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CONSTRUCTION OF PYRROLO[3,2-*c*]QUINOLINES – RECENT ADVANCES IN THE SYNTHESIS OF THE MARTINELLINE ALKALOIDS

Miklós Nyerges

Research Group of the Hungarian Academy of Sciences, Department of Organic Chemical Technology Technical University of Budapest, H-1521 Budapest P.O.B. 91. Hungary; email: mnyerges@mail.bme.hu

Abstract – The synthesis of pyrrolo[3,2-*c*]quinolines is comprehesively reviewed. Synthetic approaches to martinelline alkaloids are then considered which are based upon the endeavors in this area by three independent groups.

1. INTRODUCTION

Preparations from the root bark of *Martinella* species have been used by Amazonian Indian tribes for the treatment of a variety of eye ailments. Martinelline (**1**) and martinellic acid (**2**) (Figure 1) are two alkaloids that were isolated from an organic extract of *Martinella iquitosensis* roots by Merck Research Laboratories.[1] Both compounds contain a pyrrolo[3,2-*c*]quinoline ring system – which had not been previously described in natural products – with pendant isoprenyl-derived guanidine moieties. The biological tests revealed that these two alkaloids, especially martinelline has potent antagonist activity against some G-protein coupled receptors such as bradykinin B_1 and B_2, and α_1-adrenergic and muscarinic receptors. Interestingly these are the first examples of non-peptide natural products to be identified as bradykinin receptor anagonists.

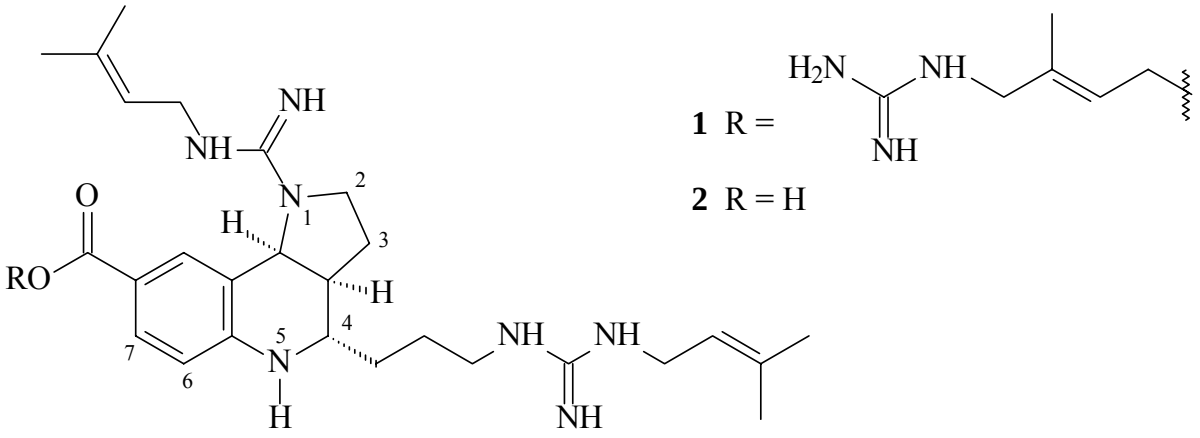
Syntheses of pyrrolo[3,2-*c*]quinolines were not particularly numerous in the literature before the initial report on these unique alkaloids: a few examples were described, with little variation in their synthetic strategies.[2] After the discovery of the interesting biological activity of martinellines, numerous research groups began work on a short, stereoselective synthesis of the pyrrolo[3,2-*c*]quinoline ring system.

Dedicated to Professor Károly Lempert on his 80th birthday.

The elaboration of the guanidine-containing side-chains at *N*-5, *C*-2 and the *C*-7 carboxylate was always envisaged as a late step in the synthesis of the martinellines. This strategy requires the synthesis of the corresponding reduced pyrroloquinoline system with the correct stereochemistry, containing a side chain at *C*-2 suitable for conversion to the natural product.

Beside the three syntheses of martinelllic acid (**2**) and the two of martinelline (**1**), several new methods for the synthesis of the pyrrolo[3,2-*c*]quinoline ring system have been reported, which can be classified into eight main categories according to their strategies. These will be treated in the present review and followed by a short summary of the total synthesis of martinellines.

Figure 1

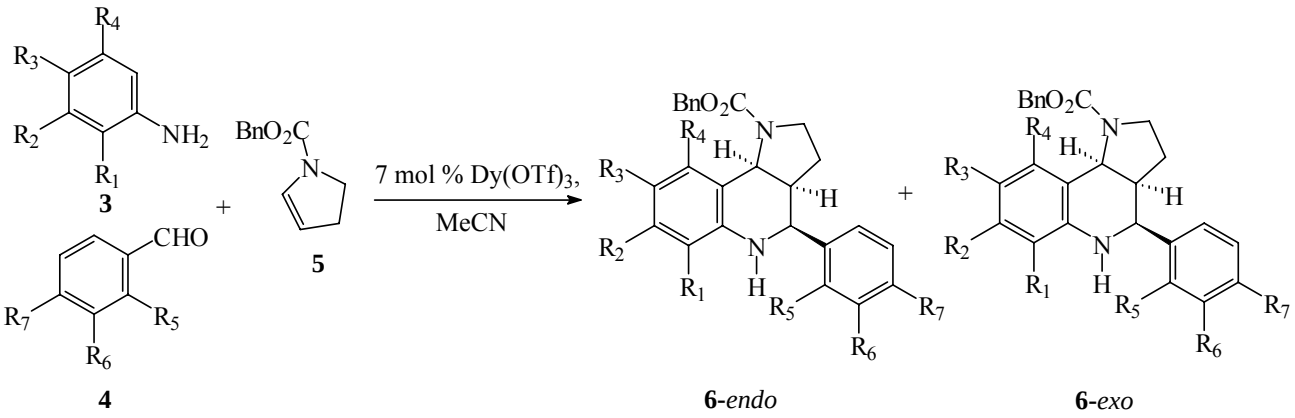


2. METHODS FOR THE SYNTHESIS OF THE PYRROLO[3,2-*c*]QUINOLINE MOIETY

2.1. Hetero Diels-Alder approach

Batey and co-workers reported a new one-pot synthesis of substituted hexahydropyrrolo[3,2-*c*]quinolines utilizing a Lewis acid promoted, three component coupling reaction of anilines (**3**), benzaldehydes (**4**) and an *N*-substituted 2-pyrroline (**5**).[3] The imine which is formed *in situ* can act as a diene, in a hetero-Diels-Alder reaction with the electron rich dienophile – the endocyclic enamines. The lanthanide triflates catalyze this addition, with $Dy(OTf)_3$ giving the best yields. The diastereoisomeric ratio was strongly solvent dependent, but the selective preparation of the required *exo*-adduct was not accomplished (Scheme 1, Table 1).

Scheme 1

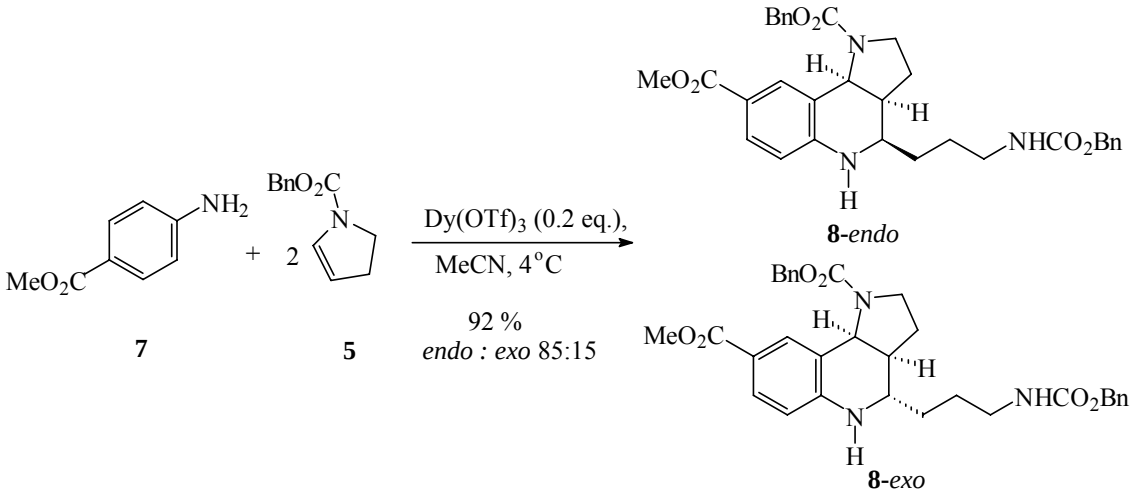


R_1	R_2	R_3	R_4	R_5	R_6	R_7	Yield (%)	*endo:exo*
H	H	H	H	H	H	H	91	51:49
H	H	H	H	H	Cl	Cl	93	57:43
H	H	H	H	H	H	MeO	84	50:50
H	H	H	H	Me	H	H	96	42:58
H	H	H	H	H	H	NO_2	96	53:47
H	H	CO_2Me	H	H	H	H	61	50:50
Cl	H	Cl	Cl	H	Cl	Cl	47	40:60
H	NO_2	H	H	H	Cl	Cl	65	55:45
-N=CHCH=N-		H	H	H	Cl	Cl	78	63:37

Table 1

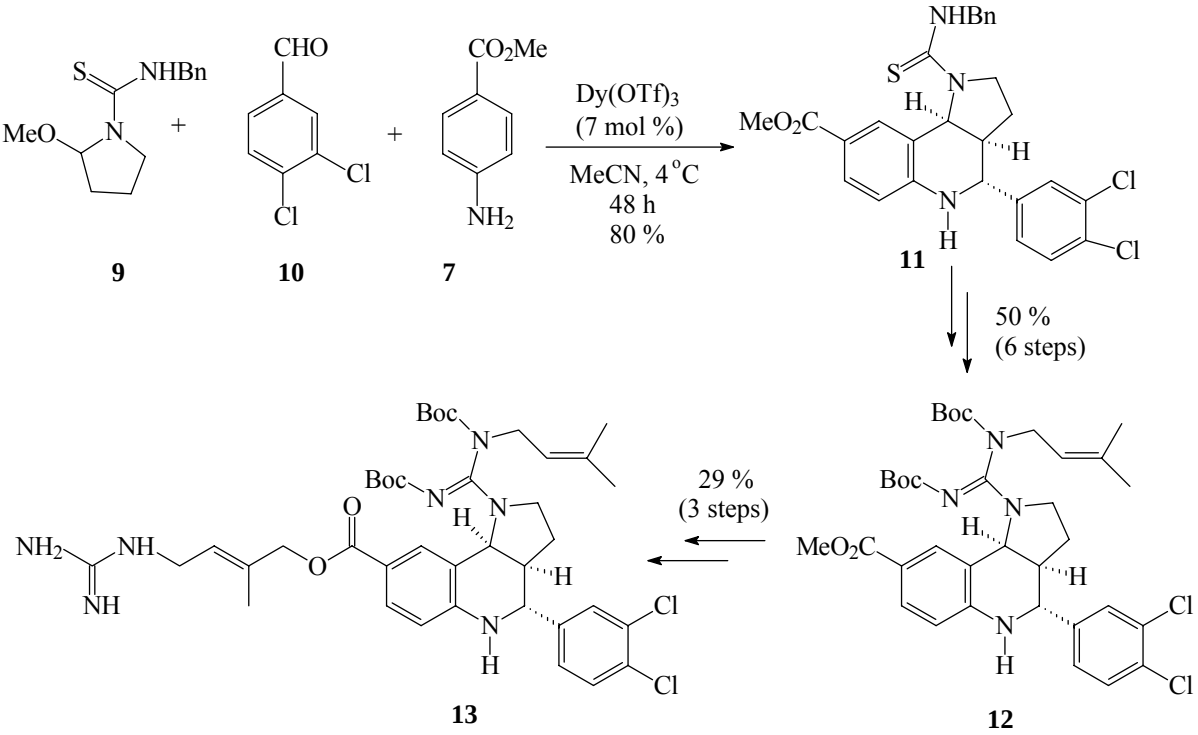
Interestingly, in the absence of an aldehyde, anilines coupled with two equivalents of the pyrroline. The 2-pyrroline derivatives (**5**) serve a dual role in this multicomponent reaction – the aniline reacts with the hydrolysis product of the pyrroline, forming an imine, which may react with the remaining enamine acting as an electron-rich dienophile. The product has strong structural similarities to martinelline but the required *exo*-isomer (**8**-*exo*) was a minor component in a 5.6:1 mixture of diastereoisomers (Scheme 2).

Scheme 2



In an attempt to improve the diastereoselectivity, the modification of the *N*-substituent on the 2-pyrroline component was investigated.[4] Since the thioureas are useful guanidine precursors, an *N*-thiocarbamoyl group was considered as an alternative *N*-protecting group. Because the synthesis and isolation of the 2-pyrroline required harsh conditions, the use of cyclic hemiaminals as *in situ* equivalents of *N*-substituted 2-pyrrolines was suggested. The lantanide triflate catalyzed reaction afforded pyrrolo[3,2-*c*]quinolines (**11**-*exo*, **11**-*endo*) as a 7:3 mixture of diastereoisomers. The main isomer (**11**-*exo*) – in a model study - was transformed into a highly functionalized derivative of martinelline containing two of the three guanidine side-chains and an aryl group in place of the *C*-4 aliphatic guanidine side chain (Scheme 3). Comparsion of the binding affinities of **13** against human bradykinin B_1 and human and rat B_2 receptors with the known effect of martinelline (**1**) and martinellic acid (**2**) suggested that the guanidine containing *C*-8 ester side-chain is of greater importance for B_2 receptor antagonist activity than the *C*-4 aliphatic guanine side-chain.

Scheme 3

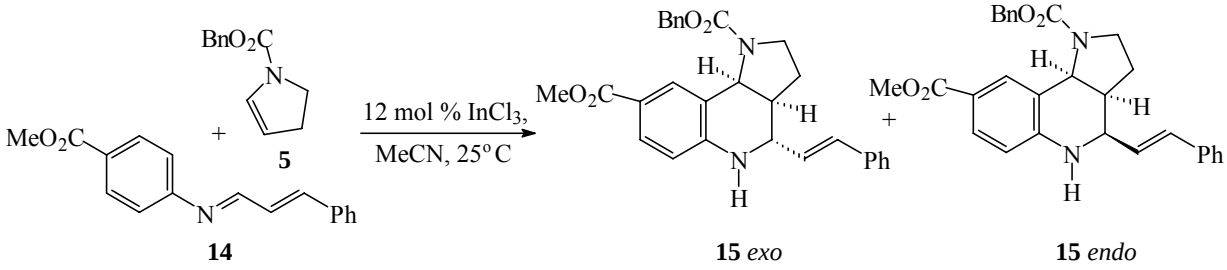


Stevenson`s group studied this three component coupling, and found the anhydrous indium trichloride to be the most effective Lewis acid catalyst. These workers aimed for a cycloadduct with an alkyl side-chain attached at *C*-2 preferably *exo*, and a group attached to nitrogen atom which was easily removable. The reaction was unsuccessful with imines derived from simple aliphatic aldehydes, while the imines derived

from methyl glyoxalate gave a low yield of mixtures of *endo* and *exo* isomers (2:1 ratio) making difficult to introduce the required 4-(3`-aminopropyl) substituent.[5,6]

The imine (**14**) derived from cinnamaldehyde with the enamide (**5**) gave the 1.1 : 1 mixture of *exo* and *endo* stereoisomers of **15**, from which the desired *exo* isomer (**15**-*exo*) was isolated in 40 % yield (Scheme 4).[7]

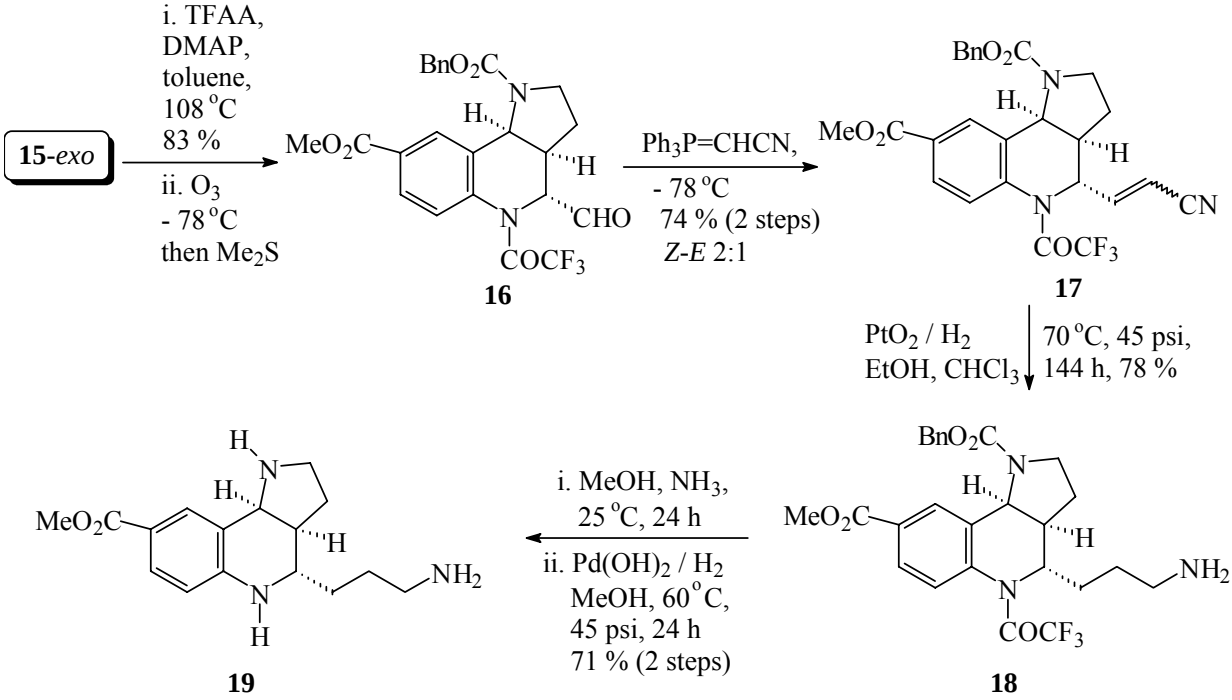
Scheme 4



After protecting the aromatic amino group in **15**-*exo,* ozonolysis gave an unstable aldehyde (**16**) which was intercepted by trapping with the nitrile-stabilised ylide prior to work up. This gave a 2:1 mixture of (*Z*)- and (*E*)-unsaturated nitriles (**17**). The introduction of the 4-(3`-aminopropyl) side-chain was completed by chemoselective reduction using Adam`s catalyst giving **18**. The sequential removal of the two nitrogen protecting groups gave **19**, which contains the central core of the martinelline alkaloids (Scheme 5).[7]

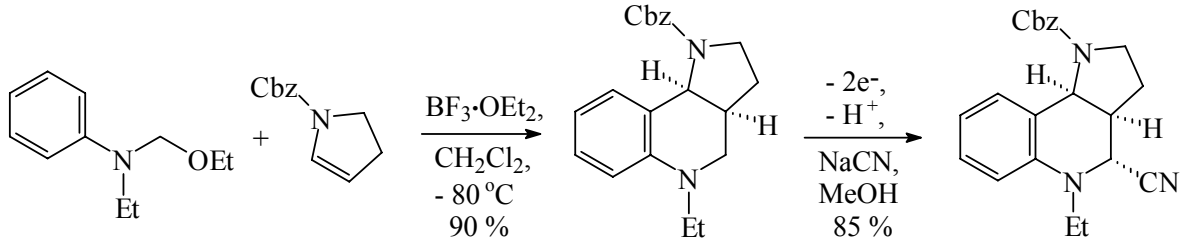
These workers also described the synthesis of parent *C*-4 unsubstituted hexahydropyrrolo[3,2-*c*]quinoline (**22**, R = H, R_1 = EtCO) from **20** and **21** in 43 % yield. Neither Lewis nor protic acids were required to effect this transformation.[6]

Scheme 5



Hurvois and co-workers reported a similar transformation using $BF_3{\cdot}OEt_2$ as the catalyst. The cycloadduct obtained (**22,** R = Et, R_1 = BnO_2C) was further functionalized at *C*-4 *via* a diastereoselective anodic cyanation (Scheme 6).[8]

Scheme 6.

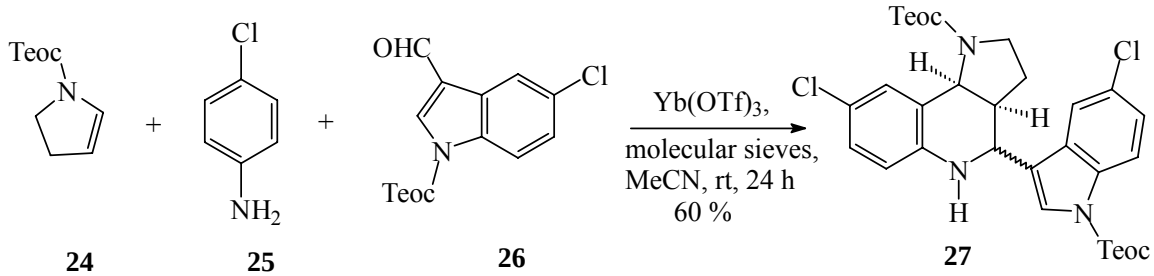


20 **21** **22** **23**

Potent antibacterial agents (*e.g.* **27**) effective against methicillin-resistant *Staphylococcus Aureus in vitro*, were prepared using hetero Diels-Alder chemistry starting from **24**, **25** and **26** in one step. The products – pyrrolo[3,2-*c*]quinolines coupled to an indole ring – were obtained as a 2:1 ratio of *cis*- to *trans*-isomers (Scheme 7).[9]

Using this imino-Diels-Alder strategy to assemble the pyrrolo[3,2-*c*]quinoline core, two independent total syntheses of martinelline were reported.[10,11]

Scheme 7.



24 **25** **26** **27**

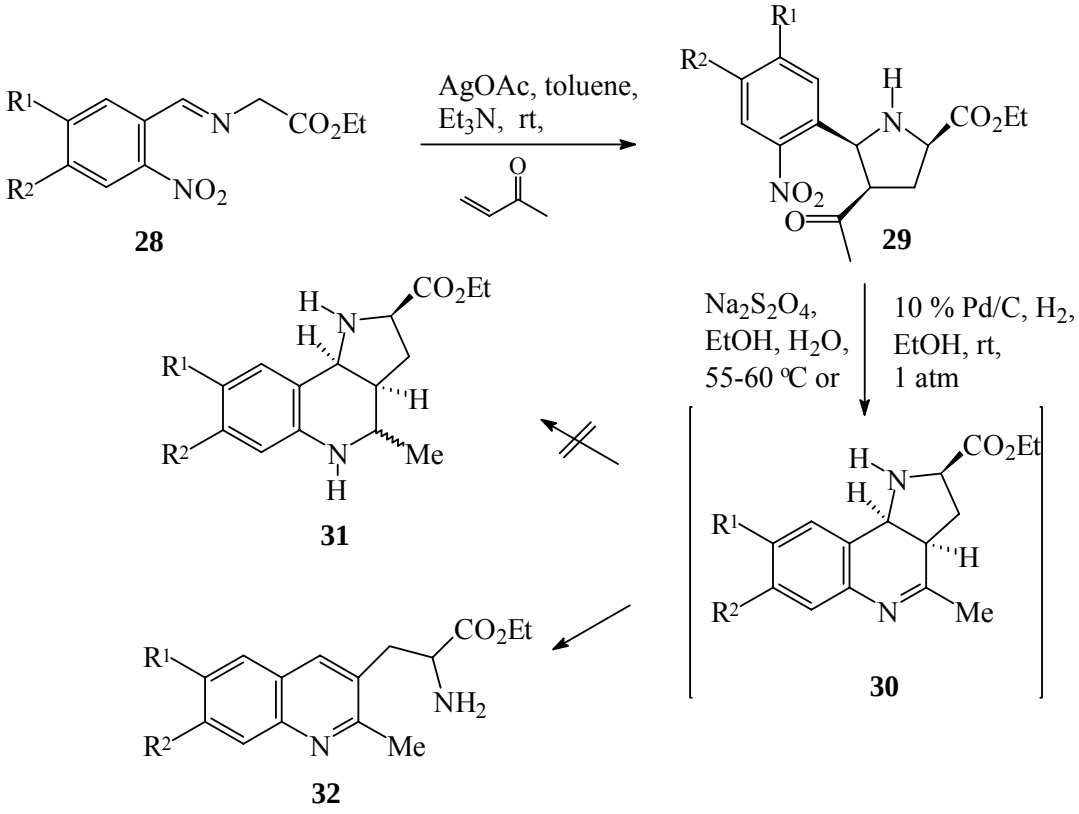
2.2. 1,3-Dipolar cycloadditions of azomethine ylides

2.2.1. Intermolecular cycloadditions of azomethine ylides

Hadden and Stevenson attempted the synthesis of hexahydropyrrolo[3,2-*c*]quinolines utilizing intermolecular cycloadditions of azomethine ylides to an olefin for the formation of suitably substituted pyrrolidine derivatives as a first step. They chose to prepare the azomethine ylides from the imine (**28**, R^1=R^2=H) derived from methyl glycinate and 2-nitrobenzaldehyde, by standard methods, using silver acetate at room temperature. The all-*cis* tri-substituted pyrrolidine (**29**) was formed in a regio- and

stereoselective manner, but the reduction with hydrogen and palladium gave none of the expected pyrrolo[3,2-*c*]quinoline (**31**), and instead gave an α-amino acid ester (**32**) (Scheme 8, Table 2).[12] This reaction was also observed in our laboratory starting from ethyl glycinate and various 2-nitrobenzaldehydes.[13] The proposed intermediate β-amino-imine (**30**) is presumably unstable, even under reducing conditions and aromatizes by loss of amine, giving the quinoline derivative (**32**).

Scheme 8

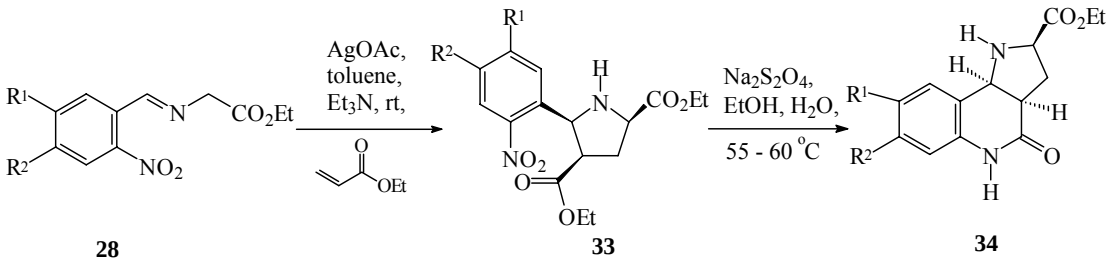


To avoid this interesting, but undesired reaction, we have generated the same azomethine ylides from **28** in the presence of ethyl acrylate as the dipolarophile. In accord with the above experiments, we obtained again the all-*cis* cycloadducts (**33**) stereoselectively. The reductions of these cycloadducts, with sodium hydrosulfite, gave the expected *cis*-fused pyrrolo[3,2-*c*]quinolines (**34**) in good yields (Scheme 9, Table 2).[14]

R^1	R^2	yield of **29** %	yield of **32** %	yield of **33** %	yield of **34** %
H	H	76	79	72	98
MeO	MeO	82	85	80	96
OCH_2O		70	81	71	92
Br	H	-	-	77	86

Table 2

Scheme 9

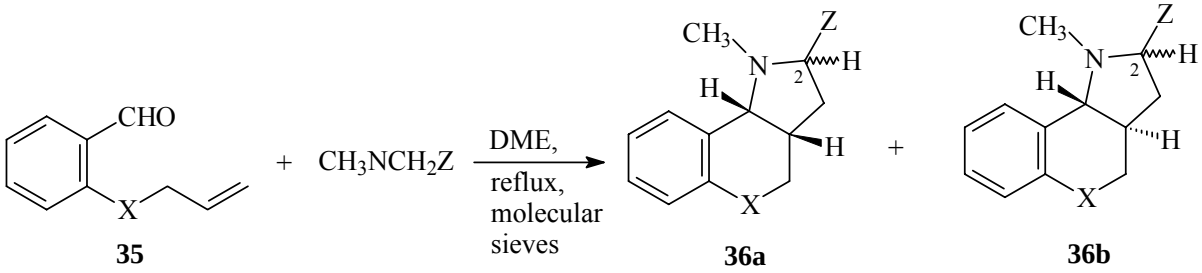


28 **33** **34**

2.2.2. Intramolecular cycloadditions of azomethine ylides

In 1999 two independent short communications[15,16] described the synthesis of the pyrrolo[3,2-*c*]quinoline tricyclic core by intramolecular 1,3-dipolar cycloadditions of non-stabilised azomethine ylides with the same general strategy applied by Martin and Cheavens[17] ten years earlier for the synthesis of various tricyclic compounds (**36**) (Scheme 10, Table 3).

Scheme 10



35 **36a** **36b**

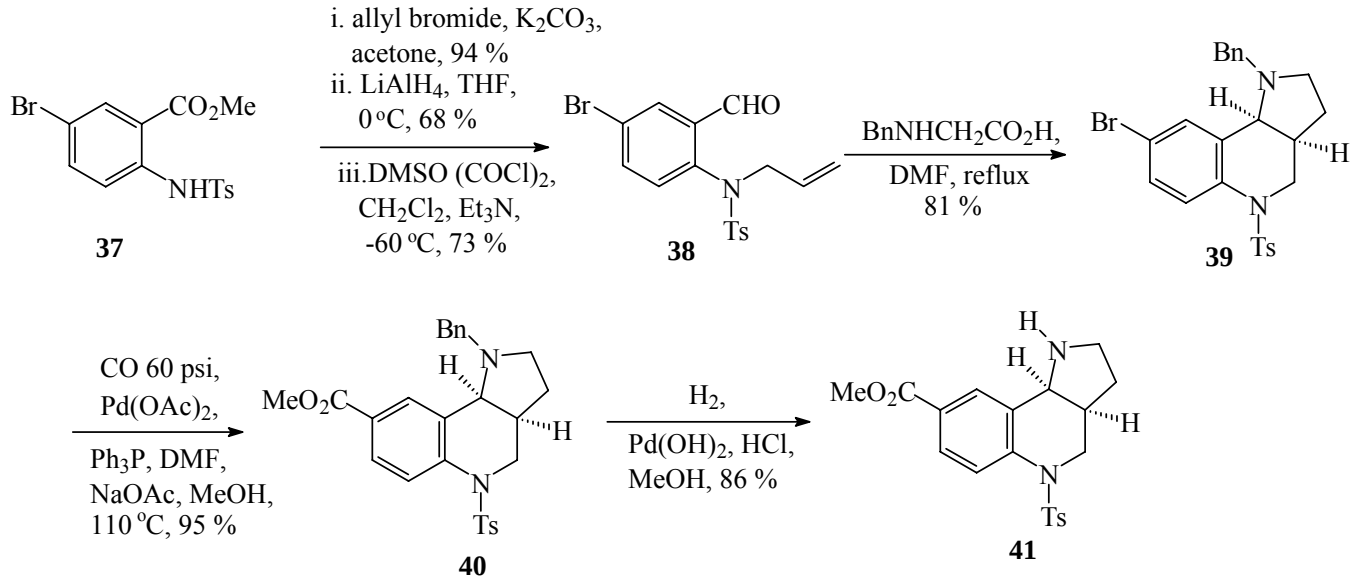
X = O, CH_2, NSO_2Me; Z = P(O)(OPr-*i*)$_2$, P(O)(OCH_2Bu-*t*)$_2$, CN

X	Z	**36a**	**36b**
O	P(O)(O-Pr-*i*)$_2$	67 % (H-2 = α) 8 % (H-2 = ß)	-
O	P(O)(OCH_2-Bu-*t*)$_2$	65 % (H-2 = α) 15 % (H-2 = ß)	-
O	CN	26 % (H-2 = α) 37 % (H-2 = ß)	1 % (H-2 = α) 6 % (H-2 = ß)
CH_2	P(O)(O-Pr-*i*)$_2$	50 % (α + ß)	-
NSO_2Me	CN	55 % (α + ß)	-

Table 3

Lovely and Mahmud evaluated an approach starting from anthranilic acid derivatives (**37**).[15] The dipolarophile olefin portion was introduced by allylation, which was followed by the two step conversion of the ester group into an aldehyde (**38**). The decarboxylative condensation with *N*-benzylglycine provided the non-stabilised azomethine ylide leading to the expected cycloadduct (**39**) in good yield. The 8-carboxyl group was incorporated through a Pd-catalyzed carbonylation protocol and the final step was the chemoselective hydrogenolysis of the benzyl protecting group to yield **41** (Scheme 11).[18]

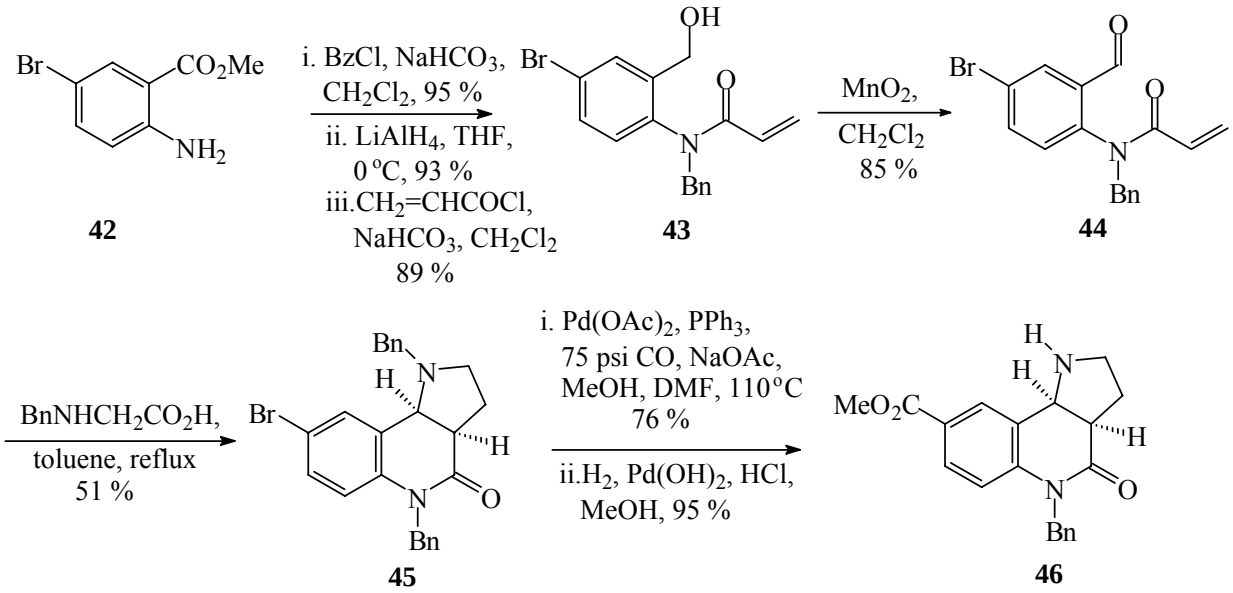
Scheme 11



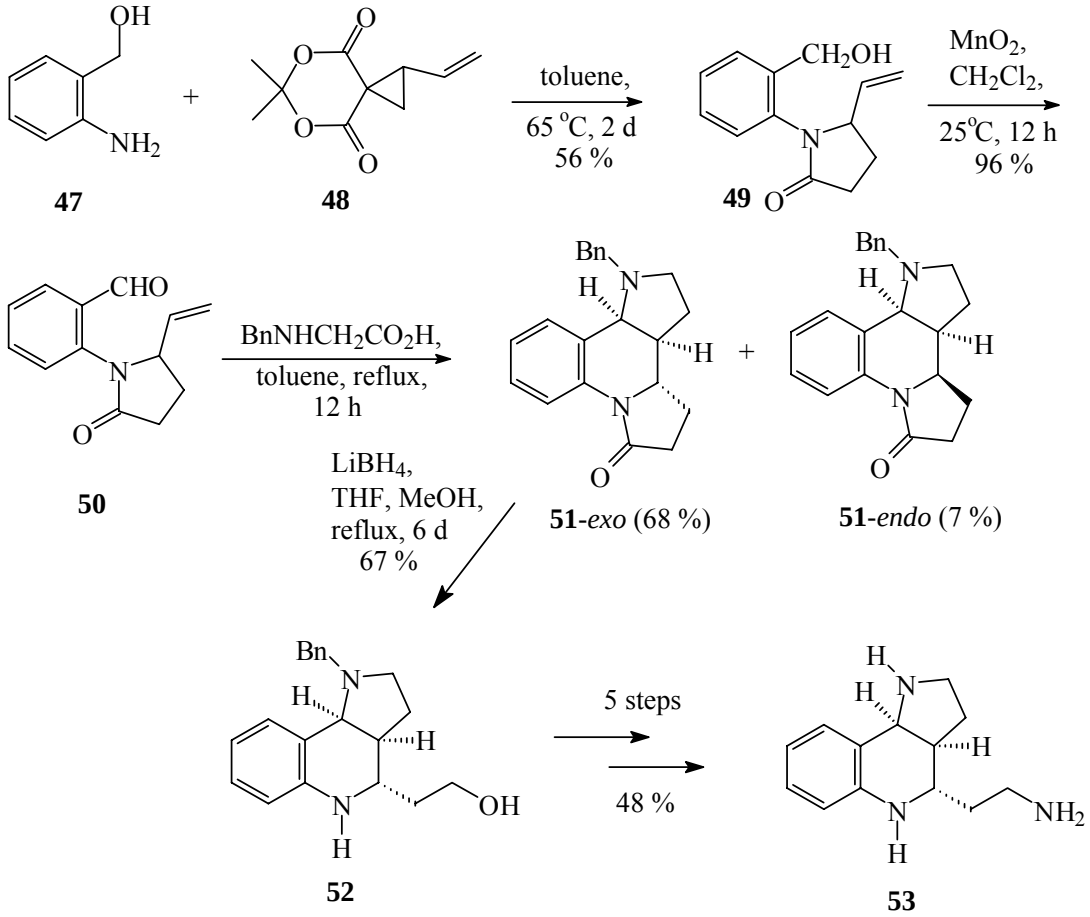
These workers then described a very similar approach in which the dipolarophile portion was introduced by acylation, which was followed by the oxidation of a hydroxy group to an aldehyde (**44**). The cycloaddition reaction, in toluene at reflux, proceeded smoothly and the desired *cis*-pyrrolo[3,2-*c*]quinoline (**45**) was obtained in good yield. The bromine substituent was converted to the methoxycarbonyl group again *via* a palladium-catalyzed carbonylation, followed by the chemoselective removal of the pyrrole benzyl group (Scheme 12).[19]

Snider and his collegues developed a stereoselective eight-step route from 2-hydroxymethylaniline (**47**) to the tricyclic triamine core (**53**) of martinellic acid.[16] The addition of 2-hydroxymethylaniline (**47**) to vinylcyclopropane (**48**), followed by oxidation with activated MnO_2 afforded the required cycloaddition precursor pyrrolidinone aldehyde (**50**). The intramolecular cycloaddition reaction of the azomethine ylide generated by the condensation of excess *N*-benzylglycine with aldehyde (**50**) gave a ≈ 9:1 mixture of the **51**-*exo* and **51**-*endo* heterocycles. The reduction of the main isomer with $LiBH_4$ afforded the amino alcohol (**52**), which was converted to the tricyclic triamine (**53**) in five steps (Scheme 13).

Scheme 12



Scheme 13

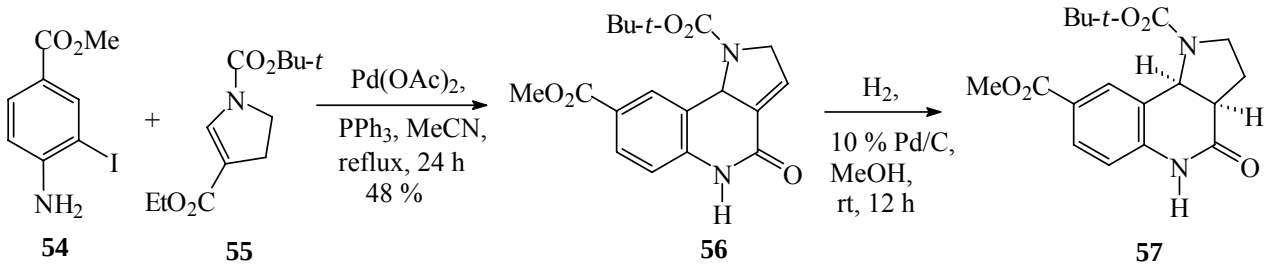


2.3. Heck reaction

A potential general strategy to construct the tricyclic pyrroloquinoline ring system based on the Heck

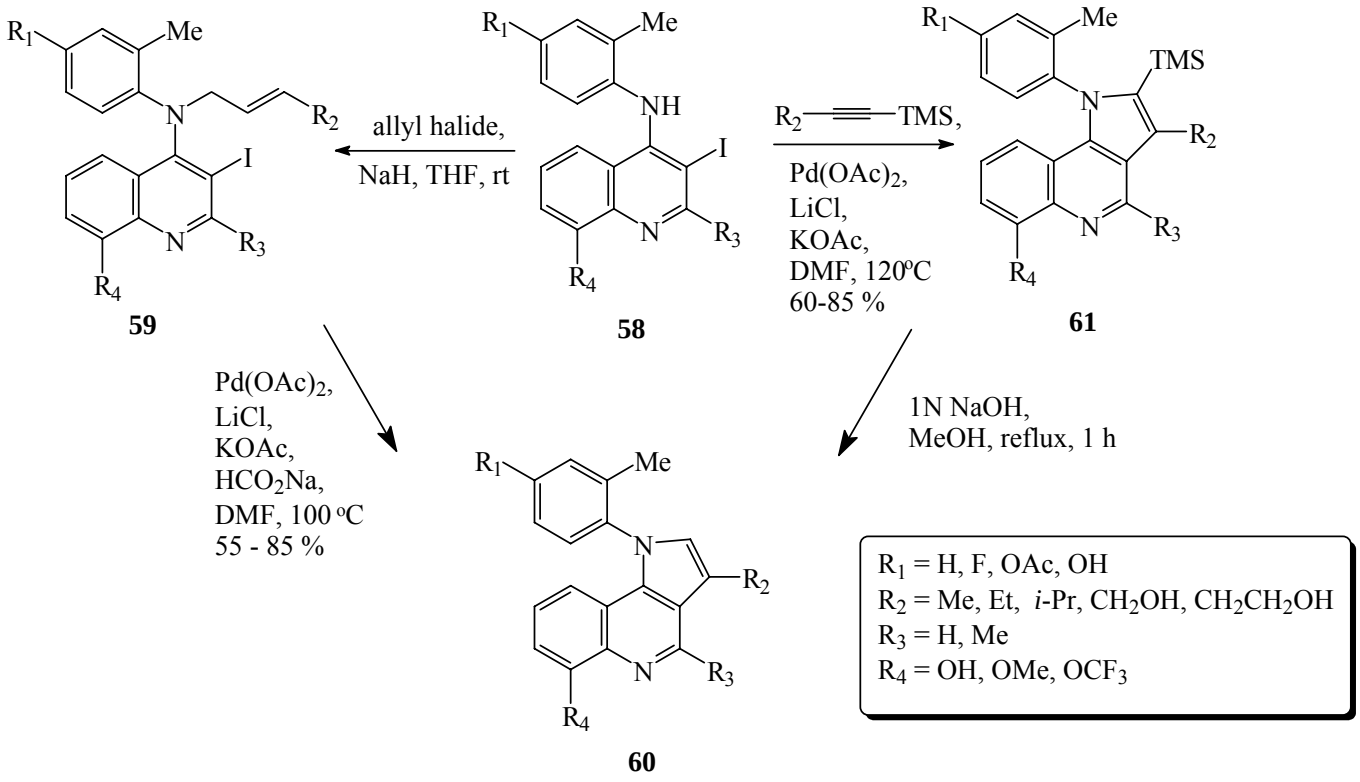
reaction was described by Gurjar and co-workers. The reaction between the 4,5-dihydropyrrole derivative (**55**) (prepared from 2-aminoethanol in 5 steps) and iodobenzene (**54**), gave the expected tricyclic compound (**56**) in one step. The palladium-catalyzed carbon-carbon bond formation was accompanied by the tandem cyclisation between the amine and the carbethoxy group. The hexahydropyrrolo[3,2-*c*]quinoline (**57**) was obtained by the catalytic reduction of the double bond of the pyrrole ring (Scheme 14).[20]

Scheme 14.



Two different methods involving palladium catalysed Heck reaction have been described for the synthesis of 3-alkyl-1-arylpyrrolo[3,2-*c*]quinolines (**60**) in order to test for their supposed anti-ulcer activity.

Scheme 15



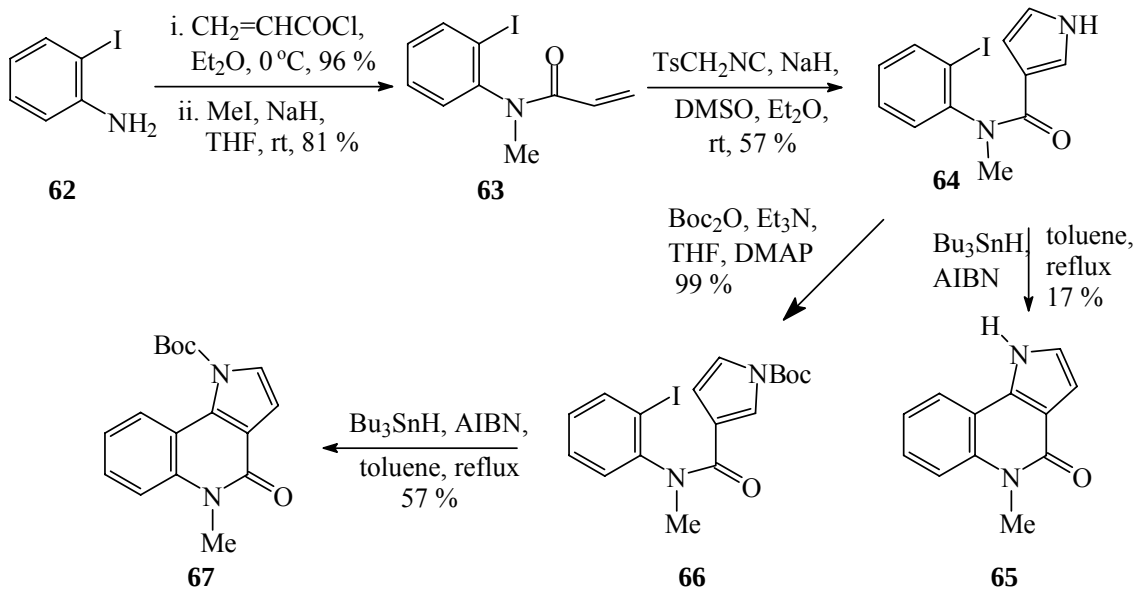
The first approach was based upon the intramolecular cyclisation of 4-(*N*-allyl-*N*-aryl)amino-3-iodoquinolines (**59**), while the same derivatives were obtained by the

palladium-catalyzed heteroannulation with 1-trimethylsilylalkynes and sequential desilylation (Scheme 15).[21,22]

2.4. Radical cyclisations

Jones achieved the synthesis of the pyrrolo[3,2-*c*]quinoline core of the martinelline alkaloids through the radical cyclisation of the *N*-(2`-iodophenyl)pyrroles (**64**). The reaction of 2-iodoaniline (**62**) with acryloyl chloride followed by methylation give the tertiary amide (**63**). Reaction with tosylmethyl isocyanide gave the radical cyclisation precursor (**64**), which was then subjected to standard reductive radical cyclisation conditions with the *N*-Boc derivative (**66**). The higher yield obtained with the *N*-Boc derivative (**66**) was explained by the electron-withdrawing effect of the Boc group (Scheme 16).[23,24]

Scheme 16

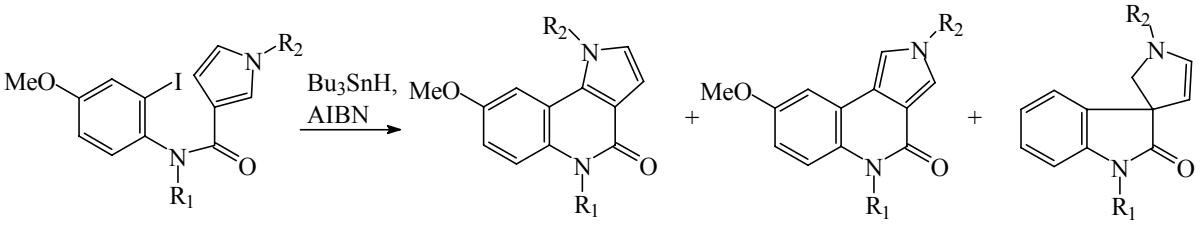


The effect of the different substituents upon the addition of aryl radicals to a pyrrole linked through the C-3 position was studied in detail. The 6-*endo* products (**69**) were formed in every case, together with the products of 6-*exo* (**70**) or 5-*exo* (**71**) cyclisations. In one case, the pyrrolo[3,2-*c*]quinoline (**69**) was the sole product in modest yield (Scheme 17, Table 4).[25]

2.5. From hydrazinoquinolines *via* Fischer-type cyclisation (Fischer Indolization)

The Fischer `Indolization` method is a general route for the synthesis of fully aromatic pyrrolo[3,2-*c*]quinolines from the 4-hydrazinoquinolines (**72**).

Scheme 17



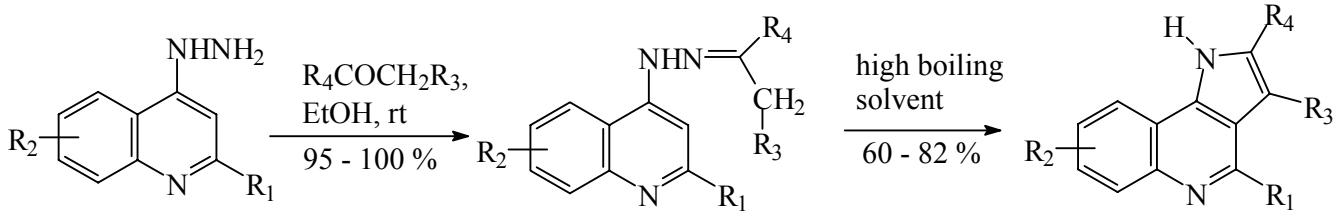
68 **69** **70** **71**

Entry	R_1	R_2	**69**	**70**	**71**
1	Me	H	37	15	-
2	SEM	H	34	18	-
3	Me	Boc	18	-	30
4	SEM	CO_2Me	15	-	32
5	SEM	Me	43	-	-

Table 4

Several groups prepared a range of 1*H*-pyrrolo[3,2-*c*]quinoline derivatives (**74,** R_1 = H, Me, R_2= H, 6-Cl, 7-Cl, 8-Cl, 6-Me, 7-Me, 8-Me, 6-OMe, 7-OMe, 8-OMe, R_3= H, Me, Et, Ph, R_4= H, Me, Et;) in excellent yields under thermal conditions for the cyclizations in diethylene glycol, diphenyl ether, or in dowtherm (Scheme 18).[26,27,28,29]

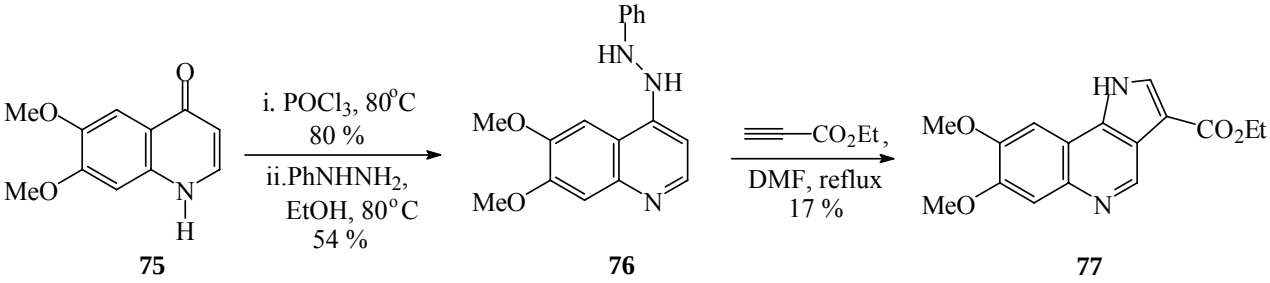
Scheme 18



72 **73** **74**

As potential topoisomerase inhibitors Henichart and co-workers synthesized some pyrrolo[3,2-*c*]quinoline esters starting from 1,4-dihydro-6,7-dimethoxy-4-oxoquinoline (**75**). The crude 4-chloroquinoline obtained from **75** was treated with phenylhydrazine, followed by a Michael addition to methyl propiolate of the more acidic NH of **76**. At higher temperatures this adduct was readily converted by Fischer indole-type synthesis to the 1*H*-pyrrolo[3,2-*c*]quinoline-3-carboxylate (**77**) (Scheme 19).[30]

Scheme 19



75 **76** **77**

2.6. From quinoline derivatives

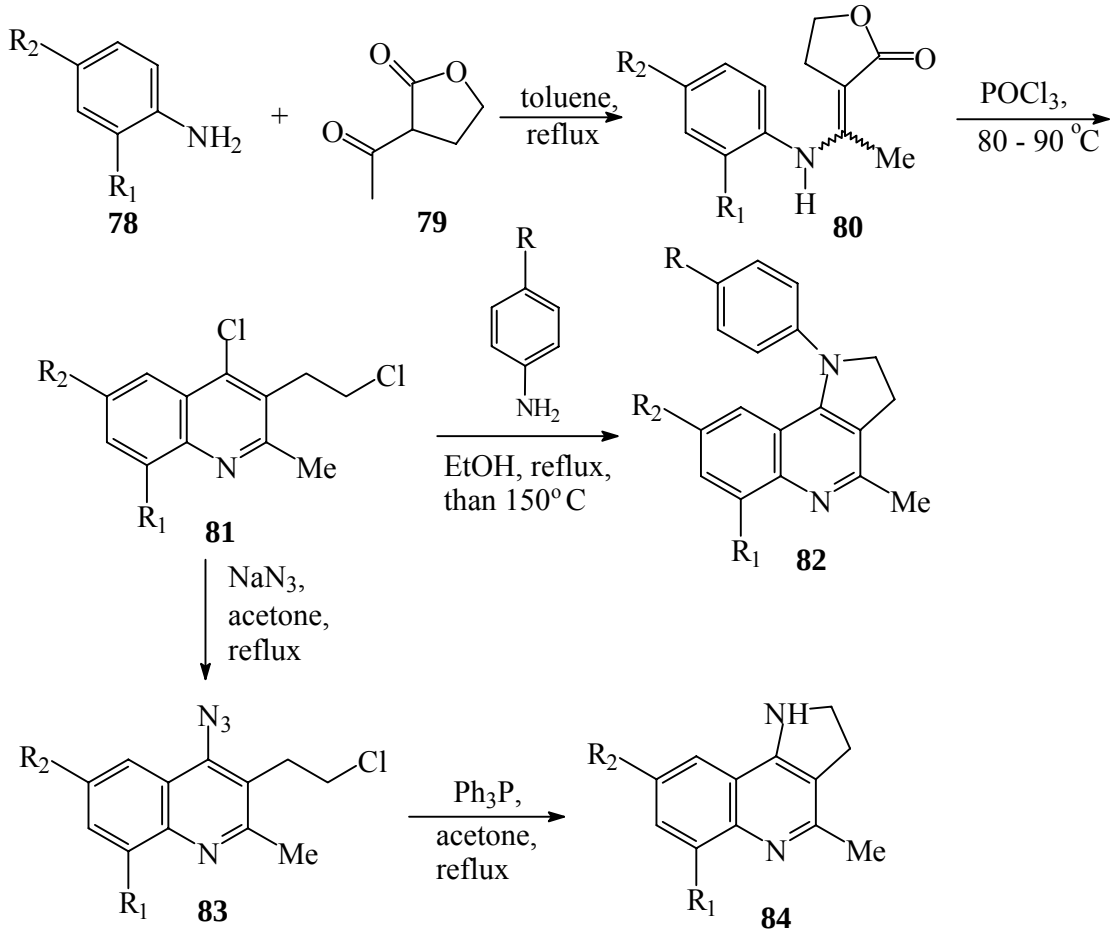
A short synthesis of some dihydropyrrolo[3,2-*c*]quinolines was patented by Schenley Industries[31] in 1952, who described these derivatives as potent amoebicides on animals *in vivo*. Meanwhile, using the same chemistry, several 1-phenyl-4-methylpyrrolo[3,2-*c*]quinolines were synthesized by Ozawa and Nagaoka[32,33] in 1957 and have been tested for their antibacterial activity.[34] This strategy was followed by Wright and co-workers during the investigation of the hypotensive properties of new 4-aminoquinolines,[35] and by Brown *et al.*[36] in a search for conformationally restrained analogues of 4-(arylamino)quinolines as reversible inhibitors of the gastric (H^+/K^+)-ATPase.

The synthesis of 1-aryl-4-methyl-2,3-dihydropyrrolo[3,2-*c*]quinolines (**82**) began with the condensation between 2-acetylbutyrolactone (**79**) and aniline derivatives (**78**). The mixture of (*E*)- and (*Z*)-enamines (**80**) was converted readily by the action of $POCl_3$ to the reactive dichloroquinoline derivatives (**81**), which were reacted with substituted anilines to give the final products (**82**). This sequence was later repeated by Badawey and Kappe,[37] who have also prepared the *N*-unsubstituted pyrrolo[3,2-*c*]quinolines (**84**) in two steps from the dichloro intermediate (**81**) (Scheme 20, Table 5).

R_1	R_2	yield of **80** %	yield of **81** %	yield of **82** %	yield of **83** %	yield of **84** %
H	Cl	93	95	-	-	78 % (R = Ph) 94 % (R = 4-Cl-C_6H_4)
H	F	90	93	98	89	72 % (R = Ph) 93 % (R = 4-Cl-C_6H_4)
Cl	Cl	87	94	95	55	97 % (R = 4-Cl-C_6H_4)
OMe	OMe	82	93	80	53	-

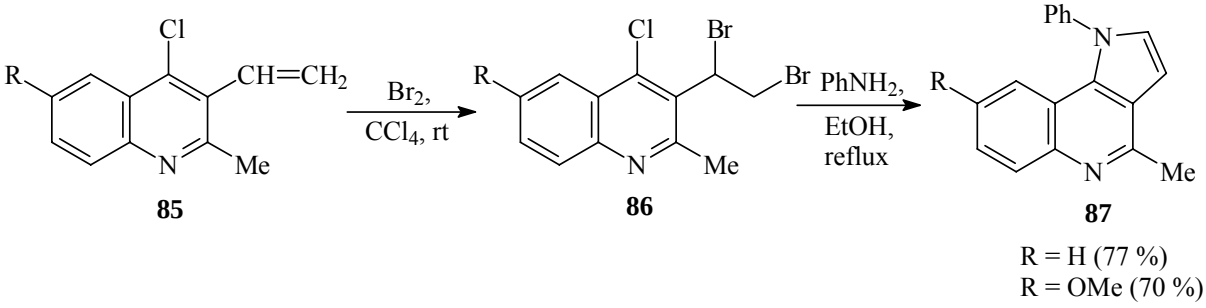
Table 5

Scheme 20



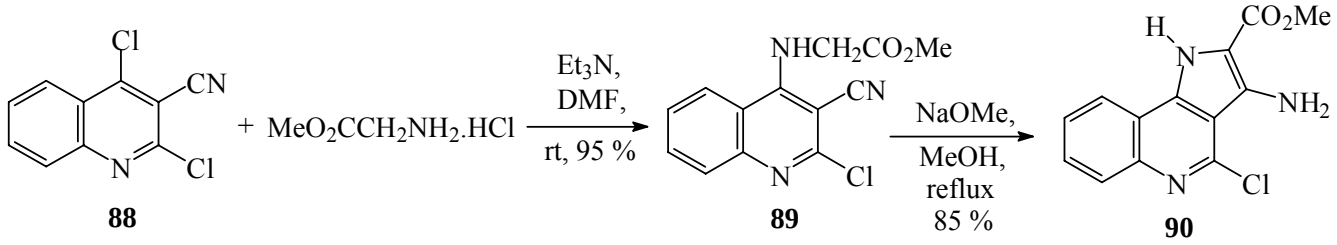
Nagaoka prepared fully aromatic 1-phenyl-pyrrolo[3,2-*c*]quinolines (**87**) by a slight variation of this method from 4-chloro-3-vinylquinolines (**85**) in two steps (Scheme 21).[38]

Scheme 21



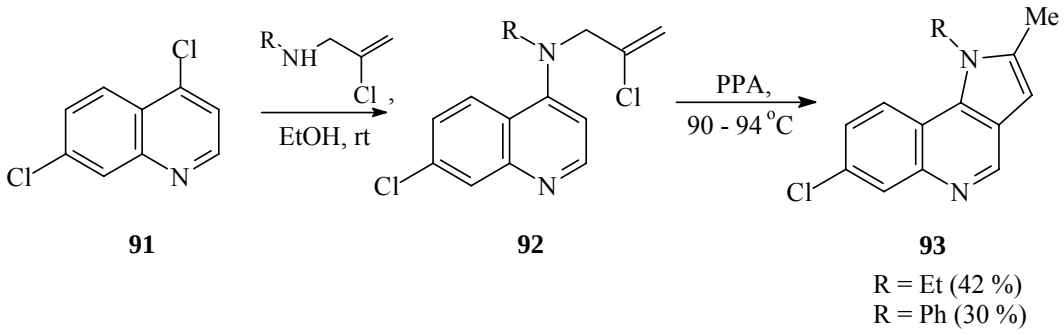
An easy and rapid synthesis of methyl 3-amino-4-chloropyrrolo[3,2-*c*]quinoline-2-carboxylate (**90**) was described by Mekheimer.[39] The 2,4-dichloroquinoline-3-carbonitrile (**88**) was reacted with an excess of methyl glycinate in the presence of triethylamine to give the 4-aminoquinoline (**89**) selectively. The cyclisation at reflux in methanol, with sodium methoxide as the catalyst, provided the target tricycle **(90**) (Scheme 22).

Scheme 22



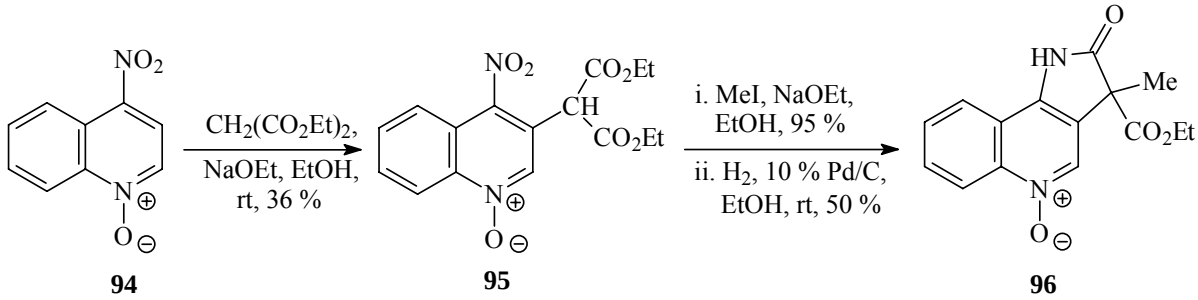
McDonald and Proctor prepared 7-chloro-2-methyl-1*H*-pyrrolo[3,2-*c*]quinoline derivatives (**93,** R = Ph, Et) from 4,7-dichloroquinoline (**91**) in simple two step synthesis. The reaction of **91** with a 2-chloroallylamine followed by the treatment of chloroalkene (**92**) with polyphosphoric acid at 90 ^{o}C, resulted in the formation of **93** in 30 – 42 % yield (Scheme 23).[40]

Scheme 23



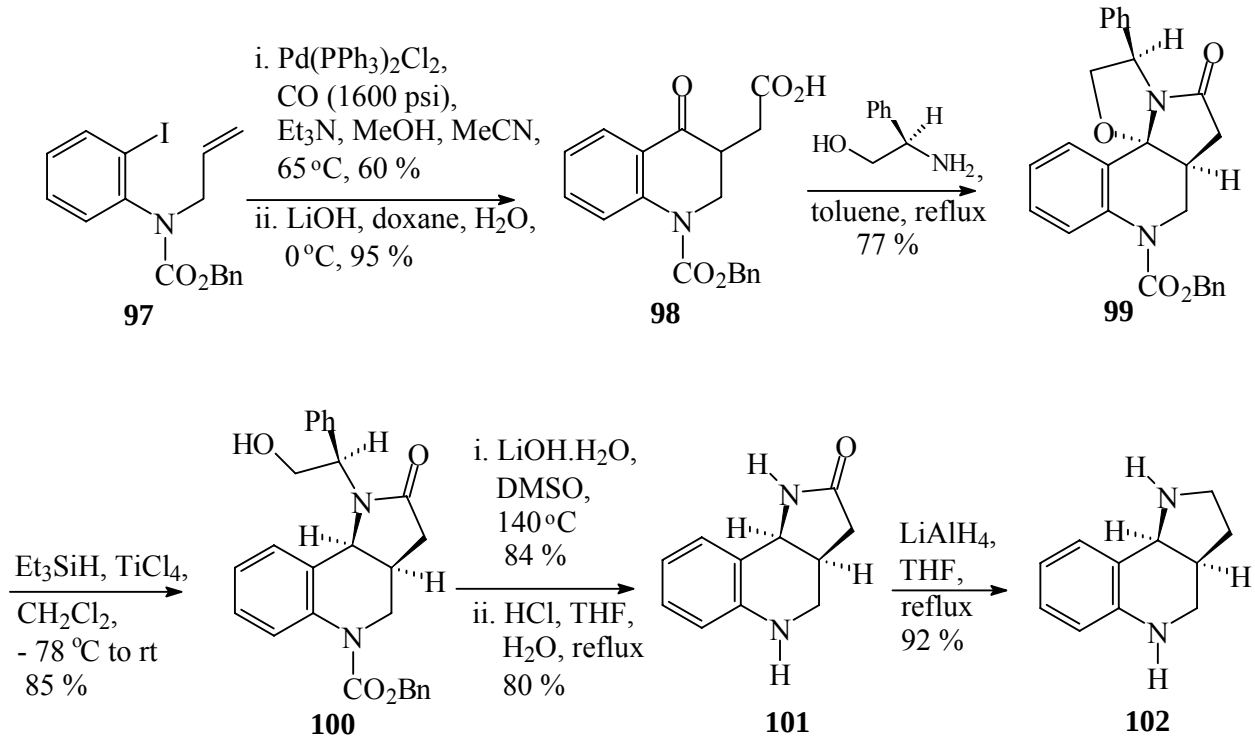
In another approach, 4-nitroquinoline *N*-oxide (**94**) was reacted with the carbanion derived from malonic ester. Substitution takes place at the 3-position, in moderate yield. Successive alkylation and reduction furnished 2,3-dihydro-3-methyl-2-oxo-1*H*-pyrrolo[3,2-*c*]quinoline-3-carboxylate *N*-oxide (**96**) (Scheme 24).[41]

Scheme 24



The first enantioselective synthesis of the martinelline core was reported by Nieman and Ennis[42] using a general methodology for the preparation of chiral, *cis*-fused bicyclic pyrrolidines using (*R*)-(-)-phenylglycinol as the source of chirality. The requisite quinoline derivative (**98)** for this synthesis was prepared *via* a palladium-catalyzed carbonylative cyclization procedure starting from the protected (Z = CO_2Bn) *N*-allyl-2-iodoaniline (**97**). The condensation of the γ-keto ester (**98**) with (*R*)-(-)-phenylglycinol generated the tetracyclic lactam (**99**) as a single isomer, which was treated with triethylsilane in the presence of titanium tetrachloride to give the pyrrolo[3,2-*c*]quinoline core of the martinelline alkaloids, partly deprotected at *N*-1. Full deprotection was achieved using a two-step elimination/hydrolysis protocol and the resulting lactam (**101**) was finally reduced with lithium aluminium hydride to the tricyclic diamine (**102**) (Scheme 25).[43]

Scheme 25



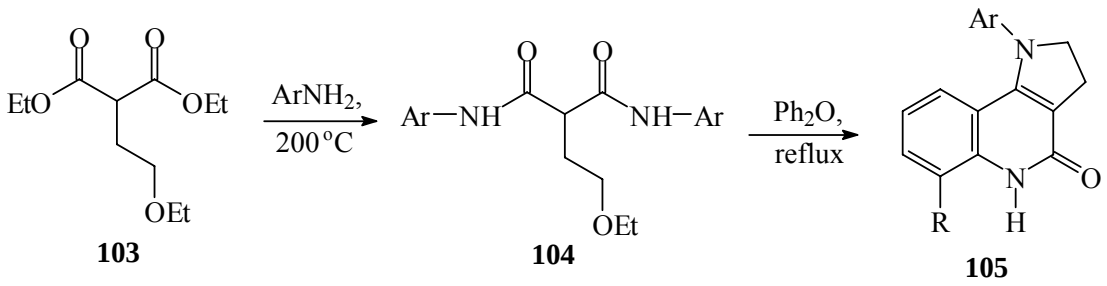
2.7. Miscellenous methods

The synthesis of the parent ring system, 1*H*-pyrrolo[3,2-*c*]quinoline was first reported in 1934, when the alkali-fusion of an indigo dye "Ciba yellow" gave a by-product, described as indolo[3,2-*c*]quinoline, which, upon oxidation with chromic acid, gave 1*H*-pyrrolo[3,2-*c*]quinoline-2,3-dicarboxylic acid. Melting of this compound produced the parent 1*H*-pyrrolo[3,2-*c*]quinoline in low yield.[44]

The synthesis of the pyrrolo[3,2-*c*]quinoline core from diethyl (2-ethoxyethyl)malonate (**103**) and aniline

was reported by Grundon and McCorkindale (Scheme 26, Ar = Ph, R = H) in boiling diphenyl ether.[45] This method was later used for the preparation of further 1-arylpyrrolo[3,2-*c*]quinolines derivatives (**105**) as reversible inhibitors of the gastric (H^+/K^+)-ATPase.[46]

Scheme 26



103 **104** **105**

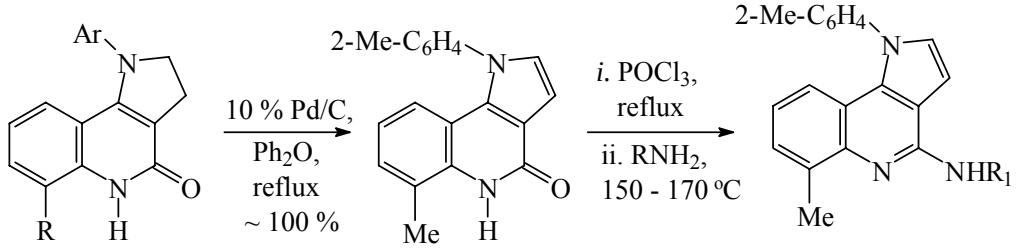
Ar	R	yield of **104** %	yield of **105** %
Ph	H	75	59
2-Me-C_6H_4	Me	67	49
2-MeO-C_6H_4	MeO	47	not reported

Table 6

The fully aromatic pyrrolo[3,2-*c*]quinoline (**106**) was conveniently prepared by dehydrogenation of a tricyclic lactam with a palladium catalyst at high temperature. After the chlorination of **106** with $POCl_3$, the product underwent substitution with a range of amine nucleophiles resulting in the formation of **107**. The lactam carbonyl of **105** could also be converted to the corresponding chloride (**108**), from which the halogen was easily removed by catalytic hydrogenation (Scheme 27).

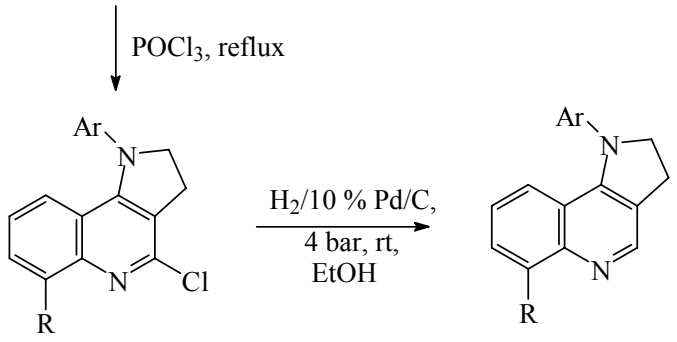
In order to avoid the symmetry constraint associated with the described route above, a modification of this methodology was applied by Grundon and co-workers[47] and others.[48] Using smaller amounts of anilines in the first step the furoquinolone (**111**) was isolated, which was ring-opened by phosphorus oxychloride yielding **112**. Heating of trichloro derivative (**112**) with aniline, however gave mainly the linear isomer (**115**) of the target pyrrolo[3,2-*c*]quinoline. After the selective hydrolisis of the 2-chloro function of **112**, the reaction of **113** with an aniline in phenol at high temperatures gave the desired lactam (**114**) (Scheme 28).[46]

Scheme 27



105 **106** **107**

R_1 = Me (42 %)
R_1 = $(CH_2)_2OH$ (72 %)
R_1 = $(CH_2)_3OH$ (51 %)
R_1 = $(CH_2)_4OH$ (66 %)

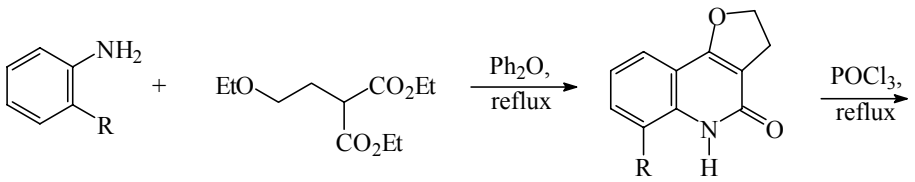


108 **109**

R = Me, Ar = 2-Me-C_6H_4 (4 %)
R = MeO, Ar = 2-MeO-C_6H_4 (56 %)

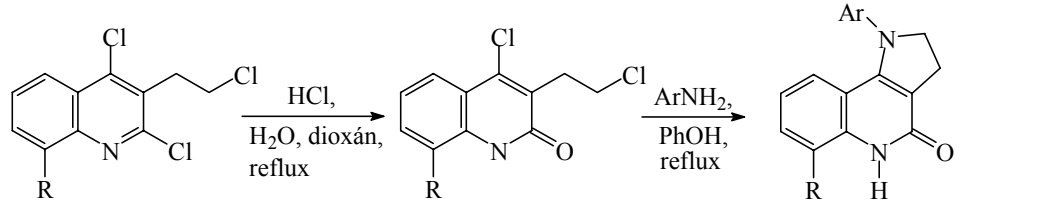
R = Me, Ar = 2-Me-C_6H_4 (31 %)
R = MeO, Ar = 2-MeO-C_6H_4 (51 %)

Scheme 28



110 **103** **111**

R = Me (52 %)
R = MeO (36 %)

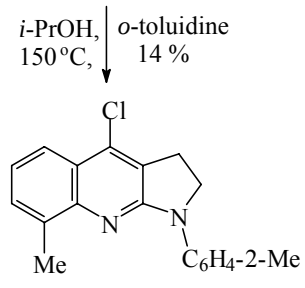


112 **113** **114**

R = Me (43 %)
R = MeO (53 %)

R = Me (39 %)
R = MeO (74 %)

Ar = 2-MeO-C_6H_4, R = Me (74 %)
Ar = 2-Me-C_6H_4, R = MeO (39 %)

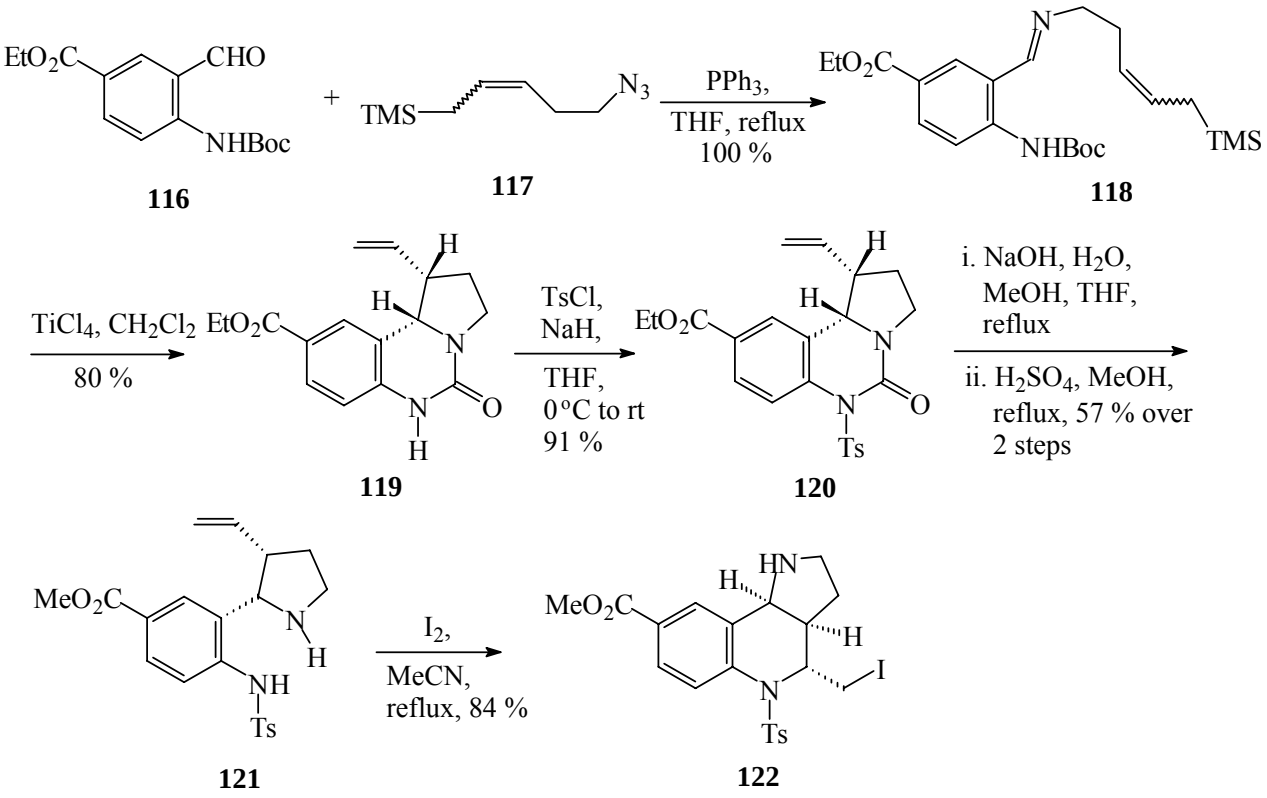


115

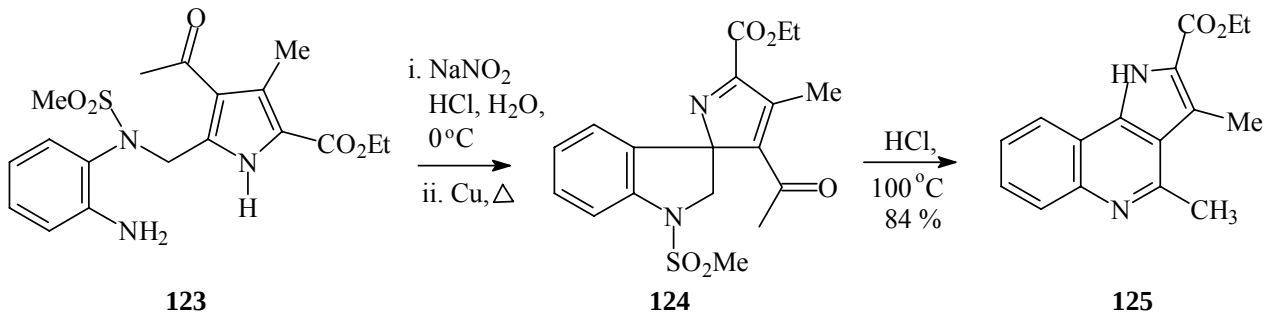
During the investigation of a hetero Diels-Alder route for the synthesis of the tricyclic core of the martinellines, an alternative Lewis-acid dependent cyclisation of precursor imines (**118**) to pyrrolo[1,2-*c*]quinazolin-5-ones (**119**) was observed. These later proved to be useful intermediate in an elegant synthesis of the tricyclic ring system of the martinellines (Scheme 29).[49]

The spiroindoline (**124**), obtained from the copper-catalyzed decomposition of the diazonium salt derived from **123**, on treatment with concentrated hydrochloric acid gave a high yield of ethyl 3,4-dimethyl-1*H*-pyrrolo[3,2-*c*]quinoline-2-carboxylate (**125**) (Scheme 30).[50]

Scheme 29



Scheme 30



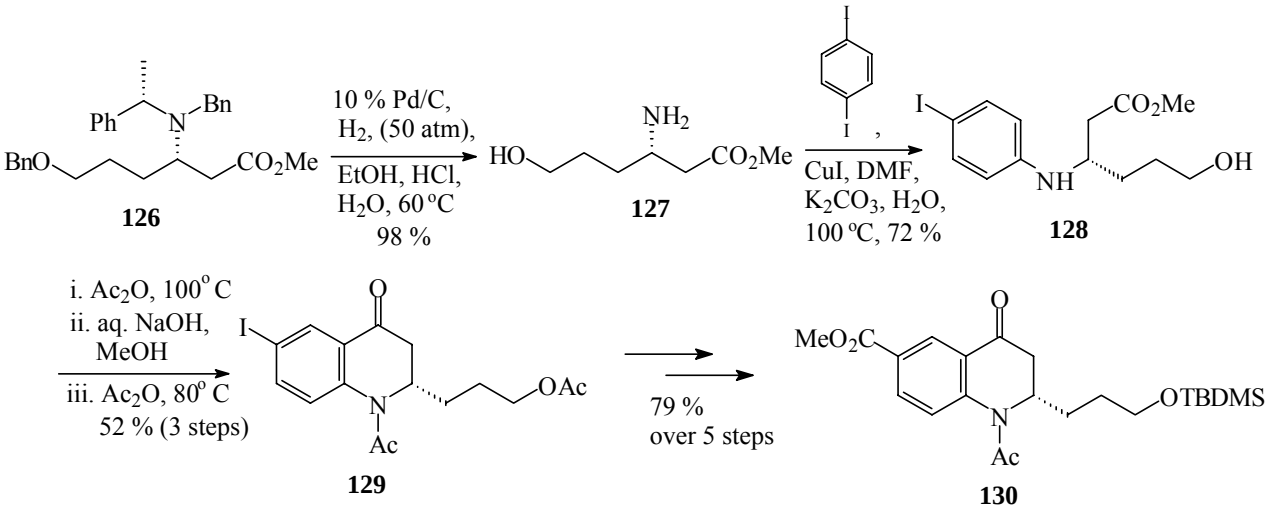
3. SYNTHESIS OF MARTINELLINE ALKALOIDS

3.1. Total synthesis of martinellic acid

3.1.1. Synthesis of Ma and co-workers

The first total synthesis of (-)-martinellic acid (**2**) was accomplished by Ma and co-workers in 2001. These workers built up the tricyclic triamine by the annellation of pyrrolidine ring to give the appropriately substituted quinoline derivative (**130**) to accomplish the synthesis in 25 linear steps with a 2.5 % overall yield.[51] Starting from the chiral *N*,*N*-disubstituted β-amino ester (**126)** the 2-substituted 4-oxoquinoline (**129**) was synthetized *via* an Ullmann type aryl amination reaction of **127** with 1,4-diiodobenzene, followed by an intramolecular acylation of **128** mediated by $AlCl_3$. The successful Pd-catalyzed carbonylation of the resulting iodoquinoline and a protective group exchange gave **130** (Scheme 31).

Scheme 31



The alkylation of 4-oxoquinoline (**130**) was carried out using $TfOCH_2CH_2Br$ (**131**) as the coupling agent, followed by the immediate conversion into the azide (**132**). Cyclization with Ph_3P/H_2O provided the tricyclic imine (**133**) which was reduced stereoselectively with $NaBH_4$ after the removal of the TBDMS group. This hexahydropyrrolo[3,2-*c*]quinoline was converted to the key intermediate triamine hydrochloride (**134**) in a series of common functional group transformations. The introduction of the guanidine moiety was accomplished by treatment with *N*-(*tert*-butoxycarbonyl)-*N*`-(3-methyl-2-butenyl)-

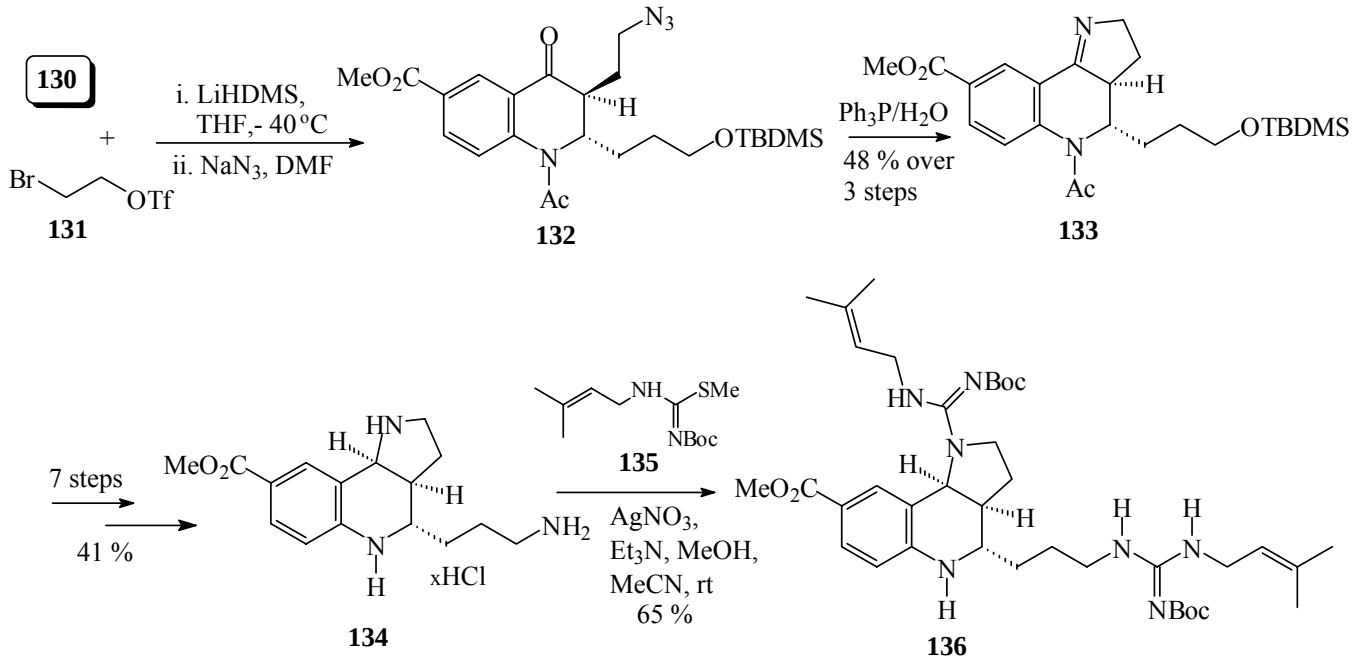
S-methylisothiourea (**135**) in the presence of $AgNO_3$ (Scheme 32). Hydrolysis of the ester, full deprotection of the side-chains and salt formation with TFA, furnished the martinellic acid TFA salt with all the spectroscopical data identical to those reported earlier by the Merck chemists.[1] The specific rotations, however, were markedly different.[52]

3.1.2. Synthesis of *Snider*

The synthesis of (±)-martinellic acid (**2**) as reported by Snider and O'Hare was based on intramolecular cycloadditions of azomethine ylides, which were already described in Section 2.2.2.

The preparation of intermediate (**137**) was achieved in a similar way to that of **52**. The conversion to tricylic triamine (**134**) – the common intermediate in all martinelline (**1**) or martinellic acid (**2**) syntheses – was achieved in nine steps. The introduction of the guanidine moiety onto the hindered secondary amine was not possible by standard methods, so these workers developed a new method for the preparation of hindered guanidines.[53]

Scheme 32



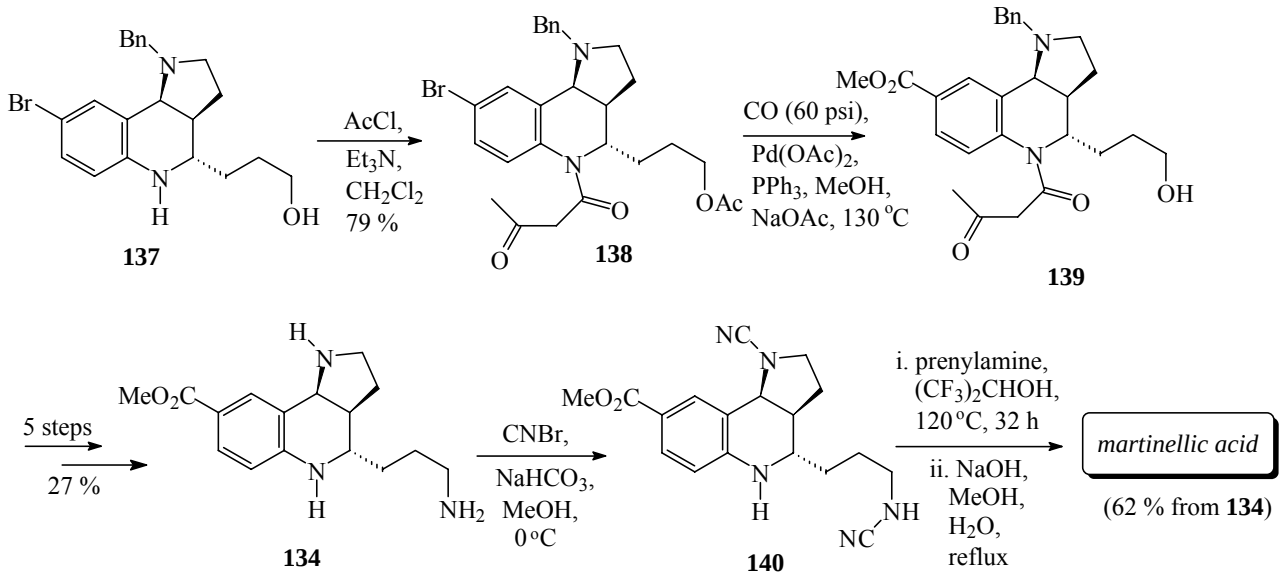
Treatment of the amine (**134**) with cyanogen bromide and $NaHCO_3$ gives the cyanamide (**140**) in quantitative yield. The reaction with prenylamine in hexafluoro-2-propanol at 120 °C provides the methyl martinellate, which was hydrolised with aqueous NaOH in methanol followed by a reversed phase chromatographic purification, to give the (±)-martinellic acid (**2**) after 14 steps in 3 % overall yield (Scheme 33).[54]

3.2. Total synthesis of martinelline

3.2.1. Synthesis of Powell and Batey

The first total synthesis of martinelline (**1**) was published by Powell and Batey[10] in 2002. These workers used the hetero-Diels-Alder strategy, which provides a very short route for the synthesis of the heterocyclic core of this biologically active substance. After much experimentation, they found that the reaction of methyl 4-aminobenzoate (**7**) with 2 equivalents of the *Z*-protected 2-pyrroline (**5**), in the presence of 5 % camphorsulfonic acid (CSA) in anhydrous THF, gives the tricyclic amine (Scheme 2, **8**-*exo*) with the correct stereochemistry. This is a remarkable change in diastereoselectivity compared to the lanthanide-catalyzed reaction. After deprotection with Pearlman`s catalyst, followed by acidification with HCl, the triamine salt (**134**) was obtained, but only in two synthetic steps and 58 % overall yield, which is, so far the best route to this key intermediate (compared to the nine or more steps in the methods of Snider[54] or Ma.[11,51,52])

Scheme 33



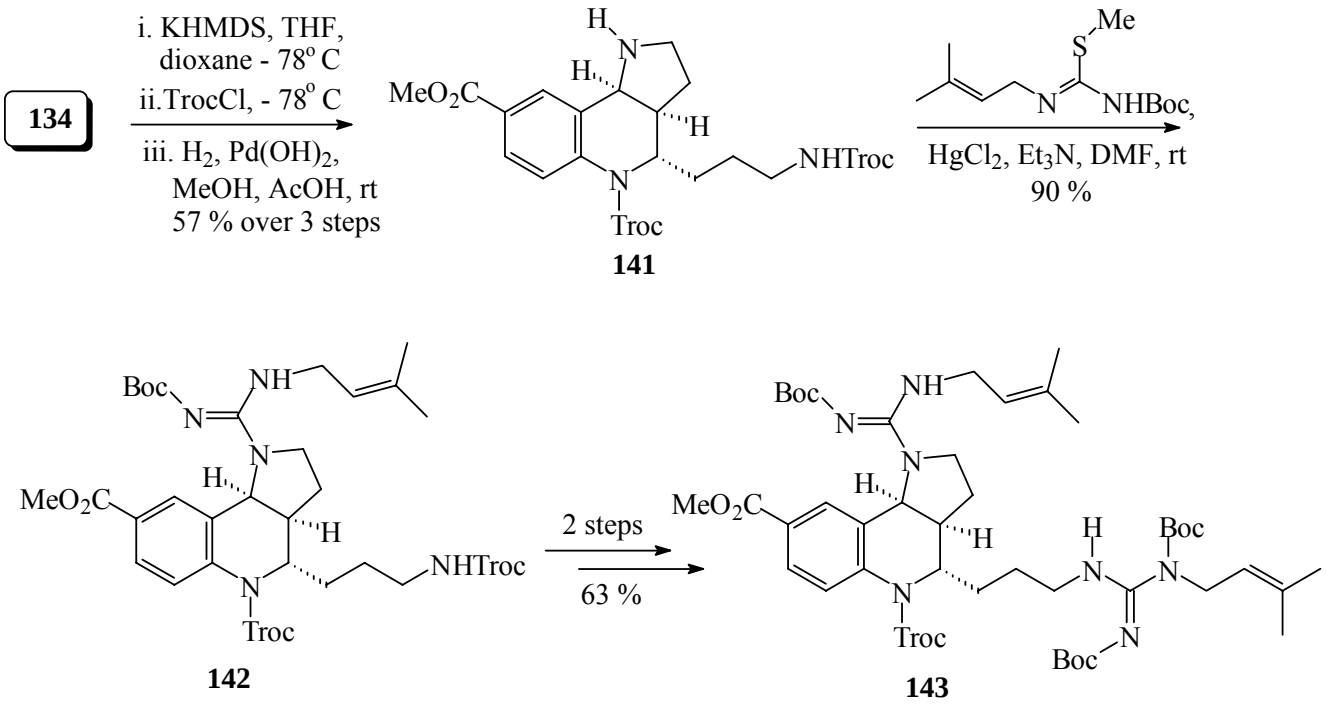
After some initial attempts to introduce both the *N*-1 and *N*-13 isopenylguanidines in one step, into **134**, these workers decided to introduce each guanidine moiety individually. The more substituted guanidine was introduced at the pyrrolidine nitrogen of **141**, and followed by protecting group manipulation, the second guanidine moiety was coupled to the side-chain nitrogen through a $HgCl_2$-promoted guanidinylation with isothiourea. The hydrolysis of the methyl ester of **143**, and the deprotection of the Boc groups, followed by HPLC purification, afforded (±)-martinellic acid (**2**). The synthesis of the allylic alcohol side-chain required for martinelline (**1**) synthesis was accomplished through a five-step sequence.

After extensive experimentation, the coupling of this fragment to martinellic acid was achieved using BOP-Cl and Hünig`s base, giving a protected martinelline derivative. The deprotection with TFA, followed by reversed-phase preparative HPLC purification, gave (±)-martinelline (**1)** in nine steps and 10 % overall yield. The ^{1}H- and ^{13}C-NMR spectra were identical to those of the original compound (Scheme 34).

3.2.2. Synthesis of *Ma*

A conceptionally very similar approach to that of Powell and Batey resulted in the second total synthesis of racemic martinelline by Ma and co-workers.[11] In contrast to Powell and Batey these workers did not attempt the diastereoselective hetero Diels-Alder reaction, instead, they realized that if some derivatives of the otherwise worthless *endo*-product could be converted to the thermodynamically more stable *exo*-isomer under basic conditions they would be able to develop a very efficient protocol for the synthesis of martinellic acid and martinelline.

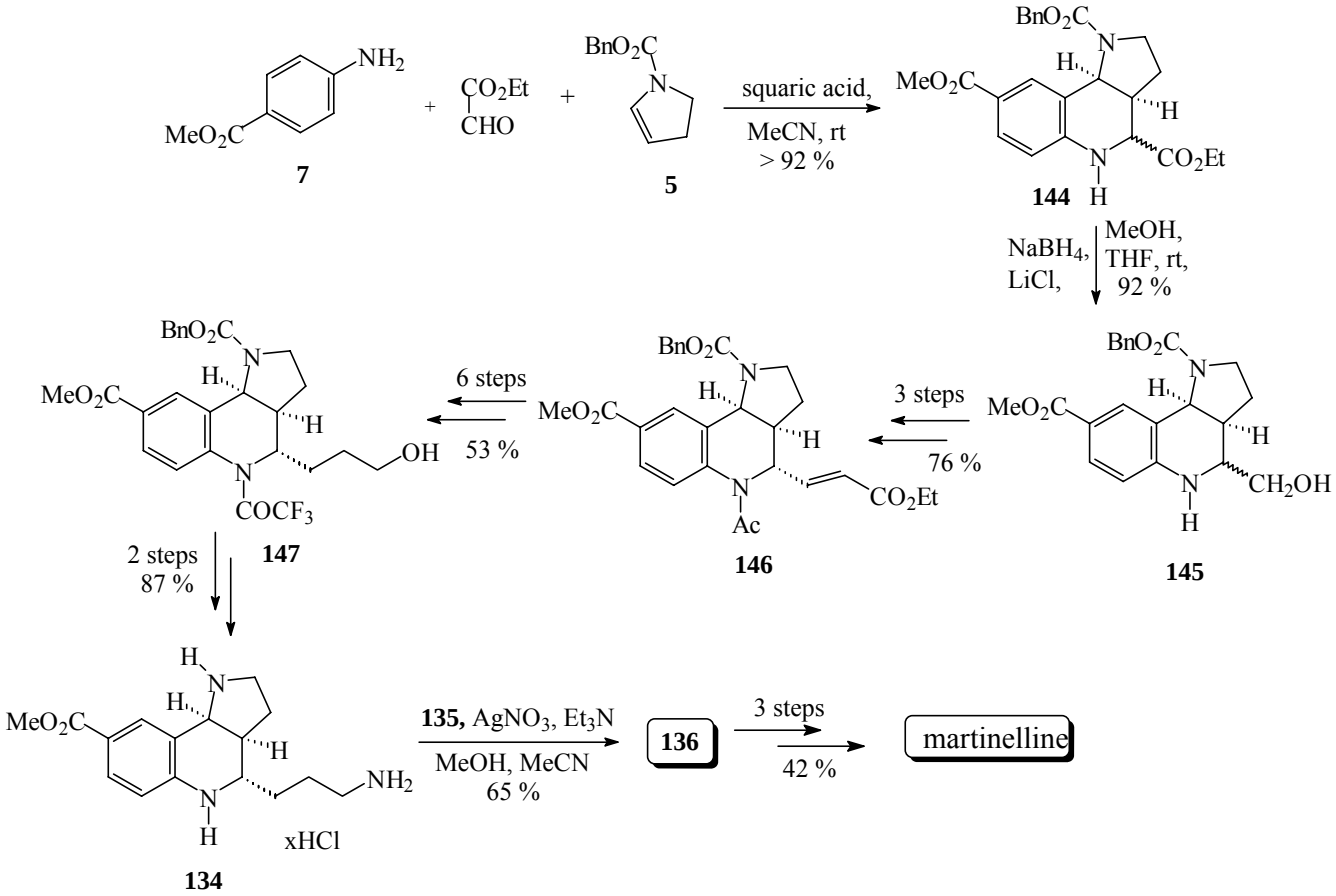
Scheme 34



These workers used unusual catalyst, squaric acid, for the Diels-Alder cycloaddition of 4-methoxycarbonylaniline (**7**), ethyl glyoxalate and the enamine (**5**), which in acetonitrile provided the *endo*- and *exo*-addition products (**144**) in a ratio of 2:1, and in greater than 92 % yield. The regioselective reduction of this diester was achieved with $NaBH_4$/LiCl. After the protection of the 1-amino group

– achieved in three steps – the *Swern*-oxidation gave the corresponding aldehyde as a mixture of *trans*- and *cis*-isomers, which showed that the expected isomerization at the 2-position had occurred. This crude aldehyde mixture was converted by a Wittig-reaction to diester (**146**) which contained only a small amount of the 2-epimer, in this manner they successfully altered the stereochemistry of the major product from the imino Diels-Alder reaction to that required for the synthesis of martinellines. This was transformed to the known tricyclic triamine (**134**) – the key intermediate for all above described martinellic acid (**2)** synthesis – which was built up in 13 steps. The transformation to martinellic acid (**2)** was accomplished as described above (see section 3.2.2.), and this was then converted to martinelline (**1)** by coupling of the allylic alcohol side-chain, mediated with EDCl, followed by the deprotection with TFA in the presence of anisole. The yield for these 17 linear steps was 8 % overall (Scheme 35).

Scheme 35



4. Conclusion

The development of efficient strategies and synthetic routes to pyrrolo[3,2-*c*]quinoline ring systems has seen increased attention as a result of the important biological activity that these compounds have been shown to display. A number of successful strategies have emerged for the construction of these

heterocycles, which are complementary in providing a diverse set of precursors and starting materials. The recent synthesis of complex martinelline alkaloids attest to the synthetic value of some of the recent developments in synthetic methodology. The structural complexity of these natural products has challenged synthetic chemists to develop ever more elaborate strategies for their synthesis.

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