Reactions of 1,2-dehydropyrrolidin-5-one with 1,3-dienes. Synthesis of *dl*-gephyrotoxin 223AB[1]

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Evidence is presented that the regiospecific and often stereospecific pseudo-Diels–Alder reactions of 1,3-dienes with *N*-acyl immonium salts, derived from 5-ethoxy-2-pyrrolidinone, are stepwise reactions. 6,7-Dehydroindolizidinones, unsaturated lactam esters, and new indene and furan derivatives are described. A synthesis of *dl*-gephyrotoxin 223AB (indolizidine 223AB) from *trans*-1,3-heptadiene was achieved.

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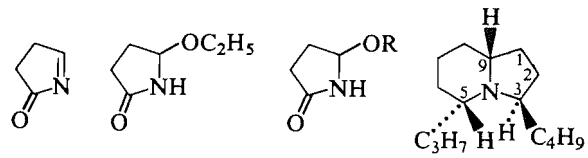
On présente des données qui suggèrent que les réactions de pseudo-Diels–Alder régiospécifiques et souvent stéréospécifiques dans dienes-1,3- avec les sels de *N*-acyl-immonium dérivés de l'éthoxy-5 pyrrolidinone-2 sont des réactions par étapes. On décrit des déhydro-6,7 indolizidinones, des esters lactames non-saturés ainsi que de nouveaux dérivés de l'indène et du furanne. On a réalisé une synthèse de la (*dl*)-géophyrotoxine 223AB (indolizidine 223AB) à partir de l'heptadiène-1,3-*trans*.

[Traduit par la revue]

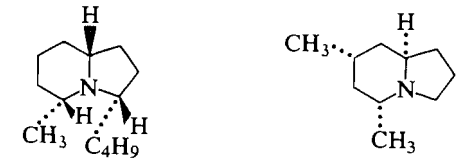
The apparent Diels–Alder reactions of *N*-acylimines or their salts have been the subject of much study (*la–f* and references therein). The initial objective of the present research was to define the mildest conditions under which intermolecular cycloaddition of simple *N*-acylimines to 1,3-dienes would take place, to obtain products from sensitive dienes. However, despite our success in isolating a steroidal *N*-acylimine with hydrogen on the imine carbon (aldimine) (2) it appeared that simpler *N*-acylaldimines such as **1** are too reactive to be readily isolated (see, however, ref. 3 for more stable electronegatively substituted examples).

We hence attempted to isolate crystalline salts of 1,2-dehydropyrrolidin-2-one **1** using the action of acetyl chloride or acetyl perchlorate on the readily available 5-ethoxy-2-pyrrolidinone **2** (4). Again this failed, although reactions showed that these salts were undoubtedly formed (see method D below).

As a consequence we changed our objective to reaction of salts of **1**, generated *in situ*, with simple 1,3-dienes, with the hope of stereo-controlled natural product synthesis. Preliminary studies using **3** (R = OCHO) or **3** (R = $OCOCH_3$), derived from **2**, as sources of the corresponding salts of **1**, using heat or triethylamine failed to give Diels–Alder adducts with 2,3-dimethylbutadiene. Success was achieved using **2** or **3** with a variety of Brönsted or Lewis acids. Low to good yields of 6,7-dehydroindolizidin-3-ones were obtained from a variety of 1,3-dienes, in addition to monocyclic addition products. In this way a precurser to *dl*-gephyrotoxin 223AB (**4**) (5) and possible precursers for monomorine (**5**) (6) and dendroprimine (**6**) (7) were generated.



1 **2** **3** **4**



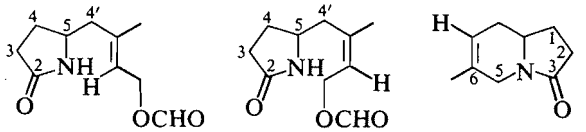
5 **6**

Results

The reaction of **2** with 1,3-dienes using methods A–E, but with some variation in relative concentrations (detailed in the Experimental), will be described under individual dienes. Method A used formic acid as solvent and catalyst; method B used methanesulfonic acid in dichloromethane; method C involved a stirred two-phase system of chloroform and 36% perchloric acid; method D used preformed salts of **1** in acetonitrile; method E was designed for use with acetoxydienes, using boron trifluoride etherate in acetic acid – acetic anhydride mixtures.

Three methods were used for reaction of **2** with isoprene. From reaction in formic acid (method A) an 80% yield of a mixture of two monocyclic formates was isolated. A negligible amount of the 6,7-dehydroindolizidinone **8** was produced. The ratio of the formates was roughly 2:1. That these had structures **7***a* and **7***b* followed from analysis, ^{1}H nmr spectra, and their nearly identical ^{13}C nmr spectra. Proton decoupling experiments showed that the vinyl hydrogen was coupled (J = 7 Hz) with the methylene carrying the formate group and that the 4′-methylene was only significantly coupled to H-5. Use of method C gave a 10% yield of 6,7-dehydro-6-methylindolizidin-3-one **8**. The complex mixture of monocyclic products was not separated. Using method D a 9% yield of **8** was isolated. The main products were monocyclic lactam dienes, which were not characterized.

The structure of **8** followed from its analysis, mass spectrum, and nmr spectra. The fact that the vinyl hydrogen and the 5-methylene of **8** were not coupled located the methyl group on C-6.



7*a* **7***b* **8**

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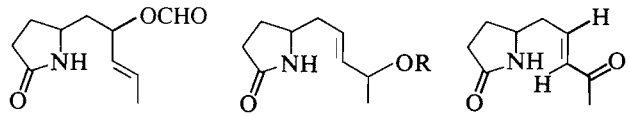
The action of formic acid on *trans*-piperylene (method A) gave a 57% yield of monocyclic formates and an 11% yield of a dehydroindolizidinone. The formate mixture was partially separated on silica, giving a 1.5% yield of a crystalline isomer, mp 102°C. This was assigned structure **9** on the basis of analysis and spectra. Its ^{13}C nmr spectrum showed the presence of a secondary formate (doublet at 72.3 ppm) and its ^{1}H nmr spectrum had signals for a vinyl methyl group (doublet at δ 1.7). The other formates were oils, but after hydrolysis and separation on silica gel these gave two crystalline lactam alcohols. One with mp 117°C (35% yield) had a three-hydrogen doublet at δ 1.22, while the other with mp 72°C (23% yield) had a comparable doublet at δ 1.24, clearly indicating with the other spectral evidence that they were stereoisomers with gross structure **10** (R = H). Oxidation of both gave the same conjugated ketone **11**



9 **10** **11**

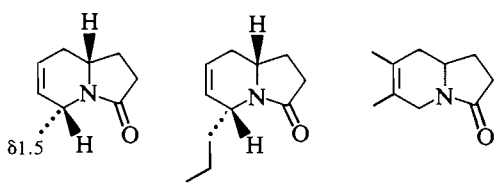
showing that the isomerism was at the secondary alcohol center. The *J* value of 16 Hz for the vinyl hydrogen signal at δ 6.17 showed that the double bond had the *E* configuration. Thus the major formates had structure **10** (R = CHO).

The dehydroindolizidinone was one isomer that from its ^{1}H and ^{13}C nmr spectra clearly had gross structure **12**. By analogy to the chemical shift of the 5-methyl group near the plane of the carbonyl in one of the isomers from 3-methyl-1,3-pentadiene (see below) we conclude that this had an equatorial methyl *anti* to the 9-hydrogen as shown in **12**. It is thus a promising precurser for the synthesis of the trail pheromone of the Pharoah ant, monomorine **5** (6), and its C-3 epimer.

Reaction of **3** with *E*-1,3-heptadiene in formic acid (Method A) gave a 15–20% yield of the desired dehydroindolizidinone **13**, and a mixture of formates that were not separated. The use of method B resulted in a 25% yield of **13**, the remainder being a mixture of lactam dienes that was not further characterized.

The dehydroindolizidinone was one isomer. By analogy to the product from piperylene we assumed that the configuration was that shown in **13** (plus its mirror image) with the 5 and 9 hydrogens *syn* to each other. This was precisely what was needed as a precurser of the proposed structure for gephyrotoxin 223AB (5*a*). As outlined below, the synthesis succeeded (see 5*b* for a preliminary account) and the stereochemistry was confirmed by X-ray analysis (8).

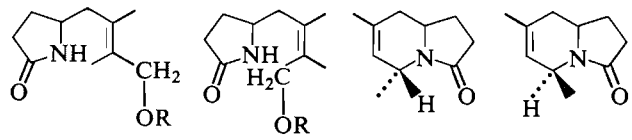
Modest yields of an indolizidinone were obtained from 2,3-dimethylbutadiene. Method A gave a 16% yield of the bicyclic lactam **14** and a 43% yield of a mixture of formates **15***a* and **15***b*



12 **13** **14**

(R = CHO). The ^{1}H nmr spectrum of the formates appeared to be that of one compound, but the ^{13}C nmr spectrum had 24 signals, showing the presence of two isomers. To our surprise, hydrolysis of the formates gave a sharp-melting lactam alcohol, mp 94–95°C. Again its ^{13}C nmr spectrum showed this to be a equimolar mixture of two very similar isomers. The ^{1}H nmr spectrum now showed the presence of two NH groups. We conclude that the isomeric alcohols were **15***a* and **15***b* (R = H) with NH signals at δ 7.7 and δ 8.5 respectively. A comparable yield of **14** (19%) was obtained using method B in benzene with *p*-toluenesulfonic acid.

trans-2-Methyl-1,3-pentadiene gave the highest yield (over 70%) of dehydroindolizidinone of any of the dienes studied, using method A. Although many other products were detected by tlc, only a small amount of formate ester was formed. The bicyclic product was a 1:1 mixture of isomers, separable on silica gel using a 1:1 acetone–hexane mixture. Their very similar ^{1}H and ^{13}C nmr spectra showed them to be stereoisomers with structures **16** and **17**. The assignment of configuration to

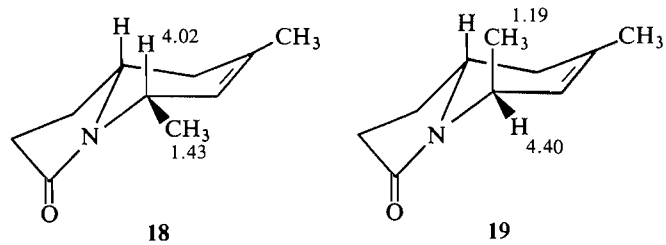


15*a* **15***b* **16** **17**

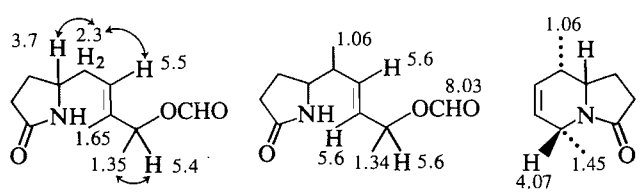
each was possible because the methyl group in the plane of the carbonyl was deshielded relative to that of it epimer (see **18** and **19**). The structure and stereochemistry of **19** make it a potentially valuable precurser of the orchid alkaloid dendroprimine **6** and its 7-epimer (7).

Reaction of *trans*-3-methyl-1,3-pentadiene with **2** following method A gave little, if any, bicyclic product. Monocyclic formates were produced in 75% yield. The ^{13}C nmr spectrum showed this to be a mixture consisting mainly of two closely related isomers. This and the ^{1}H nmr spectrum (see **20**) are consistent with this structure, with the isomers probably being the epimeric formates (see the piperylene case). Demonstrated couplings are indicated by double-headed arrows.

In reaction of *trans,trans*-2,4-hexadiene using method A, only minor amounts of bicyclic product and a 70% yield of monocyclic lactam formates were produced. The ^{13}C nmr spectrum of the formates showed this to contain two nearly identical stereoisomers. This and the ^{1}H nmr spectrum were consistent with structure **21**, with the isomers likely to be the epimeric formates. In contrast, the use of method C gave 20% of bicyclic product. Only one isomer was formed (^{13}C nmr). The chemical shift of the 5-methyl group and 5-hydrogen are close to those for



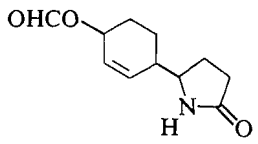
18 **19**



20 **21** **22**

18, hence we assign the stereochemistry shown in **22**, assuming retention of the original diene geometry.

When 1,3-cyclohexadiene reacted with **2** in formic acid following method A, both products of one-bond and of two-bond formation were observed. The one-bond products (42%) were a



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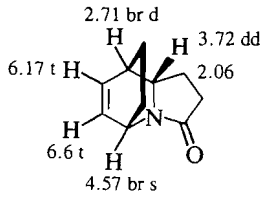

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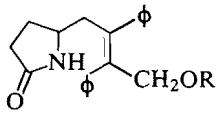
mixture of four isomeric formates. The spectra of the mixture were consistent with stereoisomers of structure **23**. In contrast, the two-bond product (40%) gave a single set of ^{13}C nmr signals, hence it was most probably one isomer. We assign structure and stereochemistry shown in **24** to it on the basis of analysis, spectra, and arguments based on maximum orbital overlap in the transition state for cyclization (see Discussion).

No dehydroindolizidinone was detected when 2,3-diphenyl-1,3-butadiene was treated with **2** in formic acid when method A was used. Instead the major products were a mixture of lactam formates and an indene derivative. The formates were hydrolysed, then the mixture separated in silica gel, giving a hydroxy lactam, mp 177°C (24%), and a second, mp 196°C (4%). The former had an uv spectrum (λ_{max} 234 nm, ε 11 800), analysis, and ^1H and ^{13}C nmr spectra consistent with structure **25**. Although the minor alcohol analysed for an isomer of **25**, its uv spectrum (λ_{max} 252 nm, ε 8440) and ^1H nmr signals were unusual. No ^{13}C nmr spectrum was obtained. Structure **26** seems a reasonable possibility, with the two vinyl hydrogens resonating at δ 4.59.



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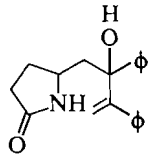

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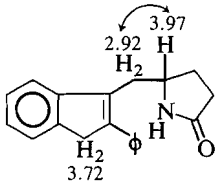
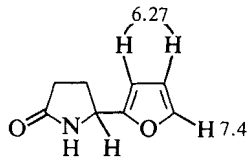


27

The most interesting product (14%) was assigned the substituted indene structure **27** on the basis of analysis, its uv spectrum (λ_{max} 289 nm, ε 14 800), and its ^1H nmr spectra and the coupling indicated by the double-headed arrow. The presence of five singlets between 134 and 145.8 ppm and eight doublets between 119.4 and 128.6 ppm in its ^{13}C nmr spectrum confirmed this structure.

The use of method C converted 2,3-diphenylbutadiene into a mixture of coupling products, which seemed to be dienes corresponding to proton elimination from original allylic cations.

As would be expected if the reaction were electrophilic attack by the *N*-acyl immonium ion from **1**, methods C and D on furan gave the 2-substituted derivative **28**, mp 82–83°C. The use of $Cu(BF_4)_2$ as catalyst in chloroform and **2** as reagent gave **28** and the product **29** of substitution on the two α positions. The simplicity of its ^1H nmr spectrum is suggestive of a *syn* relationship of the pyrrolidinone rings.



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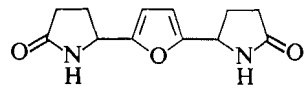
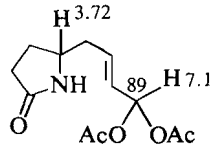


29

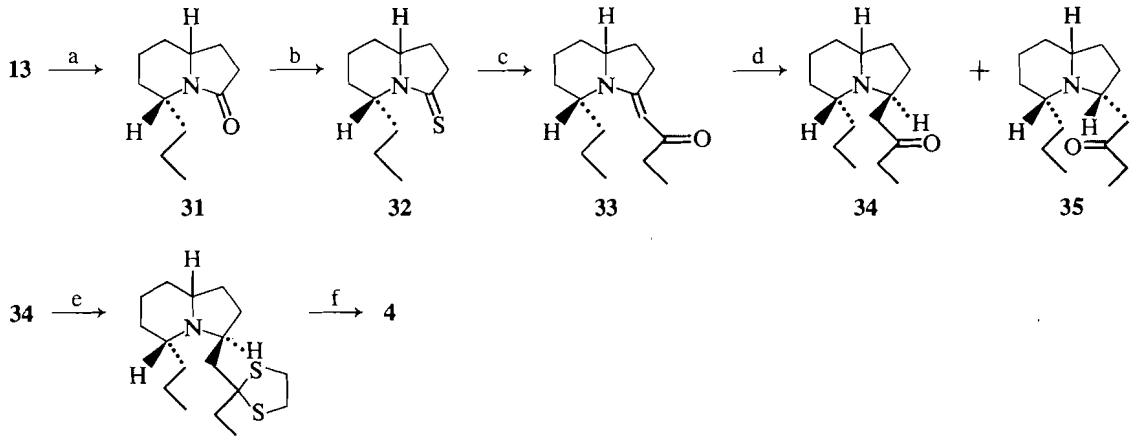
Using method E, 1-acetoxy-1,3-butadiene gave predominantly monocyclic coupling products. The major one (33%) was crystalline, mp 111–112°C. Its analysis and spectra were only consistent with structure **30** (see figure). Hydrogenation of **30** over Pd(C) gave mainly simple reduction of the double bond. The acylal hydrogen signal became a triplet (J = 5 Hz) at δ 6.8.

Reaction of the sensitive dienes 2-acetoxy- and 2-trimethylsilyloxy-1,3-butadiene with **2** and **3** (R = OAc) under a variety of conditions gave bad mixtures and no products were characterized.



30

Synthesis of *dl*-gephyrotoxin 223AB (**4**) from the dehydroindolizidinone **13** was accomplished in 15% overall yield. The 6,7-dehydro-5-propylindolizidin-2-one **13** was reduced catalytically to **31**. This was transformed using small modifications of a sequence used by Hart and Tsai (8) into **4** (see Flowsheet). The major differences from their procedure was the use of Lawes-

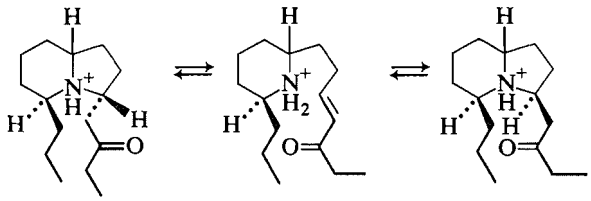


(a) H_2, Pd/C (b) Lawesson's reagent (c) 1-bromo-2-butanone, Et_3N
(d) $NaCNBH_3$,H^+ (e) $HSCH_2CH_2SH$ (f) Ni(R)

FLOWSHEET

son's reagent (9) to make the thiolactam **32** and of Raney nickel to desulfurize the dithioketal **36**. Both steps were efficient.

Two epimers at C-3 of the saturated keto lactams (**34** and **35**) were produced, distinguished by the fact that one gave a readily crystalline hydrochloride, while the salt of the other remained amorphous. However, it appeared that the amorphous salt was slowly converted into the crystalline one on standing. A mechanism exists for such an interconversion (eq. [1]), but the

[1] 

phenomenon has not been rigorously examined. The crystalline salt was used for subsequent reactions, and fortunately proved to have the desired stereochemistry shown in **34**.

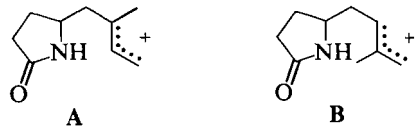
The final product had the same gc retention time as authentic gephyrotoxin-223AB[4] and gave a ^{13}C nmr spectrum identical to that found by Professor Tokuyama and co-workers for natural toxin (10). The ^{13}C nmr spectrum differed significantly from that reported by Macdonald for his synthetic isomer (11) but agreed well with that reported by Royer and Husson (12) for their synthetic optically active toxin. The structure and relative stereochemistry of the hydrobromide of our synthetic base **4** was determined by Pryzbylska and Ahmed (13) using X-ray crystallography.

A parallel series of transformations has been used to convert **12** into analogues of **32** and **33**, thus paving the way to a synthesis of *dl*-monomorine (unpublished work in these laboratories).

Discussion

The apparent Diels–Alder reactions of *N*-acyl imines or their salts have been the subject of much study. Both intermolecular and intramolecular examples have been provided (1*a–f*, and references therein). In the cases where Brönsted or Lewis acids catalysed the reactions, highly polarized acyl immonium salts[5] were present, and the possibility exists that the reactions were stepwise cationic additions. Indeed, in our own cases, the production of varying amounts of products in which only one carbon–carbon bond had been formed, the internal attack on an aromatic ring (for 2,3-diphenyl-1,3-butadiene) (see also ref. 15), and the substitution of furan all argue for a stepwise process. The regiochemistry and stereochemistry of the Diels–Alder-type products can equally well be accounted for with this mechanism (see below). The high temperature intramolecular reactions of Weinreb and Levin (1e) (in the presence of the weak acetic acid) stand a better chance of being true Diels–Alder reactions of the transient *N*-acyl imines.

The regiochemistry of the formate ester production is consistent with attack of the *N*-acyl immonium ion on an unsubstituted end of the 1,3-diene, if available. In all unsymmetrical cases except that of isoprene, this appeared to give the thermodynamically more stable cation. However, calculation of the relative energy of the cations **A** and **B** from isoprene favored **B** by 6 kcal/mol.[6] But the formate arose from **A**, hence kinetic factors determined the site of attack.



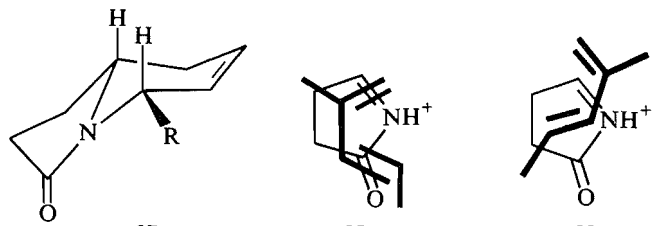
A **B**

The regiochemistry of dehydroindolizidinone formation, however, was consistent in all cases with attack on the least substituted end of the diene, leading to formation of the most substituted (lowest energy) delocalized allylic cation.

The yield of dehydroindolizidinones, using method A (formic acid), from the various dienes studied, varied from traces (isoprene) to over 70% (2-methyl-1,3-pentadiene). This is not simply a consequence of the rotamer populations in the diene. Herman[6] has calculated that only 2,3-dimethyl-1,3-butadiene has more *s-cis* than *s-trans* rotamer present at room temperature. It is also not related to the barrier to rotation or relative stability of the two delocalized allylic cations (see discussion below). Thus the origin of the difference is subtle, and may reflect nonbonded interactions in a reaction complex or transition state.

The factors involved in determining the relative stereochemistry of the bicyclic products can be illustrated with the cases of *trans*-piperylene, *trans*-1,3-heptadiene, and *trans*-2-methyl-1,3-pentadiene. The dehydroindolizidinones from the first two were essentially pure **37** (R = CH_3 and C_3H_7 respectively). These are the thermodynamically more stable isomers, but also those expected from maximum secondary orbital overlap corresponding to the Diels–Alder *endo* rule (see **38**).

That the orbital overlap is a dominant factor is supported by the case of 2-methyl-1,3-pentadiene. We suggest that in this case the steric repulsion between the 2-methyl group and a methylene group of the immonium ion as in **38** partially overrides the electronic effect, resulting in an equal contribution to the transition state of an orientation depicted in **39**. This



37 **38** **39**

rationalizes the fact that nearly equal amounts of stereoisomers **16** and **17** were formed.

Both Krow *et al.* (1*f*) and Weinreb and Levin (1*e*) have invoked similar secondary orbital interactions to account for the stereochemistry they encountered in their apparent Diels–Alder reactions.

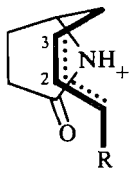
If the reactions are stepwise and the above arguments are correct, our steric results demand a good retention of stereochemistry in the initially formed allylic cations. Thus little or no rotation about the 2,3 bond takes place in the cations derived from **38** and its analogues from *trans*-piperylene and *trans*-2-methyl-1,3-heptadiene (see **40**). Herman[6] has estimated a barrier of around 15 kcal/mol (average of the two barrier heights) to rotation in the case where $R^2 = R^3 = CH_3$ (from 2-methyl-1,3-pentadiene) and R^2 = H, $R^3 = CH_3$ (from isoprene), but somewhat higher (17–21 kcal/mol) for the other dienes studied. This is adequate to provide retention of configuration in a stepwise process.

A further test of this steric control would be the geometry of

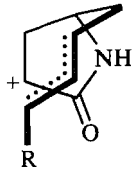
[4]We cordially thank Dr. T. F. Spande for making this observation and for other exchanges of information.

[5]In accord with traditional usage for amines, an imine should give rise to an immonium salt, not an imminium salt as has often been used.

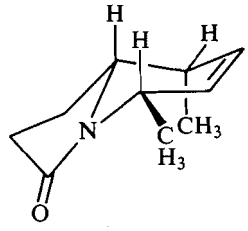
[6]We warmly thank L. Herman for these calculations, to be reported in a thesis submitted as partial requirement for the Ph.D. degree, Department of Chemistry, Carleton University.



40*a*



40*b*



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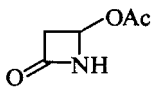
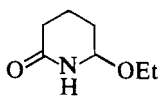
the product from *E,E*-2,4-hexadiene. The dehydroindolizidinone from this had the 5- and 9-hydrogens *syn* (see **41**), as expected for a reaction orientation related to **38**. Thus we predict that the 8-methyl group would be *anti* to the 9-hydrogen as in **41**. Unfortunately we have no evidence defining its configuration.

Our synthesis of (±) gephyrotoxin 223AB (now called indolizidine 223AB) compares favorably in yield and the use of readily available starting materials with the ingenious approaches devised by others (11, 12). The requirement of final resolution to obtain optically active material may make it inferior in practice to the synthesis of Royer and Husson (12). Synthesis of other stereoisomers of gephyrotoxin 223AB have been reported by Hart and Tsai (8), and by Stevens and Lee (16).

The above reactions should be capable of extension to other bicyclic systems fused through nitrogen, using such readily available *N*-acyl imine precursers as **42** (17) and **43** (4).



42



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Experimental

Separations were done on tlc silica gel with 13% $CaSO_4$ binder and fluorescent indicator, either in a column or 1000-μm plates, or on "flash" silica gel (50–63 μm). Infrared spectra were determined on a Perkin–Elmer model 257 grating spectrometer using dichloromethane solutions. The ^1H and ^{13}C nmr spectra were recorded using a Bruker WP-80 FT spectrometer with deuterochloroform as solvent and TMS as reference. Mass spectra were obtained using electron impact (EI), courtesy of the Ottawa–Carleton mass spectrometry center. Yields were calculated on the basis of the 5-ethoxy-2-pyrrolidinone or 5-acetoxy-2-pyrrolidinone used.

Reagents

5-Ethoxy-2-pyrrolidine 2

This was prepared from succinimide in a manner similar to that of Speckamp and co-workers (4). Simultaneous slow addition of hydrogen chloride in absolute ethanol and solid sodium borohydride, keeping the pH between 4 and 8 and cooling (0–5°C), was necessary to produce moderate yields (ca. 50%).[7] Purification of the ether-soluble product was achieved by passage in ether through a short bed (10-fold weight ratio) of activity II alumina, followed by concentration to small volume and addition of hexane. It formed large prisms, mp 56–58°C, and gave ^1H nmr signals at δ 8.1 (br, NH), 4.97 (br m, 1H), 3.5 (br m, 2H), 2.3 (m, 4H), and 1.20 (t, 3H, J = 7 Hz). More polar fractions yielded needles, mp 63–65°C, which from their ^1H nmr spectra were a 1:1 eutectic of succinimide and **2**.

5-Acetoxy-2-pyrrolidinone 3 (R = Ac)

A solution of 127 mg of 5-ethoxy-2-pyrrolidinone (**2**) in 1 mL of acetic acid and 0.75 mL of acetic anhydride was held at 70°C for 4 h. The reagents were removed under reduced pressure of 0.1 Torr (1 Torr = 133.3 Pa). The oily product (126 mg) gave ^1H nmr signals at δ 7.98 (br, NH), 6.05 (1H, m), 2.8–2.1 (4H, m), and 2.18 (3H, s). It was never obtained completely pure.

E-*1,3-Heptadiene*

A commercial sample (Wiley Organics) gave ^{13}C nmr signals at 137.5, 135.3, 131.2, 114.6, 34.7, 22.5, and 13.7 ppm. It thus appeared to be one isomer, which on the basis of the geometry of derived products (see gephyrotoxin-223AB) had the *E* configuration of the internal double bond.

E-*2-Methyl-1,3-pentadiene*

The commercial sample used (Aldrich) gave ^{13}C nmr signals at 142.2, 134.3, 125.4, 113.8, 18.7, and 18.1 ppm.

1-Acetoxy-1,3-butadiene

A commerical sample (Aldrich) was freshly distilled under reduced pressure. It was an approximately 60:40 mixture of two isomers according to its ^1H nmr spectrum. The main isomer give signals at δ 7.5 (1 H, d, J = 12 Hz), a complex set of signals between 6.5 and 4.6 (4H) and 2.2 (3H, s).

General conditions for 1,3-diene reactions[8]

Method A

A mixture of 301 mg of 5-ethoxy-2-pyrrolidinone **2**, 805 mg of freshly distilled 2,3-dimethyl-1,3-butadiene, 4 mL of 98% formic acid, and 0.6 mL of dichloromethane gave two phases. This was stirred under argon for 3 h. A trace of upper phase persisted. The solvents and the bulk of the formic acid were removed *in vacuo* in 35°C. The residue was dissolved in 15 mL of dichloromethane. The solution was washed with 3 mL of water, then 3 mL of saturated sodium bicarbonate solution. The aqueous layers were washed twice with 15-mL portions of dichloromethane. The organic layers yielded 710 mg of pleasant-smelling oil. This was hydrolysed for 1 h using 326 mg of potassium carbonate in 2 mL of water and 1 mL of methanol (stirring, room temperature). The bulk of the methanol was removed under reduced pressure, then the products were extracted into dichloromethane (3 × 7 mL). The 660 mg of oil recovered from the CH_2Cl_2 was absorbed from this solvent onto 40 g of silica gel. Elution with CH_2Cl and 0.75% methanol in chloroform gave products derived from the diene alone. A 5% methanol in chloroform mixture eluted products less polar than the desired bicyclic product **14**, followed by fractions rich in this compound (447 mg). This was followed by 64 mg of crystalline hydroxy lactam **15** (R = H). The fractions rich in **14** were separated on five silica gel plates using 5% methanol in chloroform into (*a*) 175 mg of a mixture of **14** with a monocyclic product with ν_{max} 3420 and 1696 cm^{-1} (not identified), and (*b*) 102 mg, rich in hydroxy lactam **15** (R = H). The mixture (*a*) was separated on 1000-m alumina plates using 4% ethanol in chloroform. The yield of bicyclic lactam **14** was 45 mg (12%) and of the crystalline lactam **15** (R = H) was 166 mg (39%).

If the crude reaction product was not hydrolysed the product could be separated on silica gel to give **14** (16%) and the formate **15** (R = OCHO) (43%). See also the detail for 2,3-diphenyl-1,3-butadiene.

Method B

Separate solutions of 5.6 g of *trans*-piperylene, 3.27 g of 5-ethoxy-2-pyrrolidinone in 9 mL of dry methylene chloride, and 3.13 g of methanesulfonic acid in 3 mL of methylene chloride were cooled to 0°C, then mixed. The resulting solution was left at 0°C for 64 h, then added to a stirred mixture of 10 mL of chloroform and 20 mL of water. The mixture was carefully neutralized using solid sodium bicarbonate. The layers were separated, and the aqueous layer extracted with three 30-mL volumes of chloroform. The chloroform extracts were washed with 10 mL of saturated brine, dried, and distilled. The residue was adsorbed from methylene chloride onto 200 g of silica gel and the products eluted with 25% ethyl acetate in methylene chloride. Three hundred millilitres of solvent eluted 787 mg of products derived from piperylene alone. Five percent ethanol in methylene chloride (600 mL) eluted 226 mg of unidentified products. The next 300 mL eluted 2.2 g rich in the desired bicyclic adduct but containing more polar and less polar compounds. These were removed on 1000-μm silica gel plates

[7]We thank Paul Desilets for experiments on these conditions. We were unable to obtain the high yields reported in ref. 4.

[8]These are illustrated using specific dienes.

using 5% ethanol in chloroform. The desired dehydroindolizidinone **12** weighed 530 mg (14%). See also the detail for 1,3-heptadiene.

Method C

A solution of 65 mg of 5-ethoxy-2-pyrrolidinone **2** and 200 mg of *E,E*-2,4-hexadiene in 1 mL of chloroform was cooled to −10°C. To this was added 0.5 mL of 36% perchloric acid. The mixture was stirred at −10°C for 1 week. Chloroform was added, followed by saturated sodium bicarbonate solution to neutralize the acid. The solution was dried using anhydrous sodium sulfate. The products were separated on a silica gel plate using 5% ethanol in chloroform, giving 17 mg (20%) of the dehydroindolizidinone **22**. The other major products derived from **2** appeared to be monocyclic dienes, but were not further characterized.

Method D

A solution of 123 mg of acetyl chloride in 1 mL of dry benzene was added to a solution of 300 mg of silver perchlorate in 2 mL of dry benzene. Silver chloride separated. The mixture was filtered through sintered glass under dry argon into a solution of 190 mg of ethoxy lactam **1** in 1 mL of benzene. A precipitate formed. The bulk of the benzene was removed under reduced pressure, then a solution of 217 mg of isoprene in 3 mL of dry acetonitrile was added. The mixture was left under argon for 4 days at room temperature. The solvent was evaporated, the products extracted into dichloromethane (filtered), then the solution and washings stirred with 1 mL of saturated sodium bicarbonate solution. The water was absorbed using anhydrous sodium sulfate, then the dichloromethane removed. The 263 mg of residue was adsorbed from dichloromethane onto 7 g of silica gel. The products were eluted successfully with dichloromethane, 0.5% methanol in chloroform, then 5% methanol in chloroform. The 70 mg rich in bicyclic lactam (tlc) was further separated on a 100-μm silica gel plate using 7% methanol in chloroform. The desired bicyclic product **8** (ca. 20 mg, 9%) was still contaminated with a slightly more polar product (ν_{max} 3430 and 1687 cm^{-1}), which was probably a monocyclic diene.

In other experiments using the same ratio of silver perchlorate but only half the molar equivalent of acetyl chloride, the yield of bicyclic lactam **8** remained at 9%, but a new product with slightly lower R_f in silica gel was isolated and characterized as a trimer of the *N*-acyl imine **1** with mp 205°C.

Method E

5-Acetoxy-2-pyrrolidinone **3** (R = Ac) was prepared from 127 mg of **2** as described above. This was combined with 300 mg of freshly distilled 1-acetoxy-1,3-butadiene in 0.75 mL of acetic acid and 0.4 mL of acetic anhydride. To this was added 60 mg of boron trifluoride etherate. The clear solution was left for 5 h at room temperature under argon, then the solvents removed under 0.1 Torr at 40°C. Water and dichloromethane were added, followed by enough sodium bicarbonate to bring the pH to 7 (stirring). The dichloromethane layer was separated, then the aqueous layer extracted twice with the same solvent. The organic extracts yielded 131 mg of an oil that crystallized on standing. The crystals were collected using an acetone–hexane mixture. The mother liquors were separated on a silica gel plate giving more of the crystals. The isolated yield of crude lactam acylal **30** was 70 mg (28%), mp 108–110°C.

Reactions of specific dienes

Isoprene

Using method A (516 mg of **2**, 25 mL of 98% formic acid, and 1.5 mL of isoprene for 2 h at room temperature), an 83% yield of the monocyclic formate **7** was obtained, and only a trace of indolizidinone was detected.

Using method C (65 mg of **2**, 200 mg of isoprene, 0.5 mL of 36% perchloric acid, and 0.5 mL of chloroform stirred 7 days at −10°C), a 10% yield of the indolizidinone **8** was obtained.

See also method D, above.

5,9-syn-6,7-Dehydro-6-methylindolizin-2-one 8

This was an oil with ν_{max} 1668 cm^{-1} and ^1H nmr signals at δ 5.40 (1H, br s), 4.24 (1 H, d, J = 5 Hz), 3.56 (1H, br s), 3.49 (1H, d, J = 5 Hz), 2.40 (ca. H, m), 2.12 (ca. H, br s), and 1.71 (3H, s). The vinyl hydrogen was not coupled to any of the other three low-field hydrogens.

Its ^{13}C nmr spectrum had signals at δ 173(s), 131(s), 117(d), 53(d), 40(t), 37(t), 30.5(t), 22.5(t), and 23(q). It gave m/z 152 (9), 151 (75) (M^+), 150 (15), 136 (51), 108 (24), 96 (17), 94 (23), 84 (37), 68 (100). *Anal.* calcd. for $C_9H_{13}NO$: C 71.49, H 8.67, N 9.26; found: C 71.66, H 8.84, N 9.16.

1-Hydroxy-3-methyl-4-(5'-oxo-2'-pyrrolidinyl)-but-2-en-1-ol formate 7

This was a viscous oil with ν_{max} 3430, 1723, and 1700 cm^{-1}. It gave ^1H nmr signals at δ 8.06 (1H, s), 7.1 (br s, NH), 5.43 (1H, t, J = 7 Hz), 4.69 (2H, d, J = 8 Hz), 3.82 (1H, m), and 1.75 (3H, s). Irradiation at δ 2.27 reduced the multiplet at 3.8 to a broad singlet; the doublet at 4.69 collapsed to a singlet when δ 5.4 was irradiated, and irradiation at 4.7 collapsed the triplet at 5.4 to a singlet. Its ^{13}C nmr spectrum had signals at δ 178.0(s), 160.7(d), 138.3(s), 121.0(d), 60.1(t), 52.2(d), 46.5(t), 30.1(t), 26.7(t), and 16.5(q) ppm. Extra signals for a minor isomer were present at 138.8, 121.6, 59.9, 52.5, 26.9, and 23.5 ppm with the same multiplicities as the major peaks. *Anal.* calcd. for $C_{10}H_{15}NO_3$: C 60.89, H 7.67, N 7.10; found: C 61.07, H 7.83. N 7.24.

trans-*Piperylene*

See also method B above.

Following method A(3 g of **2**, 8 mL of *trans*-piperylene in 35 mL of 98% formic acid, 2 h at room temperature), 4 g of less volatile products were obtained. Separation on 160 g of silica gel gave 2.6 g (57%) of monocyclic formates and 600 mg rich in indolizidinone. Further separation of the latter fraction using tlc plates and 5% ethanol in chloroform as solvent gave 369 mg (11%) of bicyclic lactam **12**.

The monocyclic formate was a mixture of at least four isomers. Separation on a 50-fold ratio of silica gel using 5% ethanol in chloroform gave 67 mg (1.5%) of crystalline lactam formate **9**, mp 103°C, as an early eluate. The other isomers were not cleanly separated. Comparison of their ^{13}C nmr spectra showed such close similarity that they were most likely stereoisomers. The mixture was hydrolysed using potassium carbonate in aqueous methanol and the lactam alcohols separated on silica gel, giving 1.4 g (35%) of **10***a* (R = H), mp 117°C, and 0.9 g (23%) of its isomer **10***b* (R = H), mp 72°C.

2-Hydroxy-1-(5'-oxo-2'-pyrrolidinyl)-3-pentene formate 9

This had mp 102–103°C and ν_{max} 3420, 3210, 172) (sh), and 1692 cm^{-1}. Its ^1H nmr spectrum had signals at δ 8.08 (1H, s), 6.71 (br s, NH), 5.2–6.0 (3H, m), 3.69 (1H, m), and 1.72 (3H, d, J = 4 Hz). Its ^{13}C nmr spectrum had signals at δ 178.0(s), 160.5(d), 130.7(d), 128.2(d), 72.3(d), 50.75(d), 41.6(t), 27.5(t), and 17.6(q). *Anal.* calcd. for $C_{10}H_{15}NO_3$: C 60.89, H 7.67, N 7.10; found: C 61.02, H 7.74, N 6.97.

This gave an amorphous lactam alcohol with a ^1H nmr spectrum different from either isomer described below.

Major formates 10 (R = CHO)

This mixture gave ^1H nmr signals at δ 8.08 (1H, s), 7.02 (1H, br s), 5.1–5.8 (3H, m), 3.5–3.9 (1H, m), 1.35 (3H, d, J = 6 Hz). The methyl group was coupled to a proton resonating at δ 5.5. Its ^{13}C nmr spectrum had signals at δ 178.3(s), 160.2(d), 132.6(d), 128.1(d), 70.53(d), 70.46(d), 53.7(d), 39.0(t), 30.0(t), 26.2(t), and 20.0(q) ppm. The signals at 70.53 and 70.46 correspond to epimers at the carbon carrying the formate ester.

*4-Hydroxy-1-(5'-oxo-2'pyrrolidinyl)-2-pentene 10*a (*R = H*)

This had mp 116–117°C and gave ^1H nmr signals at δ 8.57 (NH), 5.6 (2H, br m), 4.53 (1H, OH), 4.24 (1H, m), 3.7 (1H, br m), and 1.22 (3H, d, J = 6 Hz). Its ^{13}C nmr spectrum had signals at δ 179.6(s), 138.9(s), 126.4(s), 68.9(s), 55.2(s), 40.0(t), 31.0(t), 27.15(t), and 22.9(q) ppm. *Anal.* calcd. for $C_9H_{15}NO_2$: C 63.88, H 8.94, N 8.28; found C 63.72, H 9.01, N 8.18.

*4-Hydroxy-1-(5'-oxo-2'-pyrrolidinyl)-2-pentene 10*b (*R = H*)

This crystallized from concentrated ethyl acetate solution, and had mp 70–72°C. It had ν_{max} 3600, 3380, 3220, and 1685 cm^{-1} and gave ^1H nmr signals at δ 7.59 (NH), 5.68 (2H, m), 4.27 (1H, m), 3.79 (1H, t), 3.33 (1H, br s), 1.68 (1H, br s), and 1.24 (3H, d, J = 6 Hz). The

hydrogen resonating at 4.27 was coupled to the methyl group (δ 1.24). Its ^{13}C nmr spectrum had signals at δ 179.2(s), 138.0(d), 125.0(d), 67.6(d), 54.6(d), 39.0(t), 30.7(t), 26.9(t), and 22.8(q) ppm. Its EI mass spectrum gave no parent ion. The base peak was at *m/z* 84. Its CI mass spectrum gave peaks at *m/z* 170 (*M* + 1) and 152 (*M* − 18).

*Oxidation of **10**a and **10**b*

To a solution of 31 mg of **10***b* in 2 mL of dichloromethane was added 855 mg of active manganese dioxide (18) (dried at 45°C *in vacuo*). After the mixture had been stirred 1.25 h, 5 mL of 10% methanol in chloroform was added, then the solid removed by filtration. The filtrate and washings were evaporated, giving 30 mg of residue. This was purified on a 500-μm silica gel plate using 10% methanol in chloroform, giving 20 mg in a main zone. This crystallized from ethyl acetate – ether mixtures, mp 65–68°C. Jones oxidation of **10***b* in acetone gave a 30% yield of the same product.

Manganese dioxide oxidation of ***10a*** as above gave a product with mp 64–67°C. The products from both isomers proved identical (mixture mp and comparison of ir and ^1H nmr spectra).

*Keto-lactam **11***

This had mp 65–68°C and ν_{max} 3420, 3200, 1699, 1675, and 1631 cm^{-1}. Its EI mass spectrum gave no parent ion. The base peak was at *m/z* 84 ($C_4H_6NO^+$). Its CI mass spectrum (ether) gave *M* + 1 at *m/z* 168 and *M* −18 at *m/z* 149. Its ^1H nmr spectrum gave signals at δ 6.88–6.57 (1H, m), 6.55 (br m, NH), 6.17 (1H, d, *J* = 16 Hz), 3.81 (1H, m), and 2.26 (3H, s) superimposed on a 6H multiplet.

E-*1,3-Heptadiene*

The use of method A gave a mixture of formate esters with ^1H nmr signals at δ 8.0 (1H, s), 7.0 (1H, NH), 5.9–5.1 (3H, m), 3.7 (1H, m), and 0.9 (3H, t) typical of the monocyclic lactam formates described from other dienes. The yield of dehydroindolizidinone **13** (ca. 15%) was lower than that using method B, hence the latter method was used in preparative work.

In a minor modification of method B, 5.8 g (45 mmol) of **2** and 17 g (180 mmol) of *E*-1,3-heptadiene in 40 mL of dry dichloromethane was cooled to −5°C. A solution of 4.7 g (49 mmol) of methanesulfonic acid in 15 mL of dichloromethane was added to this with stirring during 15 min. The mixture was stirred at 0°C for 120 h. Separation of the products on silica gel gave two pairs of ethoxy lactams, corresponding to the formate esters from method A, and 1.3 g of pure **13** followed by 0.76 g of **13** contaminated with monocyclic adducts. The latter was purified using silica gel plates, giving a total yield of 1.7 g (21%) of **13**.

*5,9-*syn*-6,7-Dehydro-5-(1′-propyl)indolizidine-3-one (**13**)*

This distilled over a short path of 95°C under 0.05 Torr as a colorless oil. It had ν_{max} 1677 cm^{-1} and ^1H nmr signals at δ 5.75 (2H, m), 4.1 (1H, br), and 3.47 (1H, m), with peaks at 2.29, 1.00, and 0.90. Its ^{13}C nmr spectrum had signals at δ 175.4(s), 129.0(d), 123.9(d), 55.6(d), 52.5(d), 34.5(t), 31.8(t), 31.1(t), 26.6(t), 16.7(t), and 13.9(q). Its mass spectrum gave peaks at *m/z* 179 (5.3), 164 (2.9), 150 (12), 137 (39), 136 (99), and 108 (100). *Anal*, calcd. for $C_{11}H_{17}NO$: 73.70, H 9.56, N 7.81; found: C 73.52, H 9.43, N 7.69.

2,3-Dimethyl-1,3-butadiene

See method A above. The yield of the dehydroindolizidine **14** was around 16%.

*7,8-Dehydro-7,8-dimethylindolizidin-2-one **14***

This was an oil with ν_{max} 1670 cm^{-1}. It gave ^1H nmr signals at δ 4.3, 4.0, 3.56 and 3.2 (br, 3H total), and 1.68 (6H, s). Its ^{13}C nmr spectrum had signals at δ 173.4(s), 123.5(s), 121.7(s), 53.0(d), 44.0(t), 38.1(t), 29.7(t), 24.8(t), 18.7(q), and 15.7(q) ppm. It gave *m/z* 165 (100), 150 (100), 122 (34), 108 (29), 94 (23), 84 (51), 82 (100), and 67 (100). *Anal.* calcd. for $C_{10}H_{15}NO$: C 72.69, H 9.15, N 8.48; found: C 72.47, H 9.01, N 8.29.

*2,3-Dimethyl-4(2′-oxopyrrolidin-5′-yl)-but-2-en-1-ol formate **15** (R = CHO)*

This was an oil distilling over a short path at 150°C, 0.25 Torr. It had ν_{max} 3420, 1718, and 1698 cm^{-1} and gave ^1H nmr signals at δ 8.20 (1H, s) 7.8 (1H, br s), 4.70 (2H, s), 3.85 (1H, br m), and 1.80 (6H, s). Its ^{13}C nmr spectrum had signals at δ 178.2, 161.1, 132.3, 131.8, 126.3, 126.2, 64.9, 64.4, 53.2, 53.0, 52.9, 41.4, 41.1, 30.9, 30.6, 30.5, 30.3, 27.3, 27.1, 27.0, 19.1, 18.5, 17.0, and 16.9 (24 signals, i.e., two isomers). Hydrolysis of this formate in methanol containing potassium carbonate gave the crystalline alcohol **15** (R = H), mp 93°C.

*2,3-Dimethyl-4-(2′-oxopyrrolidin-5′-yl)-but-2-en-1-ol (**15** R = H)*

After recrystallization from acetone–hexane, **15** had mp 94–95°C. It had ν_{max} 3600, 3380, 3220, 3050, and 1680 cm^{-1} and gave ^1H nmr signals at δ 8.45 (0.5H, m), 7.7 (0.5H, m), 3.4–4.6 (4H), 1.9–2.2 (6H), and 1.80 (6H, s) and ^{13}C nmr signals at δ 179.7, 179.0, 131.9, 131.8, 128.3, 127.9, 63.9, 62.6, 53.5, 41.65, 41.1, 30.9, 27.9, 27.4, 19.1, 17.8, 17.4, and 17.0 (18 signals). It was thus a 1:1 mixture of two isomers. *Anal.* calcd. for $C_{10}H_{12}NO_2$: C 65.54, H 9.35, N 7.64; found: C 65.40, H 9.28, N 7.51.

trans-*2-Methyl-1,3-pentadiene*

Method A was followed. A mixture of 2.5 g of ethoxylactam **2**, 4.68 g of freshly distilled *trans*-2-methyl-1,3-pentadiene, and 20 mL of 98% formic acid was stirred under argon for 5 h. Initial cooling was needed to maintain the temperature near 20°C. The reaction mixture was still in two phases. The lower phase was separated, the upper phase washed with 5 mL of formic acid, and the layers again separated. The bulk of the formic acid was removed *in vacuo* and the work-up done as in method A. The 2.25 g (70% calcd. as **16**) of product recovered was predominantly a mixture of the two lactams **16** and **17** in a 1:1 ratio (^1H nmr). These were separated on 100 g of tlc silica gel using a 1:1 mixture of acetone in hexane for elution. Overlapping fractions were separated on 1000-μm tlc plates.

*5,9-*syn*-6-7-Dehydro-5,7-dimethylindolizidin-3-one **16***

The isomer with higher R_f on silica gel (30% acetone in hexane) was an oil, which was distilled over a short path at ca. 90°C, 0.03 Torr. It had ν_{max} 1668 cm^{-1} and gave ^1H nmr signals at δ 5.34 (1H, s), 4.0 (1H, br s), 3.5 (1H, br m), 1.8 (3H, s), and 1.43 (3H, d, *J* = 4 Hz); ^{13}C nmr spectrum, δ: 175.4(s), 130.7(s), 124.7(d), 55.9(d), 48.3(d), 36.9(t), 31.3(t), 26.5(t), 23.0(q), 20.5(q). Its mass spectrum had *m/z* 165 (25) (M^+), 150 (100), and 122 (24). *Anal.* calcd. for $C_{10}H_{15}NO$: C 72.69, H 9.15, N 8.48; found: C 72.44, H 9.03, N 8.33.

*5,9-*anti*-6,7-Dehydro-5,7-dimethylindolizidin-3-one **17***

The isomer with the lower R_f on silica gel (30% acetone–hexane) was distilled over a short path at ca. 90°C, 0.03 Torr. It had ν_{max} 1662 cm^{-1} and gave ^1H nmr signals at δ 5.35 (1H, s), 4.4 (1H, br s), 3.7 (1H, br m), 1.7 (3H, s), 1.15 (3H, d, *J* = 6.6 Hz); ^{13}C nmr spectrum, δ: 173(s), 130.7(s), 123.5(d), 50.0(d), 45.5(d), 37.2(t), 30.0(t), 25.0(t), 23.0(q), and 19.0(q). Its mass spectrum had *m/z* 165(33) (M^+), 150 (100), and 122 (26). *Anal.* calcd. for $C_{10}H_{15}NO$: C 72.69, H 9.15, N 8.48; found: C 72.42, H 9.36, N 8.20.

3-Methyl-1,3-pentadiene

Using method A (65 mg of **2**, 210 mg of 3-methyl-1,3-pentadiene in 3 mL of 98% formic acid for 2 h at room temperature), 80 mg (75%) of monocyclic formate **20** was obtained as an oil.

*5-(5′-Oxo-2′pyrrolidinyl)-3-methylpent-3-en-2-ol formate **20***

This gave ν_{max} 3440, 3220, 1720, and 1695 cm^{-1} and ^1H nmr signals at δ 8.08 (1H, s), 7.13 (1H, br s), 5.4 (2H, m), 3.70 (1H, m), 1.65 (3H, s), and 1.35 (3H, d, *J* = 6.6 Hz). The methyl doublet at δ 1.35 was coupled with a proton resonating near 5.4 (*CH*OCHO) and the singlet at 3.7 and the vinyl hydrogen near 5.5 were coupled to a methylene group resonating near 3.3. Its ^{13}C nmr spectrum showed it to be a mixture of two stereoisomers in nearly equal amounts. The major isomer gave signals at δ 178.4(s), 160.4(d), 137.2(s), 122.5(d), 75.3(d), 54.1(d), 34.5(t), 30.2(t), 26.5(t), 19.0(q), and 12.1(q). *Anal.* calcd. for $C_{11}H_{17}NO_3$: C 62.54, H 8.11, N 6.63; found: C 62.34, H 8.02, N 6.47.

E,E-*2,4-Hexadiene*

Use of method A (61 mg of ethoxy lactam **2**, 190 mg of 2,4-hexadiene in 3 mL of 98% formic acid for 2 h at room temperature) resulted in formation of 71 mg (70%) of monocyclic formate **21**. Little if any dehydroindolizinone was formed.

As described above, a 20% yield of the dehydroindolizidinone **22** was formed using method C.

5-(5'-Oxo-2'-pyrrolidinyl)-hex-3-en-2-ol formate ***21***

This was an oil with ν_{max} 3440, 3220, 1720, and 1691 cm^{-1} and ^1H nmr signals at δ 8.03 (1H, s), 7.65 (br s, NH), 5.56 (main peak of a 3H, mult.), 3.51 (1H, m), 1.34 (3H, d, J = 6 Hz), and 1.06 (3H, d, J = 6.6 Hz). Its ^{13}C nmr spectrum showed it to be a mixture of two very similar isomers. The main one gave signals at δ 178.9(s), 160.3(d), 134.1(d), 130.6(d), 70.7(d), 59.0(d), 41.9(d), 30.3(t), 24.2(t), 20.4(q), and 16.3(q). *Anal.* calcd. for $C_{11}H_{17}NO_3$: C 62.54, H 8.11, N 6.63; found: C 62.23, H 7.94, N 6.72.

*5,8,9-*syn*-6,7-Dehydro-5,8-dimethylindolizidin-3-one* (***22***)

This was an oil with ν_{max} 1675 (s) and 1650 (w) cm^{-1} and ^1H nmr signals at δ 6.1–5.4 (2H, m), 4.07 (1H, br), 3.69 (1H, br), 1.45 (3H, d, J = 6 Hz), and 1.0 (3H, d, J = 7 Hz). The methyl group resonating at 1.45 was coupled with the proton at 4.07, but the methyl at 1.0 was not strongly coupled with any low-field proton. It gave ^{13}C nmr signals at δ 176.8(s), 130.1(d), 129.5(d), 58.7(d), 48.9(d), 32.5(d), 31.2(t), 21.8(t), 21.0(q), and 14.3(q). Its mass spectrum had peaks at m/z 165 (M^+) (36), 150 (77), 122 (14), 108 (8), 94 (11), 84 (58), and 82 (100). The compound was distilled over a short path *in vacuo* for analysis. *Anal.* calcd. for $C_{10}H_{15}NO$: C 72.69, H 9.15, N 8.48; found: C 72.45, H 8.98, N 8.30.

1,3-Cyclohexadiene

Method A was used (65 mg of **2**, 190 mg of cyclohexadiene, and 0.5 mL of 98% formic acid stirred for 4 h at room temperature). After separation on silica gel, using 5% methanol in chloroform, 33 mg (40%) of tricyclic product and 44 mg (42%) of the bicyclic formate were obtained.

*8,9-*syn*-6,7-Dehydro-5,8-ethanoindolizidin-3-one* (***24***)

This distilled over a short path at 50–60°C under 0.1 Torr. It had ν_{max} 1675 cm^{-1} and gave ^1H nmr signals at δ 6.6 and 6.17 (1H each, pseudo triplets, J_1 = 8 Hz and J_2 = 5 Hz from decoupling experiments), 4.57 (1H, br s), 3.72 (1H, dd, J_1 = 9 Hz, J_2 = 5 Hz), and 2.71 (1H, br d, J = 6 Hz). The following couplings were demonstrated: 6.6–6.17; 6.6–4.57; 6.17–2.71; 3.72–2.1. It gave ^{13}C nmr signals at δ 178.1(s), 136.8(d), 130.7(d), 60.1(d), 44.8(d), 35.0(d), 31.8(t), 28.5(t), 24.5(t), and 22.9(t). Its mass spectrum had peaks at m/z 163 (5), 134 (9), 106 (5), 84 (100), 80 (88), and 79 (57). *Anal.* calcd. for $C_{10}H_{13}NO$: C 73.59, H 8.03, N 8.58; found: C 73.41, H 7.95, N 8.73.

4-(5'-Oxo-2'-pyrrolidinyl)-cyclohex-2-en-1-ol formate (***23***)

The ^{13}C nmr spectrum of this product showed it to be a mixture of four stereoisomers with correct chemical shifts and multiplicities for **23**. Its ^1H nmr spectrum had signals near δ 8.1 (CHO), 7.4–8.1 (NH), 5.95, 5.82 (vinyl hydrogens), 5.33 (CHN), and 3.6 (CHO-). It was not further characterized.

2,3-Diphenylbuta-1,3-diene

The diene (897 mg, mp 47°C) (19) and 563 mg of ethoxy lactam **2** in 3 mL of dichloromethane and 4 mL of formic acid formed two oil layers. This mixture was stirred under argon for 29 h. An extra 201 mg of ethoxy lactam **2** was added, then stirring continued (total time 71 h). The bulk of the solvent and formic acid were removed on a rotating evaporator at 50°C. The residue was dissolved in dichloromethane, then washed free of acid using aqueous sodium carbonate. The 1.12 g of oil recovered from the dichloromethane was adsorbed on a column of 15 g of tlc silica gel. Dichloromethane eluted 451 mg of diphenylbutadiene, followed by 136 mg of nitrogen-free products (formate esters). Chloroform containing 5% (v/v) of methanol eluted 505 mg of condensation products. This solvent and 10% methanol in chloroform eluted 71 mg of a mixture of more polar products, which was not further investigated.

The 505 mg contained the indene derivative **27** and two formoxy amides. This was partially separated on four 1000-μm silica gel plates using 5% methanol in chloroform. A small zone (R_f 0.7, 51 mg) contained a lactam (1682 cm^{-1}) and gave a weak NH band. It was not identified. Bands rich in indene (R_f 0.6, 218 mg) and formate ester (R_f 0.5, 80 mg) were still mixtures. They were combined and hydrolysed by refluxing for 1 h in aqueous methanol containing potassium carbonate. The product was again separated on three 1000-μm silica gel plates using 7% methanol in chloroform, giving 90 mg of indene **27** (R_f 0.65), 167 mg of hydroxy lactam **25** (R_f 0.5), and 30 mg of hydroxy lactam **26** (R_f 0.3).

In a parallel run, the indene **27** and formate mixture was carefully separated on a 50-fold ratio of flash silica gel using 5% methanol in chloroform, giving quite pure indene **27** in the early eluates and formoxy lactam **25** (R = H) as a more strongly adsorbed fraction.

2,3-Diphenyl-4-(5'-oxo-2'pyrrolidinyl)but-2-en-1-ol formate (***25***, *R = OCHO*)

This was an oil with ν_{max} 3420, 1721, and 1692 cm^{-1} and λ_{max} 233 nm, ε 11 000, Its ^1H nmr spectrum had signals at δ 7.84 (1H, s), 5.85 (br, s, NH), 4.72 (2H, s), and 3.4 (1H, t, J = 5 Hz). Its ^{13}C nmr spectrum had signals at δ 177.8(s), 160.6(d), a cluster of doublets at 127.7–129.0, 141.3, 139.5, and 135.4 (singlets), 65.6(t), 52.7(d), 42.0(t), 29.9(t), and 27.0(t). This was hydrolysed by potassium carbonate in aqueous methanol to the hydroxy lactam **25** (R = H).

2,3-Diphenyl-4-(5'-oxo-2'-pyrrolidinyl)but-2-en-1-ol (***25***, *R* = H)

Yield 24%. This crystallized from acetone as buttons, mp 176–177°C. It had ν_{max} 3380, 3220, and 1675 cm^{-1} and λ_{max} 234 nm, ε 11 800. It gave ^1H nmr signals at δ 87 (1H, br s), 7.1–7.7 (10H, m), 3.8–4.4 (3H, m, includes the OH signal) reduced to a pair of doublets at 3.90 and 4.34 (J = 11 Hz) when exchanged with D_2O, 3.4 (1H, t, J = Hz), and 1.3–2.7 (6H, m), and ^{13}C nmr signals at δ 180.0(s), 141.0(s), 140.3(s), 140.2(s), 137.5(s), 129.0, 128.6, 127.3, 126.9 (aryl doublets), 65.1(t), 53.3(d), 42.0(t), 31.0(t), and 27.1(t). *Anal.* calcd. for $C_{20}H_{21}NO_2$: C 78.14, H 6.89, N 4.56; found: C 77.96, H 6.91, N 4.17.

When warmed with a formic acid – acetic anhydride mixture this gave the formate ester (**25**, R = CHO) described above.

2,3-Diphenyl-4-(5'-oxo-2-pyrrolidinyl)but-1-en-3-ol (***26***)

Yield 4%. It crystallized from methanol–acetone mixtures as short needles, mp 195–196°C. It had ν_{max} 3430, 3300, and 1684 cm^{-1} and λ_{max} 252 nm, ε 8440. Its ^1H nmr spectrum had signals at δ 7.07 (10H), 6.55 (br s, NH), 4.59 (2H, m), 3.59 (1H, br m), 2.6–3.2 (2H, m,), 2.4 (OH), 2.0–2.6 (4H, m). *Anal.* calcd. for $C_{20}H_{21}NO_2$: C 78.14, H 6.89, N 4.56; found: C 78.02, H 7.02, N 4.38.

2-Phenyl-3-(5'-oxo-2'-pyrrolidinylmethyl)indene (***27***)

Yield 14%. This remained as a thick oil with λ_{max} 289 nm, ε 14 800, λ_{min} 248 nm and λ_{max} 227 nm. It had ν_{max} 3424 and 1694 cm^{-1} and ^1H nmr signals at δ 7.37 (10H), 6.41 (br s, NH), 3.97 (1H, m), 3.72 (2H, s), 2.92 (2H, d, J = 6.7 Hz), and 2.12 (4H, br s). The signals at δ 3.97 and 2.9 were coupled. It gave ^{13}C nmr signals at δ 177.8(s), 145.8(s), 143.9(s), 142.6(s), 137.2(s), 134.8(s), 128.6, 128.4, 128.2, 127.3, 126.5, 125.0, 123.7, 119.4 (doublets), 53.6(d), 42.3(t), 32.8(t), 30.0(t), and 27.2(t). *Anal.* calcd. for $C_{20}H_{19}NO$: C 83.01, H 6.62, N 4.84; found: C 82.88, H 6.70, N 4.72.

Furan

Method C (259 mg of **2**, 425 mg of furan, 1 mL of 30% perchloric acid, 1.5 mL of chloroform for 2 h) gave 251 mg (83%) of crude 5-(2'-furyl)-2-pyrrolidinone **28**, mp 75°C.

Method D (304 mg of **2**, 242 mg of silver perchlorate, 1.5 mL of benzene, and 117 mg of acetyl chloride, then 325 mg of furan in 1 mL of dry acetonitrile, left 4 h at room temperature. After addition of 197 mg of furan the mixture was left for 0.5 h) gave 153 mg of products. After separation on 6 g of silica gel the only compound identified was 70 mg (39%) of **28**.

Copper fluoroborate catalysis

A mixture of 202 mg of **2**, 345 mg of $Cu(BF_4)_2$, and 210 mg of dry furan in 1 mL of dry ethanol-free chloroform gave a green gum and colorless solution. This was stirred for 3 h at room temperature. The solution was diluted with dichloromethane, then washed successively with water (3 mL) and saturated sodium bicarbonate solution (3 mL). Repeated extraction (3×) of the aqueous layers gave 167 mg of oil. This was separated on two 1000-μm silica gel plates using 8% methanol in chloroform giving 40 mg of **28** (17%) and 39 mg of 2,5-bis-(5'-oxo-2'-pyrrolidinyl)furan **29**. The combined aqueous layers were evaporated to near dryness. Dichloromethane was added, then the

remaining water removed using sodium sulfate. A further 41 mg, rich in **29**, was obtained. The total yield of **29** was 70 mg (19%).

*2-(5'-Oxo-2'-pyrrolidinyl)furan (**28**)*

This crystallized as rectangular prisms from acetone–hexane, mp 82–83°C. It gave ^{1}H nmr signals at δ 7.4 (1H, M), 6.78 (1H, br s, NH), 6.27 (2H, m), 4.80 (1H, poorly resolved triplet), and 2.33 (4H, m). *Anal.* calcd. for $C_8H_9NO_2$: C 63.56, H 6.00, N 9.27; found: C 63.66, H 5.93, N 9.12.

*2,5-Bis(5'-oxo-2'-pyrrolidinyl)furan (**29**)*

This was an oil with ν_{max} 3430, 3210, and 1700 cm^{-1}. It gave ^{1}H nmr signals at δ 6.8 (2H, NH), 6.1 (2H, s), 4.8 (2H, m), and 2.0–2.7 (8H).

1-Acetoxy-1,3-butadiene

Method E (see above) gave no significant amount of bicyclic product, and the only compound characterized was the acylal **30** (28%). A comparable yield of **30** was obtained when **2** was used as the reagent. In a large run the only other product obtained reasonably pure (7% yield) was also a lactam acylal with higher R_f than **30**. Only two acetoxy groups were present (^{1}H nmr and probably 12 other carbons), hence it appeared to arise from two diene molecules and one molecule of **2**. No structure was deduced.

*1,1-Diacetoxy-4-(5'-oxy-2'-pyrrolidinyl)but-2-ene (**30**)*

After recrystallization from ethyl acetate this had mp 111–112°C and ν_{max} 3420, 3200, 1760, and 1699 cm^{-1}. It gave ^{1}H nmr signals at δ 7.0 (1H, d, J = 5 Hz), 6.8 (1H, br s, NH), 6.15–5.3 (2H, m), 3.72 (1H, m), and 2.1 (6H, s). Its ^{13}C nmr spectrum had signals at δ 178.3(s), 168.7(s), 132.5(d), 127.0(d), 89.2(d), 53.5(d), 39.1(t), 30.1(t), 26.5(t), and 20.8(q). *Anal.* calcd. for $C_{12}H_{17}NO_5$: C 56.46, H 6.71, N 5.49; found: C 56.29, H 6.66, N 5.39.

Hydrolysis of **30** using a saturated solution of sodium bicarbonate in 1:1 methanol–water gave a mixture containing an unsaturated aldehyde with ν_{max} 3420, 3330, and 1690 cm^{-1} and a ^{1}H nmr doublet at δ 9.65 (J = 7 Hz). It was not further characterized.

Lactam acylal of unknown structure

This amorphous product had ν_{max} 1760, 1680, and 1650 cm^{-1} and ^{1}H nmr signals at δ 7.1 (1H, d, J = 5 Hz), 6.3–5.3 (4H, m), 4.5 (1H, br), 3.65 (1H, br), 2.1 (6H, s). Its ^{13}C nmr spectrum had signals at δ 173.8(s), 168.6(s), 133.2(d), 127.0(d), 126.5(d), 125.0(d), 89.3(d), 51.0(d), 49.1(d), 36.3(t), 32.1(t), 30.0(t), 25.1(t) and 20.9(1) (14 signals).

Synthesis of gephyrotoxin 223AB

*5,9-syn-5(1'-Propyl)indolizidin-3-one (**31**)*

Unsaturated lactam **13** (679 mg) in 5 mL of ethanol was added to a suspension of 136 mg of 30% palladium on charcoal in 15 mL of ethanol, which had been previously saturated with hydrogen. The mixture was shaken under hydrogen. An initial rapid uptake of 30 mL of hydrogen was followed by slower reaction. After 2 h, 81 mL of hydrogen had been absorbed. The solution was filtered through a bed of Celite, and the filtrate and washings evaporated, leaving 620 mg of colorless oil. This was further purified by adsorption from dichloromethane onto a column of 50 g of silica gel (flash). Elution with 10% ethyl acetate and 2% ethanol in dichloromethane gave 24 mg of impurities, then 554 mg of quite pure (tlc on silica, 5% ethanol in chloroform) saturated lactam. An analytical sample was prepared by purification on 1000-μm silica gel plates (5% ethanol in chloroform) followed by distillation at 95°C, 0.05 Torr. It gave ^{1}H nmr signals at δ 3.2 (2H br), 2.2, 1.0, and 0.98. Its ^{13}C nmr spectrum had signals at δ 174.0(s), 59.5(d), 57.2(d), 34.4, 31.8, 31.6, 29.5, 24.9, 22.6, 19.8 (triplets), and 13.9(q). *Anal.* calcd. for $C_{11}H_{19}NO$: C 72.88, H 10.57, N 7.73; found: C 73.06, H 10.55; N 7.90.

Thiolactam 32

A mixture of 377 mg of dihydrolactam **31** and 512 mg of Lawesson's reagent (10) in 8 mL of pure dry dimethoxyethane was stirred under argon for 2 h. A further 88 mg of Lawesson's reagent was then added, and the solution left overnight at 5°C. Thin-layer chromatography still showed the presence of some starting material, so the mixture was heated to 50°C for 15 min. The bulk of the dimethoxyethane was removed under reduced pressure, then the thick oil adsorbed from dichloromethane onto 50 g of silica gel (flash). Sulphurous impurities (30 mg) were followed by 406 mg of crystalline solid. This was distilled over a short path at 135°C, 0.02 Torr, giving 390 mg (95%) of crystalline thiolactam. This had mp 52°C and ν_{max} (film) 1675 cm^{-1}. Its ^{1}H nmr spectrum had signals at δ 0.8–2.5 (ca. 14H), 2.75–3.05 (2H, m), 3.65–4.0 (1H, m), and 4.15–4.45 (1H, m). Its ^{13}C nmr spectrum had signals at δ 13.9(q), 14.7, 19.9, 21.6, 27.7, 29.4, 32.7, 44.2 (triplets), 46.2(d), 54.8(d), and 198.5(s). Its mass spectrum had m/z 197 (90), 196 (25), 168 (26), 164 (27), 155 (100), and 122 (74). *Anal.* calcd. for $C_{11}H_{19}NS$: C 66.97, H 9.71, N 7.10, S 16.22; found: C 67.08, H 9.81, N 7.20, S 16.25.

α,β-Unsaturated ketone 33

A solution of 437 mg of crystalline thiolactam **32** and 495 mg of 1-bromo-2-butanone in 5 mL of dry ether was prepared. The solution became milky and in 2.5 h an oil had separated. The ether layer was separated and evaporated. An ether extraction of the residue left more insoluble gum. The combined ether-insoluble product was dissolved in 5 mL of dry dichloromethane. Triphenylphosphine (597 mg) was added, followed by a solution of 451 mg of dry triethylamine in 2 mL of dry dichloromethane. The mixture became warm and a yellow color developed. This was left overnight at room temperature (now burgundy color). The solvent was removed *in vacuo* leaving a mush of crystals and oil. This was suspended in 10 mL of 10% ethyl acetate in hexane. The crystals were removed by filtration, then washed with 5 mL of the same solvent. The filtrate was evaporated, then extracted with more 10% ethyl acetate in hexane. This left a small amount of dark tar. The solution gave 685 mg of reddish brown oil. This was adsorbed from CH_2Cl_2 on 30 g of tlc silica gel and eluted with 20% ethyl acetate in dichloromethane. Early eluates gave 121 mg of orange crystals, followed by the desired product (567 mg). This was distilled over a short path at 150°C, 0.2 Torr, giving 434 mg (83%) of thick yellow oil. This had λ_{max} 308 nm, ε 31 000, and ν_{max} (film) 1652 and 1550 cm^{-1}. Its ^{1}H nmr spectrum had signals at δ 1.05 (3H, t, J = 7 Hz), 1.3–3.1 (15H), 3.3–3.85 (3H), and 4.85–5.15 (1H, m). Its ^{13}C nmr had signals at δ 88(d), 163.5(s), and 197.2(s). Its mass spectrum had m/z 235 (21), 206 (73), 192 (26), 164 (30), 138 (21), and 136 (100). *Anal.* calcd for $C_{15}H_{25}NO$: C 76.54, H 10.7, N 5.95; found: C 76.32, H 10.82, N 5.88.

Keto bases 34 and 35

The α,β-unsaturated keto base **33** (433 mg) was dissolved in 3 mL of methanol containing 141 mg of sodium cyanoborohydride. Bromocresol green indicator was added. A 2 N solution of hydrogen chloride in methanol was added dropwise with stirring until the solution remained yellow. After a total of 1 h the solution was evaporated, sodium carbonate solution added, and the product extracted into dichloromethane. The 456 mg of product was converted to its sulfate in methanol, then the solvent removed *in vacuo*. A cold solution of the salt in 4 mL of acetone was oxidized with a small excess of Jones' reagent (20); the excess after 10 min was destroyed with 2-propanol. The acetone solution and chromium salts yielded 379 mg of dichloromethane-soluble light brown oil. This was converted to its hydrochloride in methanol, the solvent removed, then acetone added. Addition of ether gave some crystalline hydrochloride. The remainder was separated on three 1000-μm silica gel plates using 15% ethanol in chloroform. A narrow blue band was followed by a zone rich in the crystalline hydrochloride, then one rich in amorphous hydrochloride. The crystalline hydrochloride from both zones (acetone–ether or ethyl acetate) was combined with the first crop of crystals, giving 200 mg (40%) of the hydrochloride of **34**. The amorphous hydrochloride (mainly that of **35**) weighed 198 mg (39%).

Keto base 34

The base liberated from the pure crystalline hydrochloride was an oil with ν_{max} 1712 cm^{-1} (film) and ^{1}H nmr signals at δ 2.8–3.3 (1H, m), 2.2–2.7 (4H, m), 1.13, 1.08, and 0.98. Its ^{13}C nmr spectrum had signals at δ 210.1(s), 55.8, 54.3, 52.9, 46.7, 37.0, 32.5, 29.8, 27.9, 23.4, 20.8, 19.2, 14.4, and 7.7. *Anal.* calcd. for $C_{15}H_{27}NO$: C 75.89, H 11.46, N 5.90; found: C 75.91, H 11.47, N 6.03.

Its hydrochloride crystallized from acetone–ether as needles or tiny prisms with mp 154°C, ν_{max} ($CHCl_3$) 1715 cm^{-1}, and ^{1}H nmr signals at δ 4.45 (1H br) and 3.85 (1H br). It gave ^{13}C nmr signals at δ 206, 63.3,

59.7, 56.0, 39.8, 36.8, 32.5, 27.8, 27.3, 27.1, 26.6, 22.5, 18.5, 13.5, and 7.2.

Keto base 35

The base liberated from the amorphous hydrochloride was an oil with ν_{max} 1712 cm^{-1} (film) and ^1H nmr signals at δ 3.7–4.0 (1H, br), 2.0–2.7 (7H, m), 1.16, 1.07, and 0.96. Its ^{13}C nmr spectrum had signals at δ 211.5(s), 59.4(d), 56.9(d), 55.0(d), 39.1, 37.0, 36.1, 32.3, 30.8, 29.7, 27.5, 24.7, 18.9, 14.6, and 7.9. It gave *m/z* 237 (3.2), 194 (100), 166 (90), and 122 (46). *Anal.* calcd. for $C_{15}H_{27}NO$: C 75.89, H 11.46, N 5.90; found: C 75.92, H 11.27, N 5.98.

Ethylene thioketal hydrochloride 36

Crystalline keto base **34** hydrochloride (mp 153°C, 78 mg) was dissolved in 1 mL of dry ethanol-free chloroform, then 0.3 mL of 1,2-ethanedithiol and 0.4 mL of freshly distilled $BF_3 \cdot Et_2O$ added. The mixture was left at room temperature for 4 h, then evaporated *in vacuo*. The semisolid residue was dissolved in dichloromethane, then the solution washed with dilute aqueous sodium hydroxide. The base recovered from the dichloromethane extracts was converted to its hydrochloride using HCl in methanol. The methanol was evaporated and the product crystallized from ethyl acetate, giving 93 mg, mp 173°C (90%). This was recrystallized for analysis from dichloromethane – ethyl acetate, giving tiny rosettes, mp 172–174°C. It gave ^1H nmr signals at δ 4.25 (1H, br m) and 3.32 (4H, s). *Anal.* calcd. for $C_{17}H_{32}ClNS_2$: C 58.35, H 9.22, N 4.00; found: C 60.37, H 9.62, N 4.10.

dl-*Gephyrotoxin 223AB* (*4*)

To a solution of 105 mg of ethylenethioketal **36** in 4.5 mL of absolute ethanol was added 430 mg of freshly prepared W2 Raney nickel (14). The suspension was refluxed under argon for 3.5 h, cooled, then filtered through a bed of Celite. The filtrate and ethanol washings were acidified using hydrogen chloride in ethanol, then evaporated under reduced pressure. The residue (66 mg, 87%) crystallized. This was purified on a 1000-μm silica gel plate using 15% ethanol in chloroform for development. A faint mauve band (R_f 0.6) was followed by the toxin hydrochloride. The 49 mg (63%) of salt crystallized from ethyl acetate – ether as flat needles, mp 129–131°C. The base liberated from the hydrochloride distilled over a short path at 95°C under 0.4 Torr. It gave ^{13}C nmr signals in $CDCl_3$ at δ 59.1, 58.6, 56.7, 36.0, 32.5, 31.1, 30.2, 29.3, 26.5, 25.1, 24.8, 23.0, 19.0, 14.6, and 14.2. In C_6D_6 the signals were at δ 59.0, 58.7, 56.4, 36.6, 33.1, 31.5, 30.8, 29.6, 27.1, 25.3, 23.4, 18.7, 14.9, and 14.4 (apparently two signals near 25 ppm were coincident).

The spectrum in deuteriochloroform was nearly identical to that reported by Royer and Husson (12) for their synthetic isomer, and to that recorded for natural gephyrotoxin 223AB by Professor T. Tokuyama and co-workers (10) (see glc comparison for the salt).

dl-*Gephyrotoxin 223AB hydrochloride* (*4 hydrochloride*)

The analytic specimen, mp 131°C, gave ^1H nmr signals at δ 3.85 (1H, br), 2.95 (2H, b), 2.08, 2.0, and 0.94 (center of a poorly resolved triplet) and ^{13}C nmr signals at δ 62.9(d), 59.95(d), 59.6(d), 32.6(t), 27.9(t), 27.54(t), 27.46(t), 27.36(t), 26.4(t), 24.9(t), 22.9(t), 22.4(t), 18.7(t), 13.7(q), and 13.6(q).

Comparison with various stereoisomers (glc) was kindly made by T. F. Spande[4] using a 30.5-m glass capillary column with SP-1000 stationary phase at 140°C, helium carrier gas, and flame ionization detector. The hydrochloride was shown to contain 98.6% of gephyrotoxin 223AB (**4**) (5*E*,9*E* isomer) and 1.4% of the 5*E*,9*Z* diastereoisomer.[9]

dl-*Gephyrotoxin 223AB hydrobromide*: A solution of the free base in methanol was acidified with hydrogen bromide in methanol, the solvent removed *in vacuo*, and the salt recrystallized from acetone. It formed flat needles with mp 147–150°C. Good-sized crystals grown slowly from acetone were used for X-ray crystallography (13). Its mass spectrum gave peaks at *m/z* 223 (2.8) (M^+), 222 (2.7), 180 (93), and 166 (100).

[9]This stereochemical designation gives the relation (*Z* = *syn*, *E* = *anti*) of the 5- and 9-hydrogens to the 3-hydrogen.

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