Quinolines Spiro Annulated at Heterocyclic Fragment: Synthesis and Properties

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Chemical information of the quinolines spiro annulated at heterocyclic fragment with cycloalkanes or heterocycles is reviewed. Synthetic approaches to three possible spiro-2(1*H*)-, spiro-3(4*H*)- and spiro-4(1*H*)quinoline core derivatives are analysed. Their syntheses are divided into three groups: a) chemical transformations of the substituted quinoline ring, b) construction of spiro structure from the alicyclic precursors, mainly, amine derivatives or imines preformed from cyclic ketones; c) rearrangements of more complex heterocycles leading to the spiro quinolines. Special attention is paid to spiro quinolines that display pharmacological properties. Synthetic routes to the discorhabdin alkaloids are also briefly discussed on in this review.

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1. Itroduction

Carbocyclic and heterocyclic spiro compounds [1,2] are not only parts of natural products such as sesquiterpenes and alkaloids, but also building blocks that can be used in drug preparation. Nitrogen-containing heterocycles occupy a special place among the large number of organic compounds. Many of these heterocycles have been found to play fundamental roles in biological processes and have exhibited important pharmacological activities. The appealing spiro architecture, often associated with significant biological activity, renders the spiro[pyrrolidine-3,3'-oxindole] alkaloids (Horsfiline, Rychnophylline, Elacomine) [2], spiro[piperidine-2',1-cycloalkane] frog neurotoxins (Histrionicotoxin 283A) [3] and marine products (Pinnaic acid) [4] or spiro[tetrahydroazepine-cyclohexene] shellfish toxins (Spirolides A-D) [5,6] interesting synthetic targets (Figure 1).

Quinolines and their reduced forms are of considerable interest as medicines, covering a wide spectrum of bioactivity [7-9]. It is found that several tetrahydroquinolines exhibit analgesic [10], hypertensive [11,12], antiamebic [13], insecticide [14] and fungicide [15-19] activities. Many molecules of natural origin, especially alkaloids, contain quinoline and tetrahydroquinoline rings. For example, chimanine [20,21] and cusparein [22] alkaloids were isolated from the bark of *Galipea* trees. Both molecules have been shown to have potent antileishmanial activity. Other interesting members of quinoline group are antiviral metabolite Virantmicin [23] and Pumiliotoxin C (decahydroquinoline *cis*-195A) alkaloid [24,25]. The for-

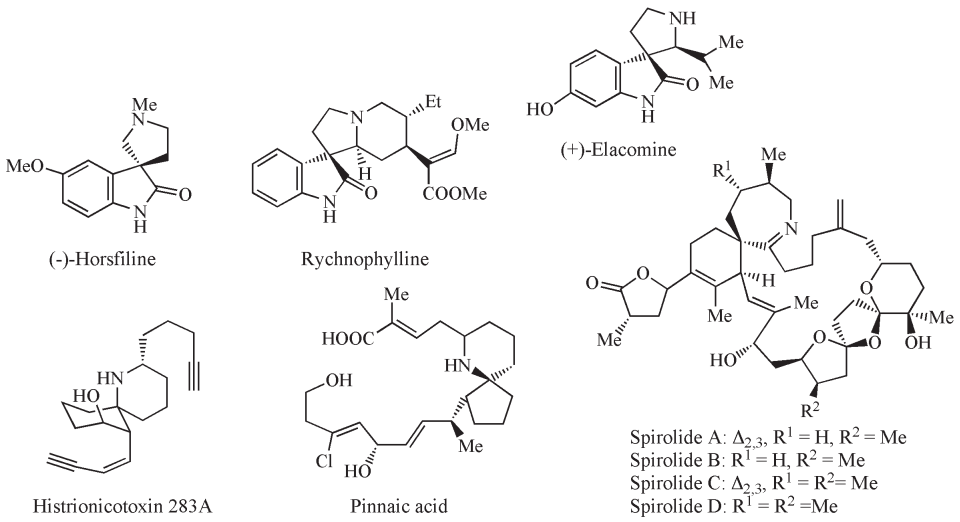


Figure 1

mer was isolated from *Streptomyces nitrosporeus*, while the latter molecule was found in the skin of neotropical frogs of the family Dendrobatidae (species *Dendrobates pumilio* and *Dendrobates auratus*) [26].

Despite the large number of published synthetic routes to quinoline derivatives, there are very few works that describe the construction of the dihydroquinoline ring spiro annulated at positions C-2, C-3 and C-4 with cycloalkanes or heterocycles [7-9,27]. The chemistry and biological activity of this type of spiro heterocompounds remain largely unexplored. Nevertheless, diverse spiro dihydroquinolines that could be useful for many sectors of the chemical industry have attracted the attention of synthetic organic chemists due to antibacterial [28], anti-inflammatory [29] and herbicidal [30,31] properties. Related substances act upon the central nervous system [32]. Other related compounds are excellent anticorrosive agents [33] or useful intermediates in the synthesis of special dyes [34].

Spiro annulations of quinoline ring with cycloalkanes or heterocycles may improve even modify the biological potency of this class of compounds. Recently, the development of efficient strategies and synthetic routes to alkaloids incorporating the spiro quinolines ring system (mainly, spiro-4-quinoline skeleton) have been given increased attention as a result of the important biological activity that these natural products have displayed.

As part of our research program on the synthesis of bioactive spiro *N*-heterocycles, we wish to review and classify all chemical transformations, which lead to the formation of diverse quinolines that contain carbo or hetero fragments spiro annulated at positions C-2, C-3 and C-4 (Figure 2).

The classic Skraup, Doebner-Miller, Friedländer, Pfitzinger, Conrad-Limpach-Knorr, Combes syntheses are

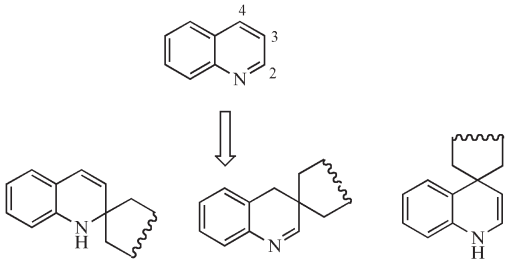


Figure 2

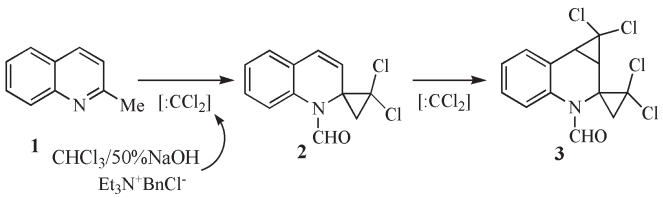
the methods usually followed to construct the quinoline cycle from alicyclic precursors *via* intramolecular cyclizations or cyclocondensations [27,35-37]. In some reactions, the substituted dihydroquinolines are intermediate products, generally not isolated. All these syntheses cannot serve in the preparation of spiro quinolines. Synthesis of these quinolines require special methods to construct the spiro structure. Synthetic approaches to three possible spiro-2(1*H*)-, spiro-3(4*H*)- and spiro-4(1*H*)quinoline derivatives can be divided into three groups: a) chemical transformations of the substituted quinoline ring, b) construction of spiro structure from the non-heterocyclic precursors, mainly, amine derivatives or imines preformed from cyclic ketones; c) rearrangements of more complex heterocycles leading to the spiro quinolines.

2. Spiro-2(1*H*)quinolines.

2.1. Synthetic Efforts to Obtain Dihydrospiro-2(1*H*)quinolines from Quinolines as Cyclic Precursors.

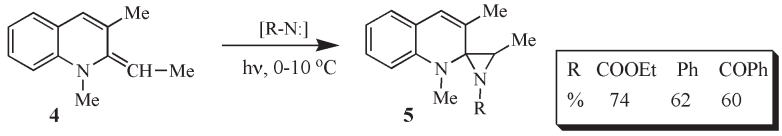
Treatment of 2-methylquinoline **1** with dichlorocarbene generated *in situ* from chloroform under biphasic conditions led to the spiro[cyclopropane-2',2(1*H*)quinoline] derivatives **2** and **3** in good yields [38,39] (Scheme 1).

Scheme 1



N-Methyl quinoline precursor **4** was used successfully in the preparation of the 1,3,3'-trimethyl-1'-R-spiro[aziridine-2',2(1*H*)quinolines] **5**. Cycloaddition of nitrenes to the exocyclic double bond of this quinoline derivative proceeded smoothly under photolysis conditions to give the spiro derivatives **5** in good yields [40,41] (Scheme 2).

Scheme 2



Walter described a simple and efficient one-pot synthesis of 4-oxo-spiro[thiazolidine-2',2(1*H*)quinolines] starting from 3,4-dihydro-1*H*-quinoline-2-thione [42]. Using sodium hydride as a base, the anion **7** was formed from 1*H*-quinoline-2-thione **6**. The treatment of this anion with the α-bromoacetamides gave no isolable intermediates **8** which reacted with other equivalent of preformed anion to afford the stable crystalline spirocyclic quinolines **9** in good to excellent yields (Scheme 3). In this case no "Eschenmoser Sulphur Extrusion" occurs [43].

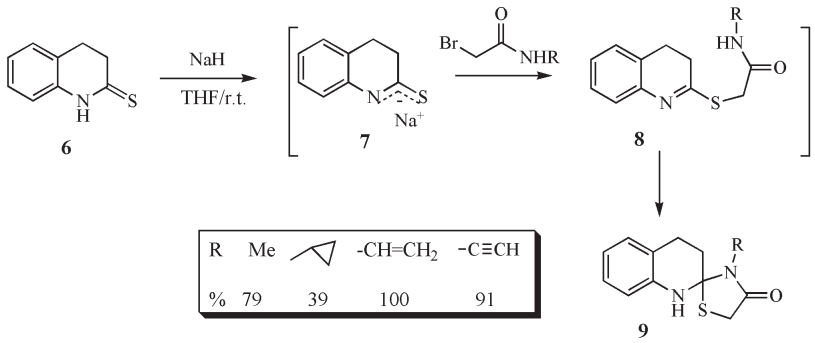
Kobayashi reported that reaction between DMAD and quinoline derivative **10** in boiling dioxane generated the quinoline **11** spiro annulated with a thiopyran ring [44] (Scheme 4).

These few examples demonstrated that synthesis of spiro-2(1*H*)quinoline derivatives starting from the quinoline precursors is not general.

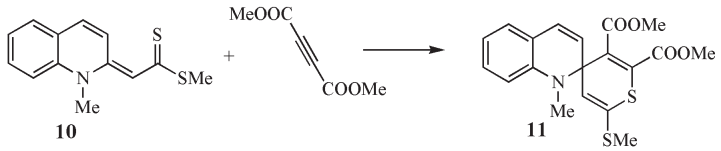
2.2. Synthetic Efforts to Obtain Dihydrospiro-2(1*H*)quinolines from Amine or Imine Precursors.

A common route to the spiro[cycloalkane-1',2(1*H*)quinoline] derivatives consists on the utilization of diverse anilines and cyclic ketones as starting materials. For example, heating primary substituted anilines with two equivalents of cyclohexanone in the presence of iodine (old method of Reddelien [45]) led to the spiro[cyclohexane-1',2-(1*H*)cyclohexano(*c*)quinoline] derivatives **12a** [46,47] (Scheme 5).

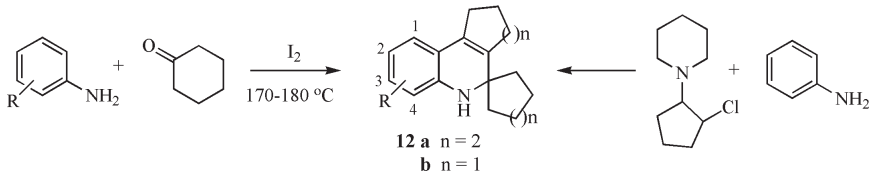
Scheme 3



Scheme 4



Scheme 5

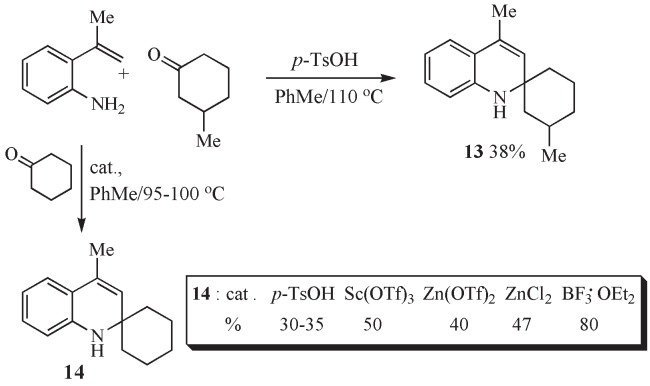


12a:	R	H	2-Me	3-Me	2-OMe	3-OMe	4-OMe
	%	52	69	62	60	69	28

Similar cyclopentano(*c*)quinoline derivative **12b** was isolated in poor yield after realizing a thermal condensation between aniline and *N*-(2-chloro-1-cyclopentyl)-piperidine [48].

Several reports described the interaction between *o*-alkenylanilines and cyclohexanones as an efficient route to the spiro-2-quinoline derivatives. Walter and co-workers reported the first synthesis of diastereoisomeric 3',4-dimethyl-spiro[cyclohexane-1',2(1*H*)quinoline] **13** from *o*-isopropenylaniline and 3-methylcyclohexanone in the presence of catalytic amounts of *p*-TsOH in toluene (110 °C). The spiro compound **13** was also obtained from aniline and (+)-R-pulegone under the same reaction condition [49] (Scheme 6).

Scheme 6



14 : cat .	*p*-TsOH	$Sc(OTf)_3$	$Zn(OTf)_2$	$ZnCl_2$	$BF_3 OEt_2$
%	30-35	50	40	47	80

The acid-mediated reaction of *o*-isopropenylaniline and cyclohexanone to form the spiro[cyclohexane-1',2(1*H*)-quinoline] **14** was also studied [50]. This study demonstrated that among diverse Lewis acids, $BF_3{\cdot}OEt_2$ was the best catalytic agent for this synthesis.

Cyclocondensation between 2-(1-phenylvinyl)anilines and α-tetralone or chromane-4-one in the presence of *p*-TsOH in boiling toluene led to the formation of spirocyclic 1*H*-quinolines **17**. The first step of this synthesis consists in the formation of ketimine **15**, which can suffer a 6π electrocyclic rearrangement to give an intermediate **16** followed by a rapid [1,5]-H shift [51] (Scheme 7).

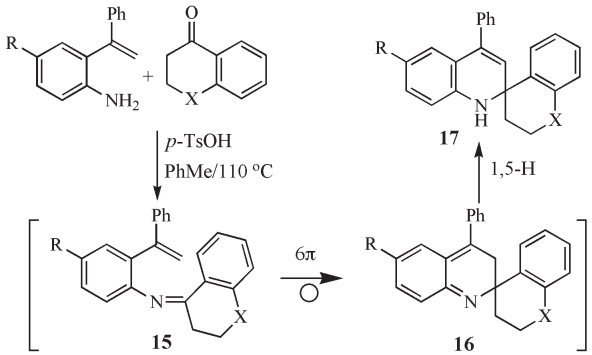
The treatment of 3,5-dimethoxyaniline with 1,2-indanedione in benzene afforded several products, among them was a polycyclic molecule with a spiro-2-quinoline structure [52].

Two-step synthesis of 1',2',3',4'-tetrahydrospiro[indoline-3,2'-quinoline]-2,4'-diones was reported by Al-Thebeiti [53]. *N*-Arylamino substituted 2-oxoindoline derivatives **19** were prepared as a result of interaction between *p*-substituted anilines and isatin derivatives **18**. Obtained products were converted into the desired spirocyclic quinolines **20** by means of triflic acid (Scheme 8).

Related spiro compounds were synthesized from a ketimine-oxoindol and an allene in the presence of $Pd(OAc)_2$, tris(2-furyl)phosphine and indium in DMF [54].

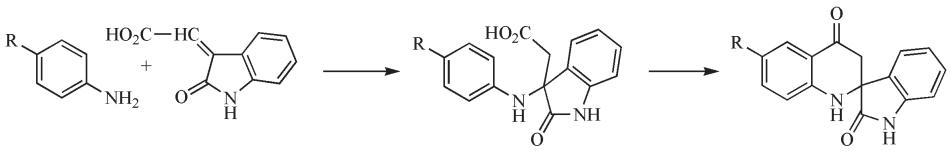
Many approaches to the spiro-2-quinolines presented above utilize ketimine intermediates, which are transformed later into the final spiro products. Imine synthons play a

Scheme 7



17:	R	H	Cl	H	Cl
	X	CH_2	CH_2	O	O
	%	86	60	22	74

Scheme 8



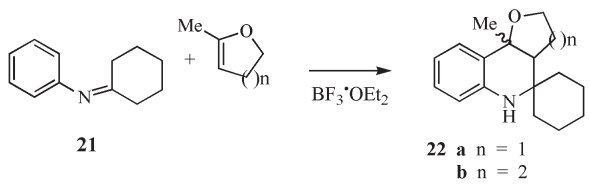
18 **19** 52-58% **20** 50-57%

R = H, Me, OMe, Cl, Br

considerable role in the preparation of diverse types of heterocyclic compounds [55,56]. Because imines derived from cyclic ketones are stable, cheap and available products, special attention has been devoted to their applications in the synthesis of spiro compounds. The utilization of *N*-benzylidenanilines (as a 2-azadiene component, where the C=C bond is part of the aromatic system) in the Diels-Alder reactions has enriched heterocyclic chemistry [57,58].

Undoubtedly, that Schiff' bases derived from cyclohexanone are the more useful starting materials to prepare 3,4-dihydro-spiro[cyclohexane-1',2(1*H*)quinoline] derivatives. The Lewis acid catalysed cycloaddition of 2,3-dihydro-5-methylfuran or 3,4-dihydro-6-methyl-2*H*-pyran to *N*-cyclohexylidenaniline **21** afforded the corresponding furo[3,2-*c*]quinoline **22a** and pyrano[3,2-*c*]quinoline **22b** spiro annulated with a cyclohexane ring [59] (Scheme 9).

Scheme 9



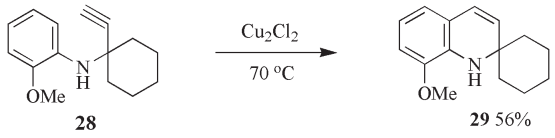
21 **22** **a** n = 1 **b** n = 2

Related ketimine precursors such as *N*-cyclohexyliden-α-naphthylamines or *N*-cyclohexyliden-β-naphthylamines were used in this reaction to obtain furo[*c*]benzo[h]quinolines or furo[*c*]benzo[f]quinolines [60] that can act as antioxidants [61,62].

Another modification of [4+2] cycloaddition that is conducive to the 3,4-dihydrospiro[cyclohexane-1',2(1*H*)-quinolines] is an "autocondensation" of *o*-quinone methide imines, which play a role as 1-azadienes as well as dienophiles. For instance, *N*-phenylindolin-2-one **23** or *N*,*N*,*N*-trimethyl-*N*-*o*-(*N*'-methyl-*N*'-trimethylsilyl) aminobenzyl ammonium bromide **24** are excellent precursors of *o*-quinone methide imines **25**. Both starting materials suffer a rearrangement under photolysis and CsF-induced conditions, respectively, that allows for the generation of the corresponding spiro-2-quinolines **26** and **27** in high yields [63,64] (Scheme 10).

1-Ethinyl-1-*o*-methoxyphenylaminocyclohexane **28** is also suitable precursor to obtain 8-methoxyspiro[cyclohexane-1',2(1*H*)quinoline] **29** through an intramolecular cyclization [65] (Scheme 11).

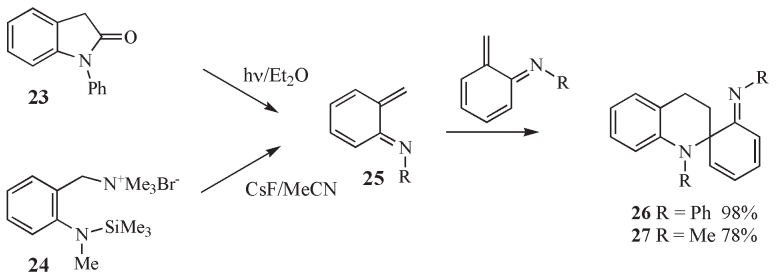
Scheme 11



28 **29** 56%

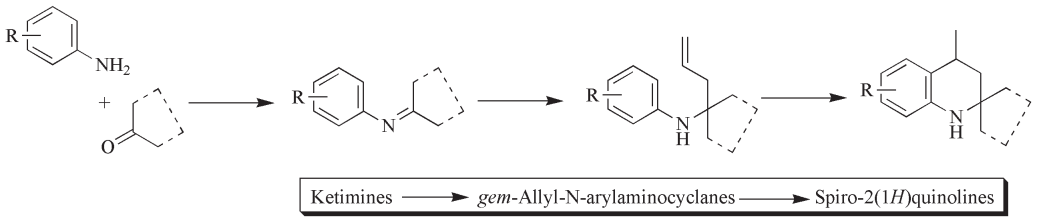
Taking into consideration that cyclic ketimines are stable, cheap and available materials, which can be easily converted into gem-allyl-*N*-arylaminocyclanes, new and efficient approaches of diverse interesting spiro-2(1*H*)quinolines using imine synthons were developed (Scheme 12).

Scheme 10

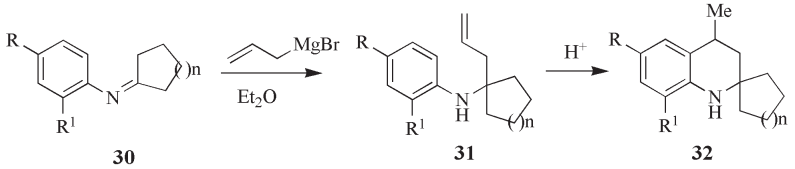


23 **24** **25** **26** R = Ph 98% **27** R = Me 78%

Scheme 12



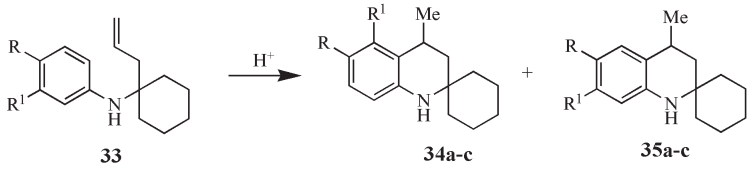
Scheme 13



30 **31** **32**

n = 1-4; R = H, Me, Et, OMe, OEt, F, Cl, Br; R^1 = H, Me, OMe, Cl

Scheme 14



33 **34a-c** **35a-c**

a R = H, R^1 = Me; **b** R = R^1 = Cl; **c** R = F, R^1 = Cl

Imines from cyclic ketones (C_5, C_6, C_7, C_8 and γ-piperidones) were taken as starting materials. Ketimines **30** were obtained in good to excellent yields by known protocol. These ketimines were transformed later into the corresponding gem-allyl-*N*-arylaminocyclanes **31** through an addition of the Grignard reagent using allyl magnesium bromide. These aminocyclanes, possessing an π-electron rich aromatic ring, a basic nitrogen atom and an allyl (electrophilic C_3 synthon) fragment, represent a versatile source of synthetic materials for constructing (1*H*)-quinolines spiro annulated at C-2. Thus, following Scheme 12, new synthesis of 6- and 8-substituted or 6,8-disubstituted 3,4-dihydro-4-methylspiro[cycloalkane-1',2(1*H*)quinolines] **32** in the presence of H_2SO_4 was accomplished in moderate to good yields depending on the electronic nature of the substituents [66-73] (Scheme 13).

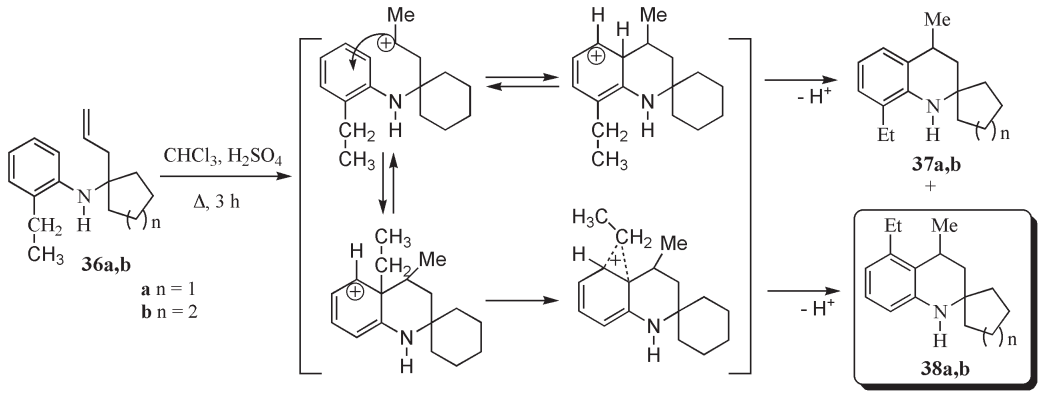
An acid cyclization of 3,4-disubstituted aminocycloalkanes **33** produced a mixture of spiro quinolines **34** and **35** in the ratio 1:1 that were easily isolated using column chromatography (Scheme 14) [66,70].

Recently, an unprecedented intramolecular Friedel-Crafts *ipso*-alkylation at the *ortho*-ethyl group in the *N*-arylamino moiety of 1-allyl-1-*N*-arylaminocycloalkanes to give alkyl substituted dihydrospiro[cycloalkane-1',2(1*H*)quinolines] was reported [74]. The acid cyclization (97%H_2SO_4/$CHCl_3$/60-65 °C/3-5 h) of *o*-ethylphenylamines **36a,b** gave the desired 8-ethyl substituted dihydrospiroquinolines **37a,b** (59, 61%) together with unexpected 5-ethyl substituted tetrahydroquinolines **38a,b** (17, 23%). Unexpected results were explained in the context of intramolecular *ipso*-substitution of ethyl groups and their 1,2-rearrangement (Scheme 15). The same cyclization of their methyl-substituted analogs proceeded smoothly to give only 8-alkyl substituted quinolines.

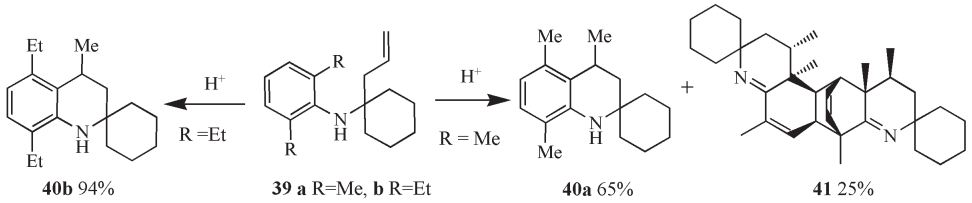
Moreover, treatment of the *ortho,ortho'*-diethyl substituted allylarylaminocyclohexane **39b** under the same reaction conditions promote cyclization that readily furnished the new expected 5,8-diethyl substituted spirane **40b** in almost quantitative yield (Scheme 16). In this case, as both *ortho*-carbon atoms attached to ethyl group are equivalent, *ipso*-attack proceeds easily followed by a 1,2-shift of the ethyl group and the loss of an H^+ to reconstitute the aromatic system. In the case of *ortho,ortho'*-dimethyl substituted allylarylaminocyclohexane **39a**, the intramolecular alkylation proceeds more fascinatingly. Besides the *ipso*-substitution product **40a**, which was obtained in 65% yield, heterocycle **41** with an unprecedented spiro structure was isolated (25%) (Scheme 16).

Unexpected results were also explained in the context of intramolecular *ipso*-substitution of alkyl groups and their 1,2-rearrangement [74,75]. The Wheland intermediate **39*a**, formed by *ipso*-attack, can be stabilize not only by a

Scheme 15



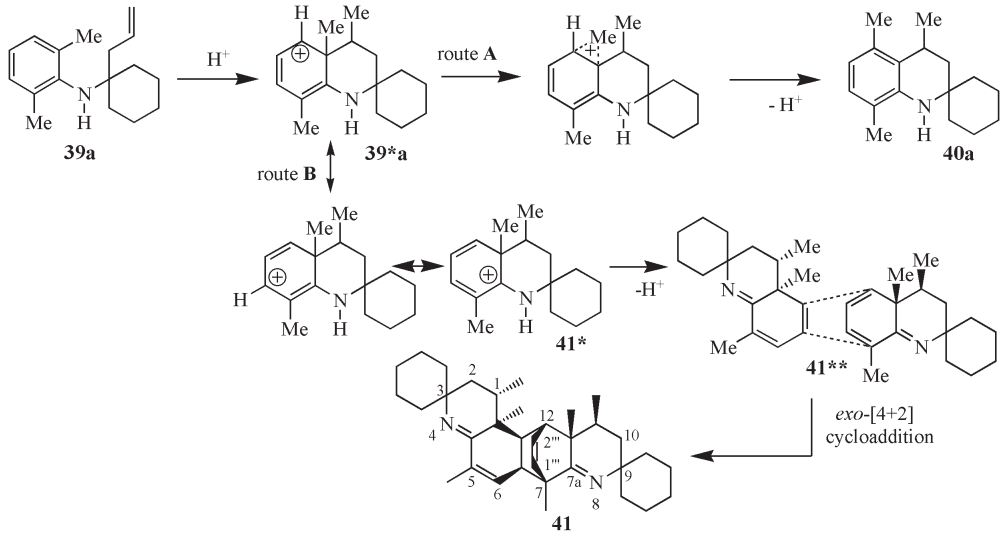
Scheme 16



1,2-shift of the methyl group giving the 5,8-dimethyl substituted spirane **40a** (route A), but by loss of H^+ from the resonance-stabilized structure **41*** (route B) offering the 2,3,4,4a-tetrahydroquinoline **41****, a precursor of dimeric product **41** (Scheme 17).

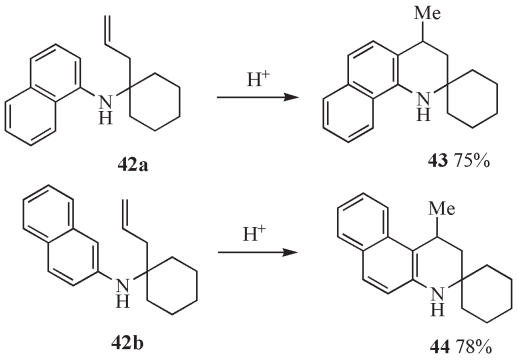
The central bicyclo[2.2.2]octene fragment of **41** has the *endo*-fusion with a piperideine cycle and the *exo*-fusion with a cyclohexene moiety. Spirocycloalkane fragments of polyheterocycle **41** have chair conformation and reduced quinoline rings bearing common unplanned spiroatoms C(1) and C(23) with cycloalkane moieties adopt "envelope" conformation where atoms C(8) and C(21) move aside from middle planes of the rest of five atom six-membered cycles at 0.67 and 0.61Å, respectively (crystallographic numbering used everywhere). Methyl groups attached to the atoms C(8) and C(21) are oriented equatorially. Their deviation from the corresponding planes constitutes 0.63 and 0.53Å. Vicinal methyl groups at C(8) and C(9) have *cis*-orientation. The other methyl groups at C(20) and C(21) are oriented in a similar manner [75].

Scheme 17



The synthetic possibilities of this method can be amplified considerably by varying the structures in both the amine and ketone components of the initial iminocyclanes. It was demonstrated that the utilization of *N*-cyclohexanyliden-α(β)-naphthylamines in this scheme allowed for the generation of the benzoannulated analogs of spiro compounds **32**. Thus, 1-allyl-1-*N*-α-naphthylaminocyclohexane **42a** and 1-allyl-1-*N*-β-naphthylaminocyclohexane **42b** gave the respective 3,4-dihydro-4-methylspiro[cyclohexane-1',2-benzo[*h*]-1*H*-quinoline] **43** and its benzo[*f*]-analogue **44** in good yields [71] (Scheme 18).

Scheme 18



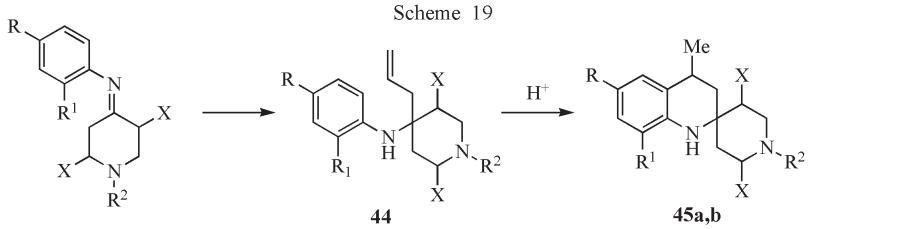
On the other hand, by varying the nature of the ketone component in 1-allyl-1-*N*-arylaminocyclanes, the first synthesis of spiro[piperidine-4,2'(1'*H*)quinoline] derivatives could be realized [76,77]. 6'-Substituted 1-benzyl(ethyl)-3',4'-dihydro-spiro[piperidine-4,2'(1'*H*)quinolines] **45a** and 6'-(8')-substituted 3',4'-dihydro-2,4',5-trimethyl-spiro-[piperidine-4,2'(1'*H*)quinolines] **45b** were obtained *via* a facile two-step hetero spiro annulation process of γ-iminopiperidines [77,78]. The key compounds, potentially bioactive 4-allyl-4-*N*-arylaminopiperidines **44a,b** were easily prepared from 4-iminopiperidines [79-81] (Scheme 19).

The spiropiperdines **45b** exit as a mixture of two diastereomers with *trans* (2e-CH_3/5e-CH_3)- and *cis* (2a-CH_3/5e-CH_3)-configurations of the piperidinic methyl groups. Dihydroquinoline ring of these compounds adopts the semi-chair conformation with the equatorial 4-CH_3 group [78].

It was reported that similar spiro[piperidine-4,2'(1'*H*)-quinolines] act as chain-breaking antioxidants [82] and related spiro[piperidine-2,2'(1'*H*)quinolines] serve as intermediates for nervous system agents and gonadotropic hormone receptor antagonists [83].

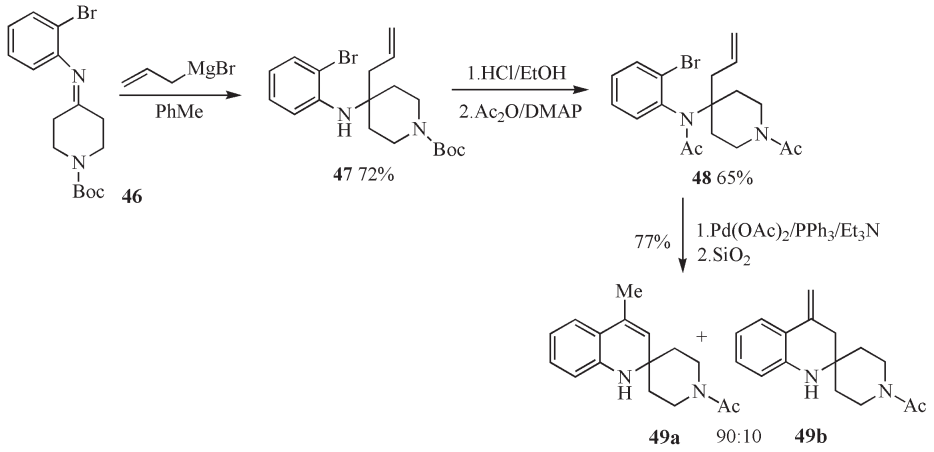
Cossy and co-workers proposed another very interesting approach based on a Heck reaction to this spiro-2-quinoline ring system [84]. The reaction between *N*-Boc protected piperidilyden-4-*o*-bromoaniline **46** and allylmagnesium

Scheme 19



a X = H; R, R^1 = H, Me; R^2 = Et, Bn
b X = Me; R, R^1 = H, Me, OMe; R^2 = Me

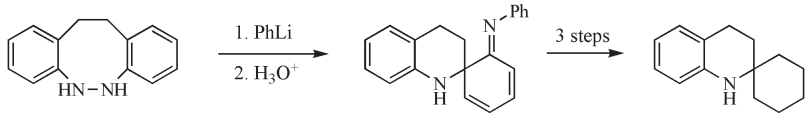
Scheme 20



bromide furnished 4,4-disubstituted piperidine **47** that was first protected (compound **48**) and subjected to a Heck reaction yielding 4'-methylspiro[piperidine-4,2'(1'*H*)quinoline] **49a** and 4'-methyliden-3,4'-dihydrospiro[piperidine-4,2'(1'*H*)quinoline] **49b** (Scheme 20).

oped which allowed for the investigation of some chemical and biological properties of this spiro heterosystem. For instance, nitration of the spiro quinoline **32a** using a nitrating mixture (HNO_3/H_2SO_4) gave the respective mono 7- and 6-nitro derivatives **52** and **53** [68]. Treatment of the

Scheme 21



50 **26** **51**

2.3. Synthetic Efforts to Obtain Dihydrospiro-2(1H)quinolines From Other Systems.

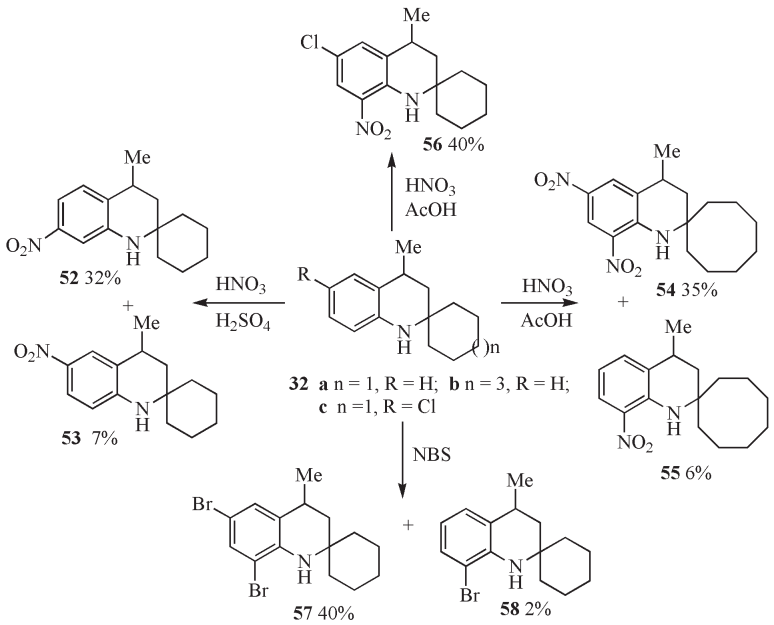
Dibenzo[*c*,*d*]-1,2-diazocine **50** was used in synthesis of spiro[cyclohexane-1',2(1*H*)quinolines]. Treatment of this exotic precursor with phenyl lithium followed by acidic workup furnished spiro compound **26** (see Scheme 10), which was converted into the 3,4-dihydrospiro[cyclohexane-1',2(1*H*)quinoline] **51** through several steps (catalytic hydrogenation of cyclohexadiene ring, hydrolysis of imino group and reduction of keto group) [85] (Scheme 21).

2.4. Some Chemical Transformations of Dihydrospiro-2(1*H*)quinolines.

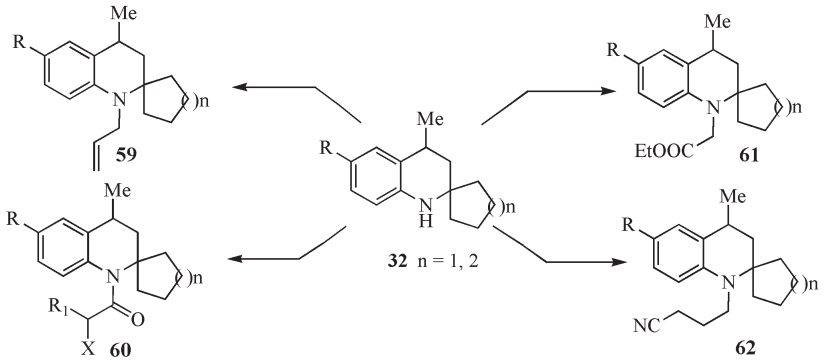
Over a period of years we were involved in the preparation of bioactive nitrogen-containing heterocycles from imines. As a result of these studies a new practical synthesis of the dihydrospiro[(1*H*)quinoline-2,1'-cycloalkanes] developed which allowed for the investigation of some chemical and biological properties of this spiro heterosystem. For instance, nitration of the spiro quinoline **32a** using a nitrating mixture (HNO_3/H_2SO_4) gave the respective mono 7- and 6-nitro derivatives **52** and **53** [68]. Treatment of the quinoline **32b** with a nitric acid and acetic acid mixture afforded the 4-methyl-6,8-dinitro-3,4-dihydrospiro[cyclooctane-1',2(1*H*)quinoline] **54** as a major product. A small amount of the 8-mononitro derivative **55** was also separated in this reaction. In the case of the 6-chloro derivative **32c** only a unique regio-isomer **56** was formed [69]. Bromination of the spiro quinoline **32a** with NBS in the presence of acetic or sulfuric acids in dichloromethane at reflux gave 6,8-dibromo spiro compound **57** as a major product [66] (Scheme 22). Thus, described electrophilic reactions are not specific of dihydrospiroquinolines **32**, which behave chemically as a 1,2,3,4-tetrahydroquinoline.

The most interesting chemical properties of these 3,4-dihydro-4-methylspiro[cycloalkane-1',2(1*H*)quinolines] **32** are related to the elegant rearrangements that their *N*-alkyl- or *N*-acyl spiroquinoline derivatives undergo. Alkylation or acylation reactions of the quinolines **32** proceeded smoothly to give the derivatives **59-62** (Scheme 23).

Scheme 22



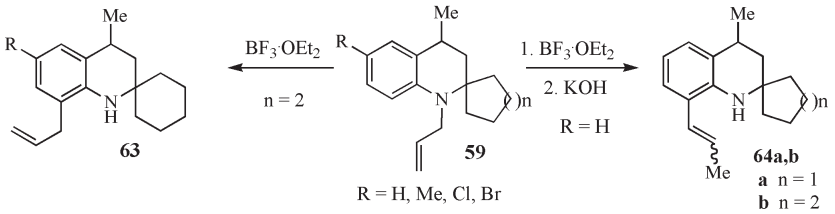
Scheme 23



The acidic rearrangements of these derivatives provided ready access to polycyclic alkaloid-type systems with interesting biological properties. For instance, the amino Claisen transposition [86] of the *N*-allylated spiranes **59** in the presence of $BF_3 \cdot OEt_2$ formed the 8-allyl substituted dihydrospiroquinolines **63** in good yields. The same *N*-allylated spiranes can give 8-propenyl substituted dihydrospiroquinolines **64** in the presence of $BF_3 \cdot OEt_2$, when a reaction mixture is treated by KOH (Scheme 24). Both obtained spiranes are useful building blocks for various alkaloids [87,88]. The obtained compounds **64a,b** represent a mixture of *Z*- and *E*-isomers in the ratio 1.0:4.5 and 1.0:4.3, respectively.

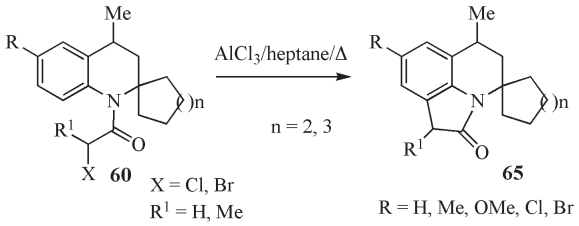
An unusual conversion of the *N*-carbethoxymethyl dihydrospiroquinolines **61** under acidic conditions (PPA at 140-150 °C) gave new 7,9-disubstituted spiro julolidines **66**. The transformation of **50** into **55** apparently proceeds by an unanticipated rearrangement. It was suggested that the resulting protonated species produces ethanol, which immediately reacts with excess PPA with ethylene and iminium cation formation *via* decarboxylation. Subsequent electrophilic addition of iminium ion to incipient ethylene gives rise to the phosphoric ester with nonprotonated nitrogen atom. This last intermediate would accommomodate the *ortho* intramolecular electrophilic aromatic substitution to form a saturated julolidine ring as depicted in

Scheme 24



Classical intramolecular Friedel-Crafts acylation reaction of the *N*-α-halogenacyl spiro quinolines **60** in the presence of $AlCl_3$ afforded the unnatural spiro analogs of lilolidine alkaloids - lactams **65** [89,90] (Scheme 25). The pyrrolo[3,2,1-*ij*]quinolines possess a large spectrum of physiological properties [91-93].

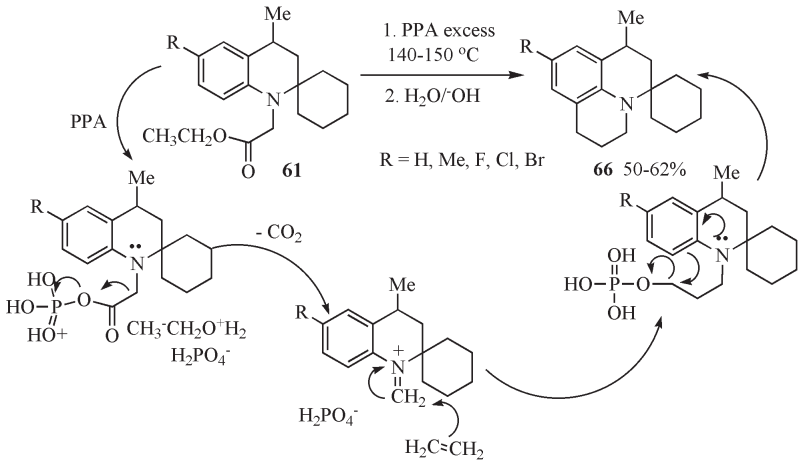
Scheme 25



Scheme 26. This simple route provides a novel, very attractive approach to unknown spiro julolidines [94].

Rearrangement of the *N*-acylated 3,4-dihydroquinolines **60** in the presence of H_2SO_4, H_3PO_4 or PPA offered a facile and new route to amido substituted 3-methylspiro-[indane-1,1'-cycloalcanes] **67** (Scheme 27) [88,95]. The latter compounds were converted into the spiroanalogs **68** of marine alkaloids isolated from various marine sponges (*Axinell sp*., *Trikentrion flabelliforme* and *Ectyonanchora flabellata*) and named trikentrins and herbindoles, which exhibit a growth inhibitory against gram positive bacteria and show cytotoxic activity [96-98]. Thermal treatment of the polyheterocycles **65** in the presence of $AlCl_3$ in heptane at 90 °C gave the spiro-hydrocylcopent[*g*]indolinones **69** in good yields [94] (Scheme 27). The rearrangement of

Scheme 26

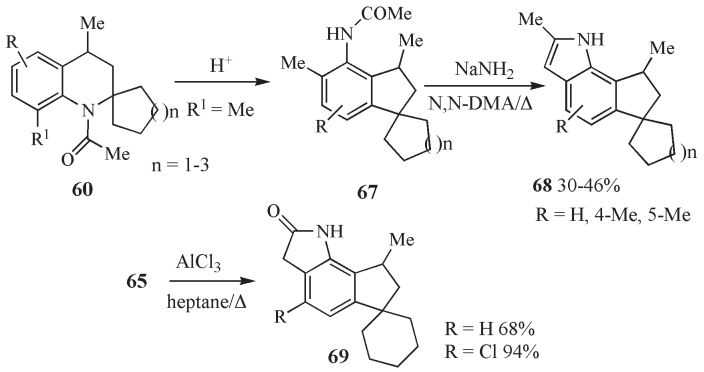


60 and **65** into respective compounds **67** and **69** involves cleavage of the C_{spiro}-N bond and formation of a cation stabilized by the spiro group that was demonstrated by prof. Meth-Cohn [99].

lized by the spiro group and a simultaneous formation of pyrrolidine ring [100] (Scheme 28).

Acetylation of the mixture **49a,b** (see Scheme 20) gave the more thermodynamically stable N-derivative **72** that

Scheme 27

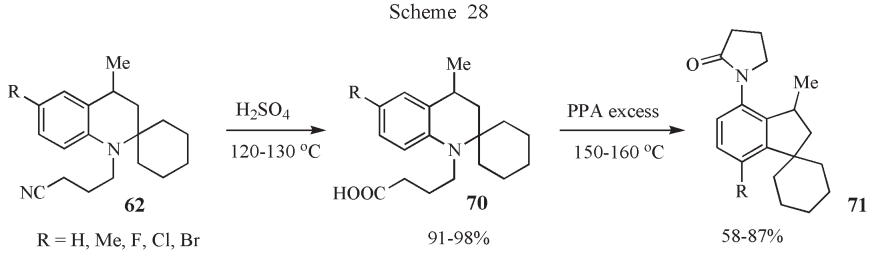


Finally, interesting transformation of spiro quinolinyl γ-aminoacids **70**, obtained from the *N*-(γ-cyanopropyl) spiro quinolines **62**, in PPA at 150-160 °C can be a suitable route towards the synthesis of 3-methyl-4-(2-oxo-pyrrolidinyl)spiro[indane-1,1´-cyclohexanes] **71**. The rearrangement of **70** into respective compounds **71** involves a cleavage of C_{spiro}-N bond and the formation of a cation stabi-

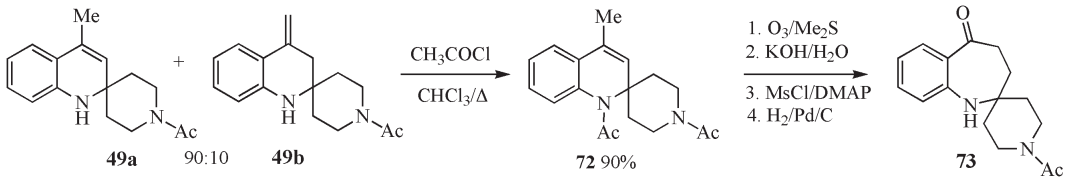
was transformed in several steps, in which an ozonolysis and aldol reactions were principal reactions for the transformation into the spiro[benzazepine-2,4'-piperidine] derivative **73**, a very perspective bio-target [101] (Scheme 29).

The above discussed acidic rearrangements of the *N*-alkyl- or *N*-acyl spiroquinoline derivatives are sometimes specific reactions of dihydrospiro-2(1*H*)-quinolines.

Scheme 28



Scheme 29



3. Spiro-3-quinolines.

Synthesis and chemical properties of spiro-3-quinoline derivatives are scantily known. There are very few works that describe their chemistry in the scientific literature.

3.1. Synthetic Efforts to Obtain Spiro-3-quinolines from Quinolines as Cyclic Precursors.

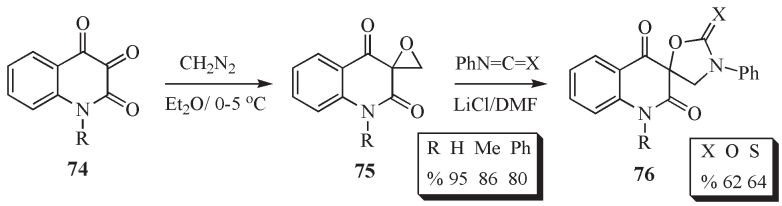
Reaction between *N*-substituted 2,3,4-trioxoquinolines **74** and diazomethane resulted in the formation of spiro[quinoline-3,2'-oxiranes] **75**, which were reacted with phenyl(thio)isocyanates yielding 2,4-dioxospiro[quinoline-3,5'-oxazole] derivatives **76** [102-104] (Scheme 30).

3.2. Synthetic Efforts to Obtain Spiro-3-quinolines from Amine or Imine (enaimine) Precursors.

Intramolecular cyclization of imines **79**, derived from corresponding amines and diverse aldehydes or ketones, was conducted to form quinolines **80**, which are spiro annulated at C-3 with a pyrazoline ring, in good yields [106] (Scheme 32).

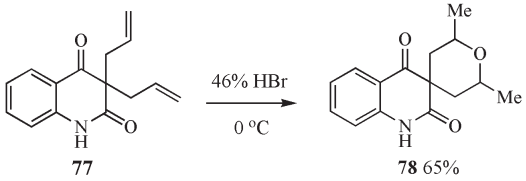
Reductive cyclization of compounds **81** represents the older example of the preparation of spiro heterocycles [107,108]. The bis-spiro-3,3'-quinolones **82** were obtained by Radulescu in 1911 [107] (Scheme 33).

Scheme 30



An acidic cyclization of diallylated quinolindione **77** in the presence of 46% HBr gave the 2,4-dioxodihydroquinoline **78** spiro annulated with a tetrahydropyran ring in 65% yield (Scheme 31) [105].

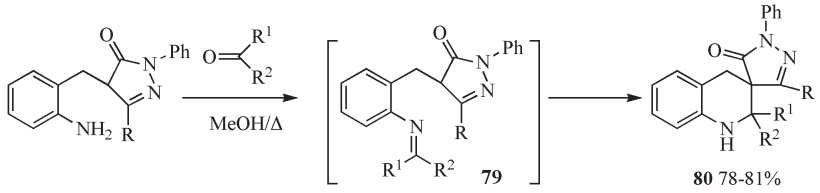
Scheme 31



Condensation of cyclic enamines **83** derived from dimedone in the presence of formaldehyde and a mineral acid at room temperature afforded the spiro-3-octahydroquinoline derivatives **84** [109] (Scheme 34).

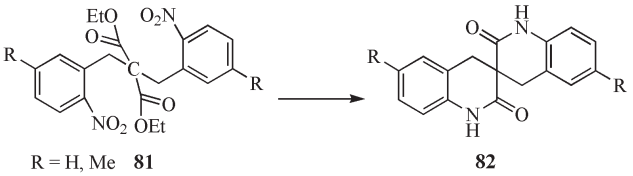
Recently, the interesting aza-Diels-Alder reaction of methylenecyclopropanes with various *N*-benzylidenanilines in the presence of $Sc(OTf)_3$ to give the spiro-[cyclopropane-1',3(4*H*)quinoline] derivatives **85** in excellent yields was described by Shi and co-workers [110] (Scheme 35). An interesting finding in this work is that in this reaction, the cyclopropyl ring of methylenecyclopropanes remains unopened in the presence of Lewis acids.

Scheme 32



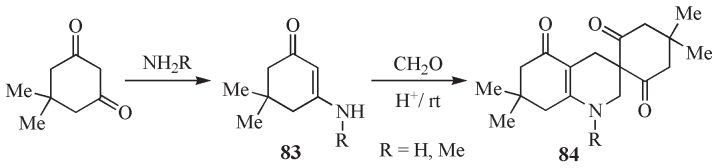
R = Me, Ph; R^1 = H, Me; R^2 = Me, Et, Ph

Scheme 33

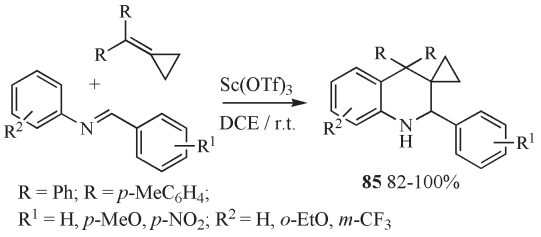


Highly enantioselective synthesis of spiro-3-quinolines **87-89** bearing an exomethylene carbomethoxy moiety was reported by Mikami and co-workers [111]. Enyne substrate **86a**, which have a five membered cyclic olefin, gave the chiral spiro ring product **87a** (62 % yield and 71 % ee) and product **88a** (38 % yield) of achiral olefin migration. The six

Scheme 34



Scheme 35

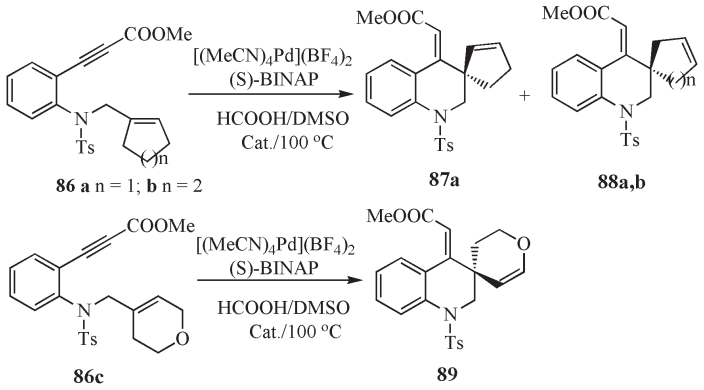


R = Ph; R = *p*-MeC$_6$H$_4$;
R^1 = H, *p*-MeO, *p*-NO$_2$; R^2 = H, *o*-EtO, *m*-CF$_3$

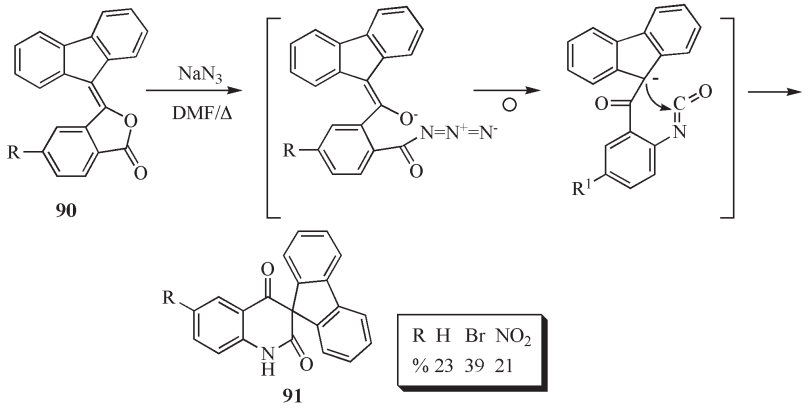
membered ring analogue **86b** gave completely olefin migrated spiro quinoline **88b** (96 % yield and 44 % ee). Cyclization of enyne **86c** with a pyran as a cyclic olefin proceeded successfully to give spirane **89**, achieving the spiro ring formation in quantitative yield and 98% ee (Scheme 36).

The cyclization of these enynes was performed by a combination of 5 mol % of a cationic Pd (II) catalyst such as [(MeCN)$_4$Pd](BF$_4$)$_2$, 10 mol % of (*S*)-BINAP as a chiral bidentate PP-ligand, and 1 equiv of formic acid, in DMSO.

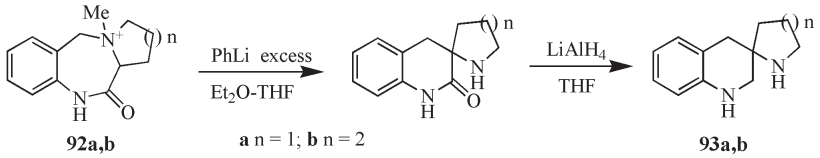
Scheme 36



Scheme 37



Scheme 38



3.3 Synthetic Efforts to Obtain Dihydrospiro-3-quinolines from Other Systems.

It was reported that the reaction between fluorenyliden phthalides **90** and sodium azide in DMF gave the spiro compounds **91** in poor yields [112] (Scheme 37).

Treatment of quaternary salts of benzodiazepine derivatives **92a,b** with an excess of phenyl lithium followed by conventional reduction with $LiAlH_4$ afforded the corresponding 2'-oxodihydrospiro[pyrrolidine-2,3'(4'*H*)quinoline] **93a** and 2'-oxo-dihydrospiro[piperidine-2,3'(4'*H*)-quinoline] **93b**, which were patented as valuable semi products in medicinal chemistry [113,114] (Scheme 38).

4. Spiro-4(1*H*)quinolines.

The spiro-4-quinoline ring system is found at the core of a number of alkaloids, which possess significant biological activity and are interesting targets for chemical synthesis. For instance, discorhabdins [115] and prianosins [116], an interesting class alkaloids, have been isolated as the major cytoxic pigments from marine sponges such as New Zealand sponges of the genus *Latrunculia*, Okinawan sponge *Prianos melanos*, Fijian sponge *Zyzzya cf. Marsailis* and from deep-water Caribbean sponges of genus *Batrella* [117,118]. Their unique structural features involve a hitherto pyrroloquinoline ring with spiro-C-4-annulated cyclohexenone and an additional sulfur bridge. Both of these groups are distinguished by their strong cytotoxic and antimicrobial activity. Discorhabdin D (priasonin D) exhibits significant *in vivo* antitumor activity against cells P388 and L1210 leukaemia. Moreover, four novel pyrroloiminoquinone alkaloids that are different members of the discorhbadin/prianosin family, epinardins A-D have been isolated recently from undetermined deep-water green demosponges collected in pre-Antarctic waters [119] (Figure 3). Epinardin C proved strongly cytotoxic toward doxorubicin-resistant L1210/Dx tumoral cells *in vitro*.

Since these marine alkaloids possess unusual heterocyclic ring structures and have potent cytotoxic activity, much attention has been paid for its total synthesis after its isolation. All known synthetic attempts to build this heterocyclic core start from amine precursors where the spiro annulation process into the spiro[cyclohexadiene-

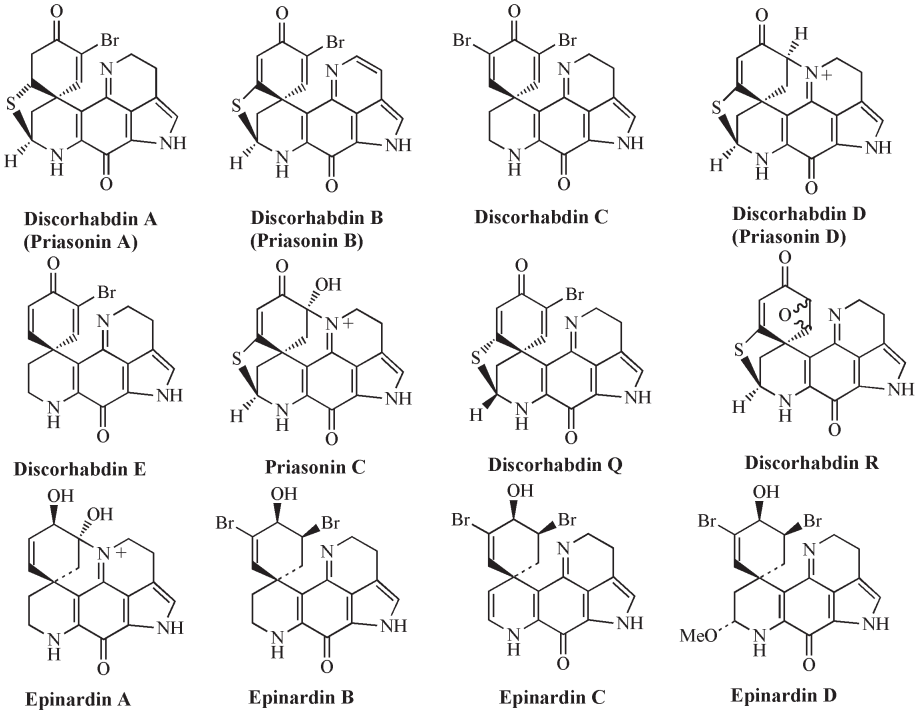


Figure 3

4',4(1*H*)quinoline] fragment plays a pivotal role.

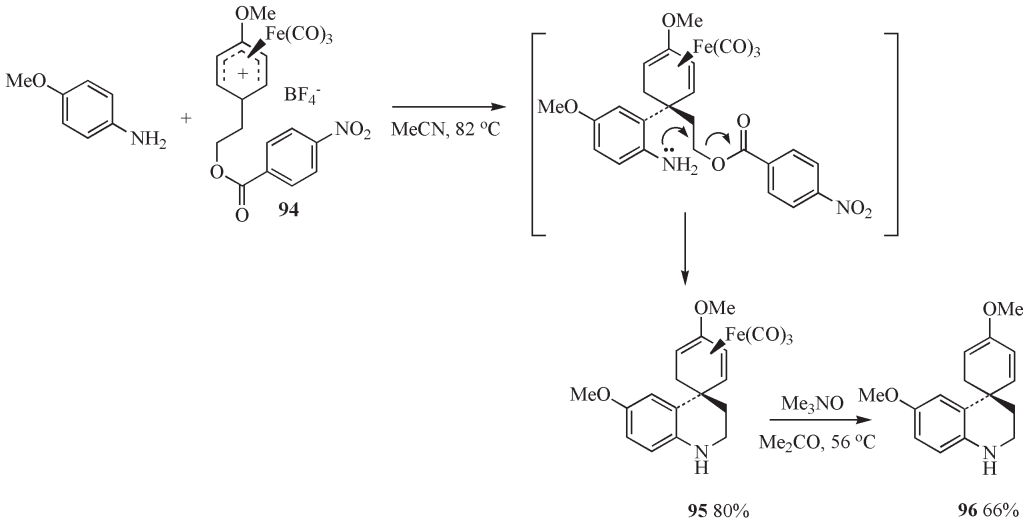
4.1. Synthetic Efforts to Obtain Dihydrospiro-4(1*H*)quinolines from Amine or Imine Precursors: Total Syntheses of Discorhabdin A, Discorhabdin C and Discorhabdin E.

Reaction of *p*-anisidine and complex salt **94** (obtained from *p*-methoxyphenylacetic acid in four step procedure [120]) in acetonitrile at reflux led regio- diastereoselectively in 80% yield to the 2,3-dihydrodimethoxy spiro-4(1*H*)quinoline **95** involving a sequence of electrophilic substitution of *p*-anisidine and *in situ* nucleophilic substitution of the leaving group in the side chain. Spiro-

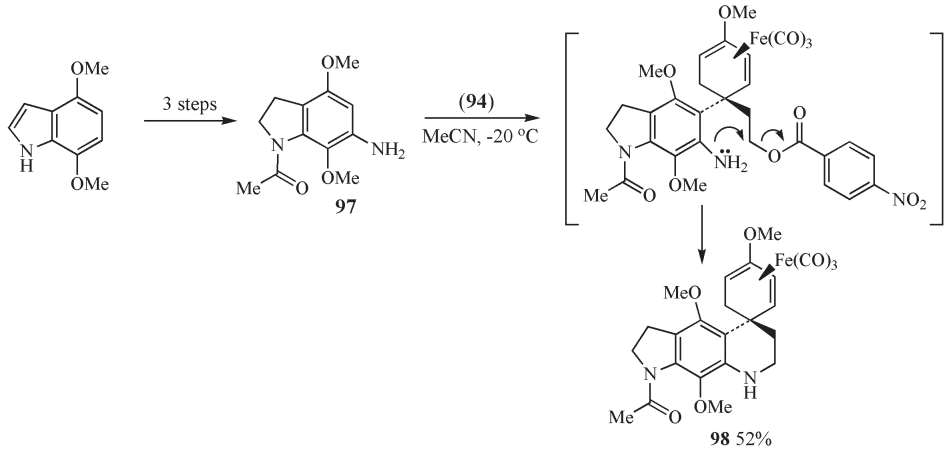
The methodology of using tricarbonyl-iron-complexed cyclohexadienyllium cations (like as **94**) as electrophiles in the substitution of arylamines *via* spiro annulation [123] allowed to build the ABCD ring system of these alkaloids in a straight-forward way. Reaction between 6-acetyl-4,7-dimethoxyindole **97** (obtained from 6-amino-4,7-dimethoxyindole in three steps [124]) and the salt **94** gave the spiropyrroloquinoline iron-complex **98** [125] (Scheme 40).

Prof. Kita and co-workers reported a very efficient intramolecular cyclization of *p*-substituted phenolic aminoquinones **99a,b** using PIFA that led to the spiro-4(1*H*)quino-

Scheme 39



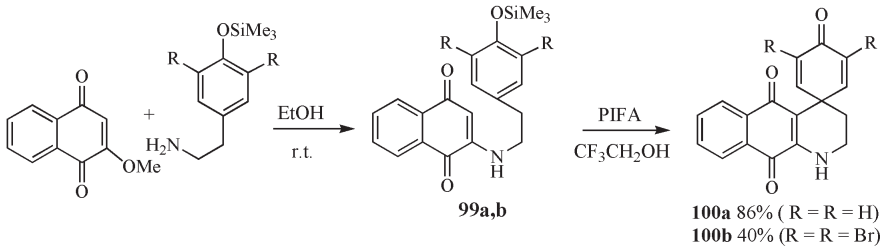
Scheme 40



4(1*H*)quinoline **95** was converted into the free ligand **96** through the demetalation with trimethylamine *N*-oxide as outlined in Scheme 39 [121,122].

line derivative **100a,b** as shown in Scheme 41. Hyper iodine oxidation of *O*-silylated phenols bearing various types of aminoquinones at the *para*-position in 2,2,2-trifluoroethanol

Scheme 41

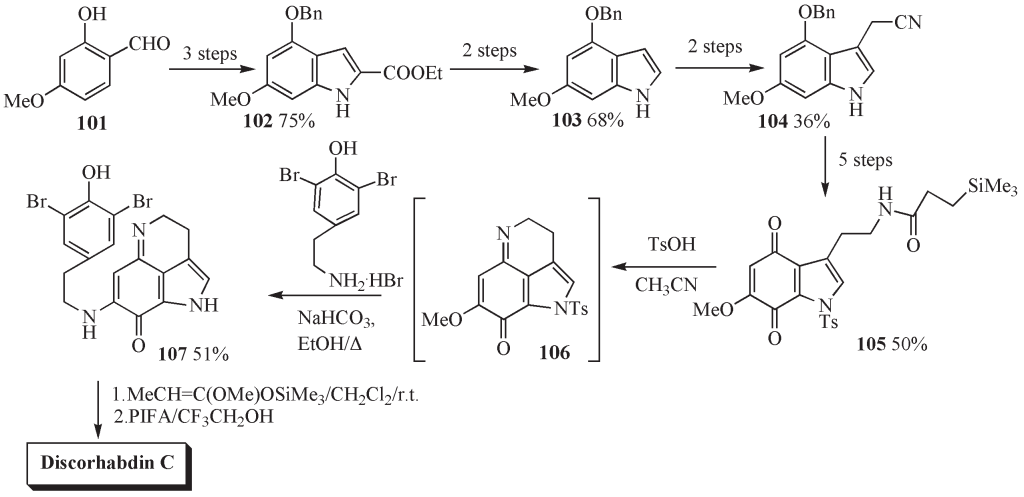


gave azacarbocyclic spiro dienones in good yields [126-128].

This elegant spiro cyclization is a key to the first total synthesis of Discorhabdin C from commercially available 2-hydroxy-4-methoxybenzaldehyde **101** [129]. Enormous synthetic efforts were made to afford desired indoloquinone imine **106**, which was treated with 3,5-dibromotyramine hydrobromide in ethanol to give the phenolic aminoindoloquinone imine **107**. The conversion of compound **107** into its corresponding silyl ether and a subsequent oxidative coupling reaction using PIFA gave rise to discorhabdin C (Scheme 42).

Recently, the first stereoselective total synthesis of discorhabdin A, which contains a labile and highly strained *N,S*-acetal (sulfur-cross-linked) core, was achieved using effectively in the presence of MK10 to give **111** as a mixture of two diastereomers in 45% yield. This diastereomeric mixture was desilylated, and converted into the diastereomeric methoxy derivative **112**. Among various sulfur nucleophiles, *p*-methoxybenzylthiol was selected to give unstable **113** as a diastereomeric mixture. This product was treated with 30% HBr-AcOH followed by workup with $NaHCO_3$ to give 11% yield of *N*-tosylated discorhabdin A **114**. However, the authors have found an efficient one-pot transformation procedure yielding **114** in 22% from **112**. The procedure used *p*-methoxybenzylthiol in 30% HBr-AcOH followed by treatment with aqueous $MeNH_2$ and gave mainly **114** as well the undesired debrominated compounds. Removal of the Ts group

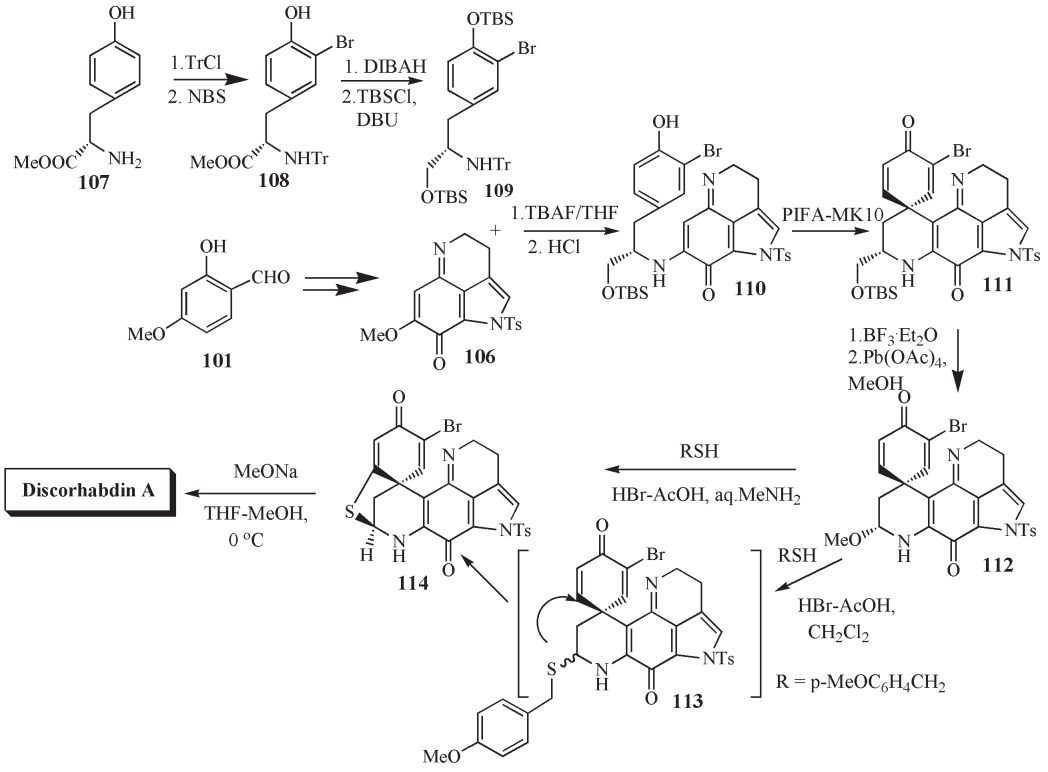
Scheme 42



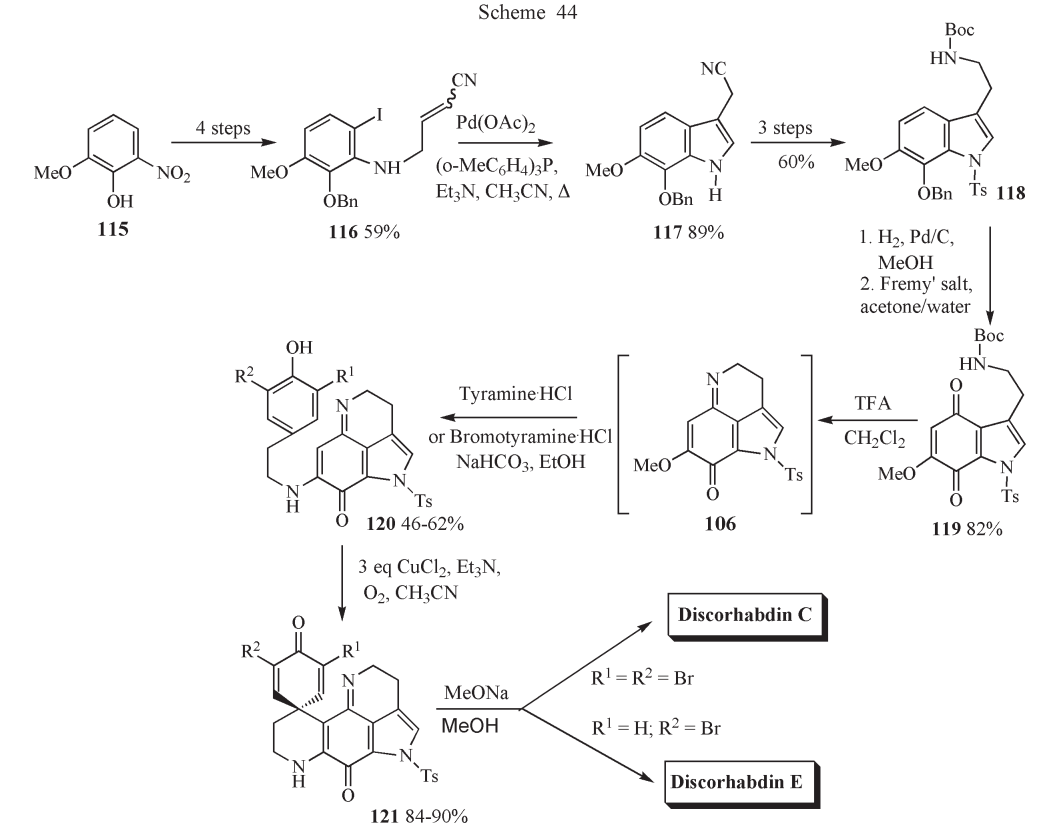
this methodology [130,131]. This synthesis starts with tritylation of commercially available (L)-tyrosine methyl ester **107**, followed by monobromination with NBS to yield **108**, which was converted into bissilylated derivative **109**. Selective desilylation of this derivate with TBAF in THF, followed by a coupling reaction with 1-tosylated pyrroloiminoquinone derivative **106** yielded **110**. Spirodienone formation using PIFA proceeded of **114** with sodium methoxide provided discorhabdin A in 65% yield (Scheme 43).

The crucial phenolic oxidation of the appropriate phenol can be achieved by electrochemical methodology. By the use of anodic oxidation of the appropriate phenol at a constant current in MeCN in the presence of $LiClO_4$, the target discorhabdin C was obtained in 24% yield together with the ring-expanded product in 6.2 % yield [132,133].

Scheme 43



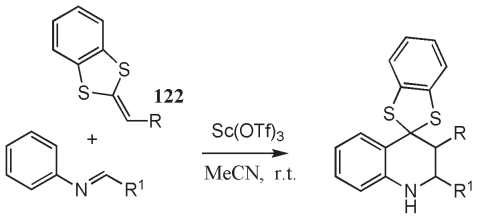
Scheme 44



The total syntheses of discorhabdins C and E were realized by prof. Heathcock and co-workers [134]. 2-Nitroguaicol **115** was chosen as a starting material to obtain 7-methoxyindole derivate **117** that was converted into a key precursor **106** in several steps (Scheme 44). The derivatives **120** were subjected to mild oxidation (3 eq $CuCl_2$, Et_3N, O_2, CH_3CN) and deprotection of N-tosyl group (MeONa, MeOH) (compounds **121**) to complete the discorhabdin core using a biomimetic approach [135].

In these discussed syntheses the spiro annulation process of the precursors **107**, **110** and **120** into the spiro[cyclohexadiene-4',4(1*H*)quinoline] fragment plays a pivotal role.

Scheme 45



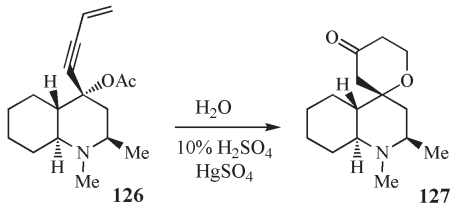
Beaton and co-workers successfully demonstrated that the aza-Diels-Alder reaction between *N*-benzylidenanilines and 1,4-benzodithiafulvenes **122** allows to construct efficiently the spiro-4-tetrahydroquinoline core derivatives **123** [136] (Scheme 45). Subsequent chemical manipulations of these spiro compounds provide a concise and divergent approach to the synthesis of 2,3-tetrahydroquinolines, 2,3-dihydro-4-quinolones, and 4-quinolones.

4.2. Synthetic Efforts to Obtain Dihydrospiro-4(1*H*)quinolines from Quinolines as Cyclic Precursors.

It was established that *trans*-1-alkyl-2,2-dimethyl-4-hydroxy-4-oxiranyldecahydroquinolines **124** in the presence of sodium hydroxide or barium hydroxide, and thiourea undergo an isomerization through a migration of the epoxy ring to give the corresponding spiro[oxirane-2',4-quinoline] derivatives **125** [137,138] (Scheme 46).

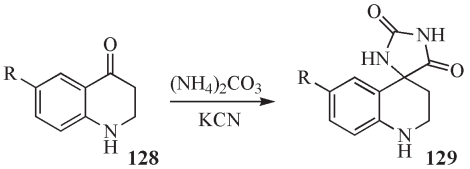
Treatment of substituted decahydroquinoline **126** with diluted sulfuric acid in the presence of $HgSO_4$ afforded 1,2e-dimethyl-*trans*-decahydroquinoline-4-spiro-2-tetrahydropyran-4-one **127** that showed considerable antiarrythmic activity [139] (Scheme 47).

Scheme 47



Dihydro spiro-4(1*H*)quinolines **129** annulated with an imidozoline ring were patented as aldose reductase inhibitors. These derivatives were obtained through a condensation between 6-substituted 4-(1*H*)quinolones **128** and $(NH_4)_2CO_3$/KCN [140,141] (Scheme 48).

Scheme 48

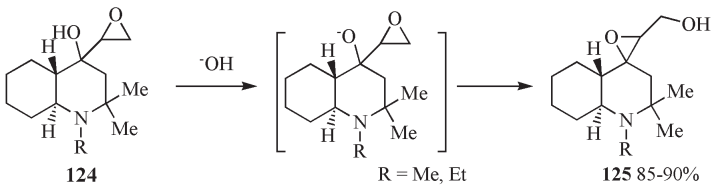


4.3. Synthetic Efforts to Obtain Dihydrospiro-4(1*H*)quinolines from Other Systems.

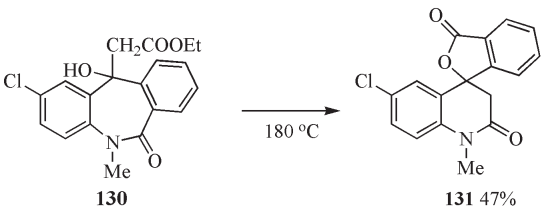
Studying chemical transformation of morphanthridines, Coppola and co-workers demonstrated that heating of morphanthridine derivatives **130** led to the rearranged product **131** with a spiro structure [142] (Scheme 49).

The first two-step synthesis of dihydrospiro[cyclohexane-1',4(1*H*)quinolines] was described by Schwartzmann in 1950. Substituted spiro-3-indan-2-ones **132** were subjected to a Schmidt rearrangement to give spiranes **133**, which were reduced to **134** in a common way [143,144] (Scheme 50). Obtained spiro-4-quinolines **134** and their 2-oxo analogs **133** possess strong analgesic activity [145].

Scheme 46

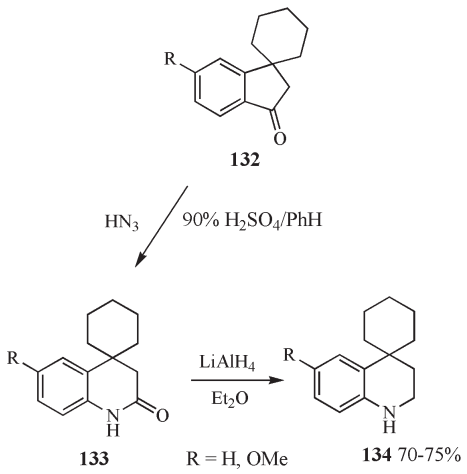


Scheme 49



130 **131** 47%

Scheme 50



132 **133** R = H, OMe **134** 70-75%

5. Conclusions.

In conclusion, spiro quinolines constitute an interesting class of heterocycles. The spiro quinoline ring system is found at the core of a number of alkaloids, which possess significant activity being interesting targets for chemical synthesis and their structure occur in some alkaloids. Without doubts, these compounds will be useful for many sectors of the chemistry industry. Because spiro-2(1*H*) and -4(1*H*)quinolines display important physiological properties, their syntheses are quite developed. In contrast to this, spiro-3(4*H*)quinoline preparations remain still underdeveloped. Syntheses of these quinolines require special methods for the spiro structure.

6. Abbreviations.

Δ	heating to reflux
hν	ultraviolet irradiation
Ac	acetyl
BINAP	2,2'-bis(dipehylphosphino)-1,1'-binaphthyl
Boc	*tert*-butoxycarbonyl
Bn	benzyl
Bu	butyl
DCE	1,2-dichloroethane
DMAD	dimethyl acetylenedicarboxylate
DMF	dimethylformamide
DME	dimethoxyethane
DMSO	dimethylsulfoxide
ee	enantiomeric excess
Et	ethyl
HMPA	hexamethylphosphoric triamide
LDA	lithium diisopropylamide
MeO	methoxy
Me	methyl
MK-10	montmorillonite K-10
NBS	N-bromosuccinimide
N,N-DMA	N,N-dimethylaniline
Ph	phenyl
PIFA	phenyliodine (III) bis(triflouroacetate)
PPA	polyphosphoric acid
TBS	*tert*-butyldimethylsilyl
THF	tetrahydrofuran
Ts	tosyl (*p*-toluenesulfonyl)
Tr	trityl (triphenylmethyl)

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