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The Azomethine Imine Route to Guanidines. Total Synthesis of (\pm)-Saxitoxin

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Azomethine imines may be readily generated through the interaction of aldehyde acetals with carboxylic acid hydrazides. These reactions are most highly favored in polar aprotic solvents and acid catalysis is required. With suitably functionalized hydrazides these substances undergo a facile intramolecular addition to give fused-ring pyrazolidine derivatives. As a part of these studies, (\pm)-Saxitoxin (7), the paralytic agent of the Alaska butter clam *Saxidomas giganteus*, has been synthesized in a totally stereospecific fashion through a sequence involving as the key steps: (a) intramolecular 1,3-dipolar addition of an azomethine imine to a 2-imidazolone; (b) reductive cleavage of the resulting pyrazolidine ring followed by intramolecular acylation; and (c) final elaboration of a bis-pseudourea to the requisite guanidine functionality.

INTRODUCTION

In recent years there has been an enormous outpouring of effort directed toward the total synthesis of naturally occurring guanidines. Much of this activity has been stimulated by the discovery of a variety of novel structures, but of greater importance, many members of this class have exceptional biological activity. Representative examples include Ptilocaulin (1) and Isoptilocaulin (2), the antimicrobial and cytotoxic principles of the Caribbean sponge *Ptilocaulis* aff. *P. spiculifer*;¹ Streptolidine lactam (3), the heterocyclic nucleus of the Streptothricin antibiotics (4);² Tetrodotoxin (5), the notorious fugu poison found in the liver, ovaries and intestines of the puffer fish;³ and the Gonyautoxins (6), a family of neurotoxins derived from the *Gonyaulax* genus of dinoflagellates⁴ (Figure 1). Of this latter group, Saxitoxin (7), whose synthesis forms the subject of the present report, has long been recognized as one of the most toxic of the non-protein poisons known. With an LD₅₀ in mice of about 8 μ g/kg, it has been estimated that a single dose of 0.2—1.0 mg would prove fatal in humans. It is thus about 100 times more poisonous than strychnine, 200 times more potent than mushroom toxins, almost 1000 times more deadly than a typical synthetic nerve gas, and 2000 times more toxic than sodium cyanide.⁵ With such properties one might legitimately

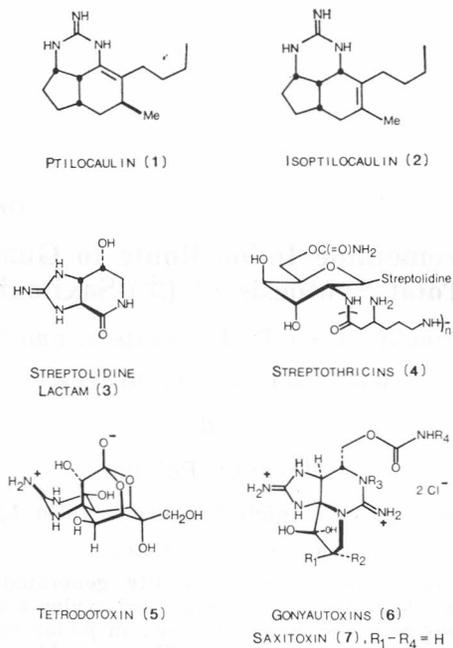


Figure 1.

question the motivation for synthetic activity in this area. However, as described below, the reasons for this activity are sound.

Saxitoxin has a relatively long history, but it was first isolated in the pure state in 1957 by Schantz and co-workers, then at Northwestern University, from clams and mussels collected on the west coast of the USA,⁶ and more recently from clams collected on the east coast while feeding on certain marine dinoflagellates.⁷ When conditions of temperature and light are right, these organisms reproduce (or bloom) so rapidly as to discolor the sea, producing the so-called »red tide«. Shellfish, especially clams and mussels, feeding on the dinoflagellates at this time become poisonous to man, causing paralytic shellfish poisoning. This poisoning is due to 7 ingested by the shellfish, which is stored for weeks in mussels, and for many months in clams. Symptoms of poisoning in man begin with a numbness in the lips, tongue and fingertips within a few minutes after ingestion. This is rapidly followed by weakness in the legs, arms and neck, which progresses to a general muscular incoordination. Death occurs from respiratory paralysis.

Saxitoxin acts by selectively blocking the entrance to sodium channels in neuron membranes, thereby preventing the transient Na^+ ion conductance increases associated with action potentials.⁸ The presence of 7 appears to have no effect on K^+ or Cl^- ion currents, or on acetylcholine release. The blockage of the sodium channel, although very strong, is also totally reversible, and, in fact, 7 and common nerve blocks at very low concentrations.⁹ Of greater importance, however, the toxin's physiological behavior makes it ideally suited for use as a probe of normal and afflicted tissue, and it is an excellent tool for the study of synaptic and neuromuscular trans-

missions.¹⁰ Medical researchers now use this agent for the labelling, characterization and isolation of sodium channel components, which has opened new avenues in the study of various nerve disorders.¹¹

Establishing a structure for 7 was complicated by the nonvolatile and noncrystalline nature of its salts. Extensive chemical degradations were carried out by Rapoport at Berkeley,¹² but the correct structure was only determined by X-ray analysis of crystalline derivatives, carried out independently by Clardy and Schantz,¹³ and Rapoport.¹⁴ Possessing both an unusual structure and potential medical importance, 7 became an attractive target for synthesis as soon as its structure was firmly established. The first total synthesis, by Kishi et. al., was reported in 1977.¹⁵

DISCUSSION

Our own efforts in this area were stimulated by the report that hydrazides of general structure 8 can be smoothly converted to azomethine imines 9, which, without isolation, undergo an intramolecular 1,3-dipolar cycloaddition to give adducts of type 10 in excellent overall yield (Figure 2).¹⁶

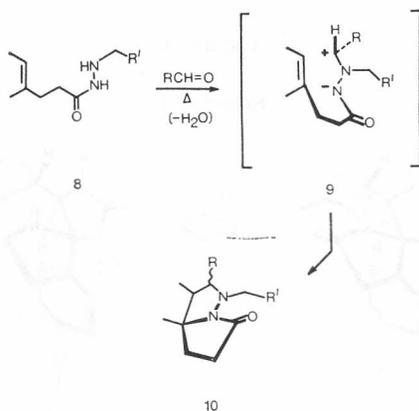


Figure 2.

Such adducts bear a number of structural features in common with Saxitoxin (7), and by analogy one might reasonably predict that hydrazides of general structure 11 should afford adducts of type 13, which could be efficiently utilized in the synthesis of perhydropurines (Figure 3). Thus, it is well known that similar heterocyclic species can be readily cleaved under a variety of reductive conditions,¹⁷ and in principle, at least, such a procedure might be utilized in a ring expansion process to give cyclic ureas or guanidines. By way of summary, then, our initial strategy for the synthesis of 7 is diagrammed in Scheme 1.

Several features of this approach are worthy of special attention. It will be recognized, for example, that pyrazolidines of type 14 contain all of the stereochemical centers of 7 in their proper relative configurations, and furthermore, there was excellent precedence for the overall conversion of 14 to 15 under non-epimerizing conditions.¹⁷ Of particular interest, however, it seemed likely that 15 could be directly converted to thiourea derivatives

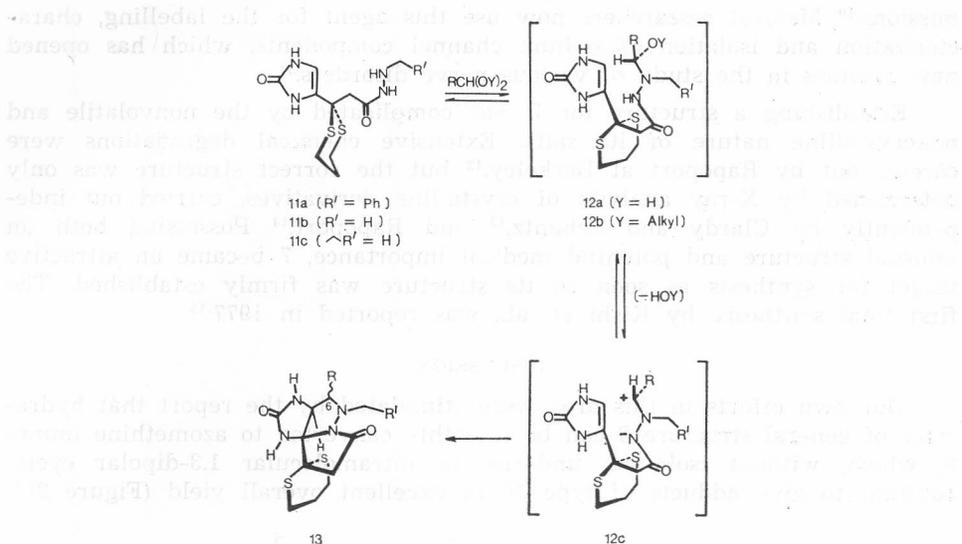
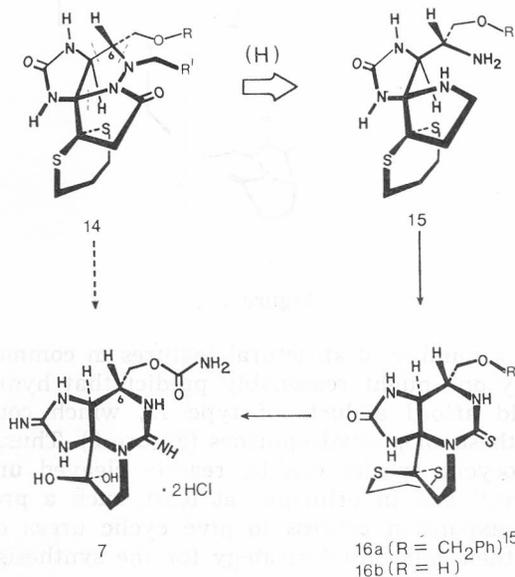


Figure 3.

Scheme 1.

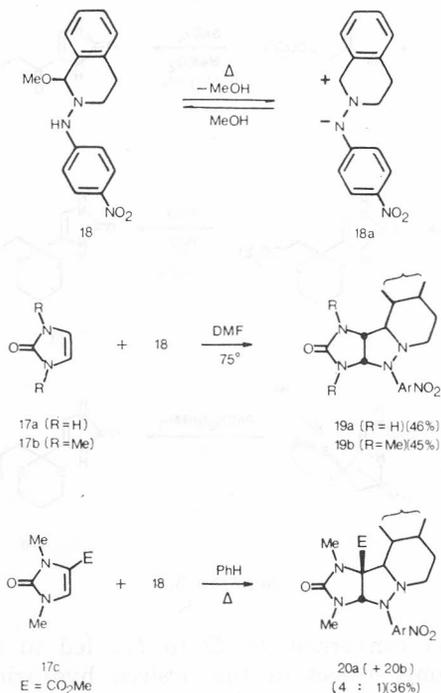


of type 16 by bridging with thiocarbonyldiimidazole,¹⁸ and if such were the case, then the present synthesis might converge with that of Kishi et. al. (cf. 16a).¹⁵ At the outset, however, three were two questions which remained to be settled. First, we could find no information pertaining to the reactivity of imidazolones as 1,3-dipolarophiles; and second, although 14 was clearly in the thermodynamically most favored configuration (vide infra), the stereo-

chemical outcome of such dipolar additions under kinetic control was far from certain (cf. C-6 in 13).¹⁶

For practical reasons, our initial studies were carried out with *inter*-molecular trials, where advantage could be taken of the ready availability of various 1,3-dipolar species. Thus, dihydroisoquinoline 18 served as a stable, convenient, and neutral source of the highly reactive azomethine imine 18a,^{19,20} and model studies were carried out with 2-imidazolone (17a), *N,N*-dimethyl-2-imidazolone (17b) and the methyl ester 17c in a variety of polar and non-polar solvents (Scheme 2). As indicated, adducts 19a and 19b were

Scheme 2.

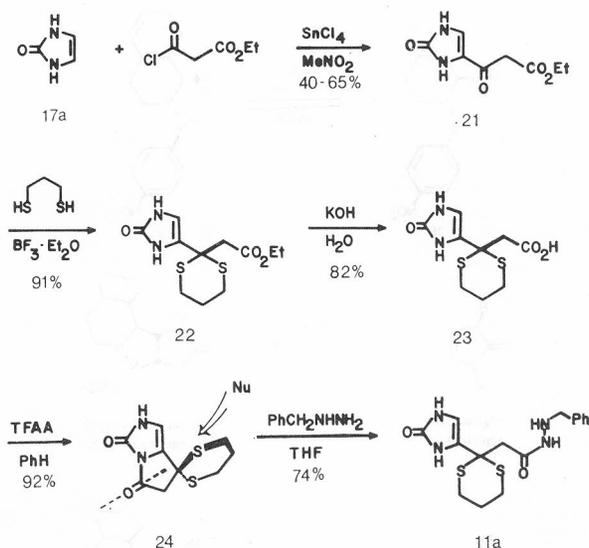


formed in moderate yield after chromatographic purification, while the less electron rich 17c afforded a 36% combined yield of regioisomers 20a and 20b in a 4:1 ratio. In addition, it is worth noting that significant solvent effects were observed in all of these model studies. Thus, both 17a and 17b gave appreciable amounts of 19 only in dipolar aprotic solvents, while 17c reacted exclusively in benzene. In solvents other than those noted for each individual case, unreacted dipolarophile and dimeric material derived from 18a were the only products recovered.

Many examples of such solvent effects have been reported,²¹ and Kadaba has postulated that they are a result of specific interactions between a partially charged transition state and solvent molecules.²² For our purposes, however, the primary importance of these model studies lay in the demonstration that imidazolones can function as dipolarophiles with azomethine

imines, and they also provided insight into the possible experimental conditions and solvents required in our intramolecular studies.

We next turned our attention to the question of stereochemical control, a factor which would be of crucial importance in the preparation of **14** but which was not investigated in our intermolecular studies. In order to address this issue it was first necessary to develop a practical synthesis of the requisite hydrazides **11**, and, as summarized below, our solution to this problem was relatively straightforward (Scheme 3).²³ It is worth noting, however, that all



Scheme 3.

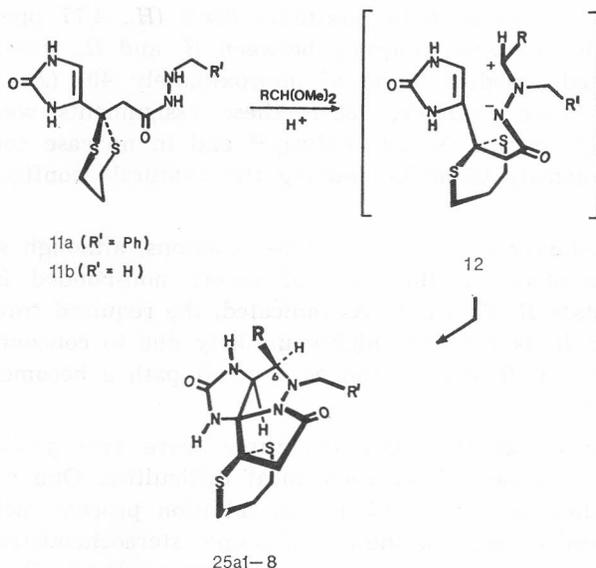
attempts at the direct conversion of **22** to **11a** led to complex mixtures of products containing only traces of the desired hydrazide. This failure was partly due to the usual problem of selectivity, frequently encountered in the acylation of mono-substituted hydrazines,²⁴ as well as the forcing conditions required for this particular reaction (strong propanedithiol odor evident). By way of contrast, however, the highly electrophilic imide **24** reacted smoothly at ambient temperatures and the desired isomer **11a** separated cleanly from the reaction mixture. In this case, we presume, the nucleophilic trajectory of benzyl hydrazine must pass in close proximity to the spirocyclic dithiane ring,²⁵ leading, in turn, to considerable steric crowding and to a more favorable outcome in the regiochemical course of reaction. In the event, the described procedures allowed for the convenient preparation of hydrazides **11** on multigram scales with no chromatographic separations.

We were less fortunate in our initial attempts at generating dipolar species of type **12c** (cf. Figure 3). Thus, for example, under the usual conditions

we could find no evidence for the desired reaction between *11a* and benzaldehyde, obtaining in every case a quantitative return of starting materials (Ph—CH=O, refluxing xylene, continuous removal of water).¹⁶ Furthermore, this outcome was unaffected by a variety of modifications in the experimental parameters and we found a similar lack of reactivity with other aldehydes which previously been employed with marked success in simpler model systems.¹⁶ A contributing factor in these difficulties was the highly insoluble nature of *11a* in all but the most polar of organic solvents. We should emphasize, however, that this impediment alone was not of crucial nature, since we had previously found that equally insoluble derivatives readily combined, in an intermolecular fashion, with suitably generated azomethine imines (cf. Scheme 2). Of greater importance, we believe, the available evidence was suggestive of an extremely unfavorable equilibrium between *11a* and *12a*, leading, in turn, to a retarding influence on the required 1,3-elimination of water. In order to circumvent this problem we focused our attention next on the potential utility of aminoacetals of type *12b*, expecting, in this case, that an equilibrium process as suggested above would be untenable (cf. also *18* in Scheme 2).

After considerable effort, in fact, we were pleased to find that excellent yields of adducts of general structure *13* could be attained under conditions which strongly implicate the intermediacy of aminoacetals *12b* (Scheme 4).²⁶

Scheme 4.



As one example, a mixture of 1.82 g (5.0 mmol) of hydrazide *11a* and 1.14 g (1.25 equiv) of benzaldehyde diethyl acetal was heated at 80 °C, with vigorous stirring, in 50 mL of freshly distilled DMF containing a catalytic amount of TsOH (careful exclusion of moisture). Solution (bright yellow) was generally complete within 1 h, and after a total of 5 h the reaction was concentrated

and chromatographed to give 1.88 g (83%) of adduct *25a-1* ($R, R' = Ph$) as a colorless, crystalline solid. Similarly prepared were the following ($R' = Ph$): (Compound, R , % yield): *25a-2*, *p*-methoxyphenyl, 90%; *25a-3*, *p*-methylphenyl, 91%; *25a-4*, *p*-nitrophenyl, 52%; *25a-5*, 2-furyl, 68%; *25a-6*, 2-thienyl, 80%; *25a-7*, H , 64%; *25a-8*, benzyl, 17%. All of these reactions were highly dependent upon the nature of the solvent, proceeding only moderately well in acetonitrile and not at all in glyme or less polar solvents.²² Furthermore, they failed completely in the absence of $TsOH$. $TsOH$, we believe, serves mainly in the capacity of bringing about an initial ionization of the aldehyde acetal, which is subsequently trapped by the strongly basic nitrogen of hydrazide *11a*. In agreement with this hypothesis, the relative rates for these conversions varied in a manner fully consistent with the ability of R to stabilize a developing cationic center (i. e., *25a-2*, *25a-5* > *25a-1*, *25a-3*, *25a-6* > *25a-7* > *25a-4*). Also, as indicated, aliphatic acetals either failed to react under these conditions or they gave much lower yields of adducts (17% with phenylacetaldehyde diethyl acetal to give *25a-8*).

The stereochemical assignments for these adducts followed readily from their highly characteristic NMR spectra, which invariably contained two features that are worthy of special comment (Figure 4). One of these is the extremely low field of absorption exhibited by H_5 (4.9—5.3 ppm), which undoubtedly derives from the strongly deshielding environment provided by a proximate dithiane ring. In this regard it is interesting to note that a similar effect is operative in Saxitoxin itself (H_5 , 4.77 ppm).¹³ Secondly, in every case the observed coupling between H_5 and H_6 was in full accord with an expected dihedral angle of approximately 40° ($J = 4.8 - 5.2$ Hz). For a representative example, *25a-1*, these assignments were completely verified by single crystal X-ray analysis,²³ and in no case could we detect a measurable quantity of adduct having the »natural« configuration at C-6 with $R' = Ph$.

The extraordinary selectivity of these reactions, although surprising, can be readily understood on the basis of severe non-bonded interactions in *exo* transition state *B* (Figure 5). As indicated, the required *trans* relationship between H_5 and H_6 is rendered highly unlikely due to concomitant eclipsing interactions between R and R' , and as a result path *a* becomes the reaction route of choice.²⁷

Having arrived at this juncture, there were two possible means of circumventing the observed stereochemical difficulties. One of these would involve a modification of the 1,3-dipolar addition process such that kinetic control might lead directly to adducts of proper stereochemistry. In principle, at least, this goal might be achieved by either drastically reducing the steric bulk of both R and R' ,²⁷ or by joining together R and R' in such a fashion as to ensure the necessary *trans* relationship between H_5 and H_6 (cf. path *b*, Figure 5). Alternatively, we believed, an epimerizable group at C-6 should allow for a facile thermodynamic equilibration to the more stable isomer *25b*. Each of these approaches will be discussed in turn.

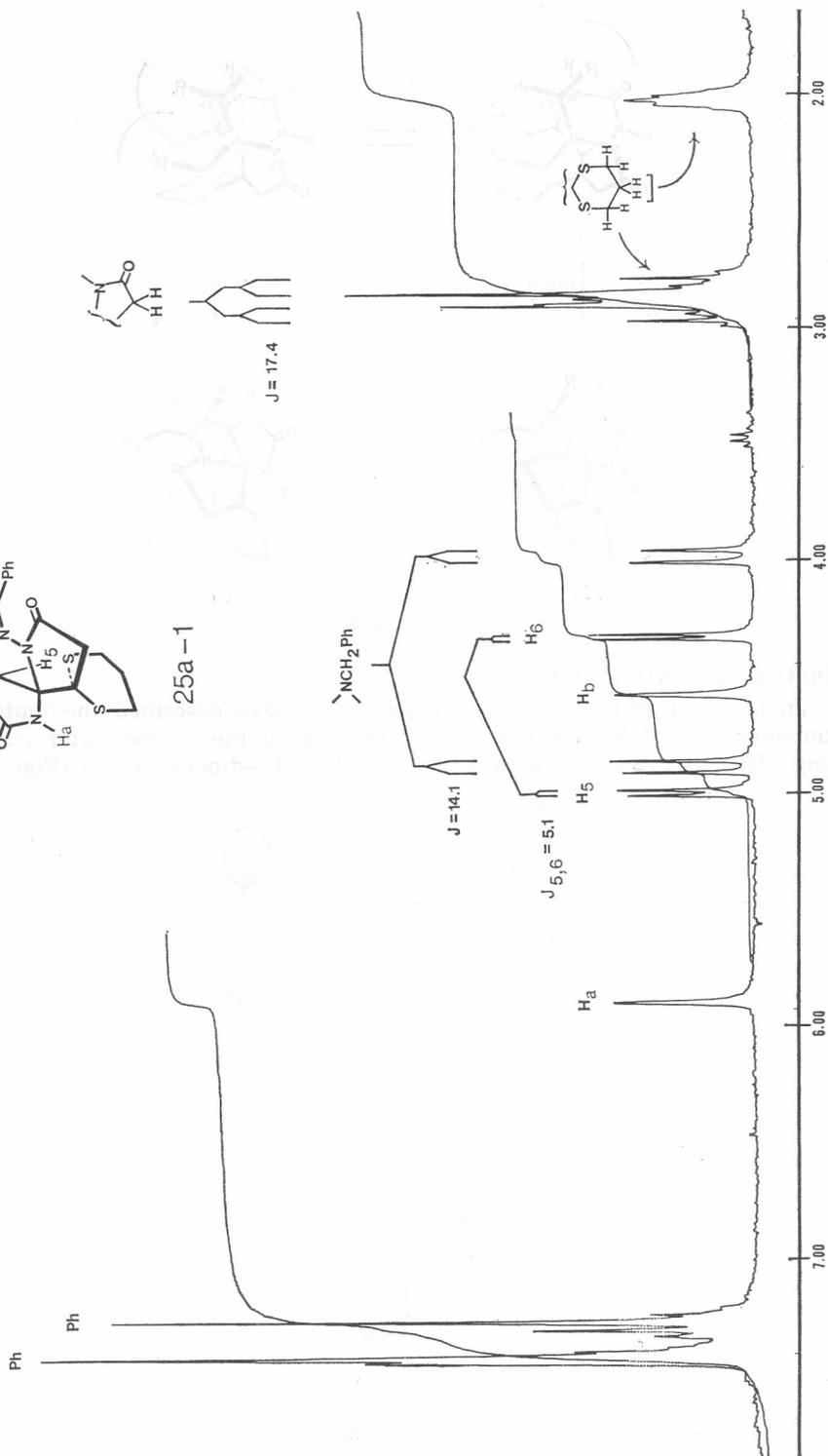


Figure 4.

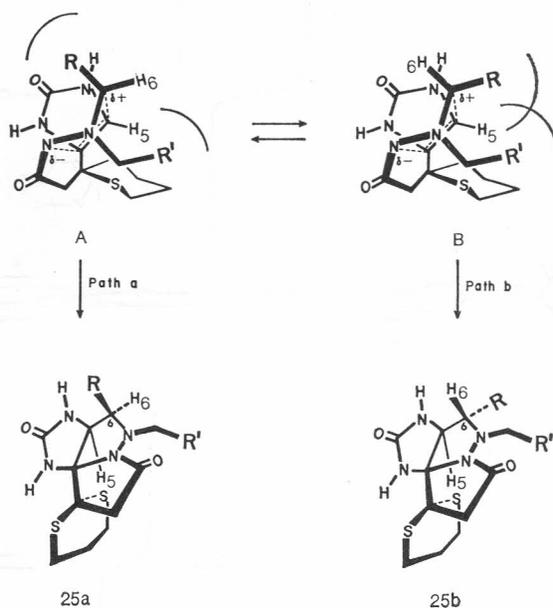


Figure 5.

Kinetically Controlled Processes

In a recent series of papers Grigg et. al. have described the tautomeric interconversion of hydrazones with azomethine imines, these latter materials being efficiently trapped with highly reactive 1,3-dipolarophiles (Figure 6).²⁸

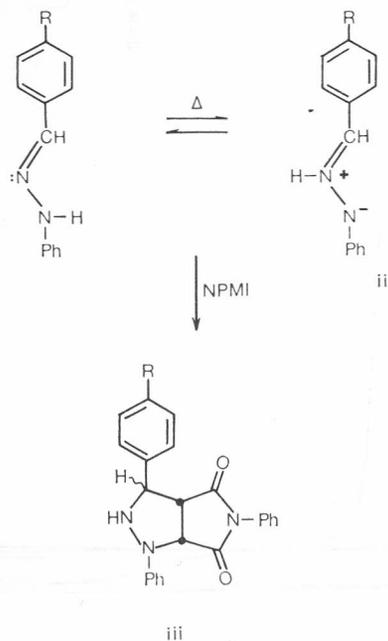


Figure 6.

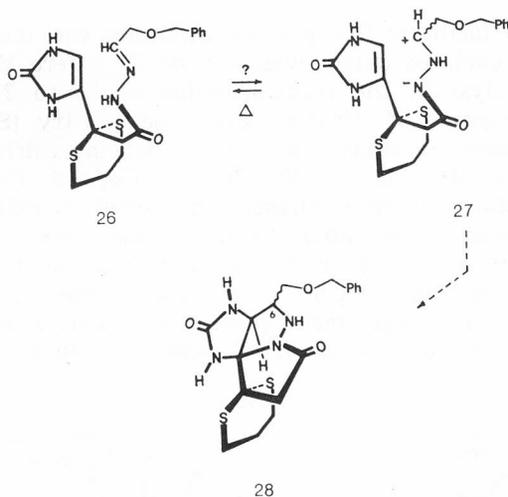
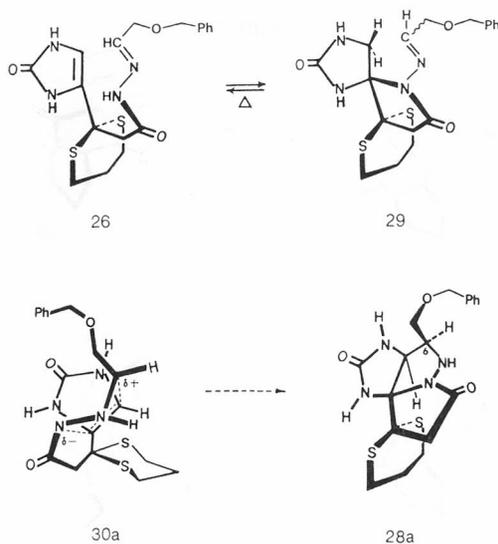


Figure 7.

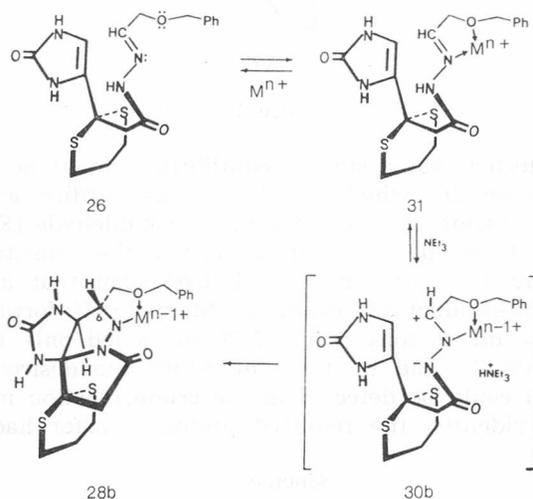
These results suggested that a similar equilibrium might be established with the benzyloxyhydrazide 26, which, in turn, was readily available via the condensation of hydrazide 11c with benzyloxyacetaldehyde (Figure 7). If such were the case, we believed, steric interactions in the transition state leading to adduct 28 might be sufficiently minimized such that a favorable ratio of the desired *alpha*-product 28b could be obtained.²⁹ Unfortunately, however, all attempts at the direct conversion of 26 to 28 led only to the reversible formation of lactam 29, and no trace of either the desired adduct 28b or its *beta*-isomer 28a could be detected in the crude reaction mixtures (Scheme 5). In this case, evidently, the required proton transfer had occurred.

Scheme 5.

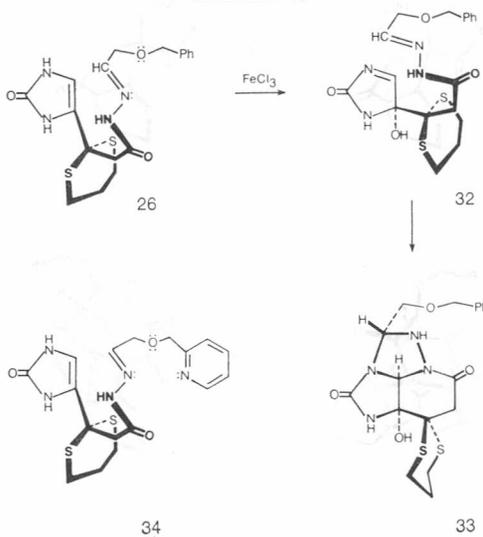


In an effort to facilitate this process, attention was next focused on the potential utility of chelated derivatives of type 31, where M^{n+} can be viewed as an internal catalyst in the transformation of 26 to 28b, as well as a template for the control of developing stereochemistry (Scheme 6). Along these lines, an exhaustive study was carried out in which M corresponded to Be, Mg, Ca, Mo, Mn, Fe, Co, Ni, Cu, Zn, Ga, Cd, Pd, Pt, and Hg in various oxidation states. Suitable changes in solvent, reaction conditions and counterions were also investigated. In most cases either no reaction was observed or total decomposition of 26 occurred at ambient temperatures and below. This is perhaps not surprising in view of the many sites available for coordination. In one experiment ($FeCl_3$), however, a smooth conversion to the tri-cyclic species 33 was observed even at $-40^\circ C$ (Scheme 7). Since

Scheme 6.



Scheme 7.



33 most likely arises from an initial oxidation of 26 to 32, followed by a rapid ring closure as indicated, the pyridyl ether 34 was subsequently prepared in an attempt to achieve greater selectivity. Unfortunately, however, the results obtained with 34 exactly paralleled those already described for 26.

Finally, in a related series of experiments, we briefly explored the possibility that an intramolecular alkylation might be employed as a means for generating the requisite dipolar species (Figure 8). Such an approach

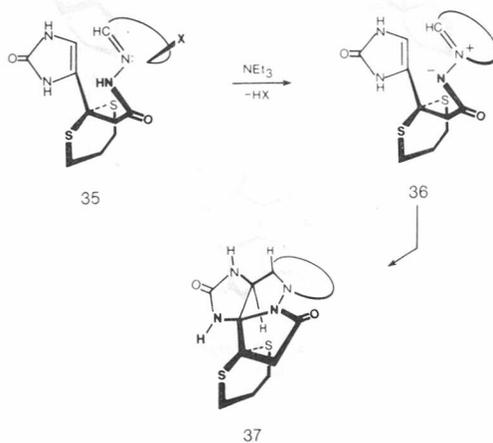
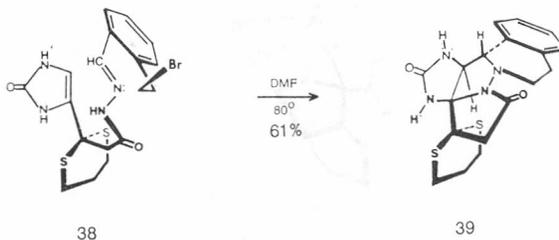


Figure 8.

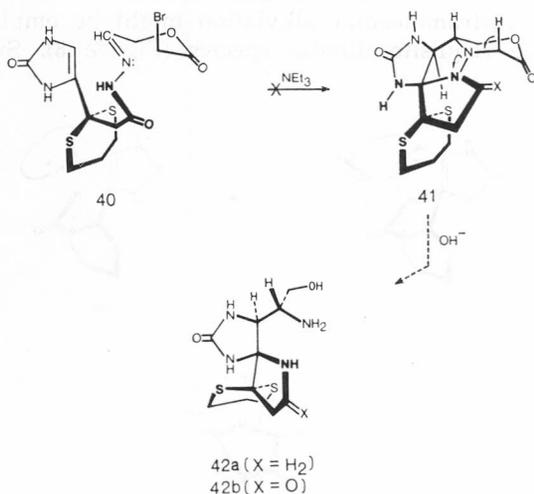
has previously been utilized in the synthesis of azomethine imines (cf., for example, 18a),^{19,20} and, if successful, should be geometrically biased in favor of adducts having the »natural« configuration at C-6 (vide supra, cf. 36 \rightarrow 37). This hypothesis was readily tested with a number of hydrazones 35, and in certain cases the results obtained were highly encouraging. Hydrazone 38, for example, gave an excellent yield of the corresponding adduct 39 merely on warming in anhydrous DMF at 80 °C (Scheme 8). Unfortunately, however, the success of these reactions was highly dependent upon the nature of the bridging alkyl halide, and satisfactory results were only obtained when this appendage incorporated a benzene ring. Hydrazone 40, for example, gave none of the expected adduct 41, a species which we believed could be readily

Scheme 8.



converted to 42a and 42b (Scheme 9). In view of this fact, increasing attention was devoted to processes which would establish the crucial stereochemistry at C-6 under thermodynamic control.

Scheme 9.



Thermodynamically Controlled Processes

In contrast to the results presented above, there could be little doubt but that the thermodynamically most favored configuration for adducts of general structure 43 would be that having the desired *alpha*-orientation at C-6 (Figure 9). In particular, with a *cis* ring juncture assured the »unnatural«

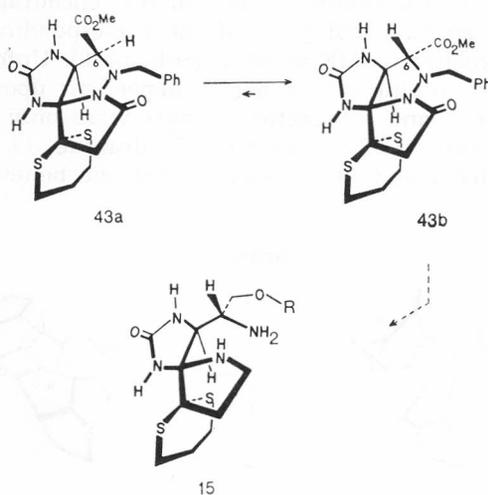
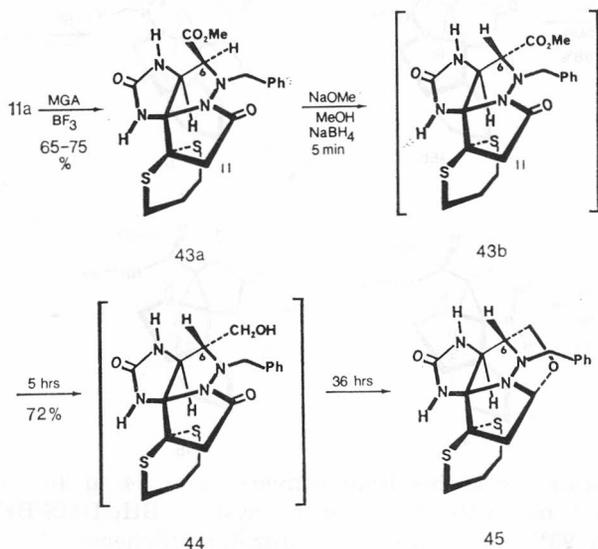


Figure 9.

isomer **43a** not only requires that a sterically demanding group be oriented on a highly concave surface, but it also suffers from strongly eclipsing interactions at positions 2, 3 and 4 of the pyrazolidine ring. These same interactions are clearly discernible in the X-ray crystal structure of **25a-1**,²³ in which all three substituents are forced into a *sun*-relationship as a consequence of the non-planar lactam ring. Adduct **43b**, on the other hand, exists in a perfectly staggered configuration and it should be highly favored at equilibrium. It was our intention, therefore, that **43b** would ultimately be converted to the desired target compound **15** through a series of reductive transformations.

In our initial efforts, however, we were disappointed to find that adducts of general structure **43** could not be prepared using our previously developed conditions (TsOH/DMF, 80 °C; see also Ref. 16). Thus, various combinations of hydrazide **11a** with methyl glyoxylate (MG),³⁰ methyl glyoxylate hemi-methylacetal (MGA),³¹ or methyl glyoxylate dimethylacetal (MGDA) all either failed to react (MGA, MGDA),³² or led to total decomposition of starting materials (MG). This last difficulty was clearly a result of random condensation reactions involving the highly electrophilic aldehyde group in MG. Eventually, however, we were pleased to find that the desired adduct **43a** could be obtained in 65–75% yield upon treatment of **11a** with 2.0 eq of 1:1 MGA/BF₃·Et₂O in dry acetonitrile at reflux (Scheme 10). These more forcing conditions presumably expedite what is undoubtedly an unfavorable ionization leading to the 1,3-dipolar species, and on several occasions, in fact, stable aminoacetals of general structure **12b** could be isolated from the crude reaction mixtures (cf. Figure 3, R = CO₂Me, Y = Me, R' = Ph).

Once in hand the desired epimerization of **43a** to **43b** could be cleanly accomplished with NaOMe/MeOH under carefully defined conditions (**43b** : **43a** > 99 : 1, NaBH₄, RT, 5 min). It is worth noting in particular that

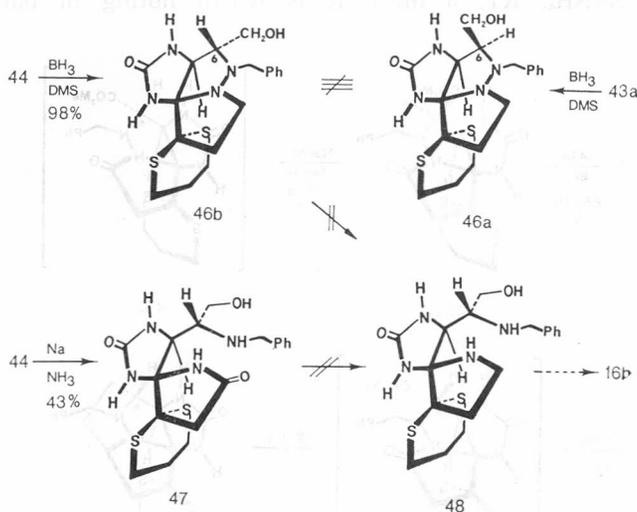


Scheme 10.

enolization at C-11 played a competing role in this transformation, since it could be readily demonstrated that 43b was in equilibrium with the enone derived by a retro-Michael opening of the dithiane ring under basic conditions (not shown). In the presence of air, for example, this open chain isomer was irreversibly trapped in the form of its oxidative dimer, and it could also be efficiently intercepted with a variety of electrophilic species. Fortunately, however, oxidative dimerization was completely eliminated through the addition of equivalent amounts of NaBH_4 . Under these conditions, we found, the disulfide bond was readily cleaved to regenerate 43b by a 5-*exo-dig*-cyclization,²⁵ and the desired product could be isolated in excellent overall yield. That 43b was actually in hand was clearly evident from its high resolution ^1H NMR spectrum, which had $J_{5,6} = 1.6$ Hz as opposed to $J_{5,6} = 4.8$ Hz for 43a.

In addition, we were pleased to find that 43a could also be directly converted to the amino-alcohol 44 upon somewhat longer exposure to $\text{NaBH}_4/\text{NaOMe}$. On a preparative scale this transformation was routinely carried out on multigram scales, under exceedingly mild conditions, to afford 44 in 70–85% yield after crystallization 5h, 10 eq NaBH_4 , RT). It is well known that such highly polarized esters can frequently be reduced with NaBH_4 at ambient temperatures and below,³³ and therefore this result offered little occasion for surprise. Of perhaps greater interest, however, after 36 h or longer the novel hemi-aminal species 45 was formed by partial reduction of the lactam ring followed by intramolecular cyclization; and ultimately, catalysis with Lewis acids resulted in the further transformation of 45 to the fully reduced pyrrolidine derivative 46b (cf. also Scheme 11 below).³⁴

Scheme 11.



For large scale work this final conversion of 44 to 46b was more conveniently carried out with the reagent system $\text{BH}_3 \cdot \text{DMS}/\text{BF}_3 \cdot \text{Et}_2\text{O}$, which afforded 46b in 98% yield after crystallization (Scheme 11).³⁵ The material thus obtained was identical in all respects with that prepared as described

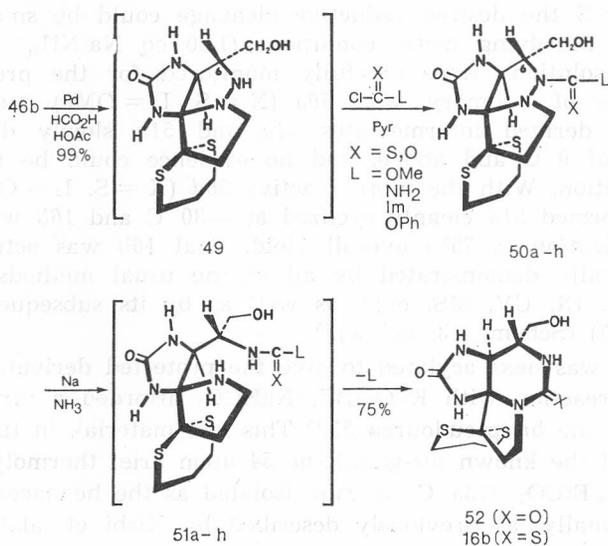
above, and was directly compared to the isomeric compound **46a** derived by reduction of the *beta*-ester **43a** under non-epimerizing conditions [$\text{BH}_3 \cdot \text{DMS}/\text{BF}_3 \cdot \text{Et}_2\text{O}$, THF, reflux; $J_{5,6}$ (**46b**) = 3.2 Hz as opposed to $J_{5,6}$ (**46a**) = 6.8 Hz]. With a ready supply of **43b**, **44** and **46b** thus secured, the suitability of each of these materials for the synthesis of **7** was carefully examined.

Our initial experiments were carried out with the lactam-alcohol **44** and we quickly discovered that this material could be selectively cleaved, in good yield, to afford the spirocyclic intermediate **47** (Na/NH_3 , -78°C).³⁶ Unfortunately, however, all attempts at the further reduction of **47** to **48** gave only complex mixtures of products containing none of the desired material.³⁷ This result was rather surprising in view of the extraordinary ease of conversion of **44** to **46b**, and is most likely due to an inherent instability of compounds of type **48** rather than a lack of chemoselectivity. On several occasions, in fact, decomposition products arising from **48** could be detected in the crude reaction mixtures.

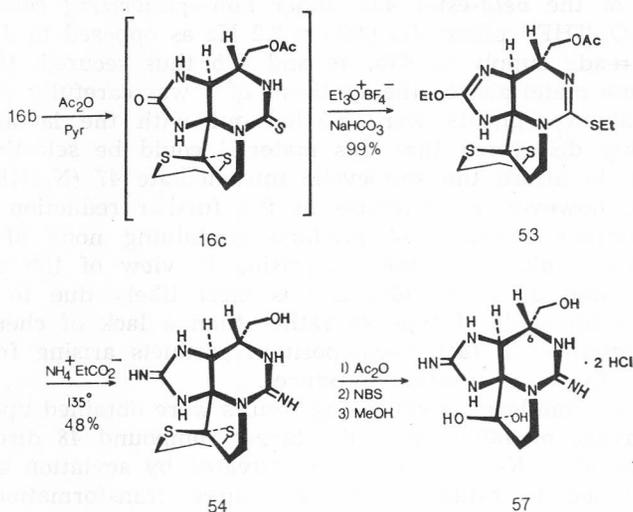
Furthermore, similarly discouraging results were obtained upon attempted reductive cleavage of **46b** to give the target compound **48** directly. In this case the pyrazolidine *N*-*N* bond is not activated by acylation and a variety of reagents failed to bring about the desired transformation. Thus, for example, **46b** was virtually inert to Na/NH_3 in the absence of a proton donor (-78°C), and with added alcohol it was rapidly converted to desulfurized products as well as mixtures derived from Birch reduction of the aromatic ring. In no case could we isolate products corresponding to the desired **48**, and we might also add that simple *N*-debenzylation was never observed under dissolving metal conditions.

As an alternative approach, however, we now found that **46b** could be smoothly debenzylated by catalytic transfer hydrogenation (Pd, HOAc, HCO_2H),³⁸ and selectively acylated to give a range of (regio-isomerically) activated species **50a-h** in excellent overall yield (Scheme 12). It was our

Scheme 12.



Scheme 13.



hope in this case that intermediates of type 51 might undergo an intramolecular ring closure at a rate competitive with decomposition.

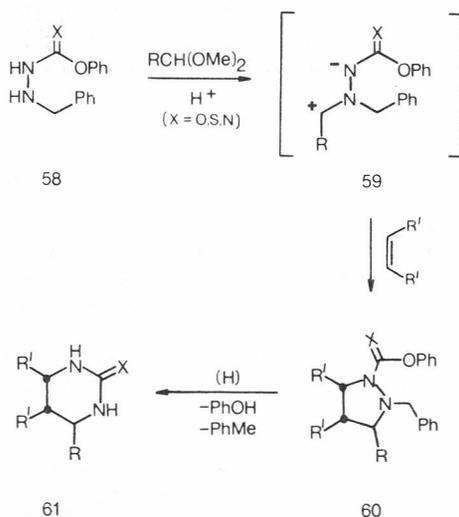
The reaction of a variety of carbamates 50 with the reagent systems Na/NH₃ or Pd/HOAc/HCO₂H followed diverse reaction pathways. With 50a (X = S, L = OMe), for example, transfer hydrogenation served only to regenerate the parent system 49, a phenomenon which was also observed with 50c-d (X = S; L = Imidazole, OPh). Compound 50e (X = O, Y = OMe), on the other hand, readily underwent N—N bond reduction to give the expected intermediate 51e (X = O, Y = OMe), but this latter material was only marginally stable and could not be cyclized to 52. Finally, however, we found that with X = S the desired reductive cleavage could be smoothly accomplished under dissolving metal conditions (1.20 eq Na/NH₃, -78 °C),³⁹ and the resulting solutions were carefully monitored for the presence of 16b (TLC). By way of summary, with 50a (X = S, L = OMe) and 50b (X = S, L = NH₂) the derived intermediates 51a and 51b slowly decomposed at temperatures of 0 °C and above, and no evidence could be found for the desired cyclization. With the more reactive 50d (X = S, L = OPh), however, the initially formed 51d cleanly cyclized at -30 °C and 16b was isolated by direct crystallization in 75% overall yield. That 16b was actually in hand was unequivocally demonstrated by all of the usual methods of characterization (NMR, IR, UV, MS, etc.), as well as by its subsequent conversion to Saxitoxin (7) (Scheme 13, below).¹⁵

Thus, 16b was next acylated to give the protected derivative 16c, which upon careful reaction with Et₃O⁺·BF₄⁻/NaHCO₃ afforded a virtually quantitative yield of the bis-pseudourea 53.¹⁵ This last material, in turn, then gave a 48% yield of the known bis-guanidine 54 upon brief thermolysis in strictly anhydrous NH₄⁺EtCO₂⁻ (135 °C, 30 min, isolated as the hexaacetate derivative 55).^{15,40} And finally, as previously described by Kishi et. al.,¹⁵ deprotection

and treatment of the resulting Descarbamoyl saxitoxin (57) with chlorosulfonyl isocyanate afforded (±)-7 as an amorphous solid which was indistinguishable from the natural product by TLC⁴¹ and NMR analysis.^{41,43}

Conclusion and Future Directions

It remains only to add that conversions of the general type 50 → 16b/52 might find considerable application in the synthesis of other naturally occurring guanidines and/or ureas. As one example we are currently exploring the potential utility of azomethine imines of general structure 59, with the eventual goal of developing a practical synthetic approach to highly substituted ring systems of type 61 (Scheme 14). The enormous variety of such



Scheme 14.

compounds found in Nature, as well as their sometimes exceptional biological activity, convinces us that such a goal is well worth pursuing.

EXPERIMENTAL SECTION^{44,45}

Infrared spectra were recorded on a Perkin-Elmer Model 1500 ET Spectrophotometer. The 200 MHz ¹H NMR and 50.3 MHz ¹³C NMR spectra were obtained on a Varian XL-200 Spectrometer. Chemical shifts are expressed in parts per million relative to internal tetramethylsilane. Ultraviolet spectra were recorded on a Cary 14 Spectrophotometer. All melting points were determined on a Thomas-Hoover capillary apparatus and are uncorrected. Elemental analyses were performed at the Baron Consulting Company in Orange, Connecticut. Mass spectra were determined on a Hitachi Perkin-Elmer RMU-6E Spectrometer at an ionization potential of 70 eV.

1,3-Dimethyl-2-imidazolone-4-carboxylic Acid, Methyl Ester (17c)

A 100 mL side arm test tube filled with Et₂O was fitted with a one-hole rubber stopper through which was inserted a fire polished Pasteur pipet immersed

below the surface of the Et_2O . Tygon tubing was connected to the side arm which, in turn, was connected to a second fire polished pipet inserted through a rubber stopper and immersed into a second side arm test tube containing 20 mL of Et_2O , 20 mL of MeOH and 10 mL of 30% aqueous KOH. The side arm of this generator was connected with tubing to a polished pipet immersed in a open 100 mL flask containing 1.0 g (6.4 mmol) of 1,3-dimethyl-2-imidazolone-4-carboxylic acid⁴⁶ suspended in 50 mL of MeOH. Diazald® (*p*-toluenesulfonylmethylnitrosamide) was added in 0.10 to 0.30 g quantities to the generator, during which time a slow stream of N_2 was passed through the entire apparatus via the pipet of the first test tube. Periodically the contents of the generator were replaced when it became too gelatinous by first allowing the N_2 to decolorize the gel. The entire process was continued until the reaction flask became homogeneous and a lasting yellow color persisted. At this point the N_2 flow was continued until the entire apparatus was colorless. The solvent was then evaporated and the residue crystallized from THF-petroleum ether to yield 1.03 g (95%) of 17c in the form of colorless needles, m. p. 127–127.5 °C, Rf 0.60 (silica gel, 10% MeOH/ CHCl_3). Mass spectrum, *m/e* 170 (M^+); IR(KBr) 1710 cm^{-1} (ester C=O); NMR (CDCl_3) δ 3.35 (s, 3H, NCH_3), 3.50 (s, 3H, NCH_3), 3.80 (s, 3H, OCH_3), 7.10 (s, 1H).

3,4-Dihydroisoquinoline Adduct (19a)

A mixture of 84 mg (1.0 mmol) of 2-imidazolone (17a)⁴⁷ and 299 mg (1.0 mmol, 1.0 equiv) of dihydroisoquinoline 18^{19,20} in 10 mL of dry DMF was heated at 80 °C with stirring and protection from moisture for a period of 42 h. The reaction mixture was then concentrated at 0.1 mm/30 °C and the residue was chromatographed on silica gel with 10% MeOH/ CHCl_3 . The material thus obtained was crystallized from DMF to afford 160 mg (46%) of adduct 19a in the form of yellow crystalline needles, m. p. 258–259 °C, Rf 0.50 (silica gel, 10% MeOH/ CHCl_3). Mass spectrum, *m/e* 351 (M^+); IR(KBr) 3300 (NH), 1720 (C=O), and 1570 (NO_2) cm^{-1} ; NMR ($\text{DMSO}-d_6$) δ 2.85–3.30 (m, 4H), 4.25 (d, 1H, $J = 6.0$ Hz), 4.85 (m, 1H), 5.65 (d, 1H, $J = 7.0$ Hz), 7.10–8.15 (m, 8H), NH's not observed.

3,4-Dihydroisoquinoline Adduct (19b)

This material was prepared from 1,3-dimethyl-2-imidazolone (17b)⁴⁶ and dihydroisoquinoline 18^{19,20} by an identical procedure as that described above for adduct 19a to afford a 45% yield of 19b as a yellow crystalline solid, m. p. 215–225 °C (from CH_2Cl_2 -petroleum ether), Rf 0.70 (silica gel, 5% MeOH/ CHCl_3). Mass spectrum, *m/e* 379 (M^+); IR (KBr) 1700 (C=O) and 1570 (NO_2) cm^{-1} ; NMR (CDCl_3) δ 2.25 (s, 3H, NCH_3), 2.80–3.35 (m, 4H), 3.10 (s, 3H, NCH_3), 4.30 (d, 1H, $J = 5.0$ Hz), 4.50 (dd, 1H, $J = 7.0, 5.0$ Hz), 5.55 (d, 1H, $J = 7.0$ Hz), 7.20–8.25 (m, 8H).

3,4-Dihydroisoquinoline Adducts (20a) and (20b)

A mixture of 40 mg (0.24 mmol) of methyl 1,3-dimethyl-2-imidazolone-4-carboxylate (17c) and 70 mg (0.24 mmol) of dihydroisoquinoline 18^{19,20} in 5 mL of dry benzene was stirred at reflux for a period of 88 h. The resulting solution was then concentrated under reduced pressure and the residue chromatographed on silica gel with 5% MeOH/ CHCl_3 . The material thus obtained consisted of 38 mg (36%) of a 4:1 mixture of adducts 20a and 20b as a pale yellow oil, Rf 0.75 (silica gel, 5% MeOH/ CHCl_3). Mass spectrum, *m/e* 437 (M^+); NMR (CDCl_3) (20a) δ 2.20 (s, 3H, NCH_3), 2.80–3.50 (m, 4H), 3.10 (s, 3H, NCH_3), 3.90 (s, 3H, OCH_3), 5.02 (s, 1H), 5.48 (s, 1H), 7.05–8.25 (m, 8H).

4-Carboethoxyacetyl-4-imidazolin-2-one (21)

A solution of 8.40 g (0.10 mol) of sublimed 2-imidazolone (17a)⁴⁷ and 26.10 g (0.10 mol) of anhydrous stannic chloride in 150 mL of dry nitromethane was stirred at ambient temperature for 1 h in a stoppered flask protected from

moisture. A second solution consisting of 22.60 g (0.15 mol) of freshly prepared ethyl malonyl chloride⁴⁸, 39.10 g (0.15 mol) of distilled stannic chloride and 150 mL of dry nitromethane was then prepared and also stirred for 1 h at ambient temperature with protection from moisture. The previously prepared solution of 17a/SnCl₄ was then added slowly to the ethyl malonyl chloride solution to give an initially deep orange reaction mixture. After stirring an additional 48h at ambient temperature the resulting dark orange-red solution was slowly poured into a blender containing 300 g of crushed ice and 180 mL of CHCl₃. A light tan emulsion formed as the blending was continued until all of the ice had melted. The thick suspension was then filtered, washed with ice cold water, and dried to yield 9.72 g of 21 as a tan solid. Crystallization of this material, with hot filtration, from 100 mL of 50% aqueous EtOH then yielded 8.30 g (42%) of 21 as colorless needles, m. p. 224—226 °C, Rf 0.60 (silica gel, 10% EtOH/CHCl₃). Mass spectrum, *m/e* 198 (M⁺); IR (KBr) 1725 cm⁻¹; NMR (DMSO-d₆) δ 1.18 (t, 3H, *J* = 7.0 Hz), 3.75 (s, 2H), 4.15 (q, 2H, *J* = 7.0 Hz), 7.75 (s, 1H), 11.17 (br s, 1H), 11.42 (br s, 1H); ¹³C NMR (DMSO-d₆) 13.9, 43.0, 60.6, 123.2, 123.6, 154.0, 167.6, 185.1.

Anal. C₈H₁₀N₂O₄S Calc'd: C 48.88; H 5.09; N 14.14.

Found: C 48.82; H 5.30; N 14.16.

4-(2-Carbethoxyethyl-1-spiro-2'-[1',3'-dithianyl])-4-imidazolin-2-one (22)

A solution of 7.50 g (0.038 mol) of ester 21 in 40 mL of glacial acetic acid/20 mL of freshly distilled BF₃·Et₂O was treated with 15 mL (0.15 mol) of 1,3-propanedithiol. The resulting yellow solution was then stirred at ambient temperature in a stoppered 200 mL round bottom flask for 36 h before concentrating, at reduced pressure, to a viscous gold oil. Crystallization of this material from 50 mL EtOH/25 mL H₂O afforded 9.9 g (91%) of 22 of m. p. 210—214 °C. Recrystallization from absolute EtOH then gave 8.7 g (80%) of analytically pure 22 as colorless crystals, m. p. 225—226 °C, Rf 0.70 (silica gel, 10% MeOH/CHCl₃). Mass spectrum, *m/e* 288 (M⁺); IR (KBr) 1735 and 1704 cm⁻¹; NMR (DMSO-d₆) δ 1.10 (t, 3H, *J* = 7.0 Hz), 1.85 (m, 2H), 2.80 (m, 4H), 3.05 (s, 2H), 3.95 (q, 2H, *J* = 7.0 Hz), 6.30 (s, 1H), 9.80 (br s, 1H, exchanges with D₂O), 9.88 (br s, 1H, exchanges with D₂O); ¹³C NMR (DMSO-d₆) 13.9, 24.1, 26.8, 45.3, 46.8, 59.9, 108.8, 121.2, 154.5, 167.1.

Anal. C₁₁H₁₆N₂O₃S₂ calc'd: C 45.81; H 5.59; N 9.71 S 22.24.

found: C 45.52; H 5.82; N 9.51; S 22.48.

4-(2-Carboxyl-1-spiro-2'-[1',3'-dithianyl])-4-imidazolin-2-one (23)

A suspension of 10.0 g (0.035 mol) of dithiane ester 22 in 300 mL of 5 M KOH (9.8 g 85% KOH) was stirred vigorously at ambient temperature for a period of 1.5 h to give a nearly homogeneous solution. Insoluble materials were then removed by filtration, through Celite® and the clear filtrate was acidified to pH 3 by slow addition of 6 N HCl. The resulting suspension was then cooled, and the collected 23 crystallized from 50% aqueous EtOH to afford 7.48 g (82%) of analytically pure 23 as colorless needles, m. p. 242—243 °C. Mass spectrum, *m/e* 260 (M⁺); IR (KBr) 3300, 1707, and 1688 cm⁻¹; NMR (DMS-d₆) δ 1.80 (m, 2H), 2.80 (m, 4H), 2.95 (s, 2H), 6.25 (s, 1H), 9.60 (br s, 2H), —CO₂H not observed; ¹³C NMR (DMSO-d₆) 24.1, 26.8, 45.3, 46.7, 108.8, 121.6, 154.5, 168.8.

Anal. C₉H₁₂N₂O₃S₂ calc'd: C 41.24; H 4.86; N 10.44; S 24.88.

, found: C 41.52; H 4.65; N 10.78; S 24.63.

5-Oxo-7-spiro-2'-(1',3'-dithianyl)pyrrolo(1,2-c)imidazol-3-one (24)

A suspension of 5.2 g (0.02 mol) of acid 23 in 200 mL of dry benzene was treated with 12.6 g (0.06 mol) of trifluoroacetic anhydride. The resulting mixture was stirred at ambient temperature, with protection from moisture, for a period of 0.5 h, and was then heated under reflux for 3 h to give a homogeneous solution. After concentration under reduced pressure, and azeotropic removal of trifluoroacetic acid with 2 × 200 ml portions of benzene, the orange-yellow residue was crystallized rapidly from 600 mL of hot absolute EtOH to yield 4.43 g (92%) of imide 24 as a yellow crystalline solid, m. p. 232—233 °C, Rf 0.70 (silica gel,

10% EtOH/CHCl₃). Mass spectrum, m/e 242 (M^+); IR (KBr) 1790, 1765, and 1694 cm^{-1} ; NMR (CDCl₃) δ 2.05 (m, 2H), 3.07 (m, 4H), 3.25 (s, 2H), 6.55 (d, 1H, $J = 2$ Hz), NH not observed; ¹³C NMR (DMSO-d₆) 24.1, 27.2, 45.1, 46.8, 107.6, 124.0, 154.6, 167.2.

Anal. C₉H₁₀N₂O₂S₂: calc'd: C 44.60; H 4.16; N 11.56; S 26.46.
found: C 44.80; H 4.41; N 11.64; S 26.06.

4-(2- β -N-Benzylhydrazidoethyl-1-spiro-2'-[1',3'-dithianyl])-4-imidazolin-2-one (11a)

A suspension of 2.42 g (10.0 mmol) of imide 24 in 200 mL of dry THF was treated with 2.44 g (20.0 mmol) of freshly prepared benzyl hydrazine⁴⁹ and the resulting reaction mixture was stirred vigorously at ambient temperature for 48 h. During this period a thick white precipitate formed which was collected and washed thoroughly with EtOH. Crystallization of this material from 120 mL of hot *N,N*-dimethylacetamide (120–130 °C) then afforded 2.70 g (74%) of benzylhydrazide 11a as an amorphous white solid, m.p. 258–259 °C, *R_f* 0.40 (silica gel, 10% EtOH/CHCl₃). Mass spectrum, m/e 364 (M^+); IR (KBr) 2900–3400 (NH), 1691 (C=O), 1658 (C=O), 750, and 700 (monosubstituted Ph) cm^{-1} ; NMR (DMSO-d₆) δ 1.85 (m, 2H), 2.80 (m, 4H), 2.93 (s, 2H), 3.85 (s, 2H), 5.20 (br s, 1H), 6.30 (s, 1H), 7.35 (s, 5H), 9.35 (br s, 1H), 9.80 (br s, 2H); ¹³C NMR (DMSO-d₆) 24.2, 26.8, 44.2, 46.9, 54.5, 108.4, 122.1, 126.9, 128.1, 128.6, 138.6, 154.3, 165.9.

Anal. C₁₆H₂₀N₄O₂S₂: calc'd: C 52.72; H 5.53; N 15.37.
found: C 52.53; H 5.71; N 15.09.

4-(2- β -N-Methylhydrazidoethyl-1-spiro-2'-[1',3'-dithianyl])-4-imidazolin-2-one (11b)

A suspension of 242 mg (1.0 mmol) of imide 24 and 3 mmol of 1-*t*-butoxycarbonyl-1-methylhydrazine⁵⁰ in 10 mL of dry THF was stirred under reflux, with exclusion of moisture, for a period of 72 h. The resulting dark yellow solution was the concentrated under reduced pressure and the residue crystallized from EtOH/Et₂O to provide 320 mg (82%) of the *t*-butoxycarbonyl derivative of 11b, m.p. 189–190 °C, NMR (CDCl₃) δ 1.42 (s, 9H), 2.62 (m, 2H), 2.81 (m, 4H), 3.01 (s, 3H), 6.43 (s, 1H), 9.87 (br s, 2H), exchanges with D₂O), plus others. This material was used directly for conversion to 11b.

Thus, a solution of 235 mg (0.61 mmol) of the *t*-butoxycarbonyl derivative thus obtained in 1.5 mL of trifluoroacetic acid was stirred at ambient temperature for a period of 1 h, during which time a vigorous evolution of CO₂ occurred. The resulting orange solution was then concentrated to dryness at 0.5 mm and the residue crystallized from EtOH/Et₂O to afford 217 mg (99%) of 11b as a white amorphous solid which decomposed over a broad range beginning at 173 °C. NMR (CDCl₃) δ 1.82 (m, 2H), 2.54 (m, 2H), 2.96 (m, 4H), 2.97 (s, 3H), 6.42 (s, 1H), 9.58 (br s, 1H, exchanges with D₂O), 9.95 (br s, 1H, exchanges with D₂O), 10.01 (br s, 1H, exchanges with D₂O).

4-(Hydrazidoethyl-1-spiro-2'-[1',3'-dithianyl])-4-imidazolin-2-one (11c)

This material was prepared from imide 24 and hydrazine hydrate by an identical procedure as that described above for hydrazide 11a to afford a 98% yield of 11c as an amorphous white solid, m.p. 219–220 °C, characterized as its benzylhydrazone derivative: m.p. 245–246 °C, *R_f* 0.20 (silica gel, 5% MeOH/CHCl₃); Mass spectrum, m/e 362 (M^+); IR (KBr) 1625 cm^{-1} ; NMR (DMSO-d₆) δ 1.90 (m, 2H), 2.80 (m, 4H), 3.00 (s, 2H), 6.30 (s, 1H), 7.55 (m, 5H), 8.00 (s, 1H), 8.15 (s, 1H), 9.80 (br s, 2H, exchanges with D₂O).

Anal. C₁₆H₁₈N₄O₂S₂ · ½H₂O: calc'd: C 51.73; H 5.16; N 15.08.
found: C 51.99; H 5.26; N 15.45.

(3'α, 4'β, 9'aR)-(±)-Octahydro-2',7'-dioxo-4'-phenyl-5'-(phenylmethyl)spiro [1,3-dithiane-2,9'-[9H]imidazo[4,5-c]pyrrolo[1,2-b]pyrazole] (25a-1)*

A suspension of 1.82 g (5.0 mmol) of hydrazide **11a** and 1.14 g (6.3 mmol, 1.25 equiv) of benzaldehyde diethylacetal in 20 mL of dry DMF was treated with a catalytic amount (2–3 mg) of *p*-TsOH · H₂O and the resulting mixture was heated with stirring and protection from moisture in an oil bath maintained at 80 °C. Solution (bright yellow) was complete within 1 h, and after a total of 5 h the reaction was concentrated at 0.1 mm/30 °C to give an orange gum. Chromatography of this material on silica gel using 2% EtOH/CHCl₃ as eluent then afforded 1.88 g (83%) of adduct **25a-1** as colorless needles, m. p. 258–259 °C (from *n*-PrOH), *R*_f 0.55 (silica gel, 5% EtOH/CHCl₃). Alternatively, direct crystallization of the crude material as obtained above from *n*-PrOH gave 1.75 g (77%) of slightly less pure adduct **25a-1**. Mass spectrum, *m/e* 452 (*M*⁺); IR(KBr) 1710 cm⁻¹ (lactam C=O); NMR(CDCl₃) δ 2.02 (m, 2H), 2.82 (d of AB, 1H, *J* = 17.4 Hz), 2.88 (m, 4H), 2.94 (d of AB, 1H, *J* = 17.4 Hz), 3.98 (d of AB, 1H, *J* = 14.1 Hz, NCH₂Ph), 4.33 (d, 1H, *J* = 5.1 Hz), 4.58 (br s, 1H, exchanges with D₂O), 4.88 (d of AB, 1H, *J* = 14.1 Hz, NCH₂Ph), 4.99 (d, 1H, *J* = 5.1 Hz), 5.90 (br s, 1H, exchanges with D₂O), 7.23–7.44 (m, 10H, ArH).

Anal. C₂₃H₂₄N₄O₂S₂: calc'd.: C 61.04; H 5.34; N 12.38.
found: C 61.28; H 5.55; N 12.73.

Similarly Prepared Were the Following (Compound, Heating Time, % Yield, Physical and Spectral Data)

25a-2, 2 h, 90%, colorless needles from CH₃CN, m. p. 204–205 °C, *R*_f 0.50 (silica gel, 7% EtOH/CHCl₃); Mass spectrum, *m/e* 482 (*M*⁺); IR(KBr) 1700 cm⁻¹ (lactam C=O); NMR(CDCl₃) δ 2.05 (m, 2H), 2.85 (m, 4H), 2.87 (d of AB, 1H, *J* = 17.2 Hz), 2.95 (d of AB, 1H, *J* = 17.2 Hz), 3.80 (s, 3H), 3.98 (d of AB, 1H, *J* = 13.9 Hz, NCH₂Ph), 4.29 (d, 1H, *J* = 5.1 Hz), 4.76 (d of AB, 1H, *J* = 13.9 Hz, NCH₂Ph), 4.91 (d, 1H, *J* = 1 Hz, exchanges with D₂O), 4.95 (dd, 1H, *J* = 5.1, 1.0 Hz), 6.27 (br s, 1H, exchanges with D₂O), 6.91–7.41 (m, 9H, ArH).

Anal. C₂₄H₂₆N₄O₃S₂: calc'd.: C 59.73; H 5.43; N 11.61.
found: C 59.92; H 5.67; N 11.32.

25a-3, 2 h, 91%, colorless needles from CH₃CN/Et₂O, m. p. 223–224 °C, *R*_f 0.60 (silica gel, 7% EtOH/CHCl₃); Mass spectrum, *m/e* 466 (*M*⁺); IR(KBr) 1700 cm⁻¹ (lactam C=O); NMR(CDCl₃) δ 2.05 (m, 2H), 2.35 (s, 3H), 2.84 (d of AB, 1H, *J* = 17.2 Hz), 2.88 (m, 4H), 2.96 (d of AB, 1H, *J* = 17.2 Hz), 3.99 (d of AB, 1H, *J* = 13.9 Hz, NCH₂Ph), 4.32 (d, 1H, *J* = 5.1 Hz), 4.78 (d of AB, 1H, *J* = 13.9 Hz, NCH₂Ph), 4.86 (s, 1H, exchanges with D₂O), 4.97 (d, 1H, *J* = 5.1 Hz), 6.26 (br s, 1H, exchanges with D₂O), 7.20–7.42 (m, 9H, ArH).

Anal. C₂₄H₂₆N₄O₃S₂: calc'd.: C 61.78; H 5.62; N 12.01.
found: C 62.02; H 5.81; N 12.31.

25a-4, 28 h, 52%, yellow needles from DMF/EtOH, m. p. 297–298 °C, *R*_f 0.40 (silica gel, 7% EtOH/CHCl₃); Mass spectrum, *m/e* 497 (*M*⁺); IR(KBr) 1710 cm⁻¹ (lactam C=O); NMR(DMSO-*d*₆) δ 1.74 (m, 1H), 2.08 (m, 1H), 2.92 (m, 4H), 3.16 (d of AB, 1H, *J* = 15.7 Hz), 3.24 (d of AB, 1H, *J* = 15.7 Hz), 3.86 (d of AB, 1H, *J* = 14.3 Hz, NCH₂Ph), 4.40 (d of AB, 1H), *J* = 14.3 Hz, NCH₂Ph), 4.46 (d, 1H), *J* = 4.8 Hz), 4.92 (dd, 1H, *J* = 4.8, 2.9 Hz), 7.03 (d, 1H, *J* = 2.9 Hz, exchanges with D₂O), 7.18–8.25 (m, 9H, ArH), 8.27 (br s, 1H, exchanges with D₂O).

Exact mass (M⁺) C₂₃H₂₃N₅O₄S₂: calc'd.: 497.1191.
found: 497.1199.

25a-5, 2 h, 68%, colorless needles from *n*-PrOH/Et₂O, m. p. 250–251 °C, *R*_f 0.50 (silica gel, 10% EtOH/CHCl₃); Mass spectrum, *m/e* 442 (*M*⁺); IR(KBr) 1700 cm⁻¹ (lactam C=O); NMR(CDCl₃) δ 2.05 (m, 2H), 2.87 (m, 4H), 2.99 (d of AB, 1H, *J* = 16.5 Hz), 3.05 (d of AB, 1H, *J* = 16.5 Hz), 4.01 (d of AB, 1H, *J* = 13.2 Hz, NCH₂Ph), 4.09 (d of AB, 1H, *J* = 13.2 Hz, NCH₂Ph), 4.65 (d, 1H, *J* = 5.1 Hz), 5.13 (d, 1H, *J* = 5.1 Hz), 5.86 (br s, 1H, exchanges with D₂O), 6.42 (A of ABX, 1H, Furyl), 6.61 (B of

ABX, 1H, Furyl), 6.83 (br s, 1H, exchanges with D₂O), 7.20–7.37 (m, 5H, ArH), 7.50 (X of ABX, 1H, Furyl).

Anal. C₂₁H₂₂N₄O₃S₂: calc'd.: C 56.99; H 5.01; N 12.66.
found: C 56.86; H 5.27; N 12.41.

25a-6, 3 h, 80%, colorless needles from CH₃CN/Et₂O, m. p. 225–226 °C, *R*_f 0.50 (silica gel, 10% EtOH/CHCl₃); Mass spectrum, *m/e* 458 (M⁺); IR(KBr) 1700 cm⁻¹ (lactam C=O); NMR(CDCl₃) δ 2.05 (m, 2H), 2.84 (m, 4H), 2.96 (s, 2H), 4.03 (d of AB, 1H, *J* = 13.2 Hz, NCH₂Ph), 4.41 (d of AB, 1H, *J* = 13.2 Hz, NCH₂Ph), 4.78 (d, 1H, *J* = 4.8 Hz), 5.07 (dd, 1H, *J* = 4.8, 2.0 Hz), 5.74 (d, 1H, *J* = 2.0 Hz, exchanges with D₂O), 6.68 (br s, 1H, exchanges with D₂O), 7.07 (A of ABC, 1H, Thienyl), 7.22–7.39 (m, 5H, ArH), 7.31 (B of ABC, 1H, Thienyl), 7.38 (C of ABC, 1H, Thienyl).

Anal. C₂₁H₂₂N₄O₃S₂: calc'd.: C 54.99; H 4.84; N 12.22.
found: C 54.79; H 5.07; N 12.27.

25a-7, 5 h, 64%, colorless needles from *n*-PrOH/Et₂O, m. p. 246–247 °C, *R*_f 0.50 (silica gel, 10% EtOH/CHCl₃); Mass spectrum, *m/e* 376 (M⁺); IR(KBr) 1710 cm⁻¹ (lactam C=O); NMR(CDCl₃) δ 2.05 (m, 2H), 2.90 (m, 4H), 3.02 (d of AB, 1H, *J* = 16.5 Hz), 3.10 (d of AB, 1H, *J* = 16.5 Hz), 3.30 (m, 2H), 4.16 (d of AB, 1H, *J* = 12.3 Hz, NCH₂Ph), 4.29 (d of AB, 1H, *J* = 12.3 Hz, NCH₂Ph), 5.00 (m, 1H), 5.27 (br s, 1H, exchanges with D₂O), 6.08 (br s, 1H, exchanges with D₂O), 7.26–7.46 (m, 5H, ArH).

Anal. C₁₇H₂₀N₄O₂S₂: calc'd.: C 54.25; H 5.35; N 14.88.
found: C 54.50; H 5.48; N 15.04.

(3'*α*, 4'*β*, 9'*aR**)-(±)-Octahydro-2',7'-dioxo-4'-(phenylmethyl)5'-(phenylmethyl) spiro[1,3-dithiane-2,9'-[9H]imidazo[4,5-*c*]pyrrolo[1,2-*b*]pyrazole] (25a-8)

A suspension of 182 mg (0.5 mmol) of hydrazide **11a**, 300 mg (2.5 mmol) of phenylacetaldehyde, and 485 mg (2.5 mmol) of phenylacetaldehyde diethyl acetal in 20 mL of dry EtOH was treated with a catalytic amount (2–3 mg) of TsOH · H₂O and the resulting mixture was heated at reflux with stirring and protection from moisture for a period of 72 h. The resulting solution was then concentrated under reduced pressure to a bright yellow oil which was chromatographed on silica gel using 3% EtOH/CHCl₃ as eluent to give 40 mg (17%) of adduct **25a-8**. The analytical sample crystallized from MeOH/Et₂O in the form of colorless needles, m. p. 275–276 °C, *R*_f 0.50 (silica gel, 5% EtOH/CHCl₃). Mass spectrum, *m/e* 466 (M⁺); IR(KBr) 1710 cm⁻¹ (lactam C=O); NMR(CDCl₃) δ 1.83 (m, 1H), 2.03 (m, 1H), 2.82 (m, 4H), 2.92 (d of AB, 1H, *J* = 16.3 Hz), 3.05 (d of AB, 1H, *J* = 16.3 Hz), 3.06 (dd, 1H, *J* = 16.2, 3.0 Hz, CH₂Ph), 3.36 (dd, 1H, *J* = 16.2, 5.5 Hz, CH₂Ph), 3.87 (ddd, 1H, *J* = 5.5, 5.1, 3.0 Hz, H₆), 4.10 (d of AB, 1H, *J* = 12.3 Hz, NCH₂Ph), 4.31 (d of AB, 1H, *J* = 12.3 Hz, NCH₂Ph), 4.63 (dd, 1H, *J* = 5.1, 2.9 Hz, H₅), 5.21 (d, 1H, *J* = 2.9 Hz, exchanges with D₂O), 6.35 (br s, 1H, exchanges with D₂O), 7.25–7.47 (m, 10H, ArH).

Anal. C₂₄H₂₆N₄O₂S₂: calc'd.: C 61.78; H 5.62; N 12.01.
found: C 61.73; H 5.82; N 12.23.

Benzylloxyethylidene Hydrazone (26)

A suspension of 2.43 g (8.88 mmol) of hydrazide **11c** and 1.46 g (9.75 mmol) of benzylloxyacetaldehyde in 170 mL of 90% EtOH/H₂O was heated at reflux for a period of 3 h with vigorous stirring, and the resulting solution was then cooled briefly in an ice bath to give 3.19 g (89%) of **26** as colorless needles, m. p. 195–196 °C, *R*_f 0.40 (silica gel, 10% MeOH/CHCl₃). Mass spectrum, *m/e* 406 (M⁺); IR(KBr) 1650 cm⁻¹; NMR(DMSO-*d*₆) δ 1.85 (m, 2H), 2.80 (m, 4H), 2.90 (s, 2H), 4.15 (d, 2H, *J* = 5.0 Hz), 4.56 (s, 2H), 6.25 (s, 1H), 7.35 (s, 5H), 9.85 (br s, 2H, exchanges with D₂O), 11.25 (d, 1H, *J* = 5.0 Hz).

2-Picolylloxyethylidene Hydrazone (34)

A suspension of 1.25 g (4.56 mmol) of hydrazide **11c**, 3.45 g (22.8 mmol) of 2-pyridyl acetaldehyde, and 40 mg of TsOH · H₂O in 50 mL of 90% EtOH/H₂O was heated under reflux for a period of 1 h with vigorous stirring and then concentrated

under reduced pressure to an orange gum. Crystallization of this material from CH_3CN afforded 1.25 g (68%) of **34** as colorless crystals, m. p. 188–191 °C, *Rf* 0.28 (silica gel, 25% $\text{MeOH}/\text{CHCl}_3$). Mass spectrum, *m/e* 407 (M^+); IR(KBr) 1660 cm^{-1} ; NMR($\text{DMSO}-d_6 + \text{D}_2\text{O}$) δ 1.82 (m, 2H), 2.76 (m, 4H), 3.36 (s, 2H), 4.18 (s, 2H), 4.59 (s, 2H), 6.23 (s, 1H), 7.24–8.02 (m, 4H), 8.57 (s, 1H).

Anal. $\text{C}_{17}\text{H}_{21}\text{N}_5\text{O}_3\text{S}_2$: calc'd.: C 50.11; H 5.19; N 17.19.
found: C 50.14; H 5.04; N 17.12.

Tricyclic Adduct (33)

A freshly prepared solution of 1.17 g (7.2 mmol) of anhydrous FeCl_3 in 50 mL of dry CH_3CN was added in one portion to a well stirred suspension of 580 mg (1.43 mmol) of hydrazone **26** in 100 mL of dry CH_3CN under N_2 , and the resulting mixture was stirred at ambient temperature for 1 h. Ethylenediamine (2.22 g) was then added and after stirring for an additional 15 min the mixture was filtered through Celite®, washed thoroughly with CH_3CN , and concentrated to dryness. Chromatography on silica gel using 2% MeOH/EtOAc as eluent then afforded 50 mg of tricyclic adduct **33** as colorless crystals (from $\text{CH}_3\text{CN}/\text{Et}_2\text{O}$), m. p. 169–170 °C, *Rf* 0.62 (silica gel, 10% $\text{MeOH}/\text{CHCl}_3$). Mass spectrum, *m/e* 422 (M^+); NMR(CDCl_3) δ 1.82 (m, 2H), 2.14 (m, 2H), 2.56 (m, 2H), 2.55 (d, 1H, $J = 18.0$ Hz), 2.85 (d, 1H, $J = 18.0$ Hz), 3.46 (d, 1H, $J = 12.0$ Hz), 3.59 (d, 1H, $J = 11.2$ Hz), 3.74 (d, 1H, $J = 12.0$ Hz), 4.46–4.74 (m, 3H), 4.85 (s, 1H), 5.03 (br s, 1H, exchanges with D_2O), 6.18 (br s, 1H, exchanges with D_2O), 7.30 (m, 5H). ^{13}C NMR(CDCl_3) 21.4, 26.2, 41.8, 45.8, 66.2, 71.8, 72.3, 79.1, 88.2, 126.9, 127.4, 127.5, 136.2, C=O's not observed. X-ray analysis confirmed the proposed structure.⁵¹

4-(2-Hydrazidoethyl-[2-bromoethyl]benzylidene-1-spiro-2'-[1',3'-dithianyl])-4-imidazolin-2-one (38)

A suspension of 274 mg (1.0 mmol) of hydrazide **11c** and 426 mg (2.0 mmol) of *o*-(2-bromoethyl)benzaldehyde^{19,20} in 20 mL of absolute EtOH was treated with 10 mg of $\text{TsOH} \cdot \text{H}_2\text{O}$, and the resulting mixture was heated with stirring under reflux for 5 min before cooling and concentrating to dryness under reduced pressure. The material thus obtained was triturated with cold CHCl_3 and recrystallized from EtOH to afford 270 mg (58%) of **38** as colorless crystals, *Rf* 0.30 (silica gel, 10% $\text{MeOH}/\text{CHCl}_3$). Mass spectrum, *m/e* 469 (M^+); NMR($\text{DMSO}-d_6$) δ 1.80 (m, 2H), 2.30–3.40 (m, 6H), 2.90 (d, 1H, $J = 16.8$ Hz), 3.14 (d, 1H, $J = 16.8$ Hz), 3.76 (m, 4H), 4.07 (br s, 1H, exchanges with D_2O), 4.22 (br s, 1H, exchanges with D_2O), 6.80–7.38 (m, 4H), 7.76 (s, 1H).

Tetracyclic Adduct (39)

A solution of 220 mg (0.47 mmol) of hydrazone **38** in 10 mL of dry DMF was stirred at 80 °C for 2.5 h under N_2 before concentrating under reduced pressure to give a dark yellow residue. Chromatography of this material on silica gel with 4% $\text{MeOH}/\text{CHCl}_3$ as eluent then afforded 110 mg (61%) of adduct **39** as a colorless crystalline solid, m. p. 271–272 °C, *Rf* 0.48 (silica gel, 10% $\text{MeOH}/\text{CHCl}_3$). Mass spectrum, *m/e* 388 (M^+); NMR(CDCl_3) δ 1.90 (m, 2H), 2.69 (m, 4H), 2.87 (m, 2H), 2.90 (d, 1H, $J = 16.8$ Hz), 3.04 (d, 1H, $J = 16.8$ Hz), 3.41 (m, 1H), 3.72 (m, 1H), 4.34 (d, 1H, $J = 6.4$ Hz), 4.64 (d, 1H, $J = 6.4$ Hz), 5.73 (br s, 1H, exchanges with D_2O), 6.01 (br s, 1H, exchanges with D_2O), 7.18 (m, 4H).

Anal. $\text{C}_{18}\text{H}_{20}\text{N}_4\text{O}_2\text{S}_2$: calc'd.: C 55.65; H 5.19; N 14.42.
found: C 56.15; H 5.18; N 14.20.

Also isolated was a trace amount (7%) of adduct epimeric at C-6: *Rf* 0.55 (silica gel, 10% $\text{MeOH}/\text{CHCl}_3$), m. p. 205–206 °C. Mass spectrum, *m/e* 388 (M^+); NMR(CDCl_3) δ 1.84–2.23 (m, 2H), 2.65–3.42 (m, 10H), 4.62 (d, 1H, $J = 4.8$ Hz), 4.71 (br s, 1H, exchanges with D_2O), 5.16 (d, 1H, $J = 4.8$ Hz), 6.96 (br s, 1H, exchanges with D_2O), 7.06–7.30 (m, 4H).

Anal. $\text{C}_{18}\text{H}_{20}\text{N}_4\text{O}_2\text{S}_2$: calc'd.: C 55.65; H 5.19; N 14.42.
found: C 56.26; H 5.21; N 14.14.

(3' α , 4' α , 9'aR*)-Octahydro-2',7'-dioxo-5'-(phenylmethyl)spiro[1,3-dithiane-2,9'-[9H]imidazo[4,5-c]pyrrolo[1,2-b]pyrazole-4'-carboxylic Acid
(\pm)-Methyl Ester (43b)

A solution of 43.5 mg (0.1 mmol) of β -ester **43a**⁴⁵ in 5 mL of anhydrous MeOH was treated with 11 mg (0.2 mmol) of NaOMe in one portion with vigorous stirring at ambient temperature. After a period of 1 h, 19 mg (0.5 mmol) of NaBH₄ was added and stirring was continued for an additional 5 min before diluting with 10 mL of pH 7 buffer and extracting with 3 \times 10 mL of CH₂Cl₂. The combined organic layers were washed with 20 mL of saturated brine, dried over Na₂SO₄, and concentrated to give a slightly off-white solid. Crystallization of this material from *i*-PrOH then afforded 30.0 mg (62.1%) of **43b** as colorless crystals, m. p. 206—208 °C, *R*_f 0.50 (silica gel, 10% MeOH/CHCl₃). Mass spectrum, *m/e* 434 (M⁺); NMR(CDCl₃) δ 2.02 (m, 2H), 2.83 (m, 4H), 2.89 (d, 1H, *J* = 16.4 Hz), 2.98 (d, 1H, *J* = 16.4 Hz), 3.70 (s, 3H), 3.99 (d, 1H, *J* = 1.6 Hz), 4.27 (d, 1H, *J* = 12.8 Hz), 4.43 (d, 1H, *J* = 12.8 Hz), 5.30 (dd, 1H, *J* = 1.6, 2.4 Hz, collapsing to a d, *J* = 1.6 Hz upon addition of D₂O), 5.84 (br s, 1H, exchanges with D₂O), 6.62 (br s, 1H, exchanges with D₂O), 7.23—7.57 (m, 5H).

Spirocyclic Lactam (47)

A solution of 250 mg (0.62 mmol) of pyrazole lactam **44** in 50 mL of freshly distilled (Na) liquid NH₃ at -78 °C was treated with 57 mg (4.7 mmol) of Na in 4 portions at 15 min intervals. After the last aliquot of Na had been added, the resulting deep blue reaction mixture was quenched with an excess of solid NH₄Cl at -78 °C and the NH₃ was allowed to evaporate under a stream of dry N₂. The residue thus obtained was extracted with 2 \times 25 mL of hot absolute EtOH, filtered while hot, concentrated and cooled to afford 108 mg (43%) of **47** as a white amorphous solid m. p. 145—150 °C, *R*_f 0.28 (silica gel, 10% MeOH/CHCl₃). Mass spectrum, *m/e* 408 (M⁺); IR(KBr) 1687, 1645 cm⁻¹; NMR(CDCl₃) δ 1.78—2.14 (m, 4H), 2.60—3.18 (m, 6H), 3.52—3.86 (m, 4H), 4.69 (d, 1H, *J* = 4.8 Hz), 6.61 (br s, 1H, exchanges with D₂O), 7.12—7.32 (m, 5H), 7.58 (br s, 1H, exchanges with D₂O), 8.74 (br s, 1H, exchanges with D₂O).

(3' α , 4' α , 9'aR*)-(\pm)-Octahydro-2'-oxo-4'-(hydroxymethyl)-5'-(methoxythio-carbonyl)spiro-[1,3-dithiane-2,9'-[9H]imidazo[4,5-c]pyrrolo[1,2-b]pyrazole] (50a)

This material was prepared in 73% yield by a procedure which was exactly analogous to that previously reported for **50d**.⁴⁵ *R*_f 0.55 (silica gel, 10% MeOH/CHCl₃); Mass spectrum, *m/e* 376 (M⁺); NMR(CDCl₃ + CD₃OD) δ 1.86 (m, 2H), 2.22 (m, 2H), 2.68 (m, 5H), 3.52 (m, 3H), 3.82 (s, 3H), 4.51 (m, 1H), 4.62 (br s, 1H).

(3' α , 4' α , 9'aR*)-(\pm)-Octahydro-2'-oxo-4'-(hydroxymethyl)-5'-(1-imidazothio-carbonyl)spiro-[1,3-dithiane-2,9'-[9H]imidazo[4,5-c]pyrrolo[1,2-b]pyrazole] (50c)

This material was prepared in 68% yield by a procedure which was exactly analogous to that previously reported for **50d**.⁴⁵ *R*_f 0.65 (silica gel, 20% MeOH/CHCl₃); Mass spectrum, *m/e* 412 (M⁺); NMR(CDCl₃ + CD₃OD) δ 1.91 (m, 2H), 2.31 (m, 2H), 2.73 (m, 4H), 2.94 (m, 1H), 3.24 (m, 1H), 3.84 (dd, 1H, *J* = 7.2, 11.0 Hz), 4.09 (dd, 1H, *J* = 3.2, 11.0 Hz), 4.66 (m, 1H), 4.70 (br s, 1H), 6.85 (s, 1H), 7.65 (s, 1H), 8.30 (s, 1H).

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POVZETEK

Azometiniminska pot do gvanidinov. Totalna sinteza (\pm) -saksitoksina.

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Azometinimini zlahka nastanejo pri reakciji med aldehyd acetali in hidrazidi karboksilnih kislin. Tovrstne reakcije potekajo najboljše v polarnih aprotičnih topilih, potrebna pa je tudi kislinska kataliza. Te spojine se nato s primerno funkcionaliziranimi hidrazidi pretvorijo v kondenzirane derivate pirazolidina. Kot sestavni del teh raziskav smo sintetizirali (\pm) -saksitoksin (7), spojino s paralitskim učinkom iz *Saxidomas giganteus*. Spojino smo sintetizirali na popolnoma stereospecifičen način v zaporedju reakcij, ki obsegajo sledeče ključne stopnje: a) intramolekularna 1,3-dipolarna cikloadicija azometinimina na 2-imidazolon; b) reduktivni razcep nastalega pirazolidinskega obroča s sledečim intramolekularnim aciliranjem; in c) končna pretvorba bis-psevdosečnine v zahtevano gvanidinsko funkcionalnost.