STUDIES DIRECTED TOWARD THE TOTAL SYNTHESIS OF PERHYDROHISTRIONICOTOXIN

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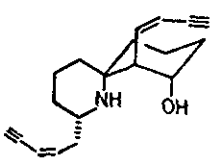
Variations on a new synthetic approach to perhydrohistrionicotoxin (2) are described.

Histrionicotoxin (1), a spirocyclic alkaloid isolated from the skin of the brightly colored frog Dendrobates histrionicus,[1] and various structural analogs possess unique properties as cholinolytics and modifiers of specific ionic channels in nerves.[2] The perhydro derivative 2, which is not a naturally occurring form,



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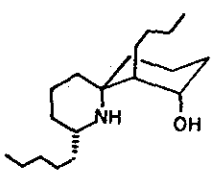
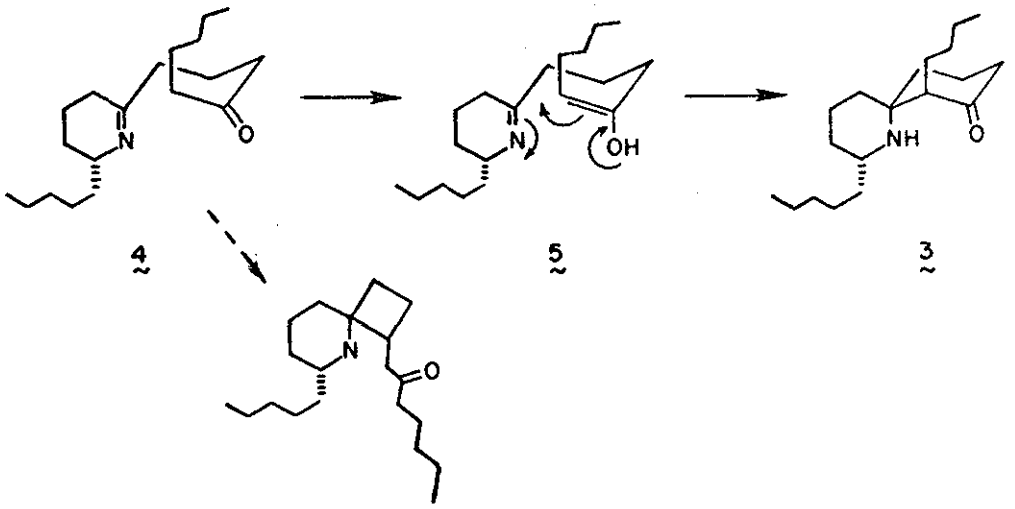


2

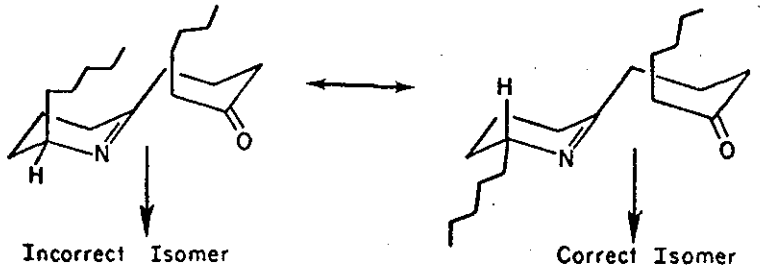
has comparable activity. Recent studies of synaptic transmission of nerve impulses have indicated that perhydrohistrionicotoxin (2) can cause transient depolarization of the nerve membrane, apparently by increasing its permeability toward potassium ions and to a lesser extent sodium ions.[2] However, the use of naturally derived 1 or its derivatives as probes for the study of nerve impulse transmission is limited by their scarcity, as each frog skin contains only 200 μg of 1. For this reason several synthetic routes to these compounds have been developed.[3,4] In continuation of work in these laboratories, still other approaches to the total synthesis of perhydrohistrionicotoxin (2) have been explored, and these are described herein.

Perhydrohistrionicotoxin (2) is a [5,5] spirocyclic compound in which one ring contains a secondary nitrogen atom adjacent to the ring junction, while the second ring bears a hydroxyl group in a 1,3 diaxial relationship to this nitrogen atom. The synthetic routes outlined here were based on the assumption that perhydrohistrionicotoxin (2) might be formed stereospecifically by reduction of the carbonyl group in the

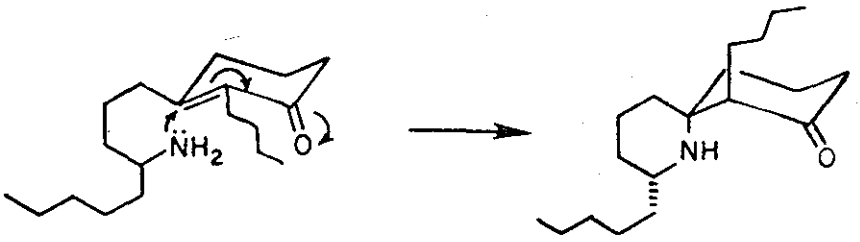
β-aminoketone 3, an intermediate which might be derived in a simple way using either of two standard condensation reactions. The first is the intramolecular Mannich reaction of a ketone and an imine (i.e., 4→5→3):[5]



It seemed reasonable that the [5,5] spirocyclic product 3 rather than the isomeric cyclobutane should be obtained in this process. Further, the chiral center bearing the amyl side chain might provide stereochemical direction since steric interaction between the amyl and butyl groups should hinder formation of the undesired epimer.



The second approach involves the intramolecular 1,4 addition of an amine to an enone (i.e., the conversion of 6 to 3). Similar 1,4 addition reactions have been used to prepare fused ring systems.[6] As in the Mannich reaction (vide supra), the desired orientation of the amyl side chain would be expected. Both of these reaction sequences have been examined with the results described below.



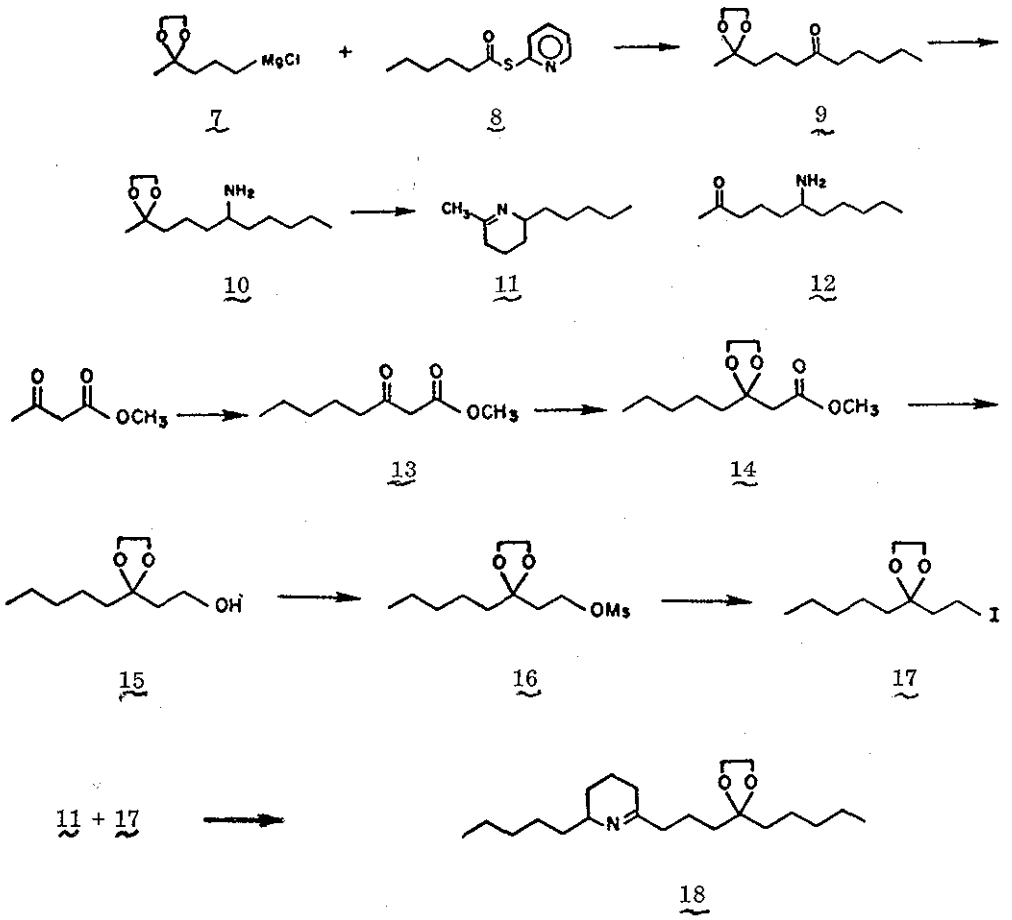
6 3

RESULTS AND DISCUSSION

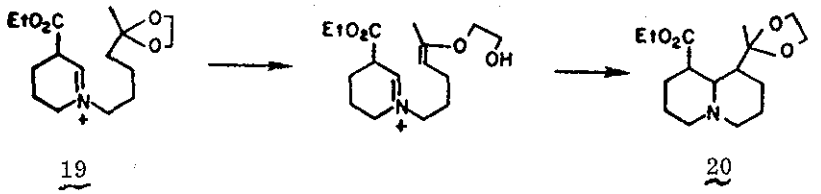
The Mannich Approach. The preparation of the requisite tetrahydropyridine derivative 4 was straightforward and involved the convergent synthesis illustrated in Scheme I. The Grignard reagent derived from 5-chloro-2-pentanone ethylene ketal (7)[7] was condensed with the 2-thiopyridine ester of hexanoic acid (8), affording the ketal-ketone 9 in high yield.[8] Reductive amination using ammonia and Raney nickel under high pressure gave the amine 10 in 70% yield.[9] Finally, extraction of the amine into aqueous hydrochloric acid, neutralization, and re-extraction into ether furnished the imine 11 in 57% overall yield from 8.[10] None of the acyclic aminoketone 12 was observed.

The side chain of 4 was constructed via a simple five-step procedure: the dianion of methyl acetoacetate was allowed to react with butyl bromide to give the ketoester 13 in 50% yield.[11] Ketalization followed by lithium aluminum hydride reduction afforded the hydroxy ketal 15 in high yield. Finally, treatment of the corresponding mesylate with sodium iodide in acetone[12] produced the iodide 17 (38% overall yield from methyl acetoacetate). Following the procedure of Evans,[13] the anion of 11 was allowed to react with excess 17 in tetrahydrofuran, initially at -78° followed by warming to room temperature; the iminoketal 18 was isolated in 63% yield after chromatography.

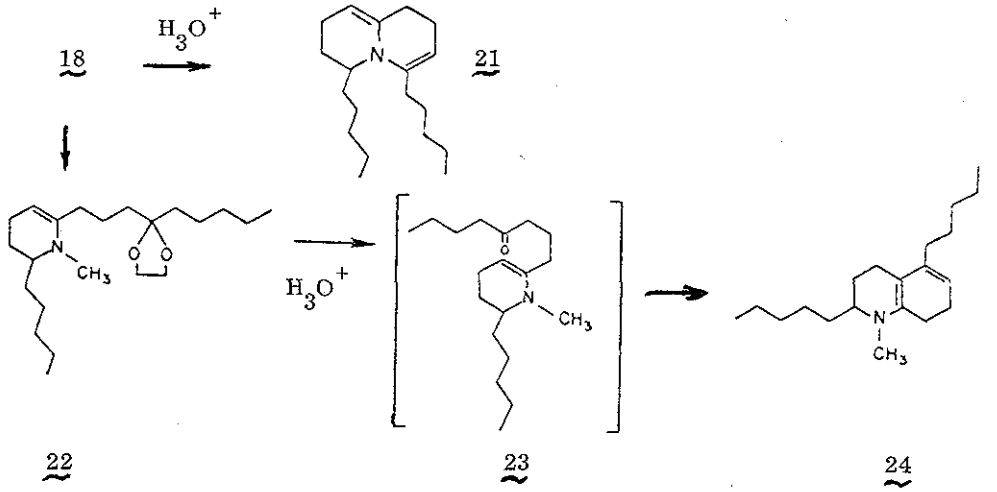
SCHEME I



With the desired imine in hand, investigation of the Mannich reaction was begun. Initial experiments centered on effecting cyclization by participation of the ketal group. Wenkert had found that imine 19 underwent cyclization to give amine 20 in high yield upon treatment with anhydrous acid.[14] However, on exposure of 18 to mild acid no reaction was observed, and upon treatment with strong acid only polymeric material was obtained.



The imino ketal 18 could be hydrolyzed to give the ketone 4 by a rapid acid extraction. The desired iminoketone was isolated and characterized by its spectral properties but was found to be very unstable. Upon prolonged exposure to a wide range of acidic conditions, 4 was converted to the dienamine 21. In an effort to suppress this reaction, 18 was treated with 1.0 equivalent of methyl fluorosulfonate[15] affording the enaminoketal 22 in 83% yield. However, upon hydrolysis of the ketal a second undesired cyclization occurred to give diene 24.



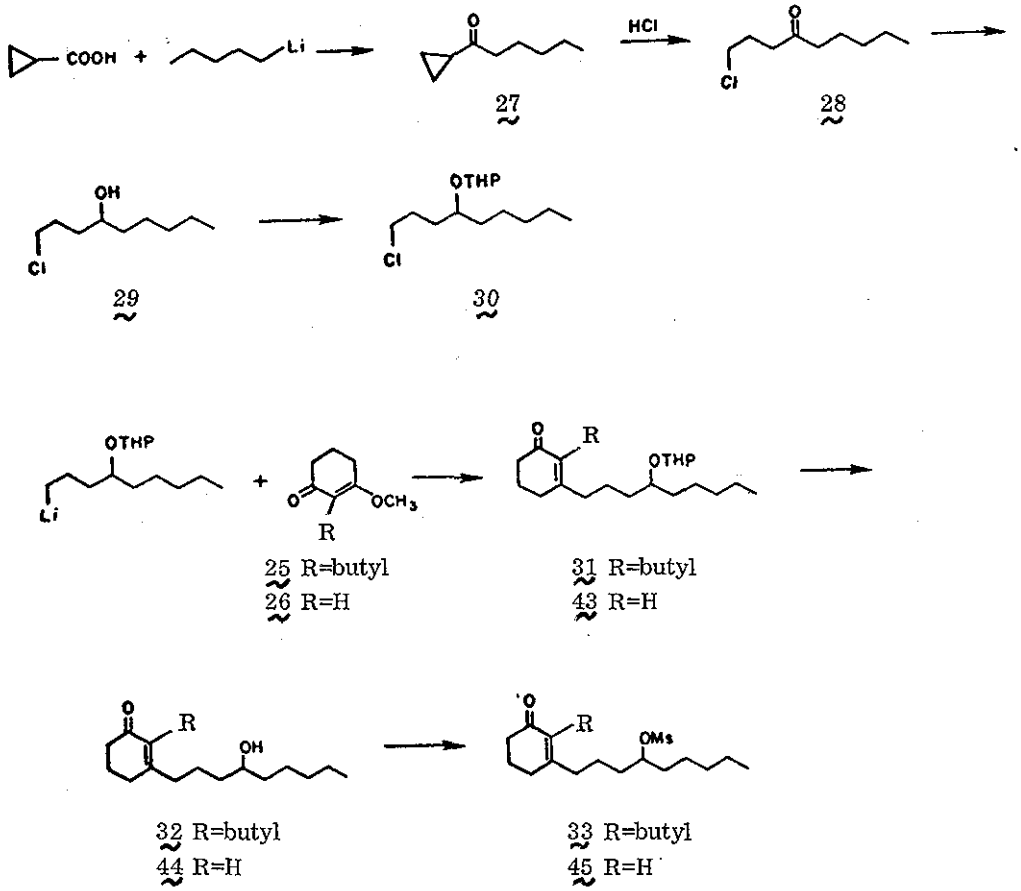
22 23 24

THE MICHAEL ADDITION APPROACH. Since formation of the spirocyclic system via the Mannich reaction could not be achieved, attention was directed at the intramolecular 1,4 addition of the primary amine 6. To begin, 1-chloro-4-nonanol tetrahydropyranyl ether (30) was prepared by a four-step procedure (Scheme II): addition of two equivalents of amyllithium to cyclopropane carboxylic acid gave amyl cyclopropyl ketone (27).[16] Reaction of 27 with dry hydrogen chloride in ether furnished the δ-chloroketone 28,[17] which upon reduction with lithium aluminum hydride at -78° and protection with dihydropyran afforded 30 in 41% overall yield.

The lithium reagent derived from 30 was added to 2-n-butylcyclohexan-1,3-dione methyl enol ether (25) giving enone 31 in 67% yield after chromatography. Cleavage of the tetrahydropyranyl group with acetic acid produced the alcohol 32 in quantitative yield. Finally, the mesylate 33 was formed in the usual manner with the mesyl

chloride--triethylamine reagent.[18]

SCHEME II



27 28 29 30

25 R=butyl
26 R=H

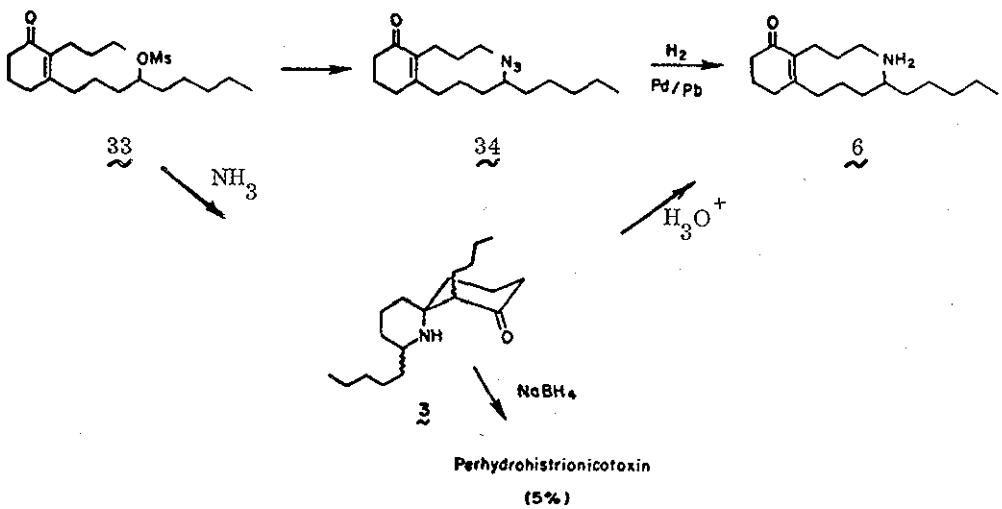
31 R=butyl
43 R=H

32 R=butyl
44 R=H

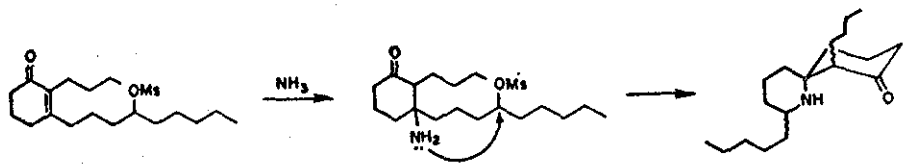
33 R=butyl
45 R=H

Two possible pathways from mesylate 33 to amine 6 were examined. First, mesylate 33 was converted to azide 34 by reaction with lithium azide in wet tetrahydrofuran.[19] Hydrogenation over Lindlar catalyst[20] gave the amine 6 in 81% yield overall from the mesylate. The infrared spectrum of this intermediate contained a single carbonyl band due to the enone; no evidence for the formation of the Michael adduct 3 was observed (i.e., there was no saturated carbonyl band in the infrared spectrum at ca. 1700 cm^{-1}). Alternatively, when an ethanolic solution of 33 was saturated with ammonia and heated at 60° for 18 hours in a sealed tube, the infrared spectrum of the crude reaction mixture indicated ca. 40% conversion to a

saturated carbonyl compound. When this material was allowed to stand at room temperature for 10 hours, however, the infrared spectrum showed complete conversion to the enone 6. Furthermore, extraction of the mixture into aqueous acid, neutralization, and re-extraction into ether, afforded only enone 6. Immediate treatment of the crude reaction mixture with sodium borohydride in methanol yielded a complex mixture of alcohols. One of the products isolated in 5% yield was indistinguishable from perhydrohistrionicotoxin (2) by thin layer chromatography and clearly different from various stereoisomers described below. Although the material obtained was insufficient for measurement of pmr and ir spectra, the mass spectrum of this compound was superimposable with the spectrum of a natural sample of 2.



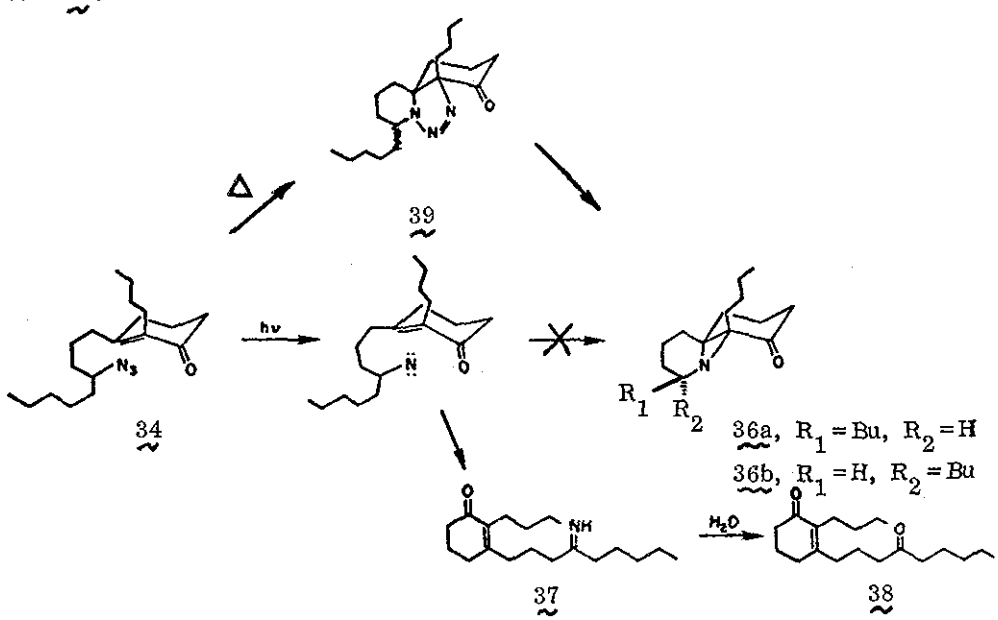
Further experiments were performed in an effort to determine the pathway of this interesting reaction. When the amine 6 was treated with ammonia in the same fashion as described for the mesylate 33, no cyclization was observed. This implies that ammonia first attacks the enone portion of 33 giving 35, with subsequent displacement of the mesylate by the amine in an intramolecular fashion. No control over stereochemistry is anticipated from this mechanism.



33 35 3

Numerous attempts to convert amine 6 to the bicyclic β-aminoketone 3 under various acidic and basic conditions failed. Our attention then turned to a possible intramolecular photochemical ring closure. It is known that alcohols can undergo photochemical addition to enones.[21] However, upon exposure of amine 6 to ultraviolet light (Corex filter) in various solvents for prolonged periods, no reaction was observed.

The Aziridine Approach. At this point studies using amine 6 were abandoned and attention was directed to azide 34. Photolysis of an azide affords a nitrene intermediate,[22] which can either add to an olefin to form an aziridine or undergo hydrogen shift giving an imine.[23] It was hoped that irradiation of the azido enone 34 would furnish the tricyclic aziridine 36a. However, the imine 37 was the sole product of this reaction. The structure of 37 was indicated by ready hydrolysis to the ketone 38.



Azides also undergo thermal [3+2] cycloaddition to strained olefins to form triazolines. Cyclopentene, for example, reacts with phenyl azide at room temperature to furnish a triazoline which can be converted thermally to an imine or photochemically to an aziridine.[24] It was anticipated from mechanistic considerations that the azide group of 34 might undergo an intramolecular 1,3 dipolar addition to the enone system to give the triazoline 39. Surprisingly, when 34 was heated in refluxing xylene for 6 hours, the tricyclic aziridine 36 was isolated in high yield. During the reaction, an intermediate product appears by thin layer chromatography, presumably the unstable triazoline 39. Apparently, the rate of decomposition of 39 at this temperature is comparable to its rate of formation.

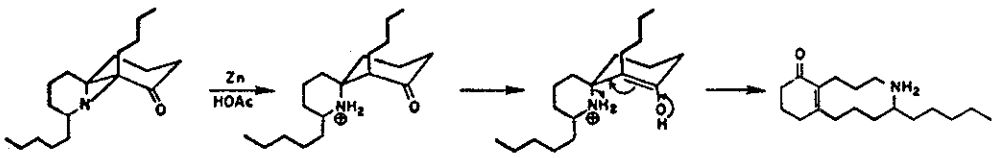
Vpc analysis of the tricyclic product 36 indicated it to be a mixture of diastereomers differing in orientation of the amyl substituent in a 2:1 ratio. At this stage in the synthesis it was not clear which of isomers 36a or 36b was the desired product. Further studies indicated that at lower temperatures the selectivity of the reaction increased; in refluxing benzene only one isomer was formed. These reactions are summarized in Table I.

Table I. Thermal Intramolecular Additions of Azide 34.

solvent	temp (°C)	36a/36b epimer ratio	yield (%)	reaction time (hr)
xylene	136	2:1	60	6
toluene	110	4:1	75	36
heptane	98	6:1	86	120
benzene	80	1:0	ca. 90	ca. 336
dimethylformamide	156	1:1.5	50	1.5

Conversion of the tricyclic aziridine to perhydrohistrionicotoxin (2) would require reductive cleavage of the three membered ring giving the spirocyclic ketone 3, followed by selective reduction of the ketone to the axial alcohol. Upon treatment of the major aziridine isomer 36a with zinc in acetic acid at room temperature, the aziridine bond was indeed cleaved. However, the sole isolated product was not the spirocyclic aminoketone 3, but rather the monocyclic amino enone 6 resulting

from a retro-Michael reaction. Since the spirocyclic β-aminoketone apparently is extremely sensitive to acid, the reduction was attempted under non-acidic conditions. Treatment of 36 with aluminum amalgam gave no reaction. However, exposure of 36a to

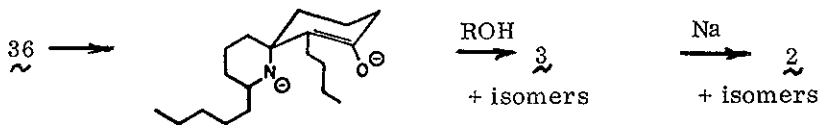


36 6

sodium in isopropyl alcohol did effect reduction of the tricyclic system to the bicyclic β-aminoketone 3. Under the reaction conditions, the ketone group of 3 was also reduced, affording a 1:1 mixture of two unnatural isomers of perhydrohistionicotoxin. These compounds were characterized by their pmr and mass spectra. The mass spectra were similar to the spectrum of 2 except for small differences in relative peak intensities.

In the sodium--isopropanol reduction, the first intermediate is the dianion 40, which is not susceptible to further reduction. However, protonation of 40 by the solvent yields the β-aminoketone 3, which is then reduced further to give an isomeric perhydrohistrionicotoxin derivative.

These results hinted that reduction of 36 under aprotic conditions might



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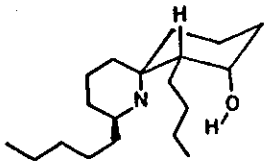
furnish the desired spirocyclic ketone 3. Thus the major azirdine isomer was treated with 2.2 equivalents of lithium in ammonia at -33° in the absence of a proton source. After the blue color had dissipated, the ammonia was evaporated. The product was isolated by ether extraction after quenching with water. Its infrared spectrum

contained a carbonyl band at 1700 cm^{-1}, consistent with the formation of 3; there were no bands which indicated that enone 6 or over reduced products were present. Without delay this material was reduced with sodium borohydride in methanol at -40°. The major isolated product was the epi-amyl-epi-butylperhydrohistrionicotoxin isomer 41, identical to a sample prepared in these laboratories.[3e] The structure of this compound has been established by X-ray crystallography. This result indicated that aziridine isomer 36a, possesses the incorrect orientation of the amyl side chain.

To confirm these structural assignments, the minor isomer 36b was purified and subjected to the two-step reduction process. As expected, the product mixture contained none of epi-epi 41. It did contain ca. 15% of perhydrohistrionicotoxin (2) which was identified by comparison with an authentic sample.

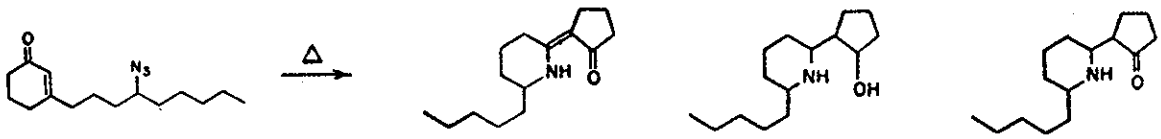
A major difficulty inherent in this approach is the lack of control over the stereochemistry of the butyl side chain which is established via protonation of an enolate ion (i.e., 40 → 3). In contrast, it was anticipated that the introduction of the butyl group by a nucleophilic attack on the aziridine ring of 42 would ensure formation of the desired butyl epimer. The preparation of aziridine 42 was



41

undertaken by a route analogous to that used in the synthesis of 36 (Scheme II, R = H). The azido enone 46 was heated in refluxing xylene for 10 hours affording a

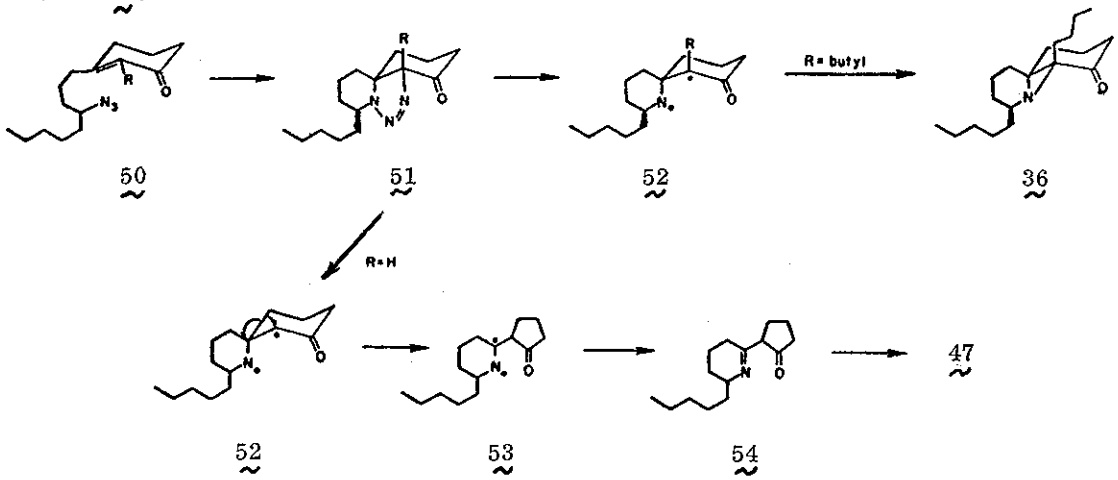
42 → 3



46 → 47, 48, 49

single product in high yield. However, the desired tricyclic aziridine 42 was not obtained. The infrared spectrum of the product contained sharp bands at 1623 and 1580 cm^{-1} and its ultraviolet spectrum had a strong absorption at 3310 Å.[25] This data, coupled with a mass spectrum and elemental analysis, indicated that the vinylogous amide 47 had been formed. Further proof for this structure was obtained by conversion of 47 to 48 by catalytic reduction, followed by reoxidation to give cyclopentanone 49, ir max (CH_2Cl_2) 1740 cm^{-1}.

The origin of the vinylogous amide 47 and the factors responsible for the differing behavior of the azides 34 and 46 may be rationalized by consideration of various pathways for decomposition of the intermediate triazolines. In the case of the azide 50 with either R = H or alkyl addition to the enone system should form the triazoline of type 51. Thermal decomposition of the triazoline can be expected to afford the triplet diradical 52.[24] When R = alkyl, the tertiary radical at carbon is relatively stable and probably is sufficiently long lived to give the singlet diradical which immediately closes to form the aziridine ring system 36b. However, when R = H, the unstable secondary radical possibly does not survive long enough for the spin inversion to occur and instead suffers rearrangement to the tertiary radical 53 from which the iminoketone 54 results; this isomerizes to give the vinylogous amide 47.

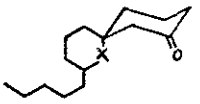


50 51 52 36

52 53 54 47

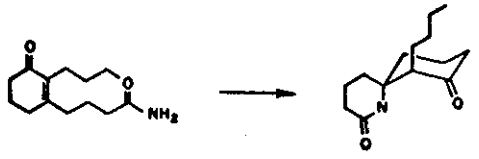
Further Examples of the Michael Reaction. During examination of the trisubstituted enone system, two interesting Michael reactions were observed. Upon

hydrolysis of the tetrahydropyranyl ether of 43 with strong acid (i.e., aqueous hydrochloric acid), none of the hydroxy enone 44 could be isolated. Instead a 1:1 mixture of epimeric spirocyclic ethers 55 were obtained in high yield. The tetrasubstituted enone tetrahydropyranyl ether 31 did not undergo this reaction. Further hydrogenolysis of the trisubstituted azido enone 46 over Lindlar catalyst afforded a 1:1 mixture of isomeric spirocyclic amines 56 in quantitative yield. These cyclization reactions are consistent with earlier findings.[6] The failure of



55, X=O
56, X=NH

the amine 6 to undergo the synthetically crucial intramolecular Michael reaction is likely due to unfavorable steric repulsion between the two side chains and the nearby ring hydrogens upsetting a delicate balance which disfavors the [5,5] spiro system only when both side chains are present. From this analysis one might expect that spiro cyclization would occur if the amyl group of 6 were lacking. In fact, Kishi et al. have recently shown that a Michael addition of 57 proceeds readily to give the spirocyclic lactam 58.[3c]



57 58

EXPERIMENTAL SECTION

General. All reactions involving oxygen or moisture sensitive compounds were conducted under an atmosphere of argon introduced by alternately evacuating and filling the reaction vessel with argon at least three times. During the reaction a positive inert atmosphere was maintained by opening the system to an argon filled balloon. Liquids were introduced or removed from the reaction vessel by syringe through a rubber serum cap attached to a side-arm of the reaction vessel. Solvent mixtures are expressed in parts by volume. Organic solutions of reaction products were dried by washing with saturated sodium chloride solution, followed by treatment with anhydrous magnesium sulfate, unless otherwise noted. Removal of solvent was effected at room temperature using a Buchi rotary evaporator at aspirator pressure unless otherwise noted. Infrared (ir) spectra were recorded using either a Perkin Elmer Model 137 or Model 267 spectrophotometer. Ultraviolet (uv) spectra were determined in ethanol using a Perkin Elmer Model 202 instrument. Proton magnetic resonance (pmr) spectra were determined in deuteriochloroform with 1% tetramethylsilane (TMS) as an internal standard unless otherwise noted using either a Varian A-60, T-60, HA-100, or XL-100 spectrometer. Data are reported as δ in parts per million shift downfield from TMS. Mass spectra were determined using an AEI Model MS-9 spectrometer. A Hewlett-Packard Model 5750 gas chromatograph (nitrogen carrier gas, 30 ml/min, flame ionization detector) was used for analytical gas-liquid chromatography. Analytical thin layer chromatography (tlc) was carried out using Merck precoated, glass-backed silica gel F-254 or aluminum oxide F-254 Type T plates, 0.25 mm thick.

Undecan-2,6-dione 2-ethylene ketal (9). The Grignard reagent[7] derived from 5-chloro-2-pentanone ethylene ketal (16.5 g, 100 mmol) was prepared in refluxing THF (100 ml).[7] A second flask was charged with the 2-thiopyridine ester of hexanoic acid 8 (bp 135-138° (1.5 mm)) (10.5 g, 50 mmol) in 50 ml of THF and cooled to 0°. The Grignard reagent was added dropwise with rapid stirring and after one additional hour at 0°, 1 ml of water was added and a bright yellow precipitate formed. The organic layer was separated and extracted twice with 10% sodium hydroxide. Evaporation of solvent gave 6.4 g (93% yield) of the keto ketal 9; ir (neat) 1705 and 1050 cm^{-1}.

6-Amino-2-undecanone ethylene ketal (10). Undecan-2, 6-dione 2-ethylene ketal (9) (3 g, 13.2 mmol) was dissolved in 60 ml of absolute ethanol. The solution was saturated with ammonia, 1 g of Raney nickel (W2) was added, and the reaction vessel was sealed in a bomb apparatus under 1800 lbs pressure of hydrogen at 100° for 10 hr. The catalyst was removed by filtration and the solvent was evaporated *in vacuo*. The resulting cloudy liquid was dissolved in methylene chloride and was dried over magnesium sulfate. Evaporation of solvent gave 2.6 g (87% yield) of pure amine 10; ir (neat) 3380 (w) and 1050 cm^{-1}; an exact mass determination gave m/e 229.2039 (calcd for $C_{13}H_{27}NO_2$: 229.2039).

6-Pentyl-2-methyl-3,4,5,6-tetrahydropyridine (11). 6-Amino-2-undecanone ethylene ketal (10) (1 g, 4.35 mmol) was dissolved in 50 ml of ether. The ether layer was extracted three times with 25 ml portions of 10% hydrochloric acid. The combined acidic layers were washed once with ether. Neutralization of the aqueous layers with 10% sodium hydroxide, extraction with ether, and evaporation of solvent, gave 0.50 g (70% yield) of the pure imine 11 as a clear oil: R_f (alumina, ether) = 0.70; pmr (CCl_4) δ 0.90 (t, J = 6 Hz, 3 H, CH_3-CH_2-), 1.80 (d, J = 1 Hz, 3 H, N=C-CH_3), 1.95 (m, 2 H, N=C-CH_2-), and 3.05 (broad, 1 H, H-C-N=C-); ir (neat) 2915, 2860, 1660, 1460, and 1370 cm^{-1}; mass spectrum m/e (%): 167 (P, 29), 152 (18), 138 (12), 110 (100), 97 (71), and 96 (76); an exact mass determination gave m/e 167.1670 (calcd for $C_{11}H_{21}N$: 167.1674).

Methyl 3-keto-octanoate (13). Sodium hydride (350 mmol), 500 ml of THF, and 100 ml of HMPA were cooled to 0° under argon. Methyl acetoacetate (40.6 g, 350 mmol) (neat) was added dropwise over a 45-min period. Vigorous evolution of

gas ensued during the addition and the solution became light yellow in color. Butyllithium (350 mmol, 1 equiv) was added dropwise, and the orange solution was stirred for an additional 30 min. Butyl bromide (44 g, 350 mmol) in 100 ml of THF was added, and stirring was continued at 0° for 2 hr. The reaction was quenched with 50 ml of 10% hydrochloric acid. Evaporation of solvent gave 51 g of crude material. Distillation afforded the pure alkylated product 13 (32.5 g, 50% yield): bp 77-79° (1.0 mm); lit. bp 53-54° (0.4 mm).[26]

Methyl 3-keto-octanoate ethylene ketal (14). A benzene solution of the 3-keto ester 13 was treated in the standard fashion in benzene with 2 equiv of ethylene glycol at reflux under a Dean-Stark trap for 18 hr. The ketal 14 was isolated as a clear oil (100% yield): bp 97-99° (1 mm); pmr (CCl_4) δ 0.9 (m, 3 H, CH_3-CH_2-), 2.5 (s, 2 H, -$\overset{|}{\underset{|}{C}}$-$CH_2$-COO-), 3.6 (s, 3 H, CH_3O-) and 3.9 (s, 4 H, ketal).

1-Hydroxy-3-octanone ethylene ketal (15). Methyl 3-keto-octanoate ethylene ketal (14) was reduced with lithium aluminium hydride in ether at 0°. The hydroxy ketal 15 was isolated as a clear oil (90% yield): R_f (silica gel, ether) = 0.70; bp 99-100° (1mm); ir (neat) 3400-3200, 1050 cm^{-1}.

1-Iodo-3-octanone ethylene ketal (17). The mesylate of 1-hydroxy-3-octanone ethylene ketal (15) was prepared in the usual manner from the alcohol, triethylamine, and methanesulfonyl chloride.[18] The mesylate 16 was immediately dissolved in acetone and was treated with 10 equiv of sodium iodide and 1 equiv of sodium bicarbonate at 50° for 10 hr. The iodide was isolated as a pale yellow oil (overall yield 84% from 15): R_f (silica gel, ether--hexane, 1:1) = 0.80; pmr (CCl_4) δ 0.9 (t, J = 6 Hz, 3 H, CH_3), 2.2 (m, 2 H, CH_2-CH_2-I), 3.2 (m, 2 H, CH_2I), and 3.95 (s, 4 H, ketal); ir (neat) 1050 cm^{-1}.

The Imino ketal 18. Lithium diisopropylamide was prepared from 15 mmol of diisopropylamine and 1.0 equiv of butyllithium in 50 ml of THF. The solution was cooled to -78° and 6-pentyl-2-methyl-3,4,5,6-tetrahydropyridine (11) (2 g, 12 mmol) in 10 ml of THF was added. The solution was allowed to warm slowly to -30° and was stirred at this temperature for 30 min. The bright orange solution was then cooled to -78° and 1-iodo-3-octanone ethylene ketal (17) (3.94 g, 13.2 mmol, 1.1 equiv) in 5 ml of THF was added dropwise. After the addition the reaction was

allowed to warm to room temperature over 2 hr. At -15° the orange color disappeared. The reaction was quenched with water. The aqueous phase was extracted with ether and the combined organic layers evaporated affording a crude yellow oil. Preparative column chromatography on basic alumina (ether--hexane, 1:1) gave 2.5 g (63% yield) of pure imino ketal 18: pmr (CCl_4) δ 0.90 (t, J = 6 Hz, 6 H, CH_3-), 2.0 (broad, 4 H, N=C-CH_2), 3.1 (broad, 1 H, CH-N), and 3.80 (s, 4 H, ketal); ir (neat) 1660, 1080, and 1050 cm^{-1}; mass spectrum m/e (%): 337 (P, 20), 304 (60), 266 (100), 194 (4), 167 (70), 166 (50), and 143 (100); an exact mass determination gave m/e 337.2978 (calcd for $C_{21}H_{39}NO_2$: 337.2981).

The Enamine Ketal 22. Methyl fluorosulfonate (1.5 equiv) was added dropwise to a solution of the imino ketal 18 (337 mg, 1 mmol) in 10 ml of methylene chloride at 0°. The solution was stirred for 1 hr and then a saturated solution of sodium bicarbonate was added. The layers were separated and the aqueous phase extracted twice with ether. The combined organic layers were dried over magnesium sulfate and were evaporated to afford 290 mg (83% yield) of enamine 22: pmr (CCl_4) δ 0.9 (t, J = 6 Hz, 6 H, methyls), 2.6 (s, 3 H, CH_3N), 3.8 (s, 4 H, ketal), and 4.3 (broad, 1 H, vinyl); ir (neat) 1640, 1460 and 1050 cm^{-1}; an exact mass determination gave m/e 351.3134 (calcd for $C_{22}H_{41}O_2N$: 351.3137).

Amyl cyclopropyl ketone (27). Amyllithium was prepared from amyl bromide and lithium (1% sodium) wire at 0° in ether. To 8.6 g (100 mmol) of cyclopropane carboxylic acid in 100 ml of ether at 0°, was added 2.1 equiv of amyllithium over a 45 min period. A precipitate formed immediately during the addition and the solution became very viscous. However, during the addition of the second equiv of the lithium reagent, the solution became less viscous and eventually clear. The reaction was stirred at room temperature for 1 hr and then was carefully syphoned into a rapidly stirred solution of saturated ammonium chloride. The organic phase was washed with 10% sodium hydroxide solution. Evaporation of solvent gave 15 g of a crude oil. Distillation afforded 10.5 g of pure cyclopropyl ketone 27 (75% yield); bp 83-92° (24 mm); pmr (CCl_4) δ 0.60-1.1 (m, 4 H, cyclopropyl), 0.9 (m, 3 H, CH_3), and 2.5 (broad t, J = 7 Hz, CH_2-C=O); ir (neat) 1700 cm^{-1}; an exact mass determination gave m/e 140.1206 (calcd for $C_9H_{16}O$: 140.1201).

1-Chloro-4-nonanone (28). Amyl cyclopropyl ketone (27) (14.0 g, 100 mmol) was dissolved in 200 ml of ether. Dry hydrogen chloride (gas) was bubbled into the rapidly stirred solution for 10 hr. The reaction was quenched by careful addition of a saturated sodium bicarbonate solution. Extraction of the aqueous phase with ether and evaporation of the combined organic layers gave 15 g (85% yield) of the pure chloride 28: bp 79-81° (1mm); pmr (CCl_4) δ 0.9 (t, J = 6 Hz, 3 H, CH_3), 2.45 (m, 4 H, CH_2-C=O), and 3.5 (t, J = 6 Hz, 2 H, CH_2-Cl); ir (neat) 1725 cm^{-1}.

1-Chloro-4-nonanol (29). To 1.15 g (1.4 equiv) of lithium aluminum hydride in 500 ml of dry ether at -78°, was added 17.6 g (100 mmol) of 1-chloro-4-nonanone (28) (neat) dropwise over 15 min. The resulting solution was stirred at -78° for 1 hr. The reaction was quenched with 1.2 ml of water and 1.2 ml of 15% sodium hydroxide (Fieser procedure) at -78°. The solution was allowed to warm to room temperature, at which time an additional 3.6 ml of water was added. Filtration and evaporation of solvent gave 16.9 g (95% yield) of the alcohol 29: pmr ($CDCl_3$) δ 0.9 (m, 3 H, CH_3), 3.4 (t, J = 6 Hz, 2 H, CH_2-Cl) and 3.5 (m, 1 H, CH-OH); ir (neat) 3400-3200 cm^{-1}.

1-Chloro-4-nonanol Tetrahydropyranyl Ether (30). The tetrahydropyranyl ether 30 was prepared in the usual manner from 10 g (56 mmol) of chloro-alcohol 29, 6.3 g (75 mmol) of dihydropyran, and 10 mg of p-toluenesulfonic acid in 120 ml of methylene chloride at room temperature for 6 hr. The light pink reaction mixture was quenched with a saturated solution of sodium bicarbonate. Evaporation of solvent gave 13 g of a crude oil. The oil was purified by passage through a column of silica gel. The pure tetrahydropyranyl ether 30 was isolated in 67% yield (10.4 g): pmr (CCl_4) δ 0.9 (broad t, J = 5 Hz, 3 H, CH_3), 3.6-3.7 (broad m, 5 H, CH_2-O-, CH-O-, CH_2Cl), and 4.5 (broad, 1 H, -OCHO-); an exact mass determination gave m/e 262.1702 (calcd for $C_{14}H_{27}O_2Cl$: 262.1699).

The Tetrasubstituted Enone Tetrahydropyranyl Ether 31. 1-Chloro-4-nonanol tetrahydropyranyl ether (30) (1 g, 3.85 mmol) was added rapidly to 10 equiv of lithium (1% sodium) wire in 20 ml of ether--THF (1:1) at 25° under argon. After 5 min the lithium wire became shiny. The solution was cooled to 0° and rapid stirring was continued for 2 hr until the lithium wire became dull in color. The methyl enol ether of 2-n-butyl-cyclohexan-1,3-dione (25) (364 mg, 2 mmol) in 2 ml of THF was added

dropwise. After stirring for an additional 2 hr at 0°, the reaction mixture was quenched with a saturated solution of ammonium chloride. The solvent was removed and the resulting oil was purified by plc on silica gel to give 510 mg (67% yield) of the pure enone 31: R_f (ether--hexane, 1:1) = 0.65; pmr ($CDCl_3$) δ 0.9 (broad, 6 H, CH_3), 1.2-2.0 (broad, 22 H), 2.3 (broad, 6 H, ring methylenes), 3.4-4.0 (broad, 3 H, -CHOTHP, $-CH_2-O$), and 4.6 (broad, 1 H, -O-CH-O); ir (neat) 2940, 2860, 1665, 1620, 1025, and 735 cm^{-1}; an exact mass determination gave m/e 378.3130 (calcd for $C_{24}H_{42}O_3$: 378.3134).

The Tetrasubstituted Enone Alcohol 32. The tetrasubstituted enone tetrahydropyranyl ether 31 (290 mg, 0.77 mmol) was dissolved in 20 ml of THF--acetic acid--water (3:2:1). The solution was heated at 50° for 5 hr. After cooling a saturated sodium bicarbonate solution was carefully added. The aqueous phase was extracted with ether and the combined organic layers were dried and evaporated giving 226 mg (100% yield) of the pure enone alcohol 32: R_f (silica gel, ether--hexane, 1:1) = 0.15; pmr ($CDCl_3$) δ 0.9 (broad t, J = 6 Hz, 6 H, CH_3), 2.25 (broad, 6 H, ring methylenes), and 3.5 (broad, 1 H, -CH-OH); ir (neat) 3600-3200, 1660 and 1615 cm^{-1}; an exact mass determination gave m/e 294.2557 (calcd for $C_{19}H_{34}O_2$: 294.2559).

The Tetrasubstituted Enone Mesylate 33. To 60 mg (0.204 mmol) of enone alcohol 32 and 276μl of triethylamine (202 mg, 2 mmol, 10 equiv) in 10 ml of dry methylene chloride under argon at -20°, was added 78μl (115 mg, 1 mmol, 5 equiv) of methanesulfonyl chloride. After the reaction was stirred for 1 hr, it was quenched with water. The solution was extracted with cold hydrochloric acid and cold sodium bicarbonate. After drying over sodium sulfate, the solvent was removed in vacuo affording 75 mg (100% yield) of the pure mesylate 33: R_f (silica gel, ether) = 0.85; pmr ($CDCl_3$) δ 0.9 (broad, 6 H, CH_3), 2.25 (broad, 6 H, ring methylenes), 3.0 (s, 3 H, CH_3-SO_2-), and 4.8 (broad, 1 H, -CH-OMs); ir (neat) 1665 and 1620 cm^{-1}.

The Tetrasubstituted Enone Azide 34. Sodium azide (15 g, 230 mmol) and lithium chloride (8.5 g, 202 mmol) in 200 ml of dry methanol were refluxed for 5 hr.[19] The solution was cooled to 0° and the sodium chloride was removed by filtration. The methanol was removed on a rotary evaporator and the resulting lithium azide was dissolved in 200 ml of THF--water (4:1) (concentration 0.9 M).

The enone mesylate 33 (372 mg, 1 mmol) was dissolved in 11 ml (10 equiv) of the lithium azide solution and was stirred for 48 hr at room temperature (ca. 25°). Ether was added and the organic phase was washed three times with water. Evaporation of solvent gave 270 mg (85% yield) of the pure azide 34 after chromatography (silica gel, ether-hexane, 1:1); pmr (CCl_4) δ 0.9 (broad t, J = 5 Hz, 6 H, methyl), 2.25 (broad, 6 H, ring methylenes), and 3.15 (broad, 1 H, $-\underset{1}{C}H-N_3$); ir (neat) 2100, 1665 and 1620 cm^{-1}; an exact mass determination gave m/e 319.2628 (calcd for $C_{19}H_{33}ON_3$: 319.2623).

The Tetrasubstituted Amino Enone 6. The azido enone 34 (319 mg, 1 mmol) was dissolved in 10 ml of absolute ethanol. Lindlar catalyst (5% Pd on calcium carbonate poisoned with lead) (100 mg) was added and the solution was stirred under an atmosphere of hydrogen for 3 hr. The catalyst was removed by filtration and the ethanol was evaporated yielding 280 mg (95% yield) of the amine 6: pmr (CCl_4) δ 0.9 (t, J = 6 Hz, 6 H, CH_3), 2.2 (m, 6 H, ring methylenes), and 2.6 (broad, 1 H, $-CH-NH_2$); ir (neat) 3360 (vw), 3300 (vw), 1660, 1615, 1460, 1360, 1180 and 1110 cm^{-1}; mass spectrum m/e (%); 293 (P, 4), 276 (5), 222 (18), 205 (5), 179 (47), and 100 (100); an exact mass determination gave m/e 293.2715 (calcd for $C_{19}H_{35}NO$: 293.2719).

The Tricyclic Aziridines 36a and 36b. The tetrasubstituted enone azide 34 (319 mg, 1 mmol) in 25 ml of dry heptane was refluxed under argon for 5 days. After cooling, the solution was extracted three times with 10% hydrochloric acid. The aqueous layers were extracted once with ether, and all of the organic layers were discarded. The aqueous phase was neutralized with 10% sodium hydroxide to pH >10. The aqueous layer was extracted with ether. After drying evaporation of solvent gave 250 mg (86% yield) of the pure aziridine 36. Vpc analysis of this compound showed it to be a 6:1 mixture of isomeric aziridines (major isomer is the epi-amyl compound 36a): R_t (4 ft, 3% OV-1, 200°) = 2.8 min (epi isomer 36a) and 3.3 min (natural isomer 36b); pmr ($CDCl_3$) δ 0.9 (m, 6 H, CH_3) and 3.15 (broad, 1 H, -CH-N); ir (neat) 1700, 1470, 1450, 1410, 1380, 1350, 1330, 1260, 1220, 1120, 1085 and 860 cm^{-1}; mass spectrum m/e (%): 291 (P, 29), 248 (100), 234 (21), 220 (43), 206 (79), and 192 (64); an elemental analysis gave C 77.94, H 11.59, and N 4.89 (calcd for $C_{19}H_{33}NO$: C 78.29, H 11.41, and N 4.81).

The Bicyclic β-Aminoketone 3. Ammonia (30 ml) was condensed into a 100 ml round-bottomed flask containing 100 mg of lithium wire. The dark blue solution was allowed to reflux for 30 min and was then distilled into a second flask containing 1.6 mg (0.22 mmol) of lithium. The aziridine 36a (29 mg, 0.10 mmol) in 2 ml of distilled ether was added rapidly. The solution was allowed to reflux for 30 min during which time the blue color faded. Lithium (0.5 mg) was again added and the solution was refluxed until the color disappeared (ca. 10 min). The ammonia was allowed to evaporate and the white solid which remained was dissolved in ether and water. The aqueous phase was quickly extracted twice with ether and the ether extract was evaporated. Methylene chloride was added and the solution was dried over sodium sulfate. Evaporation of solvent left 33 mg of crude oil. This material was identified by tlc comparison with the product from the mesylate--ammonia reaction, and also by the ir and mass spectra: R_f (alumina, ether) = 0.85; R_f (silica gel, ether--hexane, 1:1) = 0.45; ir (CCl_4) 1700 and 1460 cm^{-1}; mass spectrum m/e: strong 293 (P) and no 100 ($CH_3(CH_2)_4$-CH=$\overset{+}{N}H_2$). This material was immediately treated with sodium borohydride.

Epimeric Perhydrohistrionicotoxins (2 and 41). (a) From sodium borohydride reduction of bicyclic ketone 3. The bicyclic β-aminoketone 3 from the above described lithium--liquid ammonia reduction (33 mg of crude material) was dissolved in 5 ml of dry methanol and was cooled to -40°. Sodium borohydride (40 mg, 0.1 mmol, 4 equiv) was added and the reaction was stirred at -40° for 1 hr. The reaction was then allowed to warm to 0° over a 2 hr period. The solution was stirred at 0° for 1 hr and was then quenched with a 10% solution of sodium hydroxide. The aqueous layers were extracted with ether and the combined organic layers evaporated to give 25 mg of crude material.

When the lithium reaction was performed on the pure aziridine with the natural configuration (36b), the sodium borohydride reduction gave a complex mixture of products. Synthetic (±)-perhydrohistrionicotoxin (2) could be isolated in ca. 15% yield by this reduction procedure: pmr ($CDCl_3$) 0.9 (m, 6 H, CH_3), 3.0 (broad, 1 H, -$\overset{|}{C}H$-N), and 4.0 (m, 1 H, -$\overset{|}{C}H$-O); an exact mass determination gave m/e 295.2881 (calcd for $C_{19}H_{37}NO$: 295.2875).

When the lithium reaction was performed on the major aziridine isomer 36a (the epimeric amyl group), the sodium borohydride reduction gave a much cleaner reaction mixture. But the major product appeared by tlc, pmr and mass spectral data to be epi-amyl-epi-butylperhydrohistrionicotoxin (41). The epi-amyl isomer of 2 was also isolated and identified by tlc comparison with a sample synthesized previously.[3a] When an epimerization reaction (t-BuOK:t-BuOH) was performed on the β-amino ketone 3 before borohydride reduction, the ratio of the epi-amyl to the epi-amyl-epi-butyl isomer increased to ca. 1:1.

(b) From sodium--isopropanol reduction of aziridine 36a. Sodium dispersion (40% in oil, 10 equiv) in 40 ml of dry toluene under argon was cooled to -78°. The aziridine ketone 36a (29.1 mg, 0.10 mmol) in 3 ml of isopropyl alcohol (distilled from sodium) was added dropwise to the heterogeneous mixture. After stirring at -78° for 2 hr, the reaction was allowed to slowly warm to room temperature during which time it became clear and colorless. Ether was added, and the organic layer was washed three times with 10% hydrochloric acid. The aqueous phase was washed once with ether and the combined organic layers were discarded. Neutralization of the acidic solution with 10% sodium hydroxide, ether extraction, and evaporation of solvent left 25 mg of material. Tlc analysis indicated two epimeric perhydrohistrionicotoxin isomers: R_f (silica gel, THF--hexane, 1:4, with ammonia) = 0.35 and 0.40; pmr ($CDCl_3$) 0.9 (m, 6 H, CH_3), 3.3 (m, 1 H, -$\underset{|}{C}$H-N) and 3.9 (m, 1 H, -$\underset{|}{C}$H-O).

The Trisubstituted Enone Tetrahydropyranyl Ether 43. This compound was prepared in a manner analogous to the tetrasubstituted case using cyclohexan-1,3-dione methyl enol ether (26). The product was isolated in 73% yield: pmr (CCl_4) δ 0.9 (broad t, 3 H, CH_3), 2.2 (broad, 6 H, ring methylenes), 3.5 (broad, 3 H, $-CH_2-O$ and -CH-OTHP), 4.8 (broad, 1 H, -O-CH-O-), and 5.8 (broad, 1 H, vinyl); ir (neat) 1665, 1615, 1080 cm^{-1}; an exact mass determination gave m/e 322.2513 (calcd for $C_{20}H_{34}O_3$: 322.2508).

The Trisubstituted Enone·Alcohol 44. This compound was prepared in a manner analogous to the tetrasubstituted case. The product was isolated in 100% yield: pmr (CCl_4) δ 0.9 (m, 3 H, CH_3), 2.2 (m, 6 H, ring methylenes), 3.5 (m, 1 H, CH-OH), and 5.8 (broad s, 1 H, vinyl); ir (CCl_4) 3620, 3500-3300, 1670, 1625

1450, 1190, 1070 cm^{-1}; an exact mass determination gave m/e 238.1938 (calcd for $C_{15}H_{26}O_2$: 238.1933).

The Trisubstituted Enone Azide 46. The azide 46 was prepared via the mesylate as described for the tetrasubstituted case: pmr (CCl_4) δ 0.9 (m, 3 H, CH_3), 2.2 (m, 6 H, ring methylenes), 3.3 (broad, 1 H, -CH-N_3) and 5.75 (s, 1 H, vinyl); ir (CH_2Cl_2) 2100, 1665, 1625, 1445, 1420, 1370, 1350, 1325, 1270, 1195, 965 and 890 cm^{-1}; an exact mass determination gave m/e 263.1998 (calcd for $C_{15}H_{25}N_3O$: 263.1998).

The Spirobicyclic Ether 55. The trisubstituted enone alcohol 44 (238 mg, 1 mmol) was dissolved in 10 ml of THF. Hydrochloric acid (10%, 2ml) was added and the reaction was stirred at 20° for 1 hr. The reaction was quenched with sodium bicarbonate, and then was extracted with ether. Evaporation of solvent gave 230 mg (98% yield) of the spiro-bicyclic ether 55 as a 1:1 mixture of stereoisomeric amyl orientational forms: R_f (silica gel, ether--hexane, 1:1) = 0.50 and 0.55; pmr (CCl_4) δ 0.9 (m, 3 H, CH_3), 2.2 (m, 4 H, CH_2-CO-CH_2), and 3.4 (broad, 1 H, -CH-O-); ir (CCl_4) 1710, 1460, 1440, 1380, 1350, 1320, 1300, 1225, 1190, 1180, 1050, 990 and 900 cm^{-1}; mass spectrum m/e (%): 238 (P, 73), 195 (100), 181 (40), and 167 (53); an exact mass determination gave m/e 238.1936 (calcd for $C_{15}H_{26}O_2$: 238.1933).

The Vinylogous Amide 47. The trisubstituted enone azide 46 (263 mg, 1 mmol) in 10 ml of xylene was heated at reflux for 10 hr. After cooling, the solution was evaporated to yield 230 mg (99% yield) of the vinylogous amide 47 as a clear oil: R_f (silica gel, ether--hexane, 2:1)=0.30; pmr ($CDCl_3$) δ 0.9 (t, J = 6 Hz, 3 H, CH_3), 3.25 (broad, 1 H, -CH-N), and 10.7 (broad, 1 H, -NH); ir (CH_2Cl_2) 1623, 1580, 1420, 1335, 1250 and 1195 cm^{-1}; UV_{max} 3310 Å ($\epsilon = 1.8 \times 10^4$); mass spectrum m/e (%): 235 (P, 18), and 164 (P-amyl, 100) and no other fragments above 5% intensity; an elemental analysis gave N 5.83 (calcd for $C_{15}H_{25}NO$: N 5.95); an exact mass determination gave m/e 235.1933 (calcd for $C_{15}H_{25}NO$: 235.1936).

Catalytic reduction of 47 with 5% Pd/C at 25° in ethanol gave the tetrahydro product 48. This amino alcohol was oxidized with Collins' reagent to the cyclopentanone 49: ir (neat) 3340 (vw) and 1740 cm^{-1}; mass spectrum m/e (%):

237 (P,8), 182 (15), 166 (100), 154 (69), 149 (46) and 82 (100); an exact mass determination gave m/e 237.2097 (calcd for $C_{15}H_{27}NO$: 237.2093).

The Spirobicyclic β-Aminoketone 56. The trisubstituted azido enone 46 (263 mg, 1 mmol) was dissolved in 10 ml of absolute ethanol containing 100 mg of Lindlar catalyst (5% Pd on calcium carbonate poisoned with lead). The mixture was stirred under an atmosphere of hydrogen for 3 hr. Filtration of the catalyst and removal of solvent gave 230 mg (99% yield) of the spirobicyclic β-aminoketone 56: pmr (CCl_4) δ 0.85 (m, 3 H, CH_3) and 3.2 (broad, 1 H, CH-N); ir (CCl_4) 1712, 1460, 1440, 1345, 1315 and 1230 cm^{-1}; mass spectrum m/e (%): 237 (P,32), 194 (57), 180 (89), 167 (87), 166 (100), and 96 (95); an exact mass determination gave m/e 235.1938 (calcd for $C_{15}H_{25}NO$: 235.1936).

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