in approximately a 1:1 ratio (36%) (Scheme I). Neither of these products was present prior to the acid quench (as visualized by TLC). Further, after a number of exploratory alternatives, we found that aqueous acid was required, and HCl provided purer products in higher yield than aqueous ammonium chloride, *p*-toluenesulfonic acid, or sodium bisulfate.

In attempt to gain some insight into the mechanism of this reduction reaction, we tested the possibility that these products might result from the reaction of in situ generation of thiomethyl anion, since borohydride might be expected to deprotonate the methanethiol. This possibility was suggested by the observation of gas evolution when the imide was added to the reducing medium, although how the imide might be required for such a deprotonation was not obvious. To test this idea, a solution first of sodium borohydride and then of the imide in methanethiol was added stepwise to a preformed solution of sodium thiomethoxide in methanethiol, generated from sodium hydride. This resulted in a high yield of the thiomethyl ester **9a** as the only product.

To explore the mechanism yet further, the pure thioether **5a** and thioacetal **6a** were resubjected separately to the reaction conditions to determine whether either was a secondary product arising from the first. The results showed that the same mixture was obtained starting from either compound and that their interconversion was occurring during the acid quench. The yield of the water-soluble thioacetal **6a** was a function of how it was handled during isolation.

Since **5a** and **6a** were not seen until the acid quench and since these compounds interconverted in acid, we postulate a common precursor was formed under the reduction conditions, which was then converted to products during the acid quench. This common precursor may be the lactam alcohol **8a**, although we had at the time no other direct evidence for its existence (Scheme II).

In recognition that it would be practical to use less methanethiol upon scale-up of the reaction, we investigated whether a few equivalents of methanethiol in an inert solvent could be used. Indeed, the amount of methanethiol could be reduced to a molar ratio of approximately 7 (compared to imide) by using methylene chloride as solvent with no apparent adverse effects on yield. Finally, it only remained to optimize the conversion of the dithioacetal **6a** to the thioether **5a**. We found that the isolated mixture

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(16) (a) Winterfeldt, E. *Synthesis* **1975**, 617–630. (b) Oostveen, A. R. C.; de Boer, J. J. J.; Speckamp, W. N. *Heterocycles* **1977**, *7*, 171–77. (c) Kim, M. Y.; Weinreb, S. M. *Tetrahedron Lett.* **1979**, 579–582. (d) Hart, D. J.; Tsai, Y. *J. Org. Chem.* **1982**, *47*, 4403–4409.
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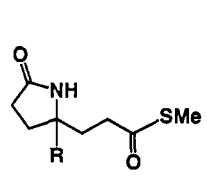
of the two adducts **5a** and **6a** could be treated with *p*-toluenesulfonic acid to afford only the cyclized thioether **5a** in as high as 56% overall yield from the imide.

Having formed **5a** in moderate yield, we employed it in our synthetic route to **1a**. Treatment of **5a** with sodium metaperiodate afforded **7a** in 93% yield.[20] Upon scale-up, the sulfoxide **7a** could not be isolated without severe decomposition. The instability appeared to be related both to the long time needed to evaporate the water and to the inorganic products from the periodate. Oxidation of **5a** with mCPBA afforded a mixture of sulfoxide **7a** and sulfone. However, slow addition of mCPBA, dissolved in CH_2Cl_2, to **5a** produced **7a** (90%) on a 10-g scale, with virtually no sulfone formation. The sulfoxide **7a** was heated in pyridine to form the enamide **1a**, in 67% yield. The final step has been plagued with inconsistent results when the scale exceeds 2.5 g of the sulfoxide. One of the byproducts of the thermal sulfoxide elimination is methanesulfenic acid.[21] This very reactive material rapidly self-condenses, giving methanethiosulfinate and water.[22] We used a drying agent ($MgSO_4$) and a base (sodium bicarbonate) to improve the yield on scale-up, and this modification permitted the preparation of **1a** in 60% yield from 18.7 g of sulfoxide **7a**.

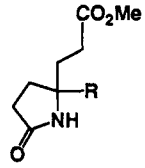
Taking advantage of what we had learned from the chemistry leading to **1a** allowed us to employ analogous procedures for the synthesis of bridgehead methyl compound **1b**. Imide **4b** was prepared by a route fashioned after a previous synthesis of this compound.[10b] Treatment of imide **4b** with sodium borohydride in methanethiol gave mainly the thiomethyl ester **9b**, with only traces of the desired thiomethyl ether. This result is still not well explained, but suggested the presence of some base in the reaction (which, presumably was also present in the synthesis of **1a**), leading to the thiomethoxide attack on the imide at a rate exceeding that of whatever may be the key step for the reduction. This problem could be completely circumvented by the addition of a small amount of acetic anhydride to the reaction, which resulted in a complete change in reaction with only the now expected mixture of the two thiomethyl compounds, **5b** and **6b**, being formed in about a 35% yield in a 1:1 ratio. In a control experiment, thiomethyl ester **9b** was resubjected to the reaction conditions containing acetic anhydride. It proved essentially inert to both the reaction and workup conditions. Completion of the synthesis of **1b** followed the procedures used for the synthesis of **1a** without event.

In order to produce an additional analogue with a more complex functional group at the 7a position, imide–ester **4c** was synthesized from nitromethane and methyl acrylate.[23] In the reduction of **4c**, as a precaution, the acetic anhydride was maintained. Although the thioether **5c** and thioacetal **6c** were formed in poor overall yield (27%), due to the hydrolysis of the ester to acid **5d**, **6c** could be recycled to **5c**, which was carried on to enamide **1c**.

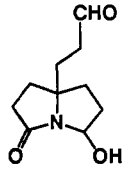
In an attempt to minimize the undesired hydrolysis of the ester, 10% HCl was used to quench the reaction and the product was extracted immediately from the aqueous fraction. Surprisingly, the lactamol **8c** and the lactam alcohol **10a** were isolated in 35% and 30%, respectively. The isolation of lactamol **8c** lends credence to our earlier conclusion that methanethiol serves only as a proton source in the reduction reaction and that thioether **5a** was formed from **8a** during the acidic workup. Further evidence was obtained by converting alcohol **8a**[17a] directly to thioether **5a** in 44% yield.



9a R=H
9b R=CH_3



10a R=$CH_2CH_2CH_2OH$
10b R=$CH_2CH_2CO_2CH_3$



11

If methanethiol functions solely as a proton source in these reductions, then another proton source, such as methanol, could replace it. The reduction of **4c** using sodium borohydride (1.00 equiv), acetic anhydride (0.36 equiv), methylene chloride as solvent, and methanol (3.00 equiv) instead of methanethiol, at room temperature, afforded the overreduced alcohol **10a** (70%) and a small amount of dimethyl ester **10b** (7%), which is also the synthetic precursor to **4c**. However, under the same conditions at −40 °C, a 63% yield of the desired lactamol **8c** was obtained. A large decrease in the rate of the reaction was evident at −60 °C. After 4 h, as judged by TLC, only a small amount of **8c** had formed, while the remainder was starting material.

Because literature methods for the reduction of imides are not compatible with the ester group of **4c**,[16,17] we decided to vary our reduction conditions, to gain a better understanding of the reaction. Omission of acetic anhydride and treating **4c** with sodium borohydride (1.00 equiv), methanol (3.00 equiv), and methylene chloride as solvent at −40 °C yielded the diester **10b** (70%), identical with authentic material. The formation of lactam **10b** must occur by attack of methoxide ion on **4c**, since methanol and sodium borohydride are known to produce trimethylborate and methoxide ion.[24]

Replacement of methanol with ethanol afforded the same product distribution yet at a slower rate. One may expect a slower reduction rate due to the lower solubility of sodium borohydride in ethanol.[25] The slower rate of decomposition of sodium borohydride in ethanol relative to methanol allowed examination of the reduction using only ethanol as the solvent. It is interesting to note that at room temperature the reduction of **4c** in ethanol gave only the overreduced alcohol **10a**. However, under the same conditions but at −40 °C only **8c** (33%) and recovered starting material (66%) were obtained after 6 h.

The successful reduction of **4c** to **8c** relies on proper choice of reaction temperature, because the rate of the reaction decreases significantly below −40 °C, whereas at higher temperatures overreduction of the lactamol occurs.

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(25) Hajos, A. *Complex Hydrides and Related Reducing Agents in Organic Synthesis*; Elsevier Scientific Pub. Co.: New York, 1979; p 100.

Table I. Reaction of Pyrrolizidinediones 4a–c with Various Reducing Reagents

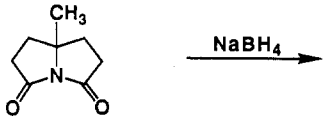
entry	product no.[a]	hydride/solvent[b]	T, °C/time	yield, %
1	8a	$LiBHEt_3$/A	−78/40 min	57
2	8a	$LiBH(sBu)_3$/A	−78/45 min	40
3	8b	$NaBH_4$/B	−40/1.5 h	51
4	8b	$Zn(BH_4)_2$/C	−10 to rt/3.5 h	32 (43)[c]
5	8b	$LiBHEt_3$/A	−78/40 min	71
6	8b	LAH/D	−40/10 min	55
7	8b	DIBAL/E	−78/30 min	68
8	8c	$NaBH_4$/B	−40/4 h	63

[a] **a**, R = H; **b**, R = CH_3; **c**, R = $CH_2CH_2CO_2CH_3$. [b] The following solvent combinations were employed: A = CH_2Cl_2/THF; B = MeOH (3.0 equiv)/CH_2Cl_2/Ac_2O (0.36 equiv); C = CH_2Cl_2/Et_2O; D = THF; E = CH_2Cl_2. [c] Yield based on unrecovered starting material.

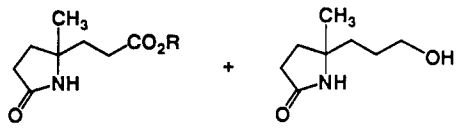
Methanol appears to be the protic cosolvent of choice as ethanol slows the rate of the reaction considerably. The success of the reaction is also dependent on the presence of acetic anhydride to prevent ring opening to the diester **10b**. To confirm the generality of this method, pyrrolizine-3,5-diones **4a** and **4b** were also reduced to **8a** (16%) and **8b** (51%).

Because **8a** and **8b** are precursors to antiatherosclerotic agents **1a** and **1b**,[5] attempts were made to maximize their yields with other reagents previously employed to reduce imides: LAH,[17] DIBAL,[16] $NaBH_4$ in MeOH,[15] and $NaBH_4$ in acidic EtOH.[14] The better results obtained with these reagents along with those from reagents which had not previously been employed for this purpose, namely $Zn(BH_4)_2$, $LiBHEt_3$, and $LiBH(sBu)_3$, are listed in Table I for the reduction of pyrrolizidinediones **4a–c**.

Of the reagents employed previously for the reductions of imides, DIBAL provided **8a** (34%) and **8b** (68%) in the highest yields. Not surprisingly, DIBAL was not chemoselective in the reduction of **4c**, as evident by the formation of **11** (3%) and **8c** (19%) along with the recovery of starting material (43%). Even lower temperatures and longer reaction times did not improve the yield of **8c**. Brossi reduced **4a** with LAH and obtained analytically pure **8a** in 15% yield.[17a] In our hands, even at −40 °C **8a** was formed in only 19% yield, whereas **8b** was formed in moderate yields (55%). Neither the method of Chamberlin,[15] eq 1, nor that of Speckamp,[14] eq 2, afforded **8b** from **4b**. Rather, imide cleavage to the esters, **12a** and **12b**, and overreduction to the alcohol, **13**, were the main results.



4b



12 **13**

MeOH, -5°C a, R=Me	4%	60%	(1)
EtOH, H+, -10°C b, R=Et	32%	26%	(2)

Among the novel reagents employed for imide reduction, Super Hydride ($LiBHEt_3$)[26,27] proved to be an excellent reagent for forming **8a** and **8b** in high yields. One equivalent of the imide was reduced with 1 equiv of Super Hydride, in CH_2Cl_2 at −78 °C, in a matter of minutes. Normally THF is the solvent of choice for Super Hydride reactions, but the limited solubility of the imides in THF led to the use of CH_2Cl_2 as a cosolvent. For these reactions a low temperature is important because Super Hydride reacts with organic halides,[26a] and at room temperature it reacts with CH_2Cl_2 exothermically and evolves gas.[28] An advantage of this hydride source over DIBAL is the mild workup conditions, which utilize saturated NH_4Cl (pH = 6), in contrast to the stronger acids required to dissolve aluminum salts. The more hindered borohydride reagent, L-Selectride, afforded **8a** in 40% yield. A reagent used previously on alkali-sensitive compounds, $Zn(BH_4)_2$,[24] proved only modestly effective in the reduction of pyrrolizidinediones.

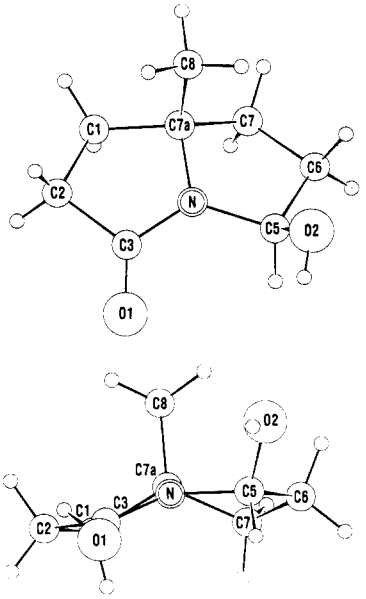


Figure 1. X-ray structure of **8b** from two views.

Despite variations in conditions and/or reagents, compound **8a** was always produced in consistently lower yield than **8b**. The yields in the $NaBH_4$/MeOH/Ac_2O reduction step decrease in the following order: **8c** > **8b** > **8a**. Because **8a** is less stable than **8b** on silica gel, as evidenced by the numerous spots observed on TLC, we rechromatographed pure **8a** and **8b** on silica gel. This led to the recovery of the hydroxy lactams in 72% and 83% yields, respectively. Clearly, the difference in yields between **8a**, **8b**, and **8c** cannot be accounted for solely on substrate stability. A contributing factor to this result may be the substituent at the ring juncture. One might expect the methyl group of **8b** and the ester side chain of **8c** to exert more of a buttressing effect on the hydroxy lactam ring than the proton of **8a**, due to the Thorpe–Ingold effect.[29] Hence, **8a** may be more prone to open to the aldehyde in situ, which can undergo further reactions.[17a]

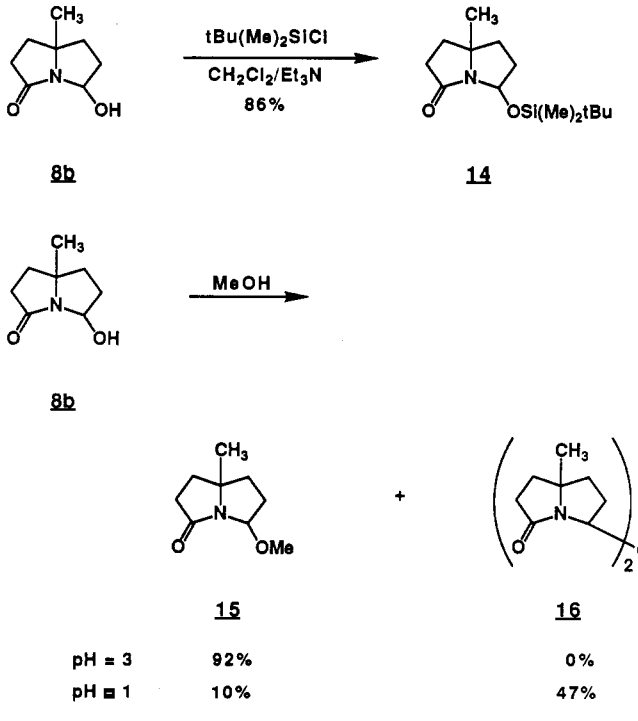
(26) (a) For use of Super Hydride in displacement reactions, see: Brown, H. C.; Krishnamurthy, S. *J. Am. Chem. Soc.* **1973**, *95*, 1669–1671. (b) For the use of Super Hydride in the reduction of ketones, see: *Ibid.* ref 9–11. (c) For the reduction of tertiary amides to alcohols with Super Hydride, see: Brown, H. C.; Kim, S. C. *Synthesis* **1977**, 635–636.

(27) Since the product of the reaction, BEt_3, is pyrophoric and may be toxic, caution should be used during workup: Odom, J. D. In *Comprehensive Organometallic Chemistry*; Wilkinson, G., Ed.; Pergamon Press: New York, 1982; Vol. I, p 270.

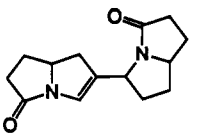
(28) This was an experimental observation.

(29) Eliel, E. L.; Allinger, N. L.; Angyal, S. J.; Morrison, G. A. *Conformational Analysis*; Wiley: New York, 1965; p 191.

Hydroxy lactams **8a–c**, synthesized by any of the methods outlined previously, were isolated as only one diastereomer. An X-ray analysis of **8b** reveals the alcohol and the methyl group at the ring juncture are cis, Figure 1. This is the same relative stereochemistry that Brossi found in the X-ray analysis of **8a**.[17a] Presumably, the stereochemistry of the alcohol and ring-juncture substituent for compound **8c** is analogous to **8a** and **8b**. One might conclude that the diastereomer isolated is the thermodynamic product, due to the aqueous acid workup, or possibly that the other diastereomer formed is unstable to the isolation conditions. One result with $Zn(BH_4)_2$ in the reduction of **4b** is particularly interesting in this regard. The ^{13}C NMR of the crude reaction revealed starting material, product **8b** (C5, 78.1 ppm; C7a, 67.8 ppm), and a third set of peaks (77.9 and 69.2 ppm), which could be the other diastereomer.[30] In an attempt to trap this unknown substance, **4b** was reduced with $Zn(BH_4)_2$ and quenched with Ac_2O or t-$Bu(Me)_2SiCl$, but no derivatives were isolated. The reaction was repeated with $Zn(BH_4)_2$ and quenched with saturated NH_4Cl. Without purification, the product was treated with t-$Bu(Me)_2SiCl$ and Et_3N.[31] Only one diasteromer was formed in 50% overall yield identical with **14**. Likewise, reaction of the crude product with acidic methanol (pH = 3) afforded only one diastereomer in 31% overall yield, identical with **15**. Under stronger acidic methanol conditions or prolonged exposure to $CDCl_3$, **8b** yields ether **16**. This material may also be prepared, as a mixture of diasteromers, by treating **8b** with aqueous acid (pH = 1). However, it does appear from the ^{13}C NMR spectrum of the crude reaction products that two diasteromers are formed. Nevertheless, attempts to isolate the second diasteromer of **8b** by eluting with different solvents or on other supports failed, and one may presume that it is unstable both to acid and to chromatography.



The elimination reactions of **8a–c** to **1a–c** require carefully controlled conditions. Brossi had dehydrated **8a** in refluxing toluene containing toluenesulfonic acid and had obtained only compound **17**.[17a] We found that these conditions for 5 min, followed by a base quench, produced **1a** (55%) and **17** (7%). The reaction time proved critical

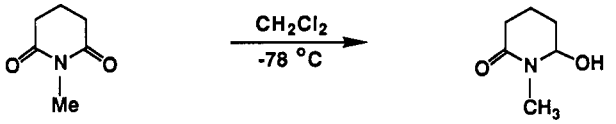


17

for the efficient formation of **1a**, since shorter (4 min) or longer (8 min) reaction times led to a decrease in the yield, 41% and 48%, respectively. Likewise alcohols **8b** and **8c** were smoothly dehydrated to the corresponding enamides **1b** and **1c** in 74% and 77% yields, respectively. When the crude intermediate **8b** was employed, **1b** was obtained in 65% overall yield from **4b**. In contrast, when **8b** was first purified the overall yield of **1b** fell to 36%. While the overall yields of compounds **1a–c** are higher in Scheme II, Scheme I is preferred for the synthesis of these compounds on large scale (>100 g).

Reduction of Methyl Glutarimide

To our knowledge, no examples of the reduction of glutarimides with Super Hydride or DIBAL are known. As stated earlier, several laboratories have shown that DIBAL is effective in reducing imides to the corresponding hydroxy lactams.[16] This prompted us to investigate the reduction of 1-methylglutarimide (**18**) with Super Hydride and DIBAL, which proved so effective for the reduction of **4a** and **4b**. Super Hydride (1.1 equiv) smoothly reduces **18**, at −78 °C, to the deliquescent lactamol **19** in 53% yield, whereas with DIBAL (1.3 equiv) under these conditions only a 3% yield was obtained.



18 **19**

LIBHEt$_3$ (1.1 eq) 53%
DIBAL (1.3 eq) 3%

Employing 4.0 equiv of DIBAL totally consumed starting material and cleanly formed the desired hydroxy lactam **19** as indicated by TLC. Quenching with a copious amount of 5% aqueous H_2SO_4, followed by exhaustive extraction of the aqueous portion, afforded only a 20% mass recovery, in which product was present as indicated by NMR.

Experimental Section

Infrared spectra were recorded on a Perkin-Elmer 297 spectrometer. ^1H NMR spectra were recorded on a Varian Associates EM-390 (90 MHz) and a Bruker Aspect 3000 (300 MHz) spectrometer and are reported in δ units, using tetramethylsilane as an internal standard. ^{13}C NMR were recorded on a Varian CFT-20 and a Bruker Aspect 3000 spectrometer and are reported in parts per million from tetramethylsilane on the δ scale. Melting points were taken on a Thomas-Hoover capillary melting point apparatus and are uncorrected. Mass spectra were obtained from a Varian MAT-CH5 spectrometer. Combustion analyses were performed by the Upjohn Physical and Analytical Chemistry Unit and by the Spang Microanalytical Laboratory. Unless specified, all Burdick and Jackson solvents and reagents purchased from Aldrich were used without further purification. CH_2Cl_2 was dried over molecular sieves.[32]

(30) For the complete ^{13}C NMR of **8b** see the Experimental Section.
(31) (a) Sommer, L. H.; Tyler, L. J. *J. Am. Chem. Soc.* **1954**, *76*, 1030–1033. (b) Lalonde, M.; Chan, T. H. *Synthesis* **1985**, 817–845.

Methyl Tetrahydro-3,5-dioxo-1*H*-pyrrolizine-7a(5*H*)-propanoate (4c). Nitromethane (5.0 g, 81.9 mmol), *tert*-butyl alcohol (1.5 mL), and Triton B (88 mg, 40% in methanol) were mixed at room temperature. Methyl acrylate (21.0 g, 254 mmol) was added dropwise, and an increase in reaction temperature was noted. After 4 h an additional 5 drops of Triton B were added. After an additional 2 h the reaction was quenched with H_2O (150 mL). The product was dissolved in CH_2Cl_2 (200 mL), and the organic portion was extracted with H_2O (3 × 50 mL). The organic portion was dried and concentrated in vacuo to 22 g of an oil. This was chromatographed (SiO_2, hexane/EtOAc 30%) to yield dimethyl 4-(3-methoxy-3-oxopropyl)-4-nitroheptanoate (17.0 g, 65%): ^1H NMR ($CDCl_3$) δ 2.40 (s, 12 H), 3.80 (s, 9 H, CH_3); IR (neat) 2996, 2956, 2851, 1738, 1541, 1439, 1352, 1324, 1261, 1202, 1176 cm^{-1}. Anal. Calcd for $C_{13}H_{21}NO_8$: C, 48.90; H, 6.63; N, 4.38. Found: C, 48.87; H, 6.70; N, 4.34. The nitro compound (50.0 g, 156 mmol; prepared by same procedure as illustrated) was hydrogenated in EtOH (750 mL), over Raney Nickel (10.0 g), at 50 psi for 4 days. The catalyst was filtered through Celite, and the solvent was removed under reduced pressure. The resulting oil was triturated with Et_2O, and after standing overnight the solid was filtered to provide dimethyl 5-oxo-2,2-pyrrolidinedipropanoate (29.0 g, 72%). Some of the lactam was recrystallized from MeOH/Et_2O, affording a white solid, **10b**: mp 74–77 °C; ^1H NMR ($CDCl_3$) δ 1.60–2.00 (m, 6 H), 2.20–2.40 (m, 6 H, O=CCH_2), 3.65 (s, 6 H, CH_3), 7.05 (b s, 1 H, NH); IR (mineral oil mull) 3166, 3078, 3032, 1730, 1701, 1325, 1287, 1210, 1190, 1179, 882, 815, 803 cm^{-1}. Anal. Calcd for $C_{12}H_{19}NO_5$: C, 56.01; H, 7.44; N, 5.44. Found: C, 56.21; H, 7.34; N, 5.43. The diester lactam **10b** (7.0 g, 27.2 mmol) (this reaction is capricious and seems to depend on the purity of the diester lactam; crude diester lactam affords product in higher yield than purified lactam) was heated at 195–210 °C under a 15-mm vacuum for 5.5 h. The product was purified by column chromatography [SiO_2, CH_2Cl_2/MeOH (5%)] to afford 2.8 g. The solid was crystallized from dioxane, yielding **4c** (2.3 g, 38%) as a white solid: mp 108–112 °C; ^1H NMR ($CDCl_3$) δ 1.80–2.90 (m, 12 H), 3.65 (s, 3 H, CH_3); ^{13}C NMR ($CDCl_3$) ppm 172.1 (s), 171.5 (s), 68.4 (s), 52.03 (q), 34.9, 33.4, 33.1; IR (mineral oil mull) 3015, 1766, 1739, 1693, 1348, 1310, 1199, 1191, 1180, 1167 cm^{-1}. Anal. Calcd for $C_{11}H_{15}NO_4$: C, 58.66; H, 6.71; N, 6.22. Found: C, 58.64; H, 6.80; N, 6.17.

Hexahydro-5-(methylthio)-3*H*-pyrrolizin-3-one (5a). Imide **4a** (20.0 g, 0.143 mol) and CH_2Cl_2 (80 mL) were placed in a flask equipped with two dry ice condensers. Methyl mercaptan (50.0 g, 1.041 mol) and acetic anhydride (2.59 g, 25 mmol) were added. After 5 min sodium borohydride (10.0 g, 264 mmol) was added cautiously via Gooch tubing. After 20 min at room temperature the reaction was poured cautiously into aqueous 5 M HCl (224 mL). The gaseous effluent was guided from the flask into two dry ice condensers followed by a KOH trap. The solvent was removed under reduced pressure in a hood, affording an oily white solid. This was extracted with $CDCl_3$ (3 × 100 mL), filtered, dried, and concentrated to yield 21.80 g of a yellow oil. The oil, consisting of **5a** and **6a**, was diluted with acetonitrile (1145 mL), and TsOH (734 mg, 84 mmol) was added. The mixture was heated at reflux for 18 h. The reaction was concentrated in vacuo to a yellow oil (21.8 g). The oil was chromatographed (SiO_2, 10% acetone/CH_2Cl_2), affording thioether **5a** (10.6 g, 44%). To obtain an analytical sample, 500 mg of the product was rechromatographed under identical conditions to give 480 mg of the sulfide. The sulfide was distilled in a Kugelrohr apparatus to produce pure **5a** (420 mg): NMR ($CDCl_3$) δ 1.10–3.00 (m, 8 H), 2.25 (s, 3 H, CH_3), 3.80–4.40 (m, 1 H, NCH), 4.95–5.30 (m, 1 H, NCHS); IR (neat) 2971, 2920, 2875, 1693, 1459, 1395, 1294, 1278, 1188, 1171 cm^{-1}. Anal. Calcd for $C_8H_{13}NOS$: C, 56.13; H, 7.65; N, 8.18. Found: C, 55.76; H, 7.65; N, 8.09.

Hexahydro-7a-methyl-5-(methylthio)-3*H*-pyrrolizin-3-one (5b). In a manner identical with the formation of **5a**, **4b** (20.0 g, 0.13 mol) was reduced, cyclized, and chromatographed to yield 13.0 g (54%) of slightly impure **5b**. A sample of this material (100 mg) was recrystallized from hexane to yield pure **5b** (90 mg): mp 53–57 °C; NMR ($CDCl_3$) δ 1.50 (s, 3 H, CH_3), 1.60–2.11 (m, 4 H), 2.35 (s, 3 H, SCH_3), 2.40–3.00 (m, 4 H), 5.10 (m, 1 H, NCHS); IR (mull) 1669, 1375, 1369, 1331, 1202, 1181 cm^{-1}. Anal. Calcd for $C_9H_{15}NOS$: C, 58.36; H, 8.16; N, 7.56; S, 17.27. Found: C, 58.03; H, 8.23; N, 7.40; S, 17.16.

Methyl Tetrahydro-3-(methylthio)-5-oxo-1*H*-pyrrolizine-7a(5*H*)-propanoate (5c). Imide **4c** (10.0 g, 44 mmol), CH_2Cl_2 (40 mL), methanethiol (25.0 g, 0.52 mol), and acetic anhydride (1.58 mL, 16 mmol) were combined at room temperature. Sodium borohydride (3.38 g, 89 mmol) was added to the reaction over 5 min. After 17 min the reaction was quenched by pouring into 5 M HCl (71.2 mL) at 4 °C. The mixture was concentrated in vacuo, and the oily solid was extracted with $CHCl_3$ (3 × 100 mL). The organic portion was dried and concentrated in vacuo to an oil. Chromatography on SiO_2 (10% acetone/CH_2Cl_2) yielded **5c** (2.4 g, 20%): ^1H NMR ($CDCl_3$) δ 1.25–3.00 (m, 12 H), 2.34 (s, 3 H, SCH_3), 3.69 (s, 3 H, OCH_3), 4.80–5.00 (m, 1 H, NCHS); ^{13}C NMR ($CDCl_3$) ppm 177.0 (s), 174.2 (s), 70.7 (s), 60.0 (d), 50.0 (q), 38.1, 33.3, 31.2, 29.6, 15.7 (q); IR (mineral oil mull) 2954, 1737, 1693, 1378, 1314, 1198 cm^{-1}. Anal. Calcd for $C_{12}H_{19}NO_3S$: C, 56.02; H, 7.44; N, 5.44; S, 12.44. Found: C, 55.93; H, 7.47; N, 5.48; S, 12.57. Continued elution of the column afforded **6c** (800 mg, 7%): ^1H NMR ($CDCl_3$) δ 1.75–2.50 (m, 6 H), 2.10 (s, 6 H, SCH_3), 3.40–3.68 (m, 1 H, SCHS), 3.68 (s, 3 H, OCH_3); IR (mineral oil mull) 3176, 3083, 1736, 1685, 1300, 1260, 1018 cm^{-1}. Anal. Calcd for $C_{13}H_{23}NO_3S_2$: C, 51.14; H, 7.59; N, 4.59; S, 20.96. Found: C, 51.42; H, 7.69; N, 4.59; S, 20.65. Further elution of the column with MeOH produced acid **5d** (3.2 g, 30%): ^1H NMR (DMSO) δ 1.30–2.80 (m, 12 H), 2.28 (s, 3 H, SCH_3), 4.80–5.00 (m, 1 H, NCHS); ^{13}C NMR (DMSO) ppm 174.6 (s), 174.1 (s), 70.3 (s), 59.5 (d), 36.8, 36.0, 33.4, 32.7, 30.2, 29.2, 14.9 (q); IR (mineral oil mull) 3000, 2762, 2691, 2636, 2591, 2540, 1720, 1645, 1407, 1300, 1289, 1189, 1159 cm^{-1}. Anal. Calcd for $C_{11}H_{17}NO_3S$: C, 54.31; H, 7.04; N, 5.76; S, 13.16. Found: C, 54.06; H, 7.12; N, 5.63; S, 12.91.

Hexahydro-5-(methylsulfinyl)-3*H*-pyrrolizin-3-one (7a). Thioether **5a** (1.65 g, 9.7 mmol), dissolved in MeOH (100 mL), was added to a stirred solution of $NaIO_4$ (2.14 g, 10.0 mmol) in H_2O (100 mL). After 1.25 h the mixture was concentrated in vacuo, extracted with $CHCl_3$ (250 mL), and filtered. The organic portion was dried and concentrated in vacuo to provide analytically pure **7a** (1.67 g, 93%): NMR ($CDCl_3$) δ 1.20–3.00 (m, 8 H), 2.60 (s, 3 H, CH_3), 3.70–4.40 (m, 1 H, NCH), 4.50–5.90 (m, 1 H, NCHS); IR 1695, 1395, 1295, 1050 cm^{-1}. Anal. Calcd for $C_8H_{13}NO_2S$: C, 51.32; H, 7.00; N, 7.48; S, 17.12. Found: C, 50.95; H, 7.35; N, 7.14; S, 17.18.

Hexahydro-7a-methyl-5-(methylsulfinyl)-3*H*-pyrrolizin-3-one (7b). *m*-Chloroperoxybenzoic acid (85% pure, 4.59 g, 26.5 mmol), dissolved in CH_2Cl_2 (65 mL), was added to **5b** (4.2 g, 23 mmol) in CH_2Cl_2 (65 mL) over a 1-h period. After an additional 1.5 h the reaction was cooled in an ice bath, and NH_3 was bubbled through the solution for 10 min. The reaction was filtered, and the solvent was removed in vacuo to yield 4.6 g of yellow oil. The oil was dissolved in CH_2Cl_2 (50 mL), and hexane (75 mL) was added. A highly crystalline solid precipitated and was filtered. The solvent was removed in vacuo from the filtrate, and 700 mg of light yellow oil was isolated. The oil was triturated with ether, and a solid formed. The solids were combined to give 3.70 g of **7b** (80%): mp 88–91 °C; NMR ($CDCl_3$) δ 1.35 (s, 3 H, CH_3), 1.60–3.06 (m + s, 12 H, CH_2 + SCH_3), 4.65 (m, 1 H, NCH); IR (mull) 1685, 1379, 1321, 1311, 1299, 1190, 1177, 1057 cm^{-1}. Anal. Calcd for $C_9H_{15}NO_2S$: C, 53.71; H, 7.51; N, 6.96; S, 15.90. Found: C, 53.37; H, 7.54; N, 6.89; S, 15.75.

Methyl Tetrahydro-3-(methylsulfinyl)-5-oxo-1*H*-pyrrolizine-7a(5*H*)-propanoate (7c). Sulfide **5c** (9.4 g, 37 mmol) and CH_2Cl_2 (150 mL) were cooled in an ice bath. A solution of *m*-chloroperoxybenzoic acid (7.63 g, 36.5 mmol, 82.5% pure), dissolved in $CHCl_2$ (150 mL), was added over a 3.5-h period. The reaction was warmed to room temperature for 0.5 h and was then recooled in an ice bath. Ammonia was bubbled through the reaction for 2–3 min. The white suspension was filtered through Celite, and the filtrate was concentrated in vacuo to a solid (9.4 g). The solid was chromatographed (SiO_2, 5% MeOH/CH_2Cl_2) to yield **7c** (8.1 g, 81%), which on standing slowly solidified: mp 118–125 °C; ^1H NMR ($CDCl_3$) δ 1.40–2.90 (m, 12 H), 2.55 (s, 3 H, $OSCH_3$), 3.65 (s, 3 H, OCH_3), 4.60–4.80 (m, 1 H, NCHS); IR (mineral oil mull) 1732, 1695, 1364, 1323, 1193, 1168, 1047 cm^{-1};

(32) Burfield, D. R.; Gan, G.; Smithers, R. H. *J. Appl. Chem. Biotechnol.* **1978**, *28*, 23–30.

MS for $C_{12}H_{19}NO_4S$, m/z (relative intensities), 211 (13), 210 (100), 178 (84), 136 (14), 135 (15), 134 (78), 123 (10), 122 (23), 94 (12). Anal. Calcd for $C_{12}H_{19}NO_4S$: C, 52.74; H, 7.00; N, 5.12; S, 11.71. Found: C, 52.71; H, 7.43; N, 4.95; S, 11.40.

1,2,7,7a-Tetrahydro-3*H*-pyrrolizin-3-one (1a). Sulfoxide **7a** (1.84 g, 9.7 mmol) was heated at 100 °C in pyridine (15 mL) for 20 h. The solvent was removed in vacuo from the cooled reaction mixture to afford a dark oil. This was chromatographed (SiO_2, EtOAc) to give 950 mg of a light brown solid. Sublimation of the solid (45 °C at 0.05 mm) afforded **1a** (810 mg, 67%): mp 65–66 °C; NMR ($CDCl_3$) δ 1.50–3.05 (m, 6 H), 4.00–4.75 (m, 1 H, NCH), 5.30–5.50 (m, 1 H, =CH), 6.50–6.60 (m, 1 H, NCH=); IR 1675, 1592 cm^{-1}. Anal. Calcd for C_7H_9NO: C, 68.24; H, 7.38; N, 11.37. Found: C, 68.04; H, 7.38; N, 11.63.

1,2,7,7a-Tetrahydro-7a-methyl-3*H*-pyrrolizin-3-one (1b). A mixture of sulfoxide **7b** (7.8 g, 39 mmol), pyridine (23 drops), $MgSO_4$ (3.65 g, 30 mmol), and $NaHCO_3$ (2.43 g, 28 mmol) was heated at 130 °C for 18 h. The crude mixture was chromatographed (SiO_2, EtOAc) to yield **1b** (2.7 g, 51%): mp 29–31 °C; NMR ($CDCl_3$) δ 1.30 (s, 3 H, CH_3), 1.80–3.10 (m, 6 H), 5.30 (m, 1 H, NC=CH), 6.50 (m, 1 H, NCH=); IR (mull) 3092, 3080, 1710, 1597, 1376 cm^{-1}. Anal. Calcd for $C_8H_{11}NO$: C, 70.05; H, 8.08; N, 10.20. Found: C, 69.69; H, 8.30; N, 10.00.

Methyl 6,7-Dihydro-5-oxo-1*H*-pyrrolizine-7a(5*H*)-propanoate (1c). Sulfoxide **7c** (1.98 g, 7.2 mmol), $MgSO_4$ (866 mg, 7.2 mmol), $NaHCO_3$ (604 mg, 7.2 mmol), and 1.8 mL of freshly distilled pyridine (from BaO) were heated at 117 °C for 18 h. CH_2Cl_2 was added to the cooled reaction, and the mixture was filtered through Celite. Removal of the solvent in vacuo yielded an oil, which was chromatographed (SiO_2, EtOAc), providing **1c** (900 mg). The solid was dissolved in Et_2O (5 mL), and upon addition of hexane (50 mL) product precipitated. The solid was filtered, affording pure **1c** (800 mg, 53%): mp 40–42 °C; ^1H NMR ($CDCl_3$) δ 1.80–3.00 (m, 10 H), 3.67 (s, 3 H, OCH_3), 5.25 (m, 1 H, CH_2CH=), 6.52 (m, 1 H, NCH=); ^{13}C NMR ($CDCl_3$) ppm 173.5 (s), 126.5 (d), 113.8 (d), 69.4 (s), 51.7 (q), 41.6, 34.7, 34.4, 34.3, 28.9; IR (mineral oil mull) 3097, 3088, 3013, 1728, 1693, 1602, 1394, 1327, 1203, 1168 cm^{-1}; MS for $C_{11}H_{15}NO_3$, m/z (relative intensities) 209 (M^+, 29), 178 (12), 155 (50), 134 (11), 123 (9), 122 (100), 80 (24), 55 (70). Anal. Calcd for $C_{11}H_{15}NO_3$: C, 63.14; H, 7.23; N, 6.69. Found: C, 63.24; H, 7.14; N, 6.75.

Hexahydro-5-hydroxy-3*H*-pyrrolizin-3-one (8a). Super Hydride (5.0 mL, 5.0 mmol, 1 M in THF) was added at 0.78 mL min^{-1} to a solution of imide **4a** (695 mg, 5.0 mmol) and CH_2Cl_2 (25 mL) at −78 °C. The cloudy mixture was stirred for 40 min and was then quenched with saturated NH_4Cl (10 mL). The aqueous portion was extracted with CH_2Cl_2 (3 × 50 mL). The organic fractions were combined, dried, and concentrated in vacuo to 1.1 g. This was chromatographed on a Waters' Prep-500 [SiO_2, $CHCl_2$/MeOH (3%)] to yield **8a** (400 mg, 57%): mp 97–100 °C; ^1H NMR ($CDCl_3$) δ 1.00–3.00 (m, 8 H), 4.12 (quintet, 1 H, J = 7 Hz, H7a), 4.41 (b s, 1 H, OH), 5.41–5.65 (m, 1 H, H5); ^{13}C NMR ($CDCl_3$) ppm 175.6, 77.8, 60.5, 36.4, 34.9, 32.3, 27.4; IR (mineral oil mull) 3433, 1689, 1430, 1422, 1412, 1295, 1266, 1062 cm^{-1}; MS for $C_7H_{11}NO_2$, m/z (relative intensity) 141 (M^+, 29), 124 (4), 113 (17), 97 (12), 84 (100). Anal. Calcd for $C_7H_{11}NO_2$: C, 59.56; H, 7.85; N, 9.92. Found: C, 59.39; H, 8.00; N, 9.88.

Hexahydro-5-hydroxy-7a-methyl-3-oxo-1*H*-pyrrolizine (8b). Diisobutylaluminum hydride (3.6 mL, 1.0 M in CH_2Cl_2) was added at 0.17 mL min^{-1} to a solution of **4b** (0.50 g, 3.27 mmol) in CH_2Cl_2 (10 mL) at −78 °C. After stirring for 0.5 h following the addition, the solution was poured onto 5% H_2SO_4 (20 mL). The organic layer was removed, and the aqueous portion was extracted with CH_2Cl_2 (3 × 30 mL). The organic extracts were combined, dried ($MgSO_4$), filtered, and concentrated in vacuo to afford analytically pure **8b** (0.34 g, 68.0%): mp 82–85 °C; ^1H NMR ($CDCl_3$) δ 1.18–3.12 (m, 8 H, CH_2), 1.41 (s, 3 H, CH_3), 4.93 (b s, 1 H, OH), 5.44–5.71 (m, 1 H, NCH); ^{13}C NMR ($CDCl_3$) ppm 175.6, 78.4, 67.5, 38.8, 35.6, 33.9, 26.4; IR (mineral oil mull) 3317, 1926, 1673, 1406, 1058, 669 cm^{-1}; MS for $C_8H_{13}NO_2$, m/z (relative intensity) 155 (M^+, 11), 140 (100), 112 (30), 98 (85), 55 (23). Anal. Calcd for $C_8H_{13}NO_2$: C, 61.91; H, 8.44; N, 9.03. Found: C, 61.54; H, 8.44; N, 8.76.

Crystal Data for 8b. $C_8H_{13}NO_2$, MW = 155.20 g/mol, monoclinic, $P2_1/c$ (14), a = 9.973 (2) Å, b = 11.194 (2) Å, c = 7.958 (1) Å, β = 116.51 (2)°, V = 795.0 (5) Å^3, Z = 4, d_c = 1.30 g/cm^3, Cu Kα, λ = 1.5418 cm^{-1}, μ(Cu Kα) = 0.7 cm^{-1}, T = 123 K, R = 0.033 for 1411 unique reflections. Compound **8b** was recrystallized from EtOAc. Chunky crystal 0.2 × 0.2 × 0.15 mm^3, Nicolet P_1 diffractometer controlled by Harris computer, graphite monochromator, Cu Kα, $2\theta_{max}$ = 138.3°, all 1411 unique reflections measured, 1153 had intensities > 2σ, 2°/min 2θ step scans, scan widths > 3.4°, 10 reflections periodically monitored showed no trend towards deterioration, $\sigma^2(I)$ was approximated by $\sigma 2(I)$ from counting statistics + $(0.012I)^2$, where the coefficient of I was calculated from the variations in intensities of the monitored reflections, cell parameters by least-squares fit of $K\alpha_1$ 2θ values (K_{α_1} = 1.5402 cm^{-1}) for 25 high 2θ reflections,[33] Lp correction appropriate for a monochromator with 50% perfect character, no absorption correction. The structure was solved by direct methods, using MULTAN80,[34] hydrogens were found in difference maps. Least-squares refinement included: all coordinates and anisotropic thermal parameters for nonhydrogen atoms. Isotropic thermal parameters for hydrogens were assigned $^1/_2$ unit higher than attached atoms. The function minimized in the refinement was $\Sigma w(F_o^2 - F_c{}^{*2})^2$, where weights w were $1/\sigma^2(F_o^2)$, and where $F_c{}^*$ was as defined by Larson.[35] Atomic form factors were from Doyle and Turner,[36] and for hydrogen, from Stewart, Davidson, and Simpson.[37] In the final refinement cycle, all shifts were <0.01σ, R = 0.033, S = 2.06, the secondary extinction parameter, g, was 13.7 × 10^{-6}, final difference Fourier peaks were <0.3 e Å^{-3}.

The CRYM system of computer programs was used.[38,39]

Table II. Molecular Dimensions for Compound 8b

bond	length, Å	bond angles	deg
C1–C2	1.536 (2)	C2–C1–C7a	104.2 (1)
C1–C7a	1.539 (2)	C1–C2–C3	103.2 (1)
C2–C3	1.514 (2)	C2–C3–N	107.5 (1)
C3–N	1.342 (2)	C2–C3–O1	127.7 (1)
C3–O1	1.235 (2)	N–C3–O1	124.8 (1)
C5–C6	1.537 (2)	C6–C5–N	102.6 (1)
C5–N	1.458 (1)	C6–C5–O2	109.2 (1)
C5–O2	1.405 (2)	N–C5–O2	113.3 (1)
C6–C7	1.534 (2)	C5–C6–C7	106.5 (1)
C7–C7a	1.533 (1)	C6–C7–C7a	103.7 (1)
C7a–C8	1.523 (2)	C1–C7a–C7	118.4 (1)
C7a–N	1.478 (2)	C1–C7a–C8	111.5 (1)
		C1–C7a–N	102.0 (1)
		C7–C7a–C8	112.2 (1)
		C7–C7a–N	100.5 (1)
		C8–C7a–N	111.0 (1)
		C3–N–C5	128.2 (1)
		C3–N–C7a	114.7 (1)
		C5–N–C7a	114.0 (1)

Hexahydro-5-hydroxy-7a-methyl-3*H*-pyrrolizin-3-one (8b). To a solution of imide **4b** (0.765 g, 5.0 mmol) and CH_2Cl_2 (25 mL), which was cooled to −78 °C, was added Super Hydride (5.0 mL, 5.0 mmol, 1 M in THF) at a rate of 0.78 mL min^{-1}. Upon completion of the hydride addition the reaction was continued for 40 min and then quenched by pouring it into 10 mL of saturated aqueous NH_4Cl. The aqueous portions were extracted with CH_2Cl_2 (3 × 50 mL). The organic fractions were combined, dried, and evaporated in vacuo to give 1.2 g. This material was chromatographed on a Waters' Prep-500 [SiO_2, CH_2Cl_2/MeOH (3%)] to yield **8b** (550 mg, 71%): mp 81–83 °C; this material was analytically pure and was identical spectrally with **8b** prepared from DIBAL reduction.

Methyl Tetrahydro-5-hydroxy-3-oxo-1*H*-pyrrolizine-7a-

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(5*H*)-propanoate (8c). Sodium borohydride (3.02 g, 79.9 mmol) was added portionwise over 2 min to a solution of imide **4c** (15.0 g, 66.6 mmol), acetic anhydride (2.09 mL, 2.22 mmol), CH_3OH (8.0 mL, 0.2 mol), and CH_2Cl_2 (150 mL) at −60 °C. After 4 h the solution was warmed to −40 °C. Two hours later 10% HCl (60 mL) was added to the solution at the reaction temperature. The reaction was removed from the cooling bath. The organic layer was removed, and the aqueous layer was extracted with CH_2Cl_2 (3 × 50 mL). The organic layers were combined, dried ($MgSO_4$), filtered, and concentrated in vacuo. The residue was chromatographed on an SiO_2 PrepPAK eluting with 2.5% CH_3OH/CH_2Cl_2. The appropriate fractions were combined and concentrated in vacuo to give **8c** as a white solid (9.53 g, 63.1%): mp 91–93 °C; ^1H NMR ($CDCl_3$) δ 1.36–3.05 (m, 12 H, CH_2), 3.70 (s, 3 H, CH_3), 5.00 (b s, 1 H, OH), 5.52–5.72 (m, 1 H, CH); ^{13}C NMR ($CDCl_3$) ppm 176.6, 173.8, 79.0, 70.1, 51.8, 37.5, 35.2, 34.0, 33.8, 32.4, 29.8; IR (mineral oil mull) 3356, 2921, 1735, 1680, 1459, 1077 cm^{-1}; MS for $C_{11}H_{17}NO_4$, *m/z* (relative intensity) 227 (M^+, 3), 196 (33), 170 (19), 140 (100), 112 (60). Anal. Calcd for $C_{11}H_{17}NO_4$: C, 58.14; H, 7.54; N, 6.16. Found: C, 57.90; H, 7.70; N, 6.02. TLC SiO_2, R_f = 0.63, 10% CH_3OH/CH_2Cl_2.

1,2,7,7a-Tetrahydro-3*H*-pyrrolizin-3-one (1a) and 2′,3′,7,7′,7a,7′a-Hexahydro[2,3′-bi-1*H*-pyrrolizine]-5,5′-(6*H*,6′*H*)-dione (17). Lactamol **8a** (85.0 mg, 0.602 mmol) was added to a refluxing solution of toluene (25 mL) and TsOH (10.0 mg). After 5 min Et_3N (2 mL) was added. The solution was cooled, and the solvent was removed in vacuo. The residue was chromatographed on a Partisil 10/50 ODS column eluting with 3% CH_3OH/CH_2Cl_2. The appropriate fractions were collected and concentrated in vacuo to afford **1a** (40.5 mg, 54.6%) and **17** (5.0 mg, 6.7%). Data for **1a**: ^1H NMR ($CDCl_3$) δ 1.64–3.14 (m, 6 H, CH_2), 4.25–4.70 (m, 1 H, NC*H*CH_2), 5.30–5.51 (m, 1 H, NCHC*H*), 6.50–6.77 (m, 1 H, NC*H*CH); HRMS for C_7H_9NO calcd 123.0684, found 123.0675, *m/z* (relative intensity) 123 (M^+, 28), 95 (11), 68 (100), 54 (14). Anal. Calcd for C_7H_9NO: C, 68.27; H, 7.37; N, 11.37. Found: C, 68.15; H, 7.29; N, 11.33. TLC (SiO_2) R_f = 0.65, EtOAc. Data for **17**: ^1H NMR ($CDCl_3$) δ 1.26–2.89 (m, 14 H, CH_2), 3.88–4.06 (m, 1 H, NC*H*CH_2), 4.34–4.56 (m, 2 H, NC*H*CH_2), 6.43–6.49 (m, NC*H*C); HRMS for $C_{14}H_{18}N_2O_2$ calcd 246.1368, found 246.1381, *m/z* (relative intensity) 246 (M^+, 100), 190 (50), 163 (54), 149 (42), 135 (47), 124 (56); TLC (SiO_2) R_f = 0.38, EtOAc.

1,2,7,7a-Tetrahydro-7a-methyl-3*H*-pyrrolizin-3-one (1b). The hydroxy lactam **8b** (0.40 g, 2.58 mmol) was added to a refluxing solution of toluene (20 mL) and TsOH (40 mg). After 5 min Et_3N (2 mL) was added, and the solvent was removed in vacuo. The residue was chromatographed on an SiO_2 PrepPAK eluting with 4/1, EtOAc/hexane. The appropriate fractions were combined and concentrated in vacuo to afford **1b** (0.26 g, 73.6%): ^1H NMR ($CDCl_3$) δ 1.13–3.03 (m, 11 H, CH_2, CH_3), 5.21–5.61 (m, 2 H, NCH, OH); IR (neat) 2965, 1695, 1393, 1195, 652 cm^{-1}; HRMS for $C_8H_{11}NO$ calcd 137.0840, found 137.0841, *m/z* (relative intensity) 137 (M^+, 79), 122 (78), 98 (32), 82 (59), 55 (100).

Methyl 3-Oxo-1,2,7,7a-tetrahydro-3*H*-pyrrolizine-propanoate (1c). Lactamol **8c** (16.0 g, 70.5 mmol) was added as a solid to a refluxing solution of toluene (900 mL) and TsOH (1.6 g), equipped with a Dean–Stark Trap. After 35 min TEA (15 mL) was added. The solution was cooled to room temperature and concentrated in vacuo. The residue was taken up in EtOAc and filtered. The filtrate was concentrated in vacuo, and the residue was chromatographed on an SiO_2 PrepPAK eluting with 4/1 EtOAc/hexane. Combination and concentration in vacuo of the appropriate fractions afforded **1c** (11.3 g, 76.7%): mp 41–43 °C; ^1H NMR ($CDCl_3$) δ 1.72–3.08 (m, 10 H, CH_2), 3.69 (s, 3 H, CH_3), 5.24–5.39 (m, 1 H, NCH=C*H*), 6.54–6.68 (m, 1 H, NCH); IR (neat) 3088, 2952, 1729, 1694, 1393, 1202, 655 cm^{-1}; MS for $C_{11}H_{15}NO_3$, *m/z* (relative intensity) 209 (M^+, 32), 178 (15), 153 (47), 134 (10), 122 (100). Anal. Calcd for $C_{11}H_{15}NO_3$: C, 63.14; H, 7.23; N, 6.69. Found: C, 63.00; H, 7.08; N, 6.52. TLC (SiO_2) R_f = 0.59, EtOAc.

Methyl 2-(3-Hydroxybutyl)-5-oxo-2-pyrrolidinepropanoate (10a). Sodium borohydride (0.386 g, 10.2 mmol) was added to a solution of imide **4c** (2.30 g, 10.2 mmol), acetic anhydride (0.347 mL, 3.67 mmol), and methanol (1.20 mL, 30.6 mmol) in CH_2Cl_2 (25 mL) at room temperature. After 0.5 h, 10% HCl (5 mL) was added, and the solution was extracted with CH_2Cl_2 (4 × 25 mL). The organic layers were combined, dried ($MgSO_4$), filtered, and concentrated in vacuo. The residue was chromatographed on an SiO_2 PrepPAK, eluting with 7% CH_3OH/CH_2Cl_2. The appropriate fractions were combined and concentrated in vacuo to afford **10a** (1.63 g, 69.7%) and **10b** (0.19 g, 7.2%, identical by SiO_2 TLC and ^1H NMR to material prepared by an alternate route. Data for **10a**: ^1H NMR ($CDCl_3$) δ 1.60–1.64 (m, 4 H, CH_2), 1.88–1.99 (m, 4 H, CH_2), 2.35–2.47 (m, 4 H, CH_2), 2.75 (b s, 1 H, OH), 3.67 (t, 2 H, *J* = 5 Hz, CH_2OH), 3.71 (s, 3 H, CH_3), 7.11 (b s, 1 H, NH); ^{13}C NMR ($CDCl_3$) ppm 177.9, 173.8, 62.3, 61.3, 51.9, 36.5, 34.7, 30.6, 29.0, 27.0, 20.7; IR (neat) 3251, 2949, 1736, 1687, 1438, 1201, 1172, 781 cm^{-1}; HRMS for $C_{11}H_{19}NO_4$ calcd 229.1314, found 229.1305, *m/z* (relative intensity) 229 (M^+, 1), 170 (100), 142 (100), 138 (66), 124 (38), 114 (19), 110 (55). Anal. Calcd for $C_{11}H_{19}NO_4$: C, 57.63; H, 8.35; N, 6.11. Found: C, 57.29; H, 8.41; N, 5.94. Corrected for 0.84% H_2O. TLC (SiO_2) R_f = 0.26, 7% CH_3OH/CH_2Cl_2.

Tetrahydro-5-hydroxy-3-oxo-1*H*-pyrrolizine-7a(5*H*)-propanal (11). DIBAL (22.0 mL, 1.0 M in CH_2Cl_2) was added at a rate of 0.45 mL/min to a solution of **4c** (4.5 g, 21.1 mmol) in CH_2Cl_2 (200 mL) at −78 °C. The solution was poured onto 10% HCl (50 mL) 10 min following the addition of DIBAL. The organic layer was removed, and the aqueous portion was extracted with CH_2Cl_2 (3 × 60 mL). The organic layers were combined, dried ($MgSO_4$), filtered, and concentrated in vacuo to a weight of 3.3 g. The aqueous portion was extracted with an additional amount of CH_2Cl_2 (4 × 25 mL). Drying ($MgSO_4$), filtering, and concentrating in vacuo the additional organic extracts afforded 0.31 g of residue. The two residues were combined with CH_2Cl_2 and concentrated in vacuo. The residue was chromatographed on an SiO_2 PrepPAK, eluting with 3% CH_3OH/CH_2Cl_2. The appropriate fractions were combined and concentrated in vacuo to afford starting material (2.05 g, 43%), lactamol **8c** (0.90 g, 19%), and aldehyde **11** (0.10 g, 3%). Data for aldehyde **11**: ^1H NMR ($CDCl_3$) δ 1.52–2.26 (m, 8 H, CH_2), 2.40–2.89 (m, 4 H, CH_2), 3.81 (b s, 1 H, OH), 5.53–5.68 (m, 1 H, NCH), 9.87 (t, 1 H, *J* = 1.7 Hz, CHO); IR (neat) 3300, 2956, 1720, 1670, 1205, 795 cm^{-1}; HRMS for $C_{10}H_{15}NO_3$ calcd 197.1052, found 197.1058, *m/z* (relative intensity) 197 (M^+, 4), 169 (48), 140 (100), 122 (30), 112 (62). Anal. Calcd for $C_{10}H_{15}NO_3$: C, 60.90; H, 7.67; N, 7.10. Found: C, 60.14; H, 7.98; N, 6.75. Corrected for 5.48% H_2O. TLC (SiO_2) R_f = 0.36, 5% CH_3OH/CH_2Cl_2.

4-Methyl-4-(3-hydroxypropyl)-2-pyrrolidinone (13). Sodium borohydride (2.47 g, 65.3 mmol) was added to a solution of **4b** (1.0 g, 6.53 mmol) in CH_3OH (60 mL) at −5 °C. After 1 h the reaction solution was partitioned between saturated aqueous $NaHCO_3$ (60 mL) and CH_2Cl_2 (60 mL). The organic layer was removed, and the aqueous portion was extracted with CH_2Cl_2 (3 × 50 mL). The organic extracts were combined, dried ($MgSO_4$), filtered, and concentrated in vacuo to 0.36 g. The aqueous portion was filtered to remove suspended solids, and the filtrate was concentrated in vacuo. The solid residue was extracted with CH_2Cl_2 (150 mL) to provide an additional 0.4 g of material. The residues were combined (0.76 g) and chromatographed on an SiO_2 PrepPAK, eluting with 7% CH_3OH/CH_2Cl_2 to afford **12a** (45.0 mg, 3.7%) and the overreduced **13** (614 mg, 59.9%): ^1H NMR ($CDCl_3$) δ 1.28 (s, 3 H, CH_3), 1.47–1.68 (m, 4 H, CH_2), 1.71–2.05 (m, 2 H, CH_2)8 2.25–2.52 (m, 2 H, CH_2), 3.37 (b s, 1 H, OH), 3.50–3.78 (m, 2 H, OCH_2), 7.37 (b s, 1 H, NH); IR (neat) 3257, 2942, 1683, 1421, 1382, 1060, 829 cm^{-1}; MS for $C_8H_{15}NO_2$, *m/z* (relative intensity) 142 (4), 124 (4), 98 (100), 70 (5), 55 (13). Anal. Calcd for $C_8H_{15}NO_2$: C, 61.12; H, 9.62; N, 8.91. Found: C, 60.99; H, 9.36; N, 8.72. Corrected for 4.18% H_2O. TLC (SiO_2) R_f = 0.41, 10% CH_3OH/CH_2Cl_2.

Hexahydro-7a-methyl-5-(*tert*-butyldimethylsiloxy)-3*H*-pyrrolizin-3-one (14). Hydroxy lactam **8b** (2.33 g, 15.0 mmol) was combined with CH_2Cl_2 (15 mL), Et_3N (3.0 g, 30.0 mmol), and *tert*-butyldimethylsilyl chloride (2.7 g, 18.0 mmol). The mixture was stirred at room temperature for 20 h. The reaction was quenched with H_2O. The aqueous portion was extracted with EtOAc (2 × 150 mL). The organic portions were combined, dried, and evaporated in vacuo to 4.5 g. This was dissolved in hexane/EtOAc, 4/1, and chromatographed in the same solvent on a Waters' Prep-500 to yield **14** (3.46 g, 86%): ^1H NMR ($CDCl_3$, 300 MHz) δ 5.29–5.21 (m, 1 H, NCHO), 2.89–2.72 (m, 1 H), 2.55–2.22 (m, 2 H), 2.07–1.88 (m, 2 H), 1.77–1.67 (m, 1 H), 1.19

(s, 3 H, CH_3), 0.87 (s, 9 H, $C(CH_3)_3$), 0.17 (s, 3 H, $SiCH_3$), 0.15 (s, 3 H, $SiCH_3$); ^{13}C NMR ($CDCl_3$) ppm 173.9, 78.1, 68.5, 38.1, 36.9, 36.4, 35.1, 25.8, 25.0, 18.2, -4.9, -5.5; IR (neat) 2956, 2929, 2857, 1710, 1352, 1060, 835 cm^{-1}; MS for $C_{14}H_{27}NO_2Si$, m/z (relative intensity) 254 (6), 213 (17), 212 (100), 154 (2), 138 (20), 75 (21). Anal. Calcd for $C_{14}H_{27}NO_2Si$: C, 62.40; H, 10.10; N, 5.20. Found: C, 62.35; H, 10.40; N, 5.13. Corrected for 0.23% H_2O.

Hexahydro-5-methoxy-7a-methyl-3*H*-pyrrolin-3-one (15). Lactam alcohol **8b** (4.38 g, 28 mmol), dissolved in MeOH (50 mL), was added to MeOH (200 mL, brought to pH = 3 with concentrated HCl) at 0 °C. After 1.5 h the mixture was concentrated in vacuo to 4.8 g. This was chromatographed on a Waters' Prep-500 [SiO_2, CH_2Cl_2/MeOH (3%)] to yield 4.35 g (92%) of **15**: ^1H NMR ($CDCl_3$, 300 MHz) δ 5.13-5.10 (m, 1 H, NCHO), 3.37 (s, 3 H, OCH_3), 2.84-2.72 (m, 1 H), 2.45-2.22 (m, 2 H), 2.14-1.84 (m, 4 H), 1.72-1.58 (m, 1 H), 1.38 (s, 3 H, CH_3); ^{13}C NMR ($CDCl_3$) ppm 176.5, 86.6, 67.6, 56.0, 38.3, 35.1, 34.0, 33.4, 27.1; IR (neat) 3570 (H_2O), 2966, 1702, 1459, 1376, 1364, 1335, 1196, 1179, 1093 cm^{-1}; MS for $C_9H_{15}NO_2$, m/z (relative intensity) 169, (M^+, 24), 154 (91), 139 (83), 138 (91), 122 (11), 98 (100). Anal. Calcd for $C_9H_{15}NO_2$: C, 63.88; H, 8.93; N, 8.28. Found: C, 63.75; H, 8.93; N, 8.19. Corrected for 0.98% H_2O. TLC (SiO_2) R_f = 0.39, EtOAc.

Bis(hexahydro-7a-methyl-3-oxo-3*H*-pyrrolizin-5-yl) Ether (16). Lactam **8b** (4.11 g, 26.5 mmol) and acidic H_2O (80 mL, pH = 1 from a few drops of 10% HCl) were combined. The mixture was evaporated in vacuo to 4.0 g. This material was chromatographed on a Waters' Prep-500 [SiO_2, CH_2Cl_2/MeOH (3%)] to yield **15** (430 mg, 10%), a fraction containing a 3:2 mixture of starting material to ether **16** (510 mg), and ether **16** (1.86 g, 47%) as a mixture of diastereomers. Data for **16**: ^1H NMR ($CDCl_3$) δ 1.20-3.00 (m, 16 H), 1.40 (s, 3.75 H, CH_3), 1.46 (s, 2.25 H, CH_3), 5.30-5.50 (m, 0.66 H, NCHO), 5.50-5.80 (m, 1.33 H, NCHO); ^{13}C NMR ($CDCl_3$) ppm (peaks of major diastereomer) 175.1, 84.8, 67.5, 38.4, 35.4, 34.5, 33.7, 26.5 (peaks of minor diastereomer) 175.7, 81.7, 67.7, 38.4, 35.5, 33.9, 26.6; IR (mineral oil mull) 2926, 1698, 1056, 1047 cm^{-1}; MS for $C_{16}H_{24}N_2O_3$, m/z (relative intensity) 292 (M^+, 0.3), 264 (0.1), 213 (0.2), 170 (1), 154 (15), 140 (10), 139 (100), 138 (62), 111 (6), 95 (15). Anal. Calcd for $C_{16}H_{24}N_2O_3$: C, 65.73; H, 8.27; N, 9.58. Found: C, 65.39; H, 8.25; N, 9.55. Corrected for 0.81% H_2O.

6-Hydroxy-1-methyl-2-piperidinone (19). Lithium triethylborohydride (220 mL, 1.0 M in THF) was added dropwise to a solution of *N*-methylglutarimide (**18**) (25.4 g, 0.2 mol) in CH_2Cl_2 (650 mL) at -78 °C. Saturated NH_4Cl (150 mL) was added to the reaction 15 min following the addition. The solution was allowed to warm to room temperature. The organic layer was removed, and the aqueous layer was extracted with CH_2Cl_2 (3 × 200 mL). The organic layers were combined, dried ($MgSO_4$), filtered, and concentrated in vacuo. The residue was chromatographed on an SiO_2 PrepPAK eluting with 5% CH_3OH/CH_2Cl_2. The appropriate fractions were combined and concentrated in vacuo. The residue was dissolved in Et_2O and allowed to crystallize. The product was collected by filtration and dried under vacuum to give **19** as an extremely deliquescent white solid (13.4 g, 52.8%): mp 36-38 °C; ^1H NMR ($CDCl_3$) δ 1.68-1.74 (m, 1 H, CH_2), 1.89-2.16 (m, 1 H, CH_2), 2.25-2.45 (m, 2 H, CH_2), 2.98 (s, 3 H, NCH_3), 4.31 (d, 1 H, J = 9.0 Hz, OH), 4.91 (dt, 1 H, J = 4.6, 8.9 Hz, NCH); IR (mineral oil mull) 3212, 2952, 1623, 1491, 1084, 987 cm^{-1}; HRMS for $C_6H_{11}NO_2$ calcd 129.0790, found 129.0789, m/z (relative intensity) 129 (M^+, 57), 101 (30), 73 (50), 60 (82), 42 (100). Anal. Calcd for $C_6H_{11}NO_2$: C, 55.80; H, 8.58; N, 10.84. Found: C, 54.97; H, 8.74; N, 10.73. TLC (SiO_2) R_f = 0.22, 5% CH_3OH/CH_2Cl_2.

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Synthesis and Alkali-Hydrolysis Reactions of Some 2,3′-(Substituted imino)pyrimidine Nucleosides Lacking a 2′-Hydroxyl Group

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2,3′-(Methylimino)- (**6a**) and 2,3′-(phenylimino)-1-(3′-deoxy-2′-*O*-methyl-β-D-lyxofuranosyl)uracil (**6b**) and 2,3′-(methylimino)- (**11a**), 2,3′-(phenylimino)- (**11b**), and 2,3′-[(*p*-methoxyphenyl)imino]-1-(2′-deoxy-β-D-*threo*-pentofuranosyl)uracil (**11c**) were synthesized. Alkaline hydrolysis of **6a**, **6b**, **11a**, and **11c** gave the corresponding pyranosyl isomers **13a-d**, while the 2,3′-(phenylimino)-bridged thymidine analogue **15** gave exclusively the C_2-N fission product **17**. Some mechanistic corroboration and difference of reactivity between 2,3′-N-bridged uracil and thymine nucleosides are described. 3′,5′-Anhydro nucleosides **12** and **16** were also isolated with **11c** and **15**.

In a recent publication,[1] we have reported that 2,3′-(substituted imino)-1-(3′-deoxy-β-D-lyxofuranosyl)uracils (**1a-d**) are convertible into their pyranosyl isomers **2a-d** under strongly alkaline conditions and that cleavage of the 2,3′-imino bridge also occurs to a similar extent to give a 3′-(arylamino)-3′-deoxy-β-D-lyxofuranosyluracil (**3a** or **3b**) when R is an aryl group (Scheme I). The results of similar hydrolysis studies on 2,2′-imino and 2,2′-(substituted imino)uracil nucleosides (**4**) have also been reported.[2] For this furanosyl-to-pyranosyl isomerization, we have proposed a general reaction mechanism involving fission of the anomeric as well as $C_{1'}$-O bond by the initial attack of a hydroxide ion on the anomeric carbon, followed by molecular reorganization with retention of chirality at the

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