SYNTHESIS OF PUMILIOTOXIN C
A TOXIC ALKALOID FROM CENTRAL AMERICAN ARROW POISON FROG, DENDROBATES PUMILIO AND D. AURATUS

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I. Introduction

Poisonous or toxic substances originated from animals have attracted increasing interest during the last years, and many chemists as well as pharmacologists are interested in studying such biologically active substances. Various kinds of amphibians produce irritating, unpleasant, and toxic

substances for defensive or offensive purpose. Tetrodotoxin[1] isolated from the western American newts of the genus Taricha, salamander alkaloids[2-5] from the skin gland secretions of various salamanders, and toad poisons (bufadienolides)[6] from the toads of the genus Bufo are well known poisonous compounds from amphibians.

The pioneering studies of Witkop and his co-workers on the toxic alkaloids from skin extracts of Central American arrow poison frogs have led to the isolation of several alkaloids (batrachotoxins, histrionicotoxins, and pumiliotoxins) of high toxic activity.[7-27] Recent works of Mosher and his collaborators on the skin (not viscera) constituents of Costa Rican and Panamanian frogs of the genus Atelopus have also led to the isolation of tetrodotoxin, chiriquitoxin, and zetikitoxin (atelopidtoxin) with high toxic activity.[28-30] The structure of tetrodotoxin, which had been isolated from poisonous pufferfishes and Californian newts, was elucidated independently by four groups in 1964.[1,31-34] The fact that tetrodotoxin is also isolated from the skin of Consta Rican frogs is of interest in connection with the widespreaded occurrence of this toxin in the animal organism.

Recent studies of Witkop and his co-workers on the toxic constituents of the skin extract of the brightly colored arrow poison frogs, Dendrobates pumilio and D. auratus have led to the isolation of three toxins, pumiliotoxin A, B, and C.[7,8] Although there had been some confusions on the absolute configuration of pumiliotoxin C in the literatures, the novel

Table 1

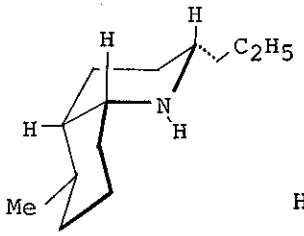
Toxins Isolated from Central American Arrow Poison Frogs

Frog species	Origin	Name of toxin	Molecular formula	Toxicity	Ref.
Dendrobates pumilio or	Panama or	Pumiliotoxin A[*1]	$C_{19}H_{33}O_2N$	2.5[*3]	7,8
D. auratus	Costa Rica	Pumiliotoxin B[*1]	$C_{19}H_{33}O_3N$	1.5[*3]	7,8
		Pumiliotoxin C (1)	$C_{13}H_{25}N$	20[*3]	7,8,27 57
Phyllobates aurotaenia	Columbia	Batrachotoxin (2)	$C_{31}H_{42}O_6N_2$	2[*4]	13-19
		Homobatrachotoxin (3)	$C_{32}H_{44}O_6N_2$	3[*4]	13-19
		Pseudobatrachotoxin[*2]			13-19
		Batrachotoxinin A (4)	$C_{24}H_{35}O_5N$	1000[*4]	13-19
Phyllobates vittatus	Costa Rica	Batrachotoxin (2)	$C_{31}H_{42}O_6N_2$	2[*4]	13-19
Atelopus varius varius	Costa Rica	Tetrodotoxin (5)	$C_{11}H_{17}O_8N_3$	10[*4]	28-30
Atelopus chiriquiensis	Costa Rica	Tetrodotoxin (5)	$C_{11}H_{17}O_8N_2$	10[*4]	28-30
		Chiriquitoxin[*1]			28-30
A. varius ambulatorius	Costa Rica	Tetrodotoxin (5)	$C_{11}H_{17}O_8N_3$	10[*4]	28-30
A. varius zeteki	Panama	Zetekitoxin[*1]			28-30

Table 1 (continued)

Frog species	Origin	Name of toxin	Molecular formula	Toxicity	Ref.
Dendrobates histrionicus	Columbia	Histrionicotoxin(HTX) (6)	$C_{19}H_{25}ON$		20-26
		Isodihydro-HTX (7)	$C_{19}H_{27}ON$		20-26
		Neodihydro-HTX (8)	$C_{19}H_{27}ON$		20
		Tetrahydro-HTX (9)	$C_{19}H_{29}ON$		20
		Isotetrahydro-HTX (10) (Allenic tetrahydro-HTX)	$C_{19}H_{29}ON$		20
		Octahydro-HTX (11)	$C_{19}H_{33}ON$		20
		Allodihydro-HTX (12)	$C_{19}H_{27}ON$		27
		Allotetrahydro-HTX (13)	$C_{19}H_{29}ON$		27
		Dodecahydro-HTX (14) *5	$C_{19}H_{37}ON$		20,27
		Desoxydodecahydro-HTX *5	$C_{19}H_{37}N$		27
		Gehyrotoxin (15) *6	$C_{19}H_{29}ON$		20,27
		Dihydrogehyrotoxin (16)	$C_{19}H_{31}ON$		27
		Alkaloid I (17)	$C_{13}H_{25}N$		27
		Alkaloid II (18)	$C_{15}H_{29}N$		27
		Alkaloid III (19)	$C_{19}H_{27}N$		27

Chart 1



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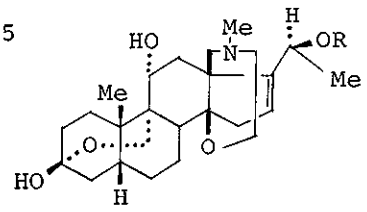
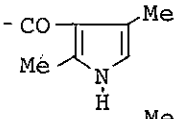
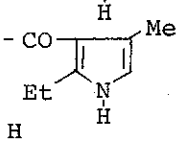


(2) R = 

(3) R = 

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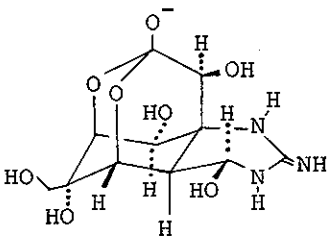

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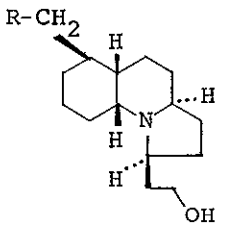
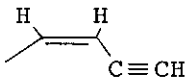
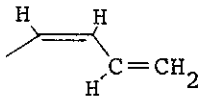
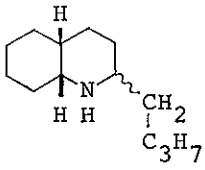


(15) R = 

(16) R = 



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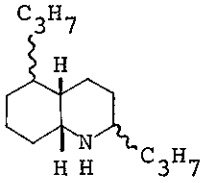

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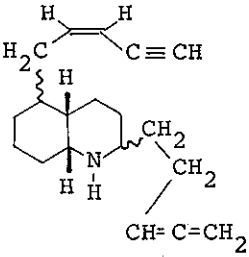


(19)

*1 Structures of these alkaloids are not clarified.

*2 Unstable and readily converted to batrachotoxinin A.

*3 LD_{50}: mg/kg in mice.

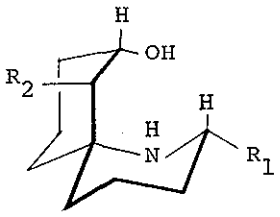
*4 LD_{50}: μg/kg in mice.

*5 Not obtained from natural source (Decahydro-HTX = Perhydro-HTX).

*6 Gehyrotoxin = Histrionicotoxin-D.

Chart 1

(continued)



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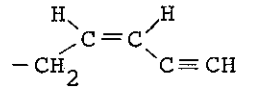
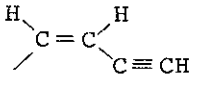
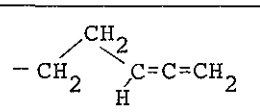
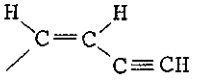
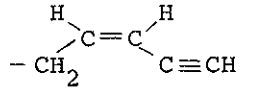
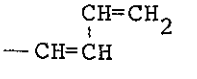
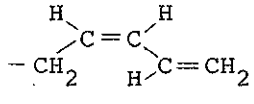
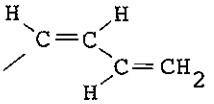
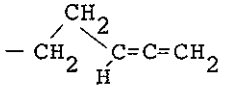
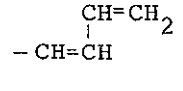
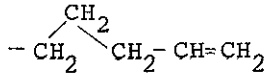
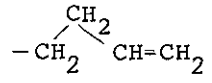
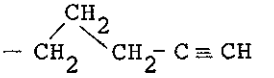
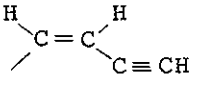
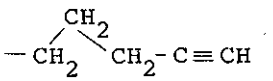
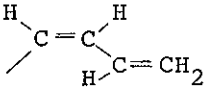
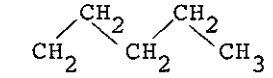
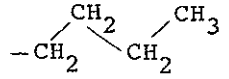
(6)		
(7)		
(8)		
(9)		
(10)		
(11)		
(12)		
(13)		
(14)		

cis-decahydroquinoline structure (1) of the toxin was elucidated by a single crystal X-ray analysis of its hydrochloride.[7,27,57] Very recently, three alkaloids (17, 18, and 19) structurally related to pumiliotoxin C (1) were also isolated from Dendrobates histrionicus collected in Columbia.[27]

Detailed treatises on the synthetic works of batrachotoxin [35], histrionicotoxins[36-54], and tetrodotoxin[55-56] have appeared and the interested reader will find the essential informations here, so we will forcus the present discussion entirely on the total synthesis of racemic and natural pumiliotoxin C.

II. Occurence and Structure of Central American Arrow Poison Frog Toxins.

Table I and Chart I give survey of the occurrence and structure of Central American arrow poison frog alakloids.

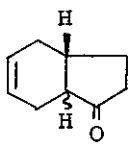
III. Synthesis of Racemic and Natural Pumiliotoxin C

Interest in the synthesis of pumilotoxin C increased not only due to the nurve-muscle activity of the toxin but for its unusual cis-decahydroquinoline structure and a limited amount of the toxin available from the natural source (15 mg from 250 frogs) has urged also chemists to establish the synthesis of the toxin. The synthetic study of the toxin has been undertaken in four laboratories with a remarkable degree of variety in the synthetic schemes culminating in seven total syntheses.[58-66]

III-A. Synthesis via Indanones

III-A-1 The first synthesis of dl-pumiliotoxin C was reported by Inubushi et al. in 1975.[59,60] A mixture of cis- and trans-tetrahydro-1-indanone (20) in the ratio 9:1 was condensed with hydroxylamine and subsequent treatment with p-TsCl in pyridine yielded a mixture of cis- and trans-octahydroquinolones (21) and (23) in 53 and 6% yields, respectively. The N-benzyl compound (22) derived from 21 was oxidized with m-chloroperbenzoic acid to give the epoxy-lactam (24) which was converted into the bromohydrin (25) by treatment with 48% hydrobromic acid. Oxidation of 25 with Jones' reagent furnished the bromo-ketone (26) which was dehydrobrominated with LiBr-Li_2CO_3 to give the α,β-unsaturated ketone (27) in 42% overall yield from 25.

The stereoselective conjugated addition of $LiMe_2Cu$ to the compound (27) afforded the methyl-ketone (28) in greater than 86% yield as a sole product. Other three possible stereoisomers (36), (37), and (38) of 28 were also synthesized with the intention of confirming the stereochemistry of the methyl-ketone (28). The thioacetal (29) derived from 28, was reduced with Raney W-2 nickel to afford the N-benzylquinolone (30) in 82% yield. Reductive debenzylation[69] of 30 gave 5-methylquinolone (31) in 71% yield, and subsequent treatment of 31 with P_2S_5 afforded the thiolactam (32). Condensation of the thiolactam (32) with bromoacetone, followed by treatment with triphenylphosphine[70] gave the vinylogous amide (33) in a 71% yield. Catalytic hydrogenation of 33 over PtO_2 and subsequent oxidation



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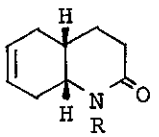

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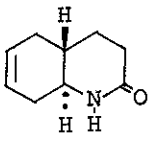
(22) R = $CH_2C_6H_5$



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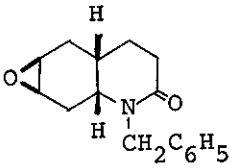

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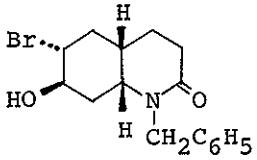

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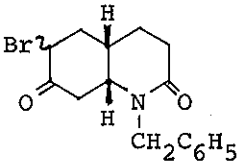

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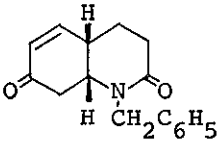

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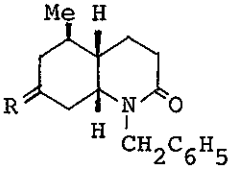
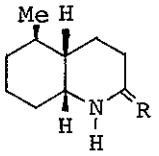


(28) R = O

(29) R = 

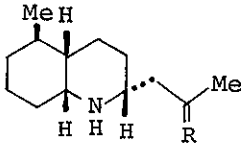
(30) R = H_2



(31) R = O

(32) R = S

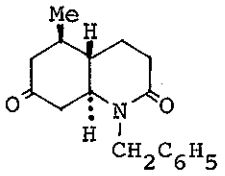
(33) R = CHCOMe



(34) R = O

(35) R = 

(1) R = H_2



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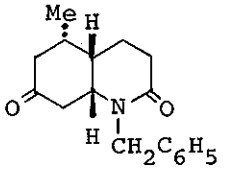

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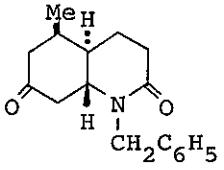


(38)

Chart 2

with Jones' reagent yielded the β-amino-ketone (34) as a single product. Finally, the thioacetal (35) derived from 34 was reduced with Raney W-2 nickel to yield dl-pumiliotoxin C (1).

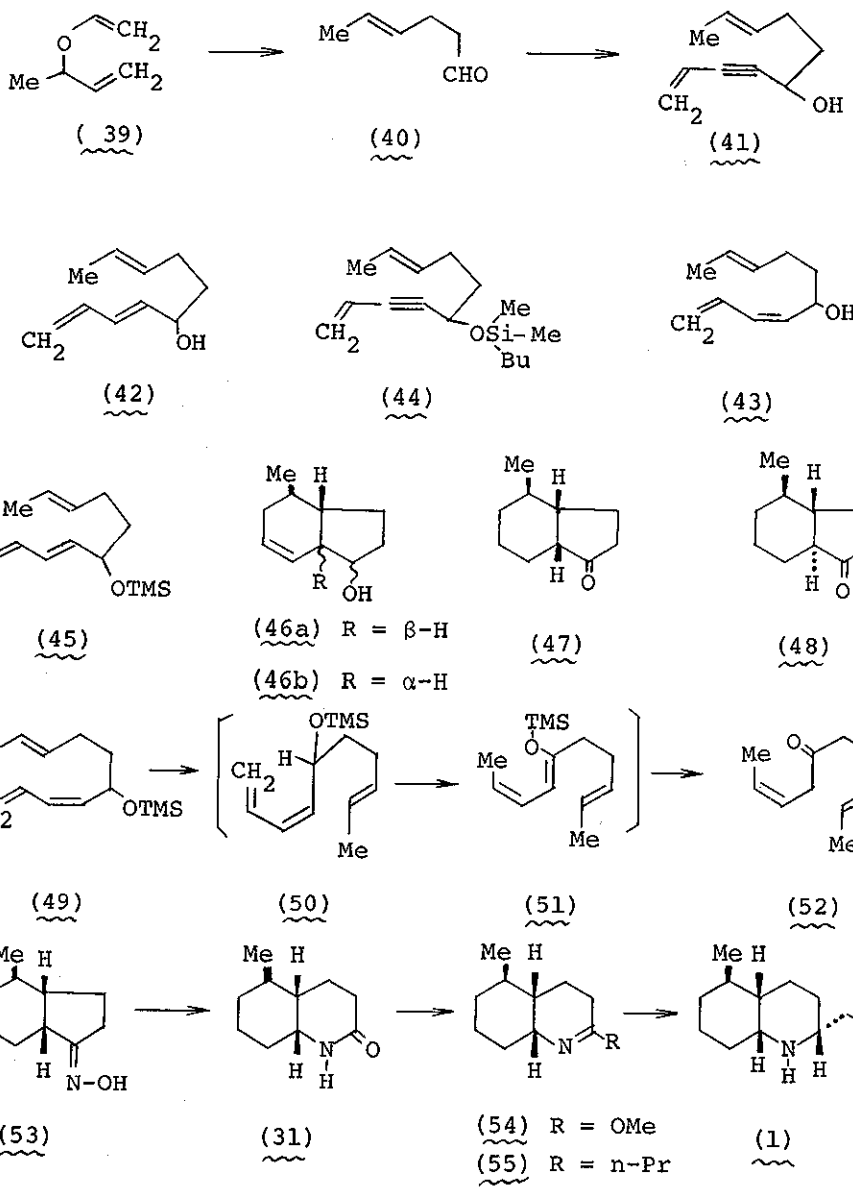
The oily synthesized toxin was characterized as its hydrochloride, and a single crystal X-ray analysis of the toxin hydrochloride provided unequivocal proof of the stereochemistry of the synthetic base.

III-A-II. For the synthesis of dl-pumiliotoxin C, Oppolzer et al. made use of the indanone (47) as an intermediate.[58] The precursor (41) for the indanone (47) was readily available by addition of vinylacetylenemagnesium bromide to the aldehyde (40) obtained from 3-vinyloxybuten-1 (39). Reduction of 41 with $LiAlH_4$-NaOMe[67] gave the trans-trienol (42). On the other hand, reaction of the acetylene (41) with Zn-KCN[68] gave a (1:2)-mixture of the trienes (42) and (43). A selective pathway to 43 (78% yield) was achieved by successive reactions of the dimethyl(t-butyl)silyl ether (44) with Zn-KCN and Si-O-bond cleavage with $(Bu)_4NF$.

No reaction took place below 240° on attempting the intramolecular cycloaddition of the trienol (42), whereas at higher temperature, dehydration products were obtained with minor quantities (10%) of the indanols (46a and 46b). Heating of the trans-trienetrimethylsilyl ether (45), followed by hydrolysis gave the indanols (46a and 46b) in 51% overall yield from 42. Catalytic hydrogenation of this mixture, followed by oxidation with CrO_3 gave a separable (2:1)-mixture of cis- and trans-fused indanones (47) and (48).

On the other hand, a similar treatment of the cis-trienetrimethylsilyl ether (49) furnished the pure cis-fused indanone

Chart 3



(39) (40) (41)

(42) (44) (43)

(45) (46a) R = β-H (46b) R = α-H (47) (48)

(49) (50) (51) (52)

(53) (31) (54) R = OMe (55) R = n-Pr (1)

(47) in only 15% yield. A careful examination of the hydrolyzed thermolysis mixture obtained from 49 showed that the main product of this reaction is the ketone (52). This suggests that the low yield of the cycloadduct (47) may be attributed to the competitive 1,5-hydrogen shift reaction (50→51). Accordingly, thermolysis of the trans-trienetrimethylsilyl ether (45) seemed to be prefered over that of the cis isomer.

The oxime (53) derived from 47 was treated with p-TsCl in aq. NaOH to give the cis-fused lactam (31) which had previously been prepared by Inubushi et al.[60] Reaction of the imino ether (54) prepared from 31 by treatment with the Meerwein reagent, with propylmagnesium bromide gave the imine (55). Hydrogenation of the imine (55) gave dl-pumiliotoxin C (1).

III-B Synthesis via the Diels-Alder Adducts

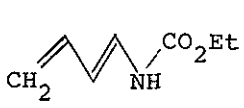
The Diels-Alder reaction in which the functionalized novel dienes[71-75] are used, has become of interest in recent years. The synthesis of dl-pumiliotoxin C using this type of the Diels-Alder reaction is described in this section.

III-B-I. Several novel 1- and 2-amino-1,3-butadiene derivatives were prepared by Overman et al.[74,75] Racemic pumiliotoxin C (1) was synthesized via the Diels-Alder adduct (57), which was obtained by using 1-acylamino-1,3-butadiene and a dienophile.[64]

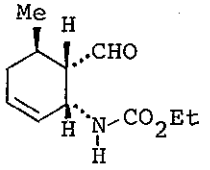
The Diels-Alder reaction of ethyl 1,3-butadien-1-carbamate (56)[75] with trans-crotonaldehyde gave the cycloadduct (57) and its isomer in 61% and 5% yields, respectively. The Diels-Alder

reaction proceeds with a high endo-stereoselectivity and a regioselectivity, so that three of four chiral centers of pumiliotoxin C (1) are formed.

Chart 4



(56)



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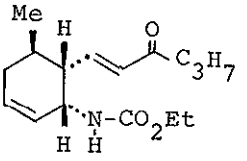
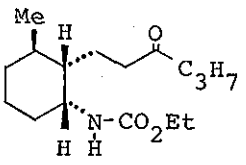


(58)



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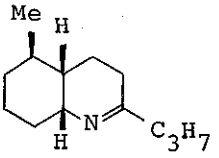
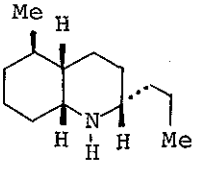


(37)

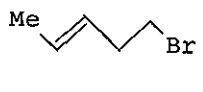


(1)

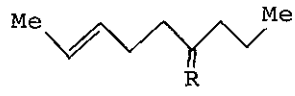
The Wittig reaction of 57 with sodio dimethyl-2-oxopentyl-phosphonate furnished the enone (58) in a 83% yield. Hydrogenation of 58 yielded the amino-ketone (59). Removal of the carbamate group of 59 with HBr-AcOH-Cu afforded the sensitive imine (37), which was immediately hydrogenated over PtO_2 to yield nearly pure dl-pumiliotoxin C (ca. 90% yield from 59). The synthetic dl-pumiliotoxin C was purified through its hydrochloride.

III-B-II. In order to achieve a stereocontrolled synthesis of substituted decahydroquinolines, Oppolzer and Frösti[76,77] developed the general synthetic method for trans-N-acyl and N-alkyl-1-amino-1,3-butadienes and they synthesized stereoselectively cis and trans octahydroquinolines by the intramolecular Diels-Alder reaction using these dienes. This synthetic route was then successfully applied to the synthesis of dl-pumiliotoxin C.[63]

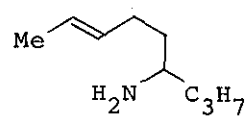
Chart 5



(60)



(61) R = O
(62) R = NOH



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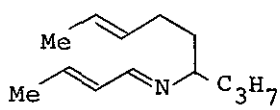

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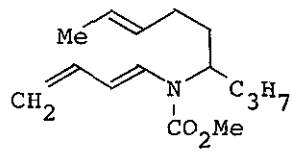

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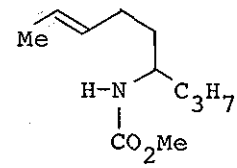

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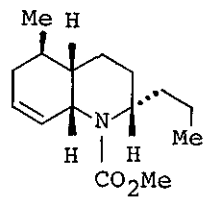

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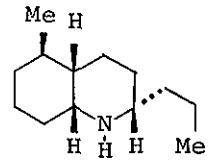


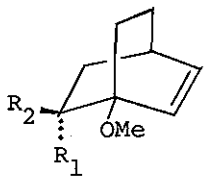
(1)

Reaction of the Grignard reagent prepared from trans-1-bromo-3-pentene with butyronitrile, followed by treatment with acid gave the ketone (61:62% yield) which was converted to its oxime (62:52% yield). Reduction of 62 with $LiAlH_4$ furnished the amine (63) which was converted into the conjugated azomethine (64) by reaction with crotonaldehyde. Treatment of 64 with sodium hexamethyldisilazane, followed by reaction with methyl chloroformate gave the trans-dienamide (65: 49% yield). Thermolysis of 65 afforded a mixture of the desired octahydroquinoline (66:25% yield) and the elimination product (67: 37% yield). On hydrogenation over Pd-C, followed by acid hydrolysis, the quinoline (66) furnished dl-pumiliotoxin C (1). The structural proof of the synthesized toxin was obtained by X-ray analysis of the base hydrogen maleate.

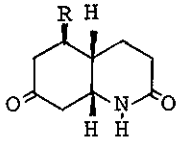
III-B-III The usefulness of the Diels-Alder reaction using cyclic and acyclic 1,3-dioxygenated dienes such as 1,3-diacetoxycyclohexa-1,3-dienes[78], 1,3-diethoxycyclohexa-1,3-dienes[79], 1,3-diethoxy-1,3-butadiene[80], and 1-methoxy-3-trimethylsiloxy-1,3-butadiene[81] for the preparation of oxygenated cycloadducts had been reported and novel cyclic and acyclic 1,3-bis(trimethylsiloxy)-1,3-dienes were prepared for the purpose of the stereoselective synthesis of dl-pumiliotoxin C at our laboratory.

An attempt was first made to convert the methoxy-nitriles (68)[84] and (69)[84] into cis-decahydroquinol-2,7-dione (70). This attempt, however, got into trouble due to the failure to

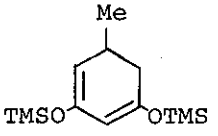
Chart 6



(68) R_1=CN, R_2=H
(69) R_1=H, R_2=CN



(70) R=H
(71) R=Me



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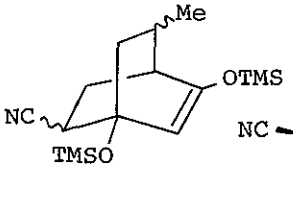

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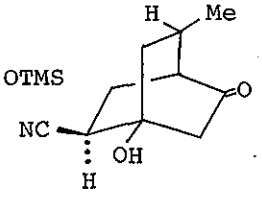
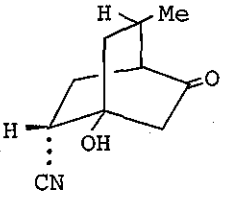
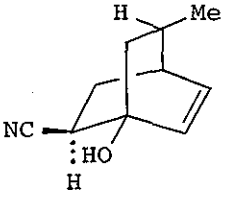


(74)



(75)



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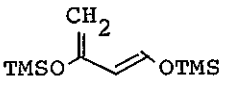

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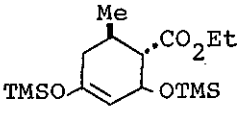

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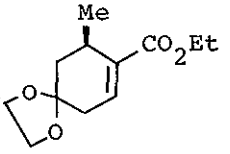

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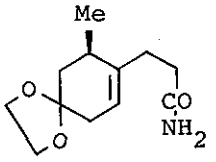

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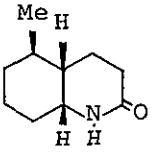

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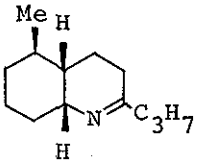

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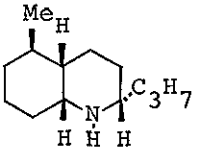


(1)

remove the methyl group of the methoxyl function. In order to overcome this difficulty, it was desired to synthesize a 1-hydroxy[2,2,2]octane derivative such as the compound (76) which would be transformed readily into the cis-decahydroquinoline derivative (71) through the retrograde-aldol type bond cleavage

and the subsequent intramolecular Michael type addition. For this purpose, 1,3-bis(trimethylsiloxy)-5-methylcyclohexa-1,3-diene (72) is suitable as a diene component in the Diels-Alder reaction since facile removal of trimethylsilyl groups from the resulting cycloadduct is expected.

The Diels-Alder reaction of the diene (72) prepared from 5-methylcyclohexa-1,3-dione and TMS-chloride, with acrylonitrile furnished a mixture of cycloadducts (73; 75% yield) which was treated with 10% HCl to give the exo-adduct (74; 51% yield)[83] and the endo-adduct (75)[83] as a minor product. Successive treatments of the compound (74) with $C_5H_5N \cdot HBr \cdot Br_2$, $NaBH_4$, and Zn-AcOH provided the exo-cyano compound (76; 64% yield). Treatment of 76 with 15% $HClO_4$-AcOH[59,60,61] gave the keto-lactam (71; 37% yield).

An alternative synthetic route to the compound (71) involves the Diels-Alder reaction using novel acyclic 1,3-bis-(trimethylsiloxy)-1,3-butadiene (77) as a diene component. Thus, reaction of the diene (77) with ethyl crotonate gave regioselectively the cycloadduct (78) which was converted into the ketal-ester (79). Successive treatments of 79 with $LiAlH_4$, TsCl, cyanomethylcopper[85], and H_2O_2-aq. NaOH afforded the ketal-amide (80). Deketalization of 80, followed by treatment with NaOMe-MeOH gave the keto-lactam (71) as a sole isolable product.

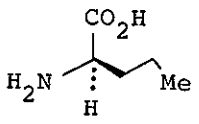
The compound (71) synthesized through the two routes described above, was converted to the lactam (35) by a method mentioned in the section III-A-I. Treatment of the lactam (35)

with NaH-butyryl chloride furnished the N-butyroyl compound which gave the imine (37) on heating with CaO.[86] Finally, catalytic hydrogenation of 37 over PtO_2 gave dl-pumiliotoxin C (1) as a sole product.[61]

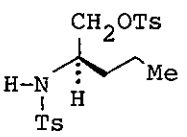
III-B-IV Natural pumiliotoxin C [(2S)-configuration] and its enantiomer [(2R)-configuration] were synthesized by Oppolzer et al. in an enantioselective manner starting from (S) or (R)-norvaline, respectively.[66]

Reduction of (R)-norvaline (81) with $LiAlH_4$, followed by treatment with TsCl-pyridine furnished the bistoluenesulfonyl derivative (82) which was converted to the N-tosyl aziridine (83) by treatment with KOH-MeOH (68% yield from (R)-81). Reaction of 83 with the Grignard reagent prepared from 1-bromo-2-butyne, gave a mixture of the allene (84) and the desired acetylene (85) in 41% and 32% yields, respectively. The acetylene derivative (85) was transformed to the trans-(R)-amine (86) by treatment with sodium in liq. ammonia. This treatment caused concurrently reduction of the acetylene function and reductive cleavage of the N-tosyl bond. Alternatively, the amine (86) was prepared starting from 1-bromo-(3R)-aminohexane hydrobromide (87). Thus, compound (87) was treated with propynyl sodium in liq. ammonia to give the acetylene (88) which on reduction with sodium in liq. ammonia furnished the amine (86). Successive treatments of 86 with crotonaldehyde, NaH, and isobutyryl chloride afforded the dienamide (89). Thermolysis of 89 gave the octahydroquinoline derivative (90) contaminated with small amounts of diastereoisomeric adducts.

Catalytic hydrogenation of the mixture, followed by reductive cleavage of the amide bond with (iso-Bu)$_2$AlH gave the free amine (91) which on treatment with MeOH-HCl provided unnatural (+)-(2R)-pumiliotoxin C (91) hydrochloride.



(81)



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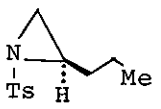

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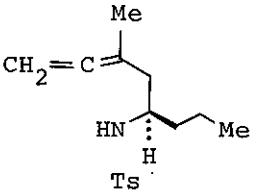

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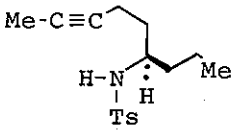

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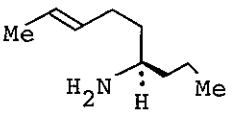

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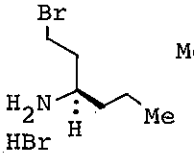

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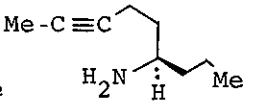

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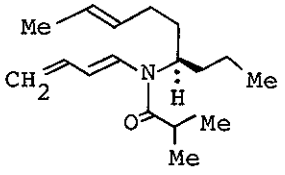

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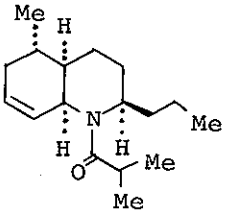

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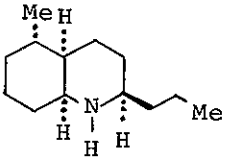

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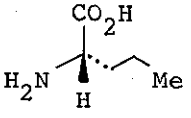

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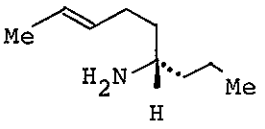

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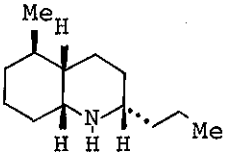


(1)

Chart 7

A similar reaction sequence starting from (S)-norvaline (92) furnished pure natural pumiliotoxin C (1) hydrochloride via the amine intermediate (93). Although there has been a confusion on the absolute configuration of the toxin[63,65], the stereostructure of the base is unambiguously established by the chemical method described above and this result is consistent with the result reported by Witkop et al.[27]

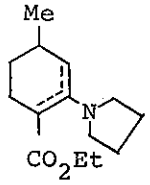
III-C Synthesis via Pyrrolidine Enamine

By application of the synthetic method of Parcell[87], racemic pumiliotoxin C[62,65] and optically active pumiliotoxin C[65] were synthesized starting from the pyrrolidine enamine (94) (see also footnotes, 8,9, and 10 of Ref. 66.). Because the synthetic method for racemic pumiliotoxin C is the same as that for the optically active toxin, the synthetic pathway for optically active pumiliotoxin C is described in this section. (The stereostructures described in Chart 8 are cited from the original paper.)

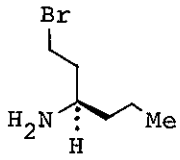
Reaction of the enamine (94) with (-)-1-(2-bromoethyl)-(1R)-butylamine (95) gave the compound (97) presumably via the intermediates (96a) and (96b). Because the imine (97) was unstable, the unisolated imine was immediately treated with 20% HCl to afford the imine (98). Catalytic hydrogenation of 98 over Pd-C furnished optically active (enantiomeric?) pumiliotoxin C (91) and an isomeric compound of unknown structure. The (2R)-configuration of the synthesized toxin (91) is not consistent with the (2S)-configuration of natural pumiliotoxin C.

Recently, it was reported that natural (2S)-pumiliotoxin C had been synthesized from (+)-1-(2-bromoethyl)-(1S)-butylamine.[27]

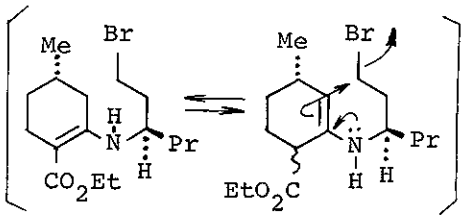
Chart 8



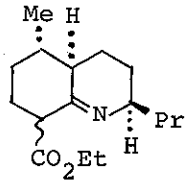
(94)



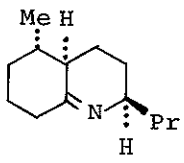
(95)



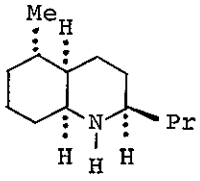
(96a) (96b)



(97)



(98)



(91)

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