SYNTHESES OF 1-AZASPIRO[5.5]UNDECANES: STEREOSELECTIVE SYNTHESES OF PERHYDRO- AND OCTAHYDROHISTRIONICOTOXIN

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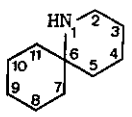
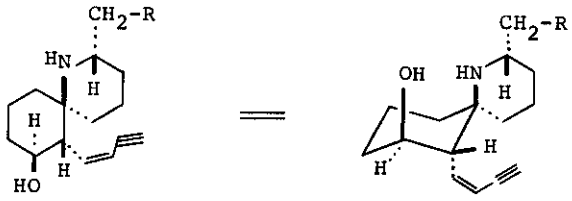
Abstract- Syntheses of 1-azaspiro[5.5]undecane derivatives, which may be potential candidates for the therapeutic application and the promising precursors for the histrionicotoxins syntheses, are described. Stereoselective syntheses of racemic octahydro- and perhydrohistrionicotoxin are also presented.

I. Introduction

Recent studies of Witkop and his co-workers on the toxic constituents of skin extracts of Neotropical arrow poison frogs, Dendrobates histrionicus and other dendrobates species, have led to the isolation of a series of alkaloids designated histrionicotoxins along with the other types of alkaloids and it has been clarified that histrionicotoxins contain the unique 1-azaspiro[5.5]undecane ring system (1).[1-8] The structures and the stereochemistries at C-2, C-6, C-7 and C-8 positions of histrionicotoxin (2) and of the congener isodihydrohistrionicotoxin (3) have been elucidated by X-ray diffraction analyses of single crystals of their hydrochloride salts.[2,3] In earlier papers, the term, "histrionictoxin"

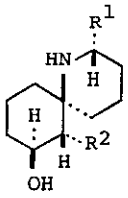


(1)



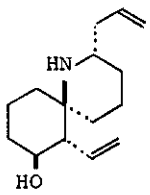
(2) R = CH=CH−C≡CH

(3) R = CH_2-CH=C=CH_2



(2 ∿ 10)

Alkaloid		R^1	R^2
Histrionicotoxin (HTX)	(2)	-CH_2-CH=CH-C≡CH	-CH=CH-C≡CH
Isodihydro-HTX	(3)	-CH_2-CH_2-CH=C=CH_2	-CH=CH-C≡CH
Neodihydro-HTX	(4)	-CH_2-CH=CH-C≡CH	-CH=CH-CH=CH_2
Tetrahydro-HTX	(5)	-CH_2-CH=CH-CH=CH_2	-CH=CH-CH=CH_2
Isotetrahydro-HTX (Allenic tetrahydro-HTX	(6)	-CH_2-CH_2-CH=C=CH_2	-CH=CH-CH=CH_2
Octahydro-HTX	(7)	-CH_2-$(CH_2)_2$-CH=CH_2	-$(CH_2)_2$-CH=CH_2
Allodihydro-HTX	(8)	-CH_2-$(CH_2)_2$-C≡CH	-CH=CH-C≡CH
Allotetrahydro-HTX	(9)	-CH_2-$(CH_2)_2$-C≡CH	-CH=CH-CH=CH_2
Perhydro-HTX	(10)	-CH_2-$(CH_2)_3$-CH_3	-CH_2-$(CH_2)_2$-CH_3



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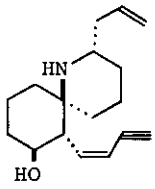

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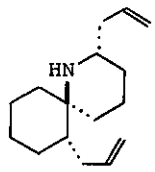

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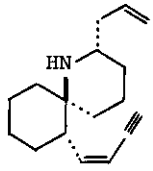

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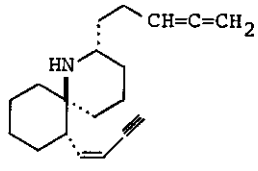


(15) 269B

has been applied only to the C_{19}-alkaloids (C_5- and C_4-side chains at C-2 and C-7 positions, respectively), but nowadays the histrionicotoxin class of alkaloids includes also the lower homologs such as alkaloids 235A (11) and 259 (12).[7,8] Other alkaloids possessing the 1-azaspiro[5.5]undecane skeleton are desoxy-histrionicotoxins such as alkaloids 219A (13), 243 (14), and 269B (15).[7]

Although histrionicotoxins are characterized, in part, by the unique allenic and acetylenic moieties, these unsaturated groups have been recently found to occur also in the pumiliotoxin C and gephyrotoxin class alkaloids.[4] These unsaturated side chains of the Neotropical poisonous frog toxins may be the first example of acetylenic and allenic moieties appearing in the animal kingdom.[1-8]

The biological activity of histrionicotoxins on vertebrate neuromuscular junctions has been studied by Albuquerque by the use of both competitive binding experiments and electrophysiology.[7-15] Qualitatively, all histrionicotoxins had a similar action to that of acetylcholine on the acetylcholine receptor-ICM (ion conductance modulator) complex, i.e., prolongation of the falling phase, or delayed rectification of the action potential and an induced densitization to repeated acetylcholine applications with concomitant neuromuscular block.[7-15] Although the O-N atomic distance resembles that in acetylcholine closely, the binding site for the histrionicotoxins is distinct from that of acetylcholine. These toxins emerged as powerful tools for the studies on the fundamental processes of neurophysiological ion transport and these spiropiperidines become candidates for the therapeutic applications.

The scarcity of natural histrionicotoxins and the unusual 1-azaspiro-piperidine framework associated with the potent biological activity have made the alkaloids highly attractive target for the synthesis. Although histrionicotoxin (2) has resisted synthetic efforts to date due to the labile cis-enyne side chains, it has been revealed that the biological activity was not associated with the unsaturated side chains since perhydrohistrionicotoxin (10) still retains the biological activity.[9]

Despite a large number of synthetic methods for the synthesis of simple 1-azaspiro[5.5]undecanes had appeared in the literatures, stereoselective synthetic routes to this ring system, which allow further elaboration of functionalizations, e.g., the hydroxyl group at C-8 and the side chains at C-2 and C-7 in the 1-aza-spirane framework, were reported by Kishi,[16,17] Corey,[18-20] Evans,[21,22] Speckamp,[23,24] Inubushi,[25,26] and Cvetovich[27] groups.

Due to page limitation, simple azaspiranes[28-35] which may be not suitable for further elaboration to the synthesis of histrionicotoxins are excluded from the present review and the authors will focus the survey on the syntheses of the useful intermediates for histrionicotoxins, the isomer of perhydrohistrionicotoxin, the formal syntheses of perhydrohistrionicotoxin, and the total syntheses of perhydro- and octahydrohistrionicotoxin.[36]

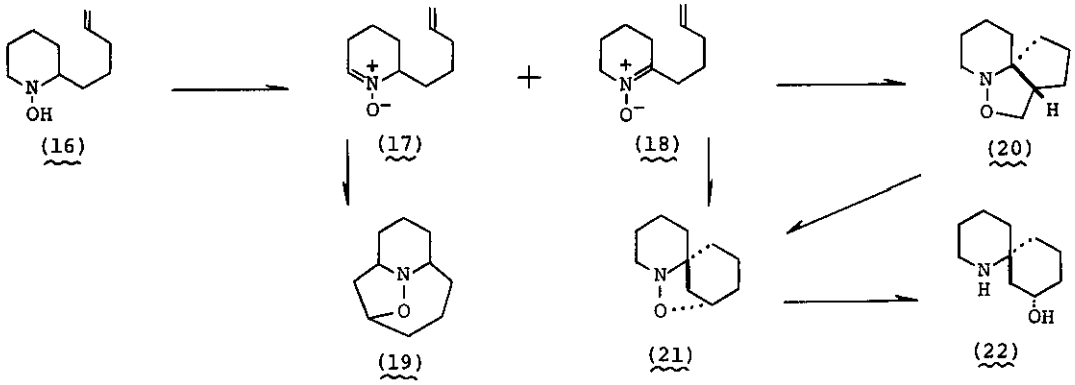
II. Syntheses of 1-Azaspiro[5.5]undecane Framework

Recently, interest in the synthesis of 1-azaspiro[5.5]undecanes increased due to the unusual spiropiperidine structure associated with the analgetic, antipyretic, and antiphlogistic activities of simple 1-azaspiranes[28] and the anticholinergic activity of histrionicotoxins. Stereoselective and nonstereocontrolled syntheses of simple 1-azaspiranes, which have a clue such as the double bond, the carbonyl group, or the hydroxyl group on the spirane skeleton for the further elaboration on the synthesis of histrionicotoxins, were described in this section.

II-A. Synthesis and Synthetic Approach by Intramolecular Oxidative Cyclization of Nitrone

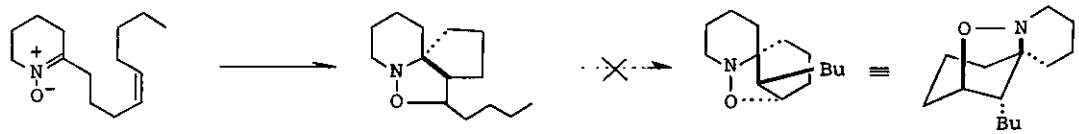
The use of nitrone in ring formation by intramolecular oxidative cyclization with an activated olefin has been well documented by many workers.[37-44]

The model study on the synthesis of histrionicotoxins by intramolecular cyclization was reported by Wehrli and his co-workers.[45] Oxidation of the hydroxylamine (16) with mercuric oxide gave a mixture of the aldonitrone (17) (1 part) and the ketonitrone (18) (9 parts). Without separation, the mixture was refluxed in toluene to yield a separable mixture of the isoxazole derivatives (19, 8%), (20, 64%), and (21, 1.2%). The undesired compound (20) was transformed



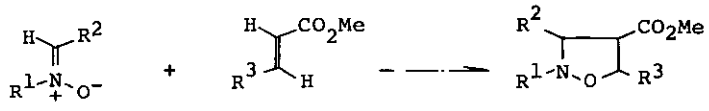
into the desired one (21) by heating in toluene in a sealed tube at 195°. Catalytic hydrogenolysis of 21 over Raney nickel afforded rel-(6S,8S)-8-hydroxy-1-azaspiro[5.5]undecane (22).

The same principle for the synthesis of perhydrohistrionicotoxin (10) was not utilized because the regiochemical control in the cyclization proved to be difficult. Thus, the nitrone (23) furnished the undesired isoxazolidine (24), which could not be transformed into the isomeric isoxazolidine (25).[45]

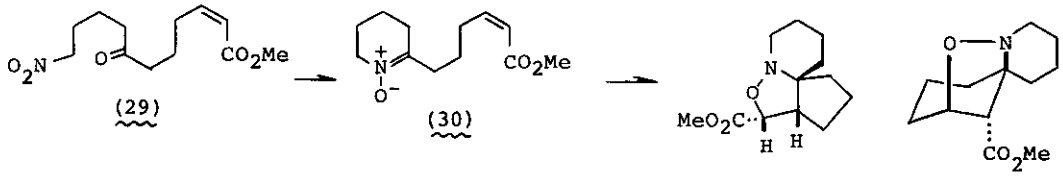


(23) (24) (25)

Another synthetic approach to histrionicotoxins by intramolecular nitrone cyclization has been reported by Tufariello and Trybulski.[46] There have been precedents which suggest that the nitrones (26) could add to the unsaturated esters (27) to yield the isoxazolidines (28).[37-40,47] Unfortunately, treatment of the nitro compound (29), a precursor of the nitrone (30), with zinc-ammonium chloride yielded the undesired isoxazolidine (31). In this 1,3-dipolar intramolecular cyclization, the desired product (32), an intermediate required for the histrionicotoxin synthesis, was not obtained.



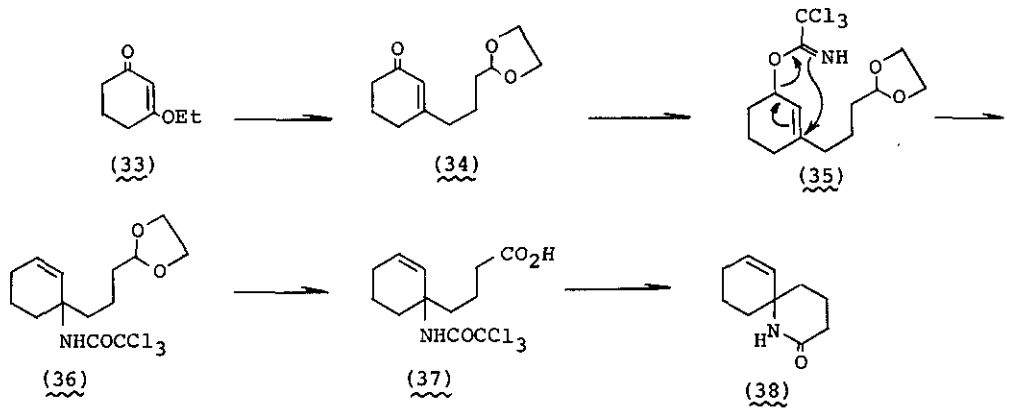
(26) (27) (28)



(29) (30) (31) (32)

II-B. Synthesis by the [3,3]-Sigmatropic Rearrangement of Allylic Trichloroimidate

The [3,3]-sigmatropic rearrangement of an allylic trichloroimidate[48] as a key step was successfully applied to the synthesis of the spiro lactam (38) by Overman.[49] Thus, reaction of the enone (33) with 4-ethylenedioxybutylmagnesium chloride followed by an acidic treatment yielded the keto-acetal (34). Reduction



(33) (34) (35) (36) (37) (38)

of 34 with lithium aluminum hydride gave an allylic alcohol, which was treated with sodium hydride-trichloroacetonitrile to yield the allylic trichloroimidate (35). The [3,3]-sigmatropic rearrangement of 35 by heating at 69° gave the amide (36) which was successively treated with oxalic acid and then silver oxide to afford the acid (37). The acid (37) was converted to the spiro-lactam (38) by a conventional method. The spiro-lactam (38) contains synthetic clues for the further elaboration of functionalization at carbons 2, 7, and 8 for the synthesis of histrionicotoxins. Unfortunately, the yield of the lactam (38) from the imidate (35) is low.

II-C. Palladium Catalyzed Synthesis of 1-Azaspirocycle

A new general route to 1-azaspirocycles via a π-allyl palladium complex as a key cyclization step has been employed for the synthesis of 1-azaspiro[5.5]-undecan-7-ene by Godleski and his co-workers.[50]

Addition of the Normant reagent[51] to the enone (33), followed by an acidic workup yielded the keto-alcohol (39). Tosylation of 39, followed by DIBAL-H reduction provided the allylic alcohol (40). This synthetic route for 40 is similar to that reported by Overman.[49] Acetylation of 40, followed by a sodium iodide catalyzed displacement of the p-TsO group by benzylamine gave the amino-acetate (41). Treatment of 41 with tetrakistriphenylphosphine palladium(0) in acetonitrile in the presence of triethylamine gave the 1-azaspirocycle (42) over

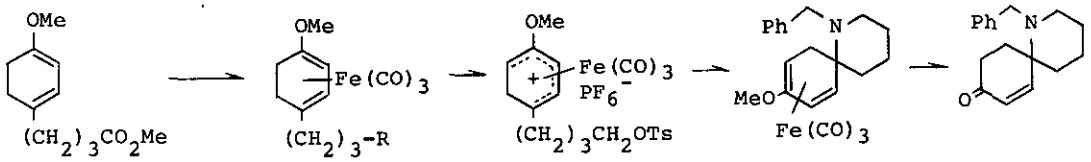
(33) R = OEt
(39) R = $(CH_2)_4OH$
(40) R^1=H, R^2=OTs
(41) R^1=Ac, R^2=$NHCH_2Ph$
(42)
(43)

95% yield presumably via the bisphosphine allyl cation (43). The compound (42) may be served as an intermediate for the synthesis of histrionicotoxins.

II-D. Synthesis via Organoiron Complex

Recently, spirocyclization of some tricarbonyldienyliumiron hexafluorophosphates has been reported by Pearson.[52-55] Application of the procedure to the synthesis of 1-azaspirocycle derivative (50) has been uncovered.[56]

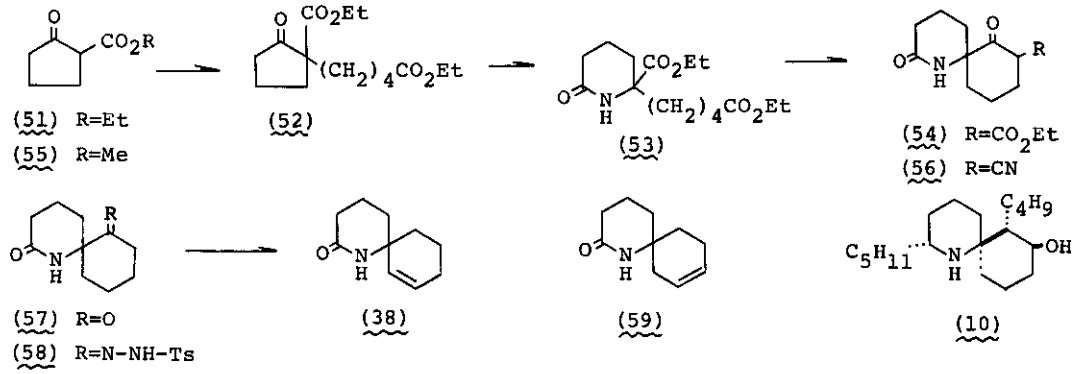
The tricarbonylcyclohexadienyliumiron complex (45), prepared from the ester (44) and pentacarbonyliron[52,53] in dibutyl ether, was reduced with DIBAL-H to the alcohol (46), which was then treated with p-TsCl-pyridine to afford the tosylate (47). Regiospecific hydride abstraction with triphenylmethylium tetrafluoroborate-ammonium hexafluorophosphate gave the hexafluorophosphate (48), which was then treated with benzylamine in nitromethane to yield the 1-azaspirocycle (49). Neither this type of reaction, nor the synthesis of cyclohexadienylium complex with this degree of functionality, has been previously reported. Removal of tricarbonyliron in 49 with trimethylamine-N-oxide, followed by an acidic hydrolysis afforded the 1-azaspirocyclic enone (50), which may be a useful intermediate for the histrionicotoxins synthesis.



II-E. Synthesis by the Beckmann or the Schmidt Reaction

Kissing and Witkop have reported the synthesis of the 1-azaspiro compound as outlined below by the Schmidt or the Beckmann reaction.[57] Thus, potassium enolate of the keto-ester (51)[58] was alkylated with ethyl 5-bromovalerate in dry DMSO to yield the diester (52). The Schmidt reaction of 52 with hydrazoic acid in $CHCl_3$ afforded the lactam (53) which was treated with sodium hydride in HMPA to give the spiro-lactam (54). By similar reaction sequences, the cyanospiro-lactam (56) was also synthesized starting from the keto-ester (55) and 5-bromovaleronitrile.

Treatment of the lactam (54) with aqueous NaOH, followed by treatment with



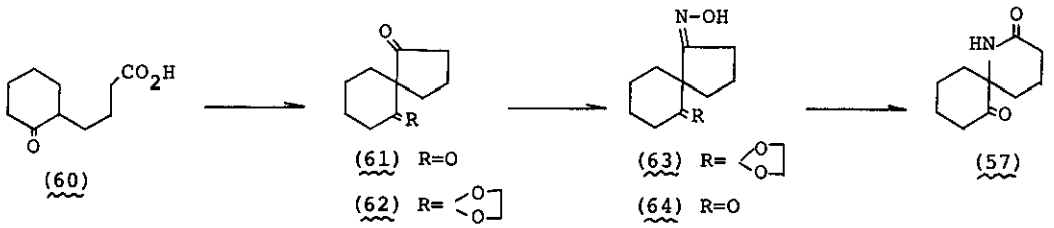
(51) R=Et
(55) R=Me
(52)
(53)
(54) R=CO_2Et
(56) R=CN
(57) R=O
(58) R=N-NH-Ts
(38)
(59)
(10)

p-toluenesulfonic acid in xylene under reflux yielded the dione (57) which already was converted to perhydrohistrionicotoxin (10) by Kishi and his co-workers.[16] p-Toluenesulfonyl hydrazone (58) of 57 was reacted with butyllithium in THF at 0° to yield the lactam (38), whereas reaction of 58 with sodium hydride in HMPA at 180° afforded the olefin (59) as a major product. The spiro-lactam (38) is the same as that prepared by an independent route by Overman.[49]

II-F. Synthesis by the Beckmann Rearrangement

Bond and his co-workers made use of the keto-acid (60), prepared from 2-ethoxycarbonylcyclohexanone,[58,60] as a starting material for the simple synthesis of 1-azaspiro[5.5]undecane-2,7-dione (57), an intermediate in Kishi's synthesis[16] of perhydrohistrionicotoxin (10). The synthesis of 57 is based on the Hill's route[35] to the ring system, with suitable modification to allow functionalization of the ring.[59]

Reaction of the keto-acid (60) with polyphosphoric acid (PPA) according to the method of Muller[61] yielded the spiro-diketone (61), which was mono-acetalized to yield the acetal-ketone (62). The acetal-oxime (63) derived from 62 was treated with PPA to furnish 1-azaspiro[5.5]undecane-2,7-dione (57). The dione (57) has been converted to perhydrohistrionicotoxin (10) by Kishi.[16]

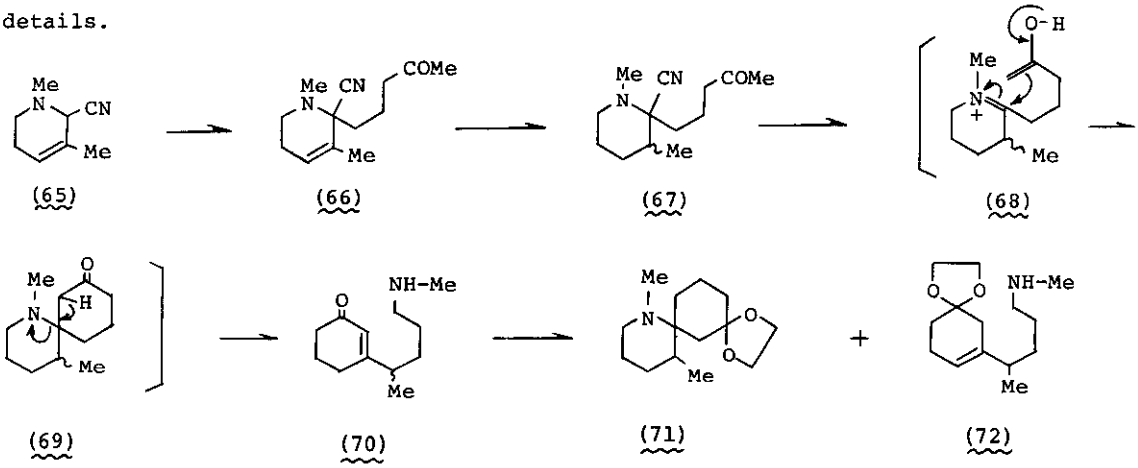


(60)
(61) R=O
(62) R= O,O
(63) R= O,O
(64) R=O
(57)

II-G. Synthesis of 1-Azaspirane by the Michael Reaction

The Model experiment in the synthesis of perhydrohistrionicotoxin (10) based on a similar strategy to that of Corey[18] has recently been published by Husson.[62] Reaction of an anion derived from the nitrile (65) with 2-ethylenedioxy-5-iodopentane, followed by an acidic workup gave the ketone (66). The cyano-ketone (67), obtained by catalytic hydrogenation of 66 over 10% palladium on charcoal, was treated with p-TsOH in refluxing benzene to furnish the amino-enone (70), presumably via the intermediates (68) and (69). It has already been demonstrated by Corey[18] that the isolation of the desired product of the type (69) was rather difficult. In order to avoid the undesired retro-Michael reaction, the enone (70) was refluxed in benzene with ethylene glycol in the presence of p-TsOH to give a mixture of the 1-azaspirocycle (71, 22%) and the ketal (72, 39%).

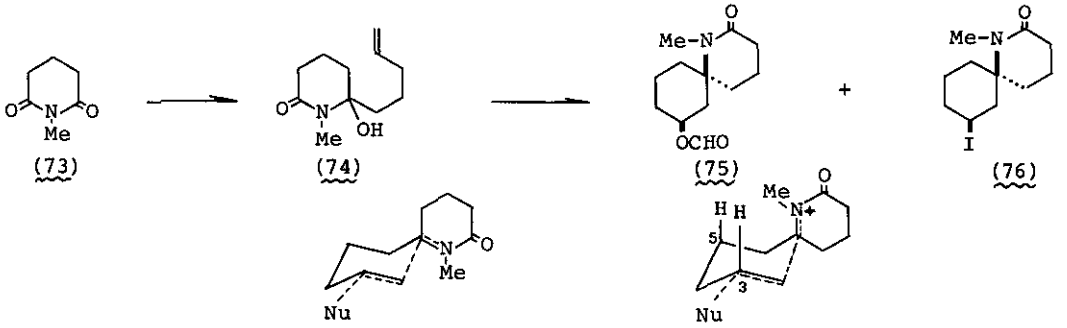
A similar synthetic route to the synthesis of perhydrohistrionicotoxin has also been proposed by Winterfeldt.[63] This report, however, lacks the experimental details.



II-H. Synthesis via the Acylimmonium Ion Intermediate

The model experiment for the perhydrohistrionicotoxin (10) synthesis has been reported by Schoemaker and Speckamp.[64] The method involves the formic acid-induced cyclization as a key step.

The crude amide (74),[65] prepared from N-methylglutarimide (73) and 4-pentenylmagnesium iodide, was treated with formic acid to yield a mixture of 1-azaspiranes, the formate (75, 45% yield) and the iodide (76, 15% yield). These two products (75 and 76) were presumably formed via the transition state (77) with synchronous formation of the new C-C and C-O bonds. Another reaction pathway via the transition state (78) is considered less likely because of steric interactions



(73) (74) (75) (76) (77) (78)

between the N-methyl group and the hydrogens at C-3 and C-5.

III. Synthetic Investigations of Isomers of Perhydrohistrionicotoxin

The potential biological activity of histrionicotoxins led to postulate the following hypothesis.[5,7] The close proximity of the two heteroatoms, a nitrogen atom and an oxygen atom of hydroxyl at C-8, would make histrionicotoxins a potential candidate for cholinergic activity or possible interaction with cholinergic or other receptor proteins.[5,7] (see Figure 1)

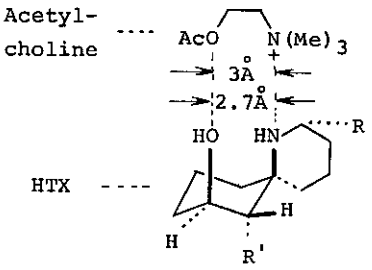
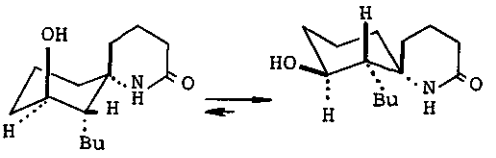


Figure 1



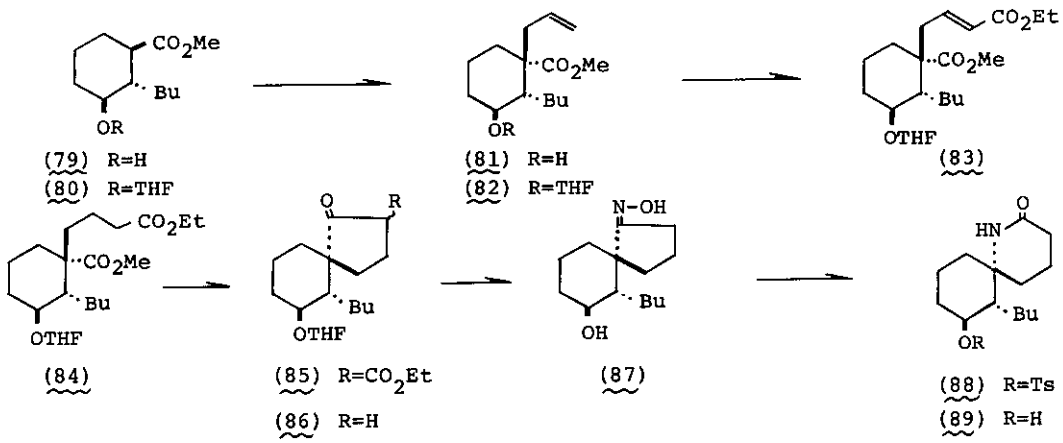
6-Epi-isomer (89)

In view of the intrinsically unique structures of histrionicotoxins and several simple 1-azaspiranes,[66] synthetic works had been directed only towards the synthesis of the natural type (6S,7S,8S)-7-alkyl-8-hydroxy-1-azaspiranes. However, stereoselective synthesis of 2,7-epi-, 6-epi, and 7-epi-1-azaspiranes has now been reported by Corey,[67] the present authors,[25] and Speckamp,[24] respectively.

III-A. Synthetic Approach to 6-Epi-perhydrohistrionicotoxin

For the purpose of pharmacological studies on the structure-activity relationship, a highly stereoselective synthesis of the rel-(6R,7S,8S) lactam (89) has recently been accomplished by the present authors.[25]

Reaction of the hydroxy-ester (79) with 2,3-dihydrofuran in the presence of



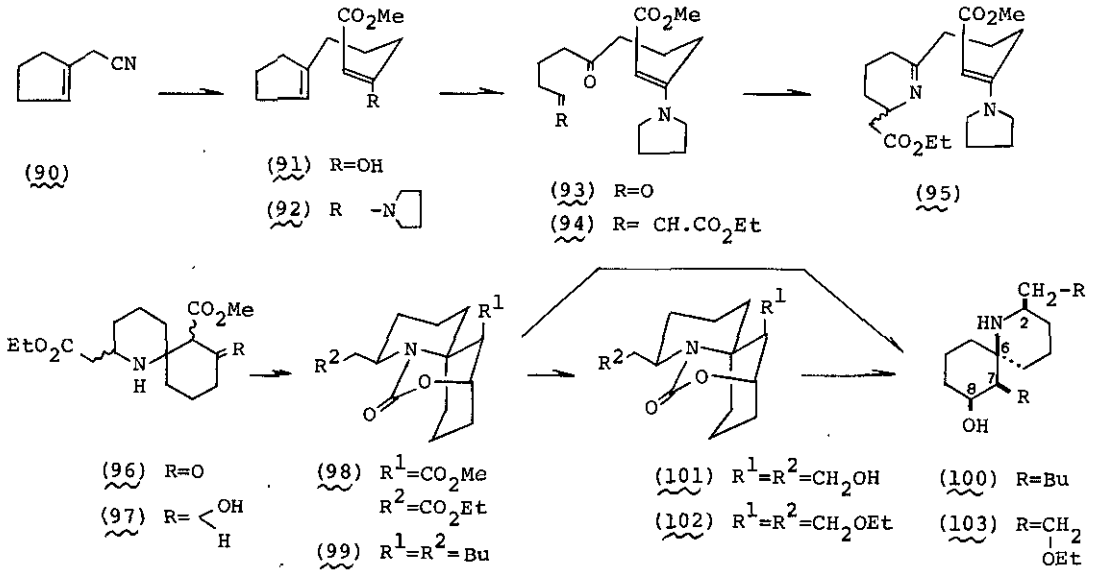
(79) R=H
(80) R=THF
(81) R=H
(82) R=THF
(83)
(84)
(85) R=CO_2Et
(86) R=H
(87)
(88) R=Ts
(89) R=H

pyridinium p-toluenesulfonte[68] gave the ester (80), which was alkylated with high stereoselectivity by successive treatments with $KN(TMS)_2$ in THF, allyl bromide, and then 5% HCl to furnish the alkylated product (81) in 65% yield. The tetrahydrofuranyl ether (82) of 81 was allowed to react with OsO_4-$NaIO_4$-N-methylmorpholine-N-oxide[69] and the resulting aldehyde was subjected to the Wadsworth-Emmons reaction to yield the enoate (83). The diester (84) resulted from 83 was subjected to the Dieckmann reaction with KH in THF[70] to yield the spirane (85), which on decarboxylation gave the five-membered ketone (86). Oximation of 86 furnished the oxime (87), which was reacted with p-TsCl-pyridine to yield the lactam-tosylate (88), and a single crystal X-ray analysis of 88 provided convincing evidence for the 6-epi- structure. Removal of p-tosyl group in 88 was achieved by using sodium-naphthalene to yield rel-(6R,7S,8S)-7-butyl-8-hydroxy-1-azaspiro[5.5]undecan-2-one (89).

III-B. Synthetic Route to 2,7-Epi-histrionicotoxins

A synthetic route to 2,7-epi-histrionicotoxin series has been developed by Corey and his co-workers.[67]

The ester (91), obtained from the nitrile (90) by a conventional method, was treated with pyrrolidine-AcOH in benzene to yield the enamine (92) in 86% yield. Glycolation of 92 followed by oxidation with Ag_2CO_3 on celite[71] gave the keto-aldehyde (93), which was converted to the enoate (94) by treatment with the anion of triethyl phosphonoacetate. The imine (95), prepared from 94 by reaction with liquid ammonia in a sealed tube, was treated with p-TsOH to afford the spirane (96), which was immediately reduced with sodium borohydride to yield an oily mixture containing 8-hydroxy-1-azaspirane (97). This mixture was allowed to react



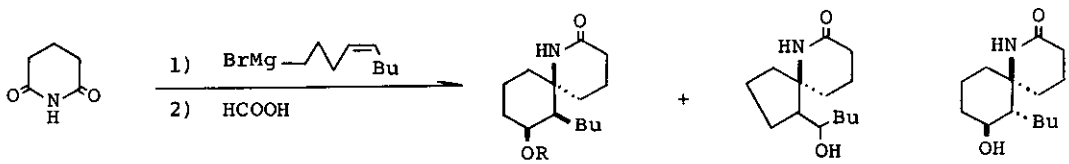
with $COCl_2$-pyridine to yield the urethane-diester (98) in rather low yield after column chromatographic separation and the structure of 98 was ascertained by a single crystal X-ray analysis. The urethane (99) was obtained from 98 by the following successive operations; 1) selective DIBAL-H reduction: 2) the Wittig olefination using a ylide prepared from allyldimethylphenylphosphonium bromide and potassium methylsulfinylmethylide: 3) catalytic hydrogenation over Pd-C. Cleavage of the urethane group was effected with Li-$MeNH_2$ to afford 2,7-epi-perhydrohistrionicotoxin (100) in 11.3% yield from 98.

The diol (101), obtained from 98 by reduction with $LiBH_4$, was treated with KH-EtI in HMPA to furnish the ether (102), which was converted to dioxa-2,7-epi-perhydrohistrionicotoxin (103) as described above for 99→100. Interestingly, the dioxa analog (103) possesses ca. one-fourth of the biological activity of naturally derived perhydrohistrionicotoxin.

III-C. Synthetic Approach to 7-Epi-perhydrohistrionicotoxin

The stereoisomer (106) of the natural type hydroxy-lactam (108) has been prepared *via* the acylimmonium ion intermediate by Speckamp.[24]

Thus, treatment of glutarimide (104) with (*Z*)-4-nonenylmagnesium bromide followed by the formic acid-catalyzed cyclization reaction yielded the formate-lactam (105, 22% yield), which on hydrolysis furnished *rel*-(6*S*,7*R*,8*S*)-7-butyl-8-hydroxy-1-azaspiro[5.5]undecan-2-one (106). The hydroxy-lactam (106) is a stereoisomer at C-7 position of the perhydrohistrionicotoxin precursor (108).



(104)

(105) R=CHO
(106) R=H

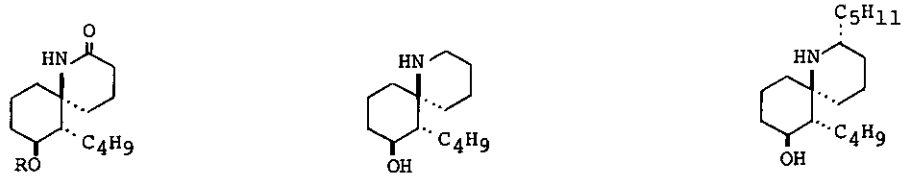
(107)

(108)

From a mixture of the hydrolyzed products, a crystalline isomeric compound, tentatively assigned the structure (107), was also isolated in 0.5% yield.

IV. Formal Synthesis of Perhydrohistrionicotoxin

Highly stereoselective synthesis of 1-azaspirane intermediates for the synthesis of perhydrohistrionicotoxin (10) has been undertaken in many laboratories



(108) R=H
(109) R=CHO
(110) R=Ac

(111)

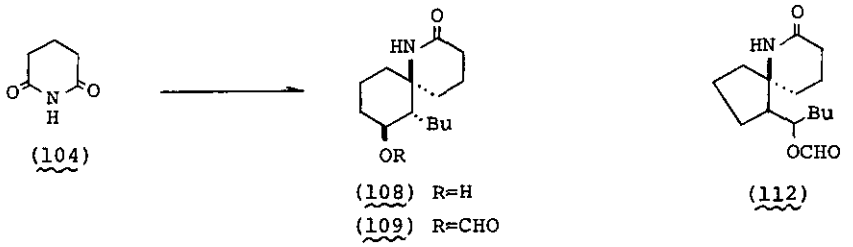
(10)

with a great variety of the synthetic schemes. Since the lactams (108-110) and the amine (111) have been transformed into perhydrohistrionicotoxin (10) by Kishi,[16,17] Corey,[19] and Evans,[22] synthesis of the lactams (108-110) or the amine (111) constitutes a formal synthesis of perhydrohistrionicotoxin.

IV-A. Synthesis via Acylimmonium Ion Intermediate

A formal synthesis of perhydrohistrionicotoxin (10) via acylimmonium ion has been presented by Speckamp.[24] (see also Section V-D)

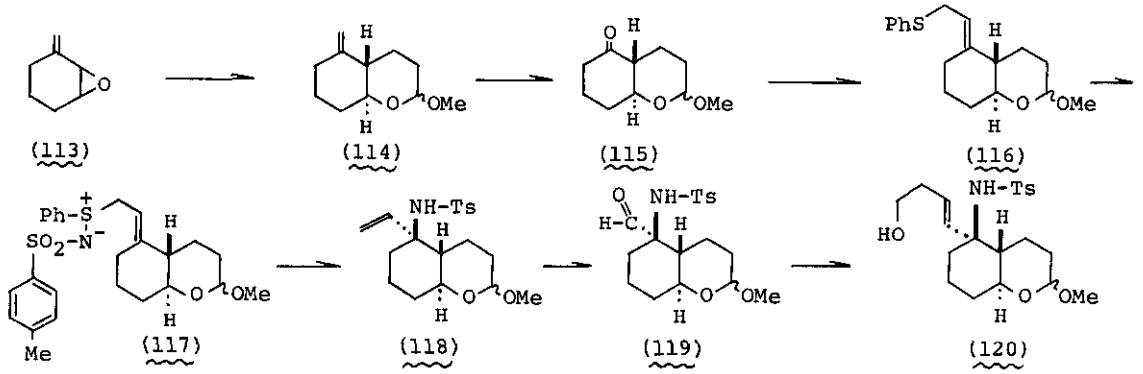
Glutarimide (104) was reacted with (E)-4-nonenylmagnesium bromide in THF and the crude product was treated with formic acid. Because of the presence of unreacted glutarimide in the crude product, the reaction was repeated with a large excess of the Grignard reagent. Chromatographic separation furnished the formate (109) in 30% yield and a by-product tentatively assigned the structure (112) was also isolated in 0.5% yield. Hydrolysis of 109 with KOH-EtOH-H_2O yielded the hydroxy-lactam (108). Since both the formate (109)[22] and the hydroxy-lactam (108)[16,17,19] have been converted into perhydrohistrionicotoxin (10), the present synthesis constitutes a formal total synthesis of perhydrohistrionicotoxin.



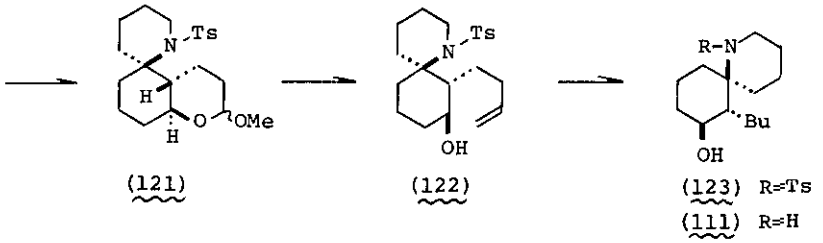
(104) (108) R=H (109) R=CHO (112)

IV-B. Synthesis via [2.3]-Sigmatropic Rearrangement of a Sulfilimine

Recently a highly stereoselective multistep synthetic route to histrionicotoxins has been reported by Cvetovich.[27] The method involves the [2.3]-sigmatropic rearrangement of the sulfilimine intermediate as a key step.



(113) (114) (115) (116) (117) (118) (119) (120)



(121) (122) (123) R=Ts (111) R=H

The epoxide (113) was allowed to react with the lithium anion of 2-(N,N-dimethylamino)ethyl allyl ether and the resulting enamine was treated with methanolic acid to yield the pyran (114), which was oxidized with ozone to furnish the keto-pyran (115) in over 85% yield. The keto-pyran (115) was successively treated with vinylmagnesium bromide, phosphorous tribromide, and then sodium thiophenoxide to yield the allyl thioether (116) in 45% yield. Reaction of 116 with chloramine-T produced the amine (118) as a single product *via* the [2.3]-sigmatropic rearrangement of the sulfilimine (117). Ozonolysis of 118 followed by successive treatments with vinylmagnesium bromide, iodomethyltributyltin, and then butyllithium afforded the homoallyl alcohol (120) *via* the aldehyde (119) in

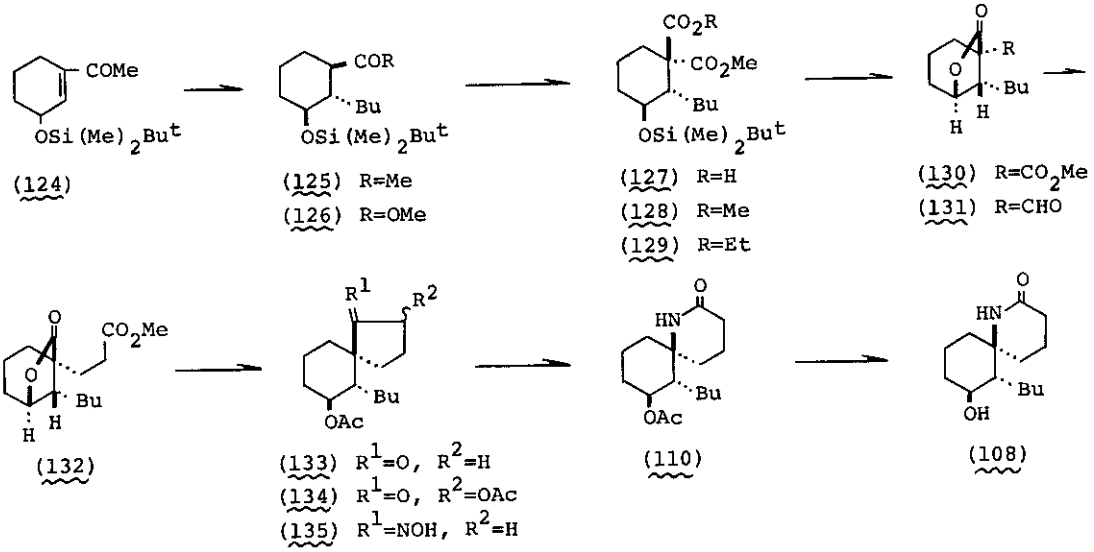
58% overall yield.

Successive reactions of 120; catalytic hydrogenation, mesylation, and then sodium hydride treatment, produced the 1-azaspirane (121). Hydrolysis of the acetal group in 121 and then the Wittig reaction with $Ph_3P=CH_2$ gave rel-(6S,7S,8S)-7-(3-butenyl)-8-hydroxy-1-tosyl-1-azaspiro[5.5]undecane (122). The n-butyl derivative (123), obtained by catalytic hydrogenation of 122, was treated with sodium-naphthalene to furnish the amine (111), which was previously been converted into perhydrohistrionicotoxin (10) by Corey.[19]

IV-C. Synthesis via Acyloin Intermediates

A simple stereoselective synthetic route to perhydrohistrionicotoxin has been recently developed by the present authors.[25] The method involves the acyloin condensation reaction for the formation of the spirocycle.

The butylated ketone (125), obtained by the conjugate addition of the enone (124) with a new reagent $BuCu.AlCl_3$,[73-76] was converted to the ester (126) in 96% yield by a conventional method. Treatment of 126 with LDA followed by carboxylation with carbon dioxide yielded the acid (127), which was allowed to react with diazomethane and diazoethane to give the diesters (128) and (129), respectively. The stereochemistry of the carboxyl group in 127 was assigned on the basis of the fact that dil. HCl treatment of both the esters (128 and 129) yielded the same lactone (130). Reaction of 130 with DIBAL-H followed by oxidation with pyridinium chlorochromate gave the aldehyde (131), which was successively treated with $(MeO)_2(O)P=CHCO_2Me$ and then H_2/PtO_2 to furnish the lactone-ester (132). The acyloin condensation[77-79] was effectively employed for the spirocyclization. Thus, treatment of 132 with sodium in the presence of TMSCl, followed by successive treatments with 5% HCl and then Ac_2O-pyridine gave the spiranes (133, 16% yield) and (134, 44% yield). The acetoxy-ketone (134) was readily reduced with Zn-AcOH to furnish the ketone (133). The acetoxy-oxime (135), obtained by a conventional method from 133, was treated with p-TsCl-pyridine to yield the 1-azaspirane (110), which on hydrolysis with NaOMe in MeOH gave rel-(6S,7S,8S)-7-butyl-8-hydroxy-1-azaspiro[5.5]undecan-2-one (108) constituting a formal synthesis of perhydrohistrionicotoxin (10).



(124)

(125) R=Me
(126) R=OMe

(127) R=H
(128) R=Me
(129) R=Et

(130) R=CO_2Me
(131) R=CHO

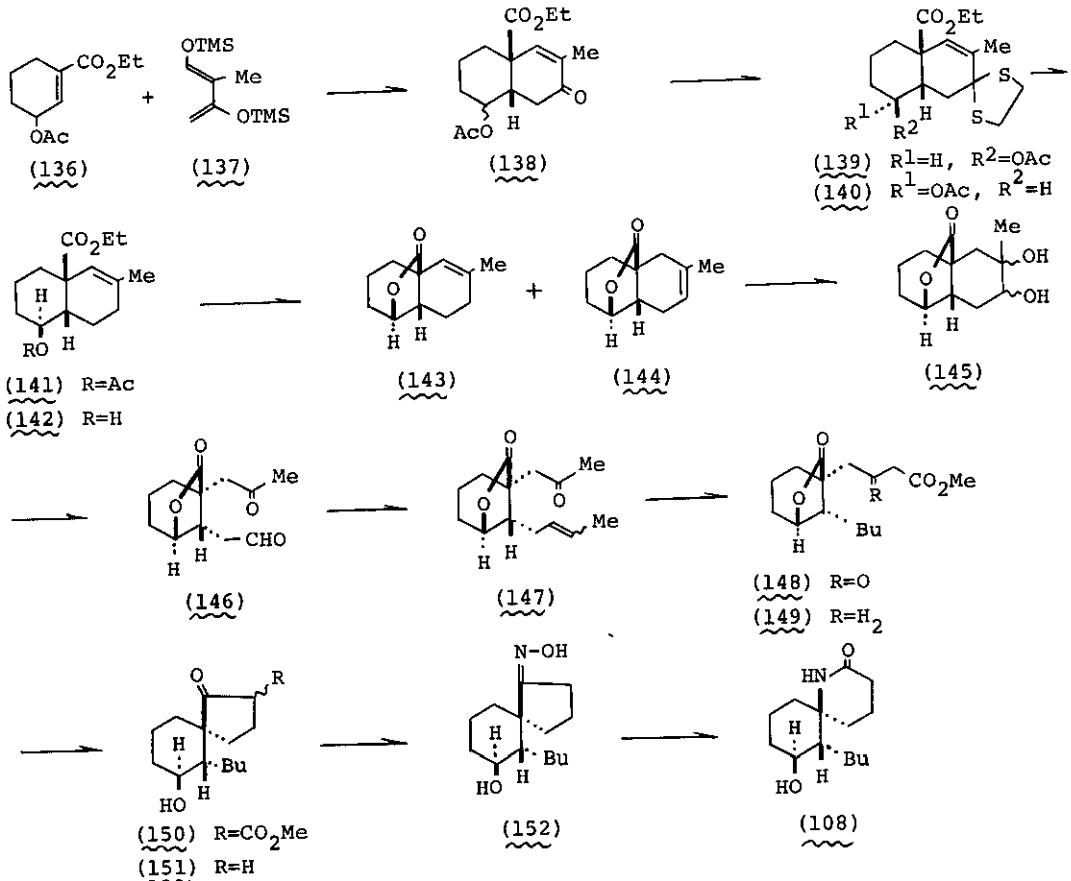
(132)

(133) R^1=O, R^2=H
(134) R^1=O, R^2=OAc
(135) R^1=NOH, R^2=H

(110)

(108)

IV-D. Synthesis of Spirocycle by the Dieckmann Condensation



(136)

(137)

(138)

(139) R^1=H, R^2=OAc
(140) R^1=OAc, R^2=H

(141) R=Ac
(142) R=H

(143)

(144)

(145)

(146)

(147)

(148) R=O
(149) R=H_2

(150) R=CO_2Me
(151) R=H

(152)

(108)

Based on the retrosynthetic analysis, the authors have stereoselectively synthesized the key intermediate for the synthesis of perhydrohistrionicotoxin.[26] By using the Diels-Alder reaction of the acetoxy-ester (136) with the diene (137), three chiral centers were constructed in the first step.

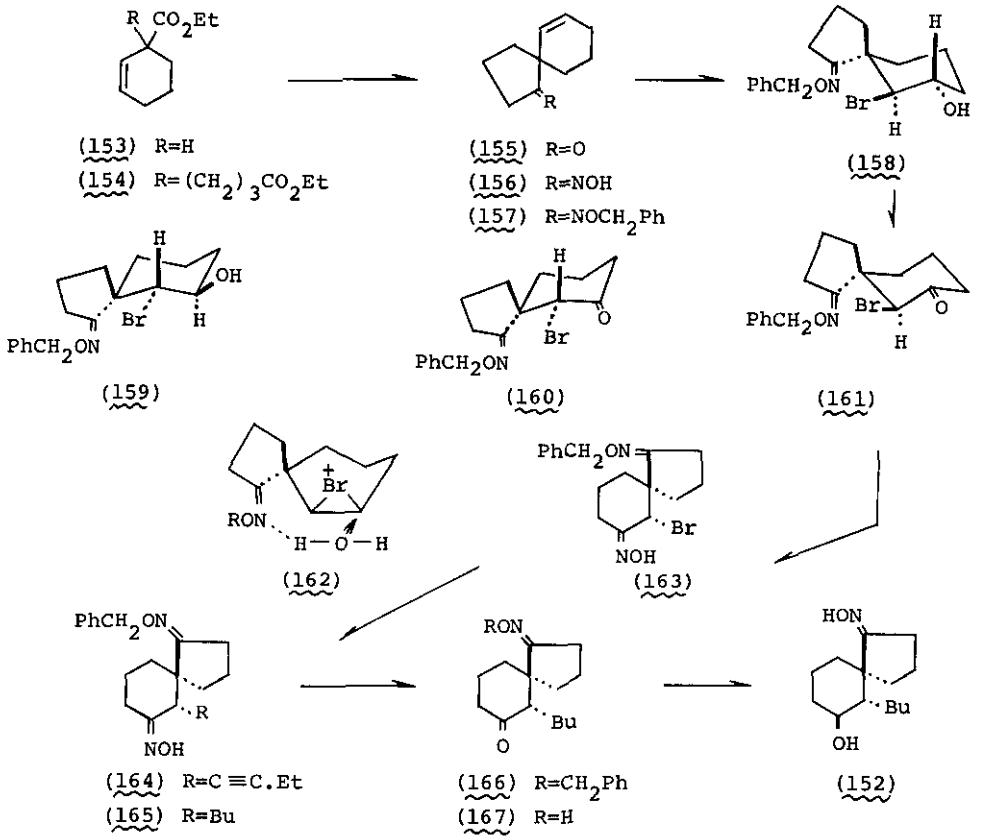
The Diels-Alder reaction of the ester (136) with the diene (137)[80] followed by hydrolysis with 5% HCl gave an inseparable mixture of the enone (138). Thioacetalization of 138 and subsequent silica gel column chromatographic separation afforded two crystalline thioacetals (139, 85% yield) and (140, 12% yield). Desulfurization of the major acetal (139) afforded the acetoxy-ester (141) which was subsequently treated with KOH-H_2O-EtOH to yield the hydroxy-ester (142) in 97% yield. Treatment of 142 in toluene with a catalytic amount of p-*TsOH* under reflux for 20 min gave a mixture of lactones (143, major) and (144, minor), but prolonged refluxing of the mixture afforded the thermodynamically stable lactone (144) as a single product. The glycol (145), obtained by oxidation with OsO_4-N-methylmorpholine-N-oxide,[81] was subjected to HIO_4 oxidation to furnish the keto-aldehyde (146) in 98% yield. The next task was a chemoselective C-C bond formation at the aldehyde group in 146. The Wittig reaction of 146 with triphenylphosphine ethylidene (1.14 equiv.) afforded the keto-lactone (147). Catalytic hydrogenation of 147 over PtO_2, followed by methoxycarbonylation according to the method of Whitlock[82] gave the keto-ester (148), which was reduced in the usual way to afford the ester (149) in 97% yield.

The Dieckmann reaction of 149 with KH provided the spirane (150), and the product was treated with 1,4-diazabicyclo[2.2.2]octane in refluxing xylene[83] to yield the hydroxy-ketone (151). Oximation of 151 gave the hydroxy-oxime (152) which was subjected to the Beckmann rearrangement to afford the spiro-lactam (108), one of the key intermediate for perhydrohistrionicotoxin, constituting a formal synthesis of perhydrohistrionicotoxin.

IV-E. Synthesis via Spiro[4.5]dec-6-en-1-one Intermediate

Starting from the ester (153), a formal synthesis of perhydrohistrionicotoxin has been achieved by Corey and his co-workers.[20,84] The two key steps involve a regiospecific addition of HOBr to the olefin (157) and the alkylation of the bromo-oxime (163) with 1-lithio-1-butyne.

The diester (154), obtained from the ester (153), was successively treated with sodium hydride in THF and then THF-H_2O-H_2SO_4 (8:2:1) to furnish the ketone



(155), which was reacted with hydroxylamine to yield the oxime (156). Reaction of the benzyl ether (157) with NBS took place with high regioselectivity in the desired direction to yield the bromohydrin (158) as a major product in 72% yield. Two by-products, the bromohydrin (159, ca. 10%) and the bromoketone (160, ca. 10%), were also isolated by chromatographic separation. The isomeric ketone (161) of 160 was obtained from 158 by oxidation with the Jones reagent. The predominant formation of the bromohydrin (158) may be due to the oxime-assisted bromonium ion formation and/or the reaction as depicted in 162. The dioxime (163) was treated with 1-lithio-1-butyne in THF to furnish the acetylenic-oxime (164), which was immediately subjected to catalytic hydrogenation to yield the oxime (165). Removal of the free oxime function in 165 with $TiCl_3$-NH_4OAc afforded the ketone (166), which on catalytic hydrogenation over palladium on charcoal furnished the keto-oxime (167). Stereoselective reduction of the carbonyl group in 167 was successfully achieved by using sodium in liquid ammonia in the presense of isopropanol to yield the hydroxy-oxime (152), and the compound (152) is convertible

to perhydrohistrionicotoxin (10) in a straightforward way.[19]

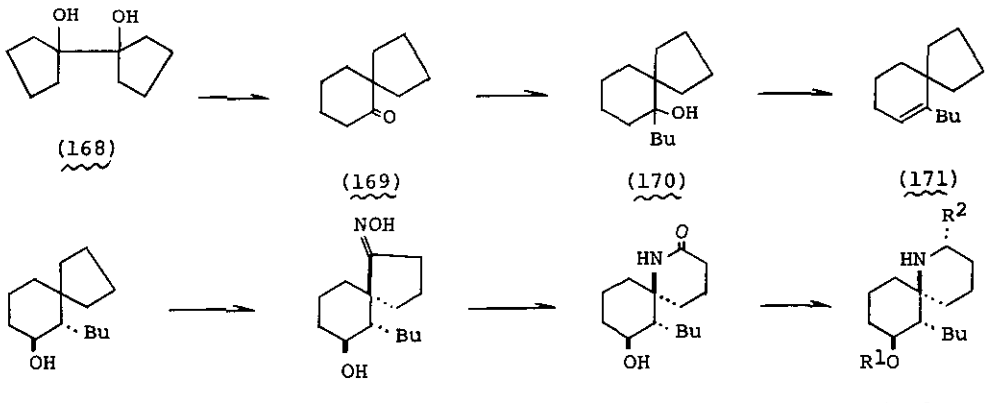
V. Total Syntheses of Perhydro- and Octahydrohistrionicotoxin

V-A. Stereoselective Synthesis by Photo-induced Rearrangement of a Nitrite Group as a key step

In the reviewer's view, the key step in the synthesis of perhydrohistrionicotoxin (10) by Corey is rearrangement of the O-nitrite group derived from the alcohol (172) to the oxime (152) by irradiation.[19]

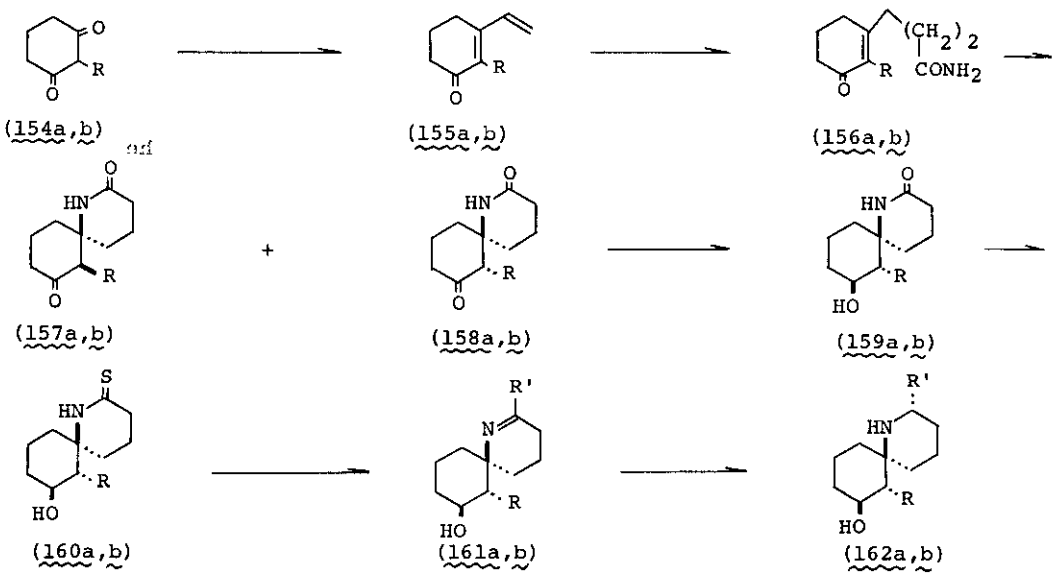
The pinacol (168), prepared in 65% yield by a modification[86] of the Mukaiyama method,[87] was converted to the spiro-ketone (169) by an acid catalyzed rearrangement. The tertiary alcohol (170), yielded by reaction of the ketone (169) with butyllithium, was dehydrated with thionyl chloride-pyridine to afford the olefin (171), which was converted to the alcohol (172) by the hydroboration-oxidation reaction in 78% yield. Irradiation of the nitrite, obtained by reaction of 172 with nitrosyl chloride-pyridine, afforded the oxime (152) in ca. 20% yield, which on treatment with p-TsCl-pyridine afforded the lactam (108). Lithium aluminum hydride reduction of 108 gave the amine (111), and the hydroxyl group in 111 was protected by the t-butyldimethylsilyl group to furnish the amine (153).

The synthesis of perhydrohistrionicotoxin (10) from 153 was completed without isolation of intermediates by treatments with the following reagents: 1) NBS in THF at 0°; 2) $KOC_5H_{11}{}^t$ in THF at -40°; 3) $LiC_5H_{11}{}^n$ in hexane at 25°; 4) $(^nBu)_4NF$ in THF at 25°.[88]



V-B. Synthesis of 1-Azaspirocycle by the Michael Reaction as a Key Step

The first total synthesis of octahydrohistrionicotoxin, one of the natural toxins, and a practical synthesis of perhydrohistrionicotoxin have been achieved by spirocyclization of the α,β-unsaturated keto-amide as a key step by Kishi.[17]



a series: $R=C_4H_9$, $R'=C_5H_{11}$

b series: $R=CH_2CH_2CH=CH_2$, $R'=CH_2CH_2CH_2CH=CH_2$

(159a)=(108); (162a)=(10)

The vinylcyclohexenone (155a), obtained from the diketone (154a) by successive treatments with EtOH-H^+ and then vinylmagnesium bromide, was reacted with methyl malonamate to yield the ester amide, which was subjected to hydrolytic decarboxylation to yield the keto-amide (156a). Spirocyclization of 156a was effectively achieved by treatment with ethyl orthoformate in ethanol containing camphorsulfonic acid to yield the epimeric keto-lactams (157a) (two parts) and (158a) (one part).

Parallel experiments, starting from the diketone (154b), afforded the corresponding vinylcyclohexenone (155b), the keto-amide (156b), and the Michael reaction of 156b gave the spiro-lactams (157b) (two parts) and (158b) (one part) in 45% overall yield.

The epimeric mixture of the spiro-lactams (157a) and (158a) was transformed to perhydrohistrionicotoxin (162a)=(10) by the established method.[16] (see Section V-C).

Equilibration of the mixture (157b and 158b) with sodium methoxide gave a new

mixture of (157b) (one part) and (158b) (four parts). The mixture of 157b and 158b was reduced with lithium in ammonia to furnish the lactam alcohol (159b) and its C-7 epimer. The thiolactam (160b), resulted from the lactam (159b), was converted to the imine (161b) by four successive operations [1) protection of the hydroxyl group as the THP derivative, 2) thioimino ether formation with the Meewein reagent, 3) DIBAL-catalyzed alkylation with pentenyllithium, 4) deprotection of the THP ether]. Reduction of the imine (161b) with aluminum hydride gave a mixture of octahydrohistrionicotoxin (162b) (six parts) and its C-2 epimer (one part).

It is also possible to apply the present procedure for the synthesis of decahydrohistrionicotoxin.

V-C. Stereocontrolled Synthesis via Acylaziridine

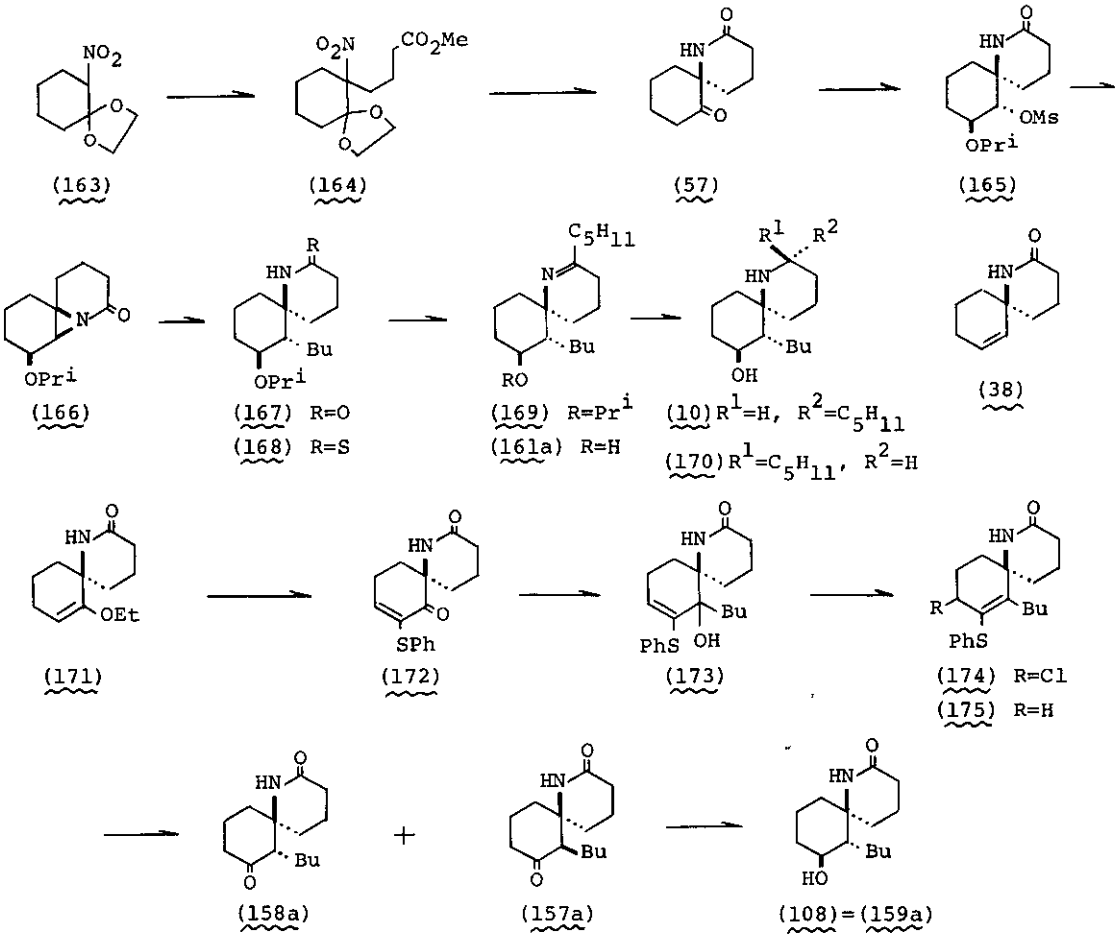
A stereocontrolled synthesis of perhydrohistrionicotoxin (10) was achieved by using a reaction of acylaziridine (166) with lithium dibutylcuprate as a key step.[16]

The nitro-ester (164), prepared from the nitro-acetal (163) in five steps by a conventional method, was hydrogenated over Raney nickel and then deacetalization of the product afforded the spirane (57).[57] Stereocontrolled synthesis of the intermediate (167) from 57 was achieved by the following reaction sequences.

Thus, the mesylate (165) was stereospecifically synthesized from 57 in 35% overall yield by six successive operations [1) $(EtO)_3CH - H^+$, 2) Δ, 3) Br_2, 4) $NaBH_4$, 5) ^iPrOH-^iPrONa, 6) MesCl-pyridine]. Sodium hydride treatment of 165 in wet benzene afforded the aziridine (166), which on treatment with lithium dibutylcuprate afforded the lactam (167) in 15% yield from 165. One of the undesired products (~30%) in this reaction was the olefin (38).

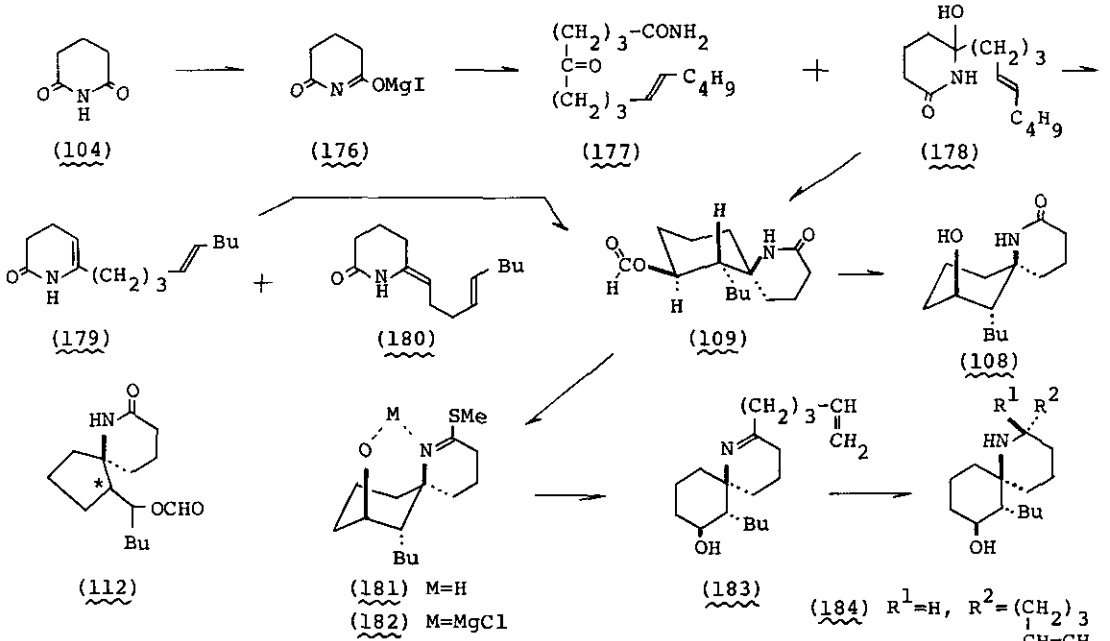
The thiolactam (168), derived from the lactam (167), was converted to the imine (169) by two steps [1) thioimino ether formation with the Meerwein reagent, 2) alkylation with pentyllithium in the presence of DIBAL]. Boron tribromide treatment of 169 gave the imine (161a), which was reduced with aluminum hydride to yield a mixture of perhydrohistrionicotoxin (10) (six parts) and 2-epi-perhydrohistrionicotoxin (170) (one part). Stereochemistry of aluminum hydride reduction is controlled by a complex formation of the reducing agent with the hydroxyl group in 161a, because $NaBH_4$ reduction of 161a or aluminum hydride reduction of 169 gave the epimer (170) or its isopropyl ether, respectively, as a major product. (see also Section V-D for the reduction of imines with aluminum hydride).

Another more efficient route to perhydrohistrionicotoxin (10) was as follows. Phenylsulfenyl chloride treatment of the enol ether (171) afforded the thiophenylenone (172), which was reacted with butylmagnesium chloride to give the carbinol (173) in 80% overall yield. Treatment of 173 with thionyl chloride afforded the chloride (174), which was reduced to the thiophenylenol (175) with Zn-HCl. Hydrolysis of 175 with conc. hydrobromic acid yielded a mixture of the lactams (158a)(three parts) and (157a)(one part). Reduction of 158a with lithium or calcium in ammonia gave the desired alcohol (108)=(159a), which is convertible to perhydrohistrionicotoxin (10) in a straightforward way according to the method established above.



V-D. Stereoselective Spirocyclization via the Acylimmonium Ion Intermediate

A practical simple synthesis of perhydrohistrionicotoxin and its congener via the acylimmonium ion intermediate has been presented by Evans.[21,22]



Following the established precedent, (E)-4-nonenylmagnesium bromide was treated with iodomagnesium salt (176) [89,90] of glutarimide (104) in ether to yield the keto-amide (177) and the carbinol-amide (178) as a 1:1 mixture. If a solution of the glutarimide salt (176) is prepared in CH_2Cl_2, the addition reaction of the Grignard reagent proceeded in nearly quantitative yield to afford the carbinol-amide (178) uncontaminated by the keto-amide (177) (compare with the method of Speckamp described in the Section IV-A). A solution of the mixture of 177 and 178 in toluene-DMF was refluxed in the presence of p-TsOH to give a separable 9:1 mixture of the enamides (179) and (180) in 75% yield. The enamide (179) was treated with formic acid to afford lactam cyclization products, from which the lactam (109) was isolated in 40% yield.

For the practical synthesis of 109, the unpurified carbinol-amide (178), prepared in CH_2Cl_2 by reaction of 176 with the Grignard reagent, was subjected to the formic acid-catalyzed cyclization to yield the formate (109) in 33% yield.

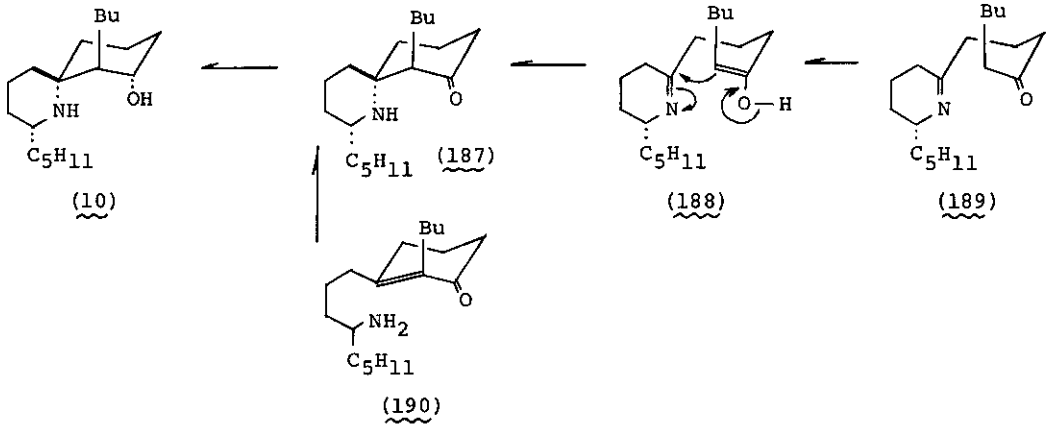
Both the enamide (179) and the carbinol-amide (178) were convertible to the formate (109) by the formic acid treatment.

Hydrolysis of 109 with NaOMe in MeOH yielded the lactam (108), a key intermediate for the synthesis of perhydrohistrionicotoxin (10). Other by-products in the formic acid-catalyzed reaction were 6-azaspiro[4.5]decane derivatives (112) (two diastereomers at the carbon atom marked with star).

Elaboration of the lactam (109) to histrionicotoxins is as follows. Successive treatments of 109 with phosphorous pentasulfide, sodium hydroxide, and then methyl iodide afforded the methyl thioimidate (181). Pretreatment of 181 with magnesium chloride gave the presumed chelate (182), which was reacted with 4-pentenylmagnesium chloride to furnish the imine (183) in 67% yield. Aluminum hydride reduction of 183 in toluene gave the desired olefin (184) and its epimer (185) (184:185=93:7). Catalytic hydrogenation of 184 yielded perhydrohistrionicotoxin (10). Elaboration of 184 to the photoaffinity labeled toxin congener (186) was also presented in the manuscript.[22]

V-E. Synthesis via the Michael Adduct or the Aziridine Intermediate

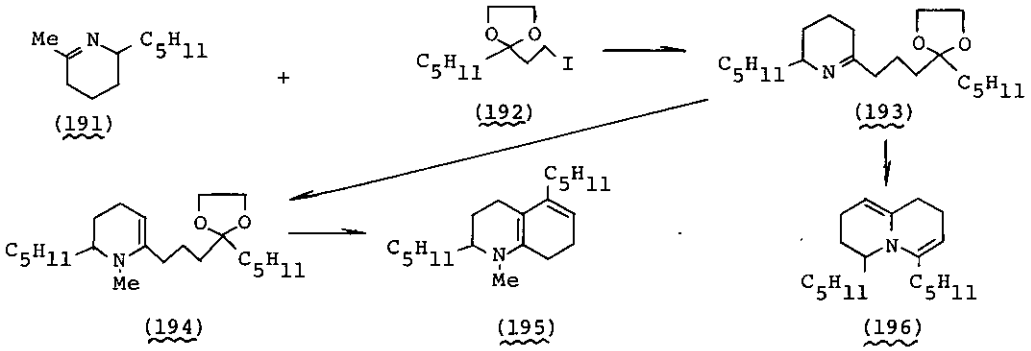
Variations on a synthetic approach to perhydrohistrionicotoxin (10) have been reported by Corey and Balanson.[18]



The synthetic routes based on the assumption that perhydrohistrionicotoxin (10) might be formed stereospecifically by reduction of the carbonyl group in the amino-ketone (187), an intermediate which might be derived in a simple way using either of two standard reactions. The first is the intramolecular Mannich reaction of a ketone and an imine (structures (189) → (188) → (187)). The second approach involves the intramolecular 1,4-addition of an amine to an enone (structures (190) → (187)).

V-E-1. The Mannich Approach

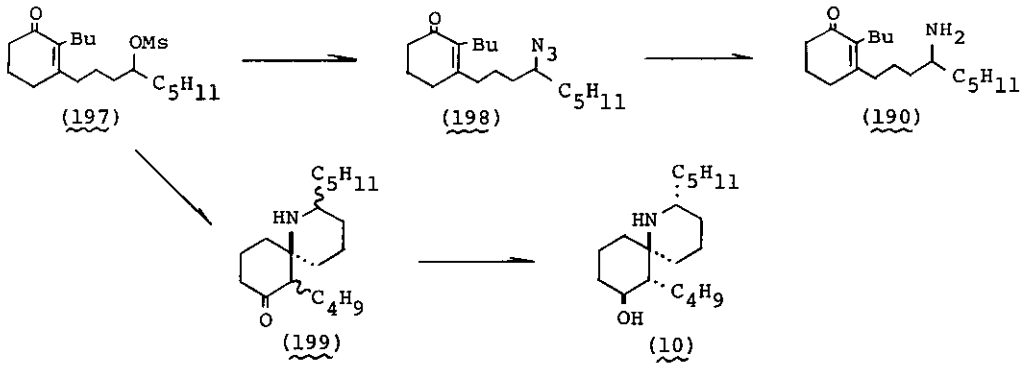
Following the procedure of Evans,[91] the anion of the tetrahydropyridine (191) was allowed to react with the iodide (192) to yield the imino-acetal (193) in 63% yield. Hydrolysis of the compound (193) was expected to give the desired ketone (189) by a rapid extraction, but the ketone (189) was found to be unstable. On exposure to a wide range of acidic conditions, 189 was converted to the undesired dienamine (196). In an effort to suppress this side reaction, 193 was treated with methyl fluorosulfonate to yield the enamino-acetal (194), which on hydrolysis gave another undesired cyclization product, the dienamine (195).



(191) (192) (193) (194) (195) (196)

V-E-2. The Michael Addition Approach

Since formation of the 1-azaspirane via the Mannich reaction route had not been achieved, the use of the Michael addition reaction was investigated.



(197) (198) (190) (199) (10)

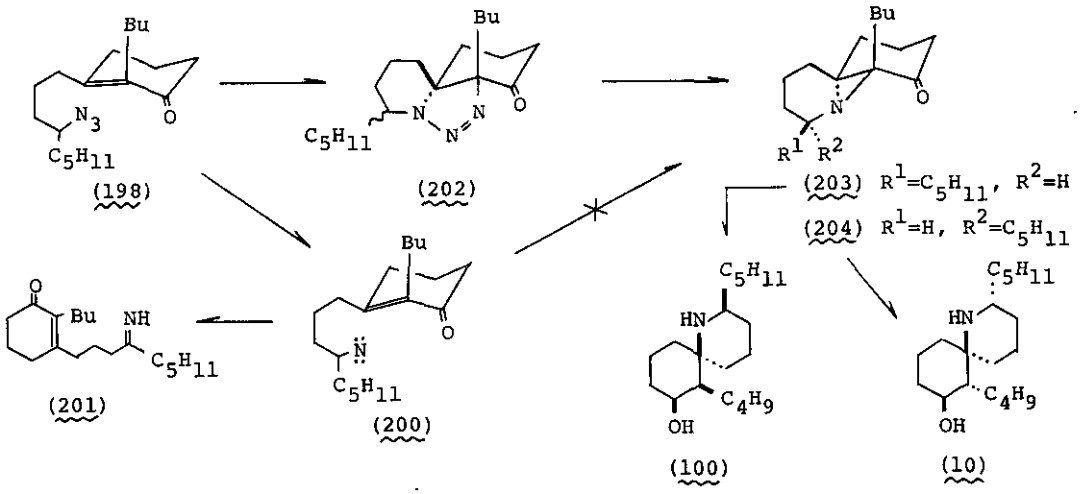
The azide (198), obtained from the mesylate (197) by reaction with lithium azide, was hydrogenated over Lindlar catalyst to furnish the amine (190) in high yield from 197. Unfortunately, no evidence for the formation of the Michael adduct (187) was obtained. When the mesylate (197) was treated with ammonia in a sealed tube, the infrared spectrum of the crude reaction mixture indicated ca.

40% conversion of 197 to the ketone mixture (199). Due to labile nature of 199, the crude mixture was immediately treated with sodium borohydride to yield a complex mixture of alcohols. One of the products isolated in 5% yield was indistinguishable from perhydrohistrionicotoxin (10) by TLC and mass spectrum.

V-E-3. The Aziridine Approach

It is well known that photolysis of an azide affords a nitrene intermediate, which can add to an olefin to form an aziridine or can undergo hydrogen shift to give an imine.

Thus, irradiation of 198 gave the undesired imine (201) presumably via the nitrene intermediate (200). When 198 was heated in refluxing xylene, a mixture of the aziridines (203 and 204) was isolated. The aziridines may be arisen from the intermediate (202). The aziridine ring cleavage of 203 was carried out with lithium in ammonia in the absence of proton source and the resulting product was immediately reduced with sodium borohydride to yield 2,7-epi-perhydrohistrionicotoxin (100). Similar two step reductions of (204) afforded perhydrohistrionicotoxin (10) in ca. 15% yield.



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