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A Strategic Development toward Tetrahydroquinoline Diversity: A Review

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ABSTRACT: Tetrahydroquinoline derivatives are a class of synthetic antibiotics with broad spectrum antibacterial as well as anti-malarial activities. The fused tetrahydroquinoline derivatives are also known to be effective in the treatment of autoimmune conditions (such as rhenumatoid arthritis) with their anti inflammatory effects. Among the numerous structurally diverse derivatives many tetrahydroquinolines show significant biological activity such as benzastatin, martinellic acid, and peniprequinolone etc. Hence, it is not surprising that this structural motif is also an important component in many of today's pharmaceuticals. Nevertheless, the diversity of tetrahydroquinoline as well as their biological and pharmaceutical relevance is still motivating academic and industrial researchers to look for new and improved syntheses for tetrahydroquinoline based natural products. Clearly, a number of practical methods have been developed for the synthesis of tetrahydroquinolines in the past century. More recently, especially transition metal catalysis has become a powerful tool for synthetic methodology but chemical and biological research has now presented a great challenge to synthesize and optimise highly efficient and cost-effective synthetic routes to some unique and novel biologically active substances. Pertinent structural, synthetic and semisynthetic studies reported in the open literature will be covered in this review.

Keywords: Antibiotic; Synthetic method; Tetrahydroquinoline and Transition metal catalyst.

INTRODUCTION: Heterocyclic compounds, especially nitrogen heterocycles, are the important class of compounds in the pharmaceutical and agrochemical industries[1]. The tetrahydroquinoline ring system, in particular, is a very common structural motif and is found in a numerous biologically active natural products and pharmacological therapeutic agents like cinchophen, plasmoquine, nupercaine, quinine, acridine dyes etc[2-8]. Due to the significance of biologically active scaffolds in drug discovery and medicinal chemistry, the development of innovative methodologies for the synthesis of tetrahydroquinoline derivatives is an interesting field for the synthetic organic chemist. During the last five years a large number of articles were published in this field. This review mainly deals with some naturally occurring potent bioactive tetrahydroquinoline moiety and few of their synthetic methodologies.

Dr. Shyamal Mondal was born in Hooghly, West Bengal, India in 1983 and attended The University of Burdwan, where he received his B.Sc degree in Chemistry in 2006. He obtained his M.Sc degree from Bengal Engineering & Science University, Shibpur in 2008. While at Shibpur, he did his post graduate research with Professor Shyamaprasad Goswami in the area of natural product isolation and synthesis methodology. In the year 2008 he qualified the CSIR-NET with distinction and nominated for the Shyama Prasad Mukherjee Fellowship. He received his Ph.D degree in 2012 at Indian Institute of Chemical Biology-CSIR under the supervision of Dr. Nirup B Mondal. He is the author of 28 scientific publications, in the field of synthetic methodology. He was a postdoctoral fellow (2012-2014) with Dr. Saleh Al-Busafi at Sultan Qaboos University, Oman, where he was involved in the synthesis of aracarpene isoflavonoids and evaluation of their antifungal activity. In 2014-Oct he moved to the University of Witwatersrand, Johannesburg, South Africa, and joined (2014-2015) with prof. Joseph P Michael, where he worked on 'Unusual Reactions of Enaminones'. At present he is working at the New Alipore College, West Bengal, India, as an Assistant Professor. His research focused on stereoselective synthesis of isoquinoline based natural alkaloids, studies on drug-DNA interactions, design and synthesis of antibiotics and biosynthetic pathways.

BIOACTIVE COMPOUNDS RELATED TO TETRAHYDROQUINOLINES: A wide variety of novel 1,2,3,4-tetrahydroquinoline molecules showed interesting biological activities, which were reported during the 1995-2010 period (Figures 1 and 2). Two naturally occurring 1,2,3,4-tetrahydroquinoline alkaloids benzastatins C and D (**A**) were isolated from *Streptomyces sp*.[9]. These two alkaloids showed inhibitory activity against glutamate toxicity and lipid peroxidation[10].

Another pyrroloquinoline alkaloid martinellic acid (**B**) was isolated from the roots of the tropical plant *Martinella iquitosensis*[11], and become synthetic targets of many research groups[12]. Penigequinolones A and B (**C**) were isolated from two active pollen-growth inhibitors of the mycelial mats of *Penicillium sp*. No. 410 by Koshino and co-workers[13]. In the search for more biologically active tetrahydroquinolines Sattler and co-workers isolated new alkaloids of the same family (**C**) and peniprequinolone (**D**) from a strain of Penicillium janczewskii which were isolated from a marine sample[14]. However an important insecticidal antibiotics yaequinolones J1 and J2 (**E** and **F**) were isolated from Penicillium sp.

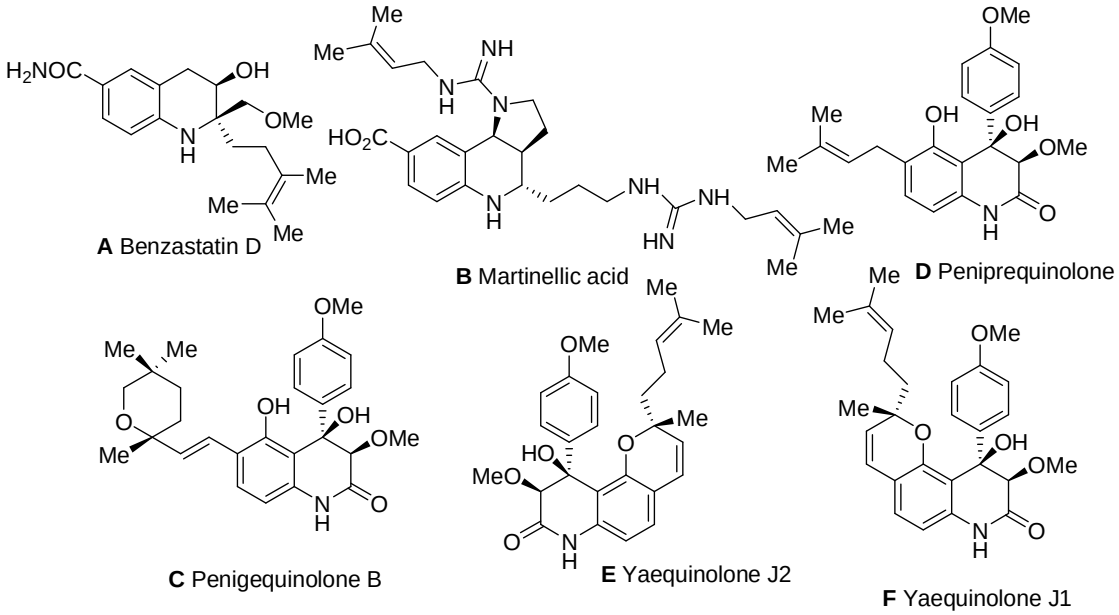


Figure 1: FKI-2140[15] and showed toxicity against *Artemia salina*.

The isomeric siderophors anachelin **L** was isolated from the cyanobacterium *Anabaena cylindrica* (NIES-19)[16] and their absolute stereochemistry was determined using the Mosher's method[17]. Tetrahydroquinolines having hydrogenation patterns different from the 1,2,3,4-tetrahydro-one are rarely present in natural products. Among those are important the Sceletium alkaloids as well as (+)-sceletium A-4, **K**, and (+)-tortuosamine[18] **I**. Haplophyllidine **H** was isolated from aerial parts of the central Asian plant *Haplophyllum perforatum*[19], and the acetyl derivatives were isolated from a Brazilian plant, *Almeidia coerulia*[20]. Two more alkaloids of this family known as megistosarcimine and megistosarconine **G**, were also isolated from the new Caledonian tree *Sarcomelicope megistophylla*[21].

Several other tetrahydroquinoline derivatives have been found to interact with retroviral targets relevant to anti-HIV therapy. However, compound **M** was found to be potent non-nucleoside[22], allosteric inhibitor of reverse transcriptase whereas 2-aryl-4-(2-oxopyrrolidin-1-yl)-1,2,3,4 tetrahydroquinolines have shown activities as inhibitors of HIV transcription.

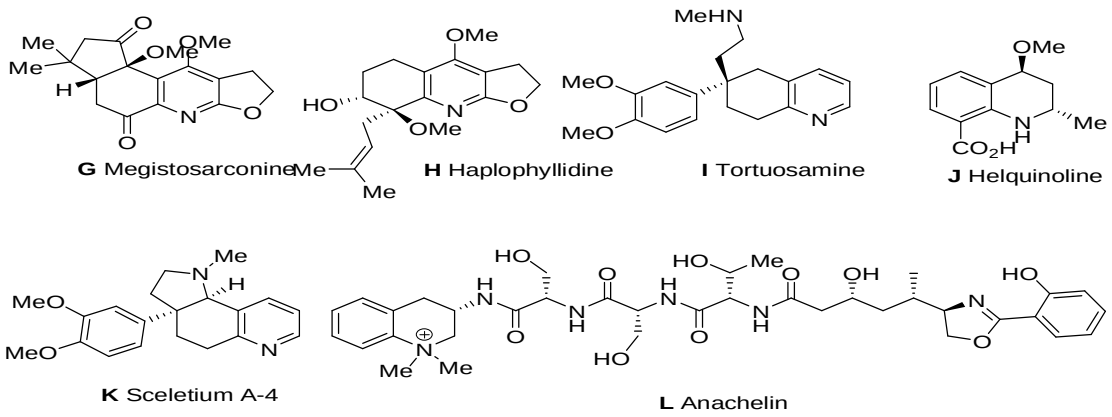


Figure 2

This fact probably explained through inhibition of the NF-kB and Sp1 transcription factors[23], and a library of 1,2,3,4-tetrahydro-6-sulphonamide derivatives have been identified as small-molecule modifiers of hepatic micro RNA function which reducing the replication of hepatitis C virus and being also active as apoptosis inducers[24].

Many tetrahydroquinolines are also active against antibacterial targets, including DNA- gyrase[25] (compound **N**) (**Figure 3**). It has been proposed as an important target in the treatment of infections because of the Gram-positive bacteria which is resistant to conventional antibiotic therapy. A number of the oxazolidinone classes of antibacterial agents contain tetrahydroquinoline-derived side chains (compound **O**). It has good activity against *Staphylococcus aureus* and *Streptococcus pneumoniae*, and act by disrupting bacterial protein synthesis[26]. However simple tetrahydroquinoline derivatives where the heterocyclic nitrogen is part of a urea moiety have shown activity against Gram-positive and Gram-negative bacteria, and also against some fungi[27].

In the course of a study on the antifungal activity of several series of homoallylamines and their analogues, compound **P** was shown to have antifungal activity[28-30]. This fact may be attributed mainly to chitin synthase inhibition, whereas imidazole substituted tetrahydroquinoline derivative **Q** have received much attention as antimalarial agents[31-38]. Those are highly cytotoxic to *Plasmodium falciparum* due to inhibition of farnesyltransferase of the parasite, while 1-benzenesulfonyl derivative **R** was shown to have good activity against *Trypanosoma cruzi*[39].

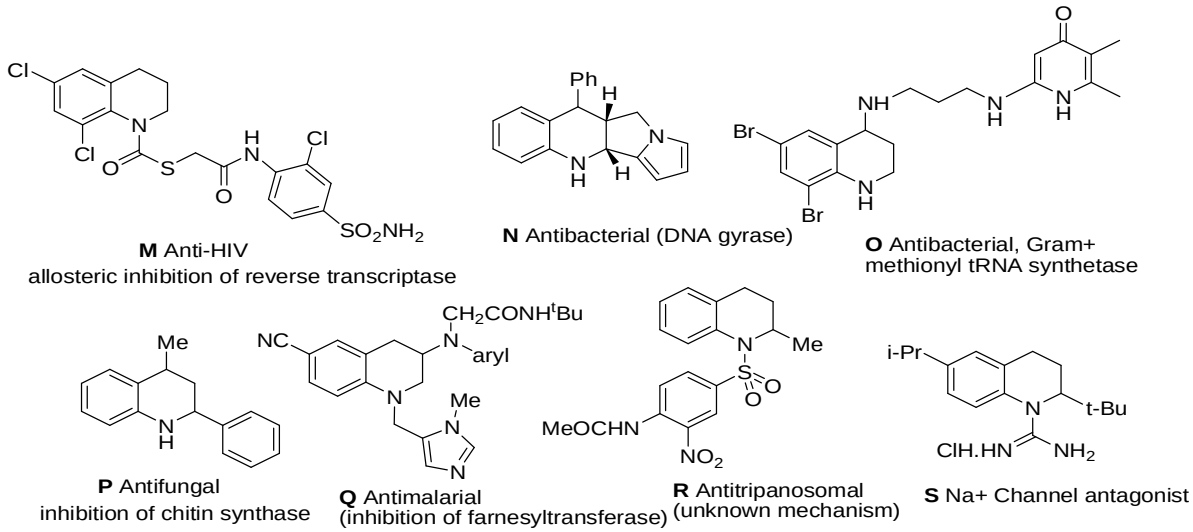
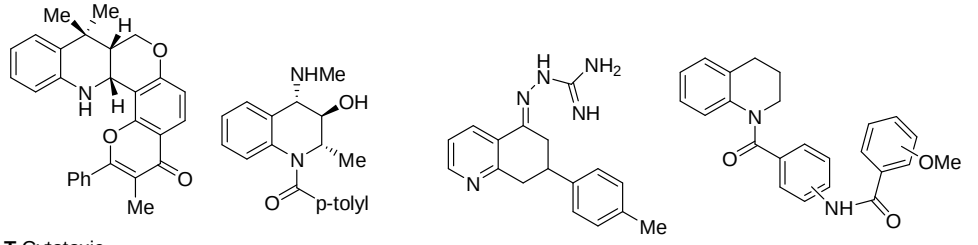


Figure 3

There are some tetrahydroquinoline derivatives whose N-1 atom belongs to a guanidine moiety (compound **S**) are antagonists of neuronal Na+ channels[40] (**Figure 4**). Another type of tetrahydroquinoline-derived guanidine compound (**T**) is an important target in the prevention of ischemia-reperfusion injury following a myocardial infarction[41].

However, through the CDK inhibition some tetrahydroquinoline compound **U** shows in-vitro cytotoxicity[42]. The 2-methyl derivative of the tetrahydroquinoline **V** (**Figure 5**) was also found to have moderate to high modulating activity in multidrug resistance[43] (MDR). This was considered as one of the main obstacles in successful anticancer chemotherapy.

Compound **W** was found to be antagonists of vasopressin receptors in the micromolar range due to its nonsteroidal hormone receptors property[44].

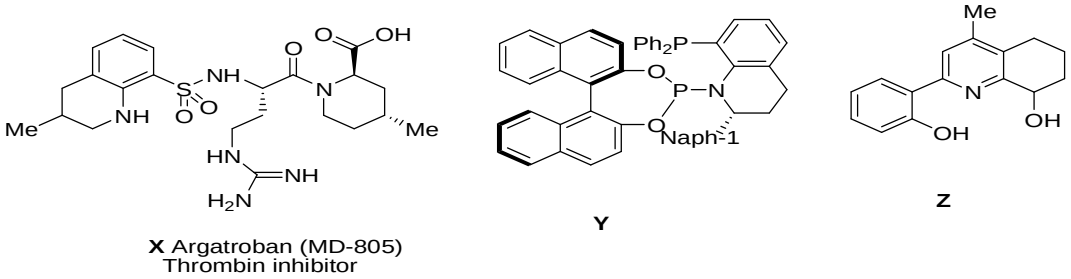


T Cytotoxic (unknown mechanism) **U** MDR Modulating activity **V** Na+/H+ Exchange inhibitor **W** Vasopressin antagonist

Figure 4

Ring-expanded analogues derived from the benzoazepine system were subsequently found to have much higher potency and higher selectivities, in favor of the V_2 receptor. Depending upon the structural characteristics another antithrombotic drug, argatroban **X** used as a thrombin inhibitor[45]. Some tetrahydroquinoline-derived chiral ligands like phosphine/phosphoramidite derivative **Y** and vanadium complexes of the chiral 8-hydroxy-5,6,7,8-tetrahydroquinoline **Z** has been used in asymmetric synthesis of Rh-catalyzed hydrogenation of acrylates[46] and chiral sulfoxides from sulfides[47] with 70% ee.

The synthetic aspects of the biologically active tetrahydroquinoline compounds can be divided into four major parts-



X Argatroban (MD-805) Thrombin inhibitor

Y

Z

Figure 5

(1) The methods involves for the construction of the saturated tetrahydropyridine ring system of the 1,2,3,4-tetrahydroquinolines starting from aryl precursors, which consisted of (a) generation of one bond (section 4); (b) generation of two bonds (section 5); and (c) generation of three or more bonds (section 6).

(2) The generation of the benzene ring of 1,2,3,4-tetrahydroquinolines (section 7), and their construction from acyclic precursors, or by means of rearrangement reactions (section 8).

(3) The synthesis of tetrahydroquinolines is based upon the reduction of quinoline systems (section 9).

(4) The functionalization of tetrahydroquinolines (section 10) and the application of simple 1,2,3,4-tetrahydroquinolines as starting materials for the synthesis of other heterocyclic systems .

SYNTHESIS OF 1,2,3,4-TETRAHYDROQUINOLINES VIA ONE BOND FORMATION: As inflected in the introduction part, suitably func-

tionalized tetrahydroquinolines possess a number of interesting biological activities. However in this section the synthesis of such bioactive tetrahydroquinoline derivatives will be discussed.

The 1,2,3,4-tetrahydroquinoline ring can be constructed by creating one new bond starting from precursors containing a benzene ring. This section describes the synthesis of tetrahydroquinoline moiety by means of generation of one new bond namely N-C_2, C_2-C_3, C_3-C_4, C_4-C_{4a}, and C_{8a}-N (**Figure 6**).

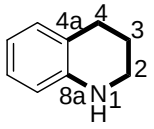
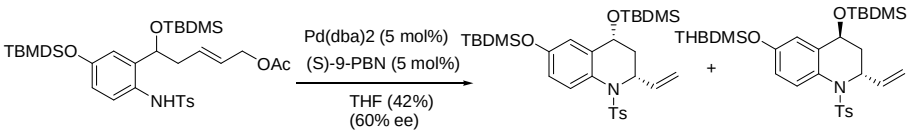


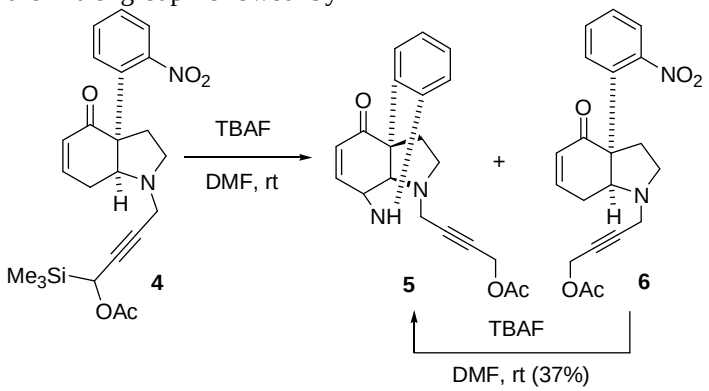
Figure 6

1. Formation of the N-C_2 Bond: The 1,2,3,4-tetrahydroquinoline ring can be constructed by creating one new bond from precursors containing a benzene ring. Initially the compound **1** was prepared from 5-hydroxyanthranilic acid using Reformatsky reaction as the key step. After some years later the same molecule was synthesized by means of intramolecular allylic amination procedure using allyl acetate **1** in the presence of a chiral phosphine (9-PBN) and Pd(dba)$_2$ which yielded diastereomeric mixture of tetrahydroquinolines **2** in moderate yields (**Scheme 1**)[48].



Scheme 1

Another work done by Solé, Bonjoch, and co-workers which involves the neucleophilic attack of the enolate on the nitro group followed by formylation with DMF to yield the intermediate R-(2-nitrophenyl) enones (**Scheme 2**)[49].



Scheme 2

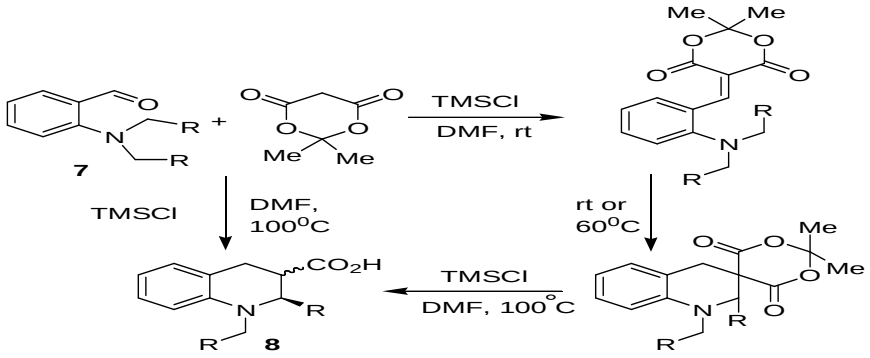
2. Formation of the C_2-C_3 Bond: Quinolines by constructing the C_2-C_3 bond is a typical and few examples that are illustrated in the literature are attributed to the tertiary amine effect. One example that describes the synthesis of 1,2,3,4-tetrahydroquinoline-3-carboxylic acids **8** which was achieved in one-pot fashion in good yields. The reaction was carried out with ortho-dialkyl amino aldehydes **7** and Meldrum's acid in the presence of chlorotrimethylsilane in DMF (**Scheme 3**)[50].

3. Formation of the C_3-C_4 Bond: An important intramolecular [**3+2**] azomethine ylide cycloaddition method was developed by Snider and co-workers. The method described the construction of the pyrroloquinoline rings system of martinellic acid and then it was successfully employed for its total synthesis[51]. The suitably substituted aryl aldehyde **9** was treated with N-benzyl glycine to generate the azomethine ylide **10**, through an iminium salt, which then underwent an intramolecular cycloaddition to afford the pyrroloquinoline **11** in acceptable yield (**Scheme 4**).

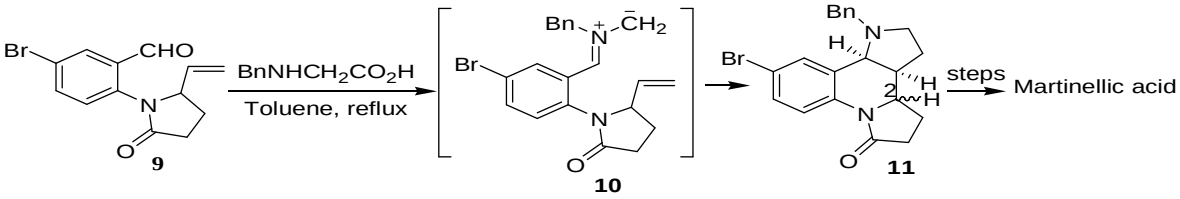
The another enantioselective synthesis of 4-amino-3-hydroxymethyl 1,2,3,4- tetrahydroquinolines **16** and **17** was attained through a strategy based on the

intramolecular 1,3-dipolar cycloaddition of nitrones (**Scheme 5**)[52].

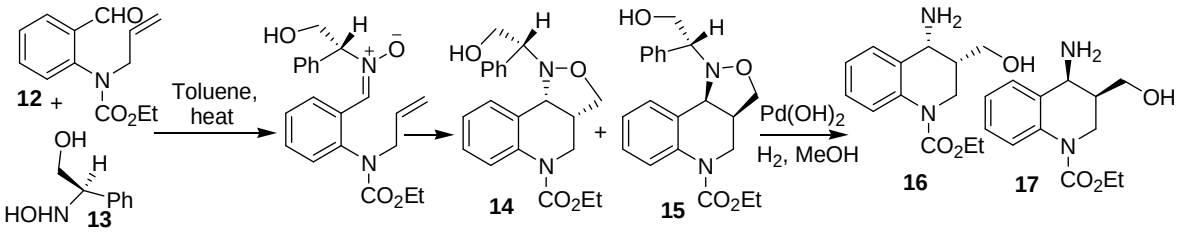
4. Formation of the C_4-C_{4a} Bond: The acid catalysed [**4+2**] cycloaddition of 1-allyl-1-aminoarylcyclohexanes was achieved by Zubkov and co-workers. This method demonstrated an efficient synthesis of tetrahydroquinolines containing an isoindolo [2, 1-a] quinoline skeleton. The reaction was started with homoallylamines, followed by acid-catalyzed intramolecular cyclization (**Scheme 6**)[53]. However an efficient route for the synthesis of enantiopure torcetrapib **24** was explored by Hii and co-workers. The tetrahydroquinoline intermediate **22** was obtained from the chiral precursor **21** through a $NaBH_4/MgCl_2$-mediated cyclization. The amide carbonyl was reduced by $NaBH_4$, and the resulting intermediate was subsequently cyclized with the help of the magnesium salt (**Scheme 7**)[54].



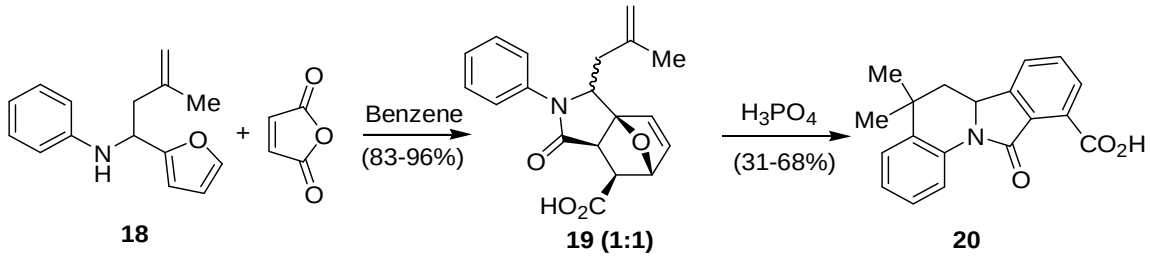
Scheme 3



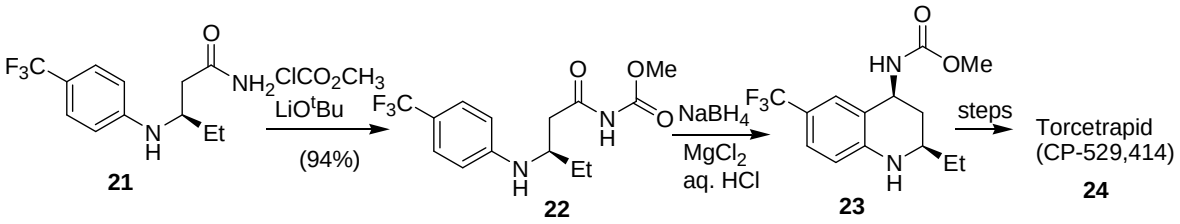
Scheme 4



Scheme 5

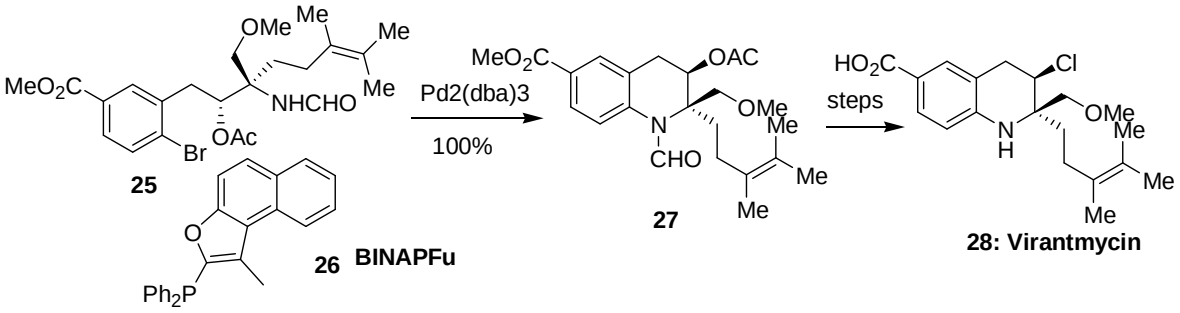


Scheme 6



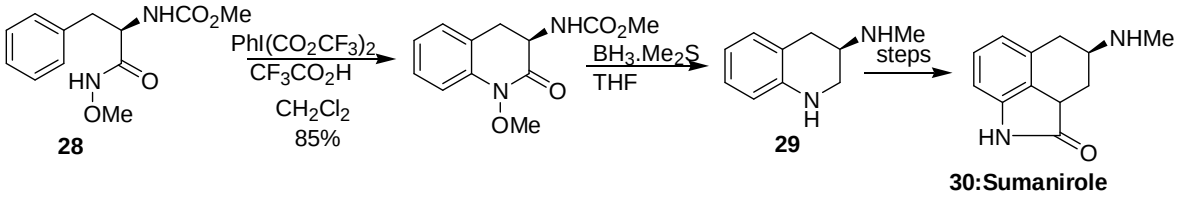
Scheme 7

5. Formation of the C_{8a}-N Bond: Back and Wulff reported the synthesis of virantmycin **27a** employing a Buckward-Hartwig aryl amination to construct the tetrahydroquinoline skeleton[55]. The reaction was initiated with formamide derivative **25**, synthesized in several steps starting from methyl 4-bromo-3-bromo methyl benzoate. This benzoate was then transformed quantitatively into the tetrahydroquinoline **27** by treatment with $[Pd_2(dba)_3]$ in the presence of the Keay ligand BINAPFu **26**, and finally led to the antiviral agent virantmycin **27a** (**Scheme 8**).



Scheme 8

The 3-(N-methylamino) 1,2,3,4-tetrahydroquinoline derivative **29** is an intermediate for the synthesis of the dopamine D_2 receptor agonist sumanirole (PNU 95666E,40) which is a naturally occurring active compound[56]. It was synthesized through the cyclization of N-methoxyamide **28** using $PhI(CO_2CF_3)_2$ followed by BH_3 reduction (**Scheme 9**).



Scheme 9

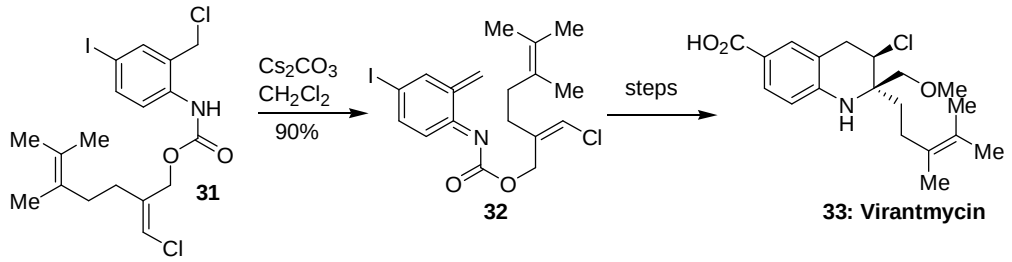
SYNTHESIS OF 1,2,3,4-TETRAHYDROQUINOLINES VIA TWO BONDS FORMATION: The synthesis of the 1,2,3,4-tetrahydroquinoline moiety can be done in several ways via formation of N-C_2 with C_{8a}-N, C_3-C_4, C_4-C_{4a} and C_3-C_4 bonds. Few interesting observations are as follows.

1. Formation of the N-C_2 and C_3-C_4 Bonds: The construction of the tetrahydroquinoline moiety can be achieved by creating the N-C_2 and C_3-C_4 bonds starting from o-substituted anilines and a C_2-C_3 fragment. For instance, Corey and Steinhagen established an efficient procedure for the synthesis of the natural antiviral agent virantmycin **27a**. The intermediate **32** was synthesized starting from 2-amino-5-iodobenzyl alcohol in a few steps, and the Cs_2CO_3 mediated intramolecular cycloaddition allowed access to the virantmycin precursor. This intermediate was then transformed into the final product **33** in four additional steps (**Scheme 10**)[57].

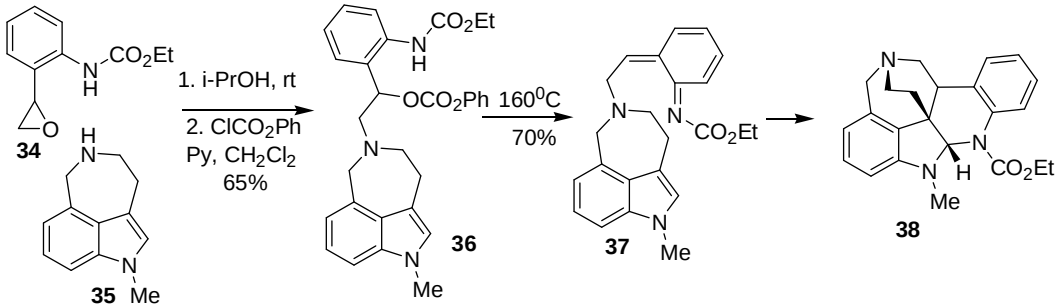
Funk and Crawley demonstrated the construction of the tetrahydroquinoline ring system of the cytotoxic natural product communesin B (**38a**) based on an intermolecular cycloaddition involving an o-quinone methide intermediate (**Scheme 11**)[58].

2. Formation of the N-C_2 and C_4-C_{4a} Bonds: Yadav and co-workers demonstrated the diastereoselective

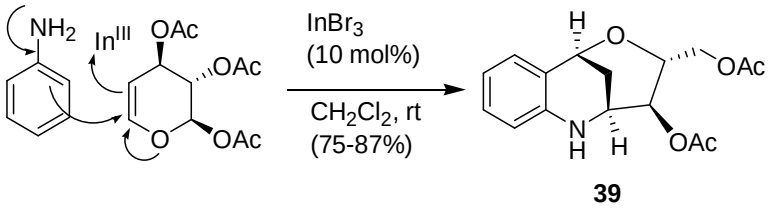
synthesis of enantiopure tetrahydroquinolines **39.** A variety of different amines bearing both electron donating and electron withdrawing groups afforded the tetrahydroquinoline rings in very good yields. The reaction was carried out using $InBr_3$ as lewis acid catalyst between arylamines and D-glucal, L-rhamnal, and D-xylal (**Scheme 12**)[59].



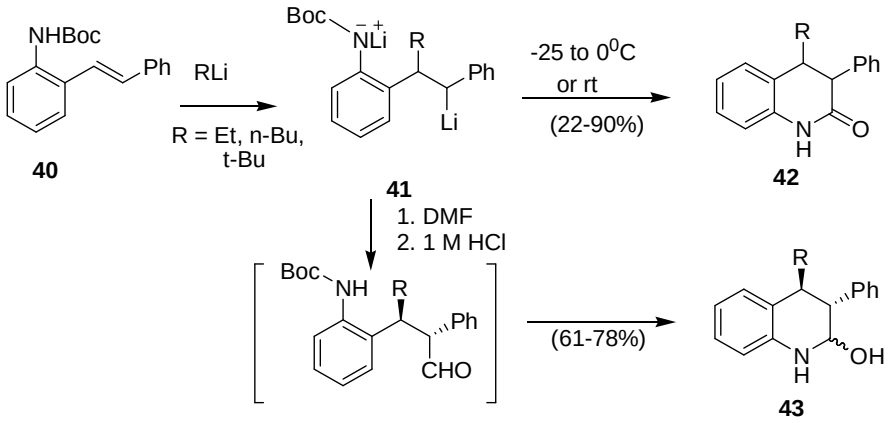
Scheme 10



Scheme 11



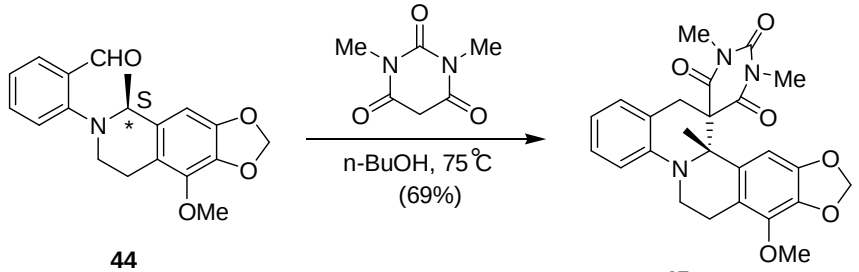
Scheme 12



Scheme 13

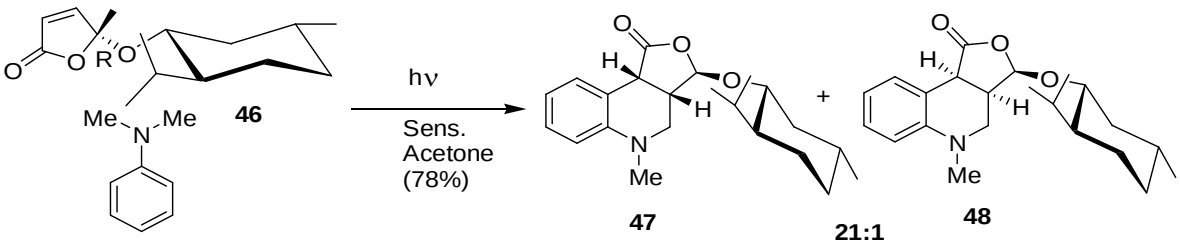
3. Formation of the N-C_2 and C_2-C $_3$ Bonds: 2-Amino-(E)-stilbenes were effectively converted into 1,2,3,4-tetrahydroquinoline derivatives where both N-C_2 and C_2-C_3 bond formed simultaneously through a regioselective carbolithiation process[60]. Initially the rection was carried out with the N-Boc-protected o-aminostilbenes **40.** After treatment of N-Boc-protected o-aminostilbenes with alkyllithium reagents gave lithiated intermediates **41** at low temperature. With gradual increase of the reaction temperature from 0°C to room temperature compound **41** converted into the corresponding tetrahydroquinolin-2- ones **42.** On the other hand, the lithiated intermediates **41** reacted with DMF followed by acid treatment to furnish 2-hydroxy-tetrahydroquinolines **43** as a mixture of two diastereo-isomers in good yields via the aldehyde intermediate **A** (**Scheme 13**).

4. Formation of the C_2-C_3 and C_3-C_4 Bonds: The derivative of (-)-anhalonine **44** reacted with N,N-dimethylbarbituric acid to give spiro-tetrahydroquinoline **45** as a single diastereo-isomer by creating the C_2-C_3 and C_3-C_4 bonds simultane-ously (**Scheme 14**)[61]. Hoffmann and co-workers illustrated the synthesis of tetrahydro-quinolines **47** and **48** in moderate yields through a domino radical reaction between N,N-dimethylaniline and furanone **46** in the presence of catalytic amount of Michler's ketone as a sensitizer under photochemical conditions (**Scheme 15**)[62].



44 **45**

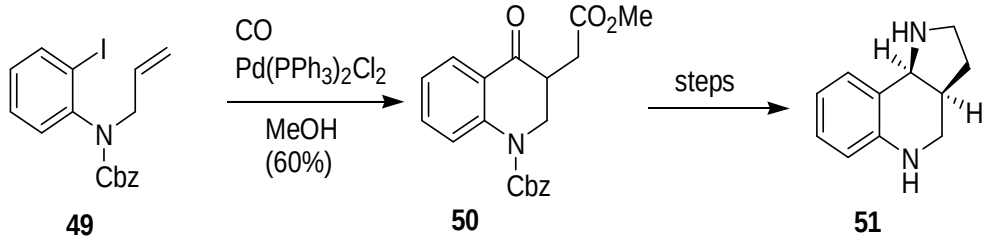
Scheme 14



46 **47** **21:1** **48**

Scheme 15

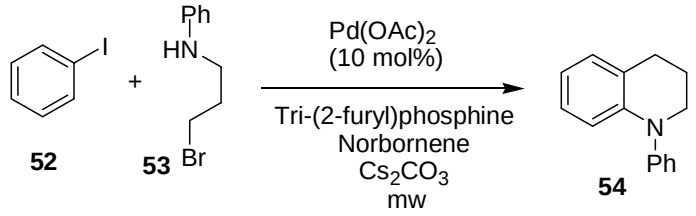
5. Formation of the C_3-C_4 and C_4-C_{4a} Bonds: The only available report for the synthesis of tetrahydroquinolin-4-one involving the creation of the C_3-C_4 and C_4-C_{4a} bonds is the palladium-catalyzed carbonylative cyclization of N-allyl-2-iodoaniline[63]. Then the tetrahydroquinolin-4-one **50** was subsequently transformed into pyrrolo-quinoline **51** in six additional steps (**Scheme 16**).



49 **50** **51**

Scheme 16

6. Formation of the C_{8a}-N and C_4-C_{4a} Bonds: The palladium-catalyzed C-C and C-N bond formation of bromoalkylamines and functionalized aryl iodides allowed the synthesis of tetrahydroquinoline derivatives (**Scheme 17**)[64]. In this tetrahydroquinoline molecule **54** both C_{8a}-N and C_4-C_{4a} bonds formed by using heck as well as buckwald reaction successively.



Scheme 17

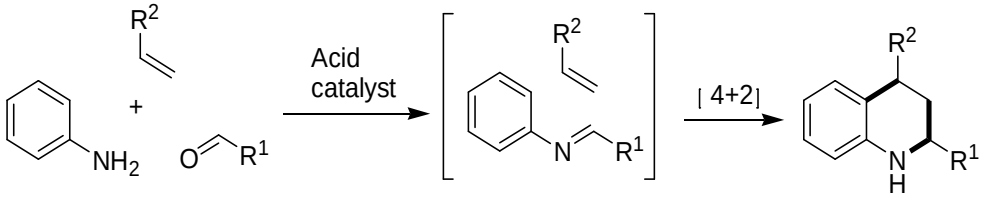
SYNTHESIS OF 1,2,3,4-TETRAHYDROQUINOLINES VIA THREE OR MORE BONDS FORMATION: The methods that allow the synthesis of 1,2,3,4-tetrahydroquinolines by creating three or more bonds in a single operation starting from a benzene derivative and two or more C_2-C_3-C_4 fragments is being discussed in this part. The best example that can specify this discussion is the Povarov reaction.

1. Formation of the N-C_2, C_2-C_3, and C_4-C_{4a} Bonds: The Povarov and Related Reactions

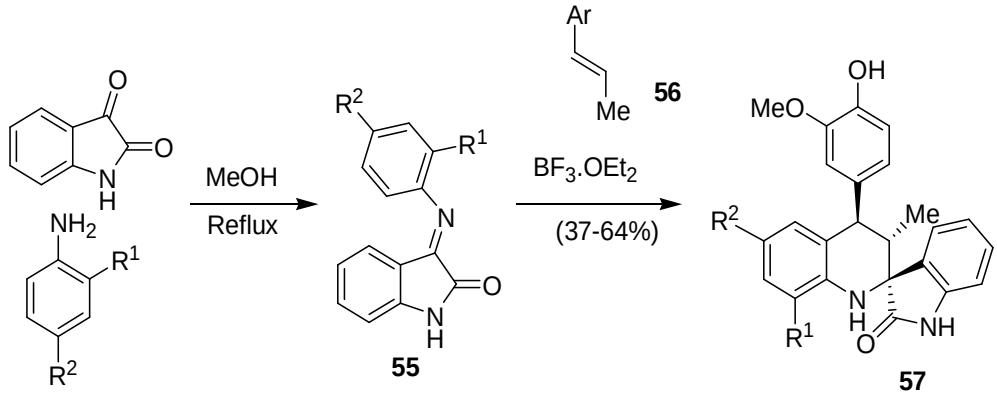
The three-component Povarov reaction allows the creation of three bonds, that is, N-C_2, C_2-C_3 and C_4-C_{4a} bonds in a single operation (**Scheme 18**)[65].

The diastereoselective synthesis of 2-spirotetrahydroquinoline derivatives **57** was achieved in moderate yields based on a $BF_3.OEt_2$-catalyzed reaction between 3-N- aryliminoisatins **55** and substituted methyl styrene **56** (**Scheme 19**)[66].

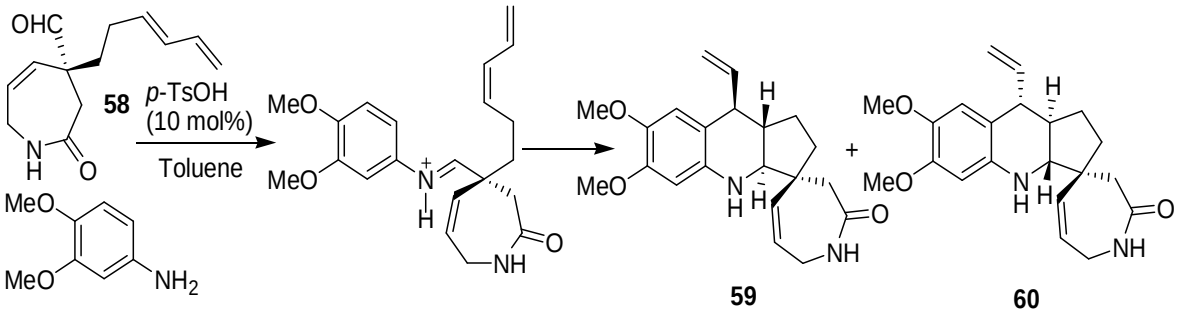
Zhou and Magomedov demonstrated an interesting intramolecular Povarov reaction for the asymmetric synthesis of tetrahydroquinoline derivatives **59** and **60** (**Scheme 20**)[67].



Scheme 18

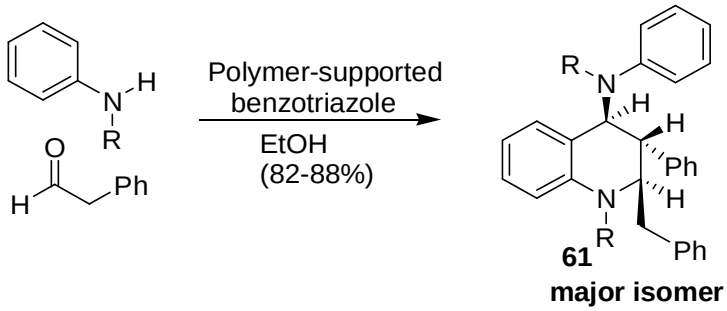


Scheme 19



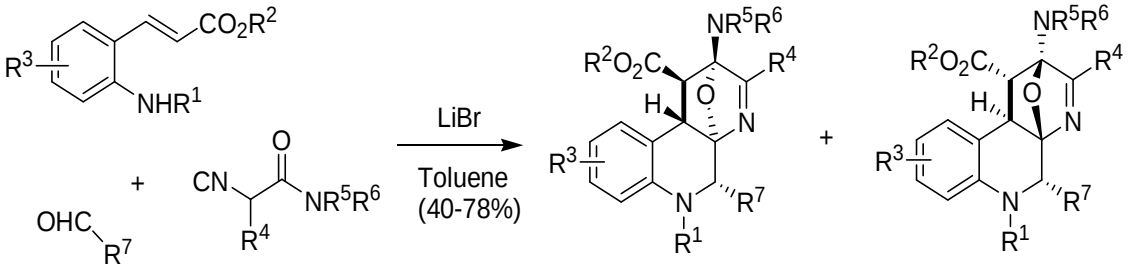
Scheme 20

2. Miscellaneous Reactions Involving the Generation of N-C_2, C_2-C_3, and C $_4$-C_{4a} Bonds: 2,3,4-Trisubstituted tetrahydroquinolines were synthesized through a reaction between arylamines and phenylacetaldehyde. The reaction was catalyzed by a polymer-supported benzotriazole that was prepared by linking 5-(hydroxymethyl)benzotriazole and benzotriazole-5-carboxylic acid with Wang resin, Merrifield resin, or (monomethoxy)poly(ethylene glycol) (**Scheme 21**)[68].



Scheme 21

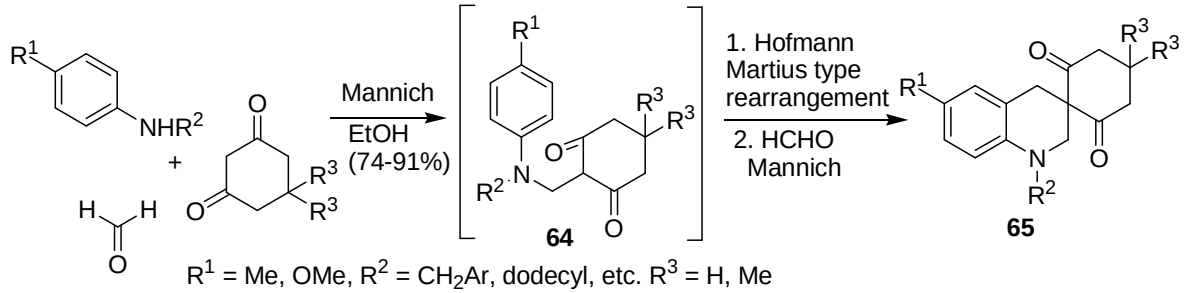
3. **Formation of the N-C_2, C_2-C_3, and C_3-C_4 Bonds:** A couple of reports by Zhu and co-workers described the synthesis of oxa-bridged tetrahydroquinolines, involving the creation of the N-C_2, C_2-C_3, and C_3-C_4 bonds in a single operation.The three-component reaction between ortho-aminocinnamates, isocyanoacetamides and aldehydes in the presence of LiBr afforded a separable dia-stereomeric mixture of oxa-bridged tetrahydroquinolines **62** and **63** by creating one C-N, one C-O, and three C-C bonds in a single operation (**Scheme 22**)[69].



R^1 = H, Me, Bn; R^2 = Me, Et; R^3 = H, Cl, OAr etc
R^4 = Ph, CH_2Ar; NR^5R^6 = piperidyl, morpholyl etc

Scheme 22

4. Formation of More than Three Bonds: The N-C_2, C_2-C_3, C_3-C_4, and C_4-C_{4a} bonds can be created in a single operation through a domino sequence (**Scheme 23**). The synthesis of 3-spiro-substituted 1,2,3,4-tetrahydroquinolines was achieved by using a three-component reaction between arylamines, formaldehyde, and β-diketones[70].

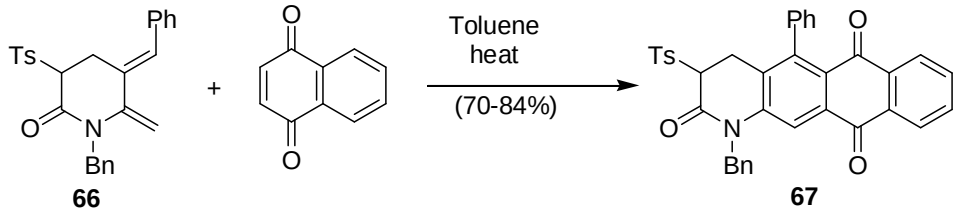


R^1 = Me, OMe, R^2 = CH_2Ar, dodecyl, etc. R^3 = H, Me

Scheme 23

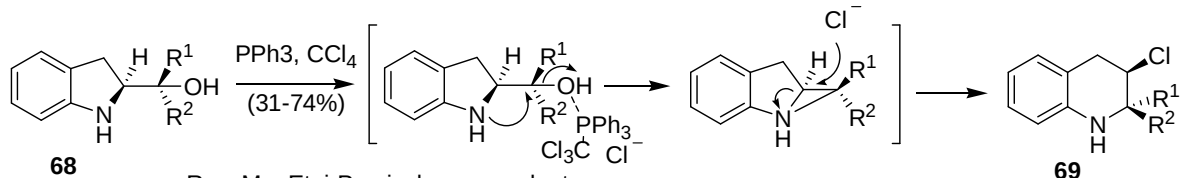
SYNTHESIS OF 1,2,3,4-TETRAHYDROQUINOLINES INVOLVING THE FORMATION OF THE ARYL OR BOTH RINGS: A few procedures are available for the construction of the aryl ring starting from a piperidine derivative or for the creation of both rings from completely acyclic precursors or from substrates bearing a furan moiety as a benzene ring precursor.

A Diels-Alder approach was developed for the synthesis of tetrahydroquinolin-2-ones and their fused analogues. For instance, the exodiene lactam **66** reacted with p-quinones to afford the fused tetrahydroquinolin-2-ones **67** in good yields. The procedure was also extended to the synthesis of hexahydro and dihydroquinoline derivatives (**Scheme 24**)[71].



Scheme 24

SYNTHESIS OF 1,2,3,4-TETRAHYDROQUINOLINES INVOLVING REARRANGEMENT REACTIONS: The literature survey shows only a few reports describing the synthesis of 1,2,3,4-tetrahydroquinolines through rearrangement reactions. Kogen and co-workers illustrated a novel rearrangement of indoline-2-methanol derivatives for the synthesis of 3-chloro1,2,3,4-tetrahydroquinolines bearing a quaternary C-2 carbon. A large variety of R,R-disubstituted indoline-2-methanols **68** were treated with triphenylphosphine (3 equiv) and CCl_4 (10 equiv) under reflux conditions to afford the corresponding 3-chloro tetrahydroquinolines **69** in good yields (**Scheme 25**)[72].

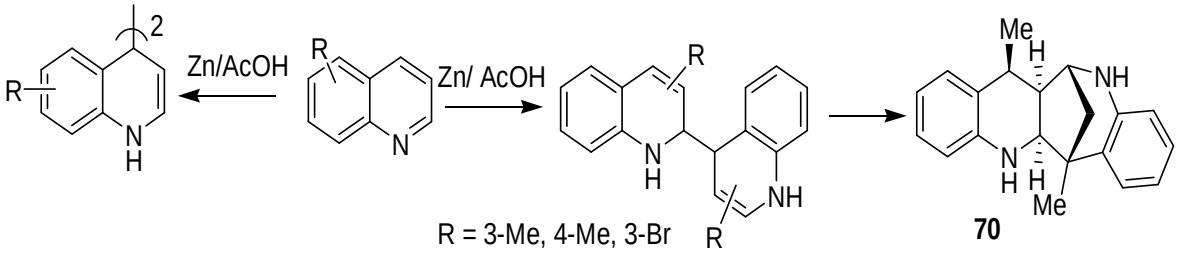


R_1 = Me, Et, i-Pr, vinyl, propergyl, etc
R_2 = Me, n-Pr, CH_2OMe

Scheme 25

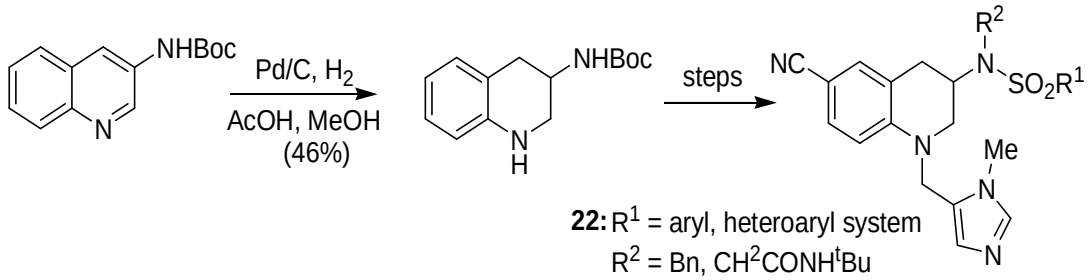
SYNTHESIS OF 1,2,3,4-TETRAHYDRO-QUINOLINES INVOLVING THE REDUCTION OF QUINOLINES: The partial hydrogenation of quinoline derivatives is a straightforward method for the synthesis of 1,2,3,4-tetrahydroquinolines. The traditional procedures for this reduction include platinum, palladium, and cobalt-catalyzed hydrogenations, metals in acids (Sn/HCl, Zn/HCOOH, Zn/CH_3COOH, etc), and hydride reduction. Whereas recent work on the partial reduction of quinolines to 1,2,3,4-tetrahydroquinolines, giving a special emphasis to the asymmetric version of this process.

1. Partial Hydrogenation of Quinolines to Racemic 1,2,3,4-Tetrahydroquinolines: Grignon-Dubois and co-workers reported a novel Zn/AcOH promoted synthesis of fused tetrahydroquinoline derivatives based on a cascade reaction of dihydroquinoline derivatives. This dimerization-cyclization cascade allowed the formation of two C-C bonds and four to five stereogenic centers (**Scheme 26**)[73].



Scheme 26

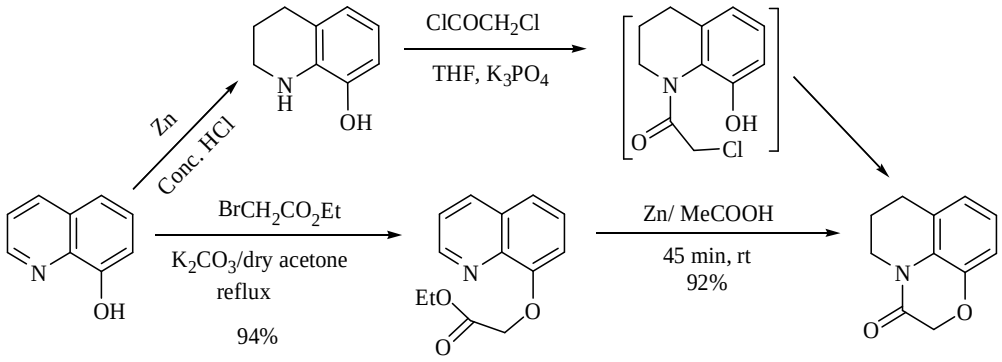
2. Synthesis of Biologically Relevant 1,2,3,4-Tetrahydroquinolines via Hydrogenation of Quinolines: Tetrahydroquinoline based farnesyltransferase inhibitors **A**, were synthesized from 3-aminoquinoline. The quinoline ring was partially hydrogenated in the presence of Pd/C to allow the corresponding tetrahydroquinoline derivative (**Scheme 27**)[74].



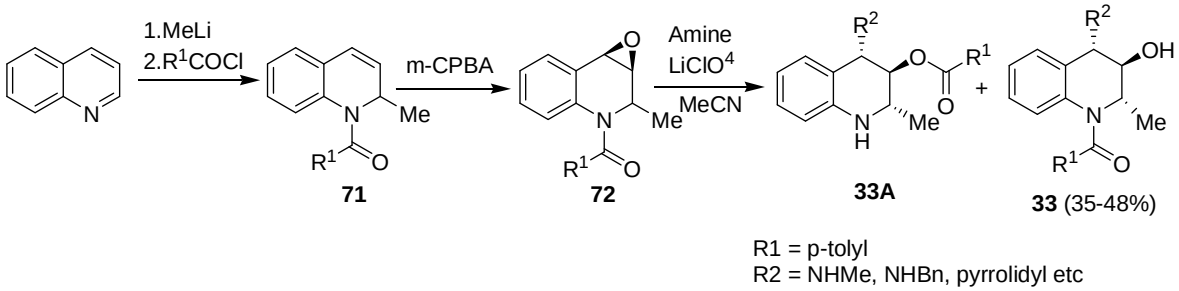
Scheme 27

3. Synthesis of tricyclic oxazino-/oxazepino-tetrahydroquinolines: Recently Mondal et.al has introduced an intramolecular partial reduction in the presence of zinc dust in acetic acid to get fused tetrahydroquinoline as exclusive product (**Scheme 28**)[75].

4. Quinoline Reduction Involving the Addition of Nucleophiles: The reductive 2-alkylation of quinoline with organolithium reagents, followed by N-acylation allowed the synthesis of 2-alkyl-1,2-dihydroquinolines **71**. Then the intermediate **71** was transformed into tetrahydroquinoline derivatives having modulating activity in multidrug resistance (MDR). Thus, epoxide **72**, obtained by oxidation of the C_3-C_4 double bond of compound **71** with mCPBA, was opened with a number of amine nucleophiles in the presence of $LiClO_4$ to afford the corresponding tetrahydroquinolines **73** and **74** (**Scheme 29**)[76].

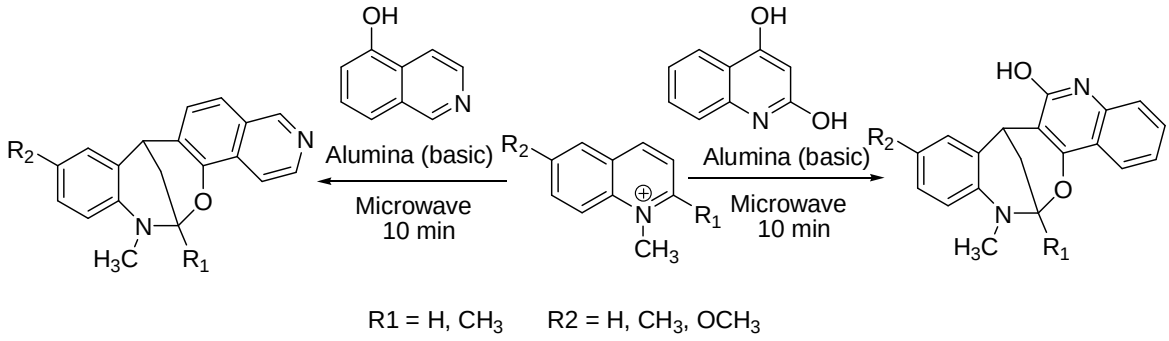


Scheme 28



Scheme 29

Another procedure that can be considered as rather similar to the previous one, with potential advantages, was developed recently for the synthesis of 1,2,3,4-terahydroquinolines substituted at C-$_2$ and C$_4$. This method involves the tandem conjugate addition-cyclisation of hydroxy-quinolines or isoquinolines to the N-aromatic system (**Scheme 30**)[77].



Scheme 30

SYNTHESIS OF TETRAHYDROQUINOLINES WITH OTHER HYDROGENATION PATTERNS: Although 1,2,3,4-tetrahydroquinolines are the most common tetrahydroquinoline system, a considerable number of reports are also available for the synthesis of 5,6,7,8-tetrahydroquinoline derivatives.

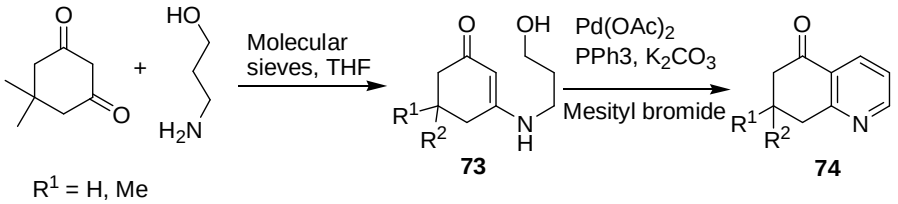
1. Synthesis of 5,6,7,8-Tetrahydroquinolines by Construction of the Pyridine Ring: The palladium-catalyzed oxidation of γ-hydroxy-enaminones **74** allowed the synthesis of 5,6,7,8-tetrahydroquinolin-5-ones **75** in moderate yields. The starting γ-hydroxy-enaminones **74** were prepared from cyclic 1,3-dicarbonyl compounds and the γ-amino alcohols were prepared under mild conditions in the presence of molecular sieves (**Scheme 31**) [78].

2. Synthesis of 5,6,7,8-Tetrahydroquinolines by Construction of the Cyclohexene Ring: A set of 6,7,8,9-tetrahydro-5H-cyclohepta[b]pyridine derivatives were found to be potent and selective opioid receptor like antagonists. This opiod was obtained from the corresponding 6,8-disubstituted 5,6,7,8-tetrahydroquinoline derivative **77**[79]. Compound **78** was in turn synthesized from 2-chloro-3-cyanopyridine in several steps, where the key reaction was the base-promoted cyclization of pyridine derivative **76** (**Scheme 32**).

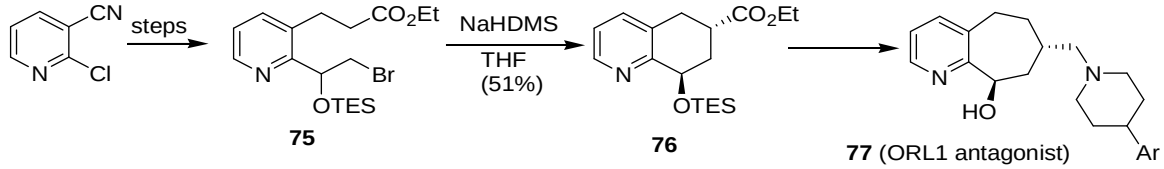
3. Synthesis of 5,6,7,8-Tetrahydroquinolines Starting from Acyclic Precursors: The creation of both rings of 5,6,7,8-tetrahydroquinoline in a single step starting from acyclic precursors is rare, and the only report of this type of transformation in the literature is the cobalt catalyzed synthesis of 5,6,7,8 tetrahydroquinolines from diynenitriles (**Scheme 33**)[80].

4. Synthesis of 1,4,4a,8a-Tetrahydroquinolines: 1,4,4a,8a-Tetrahydroquinolines are readily available using a diene-transmissive Diels-Alder strategy (**Scheme 34**)[81].

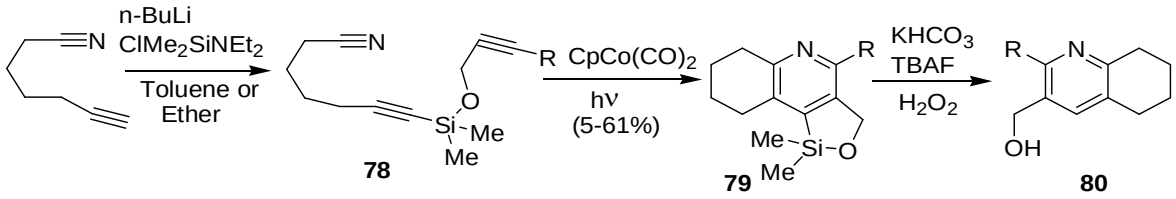
5. Synthesis of 2,3,4,4a-Tetrahydroquinolines: Povarov reactions starting from 2,6-dimethylaniline afford tetrahydroquinoline derivatives with a2,3,4,4a-tetrahydro hydrogenation pattern. This reaction cannot be transformed into the more stable 1,2,3,4-tetrahydro-one, because of the presence of a methyl group at the ring fusion (**Scheme 35**)[82].



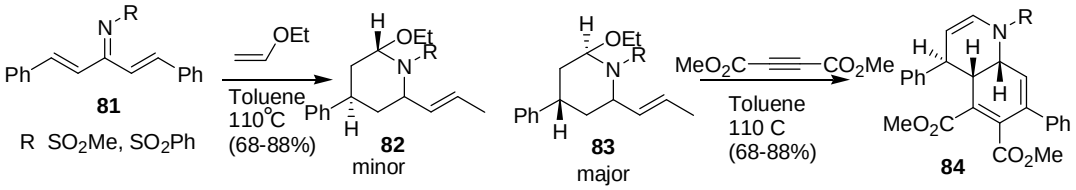
Scheme 31



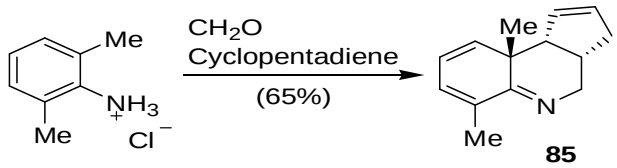
Scheme 32



Scheme 33



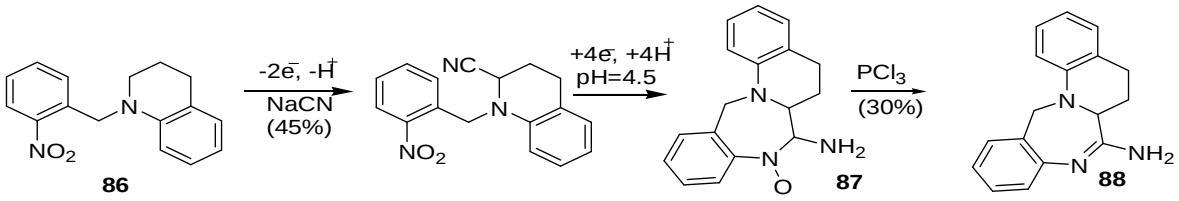
Scheme 34



Scheme 35

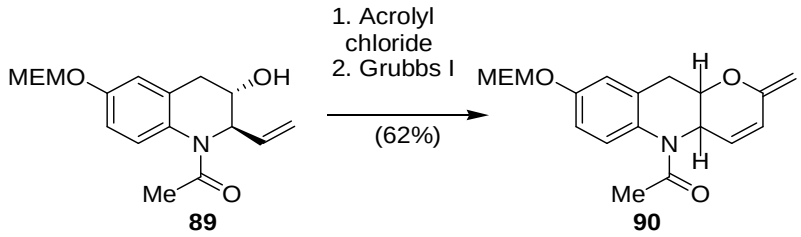
TRANSFORMATION OF TETRAHYDRO-QUINOLINES INTO OTHER HETEROCYCLES: A significant number of reports have been published documenting the creation of additional rings fused to either the tetrahydropyridine ring (N-C_2, C_2-C_3, or C_3-C_4 bonds) or the ring junction between both rings (N-C_{8a} and C_8-C_{8a} or C_4-C_{4a} and C_{4a}-C_5 bonds) of tetrahydroquinolines.

1. Methods that Create Additional Rings Fused to the N-C_2 Bond: The creation of additional rings fused to the N-C_2 bond of the 1,2,3,4-tetrahydroquinoline system has been generally achieved by introducing suitable substituents on the nitrogen atom. The target molecule was achieved by their subsequent reaction with the C-2 carbon or with substituents at C-2 (**Scheme 36**)[83].



Scheme 36

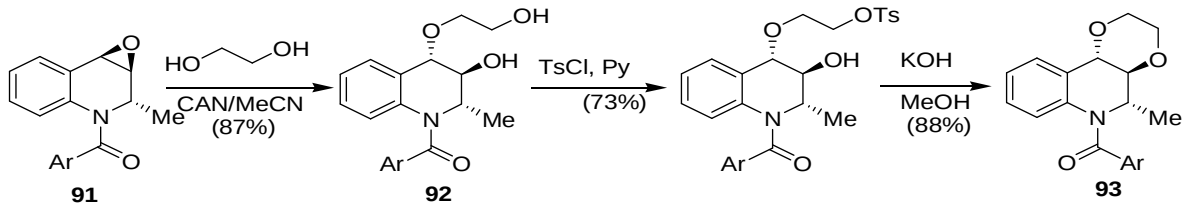
2. Methods that Create Additional Rings Fused to the C_2-C_3 Bond: The creation of additional ring fused to C_2-C_3 bond of the 1,2,3,4-tetrahydroquinoline system has been achieved by introducing suitable substitution attached to the C_2 and C_3 carbon followed by their subsequent reaction. As for example acylation of the secondary alcohol **89** with acryloyl chloride followed by a ring-closing metathesis reaction in the presence of Grubbs first generation catalyst ($C_{43}H_{72}Cl_2P_2Ru$) afforded the pyrano [3,2-b]quinoline **90** in good yields (**Scheme 37**)[84].



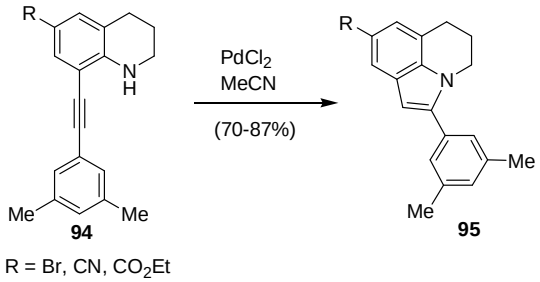
Scheme 37

3. Methods that Create Additional Rings Fused to the C_3-C_4 Bond: Another known protocol developed by Khadem and co-workers was also employed for the creation of an additional ring fused to the C_3-C_4 bond. The regioselective nucleophilic ring-opening of the readily available epoxide **91**, with alcohols in the presence of CAN afforded diastereoselectively the tetra-substituted 1,2,3,4-tetrahydroquinoline derivative **92**. Subsequent tosylation of the primary alcohol group, followed by a base-promoted cyclization, furnished the C_3-C_4-fused tetrahydroquinoline **93** (**Scheme 38**)[85].

4. Methods that Create Additional Rings Fused to the N-C_{8a} and C_8-C_{8a} Bonds: However another successful protocol was employed for the creation of an additional ring fused to the N-C_{8a} and C_8-C_{8a} bonds of tetrahydroquinolines (**Scheme 39**). The palladium catalyzed ring-closure of 2-alkynylanilines was an efficient methodology to obtain indole derivatives[86].

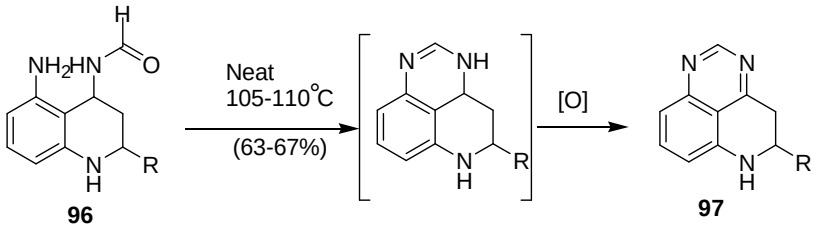


Scheme 38



Scheme 39

5. Methods that Create Additional Rings Fused to the C_4-C_{4a} and C_{4a}-C_5 Bonds: The 5-amino-substituted 1,2,3,4-tetrahydro-quinoline **96** obtained from catalytic hydrogen-ation of the m-nitro aniline. This reaction proceeds according to Katritzky's benzotriazole Povarov-like protocol. Initially it was heated at 105-110°C **under** solvent-free conditions to afford a sequence of condensation and oxidation reactions to give pyrido[4,3,2-de]quinazolines **97** in good yields (**Scheme 40**)[87].



Scheme 40

CONCLUDING REMARKS:

The interesting structural features of tetrahydroquinoline have provided the synthetic chemist with a rich and challenging set of targets. It seems likely that additional members of this family will be discovered soon and will set the stage for new biochemical and biological investigations. Moreover, knowledge concerning the biosynthesis of this family of compounds is not well advanced and constitutes yet another fascinating area of future investigation. It can be anticipated that two of the areas that will probably experience the fastest growth will be the development of step- and atom-economic methods based on the use of multi-component and domino strategies. There is every expectation that this review will provide some valuable information to the chemical community such that the work in this topic will continue in near future.

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