RECENT PROGRESS IN THE ENANTIOSELECTIVE SYNTHESIS OF ISOQUINOLINE ALKALOIDS *

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Abstract - Recent developments in the enantioselective synthesis of isoquinoline alkaloids are reviewed. They include the enantioselective modification of the traditional methods (Pictet-Spengler, Bischler-Napieralski, Pomeranz-Fritsch) as well as the modern "C-C-connective" approach.

1. Introduction.

After the pioneering work on the synthesis of optically active isoquinoline alkaloids initiated by Brossi,[1] Kametani,[2,3] Yamada[4-8] and others[9] in the 70s, intensive investigations in this field have been carried out only in the last decade. They have brought about development of a number of new synthetic methods, although some of the traditional ones have been also adapted to enantioselective synthesis.

The structure of a great number of alkaloids is based on 1-substituted tetrahydroisoquinoline skeleton. Among them 1-benzyl derivatives are the most widely distributed [10-12] and serve as precursors in the synthesis and biosynthesis[13] of other types of isoquinoline alkaloids.

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* *This paper is dedicated to Professor Arnold Brossi on the occasion of his 70 th birthday.*

The key problem in the synthesis is related to the introduction of the substituent as well as asymmetry at the C-1 position of the tetrahydroisoquinoline nucleus. Syntheses of such derivatives are the subject of this article. In many approaches to the synthesis the concept of asymmetric induction has been the basic strategy. The chiral auxiliary was placed either on or around the nitrogen of isoquinoline (or its synthon) in the form of a chiral alkyl, acyl or related groups, or in the C-1 substituent (or its synthon). Frequently natural amino acids or carbohydrates were used as chiral building bolcks or auxiliaries. The stereogenic character of sulfur has drown attention of many research teams, in particular the sulfoxide functionality has been used to control the diastereoselectivity and enantioselectivity of this synthesis. In some cases chiral catalysts,[38,39] ligands[38,39] or reagents[40-44] have been used with success.

The effectiveness of these methods is variable as far as the chemical and optical yields as well as the number of synthetic operations involved are concerned In this respect the Meyers`[63-67] amidine and Gawley`s[68-74] oxazoline chemistry, in which 1-lithiated tetrahydroisoquinolines are alkylated or treated with carbonyl compounds have provided by far the best results. The Czarnocki-MacLean-Szarek synthesis[19-21] making use of homochiral 1-formyltetrahydroisoquinoline derivatives as building blocks also deserves attention.

The steric results of these syntheses have been assessed by various methods; usually by chemical transformations into or correlation with compounds of the known stereochemistry or by nmr spectral analysis, hplc with chiral stationary phases and sometimes by X-ray crystallographic study.

The organization of this article is as follows: in the first part enantioselective modifications of the traditional methods (the Pictet-Spengler, the Bischler-Napieralski, the Pomeranz-Fritsch) are described; the second chapter gives a review of these strategies which involve the construction of the alkaloids` framework by introduction of the C-1 substituent to isoquinoline, dihydro- or tetrahydroisoquinoline derivatives (the "C-C-connective" approach). The limited size of this article does not allow the retro-synthetic analysis to be included.

As a final remark it should be added that in addition to the total asymmetric synthesis of the 1-substituted isoquinoline alkaloids reported in this paper, several other methods exploring biocatalysis[14,15] for resolution or transformations in plants and their tissue-cultured cells[16] of racemic alkaloids to get pure enantiomers has been recently worked out.

2. Enantioselective modifications of the traditional methods.

In the traditional methods of the synthesis of isoquinoline alkaloids such as the Picted-Spengler, the Bischler-Napieralski, the Pomeranz-Fritsch the closure of the isoquinoline ring is the key step, while the C-1 substituent is introduced at earlier stages. Among these methods the Pictet-Spengler reaction is the most often

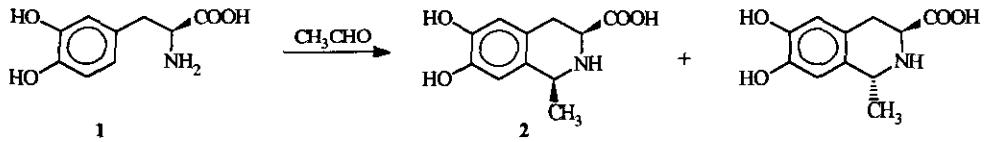
explored one. To introduce asymmetry, the Bischler-Napieralski condensation is followed by enantioselective reduction of 3,4-dihydroisoquinoline intermediate. An example of enantioselective Pomeranz-Fritsch synthesis was also desribed in recent literature.

2.1. The Pictet-Spengler condensation.

The Pictet-Spengler reaction involves the condensation of a β-arylethylamine with an aldehyde to give directly tetrahydroisoquinoline.

In order to create a stereogenic center at C-1, chiral auxiliaries were placed either in the amine component or in the aldehyde portion. Natural amino acids or carbohydrates were often used as chiral building blocks in this synthesis.

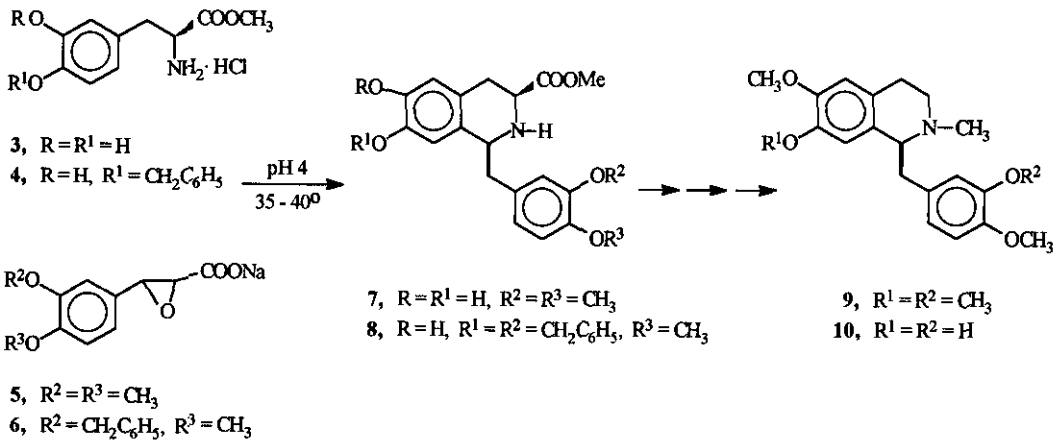
The first example of asymmetric synthesis of isoquinoline alkaloids performed with the use of natural amino acids was reported by Brossi *et al.*[1] in 1972. In a biomimetic type of process a series of 3-carboxyl substituted simple tetrahydroisoquinoline alkaloids have been prepared by treatment of the amino acid L-Dopa (1) with formaldehyde or acetaldehyde, e.g. acid-catalyzed condensation of 1 with acetaldehyde afforded in high yield a 95:5 mixture of two isomeric isoquinoline amino acids. (Scheme 1). The 1S configuration of the major product (2) was established by X-ray crystallographic study.



1 2

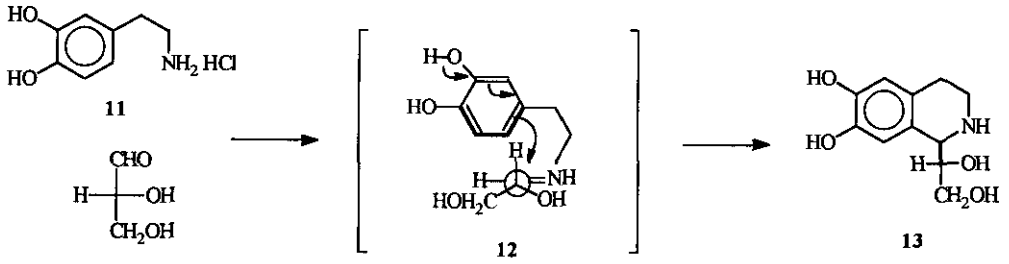
Scheme 1

Few years later Yamada *et al.*[4-6] extended this approach to include synthesis of optically active isoquinoline and indole alkaloids.[17] In the synthesis of S-laudanosine (9), R-laudanosine (ent-9) and S-reticuline (10) the starting amino acids were: L-Dopa methyl ester (3) and its monobenzyl ether (4) prepared from L-tyrosine, while sodium glycidates (5,6) served as chemical equivalents of the carbonyl component. (Scheme 2). The condensation yielded a separable mixture of diastereomeric tetrahydroisoquinolines with predominant formation of the more stable *cis*-isomers (7,8) with the C-1 and C-3 substituents in equatorial position. The major isomers(7) and (8) were then converted into alkaloids (9) and (10) by previously established methods.



Scheme 2

The critical point of this synthetic strategy was development of a method for removal of the C-3 substituent. It was accomplished by conversion of the ester into amide, then into nitrile and reductive decyanation of the latter A Canadian-Polish research group (Czarnocki-MacLean-Szarek) has used biogenic amine, dopamine (11) and enantiopure carbohydrates: D-glucose,[18] 2,5-anhydro-D-mannose[18] or R-glyceraldehyde[19-21] as substrates in enantioselective Pictet-Spengler modification The most extensively studied reaction was the condensation of dopamine (11) with R-glyceraldehyde which resulted in isoquinoline (13). (Scheme 3).

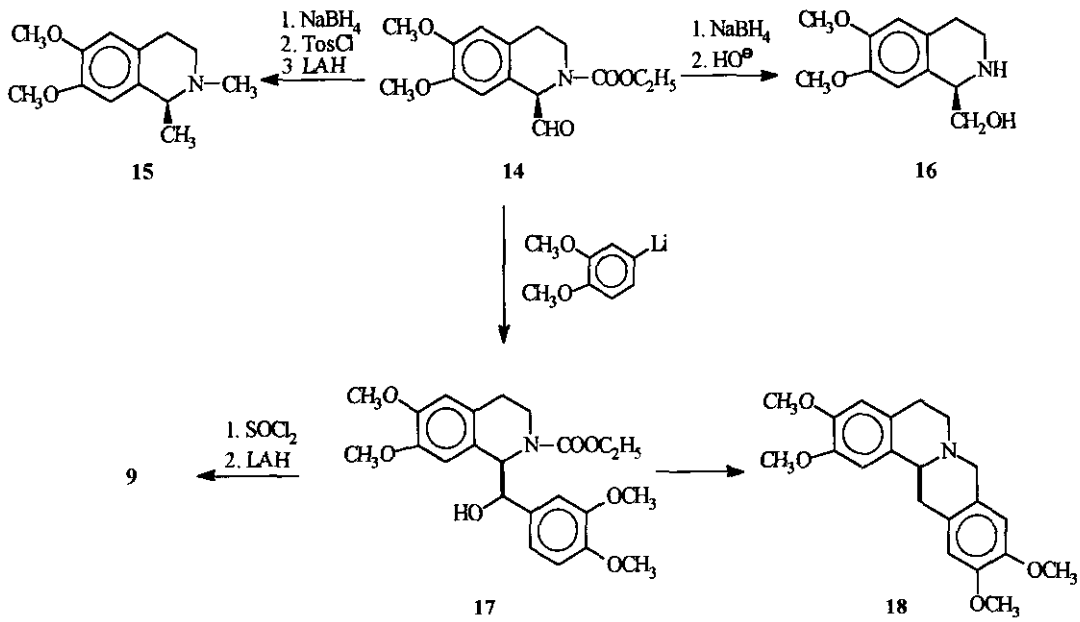


Scheme 3

The stereochemical outcome of this reaction was 9:1 in favour of the 1R diastereomer This high stereoselectivity was ascribed to the influence of the chiral center present in the intermediate iminium ion (12) in the direction of nucleophilic attack by the aromatic ring

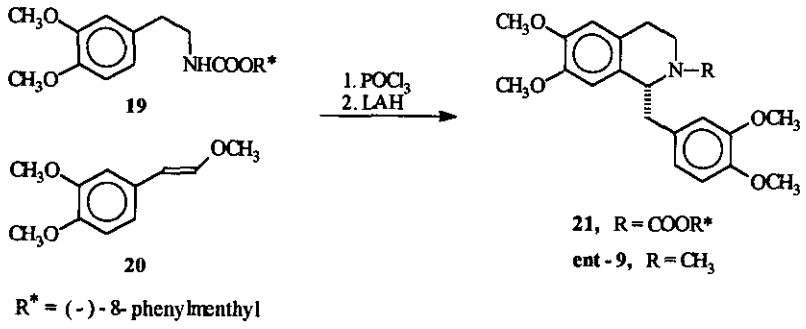
By a sequence of processes involving *N*-acylation, phenolic *O*-methylation and sodium periodate oxidation the condensation product (13) was converted into 2-ethoxycarbonyl-1-formyl-6,7-dimethoxy-1,2,3,4-tetrahydro isoquinoline (14), which then became a key intermediate in synthesis of many alkaloids. In this way 14 was

fransformed in the usual manner into homochiral simple isoquinolines. S-carnegine (15) and R-calycotomine (16) [19,20] On the other hand it was used as a chiral building block in synthesis of more complex molecules. Thus, treatment of 14 with 3,4-dimethoxyphenyllithium afforded optically active α-hydroxybenzylisoquinoline (17), which was transformed into S-laudanosine (9)[20] and into S-xylopinine (18),[21] all in good chemical yield and high enantiomeric excess (*ca.* 90%) (Scheme 4).



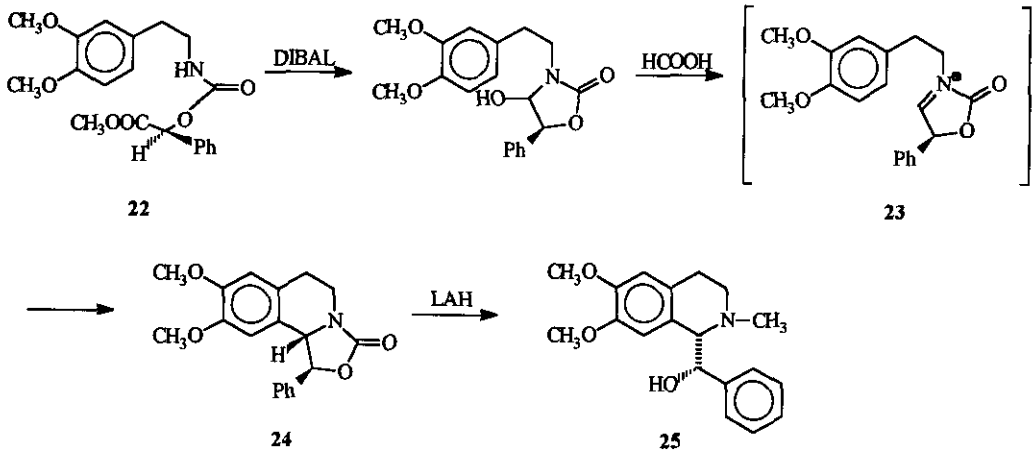
Scheme 4

Another synthesis of R-laudanosine (ent-9) by a Pictet-Spengler protocol was performed by Comins and Badawi[22] (Scheme 5) The 1,5-asymmetric induction was achieved by 8-phenylmenthyloxycarbonyl chiral auxiliary appended to the nitrogen of β-arylethylamine (19). Reaction of carbamate (19) with chemical equivalent of arylacetaldehyde (20) gave in good yield a mixture of diastereomeric isoquinolines, in which 21 was the predominant component. Lithium aluminum hydride reduction of this mixture afforded R-laudanosine (ent-9) with an enantiomeric excess of 63% as determined by optical rotation.



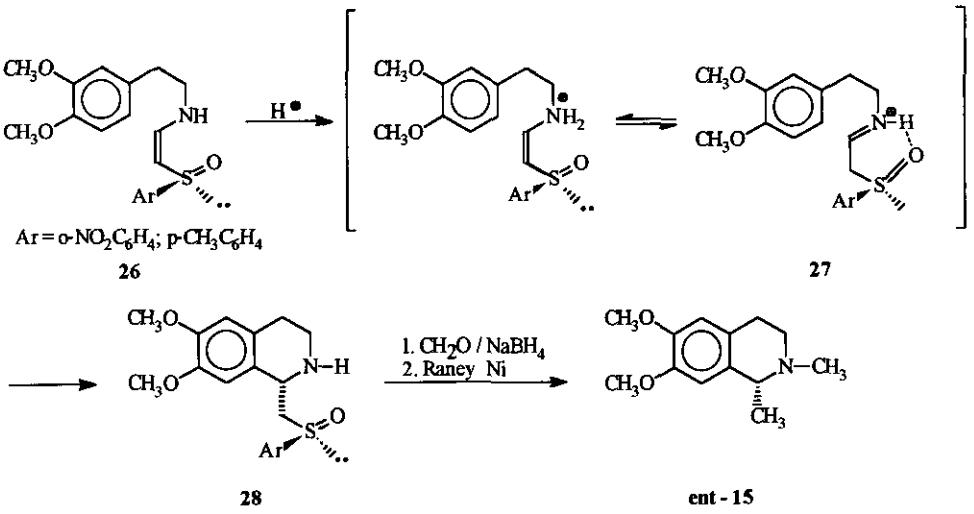
Scheme 5

In the synthesis reported by Kano *et al.*[23] the C-1 substituent was introduced as a part of chiral *N*-alkoxycarbonyl functionality in carbamate (22). (Scheme 6). DIBAL reduction followed by treatment with formic acid resulted in oxazoloisoquinoline (24), formed *via* a cyclic *N*-acyliminium intermediate (23). Reduction of 24 with LAH yielded optically active 1S,αS-hydroxybenzyltetrahydroisoquinoline (25) with excellent yield.



Scheme 6

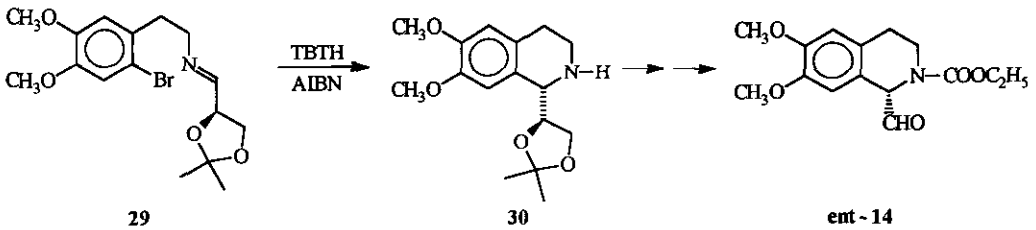
An interesting synthesis in which the chiral auxiliary was placed at the C-1 substituent has been described by Lee *et al.*.[24,25] In this case a sulfoxide functionality was used to control the steric course of this reaction. The chiral β-aminovinyl sulfoxide (26) (Ar = o-$O_2NC_6H_4$, p-$CH_3C_6H_4$), an equivalent of imine, the well established intermediate in the Pictet-Spengler reaction, cyclized in acidic medium to tetrahydroisoquinoline (28). Its stereostructure was proven by transformation to R-carnegine (ent-15). (Scheme 7)



Scheme 7

The remarkable diastereoselectivity observed in this process was postulated to be facilitated by an intramolecular hydrogen bonding, that may be formed in the protonated intermediate imine (27).

A radical cyclization of chiral imine (29), prepared from 2-bromo-4,5-dimethoxyphenylethylamine and R-2,3-*O*-isopropylideneglyceraldehyde, to give tetrahydroisoquinoline (30) in 64% yield and 97% enantiomeric excess was described.[26] The configuration of the new stereogenic center, C-1, was assigned by conversion of 30 into enantiomer of the Czarnocki-MacLean-Szarek isoquinoline (14) . (Scheme 8).



Scheme 8

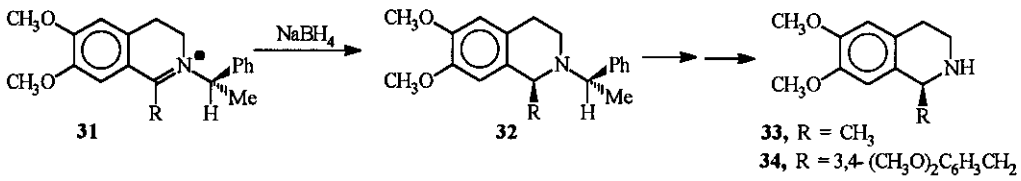
2.2. The Bischler-Napieralski - enantioselective reduction approach.

In the Bischler-Napieralski synthesis a β-arylethylamide is cyclized in an acidic medium to 3,4-dihydroisoquinoline or dihydroisoquinolinium salt which is then reduced to 1,2,3,4-tetrahydroisoquinoline system. Sodium borohydride in methanol or hydrogen in the presence of catalysts are routinely used for the reduction.

In the asymmetric synthesis the stereogenic C-1 center is created during the reduction step, by mainly the two approaches: transfer of asymmetry from a chiral auxiliary[27-36] or through chiral reducing agents.[38-44]
In one case, during the synthesis of (+)- or (-)-6,7-dimethoxy-1-methyltetrahydrisoquinoline-1-carboxylic acid the quaternary chiral center was formed by adding nucleophilic methyl group to 3,4-dihydroisoquinoline.[37]

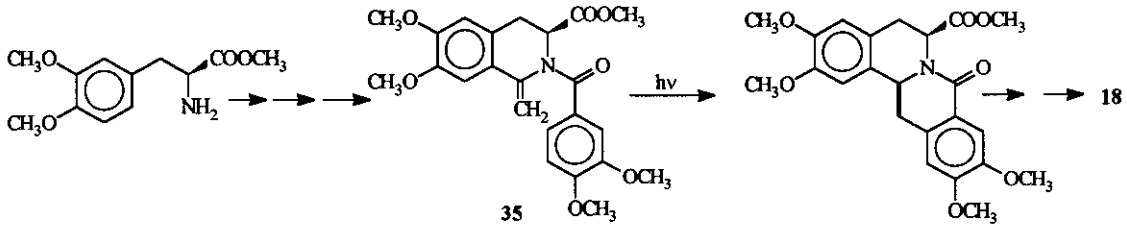
2.2.1. Chiral auxiliary mediated synthesis.

In this synthetic strategy, those intermediate 3,4-dihydroisoquinolines were used which possesed a chiral auxiliary in either the part of the molecule derived from the amine or derived from the acid.
Ishida *et al.*[27] described a synthesis of optically active 3-carboxy-substituted simple isoquinoline alkaloid (2) by cyclization of *N*-methylthiocarbonyl L-Dopa followed by sodium borohydride reduction of the resulting 3,4-dihydro derivative.
Kametani *et al.*[2,3] and Polniaszek *et al.*[28,29] applied in their very efficient and highly stereoselective syntheses optically active 1-substituted 3,4-dihydroisoquinolinium salts, type (31), with chiral α-phenethyl substituent attached to the nitrogen atom The diastereoselection of the hydride reduction step ranged from 72:28 (at 0° C)[2,3] to 94:6 (at -78°C) [28,29] (Scheme 9).



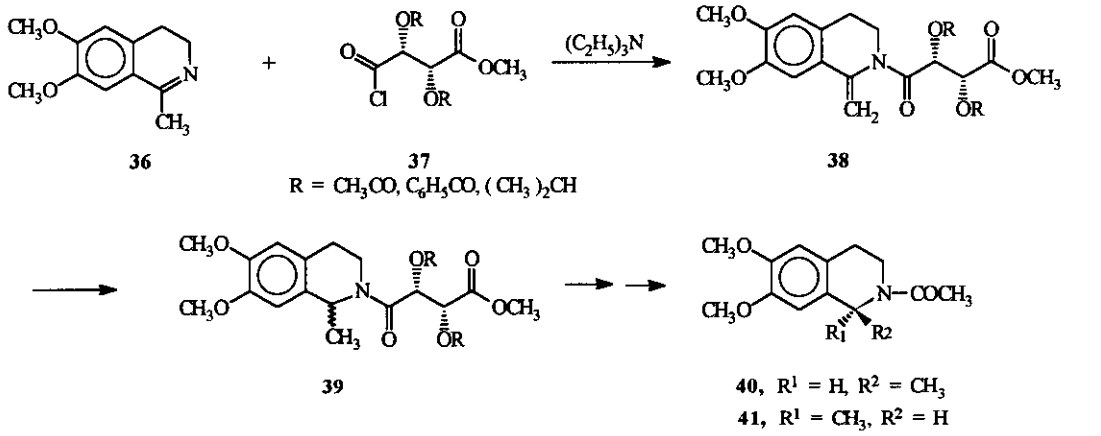
Scheme 9

The configuration of the major 1-substituted tetrahydroisoquinolines (32) was established by transformation to or chemical correlation with S-salsolidine (33) and S-norlaudanosine (34). The influence of steric crowding caused by the *N*-alkyl group on the degree of stereoselection was investigated.[29] Introduction of o-chloro- or o,o`-dichlorophenyl substituent in the *N*-alkyl group increased the diastereoselectivity of this process.
Interesting results were obtained when enamides were used as substrates in this synthesis. Kametani *et al.*[30] have performed a synthesis of S-xylopinine (18) by photochemical cyclization of amide (35) derived from L-3,4-dimethoxyphenylalanine. (Scheme10).



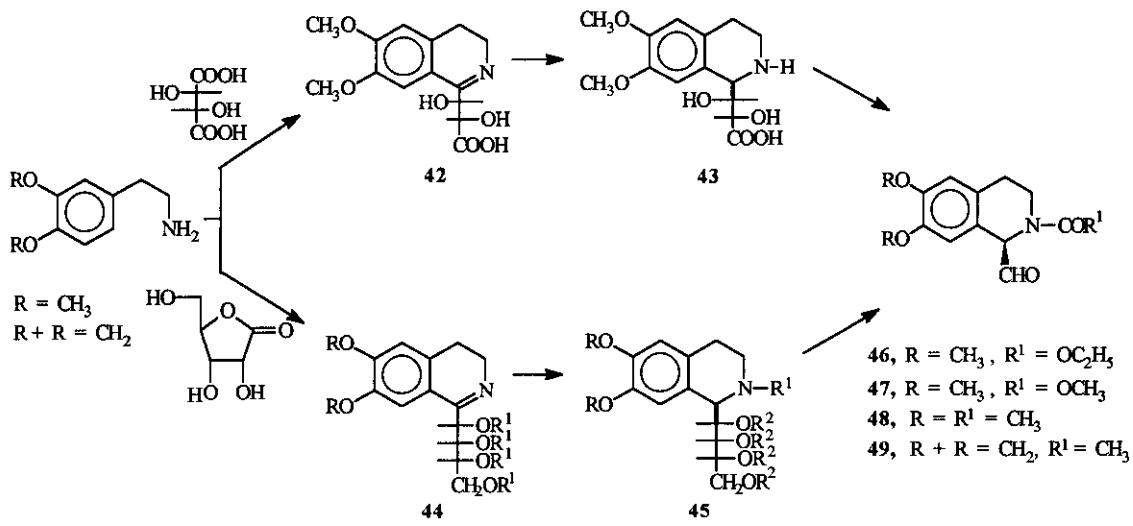
Scheme 10

Czarnocki *et al.*[31,32] have studied asymmertic reduction of various enamides, type (38), prepared from 3,4-dihydro-5,6-dimethoxy-1-methylisoquinoline (36) and D-tartaric acid derivatives (37). (Scheme 11).



Scheme 11

They have demonstrated that by applying a suitable reducing agent the resulting diastereomeric mixture of tetrahydroisoquinolines (39) could be enriched in either 1R- (40) (H_2/Pt) or 1S- (41) ($NaBH_4$, acidic medium) isomers It is worth mentioning that this complementary enantiodivergent synthesis allowed preparation of both enantiomers from a single diastereomer, albeit in a rather poor yield . The diastereoselectivity of the reduction step was assessed by converting the mixture into *N*-acetylsalsolidine (40 or 41) and a comparison of its specific rotation with the reported data.

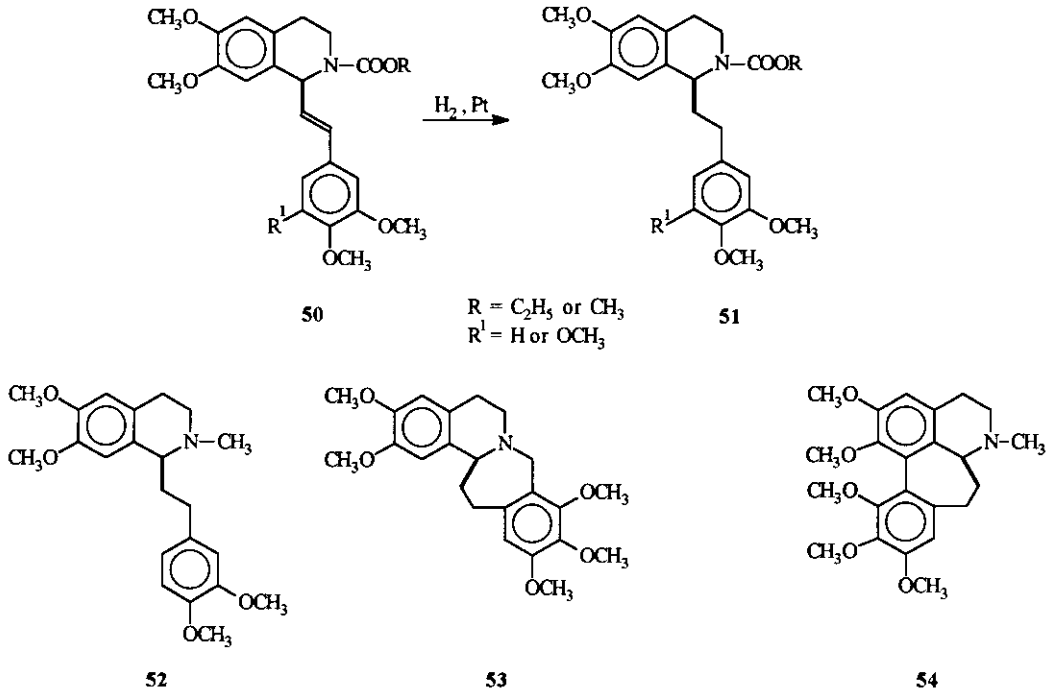


Scheme 12

Tartaric acid was used again by the same authors as a chiral building block for construction of the "acidic" part of isoquinoline (43) by the Bischler-Napieralski protocol.[33,34] In a similar way D-ribonolactone was used to give 45.[35,36] This synthetic strategy is outlined in Scheme 12. 3,4-Dialkoxyphenethylamine was condensed with either D-tartaric acid or D-ribonolactone to give, *via* the corresponding amides, the 3,4-dihydro-isoquinolines (42) and (44), respectively. Dihydroisoquinoline (42) was then reduced stereoselectively to tetrahydro derivative (43), which after *N,O*-alkoxycarbonylation, *O*-dealkoxycarbonylation and periodate cleavage of the glycolic function gave the key isoquinoline (46) or (47) in good chemical yield and high degree of stereoselectivity. Contrary to the expectations, the dihydroisoquinoline (44) (R^1=$COCH_3$), prepared from ribonolactone, turned out to be resistant towards catalytic hydrogenation as well as to hydride reduction It could be reduced to the corresponding tetrahydro derivative (45) (R^1= R^2= $COCH_3$) only after preliminary oxidation of the imine nitrogen to *N*-oxide functionality Hydrolysis followed by periodate oxidation furnished then the 1-formyl derivative (48).[35] Compound (49) was prepared in a similar fashion.[36]

The new and improved procedure for preparation of enantiomericaly pure 2-acetyl- or 2-alkoxycarbonyl-1-formyl-6,7-dialkoxy-1,2,3,4-tetrahydroisoquinolines (46 - 49) presented in Scheme 12, has extended the Czarnocki-MacLean-Szarek synthetic strategy to the synthesis of isoquinoline alkaloids, obtainable in good yields and high optical purity. Treatment of compounds (46) and (47) with a Wittig reagent derived from di- or trimethoxybenzyltriphenylphosphonium chloride resulted in condensation products (50), which upon reduction

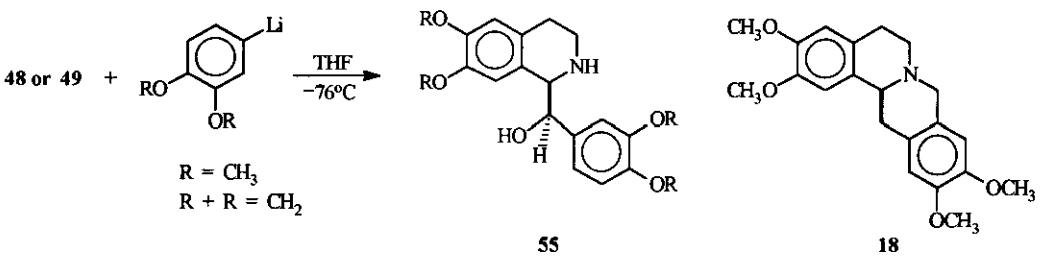
gave phenylethylisoquinolines (51) These were then transformed in straightforward steps into a series of "homo" alkaloids: S-homolaudanosine (52),[33,34] S-pentamethoxyhomoprotoberberine (53)[33,34] and homoaporphine (54).[34] (Scheme 13)



50 51 52 53 54

Scheme 13

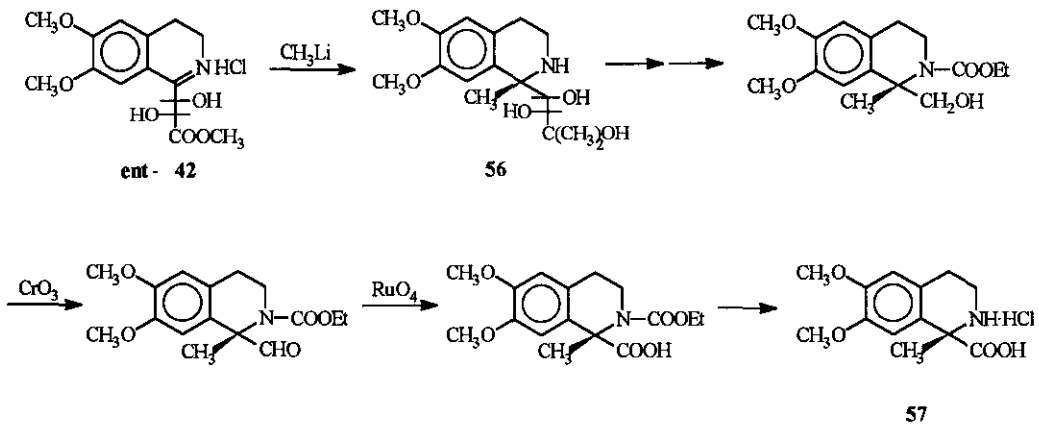
In another series of experiments involving addition of 3,4-methylenedioxy- or 3,4-dimethoxyphenyllithium to compounds (48) and (49), respectively, α-hydroxybenzyltetrahydroisoquinolines (55) were synthesized [35,36] One of them, (55, R = CH_3), after Mannich condensation followed by deoxygenation led to protoberberine (18), the other one (55, R+R = CH_2), after *N*-methylation was used to solve the "decumbensine" problem. [36] (Scheme 14).



55 18

Scheme 14

L-Tartaric acid derived dihydroisoquinoline, ent-42, was the chiral substrate in the first enantioselective synthesis of a "mammalian" alkaloid, (+)-6,7-dimethoxy-1-methyl-1,2,3,4-tetrahydroisoquinoline-1-carboxylic acid (57).[37] The quaternary chiral C-1 center was formed by adding methyllithium to the imine double bond (or to the corresponding nitrone) affording 56 as the only diastereomer. (Scheme 15). Further transformation of 56 by previously established methods, and final ruthenium tetroxide oxidation resulted in (+)-salsolidine-1-carboxylic acid (57) in 35% overall and 80% optical purity. In the same way the (-)-enantiomer was prepared with the mediacy of D-tartaric acid.



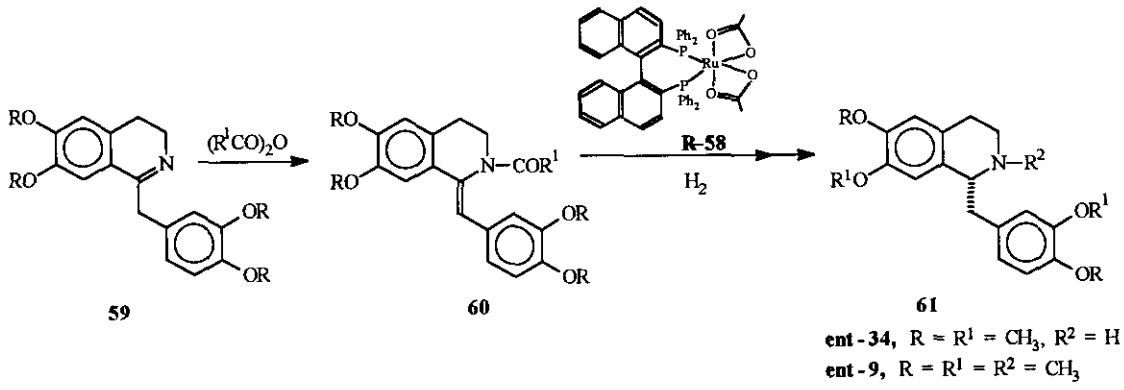
ent - 42 56 57

Scheme 15

2.2.2. Reduction of prochiral 3,4-dihydroisoquinolines with chiral reducing agent.

Another approach to chiral tetrahydroisoquinolines *via* the Bischler-Napieralski synthesis was based on the use of chiral reducing agents to reduce stereoselectively the *C*=N double bond in the 3,4-dihydrointermediates, or the $C_1 = C_\alpha$ double bond in the corresponding alkylidene derivatives.

The most outstanding results have been obtained by Noyori *et al.*[38,39] in homogeneous catalytic hydrogenation of various enamides with hydrogen over hexacoordinated ruthenium complex bearing chiral R- or S-BINAP (58) ligand. The *Z-N*-acetyl-1-alkylidenetetrahydroisoquinolines (60) prepared from 3,4-dihydroisoquinolines (59) by acylation, were hydrogenated to the corresponding saturated derivatives (61) in almost quantitative yield and with high enantiomeric excess (90-100%). (Scheme 16).

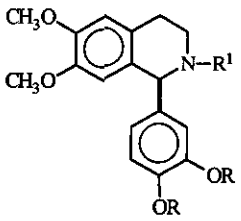


Scheme 16

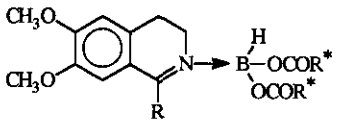
The reduction using R-58 as a catalyst gave generally the *1R* products (61), whereas the *1S enantiomers* (ent-61) were available by way of catalysis with S-58. Following the known procedures compounds (61) (R^2= $COCH_3$ or CHO) were converted into the following alkaloids: R-norlaudanosine (ent-34 = 61, R = R^1= CH_3, R^2= H), R-laudanosine (ent-9 = 61, R = R^1= R^2= CH_3), R-norreticuline (61, R = CH_3, R^1= R^2= H) and *S-salsolidine (33). This catalytic hydrogenation* allowed synthesis of both antipodal products in high enantiomeric excess to occur with equal ease provided that the appropriate ligand in the BINAP-Ru catalyst has been chosen.

There are several examples of the use of chiral hydride to introduce asymmetry at the C-1 during a reduction of the 3,4-dihydroisoquinolines. The first one to perform such an asymmetric reduction was Grundon *et al.*,[40] who studied lithium hydroalkyl-dipinan-3α-ylborate reduction of 3,4-dihydropapaverine (59, R= CH_3) and its methiodide. The optical purity of the product, R-laudanosine (ent-9 = 61, R = R^1= R^2= CH_3), was rather poor and ranged from 4% to 25%.

More satisfactory results were obtained by Yamada *et al.*,[41,42] who applied sodium borohydride modified by natural *N*-acylated amino acids. Reagents prepared from $NaBH_4$ (1 equivalent) and S-*N*-acylproline (3 equi valents) provided fair yields (55 - 60% e.e.) of S-norlaudanosine (34 = ent-61, R = R^1= CH_3, R^2= H) from 3,4-dihydropapaverine (59, R = CH_3). In the synthesis of S-salsolidine (33), S-norcryptostyline I (62, R^1= H) and S-norcryptostyline II (63, R^1= H) the e.e. ranged from 70% - 86%. An initial intermediate boron-imine complex (64) was postulated to be formed in the course of this reaction. (Scheme 17).



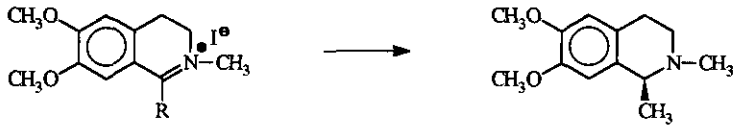
62, R + R = CH_2
63, R = CH_3



64

Scheme 17

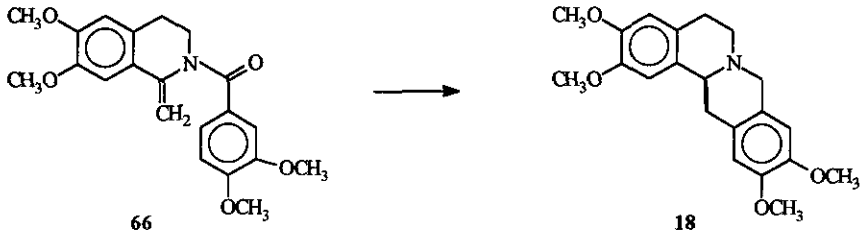
Recently, Cho *et al.*[43] have studied the asymmetric reduction of 3,4-dihydroisoquinolinium salts, type (65), by using various chiral hydride reagents such as K glucoride, Itsuno's reagent and Mosher's reagent. In the synthesis of S-carnegine (15) they have established the relative effectiveness of these reagents in the order: 52.3 % e.e. : 18 % e.e. : 66 4 % e.e., respectively. (Scheme 18).



65 **15**

Scheme 18

A 1:1 lithium aluminum hydride - quinine complex was applied by Ninomiya *et al.*[44] in a reductive photocyclization of enamide (66) to give S-xylopinine (18) in 38 % chemical and 37 % optical yield. (Scheme 19).



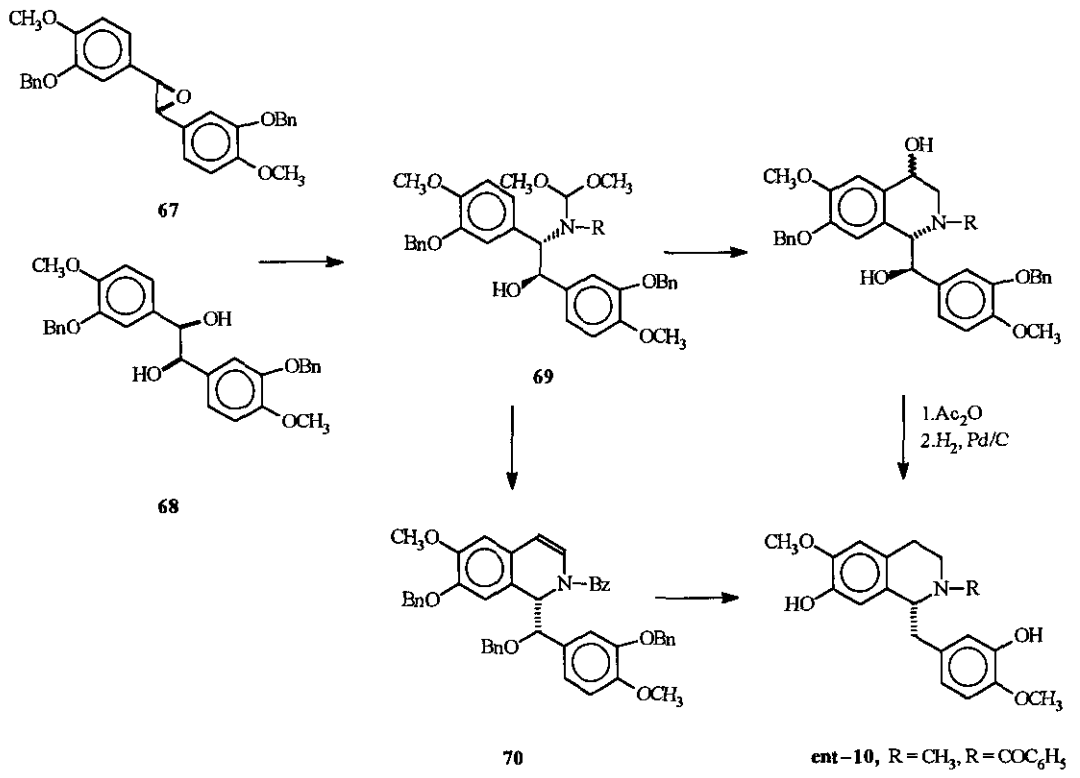
66 **18**

Scheme 19

2.3. The Pomeranz-Fritsch cyclization.

To introduce asymmetry in the synthesis of R-reticuline (ent-10) Hirsenkorn[45] used as a starting material an optically active epoxide (67) or its dihydroxy analog (68), prepared from the corresponding stilbene by

asymmetric epoxidation or Sharpless hydroxylation, respectively (Scheme 20).



Scheme 20

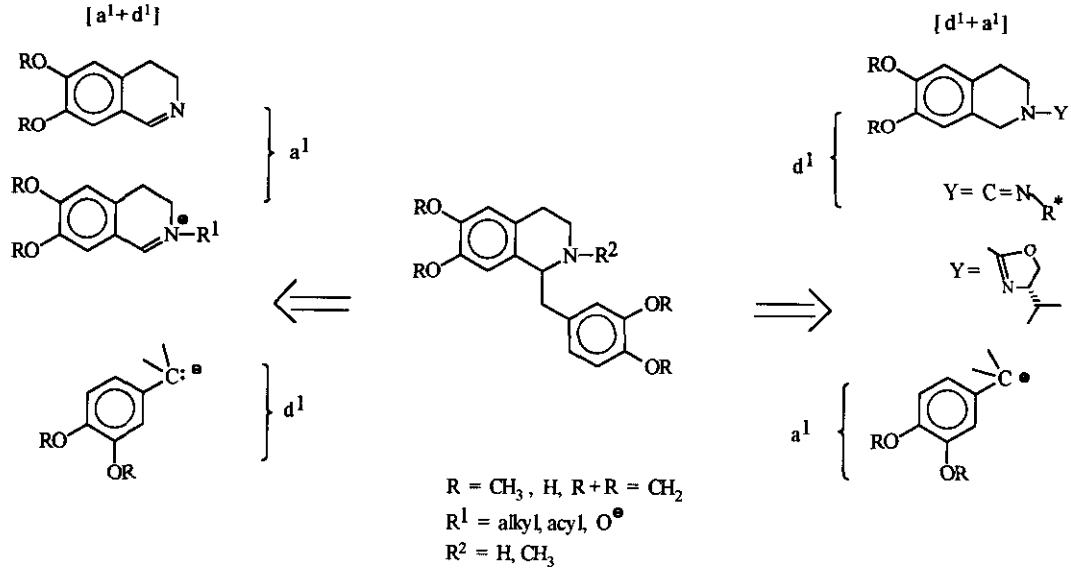
Aminolysis with amino- or methylaminoacetaldehyde dimethyl acetal proceeded with high yield and with high stereospecificity giving the 1-amino alcohols 69 (R = H or R = CH_3). Acid-catalysed cyclization of 69 (R = CH_3) followed by *O,O*-acetylation and hydrogenolysis furnished R-reticuline (ent-10) in 82 % e.e. In another experiment, compound 69 (R = H) could be converted into 1,2-dihydroisoquinoline (70), simply by treatment with benzoyl chloride. Catalytic hydrogenation of the latter afforded R-*N*-benzoylnorreticuline (ent-10, R = COC_6H_5)

The S-enantiomer (10) has been prepared in 72 % e.e. from ent-67 according to the same procedure. This strategy seems to be the shortest synthesis of reticuline; it involves 7 step sequence starting with isovanillin. Moreover, it is also economically feasible.

3. The "C-C-connective" methodology.

Recently, a number of new syntheses of isoquinoline alkaloids has been developed in which the alkaloid 's carbon skeleton was constructed by connecting two building blocks of which one was always a derivative of isoquinoline, tetrahydro- or dihydroisoquinoline. The other, containing the C-1 substituent was then introduced to form the stereogenic center at the C-1 position of the isoquinoline nucleus.

Following the concept of the retrosynthetic analysis, two general ionic strategies should be taken into consideration. (Scheme 21).



Scheme 21

One of them involves such reactions in which the isoquinoline unit is used as an a^1 synthon, whereas the other unit is a d^1 or alkylating synthon ($[a^1+d^1]$ strategy). These syntheses usually involve addition of carbanions to 3,4-dihydroisoquinolines or to the corresponding *N*-alkyl- or *N*-acylisoquinolinium salts or nitrones.

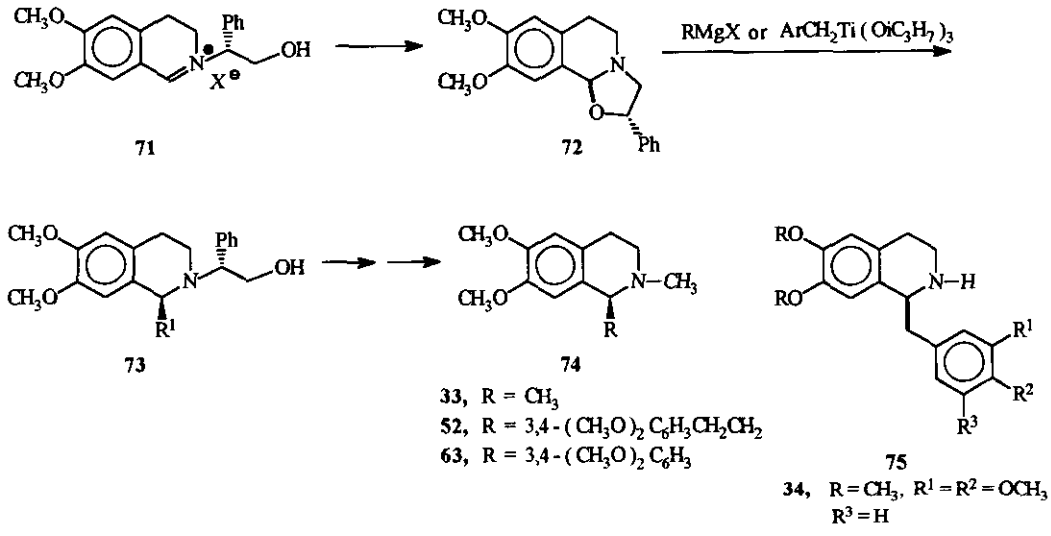
In the second strategy ($[d^1+a^1]$) the tetrahydroisoquinoline is a d^1 synthon. The Umpolung of reactivity of the C-1 atom is achieved by several *N*-activating groups. In the enantioselective synthesis best results were obtained when the isoquinoline nitrogen atom was a part of a chiral amidine or bore a chiral oxazoline substituent. In this method the second building block must be used as an a^1 or alkylating synthon. Like in the previously described synthetic methods also here the concept of asymmetric induction was the basis of these

strategies. The chiral auxiliaries were placed either in the isoquinoline synthons, usually as the *N*-substituents, or in synthons of the "lower" fragment of the target molecules.

3.1. The [a^1+d^1] *synthetic strategy.*

The use of Grignard reagents in the synthesis of isoquinoline alkaloids is well known.[10,11] Its application in enantioselective synthesis has recently been reported by many research laboratories.[46-49]

Polniaszek and Dillard[46] have performed a stereospecific synthesis of S-cryptostyline I (62, R = CH_3) by a reaction of 3,4-methylenedioxyphenylmagnesium bromide with the chiral iminium salt (31) (R = H).

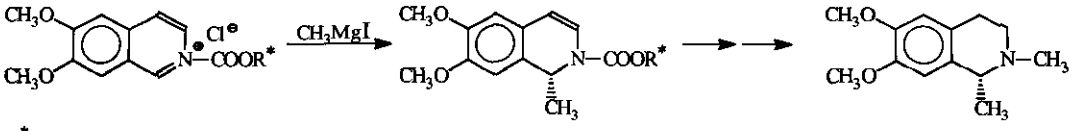


Scheme 22

Yamato *et al.*[47,48] have succeeded in carrying out a synthesis of enantiomerically pure 1-alkyl- and 1-aryltetrahydroisoquinolines *via addition of Grignard* reagent to chiral oxazolo-tetrahydroisoquinolines (72). These intermediates were prepared in 80 - 90 % d.e. by cyclization of S- or R-phenylglycinol derived 3,4-dihydroisoquinolines (71) and ent-71, respectively. *Nucleophilic substitution in 72* by a variety of Grignard reagents, activated in the case of benzylmagnesium chloride with triisopropoxytitanium chloride,[48] afforded the corresponding tetrahydroisoquinolines (73), diastereomerically pure (Scheme 22). *The synthesis was then* completed by removal of the chiral substituent by hydrogenolysis. In this way the following compounds were synthesized: S-norarmepavine (75, R = CH_3, R^1= R^3= H, R^2= OH), S-tetrahydropapaverine (34 = 75, R = CH_3, R^1= R^2= OCH_3, R^3= H), S-trimetoquinol (75, R = H, R^1= R^2= R^3= OCH_3), and after *N*-methylation:

S-salsolidine (33 =74, R =CH_3), R-salsolidine (ent-33),S-homolaudanosine (52 = 74, R = 3,4-$(CH_3O)_2C_6H_3$ CH_2CH_2) and S-cryptostyline II (63 = 74, R = 3,4-$(CH_3O)_2C_6H_3$). A similar synthetic strategy in the synthesis of R-cryptostyline I (62, R^1=CH_3) has been applied by Roussi *et. al.* [48a]

In a synthesis of R-carnegine (ent-15) Comins and Badawi[49] have performed asymmetric addition of methylmagnesium iodide to aromatic 6,7-dimethoxyisoquinoline in the presence of (-)-8-phenylmenthyl chloroformate. An *N*-acylisoquinolinium salt (76) was postulated as the first intermediate which then underwent nucleophilic attack of the methylmagnesium iodide affording an 83 · 17 mixture of diastereomeric 1,2-dihydroisoquinolines in which the 1R isomer (77) predominated. This mixture after catalytic hydrogenation followed by $LiAlH_4$ reduction gave R-carnegine (ent-15) in 62 % of optical purity. (Scheme 23).

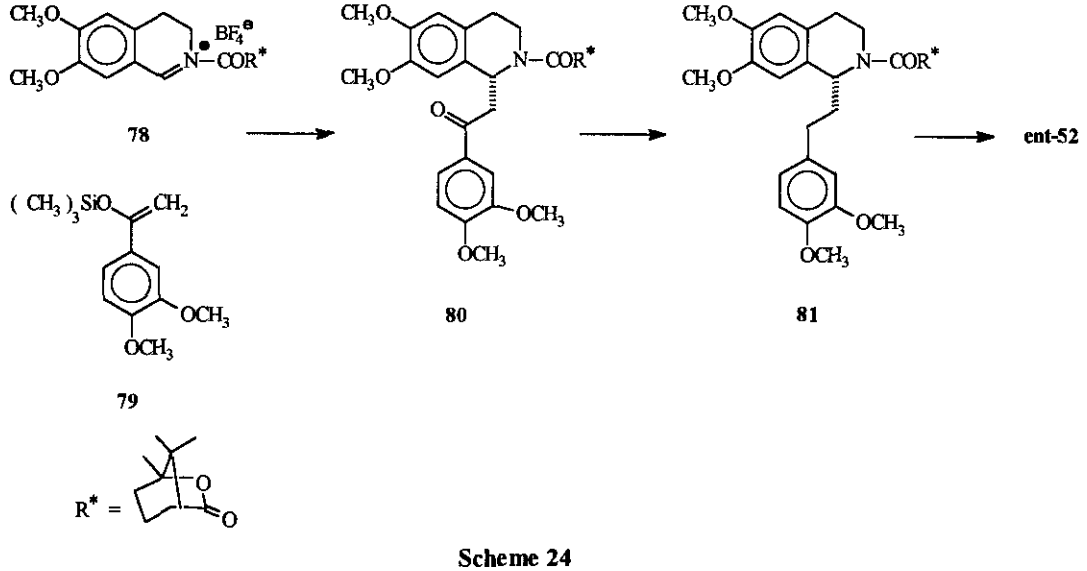


R* = (-)-8-phenylmenthyl

76 77 ent-15

Scheme 23

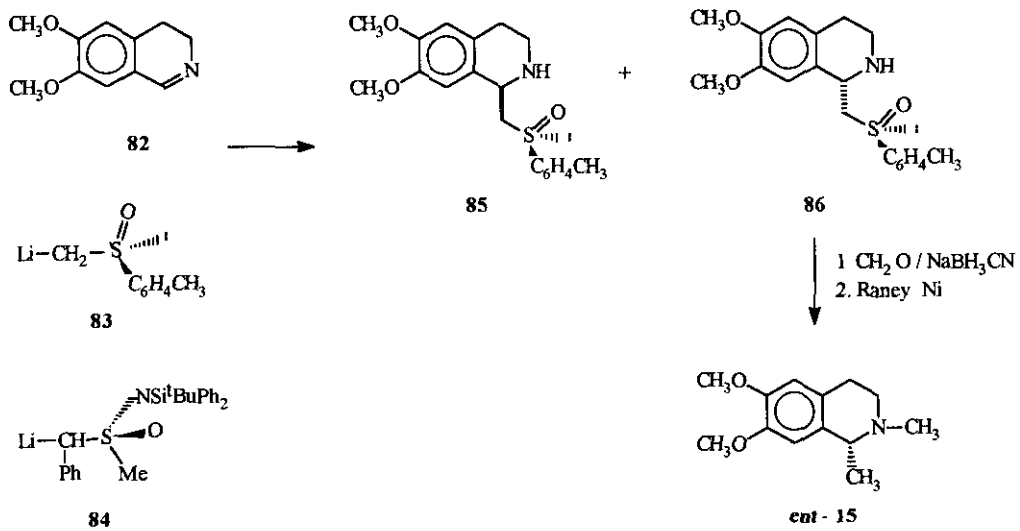
Wanner *et al.*[50,51] have synthesized 99 % pure R-homolaudanosine (ent-52) according to their asymmetric electrophilic α-amidoalkylation strategy involving addition of silyl enol ether of acetophenone derivative (79) to chiral *N*-acyl-3,4-dihydroisoquinolinium salt (78), in which the acyl group originated from camphanic acid.



Scheme 24

The unseparable mixture of diastereomeric addition products, in which 80 was the prevailing component (82 %), was hydrogenated over 10% Pd/C in acidic medium to afford 1-phenylethyltetrahydroisoquinolines, from which diastereomer (81) was separated in 38 % yield. To complete the synthesis the chiral auxiliary was removed and the secondary amine was *N*-methylated (Scheme 24).

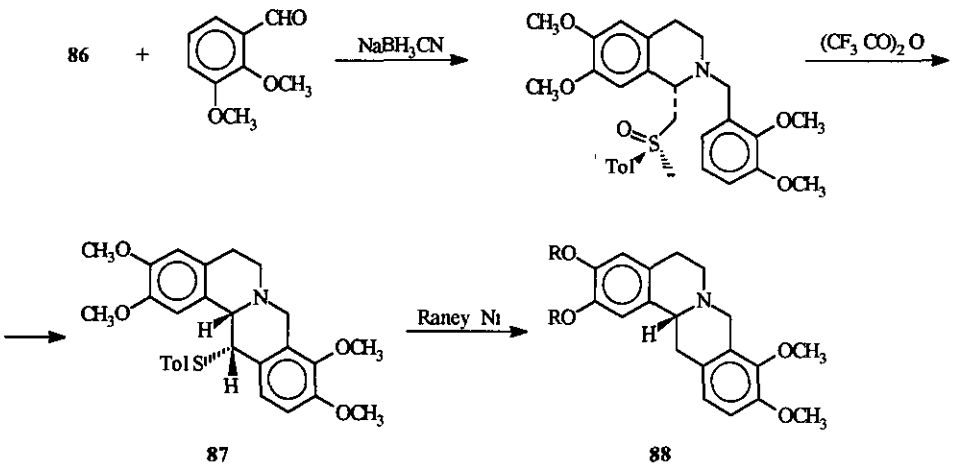
The [$a^1 + d^1$] strategy, in which the chiral auxiliary was placed in the second building block introducing the C-1 substituent, has been investigated by an Australian research group headed by Pyne.[52-56,58] In this approach the alkaloid 's carbon skeleton was build-up by the addition of chiral carbanions (83) or (84) (whose optical activity was due to the presence of stereogenic sulfur) to 3,4-dihydroisoquinolines (82) (Scheme 25).



Scheme 25

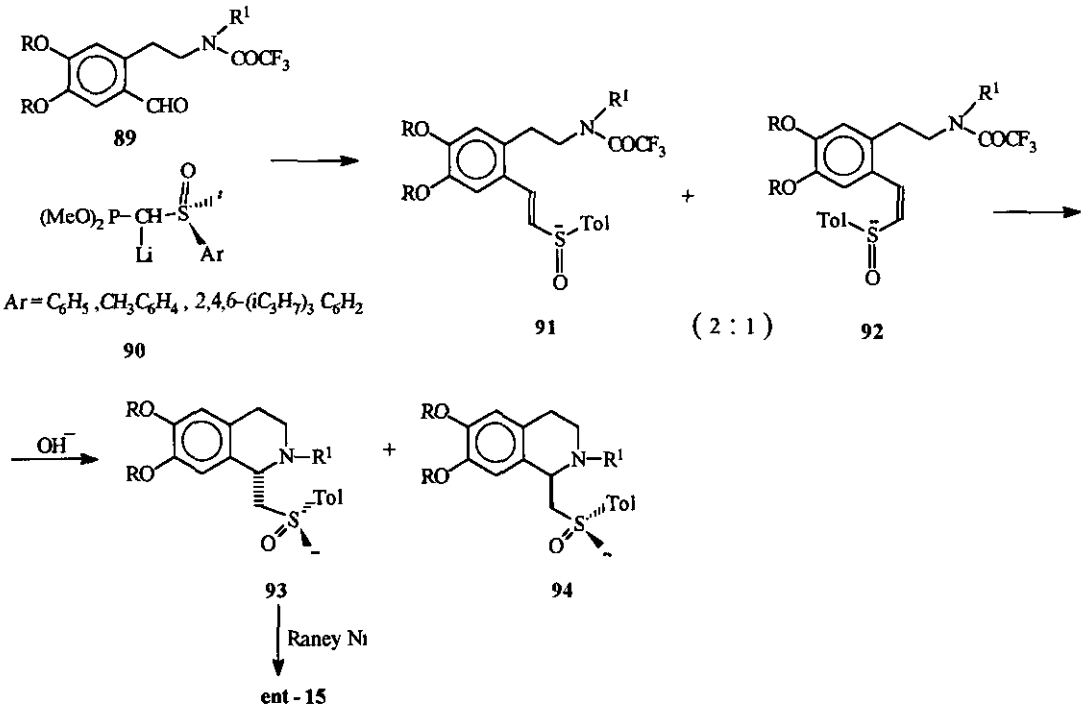
In order to increase the reactivity of the imine, a complex with boron trifluoride etherate was preformed in a few experiments, or the nitrogen atom was oxidizes to a =N-O function.[56] The latter modification was also studied by Murahashi[57]. Pyne *et al.* have found out that the diastereoselectivity of the addition step depended on the reaction temperature. In reaction of imine (82) with sulfoxide (83) it was possible, by choosing the appropriate temperature, to enhance the formation of either the 85 (at -45°C) or the more stable 86 (at 0°C). The authors suggested an equilibrium between the isomers (85) and (86) to occure *via* a reto-Mannich addition - Mannich addition reaction sequence, yet, the thermodynamic preference of 86 over 85 was not clear

To demonstrate the synthetic utility of this method Pyne's group has exploited the addition product (86) in the synthesis of R-carnegine (ent-15) and R-tetrahydropalmatine (88, R=CH_3).[55] The former alkaloid was obtained by *N*-methylation and reductive desulfurization with Raney nickel. The four-step synthesis of 88 (R=CH_3) is shown in Scheme 26. Reductive alkylation of 86 with 2,3-dimethoxybenzaldehyde and sodium cyanoborohydride followed by Pummerer rearrangement gave the tetracyclic sulfide (87) as a single isomer. Reductive desulfurization afforded R-tetrahydropalmatine (88, R=CH_3) of high optical purity.



Scheme 26

In another synthetic strategy Pyne *et al.*[59-62] have again made use of chiral sulfoxide functionality to control the steric course of the reaction. This time it was an intramolecular addition of amides to chiral vinyl sulfoxides to result in tetrahydroisoquinolines. (Scheme 27) The key vinylsulfoxides were prepared as a separable pair of *E*-91 and *Z*-92 isomers from O-aminoethyl substituted aromatic aldehydes (89) (which may be considered as an "open-chain" form of *N*-acyltetrahydro isoquinolinium hydroxide) and chiral Horner-Wittig reagent (90). Cyclization of either vinyl sulfoxide (91) (R^1 = CH_3) or 92 (R^1 = CH_3) in basic medium gave a mixture of diastereomeric isoquinolines (93) (R^1= CH_3) and (94) (R^1 = CH_3), which after separation could be transformed into alkaloids. Thus, 93 (R = R^1= CH_3) treated with Raney nickel was reductively desulfurized to R-carnegine (ent-15) in 51 % yield. From 93 (R+R = CH_2, R^1= 2,3-$(CH_3O)_2C_6H_3CH_2$) R-canadine (88, R+R= CH_2) was obtained in a sequence of transformations involving Pummerer rearrangement-cyclization and reductive desulfurization.[62] Factors that may influence the steric course of various stages of this synthesis have been discussed throughout all the publications.

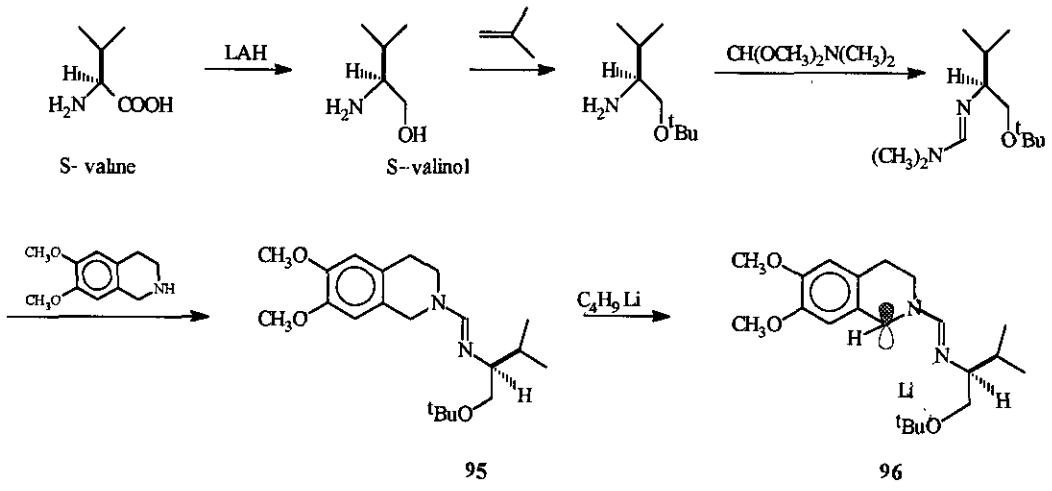


Scheme 27

3.2. The $[d^1 + a^1]$ *synthetic strategy.*

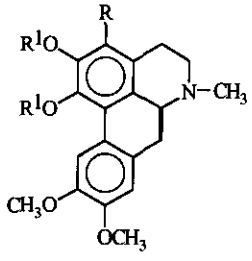
Over the past decade a powerful method of synthesis of optically pure alkaloids of the isoquinoline and indole class has been developed in Mayers` laboratories [63-67] and by Gawley`s group.[68-74]

Meyers has demonstrated that formamidines prepared from tetrahydroisoquinoline and chiral amino alcohols derived from natural amino acids give excellent optical yield in the alkylation of the C-1 prochiral center of the isoquinoline nucleus. Such a chiral auxiliary is able not only to increase the acidity of an α-proton to the nitrogen but also to stabilize the so formed carbanion by bidentate chelation (e.g 96 in Scheme 28). In Scheme 28 a typical synthesis of formamidine (95) from S-valine (*via* a dimethylformamidine prepared from t-butyl ether of valinol and DMF-acetal) and tetrahydroisoquinoline is shown.The metalation of formamidine (95) with lithium bases followed by alkylation proceeds in good yield and with very high diastereomeric excess. The synthesis is then completed by removal of the chiral auxiliary by hydrazinolysis followed by standard operations.

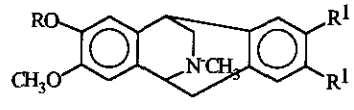


Scheme 28

Applying formamidine (95) or its analogs as building blocks and several alkylating reagents a number of isoquinolines belonging to various types of alkaloids have been synthesized They are· S-salsolidine (33)[63] a simple isoquinoline alkaloid, two benzylisoquinolines· S-laudanosine (9)[63] and S-reticuline (10),[65] S-xylopinine (18)[63] a protoberberine, two aporphines.S-glaucine (97)[64] and S-ocoteine (98),[63] three isopavines: (5S,12S)-reframoline (99),[63] (5S,12S)-*O*-methylthalisopavine (100)[66] and (5S,12S)-8,9-didemethoxythalisopavine (101)[64] and one dibenzopyrrocoline, (13S,7R)-cryptaustoline (102)[67] as well as "homo" alkaloids: S-homolaudanosine (52)[63,64] and S-homoglaucine (103).[64] (Scheme 29). All these alkaloids have been obtained in high enantiomeric purity ranging from 87 % to 99 %.

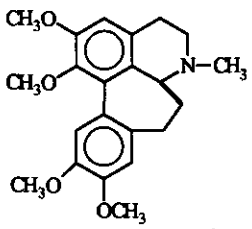


97, R = H, $R^1 = CH_3$
98, R = OCH_3, $R^1 + R^1 = CH_2$

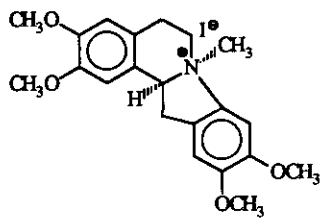


99, R = H, $R^1 + R^1 = OCH_2O$
100, R = CH_3, $R^1 = OCH_3$
101, R = CH_3, $R^1 = H$

Scheme 29



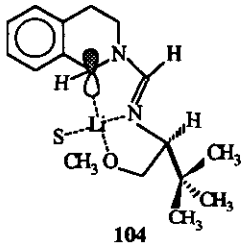
103



102

Scheme 29

In order to explain the high 1S stereoselectivity observed in the alkylation of these formamidines Meyers *et al.* have conducted mechanistic studies which allowed to postulate a mechanism which assumes the deprotonation of the α-H to occur from the α-face of the molecule. As a result a conformationally more stable anion is generated, which then undergoes alkylation from the β-face affording the 1S-diastereomer.[66] As it followed from examination of molecular models and from molecular mechanics of the two chelated carbanions (104) and (105) the latter one is less stable by 2.3 kcal/mol due to repulsive steric interaction between the formamidine vinyl hydrogen and the methyl hydrogen of the alkyl (t-butyl in Figure 1) group.



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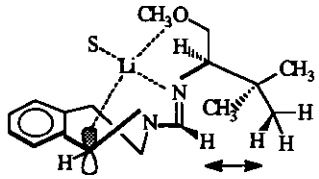


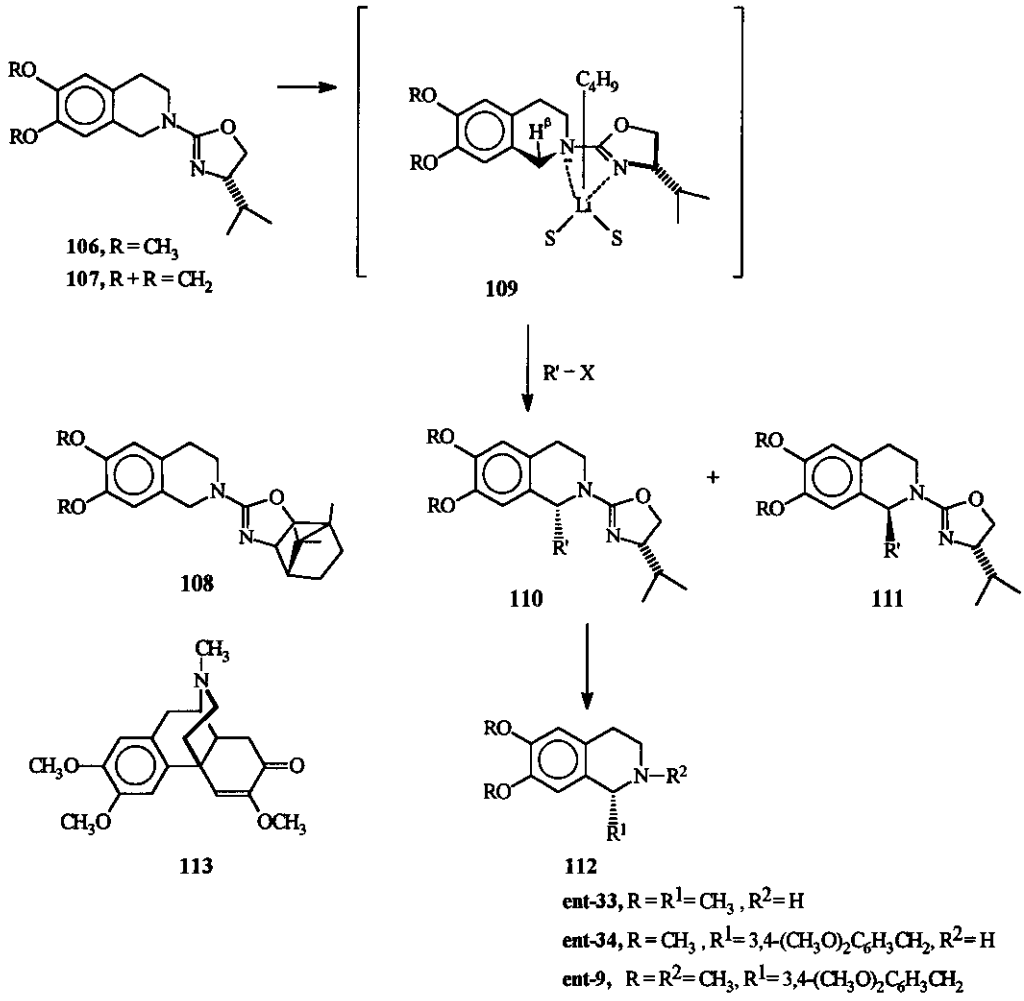
105

Figure 1

In conclusion it should be emphasized that the Meyers' formamidine chemistry not only allows to perform the synthesis in good chemical yields and with excellent optical purity but also to reach the target molecule with a predictable absolute stereochemistry.

In a closely related approach Gawley *et al.*[68-74] have utilized a chiral oxazoline affixed to the isoquinoline nitrogen for both the functionalization of the prochiral C-1 carbon to act as a d^1 synthon and for the transfer of chirality. The routinely used *N*-oxazolylisoquinolines were those derived from S-valinol (106, 107) although many others were prepared and their ability to influence the steric course of the alkylation step investigated.[70]

Recently, they have discovered that a camphor-derived oxazoline (108) is very efficient in increasing the chemical and optical yield in carbonyl addition reactions.[74] (Scheme 30).



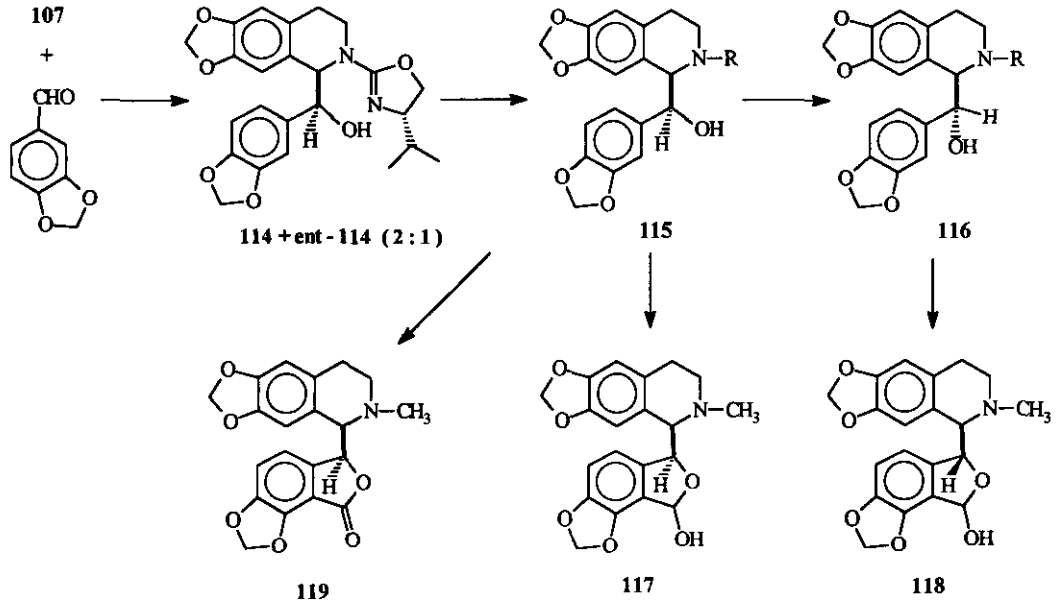
Scheme 30

The key isoquinolyloxazolines (106) and (107) were prepared by condensation of S-2-ethoxy-4-isopropyl-oxazoline with the corresponding 6,7-disubstituted tetrahydroisoquinolines. Metalation with butyllithium in THF and alkylation of the resulting anion afforded 1-substituted tetrahydroisoquinolines (110) and (111) of which the former ones were always predominant.

When methyl iodide was used for alkylation of 106 and the auxiliary removed, optically pure R-salsoldine (ent-33 = 112, R = R^1= CH_3, R^2= H) was obtained while treatment of 106 with 3,4-dimethoxybenzyl chloride followed by hydrolysis led to R-norlaudanosine (ent-34 = 112, R = CH_3, R^1=3,4-$(CH_3O)_2C_6H_3CH_2$, R^2=H). It was then *N*-methylated to give R-laudanosine (ent-9 = 112, R=R^2=CH_3, R^1=3,4-$(CH_3O)_2C_6H_3CH_2$), which after electrochemical oxidative cyclization was converted into *O*-methylflavinantine (113), an alkaloid

having the morphine skeleton. It is noteworthy that the attachment and removal of the chiral oxazoline auxiliary occurred in routinely high yields

It turned out that in the alkylation the major isomers were of 1- R-configuration. Such a steric course of this process was explained[70] by assuming the formation of an initial oxazoline - butyllithium complex (109) in which the butyl group was oriented anti to the isopropyl part of the oxazoline ring and thus in a suitable position to remove the β-H proton. It was not clear if, in order to produce 110, the alkylating agent entered from the β-face causing retention of configuration of the organolithium or from the α-face with inversion. Detailed mechanistic studies involving examination of various external and internal factors as well as semiempirical molecular orbital calculation have been carried out.[70,71]



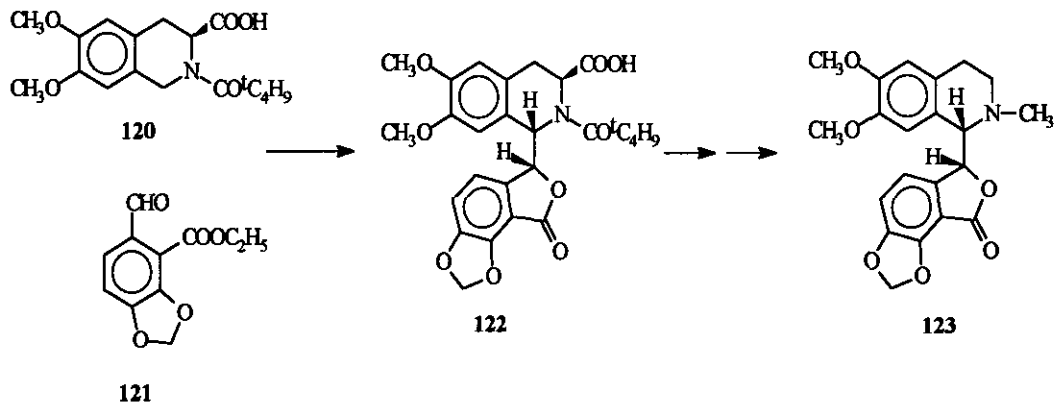
Scheme 31

The Gawley's methodology has not been limited to the alkylation reactions only but was adapted to addition of the C-1 metalated tetrahydroisoquinolines to carbonyl compounds opening a way to synthesis of C-α-oxygenated alkaloids.[72,73] In this way, starting with isoquinoline (107) and piperonal a phthalideisoquinoline alkaloid, (-)-bicuculline (119) and two phthalideisoquinoline hemiacetals, (-)-egenine (117) and (-)-corytesine (118) along with the corresponding α-hydroxybenzyltetrahydroisoquinolines (115) (R = CH_3) and (116) (R = CH_3) have been synthesized. (Scheme 31). The key step here was the addition of piperonal to 1-metalated isoquinoline (107) used as a Grignard reagent prepared from the 1-lithiated derivative by

transmetalation with magnesium bromide. In the 100 % erythro-selective process the ratio of enantiomers (114) and (ent-114) was determined as 2 : 1. Enantiomer (114) was enriched to 100 % e.e. by simple recrystallization of its (+)-tartrate salt. The absolute configuration of 114 was established by conversion to the alkaloids: (-)-egenine (117) and (-)-bicuculline (119) of known stereochemistry. This process involved a series of reactions including hydrolysis to 115 (R = H), *N*-methylation to 115 (R = CH_3) and either *C*-formylation to give 117 or *C*-carbonylation to give 119. (-)-Corytensine (118) was available from compound (116), prepared from 115 by epimerization.

It is important to notice that the carbonyl addition occurred from the opposite face to that of alkylation, leading to products with opposite configuration at C-1.

In another [d^1 + a^1] strategy Seebach and Huber[75] have performed a synthesis of the phthalideisoquinoline alkaloid (+)-corlumine (123) of high enantiomeric purity (over 80 % e.e.) from L-Dopa derived *N*-pivaloylamide (120) and 2-ethoxycarbonylpiperonal (121). In this approach two auxiliaries were present in the molecule. One of them was used to achieve the Umpolung of reactivity of the C-1 carbon ($CO^tC_4H_9$), the other for the transfer of chirality (COOH). (Scheme 32). Dilithiation of the acid (120) followed by transmetalation with magnesium bromide then by addition of the aldehyde (121) resulted in 122 formed as a mixture of diastereomers in a ratio 3 : 2.



Scheme 32

The configuration of the major isomer (122) was determined by conversion to the alkaloid (+)-corlumine (123) by a series of transformations involving anodic oxidative decarboxylation, $NaBH_3CN$-reduction, chromatographic separation, depivaloylation and final *N*-methylation.

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