PROGRESS IN TOTAL SYNTHESES OF MARINE ALKALOIDS, AAPTAMINES

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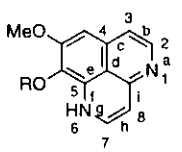
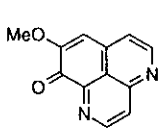
Abstract — A bright yellow aaptamine, which possesses a novel 1*H*-benzo[*d*,*e*][1,6]naphthyridine skeleton was isolated as a protonic salt from the Okinawan sea sponge *Aaptos aaptos*. Also related compounds, demethylaaptamine and demethyloxyaaptamine were isolated from same origin. We summarize here eight total syntheses containing one formal synthesis of aaptamine and related compounds.

1. Introduction

The bright yellow substance, aaptamine (**1a**), 8,9-dimethoxy-1*H*-benzo[*d*,*e*][1,6]naphtyridine, was isolated in 1982 from an Okinawan sea sponge, *Aaptos aaptos* as its hydrochloride by Nakamura and co-workers.[1] This substance has been shown to have powerful α-adrenoceptor blocking activity.[2] Demethylaaptamine (**1b**) and demethyloxyaaptamine (**2**) have since been isolated from the same origin[2] (Scheme 1). The demethylated and oxidized variants (**1b** and **2**) possess antitumor and antimicrobial activity.[3] These three compounds were the first examples of the 1*H*-benzo[*d*,*e*][1,6]naphthyridine ring system found in a naturally occurring substance.



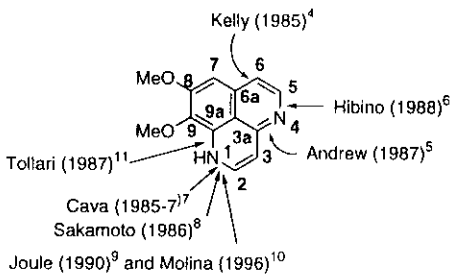
1a: R=Me
1b: R=H
1c: R=Me , HCl salt



2

Scheme 1

From a synthetic viewpoint, the 1*H*-benzo[*d,e*][1,6]naphthyridine ring system can be viewed either as quinoline or isoquinoline, but with an additional fused six-membered nitrogen-containing ring. To date, eight synthetic efforts, including one formal total synthesis, have been completed. These efforts necessitated the construction of either isoquinoline[4-6] or quinoline[7-11] at the final stage of total synthesis, depicted by an arrow in Scheme 2. Each bond position on the three ring system is represented below; the C6-C6a bond, based on the numbering indicated in Scheme 2, is an example. Work in this area of study can be divided into two broad categories, namely, synthesis of the pyridine ring fused to quinoline and synthesis of the pyridine ring fused to isoquinoline.



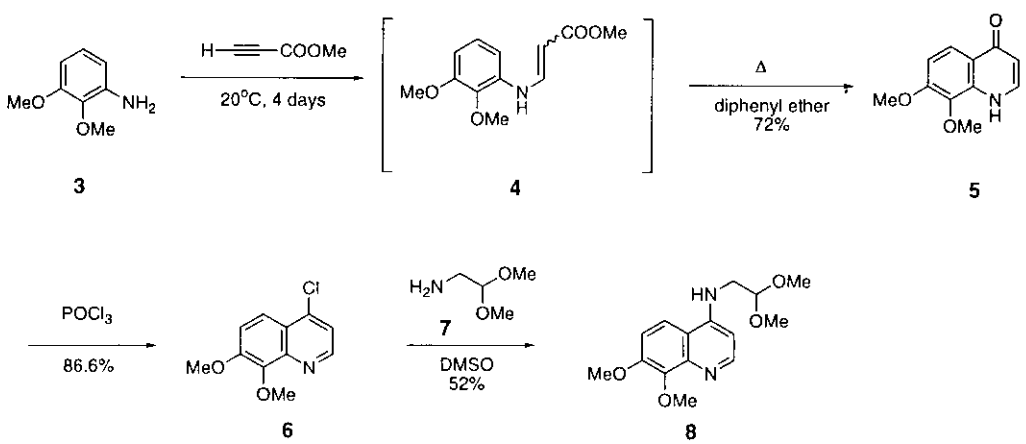
1a

Scheme 2

2. Synthesis of the Pyridine Ring Fused to Quinoline

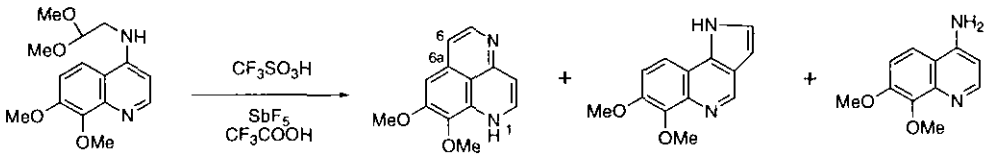
2.1 The formation of the *C6-C6a* bond

The first total synthesis was achieved by Kelly[4] through the formation of the C6-C6a bond at the final stage. Michael addition of 2,3-dimethoxyaniline (**3**) (prepared from veratrole) to methyl propiolate,



Scheme 3

followed by replacement of the solvent with diphenyl ether and the thermal cyclization at reflux temperature produced the initial quinoline (**5**). Chlorination of **5** with $POCl_3$ gave the 4-chloroquinoline (**6**), which was carried out by the reaction with aminoacetaldehyde dimethylacetal (**7**) to produce the key compound (**8**) (Scheme 3). The bicyclic key compound (**8**) was subjected to Pomerantz-Fritsch type reaction[12] to produce aaptamine (**1a**) (34%) directly together with pyrroloquinoline (**9**) in the 1:1 ratio without regioselectivity. The results were obtained by using a mixture of triflic acid and antimony pentafluoride in trifluoroacetic acid (Scheme 4).

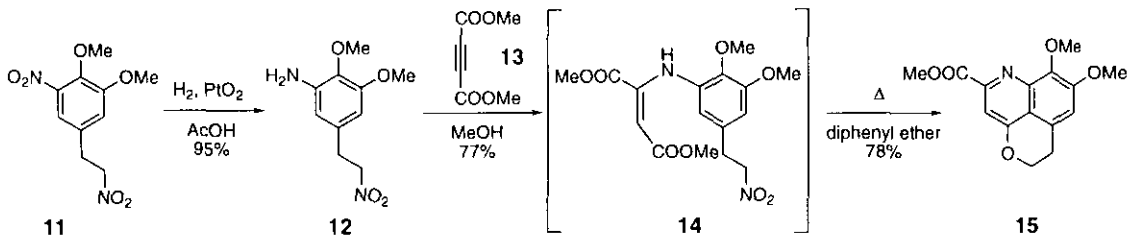


8 **1a**: 34% **9**: 33% **10**: 24%

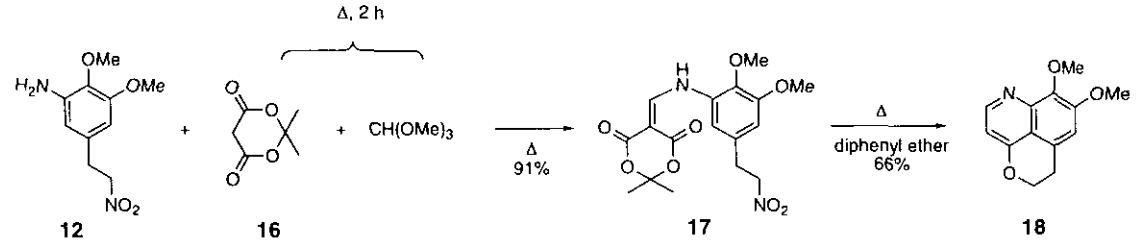
Scheme 4

2.2 The formation of the *C3a-N4* bond

Andrew and Raphael[5] chose the dinitro-compound, 1-(3,4-dimethoxy-5-nitrophenyl)-2-nitroethane (**11**), as a key compound for anticipating in two cyclizations regioselectivity without ambiguity. The dinitro compound (**11**) was prepared from 5-nitroveratraldehyde in a three step sequence. Selective catalytic hydrogenation of **11** gave the aniline (**12**), which was made to react with dimethyl acetylenedicarboxylate



11 **12** **14** **15**

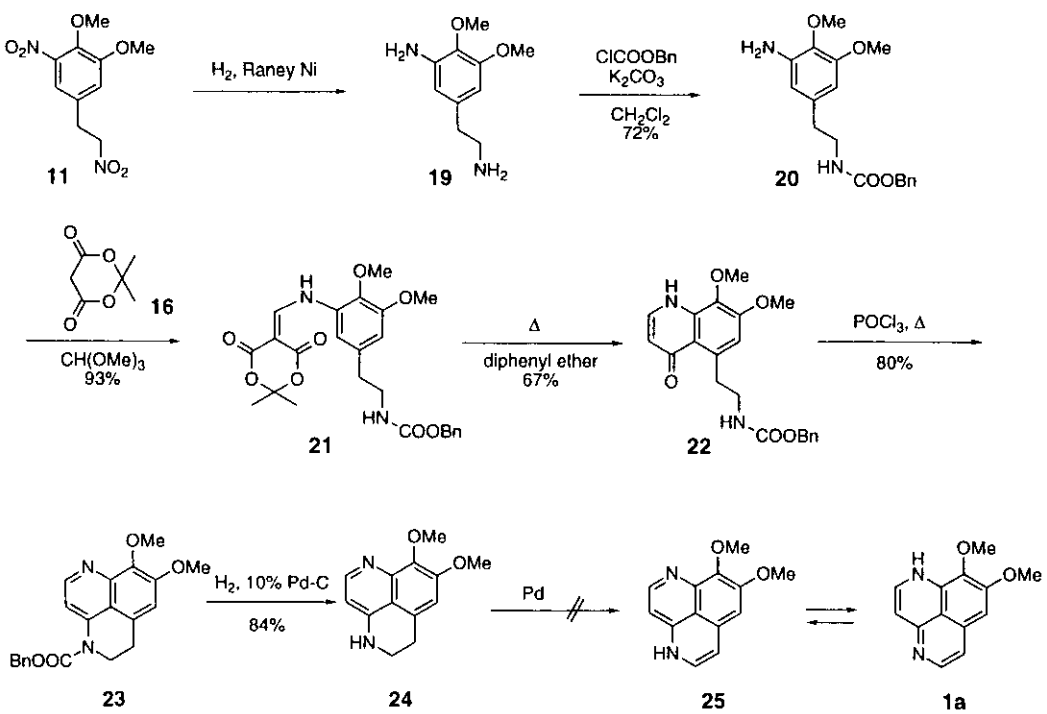


12 **16** **17** **18**

Scheme 5

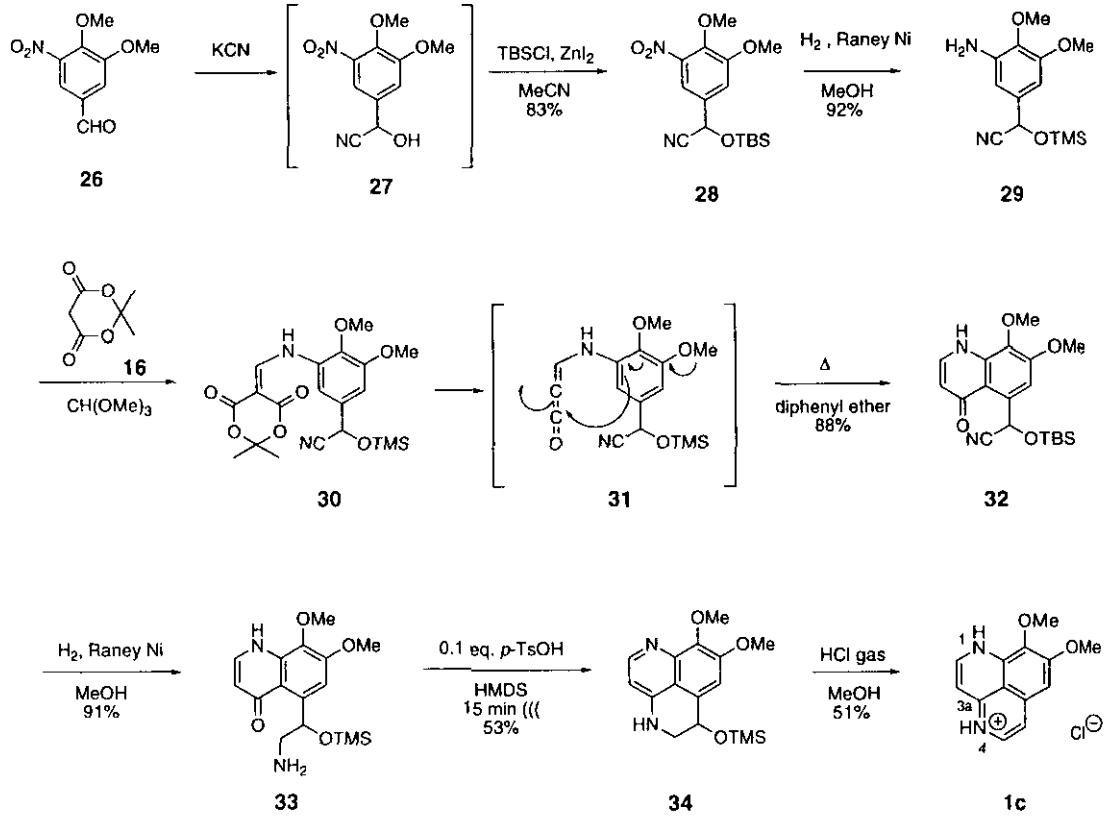
(**13**) to produce the enamino ester (**14**). The thermal cyclization[13] of **14** in diphenyl ether gave a trace of the quinolone and the tricyclic oxygen-containing compound (**15**) (78%) as a major product. In another approach to the quinolone, the nitroaniline (**12**) was condensed with methoxymethylidene Meldrum's acid [prepared form Meldrum's acid (**16**) and trimethyl orthoformate] to yield the anilinomethylidene Meldrum's acid (**17**). The thermal cyclization[13] of **17** in diphenyl ether again provided the tricyclic oxygen-containing compound (**18**) with a similar extrusion of the nitro group (Scheme 5).

Andrew and Raphael attempted to utilize the diamino-compound (**19**) for the cyclization to the quinolone. Catalytic hydrogenation of the dinitro-compound (**11**) with Raney's nickel gave the corresponding diamine (**19**), which was selectively acylated with benzyl chloroformate to afford the mono-acylated amine (**20**). Treatment of **20** with methoxymethylidene Meldrum's acid in a similar way yielded the anilinomethylidene Meldrum's acid (**21**). Thermal cyclization[13] of **21** produced the quinolone (**22**) without a trace of tricyclic oxygen-containing compound (**18**), which was directly treated with $POCl_3$ to yield the desired tricyclic compound (**23**) through the formation of the bicyclic chloroquinoline. Subsequent hydrogenolysis of **23** gave the dihydroaaptamine (**24**). However, dehydrogenation of **24** to aaptamine was unfortunately unsuccessful (Scheme 6).



Scheme 6

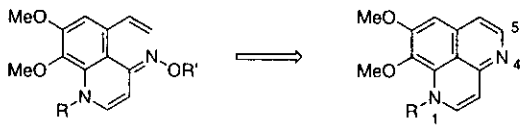
In view of an unexpected occurrence, they employed an intermediate of higher oxidation state, namely, 5-nitroveratraldehyde (**26**), which was then converted into the silylated cyanohydrine (**28**) by treatment with KCN and *t*-butyldimethylsilyl chloride (TBDMS-Cl). Hydrogenation of **28** with Raney's nickel gave the aniline (**29**), which was transformed to the anilinomethylidene Meldrum's acid (**30**). Thermal cyclization of **30** led to the quinolone (**32**). Catalytic hydrogenation of **32** afforded the corresponding phenylethylamine (**33**). The second cyclization of **33** effectively proceeded in a hexamethyldisilazane solution in the presence of *p*-TsOH, which produced the tricyclic product (**34**). Subsequent treatment of **34** with methanolic hydrochloric acid provided aaptamine hydrochloride (**1c**) through the processes of deprotection and dehydration.



Scheme 7

2.3 The formation of the *N4-C5* bond

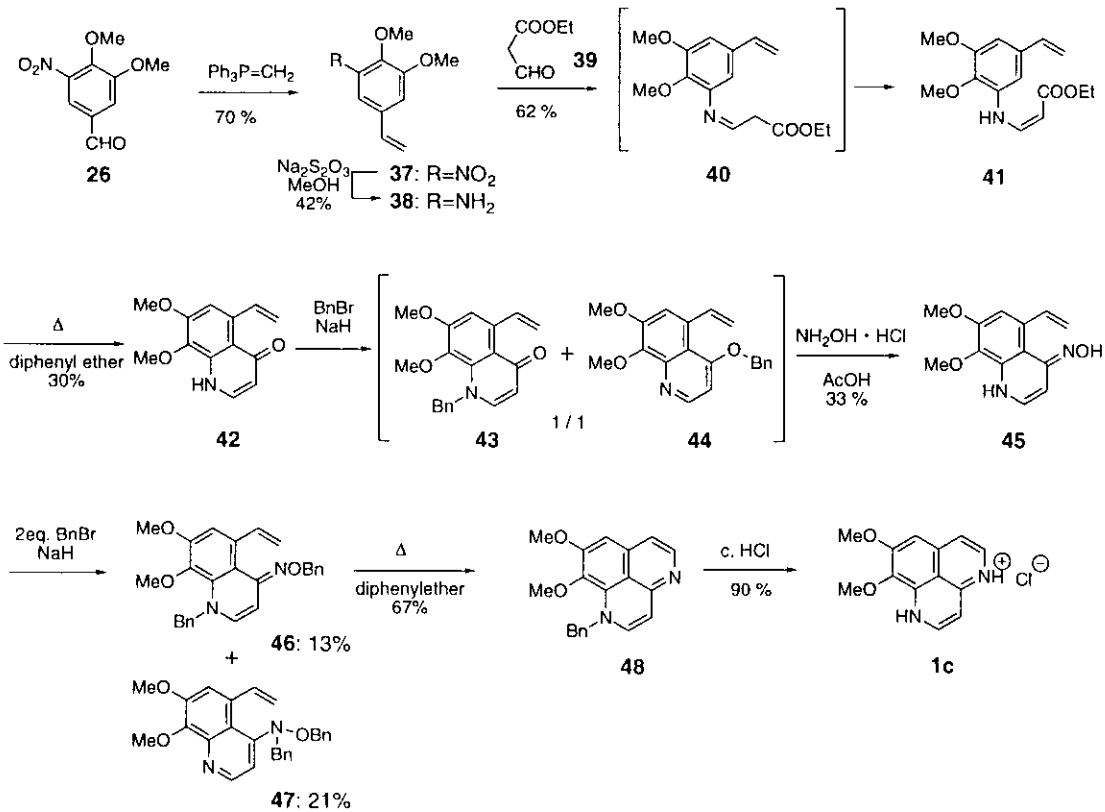
We planned to form the N4-C5 bond based on the thermal electrocyclic reaction of the 1-azahexatriene system (Scheme 8).[6,14]



35 36

Scheme 8

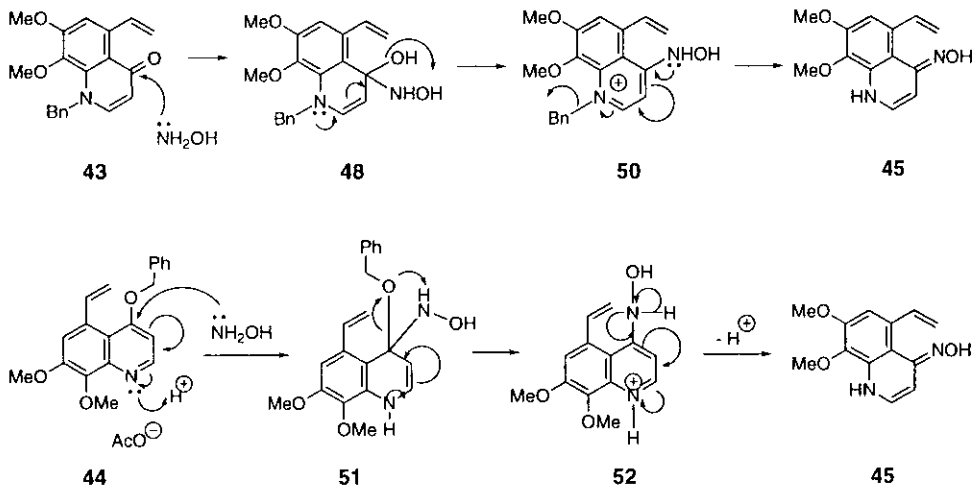
The 5-nitroveratraldehyde (**26**) was converted into the nitrostyrene (**37**) by Wittig reaction (Scheme 9). Reduction of **37** with sodium dithionate provided the aminostyrene (**38**), which was treated with 2-formylacetate (**39**) to give the enamino ester (**41**). Subsequent cyclization of **41** in diphenyl ether afforded the appropriate quinolone (**42**). However, the direct conversion of quinolone (**42**) into the oxime (**45**) failed because of the vinylogous amide. The protection of the nitrogen with benzyl bromide gave an inseparable mixture (1:1) of the *N*-benzylquinolone (**43**) and the quinoline (**44**). When a mixture of **43** and



Scheme 9

44 was refluxed with hydroxylamine hydrochloride and sodium acetate in ethanol, the deprotected quinolone oxime (**45**) was obtained in 33% yield from **42**. However, the thermal electrocyclic reaction of

45 was unsuccessful because of tautomerism between the quinolone and quinoline forms. In order to prevent the aromatization of **45**, the benzylation of **45** with benzyl bromide was carried out, giving the *N*-benzylated quinolone oxime (**46**) (13%) along with the unexpected quinoline (**47**) (21%). The thermal electrocyclic reaction[14] of the 1-azahexatriene system (**46**) afforded the *N*-benzylaaptamine (**48**) (67%), which was treated with hydrochloric acid at reflux to provide aaptamine hydrochloride (**1c**) (90%). The quinoline oxime (**45**) probably can be obtained from both compounds (**43** and **44**) in either of two ways, illustrated by the arrows in Scheme 10.



Scheme 10

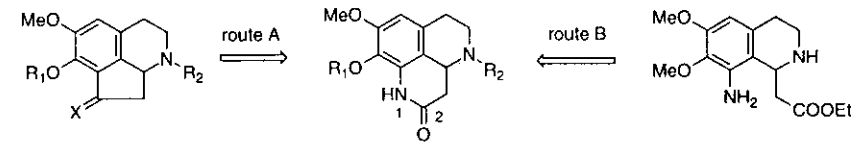
3. Synthesis of the Pyridine Ring Fused to Isoquinoline

3.1 The formation of the *N1-C2* bond

1*H*-Benzo[*d*,*e*][1,6]naphthylidine, aaptamine (**1c**) and demethyloxyaaptamine (**2**) were synthesized by Cava and Pelletier[7] through the intramolecular condensation (route B) of ethyl 8-amino-1,2,3,4-tetrahydro-1-isoquinolineacetate (**55** or **65**) derived from the common compound (**61**) sequentially.

Cava and Pelletier initially envisaged the δ-lactam (**53**) as the tricyclic ring; they chose to investigate two synthetic routes to aaptamine. The first route utilizes Beckmann rearrangement (route A, in Scheme 11) and the second (route B, in Scheme 11) is the usual condensation of amine with the ester group. Initially, the tricyclic amino ketone (**54a and b**) was treated with hydroxylamine to give the corresponding oxime (**54c** and **d**). Exposure of the oxime (**54c** and **d**) to various acid conditions conducive to Beckmann

rearrangement[15] did not afford any objective compound (**53c** and **d**). Schmidt reaction of **54c** was also unsuccessful.

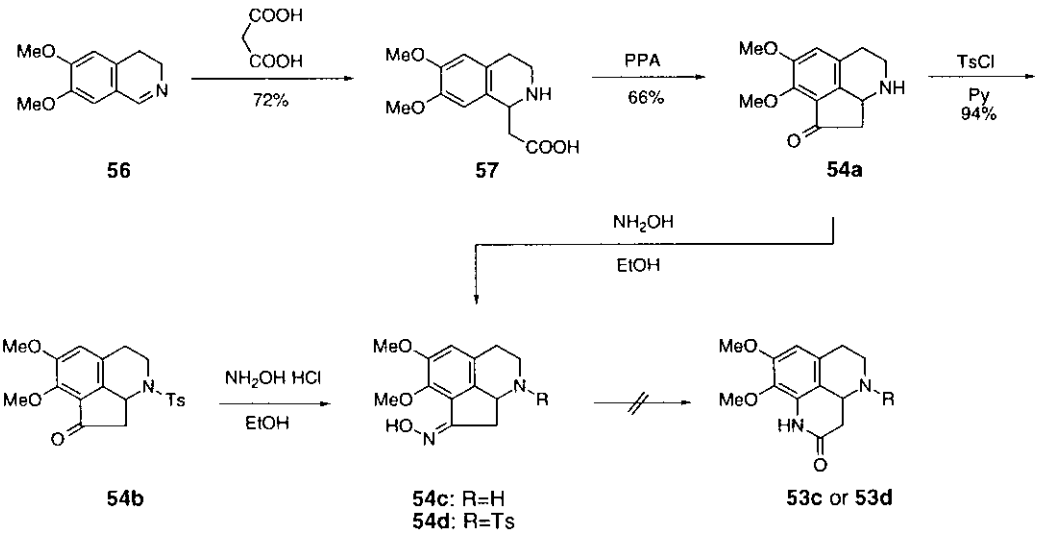


54a: R_1=Me, R_2=H, X=O
54b: R_1=Me, R_2=Ts, X=O
54c: R_1=Me, R_2=H, X=N-OH
54d: R_1=Me, R_2=Ts, X=N-OH

53a: R_1=H, R_2=H
53b: R_1=H, R_2=Ts
53c: R_1=Me, R_2=H
53d: R_1=Me, R_2=Ts

55

Scheme 11



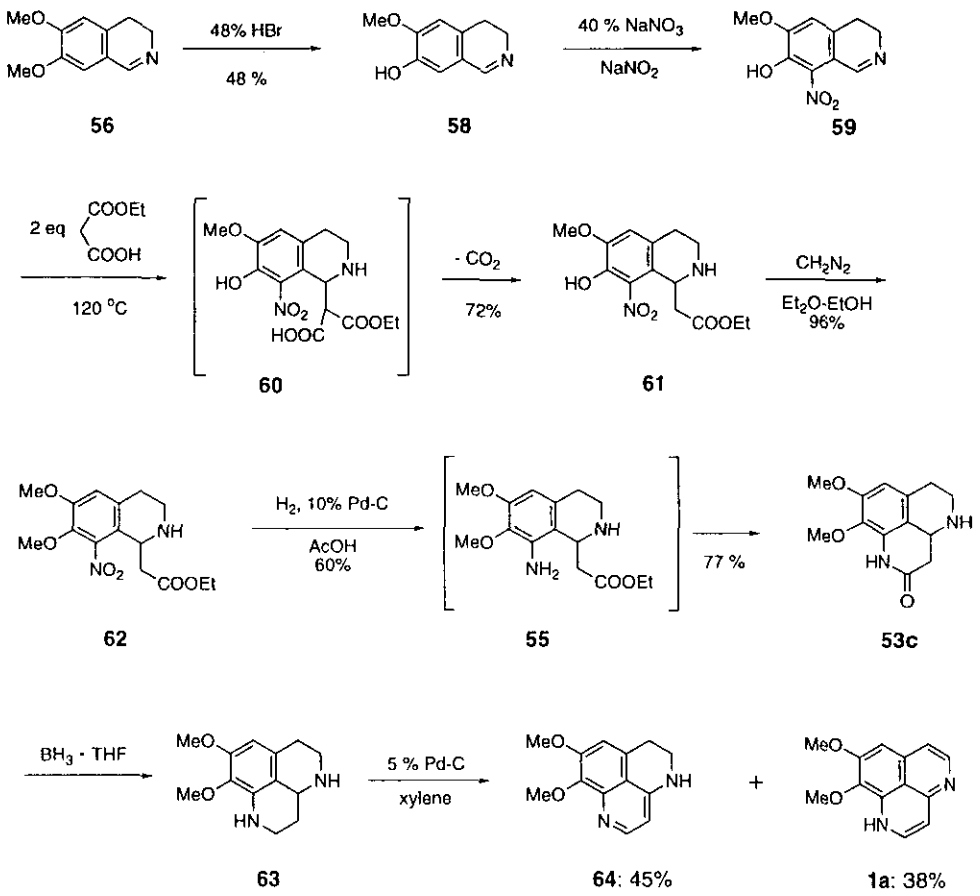
56 **57** **54a**

54b **54c**: R=H **54d**: R=Ts **53c** or **53d**

Scheme 12

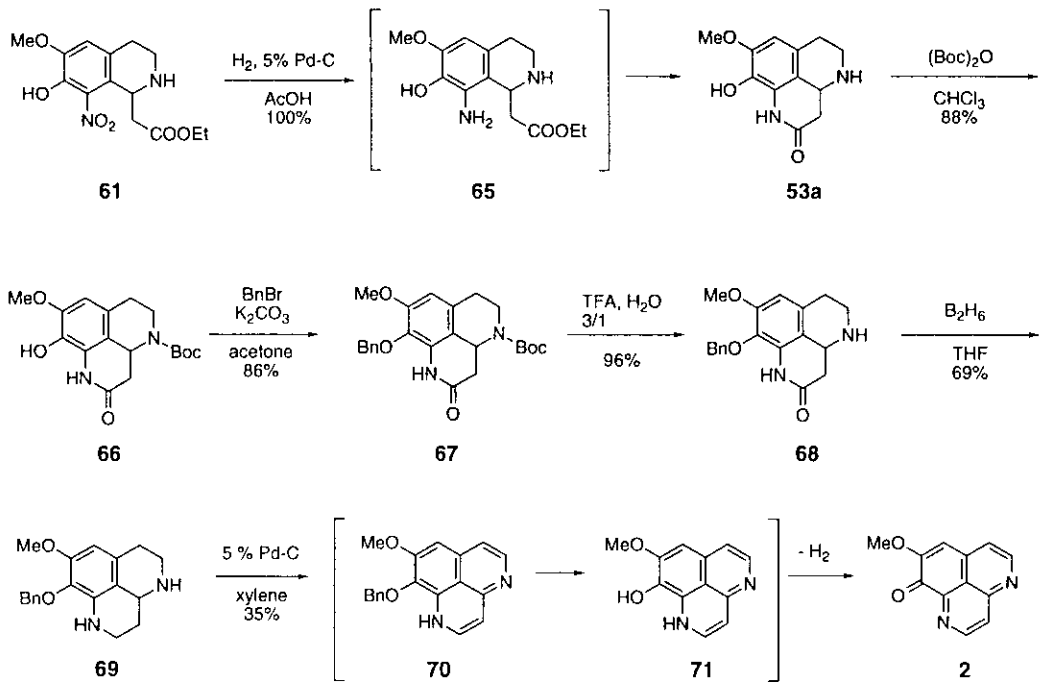
Cava and Pelletier turned to route B (Scheme 13). Selective demethylation of 6,7-dimethoxy-3,4-dihydroisoquinoline (**56**) was achieved by Brossi's procedure[16] to afford the phenolic isoquinoline (**58**). The 8-nitroisoquinoline (**59**) was obtained by nitration of **58** as the sole isolable product. It was assumed in advance that the stronger *ortho-para* directing effect of the 7-hydroxy group would promote the selective nitration of the 8-position. This compound was then heated at 120°C with malonic acid mono ethyl ester to give the nitro ester (**61**), which was subsequently methylated with diazomethane to yield the methyl ether (**62**). Hydrogenation of the nitro group of **62** in AcOH afforded the desired amino lactam (**53c**) (77%) *via* the amino ester (**55**). The conversion of amino lactam (**53c**) to aaptamine was achieved as follows. The

reduction of **53c** with diboran THF complex gave the hexahydroaaptamine (**63**), and the partial dehydrognation with 5% Pd-C afforded a 1:1 separable mixture of an aaptamine-free base (**1a**) and dihydroaaptamine (**64**). Finally, treatment of the free base (**1a**) with hydrochloric acid yielded aaptamine hydrochloride (**1c**) (33% overall yield).



Scheme 13

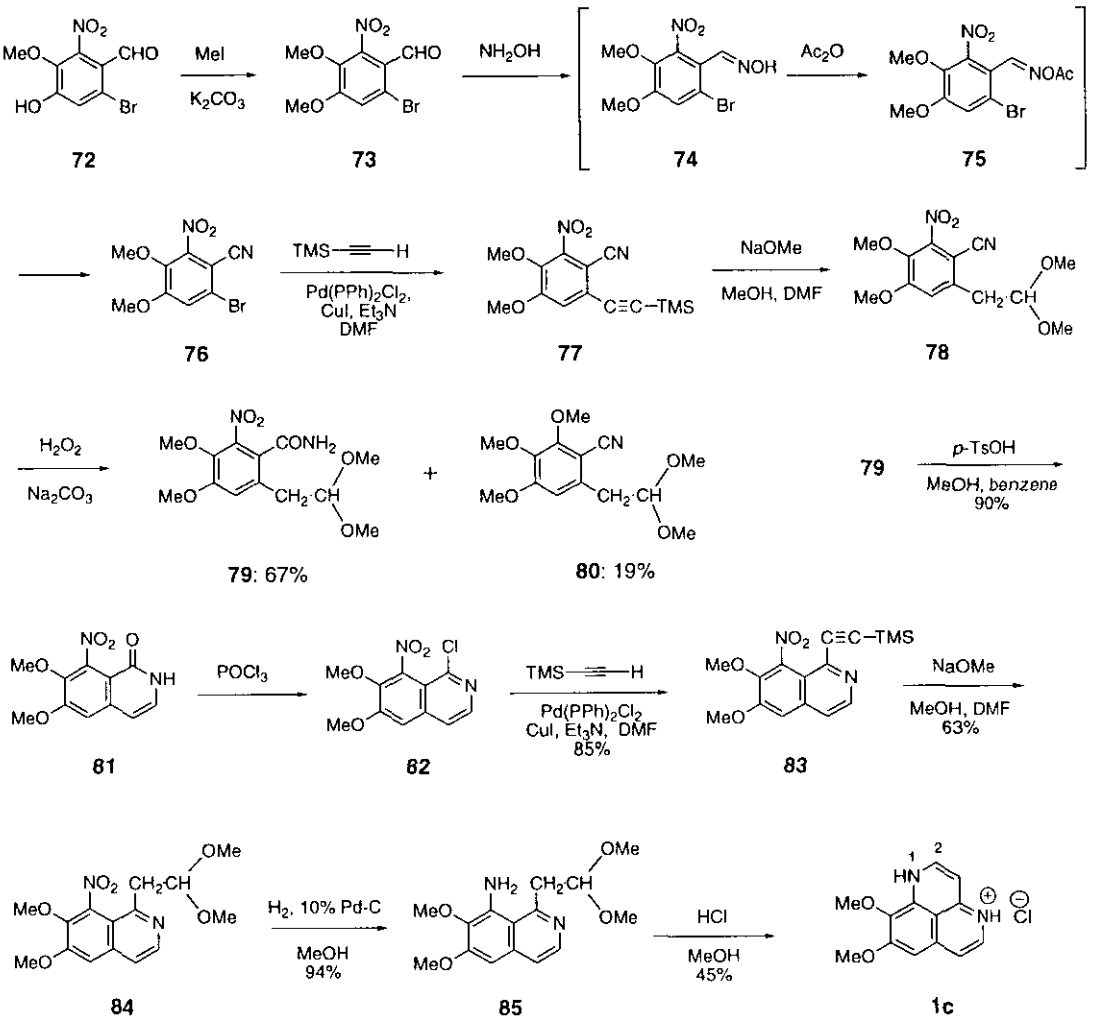
Next, the first total synthesis of demethyloxyaaptamine (**2**) was also accomplished as follows. The amino lactam (**53a**) was afforded by starting with the hydrogenation of the nitro ester (**61**). Attempts to reduce this lactam with $LiAlH_4$ or diborane were unsuccessful. This problem was overcome by protecting the free amine function as an *N*-Boc group and then benzylating the phenolic OH group of **53a** to obtain the fully protected tricyclic ring (**67**). The selective deprotection of the *N*-Boc group of **67** followed by the diborane reduction of **68** afforded the hexahydro compound (**69**), which was refluxed in xylene with 5% Pd-C to yield demethyloxyaaptamine (**2**) through a three step sequence (Scheme 14).



Scheme 14

Sakamoto *et al.* chose the isoquinoline (**81**) as a key compound for the application of palladium-catalyzed cross-coupling reactions of *o*-bromobenzaldehyde derivative (**76**) and 1-chloroisoquinoline (**82**) with trimethylsilylacetylene (TMSA) in two times.[8] Using their facile procedure[17] the isoquinoline (**81**) was obtained from 6-bromo-3,4-dimethoxy-2-nitrobenzaldehyde (**73**), and then **73** was converted to the *o*-bromobenzonitrile (**76**) from the corresponding aldoxime (**74**). The palladium-catalyzed cross-coupling reaction of **76** with TMSA in the presence of dichlorobis(triphenylphosphine)palladium was carried out. At 40-45°C, this gave the *o*-trimethylsilylethynylbenzonitrile (**77**), which was subjected to react with sodium methoxide in MeOH-DMF to obtain the *o*-(2,2-dimethoxyethynyl)benzonitrile (**78**). The partial hydrolysis of the cyano group of **78** with hydrogen peroxide under alkaline conditions gave the benzamide (**79**) along with the 2,3,4-trimethoxybenzonitrile (**80**) as a by-product. On heating with *p*-toluenesulfonic acid in MeOH-benzene, **79** cyclized smoothly to give the expected key-compound, isoquinoline (**81**). The chlorination of **81** with $POCl_3$ afforded the 1-chloroisoquinoline (**82**), which was made to react with TMSA in the presence of a palladium catalyst to yield the 1-(trimethylsilylethynyl)isoquinoline (**83**). Subsequent treatment of sodium methoxide produced the 1-(2,2-dimethoxyethyl)-8-nitroisoquinoline (**84**), which was converted to the 8-aminoisoquinoline (**85**) by hydrogenation. When **85** reacted with hydrogen

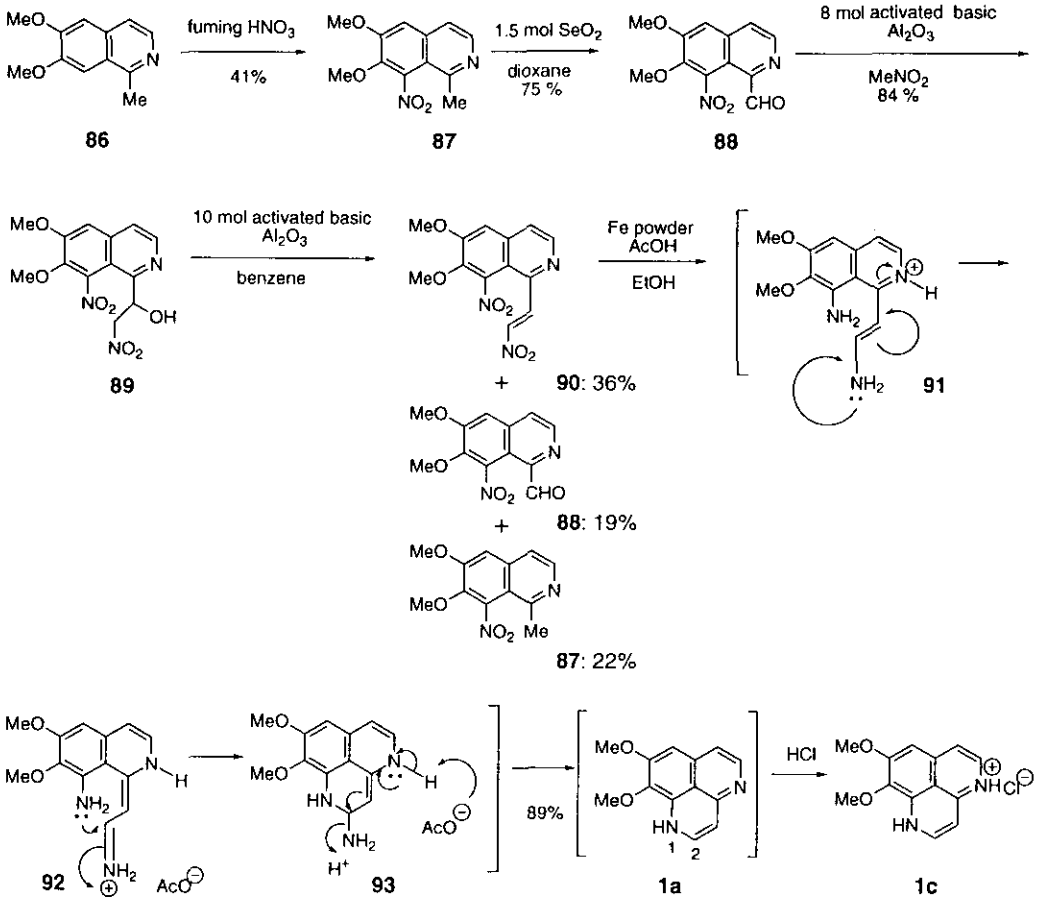
chloride in MeOH, aaptamine hydrochloride (**1c**) was obtained according to the previous cyclization method[17] (*Scheme 15*).



Scheme 15

Joule and co-workers[10] completed five-step total synthesis of aaptamine hydrochloride (**1c**) based on reductive cyclization as a key step. 6,7-Dimethoxy-1-methylisoquinoline (**86**) was nitrated directly with fuming nitric acid at a low temprature (-40 ~ - 45°C) to produce the 8-nitroisoquinoline (**81**) in a yield of 41%. The methyl group at the 1-position of the isoquinoline (**87**) was converted into the isoquinoline-1-carbaldehyde (**88**) with selenium dioxide (75%). Condensation of the aldehyde (**88**) with nitromethane was effected in the presence of basic Al_2O_3 (activated) to afford the nitro alcohol (**89**) (83%). Dehydration of the alcohol (**89**) with basic Al_2O_3 (activated) in benzene at reflux temperature gave the

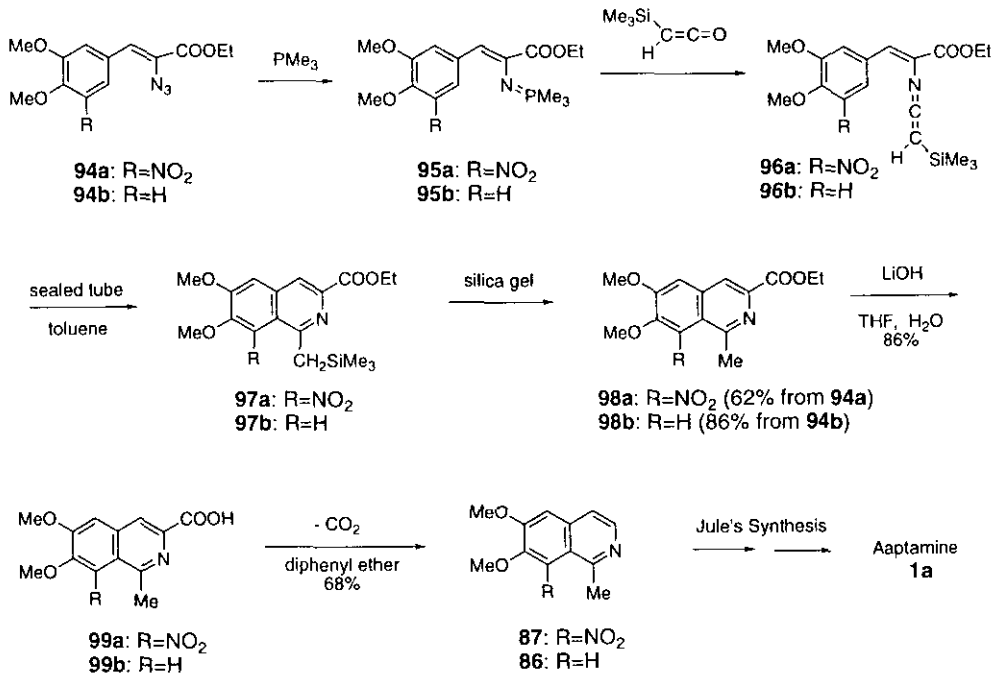
corresponding 1-nitrovinylisoquinoline (**90**) in a 36% yield, together with the original 8-nitroisoquinoline (**87**) (22%) and **88** (19%). Finally, the reductive cyclization of the nitroalkene (**90**) was effected by using iron powder in acetic acid[18] to produce aaptamine hydrochloride (**1c**) (83%). The mechanism of this reductive cyclization has been described as follows. Mildly acidic conditions in the reduction and cyclization would facilitate the step proceeding from the conjugated enamine (**91**) to **93** *via* **92**, and in the final elimination, by protonating the amino group giving rise to aaptamine as a protonic salt (**1c**) (Scheme 16).



Scheme 16

The preparation of bicyclic 6,7-dimethoxy-1-methyl-8-nitroisoquinoline (**87**) and 6,7-dimethoxy-1-methylisoquinoline (**86**) has been reported by Molina and co-workers[11] as a formal total synthesis of aaptamine (**1a**). The method is based on the tandem aza-Wittig/electrocyclic ring closure[19] of vinyl keteneimine. The vinyl azide (**94a**), prepared by condensation of 3,4-dimethoxy-5-nitrobenzaldehyde with

ethyl azidoacetate (47%), was converted into the 3-ethoxycarbonyl-6,7-dimethoxy-1-methyl-8-nitroisoquinoline (**98a**) by a one-flask procedure (62% overall yield). The conversion from **94a** to **98a** was started by an initial Staudinger reaction between the vinyl azide (**94a**) and trimethylphosphine to give the iminophosphorane (**95a**), which was used without purification. The aza-Wittig type reaction of **95a** with trimethylsilylethenone afforded the keteneimine (**96a**), which undergoes electrocyclic ring closure to give the isoquinoline (**97a**) and, finally, the carbon-silicon bond cleavage of **97a** by the action of silica gel yielded the isoquinoline (**98a**). Hydrolysis of the ester (**98a**) with lithium hydroxide followed by thermal decarboxylation provided the 6,7-dimethoxy-1-methyl-8-nitroisoquinoline (**87**) in a 58% yield from **94a** (Scheme 17). On the other hand, the vinyl azide (**94b**) which was obtained from 3,4-dimethoxybenzaldehyde and ethyl azidoacetate was transformed into the 3-ethoxycarbonyl-6,7-dimethoxy-1-methylisoquinoline (**98b**) in a similar manner (86% from **94a**). These constructions of isoquinoline derivatives (**87** and **86**) constitute a formal synthesis of aaptamine (**1a**), since **87** and **86** are starting molecules for the synthesis of the aaptamine frameworks by Joule[9] and Tollari,[10] respectively (Scheme 17).

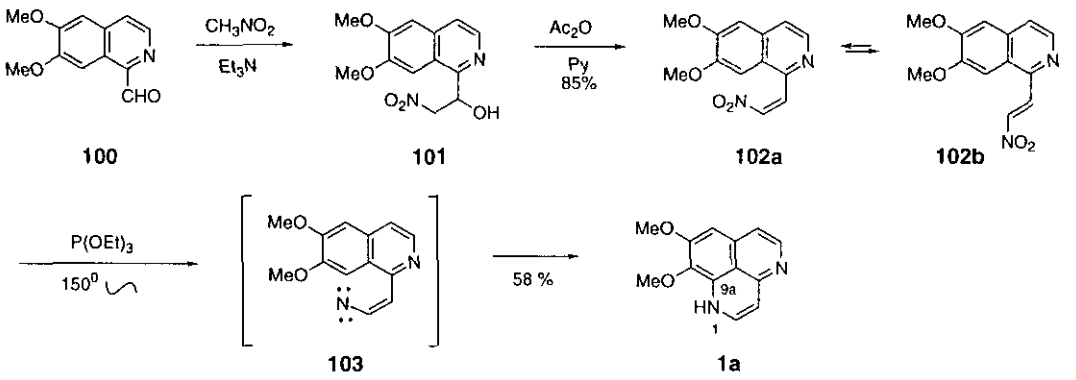


Scheme 17

3.2 The formation of the *N1-C9a* bond

A simple and selective total synthesis of aaptamine (**1a**) was accomplished by the connection of a

N1-nitrogen and a C9a-carbon bond based on the generation of a vinylnitrene intermediate[20] (**103**) requiring the functionalization of only the 1-position of isoquinoline (Scheme 18). Condensation of 6,7-dimethoxyisoquinoline-1-carbaldehyde (**100**) with nitromethane in diethylamine as a base afforded the nitro alcohol (**101**), which was dehydrated with pyridine and acetic anhydride at 0°C to provide the unsaturated nitro compound (**102**). When the triethylphosphite reduction[20] of the vinylic nitro derivative (**102**) was performed at reflux temperature, aaptamine (**1a**) was obtained through the regioselective nitrene insertion process in 58% yield. Tollari and co-workers[11] have described that the (*Z*)-form of the unsaturated nitro compound (**102a**) suitable for this cyclization reaction probably can be derived from a thermal (*E*)-(*Z*) isomerization.



Scheme 18

4. Conclusion

During the past eleven years, aaptamine (**1**) and its related natural products (**2**) have been established by eight research groups. In this paper, we have described their efforts, which are consistent with the construction of the pyridine ring fused to the appropriate quinoline or isoquinoline.

Since 1982, when aaptamine (**1** and **2**) possessing tricyclic benzo[*d,e*][1,6]naphthyridine ring was isolated as the first example of finding a naturally occurring product, the bicyclic 2,7 (or 1,6)-naphthyridine (copyrine) alkaloid, neozeylanicine (1988)[21] and the tetracyclic dibenzo[*d,e,h*][1,6]naphthyridine alkaloid, necatorone (1984)[22] have appeared in *Neonauclea zeylanica* (Rubiaceae) and fruit bodies of the toadstool *Lactarius necator*, respectively. In 1986 Rao and co-workers[23] reported the isolation and structure elucidation of the new tetracyclic aromatic alkaloid, sampangine, with a naphtho[1,2,3-*ij*][2,7]-naphthyridine ring system from the African tree *Cananga odorata* (Annonaceae). One year later, eupomatidines (oxygenated sampangines) and imbilines (higher oxygenated sampangines), possessing the

common structure, were isolated from *Eupomatia bennetti* and *E. laurina* (Eupomatiaceae) by Carroll and Taylor.[24]

Furthermore, during the past fifteen years, a number of marine alkaloids with highly condensed tetra-, penta-, hexa-, and octacyclic products have been discovered. The dominant feature is the dibenzo[*f,i,j*][2,7]naphthyridine nucleus (so-called pyrido[2,3,4-*kl*]acridine alkaloids), such as ascididemine, amphimedine, and the cystodytins in the representative members.[25,26]

On the other hand, these highly condensed aromatic alkaloids possessing a [1,6] or [2,7] naphthyridine ring system have caught the considerable attention of many synthetic organic chemists because of their diverse biological activities (Ca-releasing, antiviral, antimicrobial, cytotoxic to L1210 murine leukemia cell).[25]

Since then, the biological efforts of aaptamines (**1** and **2**) have not been developed. However, recently, the synthesis of tricyclic azakynurenic acid (5,6-dihydrobenzo[*d,e*][1,6]naphthyridine derivatives) has been reported and evaluated as a lead compound for the generation of a new class of NMDA-glycine antagonists.[27] The synthesis of the tricyclic azakynurenic acid has been estabiliched by Stille coupling reaction of 5-chloroquinoline-4-tosylamide with tributylvinyltin followed by cyclization based on the formation of the N4-C5 bond.[27]

These condensed aromatic molecules do not have special substituents, but it is thought that these compounds possess dipolemoment which is specific for planar condensed heteroaromatics. As regards condensed naphthyridine ring systems, studies of more effective or various synthetic methods are anticipated, as is further investigation of these system's biological activity and how it might lead to pharmaceutical and agricultural applications.

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