Asymmetric Synthesis of Isoquinoline Alkaloids

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Received December 5, 2003

Contents

1. Introduction

Recent methods of the asymmetric synthesis of isoquinoline alkaloids are based generally on two synthetic strategies: the stereochemical modification of the traditional, classical methods (the sequential Bischler−Napieralski cyclization/reduction, the Pictet−Spengler, various Pomeranz−Fritsch cyclizations) and introduction of nucleophilic or electrophilic carbon units into the C-1 position of isoquinoline derivatives (the C_1−C_α connectivity approach).

A great number of chiral natural isoquinoline alkaloids owe their chirality to the presence of a stereogenic center at the C-1 carbon, and development of methodologies to access this center in configurational integrity has been the subject of great interest. Thus, most of the syntheses presented in this review have been worked out for such reactions, while no resolution of racemic mixtures or interconversion between various types of chiral alkaloids has been included.

Since the publication of our first review on stereocontrolled synthesis of isoquinoline alkaloids in 1994,[1] the number of new synthetic methodologies and modifications of the traditional procedures has grown markedly; thus, a new compendium on this topic was appropriate. This review covers the literature from late 1993 until the end of 2003.

The organization of this review is similar to that of the first one.[1] It begins with a presentation of the stereochemically modified traditional methods, followed by recent achievements, obtained with the "C_1−C_α connectivity approach". At the end, other syntheses which do not fall into these categories are described.

2. Stereochemical Modification of the Traditional Synthetic Methods

2.1. Bischler–Napieralski Cyclization/Reduction

In the past decade the sequential Bischler−Napieralski cyclization/reduction has been the most frequently explored approach to the asymmetric synthesis of isoquinoline alkaloids. In this synthesis, β-arylethylamide is cyclized to 1-substituted 3,4-dihydroisoquinoline or a corresponding isoquinolinium salt, which is then reduced in the next step to the 1,2,3,4-tetrahydro derivative (Scheme 1).

The reduction process is crucial for the stereochemical outcome of the synthesis because it creates a stereogenic center. This step can be realized either by diastereoselective or enantioselective synthesis.

2.1.1. Diastereoselective Synthesis

Hydride reduction or catalytic hydrogenation of chiral 1-substituted 3,4-dihydroisoquinolines or the corresponding 3,4-dihydroisoquinolinium salts has been found to give satisfactory to excellent results. In most cases the chiral auxiliary was appended to the imine nitrogen; in some cases a C-3 chiral center was effective as well.

Rodrigues et al.[2] in their synthesis of cularine alkaloids, (+)-cularine (**2**), (+)-*O*-demethylcularine (**3**), (+)-sarcocapnidine (**4**), and (+)-sarcocapnine (**5**), used imminium salt **1** as the key intermediate, prepared from the corresponding 3,4-dihydroisoquinoline and (+)-phenylmenthyl chloroacetate (Scheme 2).

It was interesting to find that the $NaBH_4$ reduction step was accompanied by an unprecedented hydrolysis/decarboxylation of the chiral auxiliary, leading directly to the *N*-methyl derivatives **2**−**5**, formed practically as single enantiomers from axially chiral imines **1**. The postulated (*S*)-configuration of the products was supported by molecular modeling, ac-

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10.1021/cr030692k CCC: $48.50
Published on Web 06/19/2004

Maria Chrzanowska was born in Poznań, Poland. She received her M.Sc. degree in chemistry at the Technical University in Poznań. In 1981 she joined the research group of Professor Maria D. Rozwadowska at the Adam Mickiewicz University in Poznań. In 1986 she received her Ph.D. degree working on the total synthesis of secoisoquinoline alkaloids and their analogues, elaborating the dithiane method. She was a postdoctoral fellow with Dr. Arnold Brossi at National Institutes of Health, Bethesda, MD, where she was involved in the synthesis of optically active mammalian alkaloids, transformations of colchicine alkaloids, and tubuline binding to colichicine. At present she is working at the Adam Mickiewicz University; her research is focused on stereoselective synthesis of isoquinoline alkaloids and their analogues belonging to simple isoquinoline and protoberberine groups. Her research interests include enantio- and diastereoselective addition of carbon nucleophiles to imines as well as other topics connected with metalloorganic and organic sulfoxide chemistry.

Maria Danuta Rozwadowska received her M.S. degree in chemistry from the Adam Mickiewicz University (UAM) in Poznań, Poland. After one year of teaching chemistry at Zamoyska High School in Poznań in 1959/60 she was awarded a doctoral scholarship at the Institute of Organic Chemistry, Polish Academy of Sciences, where she worked with Professor Jerzy Suszko on isolation and structure elucidation of wild-poppy alkaloids. After receiving her Ph.D. degree in 1964, she was a NRC postdoctoral fellow in the group of Professor John ApSimon at the Carleton University in Ottawa, Canada, in 1965/67. In 1973 she joined the Faculty of Chemistry, UAM, as an adjunct, was promoted Docent in 1979, and in 1990 became full Professor. Since that time she has been involved in teaching organic chemistry at various levels and in charge of a research group. In the years 1979/80 and 1987/89 she was appointed as a visiting scientist at NIDDK, National Institutes of Health in Bethesda, working with Dr. Arnold Brossi on transformations of morphine-type alkaloids and synthesis of isoquinoline alkaloids. Her current research activities are focused on the synthesis of chiral nonracemic amines (including alkaloids) and sulfoxides and utilization of waste products in the manufacture of chloramphenicol-type antibiotics. Professor Rozwadowska is the Honorary Advisor to the Editorial Board of *Heterocycles*.

cording to which the conformer of **1**, which would give the (*S*)-isomer, was also the energetically favored one.

Chiral *N*-acyliminium salts, type **6**, generated in situ from dihydroisoquinoline and several acid chlorides, most of them derived from *N*-protected amino acids, D-phenylalanine, D- and L-alanine, and L-proline, were used by Czarnocki's group[3] in the synthesis of (*R*)-(−)-(**7**) and (*S*)-(+)-cryptostyline II (*ent*-**7**) (Scheme 3).

The highest degree of asymmetric induction was achieved in reduction of 6, which was prepared from *N*-tosyl-D-alanine (**6**, R = H, R^1 = Me) and *N*-tosyl-L-proline (**6**, R + R^1 = $(CH_2)_3$) chlorides with tetrabutylammonium borohydride. The crude products were subject in situ to hydrazinolysis followed by *N*-methylation to afford (*R*)-cryptostyline II (**7**; 58.5% ee) and the (*S*)-enantiomer (*ent*-**7**; 65.9% ee), respectively. The configuration of the product was determined by the configuration of the auxiliary amino acid.

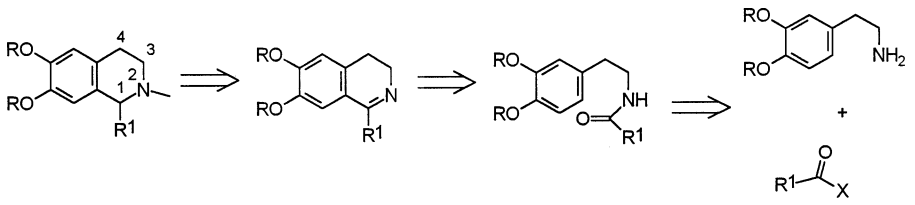
Dihydroisoquinolinium salts **8a**,**b**, incorporating a chiral hydrazonium functionality, were used as substrates by Kibayashi et al.[4] in the synthesis of (*R*)-(+)-salsolidine (**10**) and (*R*)-(−)-cryptostyline II (**7**) (Scheme 4). [During the publication process of this article a report on "Synthetic pathways to salsolidine" by T.S. Kaufman appeared in Tetrahedron: *Asymmetry* **2004**, *15*, 1203.] Reduction of **8a**,**b**, employing sodium borohydride as well as other metal hydride reagents resulted in tetrahydro products obtained with excellent diastereoselectivity (90−96%), with (1*R*) major diastereomers **9a**,**b**. Reductive N−N bond cleavage converted **9a**,**b** into alkaloids: (*R*)-(+)-**10** and (*R*)-(−)-**7**, respectively. The effectiveness of the asymmetric induction was postulated to arise from the pyramidal stability of the pyrrolidine sp^3-hybridized nitrogen atom and hydride-ion approach to the imine double bond from the sterically less shielded site. The energetically favored conformer **11** (Figure 1) was postulated to explain the preferential formation of (1*R*)-isomers.

Following the Polniaszek strategy,[5] Kunitomo et al.[6−9] performed the synthesis of the alkaloid (*R*)-(+)-noranicanine (**12**) and two other 1-benzyltetrahydroisoquinolines, (*R*)-**13** and (*S*)-**14a,** whose structures had been incorrectly postulated to represent two natural alkaloids, "fumarizine"[10] and "dehassiline",[11] respectively (Chart 1). Also, the synthesized[9] regioisomer (*S*)-**14b** was different from the natural product.

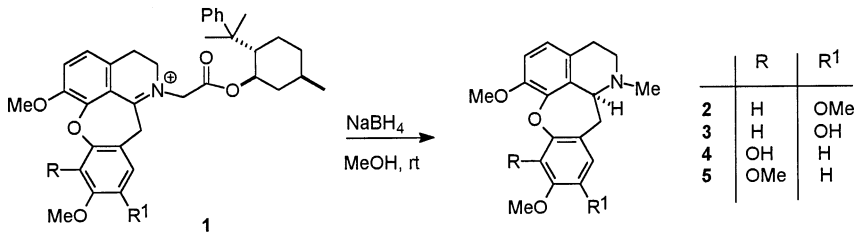
In the syntheses, amides **15** (Scheme 5) with chiral auxiliaries derived from either (*R*)-α-phenylethylamine (in the synthesis of (*R*)-**12** and (*R*)-**13**) or the (*S*)-enantiomer (in the synthesis of (*S*)-**14**) were used. Hydride reduction of the Bischler−Napieralski cyclization products **16** resulted in tetrahydroisoquinolines **17**, which were isolated as single diastereomers. Removal of the auxiliary along with the *O*-protecting groups (H_2/Pd−C) yielded (*R*)-**12** and after *N*-methylation (*R*)-**13** and both regioisomers of (*S*)-**14** as optically pure compounds. According to the authors, none of the three synthetic isoquinolines showed properties assigned to the natural products.

An unusual course of the Bischler−Napieralski cyclization/reduction synthesis was noticed when applied to amides of type **15** substituted in ring A with bromine at C-2 and ether substituents at C-4 and C-5. In the course of this process the initial

Scheme 1

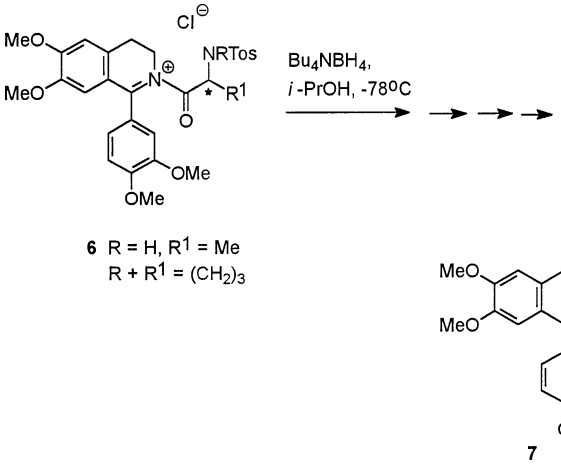


Scheme 2



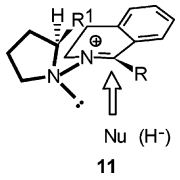
	R	R^1
2	H	OMe
3	H	OH
4	OH	H
5	OMe	H

Scheme 3



6 R = H, R^1 = Me
R + R^1 = $(CH_2)_3$

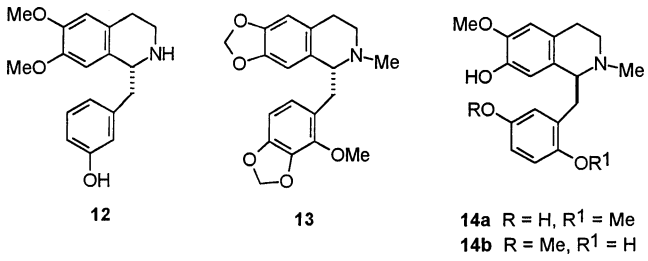
7



11

Figure 1. Energetically favored conformer **11** leading to (1*R*)-**9**.

Chart 1



12 **13** **14a** R = H, R^1 = Me
14b R = Me, R^1 = H

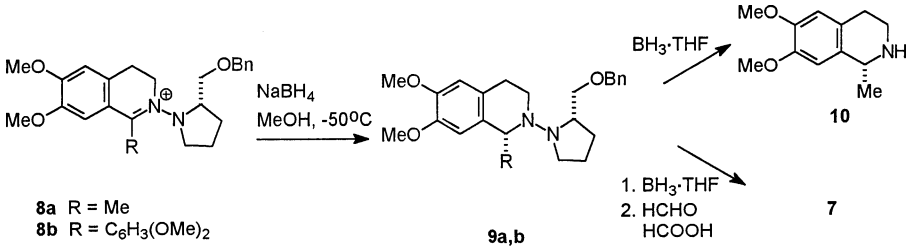
cleavage of the chiral auxiliary takes place, leading to racemic tetrahydroisoquinolines.[12,13]

(*S*)-α-Methylbenzylamine was found to be a very efficient chiral auxiliary also in the multistep synthesis of (−)-tejedine (**23**), a *seco*-bisbenzylisoquinoline alkaloid[14] (Scheme 6). The crucial intermediate, amide **21**, was prepared from chiral amine **19** (obtained from vanillin (**18**) in 13 synthetic steps) and acid **20** (synthesized from 4-hydroxybenzaldehyde in 11 steps). Cyclization of **21** with $POCl_3$ in benzene followed by reduction gave the desired regioisomer of tetrahydroisoquinoline **22** in 40% yield and with 99% de. The synthesis of the alkaloid (−)-tejedine (**23**) was completed after an additional series of transformations (in total, ca. 35).

(1*S*,*R*)-1-Benzyltetrahydroisoquinoline **25** was prepared as the main diastereomer (78% de) by stereoselective reduction of dihydroisoquinolinium salt **24** incorporating (*R*)-phenylglycinol as chiral auxiliary.[15] Hydrolysis of the *O*-protective group, reductive removal of the chiral auxiliary, and cleavage of the methylenedioxy group in **25** led to the dopaminergic (*S*)-1BTHIQ **26** (X = H), an analogue of the alkaloid (*S*)-anicamine **26** (X = OH) (Scheme 7).

Several syntheses of 1,3-disubstituted tetrahydroisoquinoline derivatives have been performed using β-phenylethylamines with a chiral center at the future C-3 carbon. In Ohba's[16] multistep synthesis of the starfish alkaloid imbricatine (**29a**), isolated as the tri-*O*-methyl ether **29b**, the substituted L-phenylalanine derivative (synthesized in five steps from 3,5-dimethoxybenzamide and 4-methoxyphenylacetyl chloride[17]) was used to prepare (*R*)-amidoester **27**. Its

Scheme 4



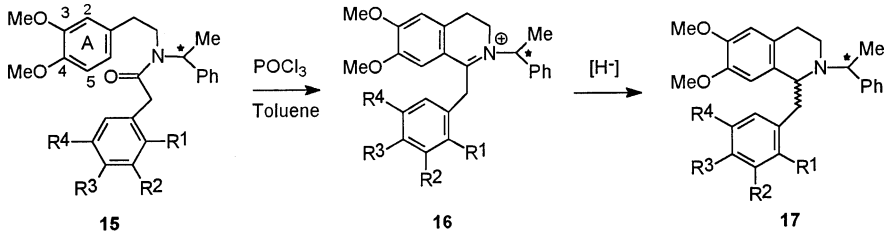
8a R = Me
8b R = $C_6H_3(OMe)_2$

9a,b

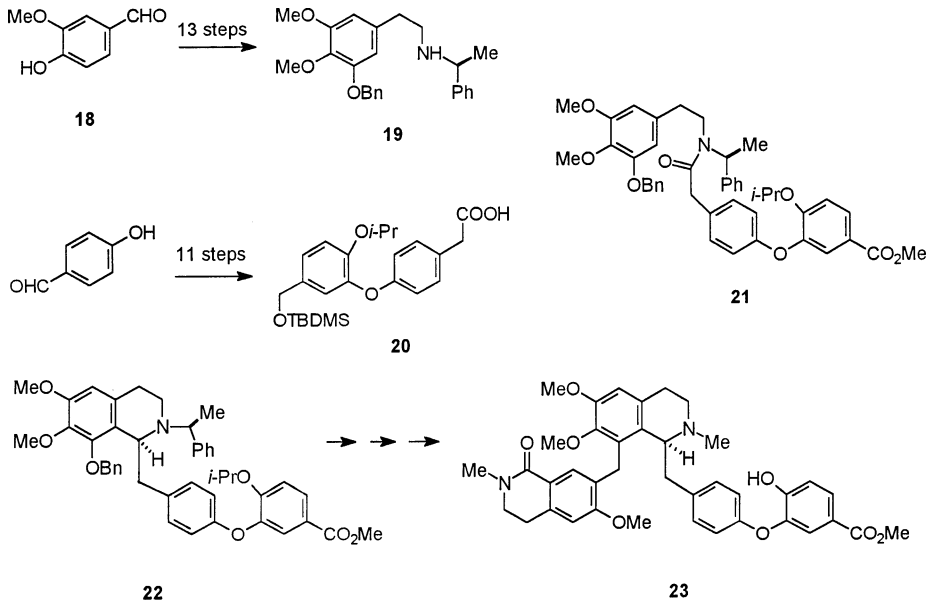
10

7

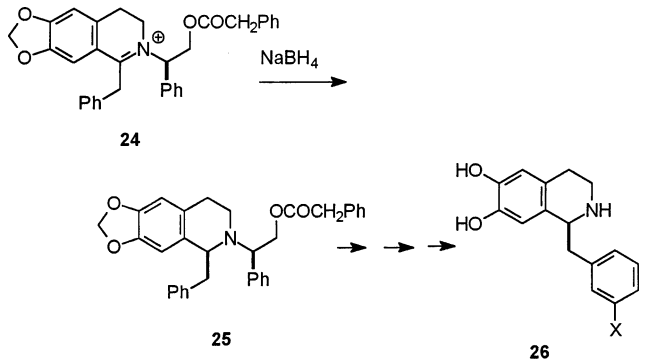
Scheme 5



Scheme 6



Scheme 7



in situ cyclization/reduction resulted in amine **28**, formed in a highly 1,3-*cis* diastereoselective and enantioselective (91% ee) process (Scheme 8). A similar selectivity was observed in the synthesis of the enantiomeric *ent*-**28**.[18] To complete the synthesis, 15 additional steps were needed to finally give the alkaloid **29b** as a single enantiomer, identical with the natural product. The structure and absolute configuration of the natural imbricatine **29a** were confirmed.

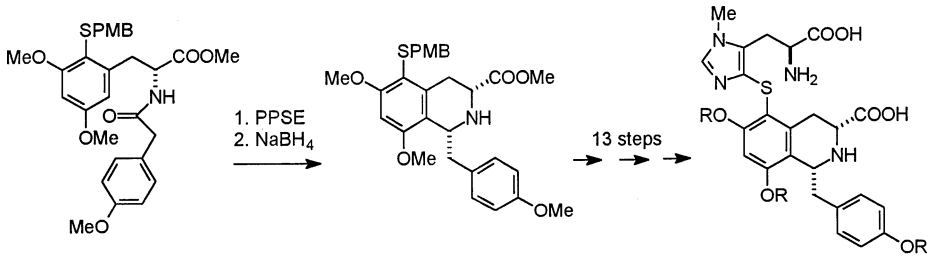
Chiral 1,3-dimethyl-3,4-dihydroisoquinolines (e.g., **31**) and 1,3-dimethyl-1,2,3,4-tetrahydroisoquinolines **32**, cis and trans, have found broad application as isoquinoline building blocks in the synthesis of naphthylisoquinoline alkaloids[19] (e.g., of korumpensamine **33** and anti-HIV active michellamine **34** type of compounds), being important due to interesting pharmacological activities. Since the earlier successful approach to the synthesis by regio- and stereoselective Bischler−Napieralski route, presented by Bringmann et al.[20] (Scheme 9), this method has been frequently explored by others.[21−27]

In this approach, acetamides **30**, prepared from chiral α-methyl-*β*-phenylethylamines, differently substituted at the aromatic ring, have been used as substrates. Depending on the reducing conditions applied, the cyclization products, dihydroisoquinolines **31**, could be converted into either *trans*- ($LiAlH_4$/Me_3Al) or *cis*-1,3-dimethyltetrahydroisoquinolines ($NaBH_4$ or H_2/Pd−C[22]) **32**. The differences among the numerous syntheses performed[20−27] lie mainly in the methods of preparation of the chiral amines, the precursors of acetamides **30**, as well as methods and stage of diaryl coupling needed for construction of the naphthylisoquinoline carbon skeleton.

The *trans*-enantiomer *ent*-**32** (R = Me, $R^1 = R^2 =$ H) was transformed into an alkaloid (−)-gentrymine B (**35**) by two-step *N*-methylation[28] (Scheme 9).

In a series of papers Czarnocki et al.[29−31] reported the synthesis of isoquinoline alkaloids according to the Bischler−Napieralski cyclization/reduction of amides **36**−**38** in which the chiral auxiliary was present as a part of the acid component. They were prepared from *β*-(6,7-dimethoxyphenyl)ethylamine

Scheme 8



27 28 29a R = H 29b R = Me

PMB = 4-methoxymethyl
PPSE = trimethylsilyl polyphosphate

Scheme 9

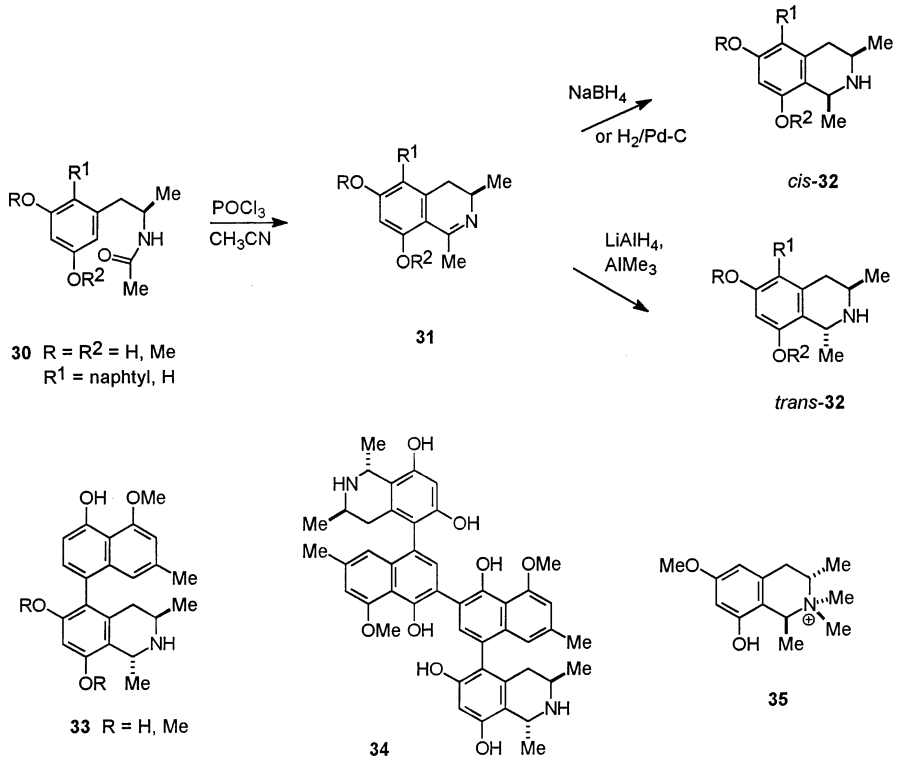
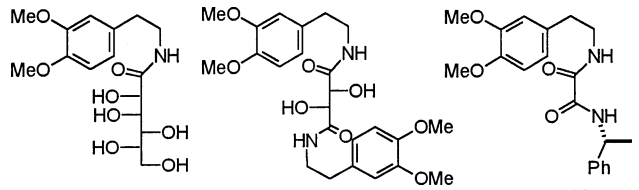


Chart 2



36 37 38

and L-(+)-ascorbic acid (**36**),[29] L-(+)-tartaric acid ethyl ester (**37**),[30] and (*S*)-phenylethyl amide of oxalic acid chloride (**38**)[31] (Chart 2).

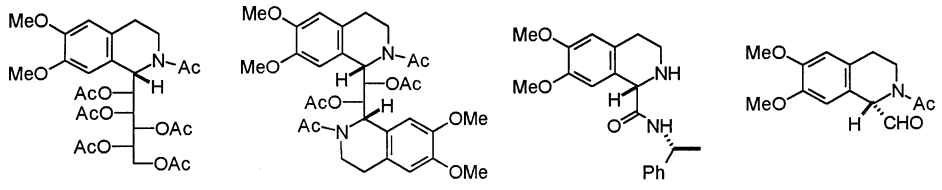
Following the standard procedures of cyclization (PCl_5/CH_2Cl_2/0 °C) the intermediate 3,4-dihydroisoquinolines were produced and subsequently reduced ($NaBH_4$) to the tetrahydro products **39**−**41**. Compounds **39** and **40** could be isolated after *N*,*O*-acylation (Chart 3). The best selectivity was observed during the reduction leading to compound **40**, which was obtained as a single diastereomer. The synthesis of **39** (via *N*-oxide) was characterized by lower selectivity (87:13 mixture of diastereoisomers). Both enantiomers, **41** and *ent*-**41**, could be obtained by choosing the appropriate reducing reagent, either hydride reduction ($NaBH_4$/EtOH/−78 °C) or catalytic hydrogenation ($H_2/RhCl(PPh_3)$/100 atm/rt), respectively.

After hydrolysis of the ester groups, metaperiodate cleavage of the glycol system in **39** and **40** afforded aldehyde **42**, which was then reduced to (*S*)-(−)-*N*-acetylcalycotomine (**43**)[30] (also prepared from **41** by hydrolysis/$LiAlH_4$ reduction[31]). Addition of 3,4-dimethoxyphenyllithium to **42** gave (−)-hydroxynorlaudanosine (**44**),[29] from which (*R*)-(−)-laudanosine (**45**)[29] was prepared by hydrogenolysis and *N*-methylation. The latter was further transformed into (*R*)-(−)-glaucine (**46**)[29] by diaryl coupling (Chart 4).

2.1.2. Enantioselective Synthesis

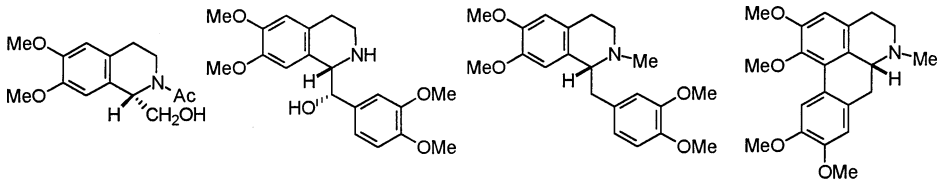
Enantioselective synthesis of isoquinoline alkaloids according to the Bischler−Napieralski cyclization/reduction approach is based on a reduction of prochiral 3,4-dihydroisoquinolines. For this purpose chiral hydride reducing agents are used or hydrogenation is carried out in the presence of chiral catalysts.

Chart 3



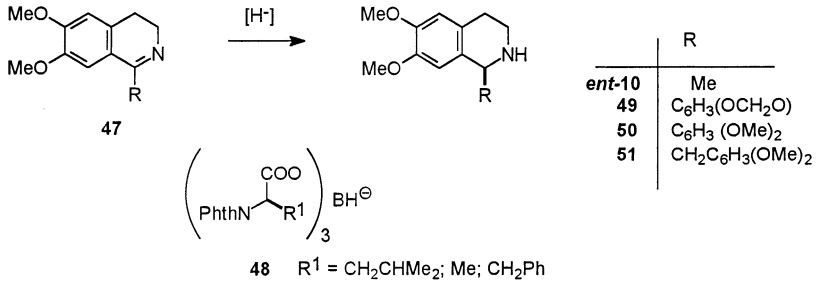
39 **40** **41** **42**

Chart 4



43 **44** **45** **46**

Scheme 10



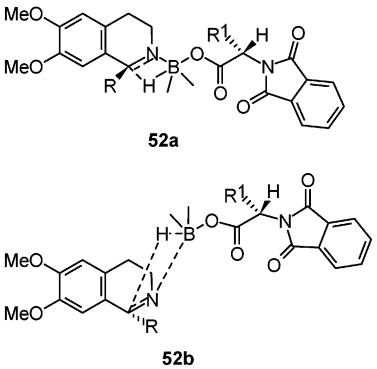
47

48 $R^1 = CH_2CHMe_2$; Me; CH_2Ph

Sodium triacyloxy borohydrides **48**, prepared from $NaBH_4$ and *N*,*N*-phthaloyl-protected (Phth) amino acids, (*S*)-leucine, (*S*)-alanine, and (*S*)-phenylalanine, were used by Hajipour and Hantehzadeh[32] in the synthesis of four isoquinoline alkaloids, (*S*)-(−)-salsolidine (*ent*-**10**), (*S*)-(−)-norcryptostyline I (**49**), (*S*)-(−)-norcryptostyline II (**50**), and (*S*)-norlaudanosine (**51**), from imines **47** (Scheme 10).

The enantioselectivity (65−75% ee) attained in reactions with (*S*)-leucine-derived **48** increased when the reduction was performed in the presence of $ZnCl_2$ (72−80% ee) or carried out under solid-state conditions (83−100% ee). The (*S*)-selectivity was postulated to arise from a transition state **52a** favoring a *re*-face attack of hydride ion rather than from **52b** (Figure 2).

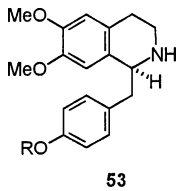
In a similar synthetic strategy, sodium borohydride, modified with (*S*)-*N*-Cbz-proline, was used for asymmetric reduction of dihydroisoquinoline intermediates in the synthesis of (*R*)-(+)-norroefractine (**53**, R = Me)[33] and (−)-norarmepavine (**53**, R = H)[34] (Chart 5).



52a **52b**

Figure 2. Transition states for the reduction of imines **47** with acyloxy borohydride **48**.

Chart 5



53

(*R*)-Salsolidine (**10**), (*R*)-norcryptostyline II (*ent*-**50**), and (*R*)-norlaudanosine (*ent*-**51**) were synthesized by Kang et al.[35] from imines **47** (R = Me, $C_6H_3(OMe)_2$, and $CH_2C_6H_3(OMe)_2$, respectively) (Scheme 10) by reduction with BH_3·THF in toluene. The reaction was carried out in the presence of a catalytic amount of a complex of organozinc reagents with chiral aminothiols. Among the catalysts investigated, thiazazincolidine complex **54** (R+R = $(CH_2)_5$, Chart 6) was shown to be the most effective one, producing **10** and *ent*-**51** with ee values in the range 62−86%. The preference of formation of (1*R*) isomers in all the synthesized alkaloids was explained by assuming that of the two working models, **55a** and **55b**, the former was less favorable because of the steric interaction between the R^1-substituent and the ethyl group on the zinc atom as well as electronic effects caused by the *syn*-relationship between the C=N double bond and the Zn−C bond.

Since the outstanding achievements of Noyori et al.[36] in asymmetric hydrogenation of cyclic imines catalyzed by diphosphine−Ru(II) complexes, other

Table 1. Asymmetric Hydrogenation of Imines Type 47 Catalyzed by Ir(I) Complexes[a]

entry	alkaloid	Ir(I)-ligand	cocatalyst	yield, %	ee, %	ref
1	salsolidine (*ent*-**10**)	(2*S*,4*S*)-BCPM (**57**)	phthalimide	95	93 (*S*)	39
2	norlaudanosine (**51**)	(2*S*,4*S*)-BCPM (**57**)	phthalimide	88	72 (*S*)	40
3	norlaudanosine (**51**)	(2*S*,4*S*)-BCPM (**57**)	F_4-phthalimide	84	88 (*S*)	40
4	norlaudanosine (**51**)	(2*S*,4*S*)-BCPM (**57**)	none	30	27 (*S*)	40
5	norhomolaudanosine (**58**)	(2*S*,4*S*)-BCPM (**57**)	phthalimide	75	87 (*S*)	40
6	norhomolaudanosine (**58**)	(*S*)-BINAP	phthalimide	89	82 (*S*)	40
7	norcryptostyline II (*ent*-**50**)	(*S*)-BINAP	phthalimide	50	31 (*R*)	40
8	calycotomine (**59**)	(*R*)-BINAP	F_4-phthalimide	85	86 (*S*)	41

[a] The hydrogenation was carried out at 5−20 °C, under hydrogen pressure of 100 atm, with 0.5−1 mol % of a catalyst in the presence of 1 mol % of an imide.

Chart 6

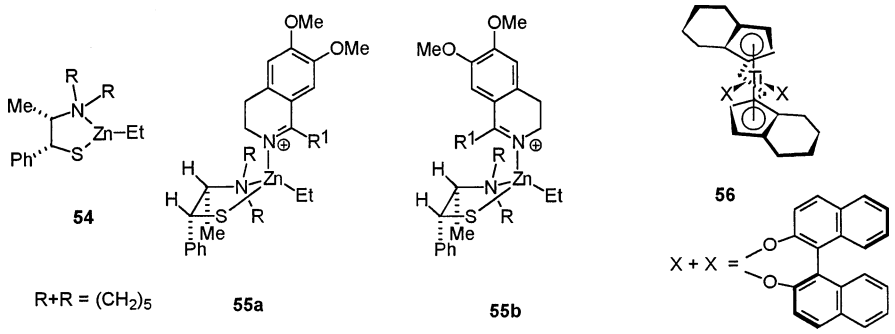
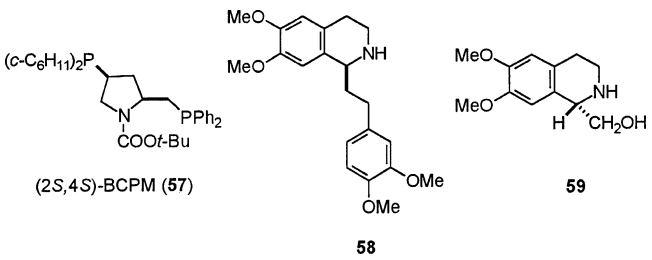
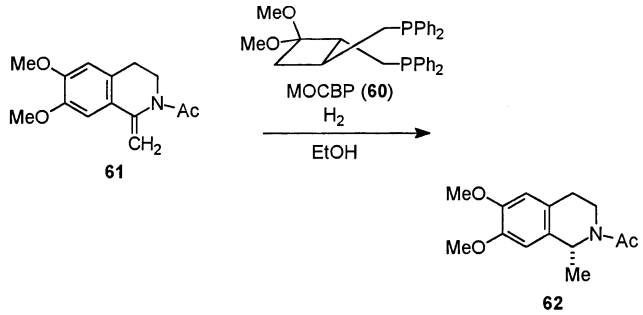


Chart 7



Scheme 11

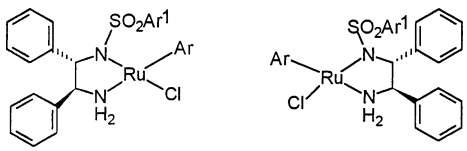


catalytic systems have been devised and applied in the synthesis of isoquinoline alkaloids.

Earlier studies by Buchwald and Willoughby,[37,38] in which chiral titanocene catalysts **56** (Chart 6) were introduced to control the stereochemistry of hydrogenation of cyclic imines, allowed the synthesis of isoquinolines with excellent levels of enantiomeric excess (95−99%). Among others, 6,7-dimethoxy-1-methyl-3,4-dihydroisoquinoline (**47**, R = Me) under the action of hydrogen at 80 or 2000 psig at 65 °C was smoothly converted into (*S*)-(−)-salsolidine (*ent*-**10**) in 79% or 82% yield with 95% or 98% ee.

Achiwa, Morimoto et al.[39−43] carried out extensive studies on catalytic asymmetric hydrogenation of various 3,4-dihydroisoquinolines **47** using various biphosphine−transition-metal complexes. They found iridium(I) complexes with (*R*)- and (*S*)-BINAP and (2*S*,4*S*)-BCPM (**57**, Chart 7) to be the most effective catalytic system, particularly when used in the presence of cyclic imides as cocatalyst. In efforts undertaken to establish the optimal reaction conditions (Table 1), isoquinoline alkaloids, (*S*)-(−)-salsolidine (*ent*-**10**), (*S*)-norlaudanosine (**51**), (*R*)-norcryptostyline II (*ent*-**50**), (*S*)-norhomolaudanosine (**58**, Chart 7), and (*S*)-calycotomine (**59**, Chart 7), have been synthesized in satisfactory yields and with high enantioselectivity.

Chart 8

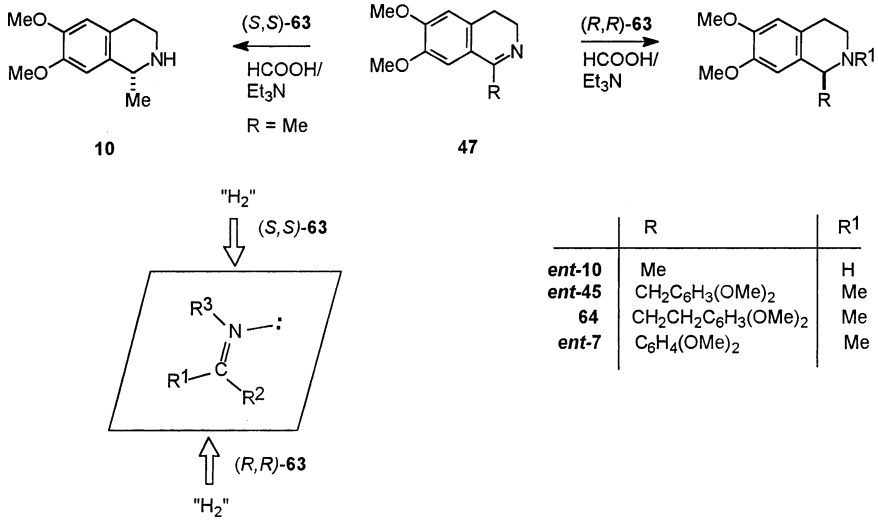


The effect of temperature, solvent, cocatalyst, and amount of catalyst used on the enantioselectivity of the process has been examined. Interestingly, a strong impact of tetrafluorophthalimide on the degree of enantioselectivity has been noticed (Table 1, entry 3 versus 4). Without the amide, e.g., (*S*)-salsolidine (*ent*-**10**) was produced with only ca. 30% ee.[40]

The same group using the rhodium(I) complex with a biphosphine ligand **60** (MOCBP) of cyclobutane framework has synthesized (*R*)-(−)-*N*-acetylsalsolidine (**62**) in quantitative yield with 80.6% ee by hydrogenation of enamide **61** (Scheme 11).[43]

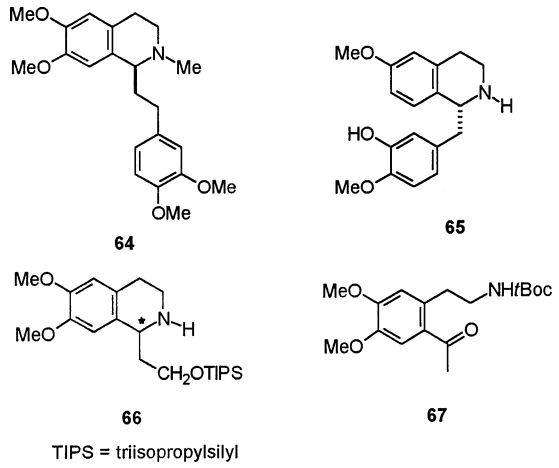
Asymmetric transfer hydrogenation of imines with formic acid/triethylamine catalyzed by suitably designed chiral *N*-sulfonated diamine−Ru(II)−η^6arene complexes of type **63** (Chart 8), attainable in both

Scheme 12



	R	R^1
ent-**10**	Me	H
ent-**45**	$CH_2C_6H_3(OMe)_2$	Me
64	$CH_2CH_2C_6H_3(OMe)_2$	Me
ent-**7**	$C_6H_4(OMe)_2$	Me

Chart 9



TIPS = triisopropylsilyl

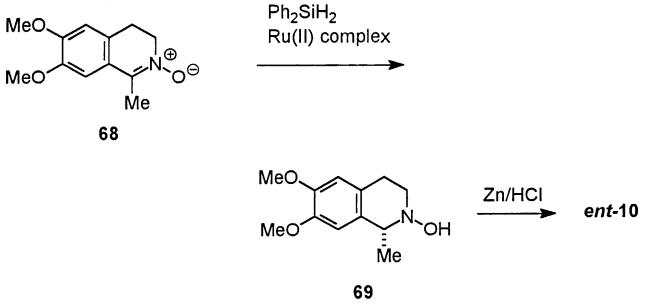
enantiomeric forms, has been developed by Noyori et al.[44,45] (Scheme 12), and since then it has became the method of choice in enantioselective reduction of cyclic imines.

Among the amines synthesized by Noyori's group, several isoquinoline alkaloids have been prepared in high yield with ee values ranging from 90% to 97%, starting with cyclic imines **47** (R = Me, $CH_2C_6H_3(OMe)_2$, $(CH_2)_2C_6H_3(OMe)_2$, and $C_6H_3(OMe)_2$). It has been shown that the stereochemistry of the catalyst determined that of the amine. As such, products with (1*R*) configuration were obtained when the (*S*,*S*)-**63** were used, whereas the (*1S*) isomers were obtained when the (*R*,*R*)-**63** were applied, as illustrated in Scheme 12.

Thus, by choosing the appropriate catalyst, any of the enantiomers of the alkaloids could be prepared, e.g., (*S*)-salsolidine (*ent*-**10**) and, after *N*-methylation, (*S*)-laudanosine (*ent*-**45**), (*S*)-homolaudanosine (**64**, Chart 9), and (*S*)-cryptostyline II (*ent*-**7**) with the (*R*,*R*)-**63** catalysts while (*R*)-salsolidine (**10**) with the (*S*,*S*)-**63**.

The same catalytic system has been successfully applied by many other research groups, affording tetrahydroisoquinolines in high yield and with a high level of enantioselectivity. Maat, Sheldon, and colleagues[46] in the synthesis of (*R*)-1-benzyl-1,2,3,4-

Scheme 13



tetrahydroisoquinoline **65** (Chart 9), a key intermediate in the synthetic route to the alkaloid morphine, applying complex (*S*,*S*)-**63** (Ar = *p*-cymene, Ar^1 = mesityl), reached an enantioselectivity up to 99%.

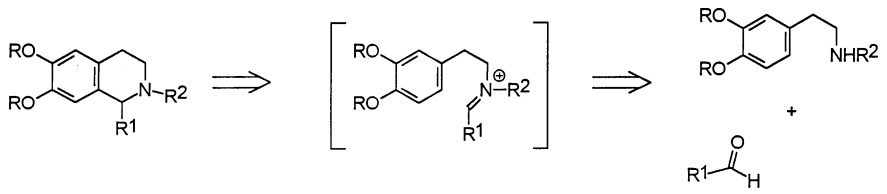
Vedejs et al.[47] obtained (*S*)-1-(2-aminophenyl)-6,7-dimethoxy-1,2,3,4-tetrahydroisoquinoline with 98% ee using (*S*,*S*)-**63** (Ar = benzene, Ar^1 = 1-naphthyl).

Tietze et al.[48] and Wills et al.[49] both used the same complex (*R*,*R*)-**63** (Ar = *p*-cymene, Ar^1 = tolyl) to control the steric course of the reduction of prochiral 3,4-dihydroisoquinolines, also achieving excellent results. Tietze's group synthesized both enantiomers of tetrahydroisoquinoline **66**, the building block of the upper fragment of the emetine alkaloid, while Wills et al. obtained (*S*)-salsolidine (**10**). The last alkaloid was also prepared by the asymmetric transfer hydrogenation of *N*-Boc-protected amino ketone **67**. The one-pot procedure involved cyclization/reduction and *N*-deprotection[49] (Chart 9).

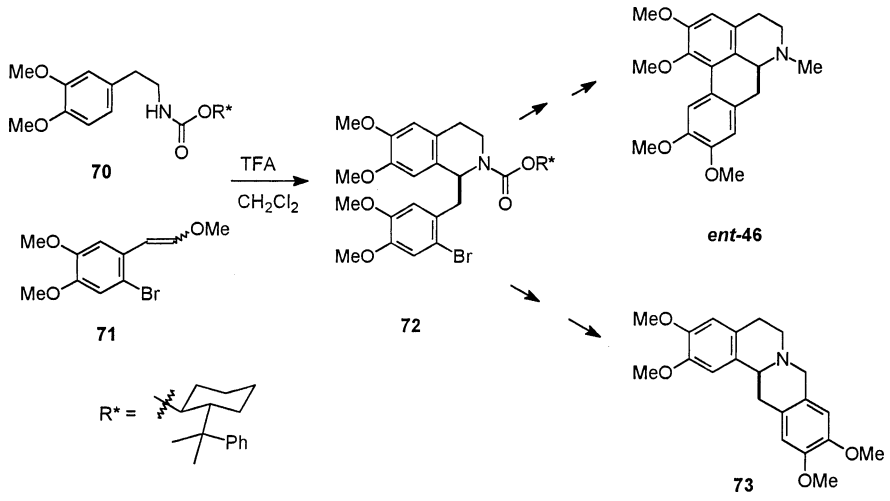
Noyori's method[44,45] using slightly modified ligands of the diamine−ruthenium catalyst **63** (Ar = cyclopentadiene, Ar^1 = tolyl) has been used by Baker and Mao[50] for reduction of imine **47** (R = Me). Depending on the configuration of the catalyst used, both enantiomers of salsolidine (**10** and *ent*-**10**) could be prepared in high yield and with ~90% ee. However, in the hydrogenation of imine **47** (R = $C_6H_3(OMe)_2$), leading to (*R*)-cryptostyline II (*ent*-**50**), the selectivity was disappointingly low (3.2%).

Enantioselective reduction of dihydroisoquinoline *N*-oxide **68** with diphenylsilane in the presence of catalytic amounts of BINAP ruthenium(II) complexes

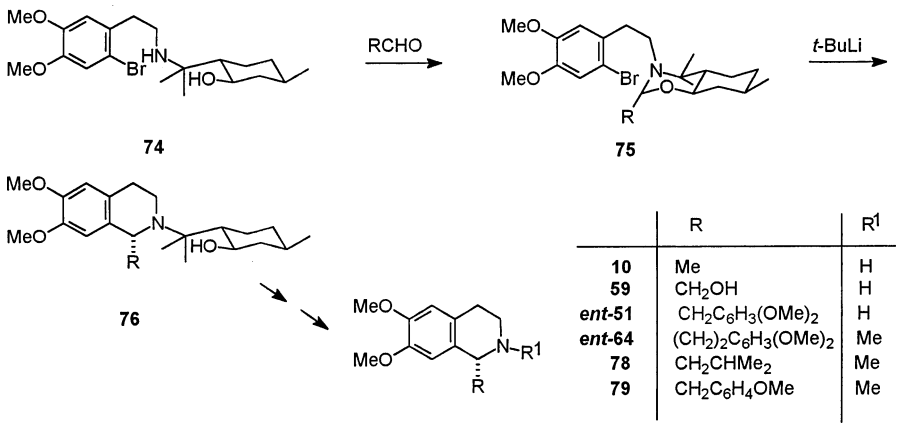
Scheme 14



Scheme 15



Scheme 16



(e.g., Ru_2Cl_4[(*S*)-(−)-*p*-TOLBINAP](NEt$_3$)) afforded hydroxylamine **69** in 99% yield with 56% ee, which, upon treatment with Zn/HCl, gave (*S*)-(−)-salsolidine (*ent*-**10**)[51] (Scheme 13).

2.2. Pictet–Spengler Synthesis

The Pictet−Spengler reaction, which involves the condensation of β-arylethylamine with an aldehyde or its synthetic equivalent, is a convenient method for the synthesis of tetrahydroisoquinoline derivatives or related heterocyclic systems.[52] In this method, the stereogenic C-1 center is generated during the ring closure in a one-pot process. In the syntheses that have been carried out in an asymmetric manner, the chirality transfer occurred from the chiral auxiliary introduced to either the β-arylethylamine or the aldehyde component, thus involving a diastereoselective synthesis.

As a continuation of the earlier study[53] on the Pictet−Spengler asymmetric synthesis of isoquinoline alkaloids, Comins and co-workers[54] investigated the influence of another chiral auxiliary, e.g., (+)-*trans*-2-(α-cumyl)cyclohexyl, appended to the amine nitrogen in **70** as well of the aldehyde equivalent **71**, substituted at C-2 with bromine, on the degree of stereoselectivity in the cyclization step (Scheme 15).

It turned out that the C-2 bromine not only caused an increase in diastereoselectivity during the cyclization step (tetrahydroisoquinoline **72** was formed as an mixture of diastereomers with 77% de) but was helpful for separation of the diastereomeric products.

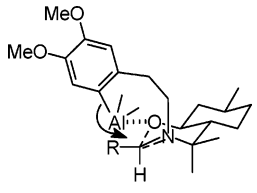
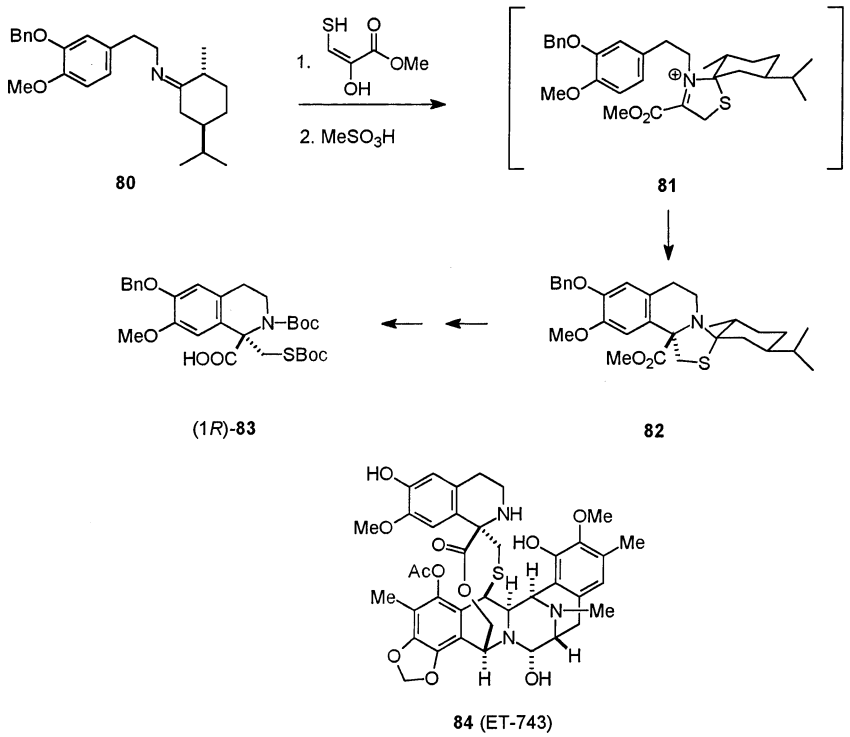


Figure 3. Transition state leading to (1*R*)-**76**.

Scheme 17



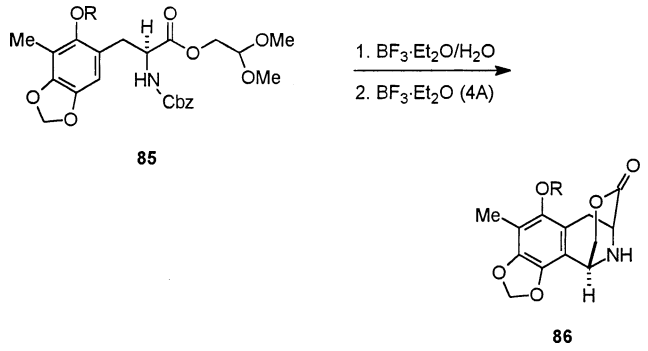
The major isomer (+)-**72** was then converted into the aporphine alkaloid (+)-glaucine (*ent*-**46**) by treatment with *n*-Bu_3SnH/AIBN and $LiAlH_4$ as well as to the protoberberine (−)-xylopinine (**73**) when treated with *t*-BuLi and Red-Al.

Another cyclohexyl-based chiral auxiliary, derived from (−)-8-aminomenthol, appended to the amine nitrogen, as in **74**, was used by Pedrosa, Andres et al.[55] to control the steric course of an intramolecular Pictet−Spengler reaction, giving products with high diastereoselectivity (Scheme 16).

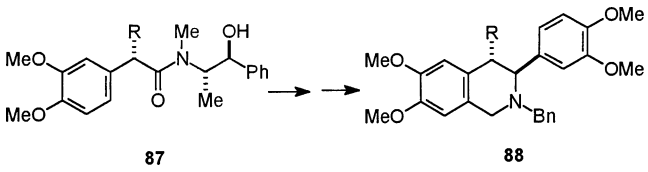
An interesting innovation of this study was to incorporate the aldehyde component into the *N*,*O*-acetal of perhydrobenzoxazine structure **75** before the cyclization step. In this situation, the intramolecular nucleophilic attack of the aromatic anion (generated by *t*-BuLi/Et_2AlCl) on the heterocycle occurred from the less hindered *si* face to create compound **76** with the (1*R*) configuration, as explained in structure **77** (Figure 3). After removal of the chiral auxiliary (PCC oxidation followed by KOH hydrolysis) and, in a few cases, *N*-methylation, enantiopure, homochiral alkaloids were synthesized. They included (*R*)-salsolidine (**10**), (*S*)-calycotomine (**59**), (*R*)-norlaudanosine (*ent*-**51**), (*R*)-homolaudanosine (*ent*-**64**), (*R*)-*O*-methyllophocerine (**78**), and (*R*)-*O*-methylarmepavine (**79**).

A chiral imine **80** obtained from *β*-arylethylamine and (+)-tetrahydrocarvone was used by Corey and Gin[56] to synthesize tetrahydroisoquinoline **83** (Scheme 17), a building block needed for construction of the "upper" isoquinoline part of the potent antitumor marine alkaloid, ecteinascidin 743 (ET-743) (**84**). In the reaction with methyl mercaptopyruvate followed by methanesulfonic acid, **80** was cyclized to a 6.5:1 mixture of diastereomeric tetrahydroisoquinolines **82** via the Pictet−Spengler intermediate iminium ion **81**. During ester hydrolysis of the diastereomeric products **82**, the desired major (1*R*) isomer hydrolyzed faster and could be transformed into the (1*R*)-**83** after separation, acetal hydrolysis, and Boc protection.

Scheme 18

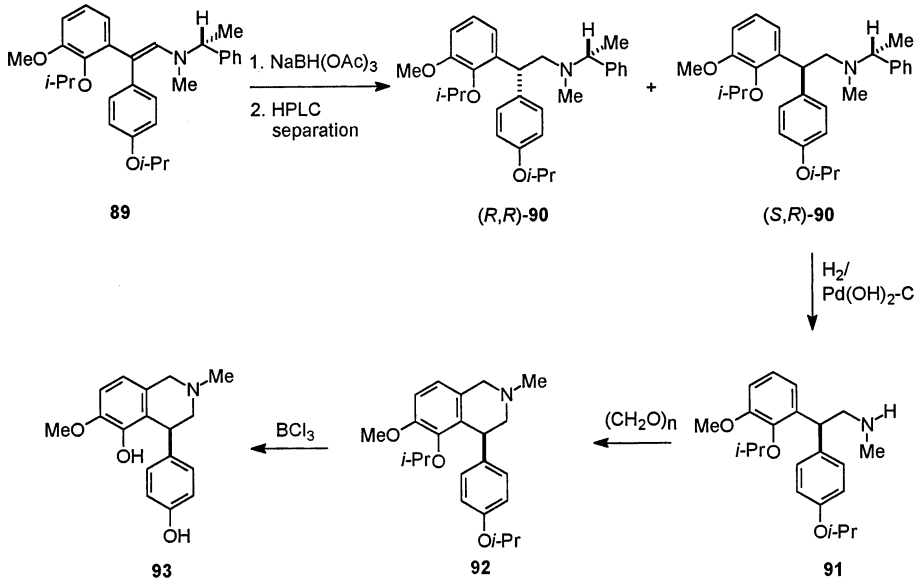


Scheme 19



The same authors[57] constructing the "lower" isoquinoline building block **86** of ET-743, again applied the intramolecular Pictet−Spengler reaction to enantiomerically enriched (96%) carbamate **85** (Scheme 18). The intermediate aldehyde, formed after acetal hydrolysis was exposed to $BF_3{\cdot}Et_2O$ in the presence of molecular sieves (4A) to be cyclized to the bridged lactone **86**, produced in 73% yield. It was further transformed into the final alkaloid via a multistep synthesis, involving, among others, a reaction with *β*-phenylethylamine to afford the "upper" isoquinoline, again via the Pictet−Spengler cyclization.

Scheme 20



The diastereoselective Pictet−Spengler reaction has also been applied by Danishefsky et al.,[58] Williams et al.,[59] Saito et al.,[60] Liu et al.,[61] Myers and Kung,[62] Ong et al.,[63] and Stoltz et al.[64] in construction of various tetrahydroisoquinoline moieties of ecteinascidine and saframycine types of antitumor alkaloids.[65]

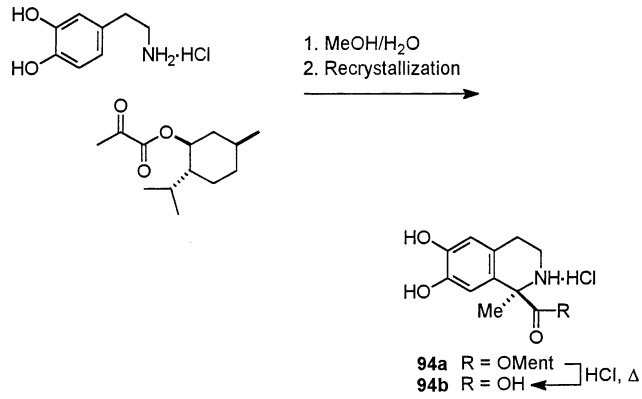
A series of tetrahydroisoquinoline derivatives **88** substituted at C-3 with dimethoxyphenyl and at C-4 with alkyl groups (substitution pattern present in molecules of few isoquinoline alkaloids) has been elaborated by the Badia−Dominquez group.[66] The key intermediate (*S*,*S*)-pseudoephedrine-derived amide **87** after hydrolysis, Friedel−Crafts acylation of 1,2-dimethoxybenzene, and Pictet−Spengler cyclization was transformed into the alkaloids' analogues **88** (Scheme 19).

The synthesis of (+)- and (−)-latifine (**93**), using enamine **89** as the key intermediate, has been prepared by Couture et al.[67] $NaBH(OAc)_3$ reduction of **89** gave a mixture (85% de) of diastereomeric amines (*R*,*R*)-**90** and (*S*,*R*)-**90**, which were separated by chromatography and converted into (+)- and (−)-latifine (**93**), respectively, in a series of transformations involving removal of the chiral *N*-auxiliary, cyclization of **91**, and *O*-deprotection of **92** (Scheme 20).

A two-step diastereoselective synthesis of (*R*)-(−)-salsolinol-1-carboxylic acid (**94b**), a biosynthetic precursor of (*R*)-salsolinol, a potent dopaminergic neurotoxin, has been presented by Kawai et al.[68] (Scheme 21). In this method, (+)-menthyl pyruvate was used as an inductor of chirality in formation of a chiral, C-1 quaternary center. The chiral carbonyl component, (+)-menthyl pyruvate, and dopamine hydrochloride were condensed to give a 56:44 mixture of diastereoisomeric menthyl esters **94a**, from which the dextrorotatory isomer was separated by crystallization and hydrolyzed to the acid (−)-**94b**.

Oppolzer's sultam[69] **95**, substituted at nitrogen with glyoxyloyl group, was applied by Czarnocki et al.[70,71] as a chiral aldehyde equivalent in the Pictet−Spengler synthesis of (*S*)-(+)-*N*-methylcalycotomine

Scheme 21

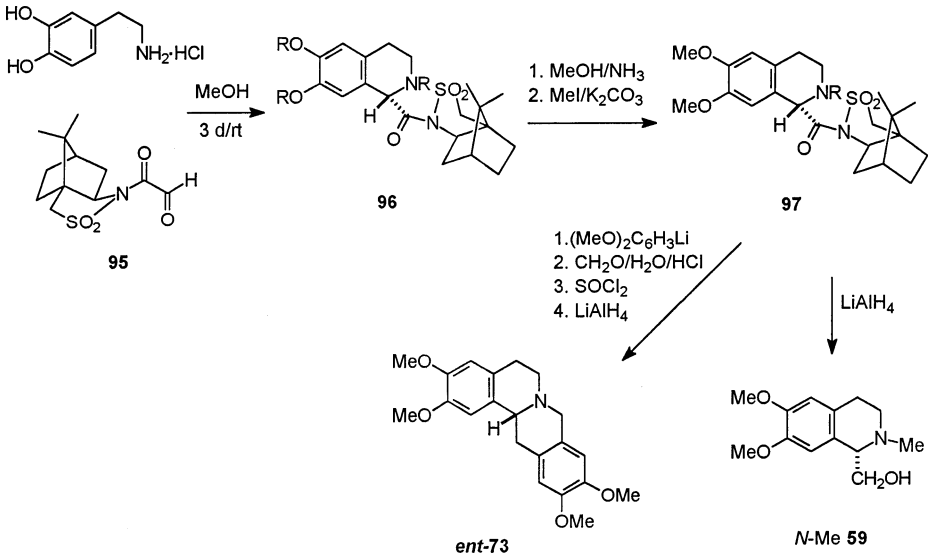


(*N*-Me **59**) and (*R*)-(+)-xylopinine (*ent*-**73**) (Scheme 22). The reaction of **95** with dopamine hydrochloride afforded the condensation product in which (1*R*)-diastereomer **96** (R = H) was formed as the major product (86% de) and isolated as a *per*-acylated derivative **96** (R = COOMe). It was then used as a key intermediate in the synthesis of the alkaloids via the dimethoxy derivative **97**. $LiAlH_4$ reduction of **97** afforded (*S*)-(+)-*N*-methylcalycotomine (*N*-Me **59**), while addition of 3,4-dimethoxyphenyllithium followed by formylation and deoxygenation led to (*R*)-(+)-xylopinine (*ent*-**73**), both alkaloids produced in high yield and enantiomeric purity.

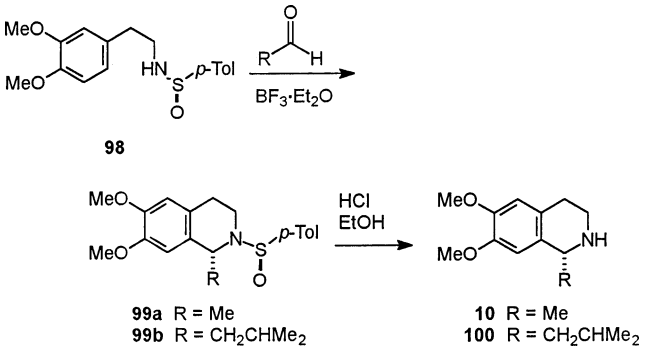
Recently, a number of asymmetric syntheses of isoquinoline alkaloids mediated by an auxiliary containing chiral sulfur have been reported. Koomen et al.[72] starting with chiral *N*-*p*-tolylsulfinylphenylethylamine **98** and aliphatic aldehydes have worked out an efficient synthesis of tetrahydroisoquinolines **99**, carried out under very mild conditions (Scheme 23). The major diastereomers, **99a** and **99b** (obtained in 93 and 92 dr, respectively), after removal of the chiral auxiliary, were transformed into the alkaloids (+)-salsolidine (**10**) and *O*-methylnorlophocerine (**100**), respectively.

A complementary synthesis of both (*R*)-(+)-carnegine (**103**) and (*S*)-(−)-carnegine (*ent*-**103**) has been

Scheme 22



Scheme 23

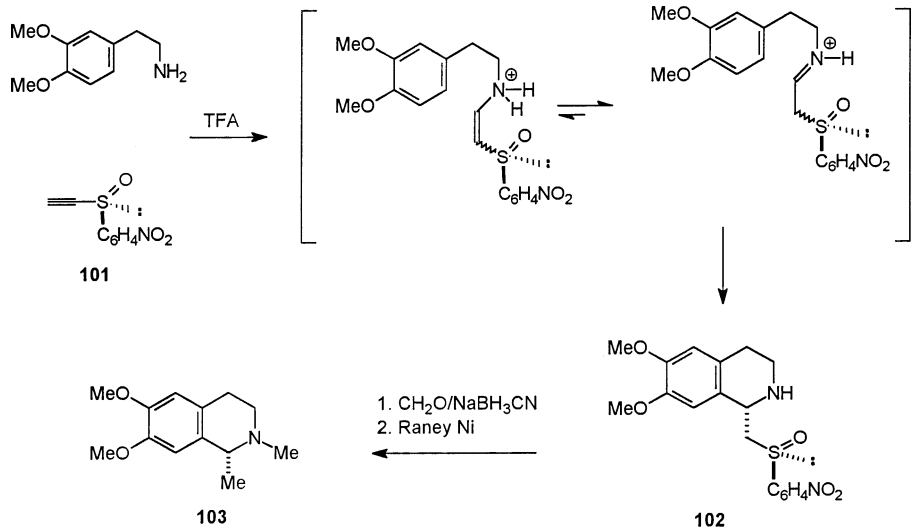


performed by Chan, Lee et al.[73,74] (Scheme 24). Having reacted homoveratrylamine with (*R*)-(+)-ethynyl *o*-nitrophenyl sulfoxide (**101**), used as a chiral synthetic equivalent of acetaldehyde, they obtained tetrahydroisoquinoline **102** as a single diastereoisomer as a result of a one-pot Michael addition−cyclization process. *N*-Methylation followed by Raney nickel desulfurization gave enantiomerically homogeneous (*R*)-(+)-carnegine (**103**) in good yield. When, instead of the primary amine, *N*-methylhomoveratrylamine was used and treated with **101** in similar reaction conditions, diastereomer **102** of reversal configuration at C-1 was produced as the main isomer (1.8:1) and transformed into (*S*)-(−)-carnegine (*ent*-**103**).

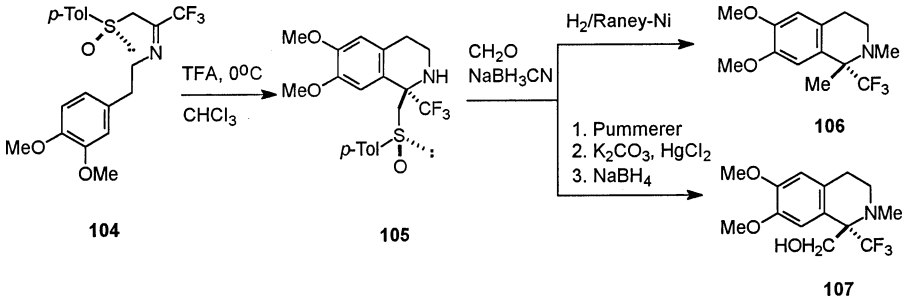
Synthesis of 1-trifluoromethyl tetrahydroisoquinoline alkaloids **106** and **107** of biological interest, based on the intramolecular Pictet−Spengler cyclization using a sulfinyl auxiliary to generate the C-1 quaternary stereogenic center, was reported by Bravo et al.[75] (Scheme 25).

The stereoselectivity achieved during the cyclization of the sulfoxide **104** to give tetrahydro derivative **105** as a 6:1 mixture of (1*S*,R_S)/(1*R*,R_S) diastereomers was postulated to result from a *cis*-geometry of the C=N double bond in **104**, with the two aromatic rings on the same side of this bond, thus minimizing the dipole−dipole interaction between the S=O and C=N bonds and hindering the *si* face of the molecule. The major condensation product (1*S*)-**105** upon *N*-methylation was forwarded to (*S*)-1-trifluoromethylcarnegine (**106**) by Raney nickel desulfurization and to (*R*)-*N*-methyl-1-trifluoromethylcalycotomine (**107**) by

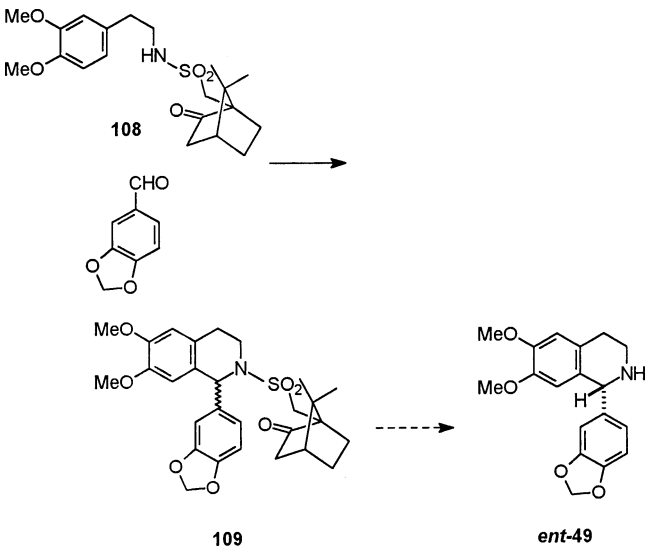
Scheme 24



Scheme 25



Scheme 26



Pummerer rearrangement followed by hydrolysis and reduction.

N-Camphorosulfonyl homoveratrylamine (**108**) and piperonal were condensed to produce a 4:3 mixture of diastereomeric tetrahydroisoquinolines **109**, intermediates in the synthesis of (*R*)- and (*S*)-norcryptostyline I (*ent*-**49** and **49**)[76] (Scheme 26).

Another example showing that structures deduced entirely from spectral analysis must be occasionally verified by synthesis (see also Chart 1 and Schemes 5 and 46) has been displayed by Simpkins et al.[77,78] For the alkaloid called "jamtine", isolated as *N*-oxide, structure **115** was postulated on the basis of spectral data analysis;[79] however, Simpkins asymmetric synthesis of the heterocyclic compound **115**, performed earlier by Padwa et al.[80,81] in racemic synthesis, revealed that the spectral characteristics of the synthetic product were not compatible with that reported for the natural alkaloid.

Simpkins' original approach to the asymmetric synthesis (Scheme 27) was based on desymmetrization by enolization of the achiral cyclic imide **110** using chiral lithium amide base **111** followed by enantioselective methoxycarbonylation to give imide **112**. Construction of the alkaloid carbon skeleton **114** was achieved by regioselective reduction of **112** ($NaBH_4$/EtOH/0 °C) and a Pictet−Spengler type of cyclization of the hydroxy lactam **113** (or rather of the corresponding *N*-acyliminium ion). The cyclization step proceeded with complete stereoselectivity, giving the dextrorotatory lactam **114**, which was next transformed in an overall yield of 20% into the target compound **115** by dehydrogenation using a selenoxide *syn*-elimination, selective reduction of the lactam carbonyl, and *m*-CPBA *N*-oxidation.

A similar synthetic strategy has been used for the synthesis of the tetracyclic carbon skeleton of erythrina-type alkaloids.[82]

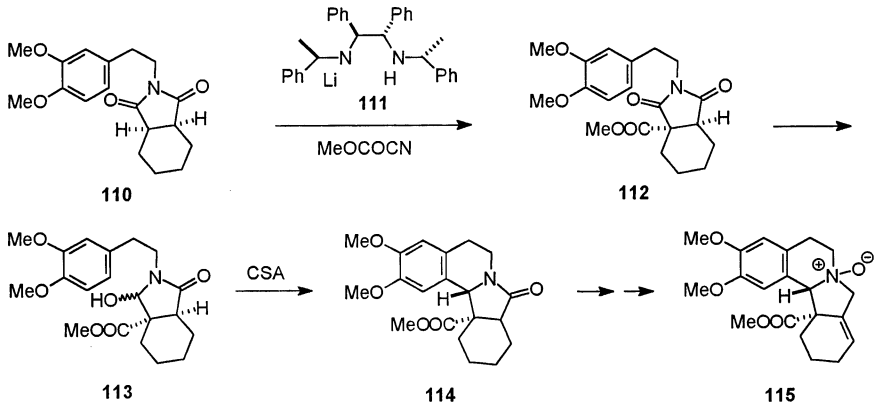
The Pictet−Spengler approach has also been explored for the syntheses of 1,3-dimethylisoquinoline derivatives, important building blocks in the synthesis of naphthylisoquinoline alkaloids.

In the Bringmann synthesis of dioncophylline B (**118**),[83] the chiral α-methyl-β-phenylethylamine **116** was treated with acetaldehyde at room temperature to give two regioisomeric tetrahydroisoquinolines **117a**,**b**, from which isomer **117b** was further converted into the target alkaloid **118** (Scheme 28).

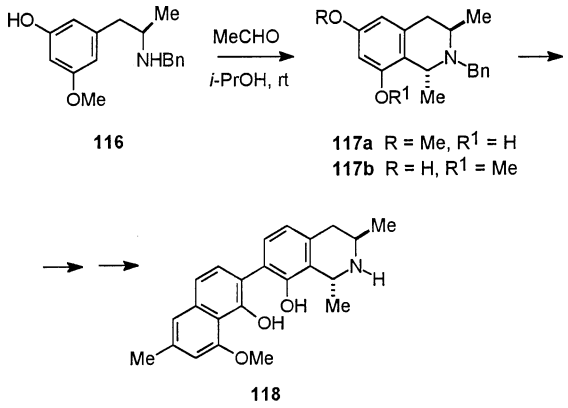
2.3. Pomeranz–Fritsch Synthesis

The term "Pomeranz−Fritsch isoquinoline synthesis" has been customarily applied to a variety of

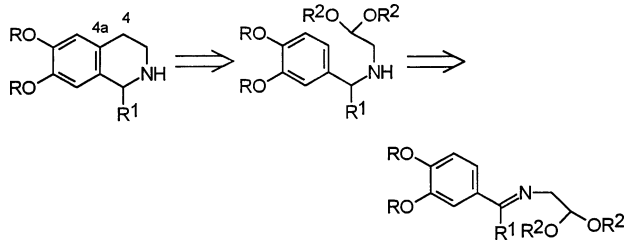
Scheme 27



Scheme 28



Scheme 29



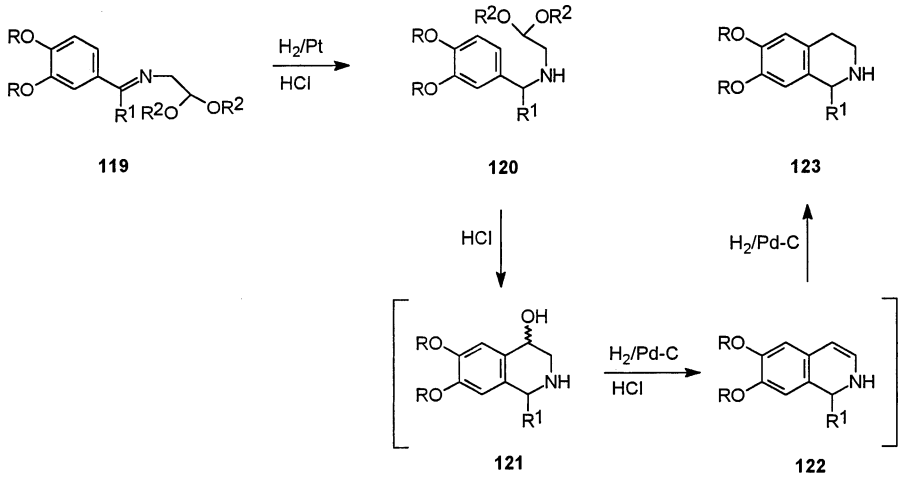
synthetic strategies in which the isoquinoline ring system was closed by formation of the C_4-C_{4a} bond (Scheme 29).

The original Pomeranz–Fritsch method, which involved an acid-catalyzed cyclization of benzalamino acetals of type **119** to give fully aromatic isoquinolines, has been improved and modified in many ways.[84] A useful modification for the synthesis of tetrahydroisoquinoline derivatives was developed by Bobbitt[85] as a two-step procedure in which the "Pomeranz–Fritsch imine" **119** was hydrogenated in situ to the aminoacetal of type **120**. This in turn was converted into tetrahydroisoquinolines **123** by an acid-catalyzed cyclization–hydrogenolysis process. In some reactions, however, depending on the conditions applied, 4-hydroxytetrahydro-**121** or 1,2-dihydro-**122** derivatives could be isolated as well (Scheme 30).

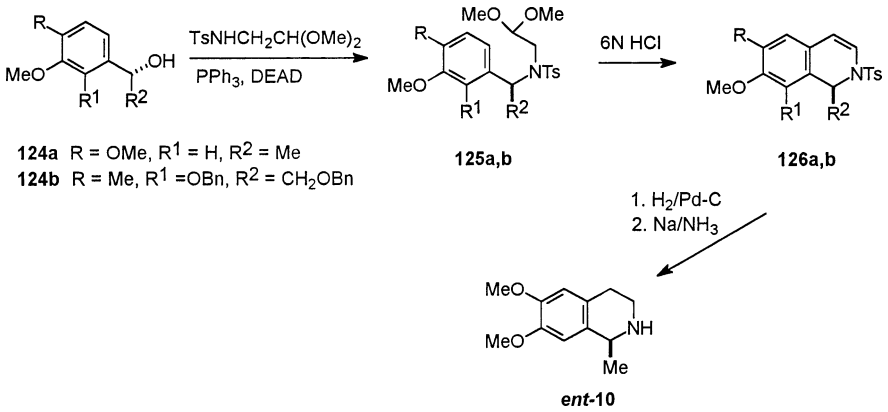
Recently, in one version of the stereoselective Pomeranz–Fritsch–Bobbitt synthesis, aminoacetals **120** were prepared either from chiral benzyl alcohols on treatment with an aminoacetaldehyde acetal under the Mitsunobu reaction conditions or by *N*-alkylation of chiral benzylamines with bromoacetaldehyde acetal. In another approach, addition of organometallic reagents to prochiral imines carried out in the presence of external controllers of stereochemistry has been performed.

In the Kaufman synthesis of (*S*)-(−)-salsolidine (*ent*-**10**)[86] and the 1,2-dihydroisoquinoline derivative **126b**[87] (a key intermediate in the synthesis of the β-adrenergic receptor antagonist MY 336-a), the substrates were chiral benzyl alcohols **124a** and **124b**, respectively (Scheme 31). The treatment with *N*-tosylaminoacetaldehyde acetal under the Mitsunobu reaction condition produced the tosylamides

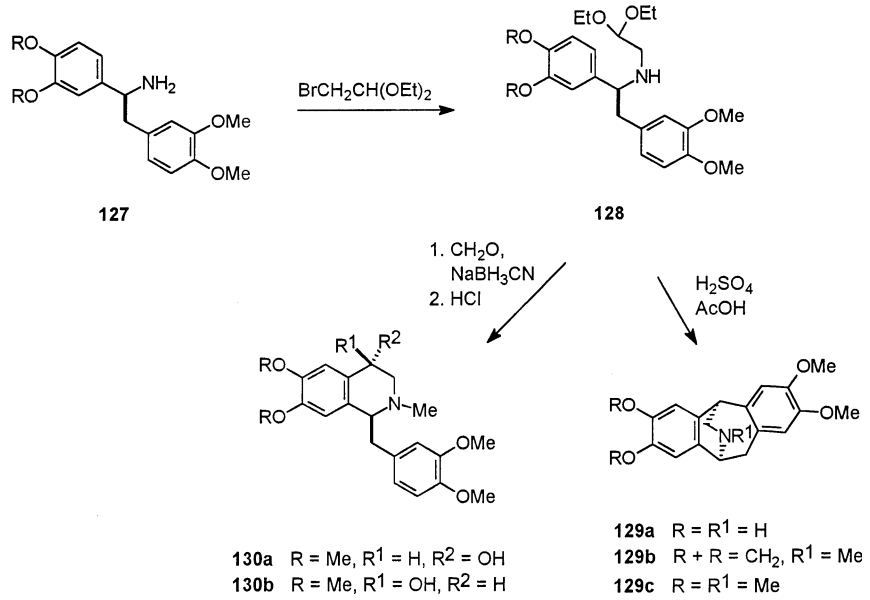
Scheme 30



Scheme 31



Scheme 32



125a,**b** (the Jackson modification[88]) in a satisfactory yield, with enantioselectivity up to 95% and inversion of configuration. (*S*)-(−)-Salsolidine (*ent*-**10**) with 95% ee was prepared from **125a** when refluxed in dioxane with 6 N HCl to form **126a**, which was further hydrogenated (H_2/Pd−C) and detosylated (Na/NH_3).

Optically active benzylamines **127** and **134** have been used by Badia's research group for the synthesis of isopavines[89] and benzylisoquinolines[90] and as precursors of protoberberine[91] and the benzo[*c*]-phenantridine[92] alkaloids (Schemes 32−34).

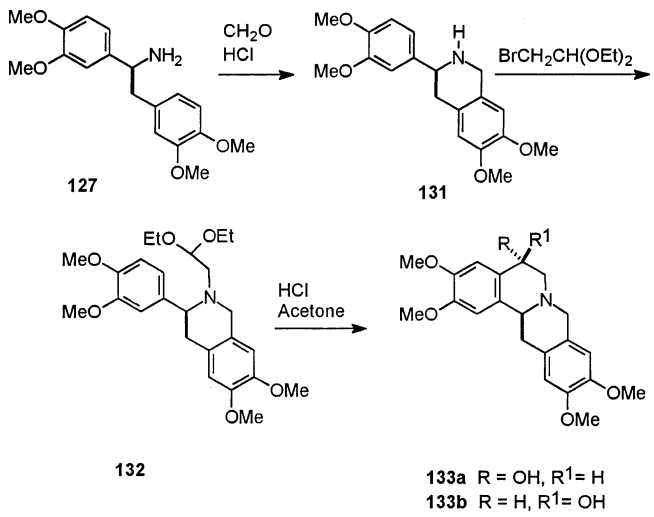
On *N*-alkylation of benzylamines **127** with bromoacetaldehyde acetal, followed by acid-catalyzed cyclization of the secondary amines **128**, the pavine carbon skeleton **129a** was constructed, and after *N*-methylation, it was transformed into (−)-amurensinine (**129b**) and (−)-*O*-methylthalisopavine (**129c**)[89] in good yield with high enantiomeric purity (Scheme 32).

When amine **128** was subject to *N*-methylation prior to the cyclization step, 4-hydroxy-1-benzyltetrahydroisoquinolines *O*-methylroemecarine (**130a**) and *O*-methyl*epi*roemecarine (**130b**) were obtained, although with poor diastereoselectivity (33%)[90] (Scheme 32).

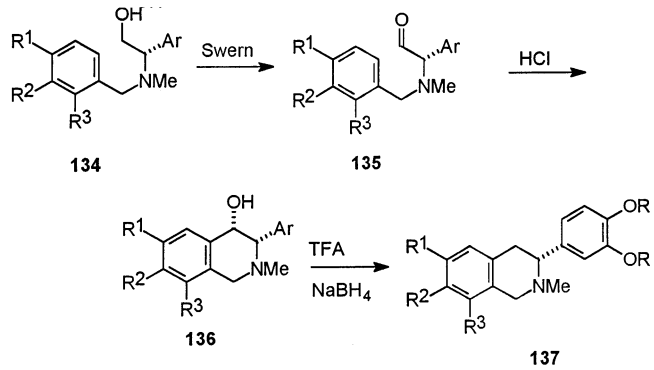
The same authors[93] in their highly stereoselective synthesis of (5*S*)- and (5*R*)-hydroxyxylopinine (**133a**,**b**) made use of two consecutive classic syntheses involving the Pictet−Spengler and Pomeranz−Fritsch−Bobbitt cyclizations. The first one was applied to amine **127**, from which tetrahydroisoquinoline **131** was produced under the action of formaldehyde/HCl. In the second, the tetracyclic protoberberine carbon skeleton was constructed by cyclization of aminoacetal **132** in concentrated HCl to a separable 1:1 mixture of (5*R*)-**133a** and (5*S*)-**133b** diastereomeric hydroxyxylopinines (Scheme 33).

In another series of experiments, chiral amines **134** were oxidized by the Swern method to the corresponding aldehydes **135**, which in turn were cyclized in acidic media to give diastereomerically pure 3,4-*cis*-3-aryltetrahydroisoquinolin-4-ols **136**,[91] possible

Scheme 33



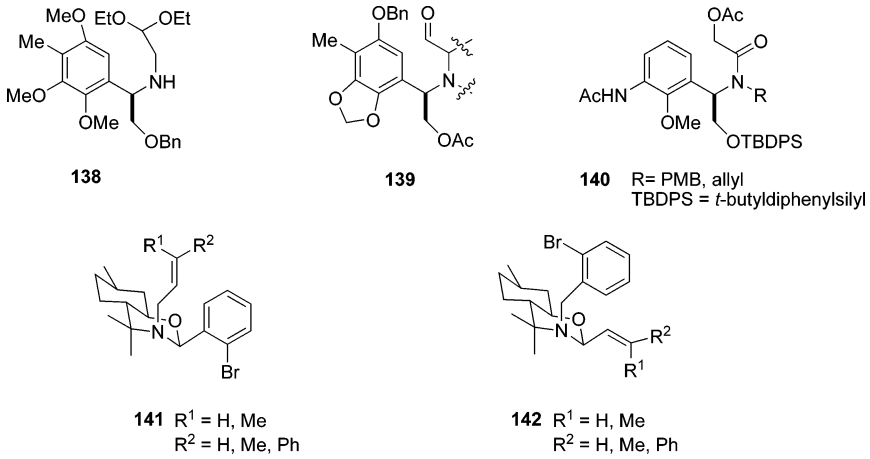
Scheme 34



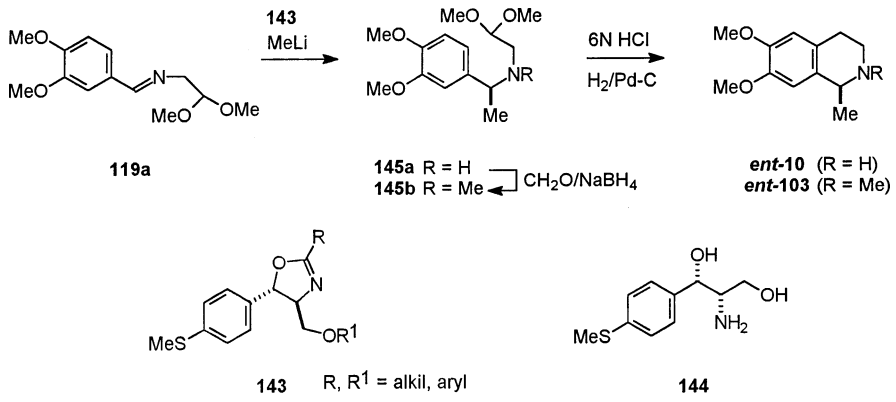
precursors of protoberberine alkaloids (e.g., ophiocarpine or papaverberine). As a continuation of this line of investigation, 4-hydroxy derivatives **136** were deoxygenated to give the 3-aryl-substituted tetrahydroisoquinolines **137**, which might be considered as intermediates en route to benzo[*c*]phenanthridines[92] (Scheme 34).

Several chiral "Pomeranz−Fritsch" amines, **138**−**140**,[94−96] have been used as important units for the

Chart 10



Scheme 35



construction of various tetrahydroisoquinolines, useful building blocks in the synthesis of saframycin and ecteinascidin type of derivatives (Chart 10).

(−)-8-Aminomenthol, which was successfully applied by Pedrosa−Andres' team[55] in the synthesis of chiral β-phenylethylamines (**74**, Scheme 16) for Pictet−Spengler cyclization, has been further elaborated to provide substrates for Pomeranz−Fritsch[97,98] synthesis. Perhydrobenzoxazines **141** and **142** (Chart 10), readily cyclized stereoselectively to tetrahydroisoquinolines by the C_4-C_{4a} bond-forming reaction under radical[97] (Bu_3SnH/AIBN) or ionic[98] (*t*-BuLi/TMEDA) reaction conditions.

The enantioselective approach to the Pomeranz−Fritsch−Bobbitt synthesis, involving enantioselective addition of organometallic reagents to the Pomeranz−Fritsch imine **119a**, carried out in the presence of external controllers of stereochemistry as a crucial step, has been studied[99] (Scheme 35).

Enantiomerically enriched (*S*)-(−)-salsolidine (*ent*-**10**) and (*S*)-(−)-carnegine (*ent*-**103**) were synthesized from aminoacetals **145a**,**b** prepared by methyllithium addition to *E*-imine **119a**, catalyzed by oxazolines of type **143**, prepared from (+)-thiomicamine (**144**), an industrial waste product. As a result of intensive investigation, the best yield (92%) and enantioselectivity (49% ee) of the addition step were achieved with oxazoline **143** (R = Ph, R^1 = Me), recently[100] improved to 76% ee with oxazoline **143** (R = R^1 = Me). The synthesis was completed by one-pot cyclization/hydrogenolysis in 6 N HCl of aminoacetals **145a**,**b**.

3. C_1-C_α Connectivity Approach

Introduction of a carbon unit at the C-1 position of the isoquinoline heterocycle has recently been explored as an alternative to the traditional synthetic methods. In this context, construction of the carbon skeleton of the alkaloids involving formation of a C−C bond between the isoquinoline ring and the C-1 substituent has been realized by two general synthetic strategies: by addition of carbon nucleophiles to isoquinolines, 3,4-dihydroisoquinolines, or the corresponding isoquinolinium ions, or by C-alkylation of tetrahydroisoquinoline derivatives with electrophilic carbon reagents. The stereogenic center is created at this stage of the syntheses.

3.1. Addition of Carbon Nucleophiles to Isoquinoline Derivatives

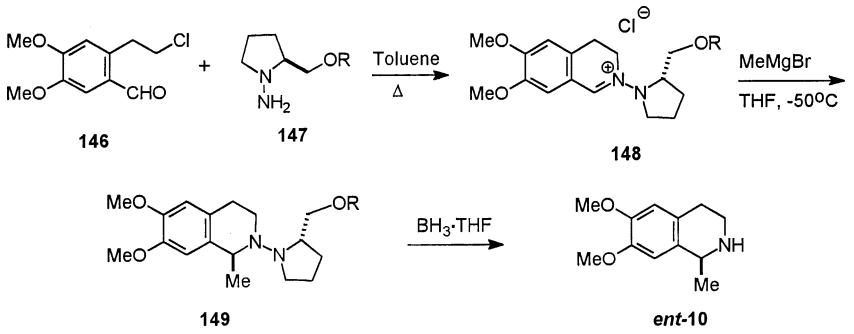
Both diastereo- and enantioselective syntheses relying upon additions of nucleophilic carbon species to the C=N double bond of the isoquinoline ring system have been developed.

3.1.1. Diastereoselective Synthesis

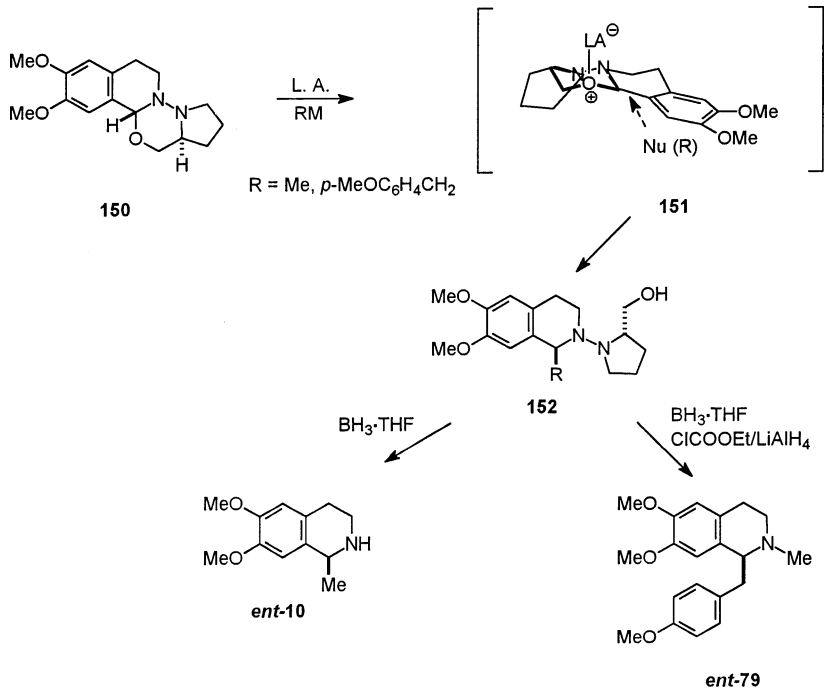
In most cases, asymmetry was induced by a chiral auxiliary appended to either nitrogen or C-3 of the isoquinoline building block or by a chiral substituent present in the carbon nucleophile.

The Kibayashi "hydrazonium ion strategy",[4] described previously (Scheme 4), based on hydride

Scheme 36



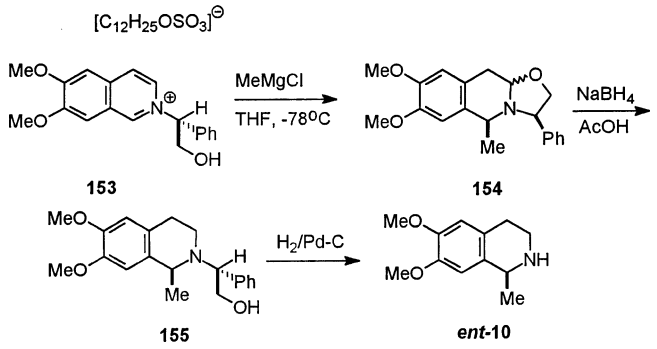
Scheme 37



additions to C-1-substituted Bischler−Napieralski dihydroisoquinolinium ions **8a** and **8b**, has also been applied for the addition of organometallic reagents to unsubstituted at C-1 dihydroisoquinoline derivatives[101] (Scheme 36). When salt **148** (R = Bn), prepared from aldehyde **146** and pyrrolidine **147** (R = Bn), was treated in situ with a methyl Grignard reagent, (1*S*)-1-methyltetrahydroisoquinoline **149** (R = Bn) was produced (96% dr). The configuration at the C-1 stereogenic center was found to be the opposite to that obtained by hydride reduction of the 1-methyl derivative **8a**. Upon removal of the chiral auxiliary, (*S*)-(−)-salsolidine (*ent*-**10**) of high optical purity was obtained in 77% yield. In this context, the two complementary methods based upon the "hydrazonium ion strategy" provide a useful way to obtain both enantiomers of salsolidine (**10**).

When, in another series of experiments,[101] **146** was treated with *O*-deprotected **147** (R = H), tetracyclic oxadiazine **150** was formed. Reactions with MeMgBr and *p*-$MeOC_6H_4CH_2MgCl$, catalyzed by Lewis acids (e.g., Et_2AlCl), proceeded with inversion of configuration at the future C-1 center (**151**), leading to tetrahydroisoquinolines **152** (R = Me, 95% dr; R = $CH_2C_6H_4OMe$, 99% dr) in satisfactory yield and excellent diastereoselectivity (Scheme 37). In this way (*S*)-(−)-salsolidine (*ent*-**10**) and (*S*)-(+)-*O*-methylarmepavine (*ent*-**79**) were synthesized from **152** after removal of the pyrrolidine *N*-substituent.

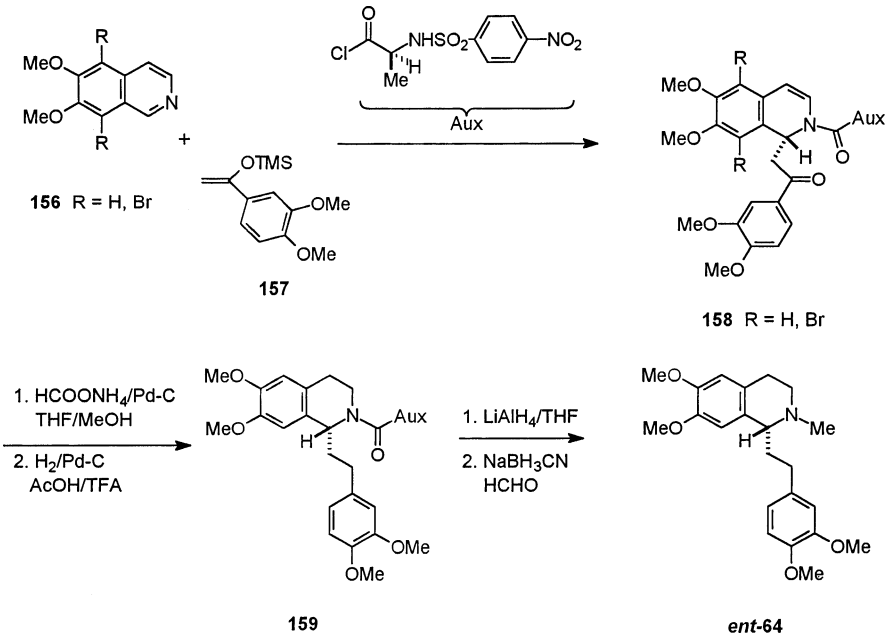
Scheme 38



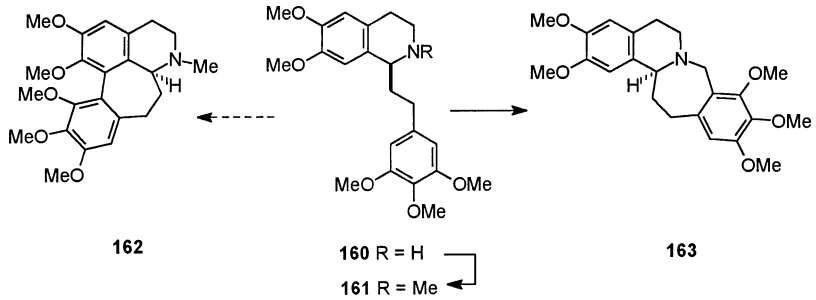
Chiral isoquinolinium dodecyl sulfate **153** prepared from the corresponding *N*-(2,4-dinitrophenyl)isoquinolinium chloride (Zinke salt) and (*R*)-(−)-phenylglycinol has been applied by Marazano, Das et al.[102,103] in the synthesis of a number of 1-mono-, 3-mono-, and 1,3-disubstituted tetrahydroisoquinoline derivatives, including (*S*)-(−)-salsolidine (*ent*-**10**) (Scheme 38).

Treatment of **153** with MeMgCl at −78 °C gave a diastereomeric oxazolidine **154**, contaminated with

Scheme 39



Scheme 40



1,2-dihydro derivative. This mixture was reduced with $NaBH_4$ in acetic acid to afford the (1*S*)-tetrahydroisoquinoline **155** with 60% de. After chromatographic separation, the major, pure (1*S*)-**155** isomer was hydrogenated to give the alkaloid *ent*-**10** in 38% overall yield.

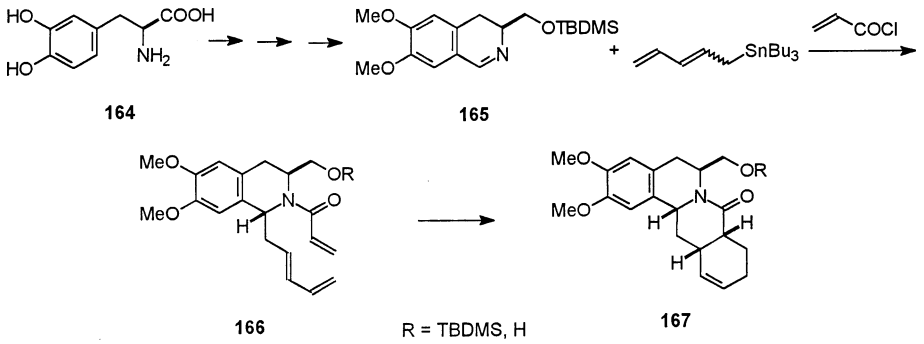
In this type of addition the methods involving the use of fully aromatic isoquinoline derivatives, acylated in situ with chiral acyl chlorides, have been found to give 1-substituted tetrahydroisoquinolines with excellent diastereoselectivity.[104] Oshawa et al.[105,106] described the synthesis of (*R*)-(−)-homolaudanosine (*ent*-**64**) employing aromatic isoquinoline **156** (R = H, Br) and silyl enol ether **157** in the reaction mediated with *N*-protected alanine derivative (Scheme 39).

To obtain the key addition product **158** with the highest possible diastereoselectivity, the authors undertook a series of experiments to establish the optimal reaction conditions. They noted that *p*-nitrophenylsulfonyl-protected alanine was the most effective chiral auxiliary. Introduction of bromine substituents at C-5 and C-8 into the isoquinoline nucleus (**156**, R = Br) not only accelerated the addition step but also enhanced the diastereoselectivity, as compared with those obtained using the unsubstituted isoquinoline (**156**, R = H). The key addition product **158** (R = Br), isolated as single isomer on crystallization of the crude reaction product (Y: 93%, 93% de), was readily converted into the alkaloid by three reduction processes. The double bond, bromine, and auxiliary nitro group were all reduced during the catalytic hydrogenation in $HCOONH_4$/Pd−C system, the carbonyl group in a TFA/AcOH solution, catalyzed also by Pd−C, and finally the chiral inductor in **159** was eliminated by $LiAlH_4$. After *N*-methylation, (*R*)-(−)-homolaudanosine (*ent*-**64**) was obtained in 33% overall yield. The (*R*)-selectivity of this process was postulated to arise from a stable conformation (calculated by the PM3 method) of the in situ formed quaternary salt.[106]

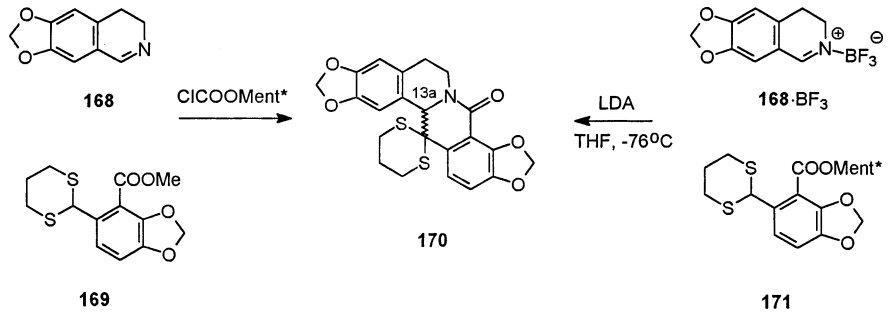
Recently,[107,108] other alkaloids of the "homo-series" have been synthesized in good yields and stereoselectivity by the same group of researchers using as a key intermediate (1*S*)-phenylethylisoquinoline **160**, prepared according to the above method. Its *N*-methylation led to (*S*)-(+)-*O*,*O*-dimethylautumnaline (**161**), a known precursor of the aporphine alkaloid (*S*)-(+)-*O*-methylkreysigine (**162**), while cyclization with formaldehyde yielded the homoberberine **163** (Scheme 40).

Stereoselective addition of tin reagents to the C=N double bond of chiral dihydroisoquinoline **165**, activated by acyl chlorides, has been explored in the synthesis of the berbane system (e.g., **167**) by Yamaguchi et al.[109] (Scheme 41). In this synthesis, chiral dihydroisoquinoline **165**, produced from L-DOPA (**164**) and the tin derivative, 2,4-pentadienyltribu-

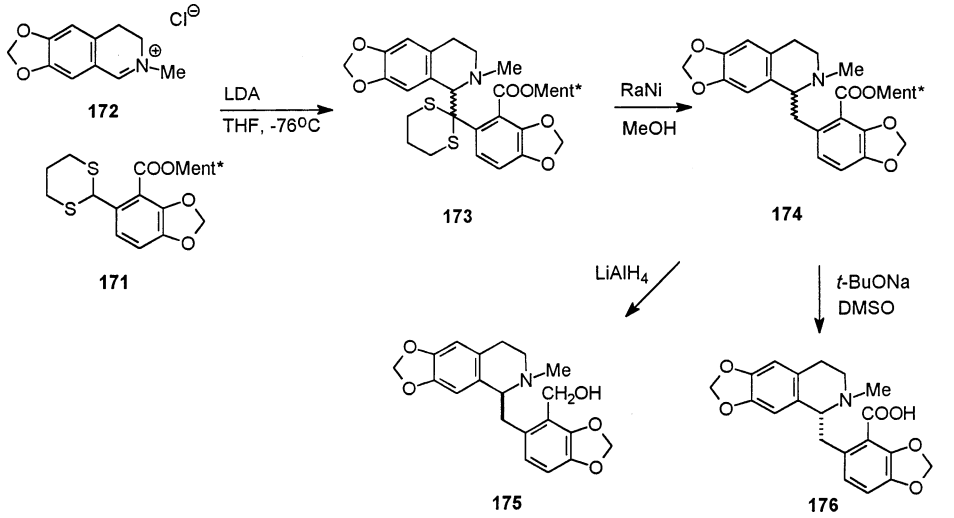
Scheme 41



Scheme 42



Scheme 43



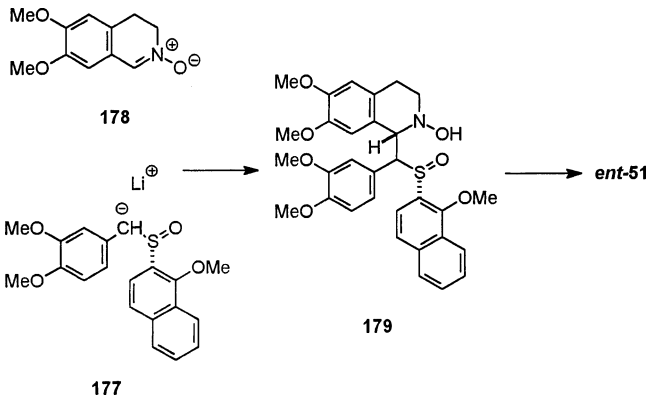
tyltin, in the presence of acryloyl chloride afforded the addition product **166**, which underwent intramolecular Diels−Alder cycloaddition to the tetracyclic berbane system **167** (95% ee). The synthesis could also be performed as a one-pot procedure. It is notable that during this synthesis, a single stereogenic center in amino acid **164** was able to introduce three other stereogenic centers in **167** in a stereoselective manner.

In an asymmetric modification of the "dithiane synthesis"[110] of isoquinoline alkaloids, 6,7-methylenedioxy-3,4-dihydroisoquinoline (**168**) was treated in situ with (−)-menthyl chloroformate in the presence of dithiane **169**. As a result, oxostylopine precursor **170** (13a*R*) was produced, albeit in very poor yield and moderate enantioselectivity (39% ee)[111] (Scheme 42). Product *ent*-**170** with 13a*S* configuration, in contrast to the above, was obtained with 21% ee when dihydroisoquinoline **168** activated with BF_3 etherate was reacted with optically pure dithiane **171**, prepared from 2-menthyloxycarbonylpiperonal. Crystallization of **170** from methylene chloride resulted in an increase in the enantiomeric excess to 86%.

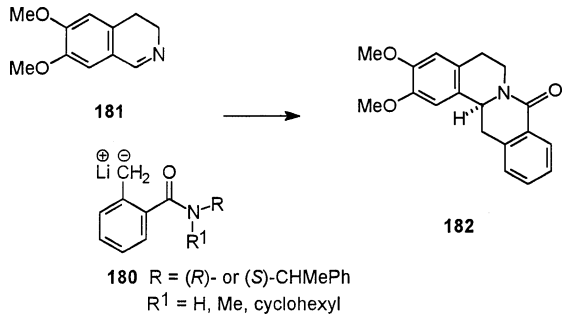
The chiral dithiane **171** and hydrastinine chloride (**172**) were used as substrates in the synthesis of (+)- and (−)-corydalisol (**175**), a *seco*berbine[111] (Scheme 43). The addition product **173** was formed as an unseparable mixture of diastereomers with low selectivity (55% dr). Desulfurization with Raney nickel of the mixture followed by repeated column chromatography gave samples of both diastereomers **174** with ca. 90% dr. $LiAlH_4$ reduction of the dextrorotatory diastereomer **174** led to (*S*)-(−)-corydalisol (**175**), obtained with 53% op, while (−)-**174** gave the (*R*)-(+)-isomer (*ent*-**175**) with 46% op.

Hydrolysis of the ester group in (−)-**174** (85% de) afforded (+)-coryximine (**176**), a *seco*phthalideiso-

Scheme 44



Scheme 45



quinoline alkaloid.[112] For this reaction to occur, drastic conditions (DMSO and sodium *tert*-butoxide under reflux) were needed, which apparently were responsible for a dramatic loss of optical purity to 6% (Scheme 43).

Optically active benzyl naphthyl sulfoxide **177** and isoquinoline *N*-oxide **178** were used in the synthesis of (*R*)-(−)-norlaudanosine (*ent*-**51**), obtained in a highly diastereoselective addition process,[113] via hydroxylamine **179** in a reaction carried out under kinetic control (Scheme 44).

Recently, lateral metalation methodology using chiral *o*-toluamides **180** with a chiral auxiliary in the amine part of the molecule has been conveniently adapted for asymmetric synthesis of protoberberine alkaloids (Scheme 45).

Reaction of 3,4-dihydroisoquinoline **181** with lithiated *o*-toluamide incorporating either (*R*)- or (*S*)-α-phenylethylamine **180** (R = (*R*)- or (*S*)-CH(Me)C_6H_5, R^1 = H, Me, cyclohexyl) was used by Warrener et al.[114] in a one-pot synthesis of both enantiomers of oxoberberine **182** and *ent*-**182** (Scheme 45). The nitrogen-R^1 substituent turned out to be an important factor for the stereochemical outcome of the reaction. It was shown that R^1 = cyclohexyl was more effective than methyl and hydrogen and allowed ee's up to 97% to be otained, although with moderate chemical yield (ca. 48%).

In an analogous experiments,[115] lithiated *o*-toluamide **183**, in which the amide nitrogen was a part of the oxazolidine heterocycle, derived from norephedrine, was added to dihydroisoquinoline **181**. Oxoberbine **182**, obtained in 31% yield, was accompanied with a ring-opened intermediate **184** (41%), which easily cyclized (*n*-BuLi, THF, −72 °C) to **182** (Scheme 46). Both compounds were produced with 98% ee and the same (*S*)-configuration of the newly generated stereogenic center.

In other series of experiments (Scheme 46) lithiated *o*-toluamide **183** and 6,7-methylenedioxy-3,4-dihydroisoquinoline (**168**) were used as substrates in the planned synthesis[116] of the so-called "gusanlung D", a protoberberine alkaloid whose structure **185** was postulated on spectral grounds.[117] As above, in this reaction two products were formed, the addition/cyclization lactam **185** (33% yield, 98% ee) and the ring-opened secondary amine **186** (31%), which was cyclized to **185** of the same ee, 98%. The ee of lactam **185** could be increased to >99% on crystallization from methanol. Finally, the physical properties and spectral data of the synthesized oxoberbine **185** were proved to differ from those reported for the natural product; therefore the structure postulated earlier for the natural gusanlung D remains to be clarified.

3.1.2. Enantioselective Synthesis

In contrast to many studies devoted to addition of organometallic reagents to the carbonyl group in aldehydes and ketones catalyzed by external chiral ligands, analogous reactions involving the carbon−nitrogen double bond have not received as much attention.[118,119]

An efficient enantioselective synthesis of protoberberine **182** based upon (−)-sparteine (**187**)-mediated addition of nonchiral *o*-toluamides **180** (R, R^1 = alkyl, cycloalkyl, heterocyclic, aromatic) with 3,4-dihydroisoquinoline **181** has been reported by Liu[120] (Scheme 45). The enantiomeric purity of the addition/cycliza-

Scheme 46

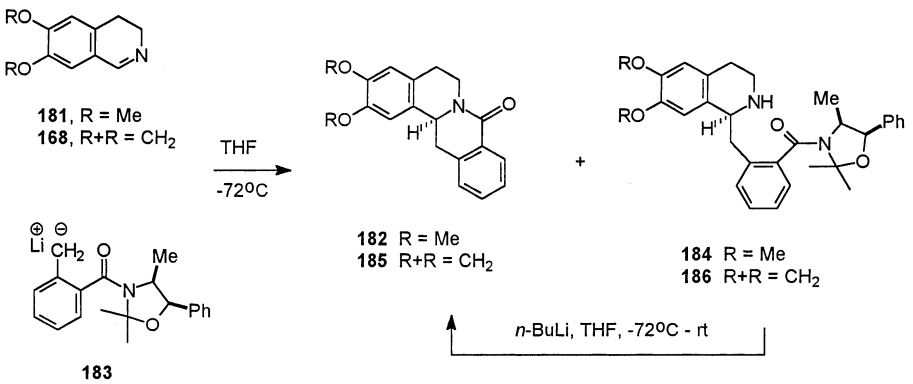
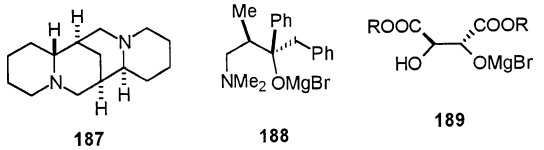
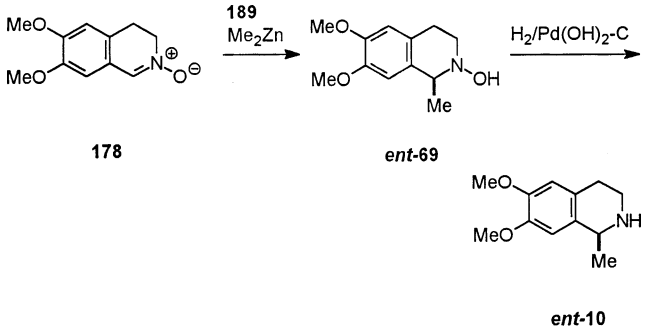


Chart 11



187 188 189

Scheme 47



178 *ent*-69 *ent*-10

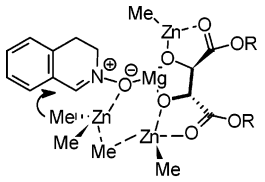
tion product **182** was strongly dependent on the nature of the R,R[1] substituents. The best results, 77% ee and 45% yield, were achieved when ethyl and phenyl groups were the substituents.

To increase the electrophilicity of the isoquinoline C=N double bond, the corresponding *N*-oxides have been utilized. Ukaji, Inomata et al.,[121−124] who studied addition reactions of organozinc compounds to nitrones including dihydroisoquinoline *N*-oxides **178**, used magnesium and zinc alcoholates derived from Chirald (**188**) and tartaric acid esters (**189**) as external chiral auxiliaries (Chart 11).

Initially, addition of Me_2Zn to nitrone **178** was carried out in the presence of Chirald-derived ligand **188**.[121] The addition product **69** (Scheme 47) was formed with 63% ee and readily converted into (*R*)-(+)-salsolidine (**10**) in high yield but at a rather moderate enantioselectivity (50% ee). The selectivity was improved significantly with magnesium zinc alkoxides of tartaric acid esters **189**; in particular, dicyclopentyl ester **189** (R = *c*-Pent) was found to be the best choice.[122,123] Thus, when nitrone **178** was slowly added to a preformed complex of this alkoxide with 3 mol equiv of dimethylzinc, (*S*)-(−)-salsolidine (*ent*-**10**) was produced in high yield and with high enantioselectivity via hydroxylamine *ent*-**69**, obtained with >99%ee.

The preferential formation of the (*S*)-enantiomer under these reaction conditions was attributed to the intermediate complex **190**, in which the carbon−nitrogen double bond was approached by the methyl group from the less hindered *si* face[124] (Figure 4).

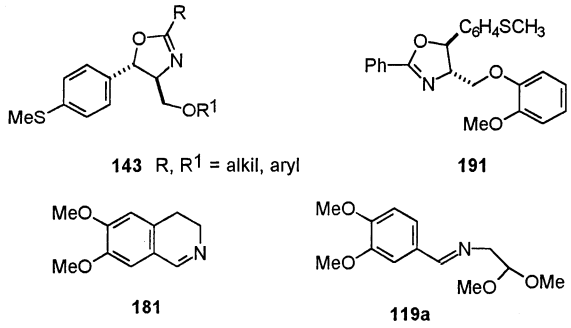
The inductive and catalytic power of other external chiral controllers of stereochemistry, such as (−)-sparteine (**187**, Chart 11),[125] oxazolines **143** (Scheme 35),[126] and **191**,[127] in addition reactions of organometallic reagents to prochiral imines **181** and **119a** as the key steps of the synthesis of simple isoquinoline alkaloids have been investigated (Chart 12). Despite the pronounced catalytic effect of the ligands, the enantioselectivity in addition of organometallic compounds to the imines was very disappointing (2−41% ee).



190

Figure 4. Intermediate complex **190** in the addition of Me_2Zn to nitrone.

Chart 12



143 R, R[1] = alkil, aryl 191 181 119a

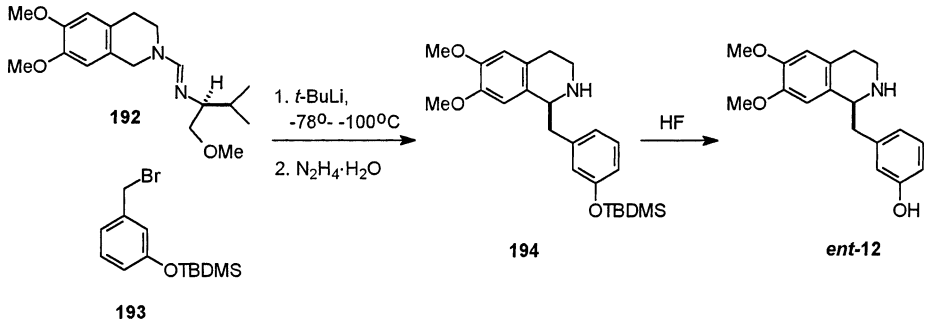
3.2. Alkylation of α-Carbanion of Tetrahydroisoquinoline Derivatives

The outstanding Meyers' formamidine carbanion chemistry,[128] applied to the synthesis of many isoquinoline alkaloids, providing products in high yield and with high enantiomeric purity, has been further developed. Syntheses of other alkaloids such as the unnatural (*S*)-(−)-noranicanine (*ent*-**12**, Scheme 48) and (−)-tetrahydropalmatine (**199**, Scheme 49) have been performed by Meyers' group[129,130] using this methodology. Starting with the well-known valinol methyl ether (VME)-derived formamidine **192** and *O*-silylated benzyl bromide **193**, the target (*S*)-(−)-noranicanine (*ent*-**12**) was prepared in 54% overall yield and with high enantiomeric purity via tetrahydroisoquinoline **194** by cleavage of the silyl ether (Scheme 48).

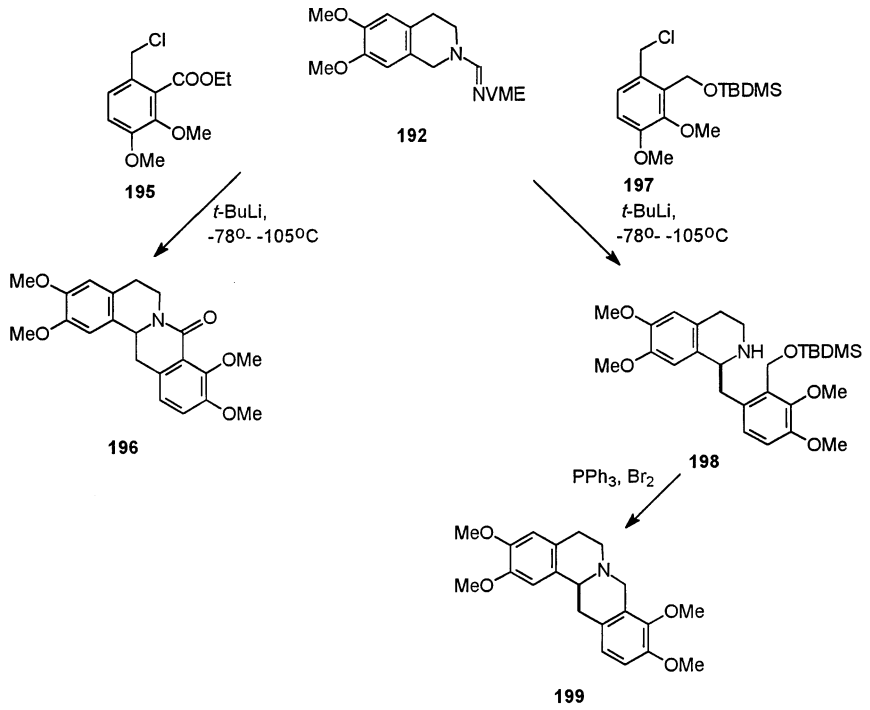
In the planned synthesis of tetrahydropalmatine (**199**), a protoberberine vicinally substituted in ring D, the reaction between formamidine **192** and benzyl chloride **195**, substituted with the ethoxycarbonyl group at C-2, was used.[130] However, the generally highly stereoselective C-alkylation process turned out to be nonselective, leading to a racemic product **196**. It was assumed that the configuration of the formamidine anion stabilized by lithium chelation, important for the steric course, was disrupted by the ester group. Thus, a nonchelating benzyl alcohol **197** was used instead, and (−)-tetrahydropalmatine (**199**) was synthesized in 65% yield with 88% ee via the intermediate secondary amine **198** (Scheme 49).

Another synthesis of protoberberine alkaloids, using Meyers' formamidine methodology, was carried out by Schore and co-workers.[131] In their approach the difficulty in the synthesis of 9,10-disubstituted protoberberines encountered above was overcome by introduction of a trimethylsilyl group at C-2 of the benzyl chloride **201** (Scheme 50). The silyl group was used to control the regioselectivity (*ipso*-directing) of the following cyclization step. Thus, the alkylation of formamidines **200** with benzyl chlorides **201** af-

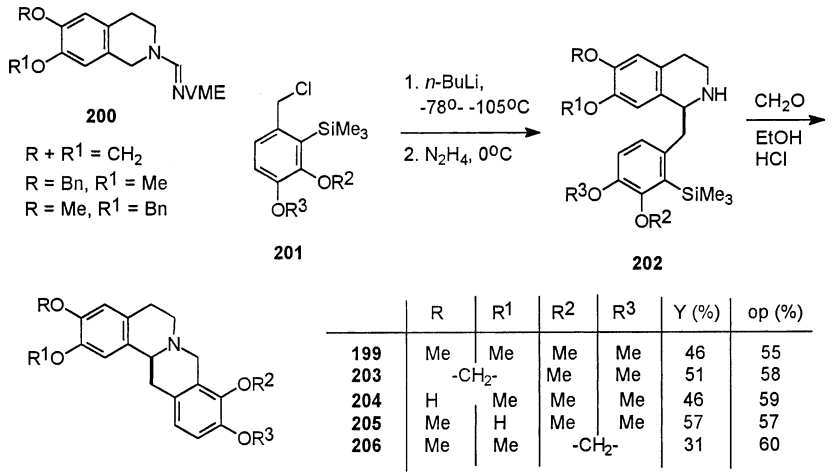
Scheme 48



Scheme 49



Scheme 50

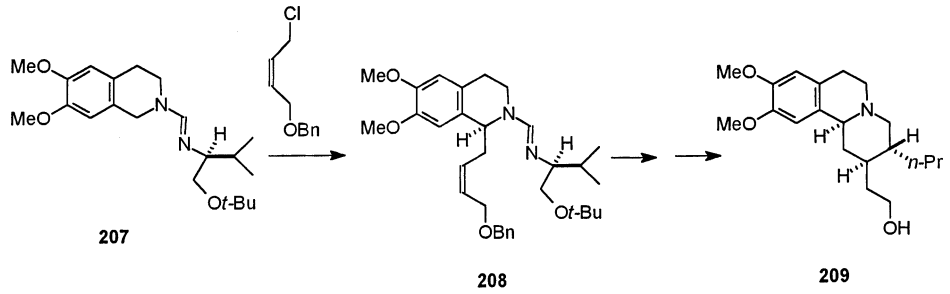


	R	R1	R2	R3	Y (%)	op (%)
199	Me	Me	Me	Me	46	55
203	-CH2-		Me	Me	51	58
204	H	Me	Me	Me	46	59
205	Me	H	Me	Me	57	57
206	Me	Me	-CH2-		31	60

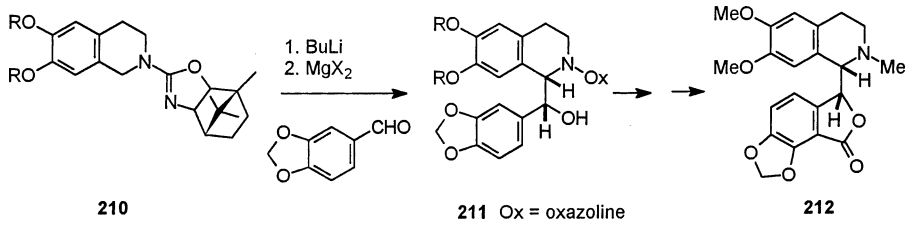
forded (1*S*)-benzylisoquinolines **202**, which on Mannich-type condensation with formaldehyde were regioselectively cyclized to tetracyclic alkaloids (*S*)-tetrahydropalmatine (**199**), (*S*)-canadine (**203**), (*S*)-corypalmine (**204**), (*S*)-isocorypalmine (**205**), and (*S*)-sinactine (**206**), albeit with a moderate optical purity. In the synthesis of (*S*)-sinactine (**206**), with methylenedioxy-substituted ring D, no selectivity was observed, and a mixture of the alkaloid and its regioisomer was produced.

C-α-Alkylation of chiral amidine **207** with *cis*-1-chloro-4-benzyloxy-2-butene to give (1*S*)-tetrahydroisoquinoline **208** with good diastereomeric excess and its further transformation into homoprotoemetinol **209** in a series of transformations has been reported by Takacs and Boito[132] (Scheme 51).

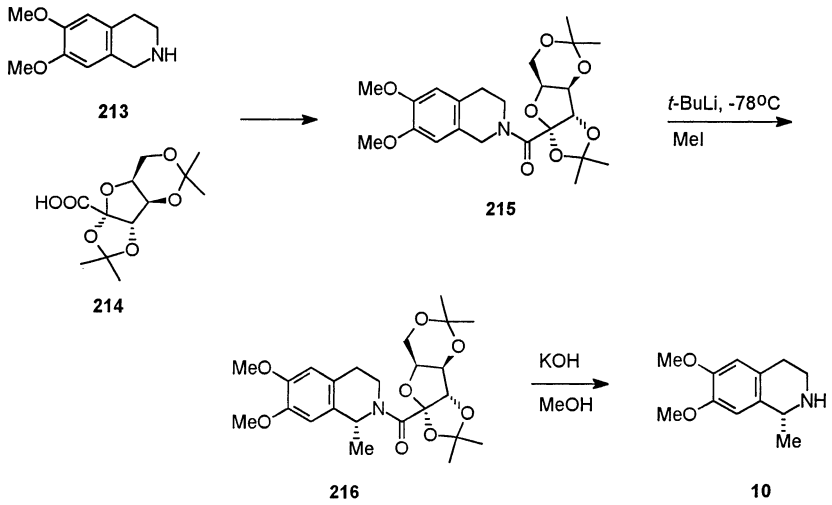
Scheme 51



Scheme 52



Scheme 53



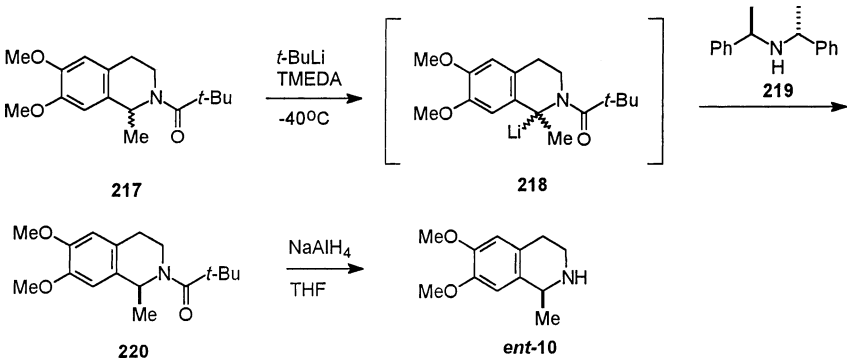
The Gawley diastereo- and enantioselective synthesis of phthalide isoquinoline alkaloids, applying camphor-derived isoquinolyloxazoline **210**,[133] has been modified by using 1-magnesiotetrahydroisoquinolines[134] instead of the 1-lithiated derivatives (Scheme 52). The synthesis started with transmetalation with magnesium halides of lithiated tetrahydroisoquinolines **210** followed by addition of piperonal. This process, which occurred with 80% *erythro*-selectivity and 100% enantioselectivity, afforded adducts **211** in good yield. From **211** substituted with methylenedioxy group (R+R = CH_2) the known precursors of (+)-egenine, (+)-bicuculline, and (+)-corytensine were obtained. In another series of experiments **211** with methoxy substituents (R = Me), after reductive removal of the oxazoline auxiliary, *N*-methylation, and metalation−carboxylation, was converted into (+)-corlumine (**212**).

Quirion et al.,[135] studying the efficiency of chiral carboxylic acids both as activators and chiral auxiliaries in α-alkylation of carbanions derived from heterocyclic amines, chose amide **215**, prepared from tetrahydroisoquinoline **213** and 2-keto-L-gulonic acid **214**, and used it as a key intermediate in the synthesis of (*R*)-(+)-salsolidine (**10**) (Scheme 53).

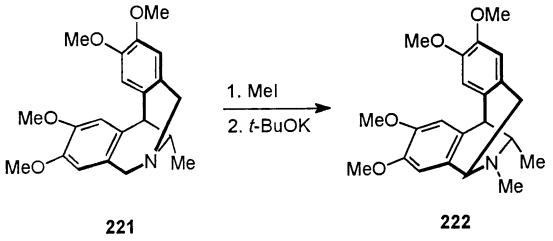
Treatment of **215** with *t*-BuLi at −78 °C, followed by methyl iodide, gave the substitution product **216** in 55% yield with 78% de. Removal of the auxiliary from the prevailing (1*R*)-diastereomer by base-catalyzed hydrolysis led to the final product (*R*)-(+)-**10** isolated with 98% ee.

Another synthetic strategy, involving formation of α-amine carbanion at C-1 of tetrahydroisoquinoline heterocycle, was reported by Simpkins and co-workers.[136] Deprotonation (*t*-BuLi/TMEDA, −40 °C) of racemic 1-substituted *N*-acylated tetrahydroisoquinoline **217** and reprotonation of the lithio derivative with chiral amines such as **219** has been developed as a simple and convenient method of the synthesis of isoquinoline alkaloids. Accordingly, (*S*)-(−)-salsolidine (*ent*-**10**) was synthesized from racemic amide **217** by reprotonation of the lithio derivative **218** at −78 °C using chiral amine **219**. The resulting *N*-pivaloyl salsolidine (**220**), enriched from 86% to 96% ee by crystallization, was treated with $NaAlH_4$ to give the alkaloid *ent*-**10** of ca. 96% ee (Scheme 54).

Scheme 54



Scheme 55



An original approach to the synthesis of a pavine alkaloid, (6*R*)-methyl-*O*-methylthalisopavine **222** employing Stevens rearrangement involving a 1,2-migration of substituent from nitrogen N-2 to carbanion at C-1, has been taken by Hanessian and Mauduit[137] (Scheme 55).

The chiral amine **221** was *N*-methylated to the corresponding quaternary salt and treated with potassium *tert*-butoxide in dioxane at 80 °C to rearrange to the isopavine **222** in a highly stereoselective process.

3.3. Miscellaneous Methods

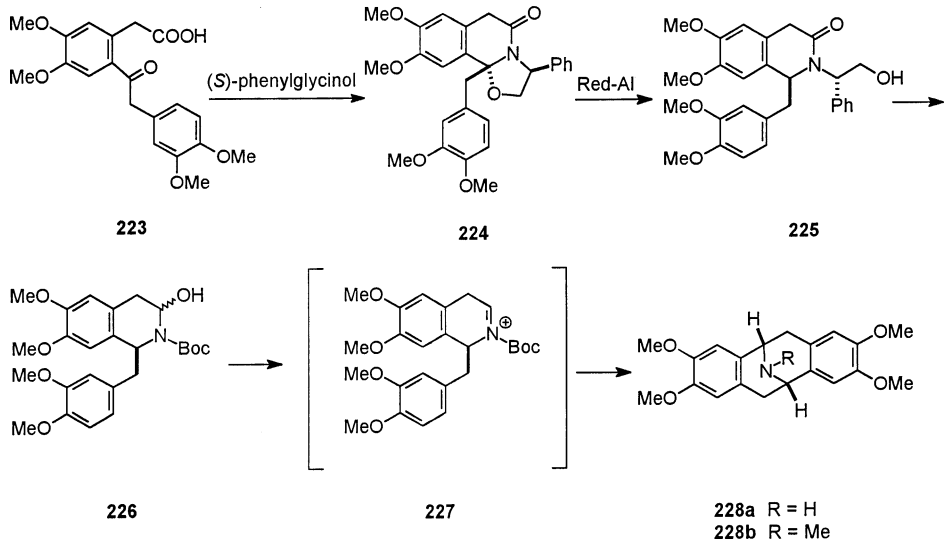
The traditional methods of the synthesis of isoquinoline alkaloids, described in the preceding sections of this review, involved the closure of the nitrogen-containing isoquinoline ring by formation of new bonds between $C_{8a}-C_1$ (Bischler−Napieralski), $C_{8a}-C_1-N_2$ (Pictet−Spengler), and C_4-C_{4a} (Pomeranz−Fritsch). There are, however, methodologies which do not fall into these categories but in which the heterocyclic ring closure occurs between C_1-N_2 and N_2-C_3 atoms as well.

The C_1-N_2 connectivity approach has been taken by Meyers and Munchhof[138] in the synthesis of several alkaloids from a common intermediate, the ketoacid **223**, containing the alkaloids' carbon framework (Scheme 56).

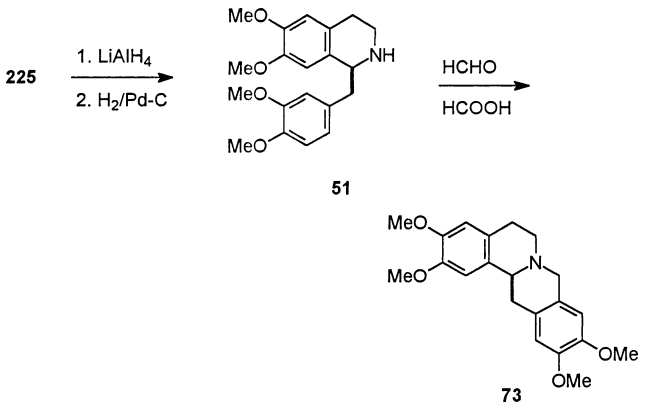
Condensation of **223** with (*S*)-phenylglycinol produced the chiral bicyclic lactam **224** as a single isomer. Selective cleavage of the aminal C−O bond without affecting the carbonyl group (Red-Al, −78 °C) resulted in lactam **225**. This strategy has opened a new entry into the pavine family of alkaloids. The next steps of pavine synthesis involved exchange of the *N*-chiral auxiliary for the Boc-protecting group, reduction ($NaBH_4$) of the lactam carbonyl to hydroxy derivative **226**, and cyclization via the intermediate iminium ion **227** to give the tetracyclic pavine skeleton **228a**. Final *N*-methylation supplied the enantiopure alkaloid (−)-argemonine (**228b**) in high yield.

The usefulness of lactam **225** in the synthesis of other types of isoquinoline alkaloids was also demonstrated,[138] as shown in Scheme 57. Reduction of the carbonyl group with $LiAlH_4$ followed by hydrogenolysis of the *N*-chiral auxiliary completed the synthesis of (*S*)-(−)-norlaudanosine (**51**), from which

Scheme 56



Scheme 57



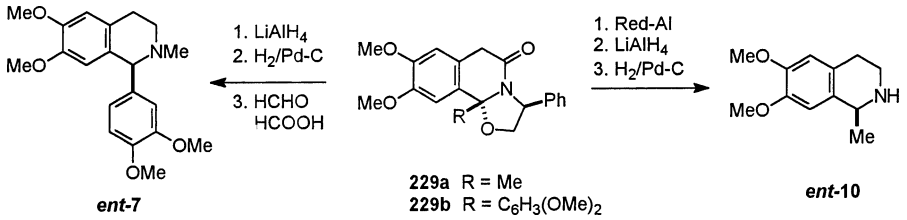
(*S*)-(−)-xylopinine (**73**) was prepared by condensation with formaldehyde.

Earlier, a similar reaction sequence was applied by the same authors[139] in the synthesis of (*S*)-(−)-salsolidine (*ent*-**10**) and (*S*)-(+)-cryptostyline II (*ent*-**7**), also based on bicyclic lactams **229a** and **229b**, respectively (Scheme 58).

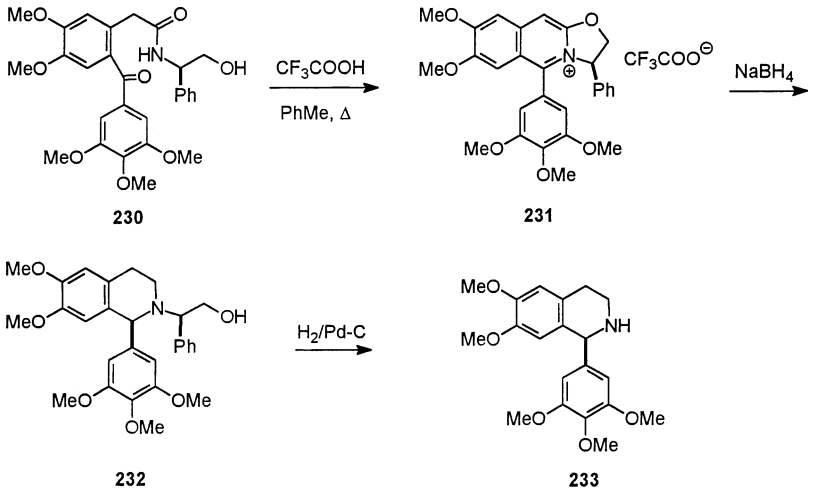
Applying a similar synthetic strategy in the synthesis of norcryptostyline III (**233**), Husson et al.[140] used keto−amide **230** as a substrate derived from (*R*)-phenylalaninol (Scheme 59). It was cyclized in acid to tetracyclic aromatic isoquinolinium moiety **231**, subsequently reduced with $NaBH_4$ to the tetrahydro derivative **232**. Removal of the chiral auxiliary transformed **232** into (*S*)-(−)-norcryptostyline III (**233**) in high overall yield.

1,3-Dimethyltetrahydroisoquinolines **238**, trans and cis, important building blocks in the synthesis of naphthylisoquinoline alkaloids,[19] have been synthe-

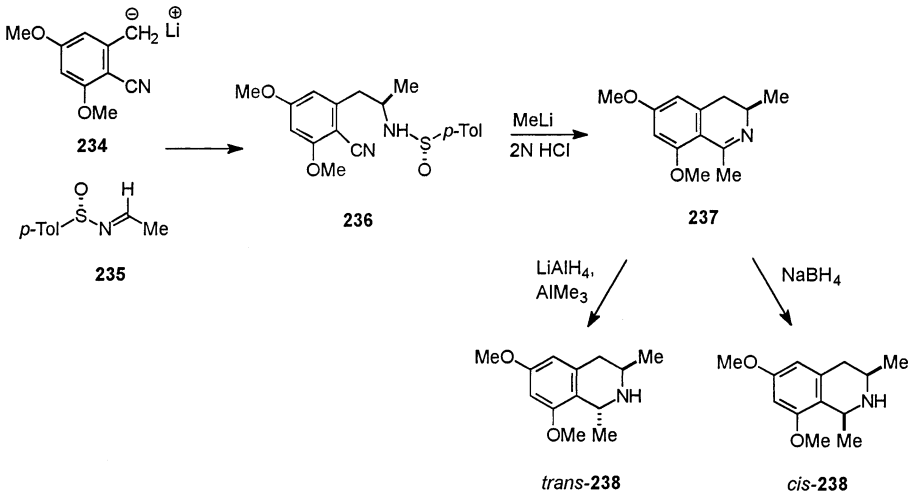
Scheme 58



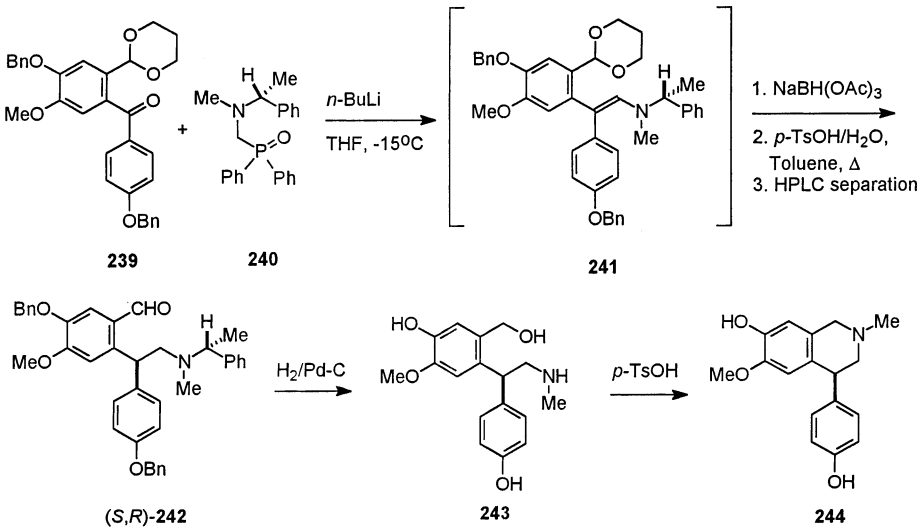
Scheme 59



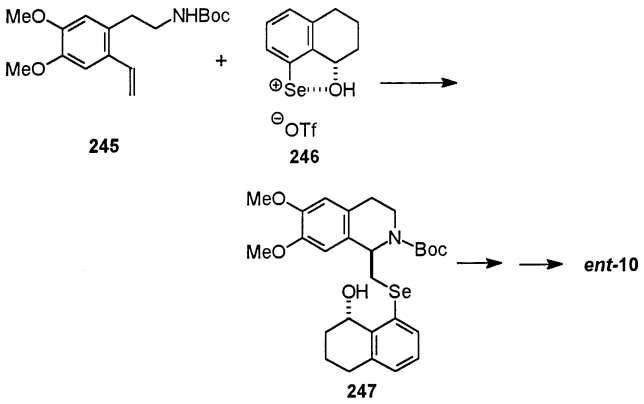
Scheme 60



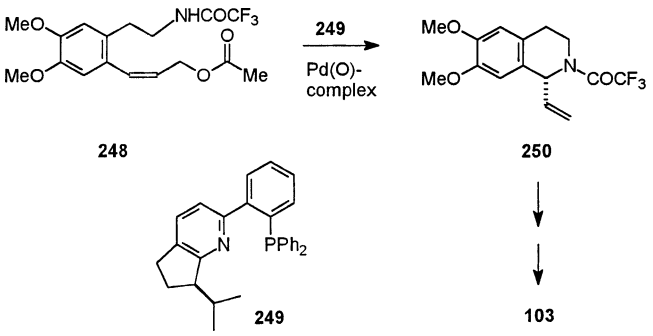
Scheme 61



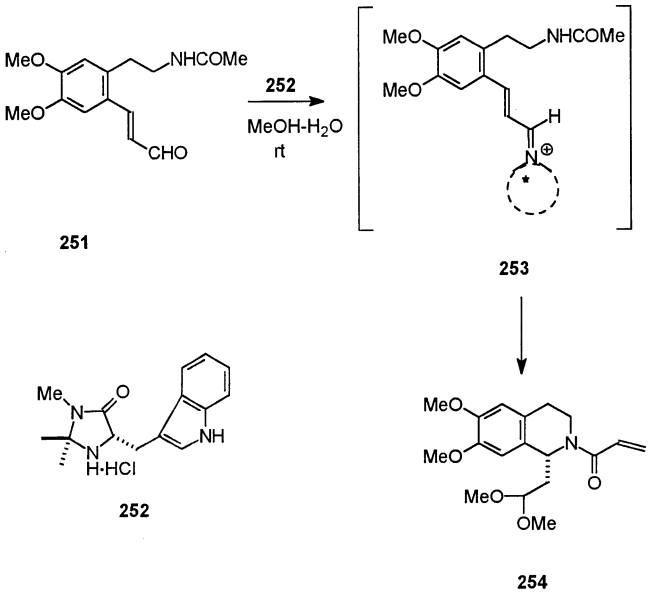
Scheme 62



Scheme 63



Scheme 64



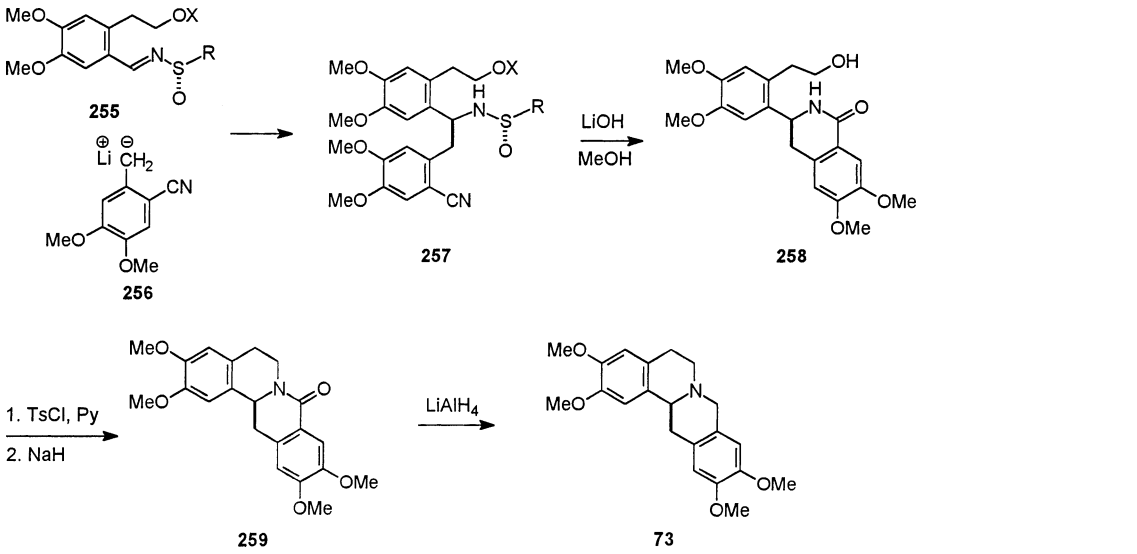
sized by Davis et al.[141] using chiral sulfinamide **236** as a key intermediate. Its preparation involved highly diastereoselective addition of the laterally lithiated nitrile **234** to sulfinimine **235**. Compound **236** on treatment with excess of methyllithium followed by acidification was directly converted into dihydroisoquinoline **237**, which was in turn reduced to either *trans*-(1*R*,3*R*)-**238** or *cis*-(1*S*,3*R*)-**238**, depending on the reducing agent used[20] (Scheme 60).

Synthesis of (*S*)-(−)-cherylline (**244**), a phenolic alkaloid substituted at C-4 of the isoquinoline unit, and the unnatural (*R*)-enantiomer *ent*-**244**, performed by Couture and co-workers,[142] involved the bond formation between C-1 and N-2 atoms in chiral amino aldehyde **242** (Scheme 61).

In this synthesis, the starting compounds diaryl ketone **239** and chiral phosphorylated amine **240** have been prepared in multistep syntheses and coupled together with *n*-BuLi. The resulting enamine **241** was reduced in situ with $NaBH(OAc)_3$ to give a mixture of diastereomeric amines **242** with 25% de, from which after hydrolysis and chromatographic separation each of the pure diastereomers (*S*,*R*)-**242** and (*R*,*R*)-**243** was obtained. During catalytic hydrogenation (H_2/Pd−C) of (*S*,*R*)-**242** (the precursor of the natural alkaloid), not only was the formyl group reduced but also the chiral auxiliary and *O*-protecting benzyl groups were cleaved affording **243**, which was easily cyclized to (*S*)-(−)-cherylline (**244**) when treated with *p*-toluenesulfonic acid. The unnatural enantiomer *ent*-**244** was synthesized from (*R*,*R*)-**242** following the same reaction sequence.

A selenium-mediated synthesis of (*S*)-(−)-salsolidine (*ent*-**10**) has been performed by Wirth and colleagues[143] as part of their study on application of selenium compounds in organic synthesis. Additions of chiral selenium electrophiles to alkenes followed by nucleophiles, known to proceed with high diaste-

Scheme 65



reoselectivity, were used in intramolecular aminoselenation of styrene−carbamate **245** to construct the tetrahydroisoquinoline system (Scheme 62). Thus, in reaction of **245** with the chiral selenium cation, e.g., **246**, prepared in situ from the corresponding diselenide and bromine/silver triflate at −100 °C, **247** was produced in a moderate yield as a result of an addition−cyclization process. The alkaloid *ent*-**10** (90% ee) was prepared by cleavage of the selenide appendage (Ph_3SnH, AIBN) and the Boc protecting group (TFA).

Asymmetric intramolecular allylic amination catalyzed with Pd(0) complexes has been used as a key step in the synthesis of (*R*)-carnegine (**103**) by Ito, Katsuki et al.[144] (Scheme 63).

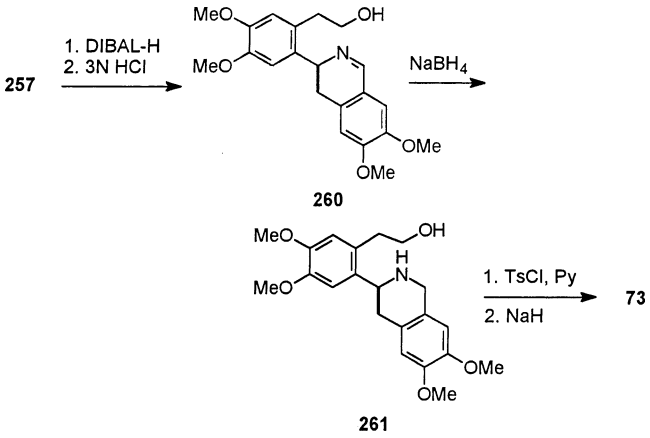
Amidocarbonate **248**, prepared in five steps from homoveratrylamine, was cyclized to 1-vinyltetrahydroisoquinoline **250** in the presence of Pd(0)-complex/chiral ligand **249** in methylene chloride. The cyclization product **250** was produced in 89% yield and with 88% ee and was further elaborated into the target alkaloid **103** in a series of transformations. They involved conversion of the vinylic function into methyl group (six steps) and exchange of the *N*-protection into *N*-methyl group (three steps).

Intramolecular cyclization of tetrahydroisoquinoline ring between amide nitrogen and vinyl group by enantioselective aza-Michael reaction, using organocatalysts under enviromentally friendly conditions, has been described by Takasu, Ihara et al.[145] (Scheme 64).

The amidoaldehyde **251**, when treated with tryptophan-derived catalyst **252** in methanol/water (95:5) for 10 days, was cyclized in 90% yield with 46% ee to (*R*)-**254**, a potential precursor of emetine-type of alkaloids. A chiral iminium intermediate **253** was postulated to be responsible for the steric outcome of the reaction.

The formation of a bond between N-2 and C-3 atoms to construct the tetrahydroisoquinoline ring system was an important step in the synthesis of (*S*)-(−)-xylopinine (**73**), performed by Davis and Mohanty.[146] Various chiral sulfinimines **255** (R = *p*-tolyl, 2-methoxynaphthyl, and *tert*-butyl), *ortho*-substituted

Scheme 66



with alkoxyethyl group, were used as substrates (Scheme 65). Treatment with laterally lithiated *o*-tolunitrile **256** gave the addition product **257** in moderate yield (ca. 68%) with dr ca. 90%. Adduct **257** (R = *p*-tolyl, X = TBDMS) was elaborated to the alkaloid in two ways (Schemes 65 and 66).

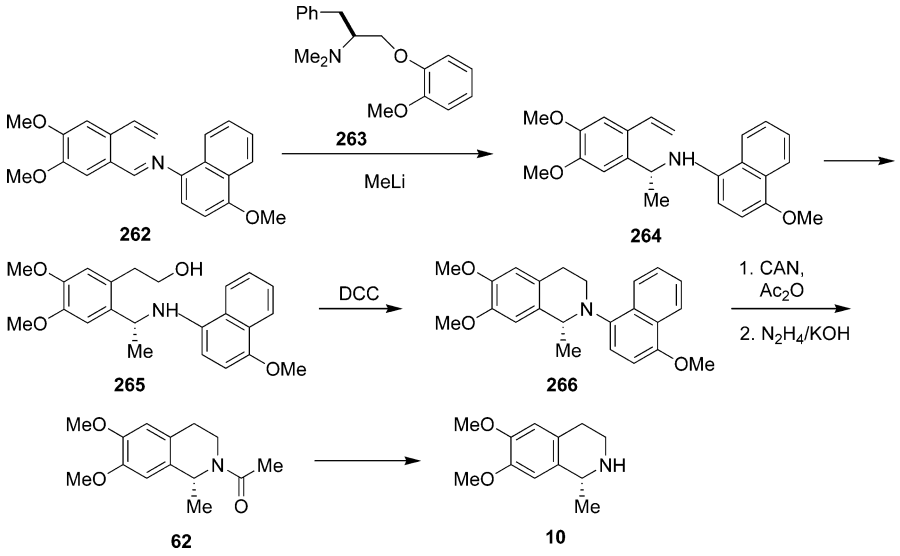
In the first sequence, hydrolysis/cyclization (LiOH, MeOH) gave the hydroxy lactam **258**, further cyclized to oxoxylopine **259** on treatment with tosyl chloride in pyridine. Finally, $LiAlH_4$ reduction afforded the target alkaloid (*S*)-(−)-**73** (Scheme 65).

In the other reaction sequence, the same sulfinamide **257** (R = *p*-tolyl, X = TBDMS) was transformed into dihydroisoquinoline **260** in a one-pot operation involving DIBAL-H reduction and hydrolysis/cyclization. A subsequent reduction of the C=N double bond with $NaBH_4$ afforded the tetrahydroisoquinoline **261**, produced as a single isomer, which was in situ tosylated and treated with NaH to complete the synthesis of (*S*)-(−)-xylopinine (**73**) (Scheme 66).

Another example in which the nitrogen-containing tetrahydroisoquinoline ring was closed by N-2−C-3 bond coupling was presented by Tomioka et al.[147] in the synthesis of (*R*)-(+)-salsolidine (**10**) (Scheme 67).

Vinylic imine **262** was subjected to enantioselective addition of MeLi at −95 °C in the reaction catalyzed by chiral ligand **263** to give amine **264** in quantitative

Scheme 67



yield with 93% ee. Hydroboration followed by DCC induced cyclization of the resulting alcohol **265** led to the tetrahydroisoquinoline derivative **266**, from which the *N*-substituent was oxidatively removed by CAN/Ac_2O to give *N*-acetylated salsolidine **62**, hydrazinolyzed to the alkaloid (*R*)-(+)-**10**.

There are several methodologies focused on the asymmetric synthesis of morphine-type alkaloids which are reviewed in detail in Bentleys' annual reports published in the Natural Products Reports and in other review articles.[148] They have not been included because the synthetic strategies are far different from those that are the focus of this review.

4. Conclusion

Tetrahydroisoquinoline alkaloids, due to their widespread occurrence in nature, diverse biological activity (including the unnatural congeneres[149]), and interesting chemical properties, have become attractive targets for organic synthesis. In the past decade a wide range of synthetic methods have been reported for the synthesis of chiral nonracemic alkaloids.

Most of the methods have been based on diastereoselective syntheses using chiral auxiliaries, usually derived from natural products, appended either to or around the nitrogen of isoquinoline (or its precursor) or in the C-1 substituent (or its equivalent). In this context, the traditional Bischler−Napieralski cyclization/reduction and Pictet−Spengler syntheses as well as the addition of carbon nucleophiles to the isoquinoline C=N double bond have been the most often explored strategies. A new approach to the synthesis of protoberberine alkaloids involving addition of laterally lithiated *o*-toluamide to dihydroisoquinoline applying either chiral amides or chiral imines or external controllers of stereochemistry should be mentioned.

Good to excellent results have been achieved also in enantioselective methodologies, in particular in the reduction of the Bischler−Napieralski imine with chiral hydride reagents or during hydrogenation using chiral catalytic systems.

Various types of isoquinoline alkaloids have been synthesized, although the simple isoquinoline alkaloids, salsolidine and cryptostylines, have attracted the most attention as target compounds, the former being used as a reference in assessment of efficiency of new synthetic approaches.

Although the 1-substituted tetrahydroisoquinoline alkaloids are readily synthesized in an asymmetric manner, there is no one general method that would secure preparation of all types of isoquinoline alkaloids with high optical purity employing simple procedures. Usually the applied methodologies suffer from various limitations such as, e.g., moderate to poor yields, unsatisfactory regio- and stereoselectivity, nonavailability or costs of starting materials or reagents, multistep procedures, etc. Therefore, the question of finding a more efficient and/or simpler synthetic strategy is still open.

5. Acknowledgments

This work was supported by a research grant from The State Committee for Scientific Research in the years 2003−2006 (KBN grant no. 4T09A 07824).

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CR030692K