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Synthetic approaches to carnegine, a simple tetrahydroisoquinoline alkaloid

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Abstract—The different approaches towards the total synthesis of carnegine, a simple tetrahydroisoquinoline alkaloid isolated from several Cactaceae and Chenopodiaceae as well as other plants, are presented. Emphasis is placed on the various enantioselective strategies leading to the natural product in chiral form.

Contents

1. Introduction

The development of organic chemistry has been closely associated to the chemistry of natural products, and natural products synthesis has clearly played a dominant role in driving the course of synthetic organic chemistry. Many extraction, separation, structural elucidation and chemical synthetic procedures have been developed and originally applied with the purpose of achieving a better understanding of the natural products, since the latter have proven to be an excellent source of novel chemical entities and extraordinary challenges to the organic chemistry community.

The toxicity of plants, which contributes to their ability to protect themselves against predation, is partially related to

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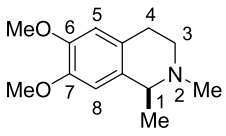
the diversity of small molecules that they synthesize. Alkaloids, which display a large variety of pharmaceutical activities and which importance in medicine has been highly publicized, compose one of the major classes of small molecules and accumulate in about 20% of all plant species.

The isoquinolines are the most numerous group among the alkaloids; they also display the widest range of structural diversity. Many of them are intensely bioactive and the biological activity attached to the isoquinoline nucleus coupled to the diversity characterizing these compounds, which is essential to the discovery of new drugs, have provided a great deal of interest in their synthesis.[1a–d] Furthermore, many natural, semisynthetic and synthetic isoquinolines with useful pharmacological properties, are currently part of mankind's therapeutic arsenal.[1e,f]

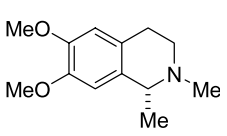
Structural diversity and biological activity of isoquinolines have long attracted the attention of synthetic chemists. The construction of the 1,2,3,4-tetrahydroisoquinoline ring system, specially in racemic form, has been a popular area of research in natural products chemistry since the early years of the past century. Activity in this field is almost as old as the discovery of the isoquinoline system itself; however, it is only in the past 20–25 years that the asymmetric synthesis of tetrahydroisoquinolines has been undertaken.

In a short compilation, Bentley listed 34 simple tetrahydroisoquinolines (methoxy, hydroxy and/or alkyl groups as substituents), 6 of their congener dihydro-isoquinolines and 6 related isoquinolines,[2] while Shamma et al. listed 99 structures belonging to natural and synthetic simple isoquinolines.[3] However, a more exhaustive listing of the most important plant isoquinolines and their natural sources has been recently collected by Shulgin and Perry, comprising approximately 45 isoquinolines, over 20 dihydroisoquinoline derivatives and more than 150 tetrahydroisoquinolines, including among the latter around 70 1-benzyl tetrahydroisoquinolines and tetrahydroisoquinolinium salts.[4] Numerous other natural products containing the isoquinoline moiety or derived from isoquinolines are known.

Carnegine (**1**, 1,2-dimethyl-6,7-dimethoxy-1,2,3,4-tetrahydroisoquinoline, CAS 490-53-9) is a simple tetrahydroisoquinoline isolated from different plants around the world. Besides its simplicity, this natural product has one chiral carbon attached to nitrogen, an *N*-methyl moiety and a 6,7-dimethoxy substitution pattern on its aromatic ring as prominent structural features (Fig. 1), the establishment of all of which by synthetic means has been the subject of numerous research endeavors.



S-(-)-Carnegine, (-)-1



R-(+)-Carnegine, (+)-1

Figure 1. The enantiomers of carnegine.

Carnegine has been repeatedly employed during the last three decades as a model compound, serving as a superb test field where advantages of novel synthetic strategies, reactions and reagents were challenged and their disadvantages and limitations put in evidence; moreover, a phosphorus isostere of carnegine was proposed as test molecule during the study of the performance of a computer program designed for the analysis of synthetic routes towards organophosphorus compounds.[5]

According to Kametani,[6a] the synthetic approaches towards isoquinoline alkaloids and derivatives can be divided systematically into 15 different types, taking into account the mode of formation of the heterocyclic (1–8 and 15) and the homocyclic (9–14) rings.

Types 6–8 and 14 involve cycloaddition reactions, while type 15 entails a rearrangement. The 15 types are schematically represented in Figure 2. A previous and simplified classification presented earlier by Manske, useful for sorting carnegine syntheses, contained only the first five types.[6b,c]

Type 1 synthesis involves closure between the benzene ring and the carbon atom that forms *C*1 of the resulting isoquinoline ring. Pictet–Spengler and Bischler–Napieralski classical isoquinoline syntheses belong to this type. On the other hand, type 2 describes a synthesis in which the ring closure is made between the nitrogen atom and *C*1, while a type 3 synthesis entails *C–N* bond formation with *C*3. Analogously, types 4 and 5 are reserved for those syntheses in which the closing *C–C* bond is formed between *C*3 and *C*4, and *C*4 and the aromatic ring, respectively.

The most common syntheses of tetrahydroisoquinolines involve strategies of types 1, 2 and 5 and the literature does not record examples of the synthesis of carnegine employing types 3, 4 and 6–15. Noteworthy, however, this natural product was elaborated several times starting from an isoquinoline derivative, built according to one of the Kametani types described above.

Many of the most interesting isoquinolines are 1-substituted tetrahydroisoquinoline derivatives which, like carnegine, have been isolated or synthesized either as racemates or as pure enantiomers.

The absolute configuration of several 1-substituted tetrahydroisoquinolines, including that of carnegine, has been deduced by chemical correlations, thanks to the seminal work of Battersby and Edwards, which allowed unequivocal establishment of the absolute configuration of *S*-salsolidine (**8**).[7] As shown in Scheme 1, this was based on the oxidation of (−)-*N*-formyl salsolidine (**2**) with ozone to give the triformyl intermediate **3**, which was cleaved with hydrogen peroxide in formic acid to diacid **4** and hydrolyzed under acidic conditions to furnish *N*-carboxyethyl-L-alanine (**5**). This was compared with an identical material produced by Michael addition of L-alanine (**7**) onto acrylonitrile, followed by acid hydrolysis of the nitrile (**6**).

For correlation purposes, carnegine was accessed by Eschweiler Clarke *N*-methylation of natural *S*-salsolidine

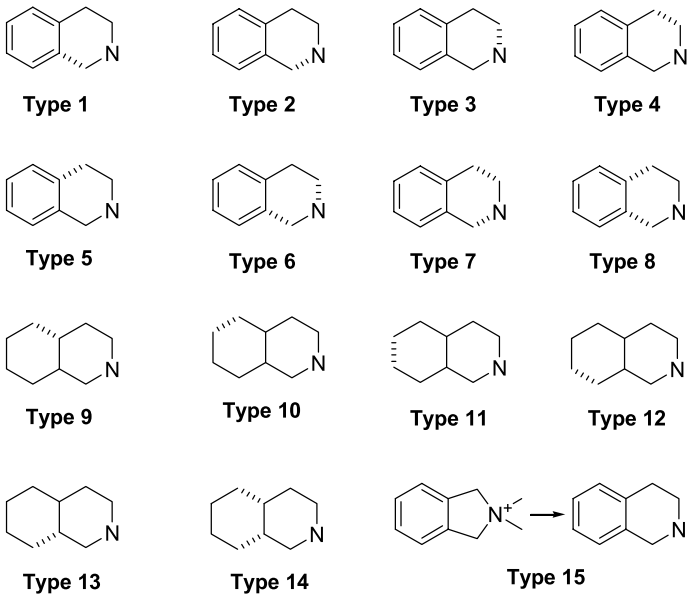
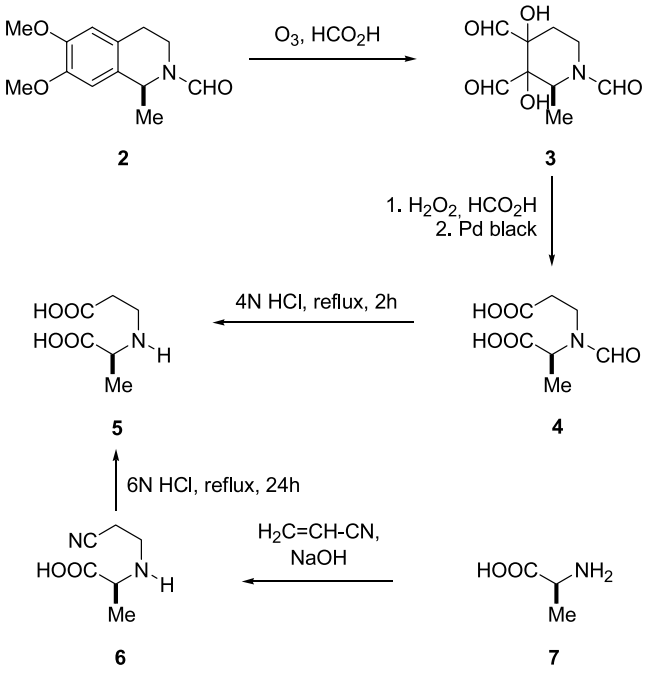


Figure 2. Synthetic strategies for the elaboration of the isoquinoline ring system, according to Kametani.

(**8**) with formaldehyde and formic acid,[8] in a procedure similar to that previously used by Orekhov.[9] Employing this correlation, Battersby and Edwards were able to demonstrate that natural carnegine possesses the 1-*S* configuration,[8b] observing that *S*-**1** is dextrorotatory in 1N HCl and levorotatory in benzene and EtOH. Correlating gigantine (**9**) to carnegine, Brown et al. established that the former also possesses the 1-*S* configuration.[10a] Similarly, Bobbitt deduced the absolute configuration of both enantiomers of **13b** by correlating them to carnegine[10b] and Brossi et al. correlated *N*-methyl salsolinol **13c** to the natural product.[10c] In both cases, smooth *O*-methylation with diazomethane brought about the required derivatized product.

As early as in 1987, Huber and Seebach[11] pointed out that



Scheme 1.

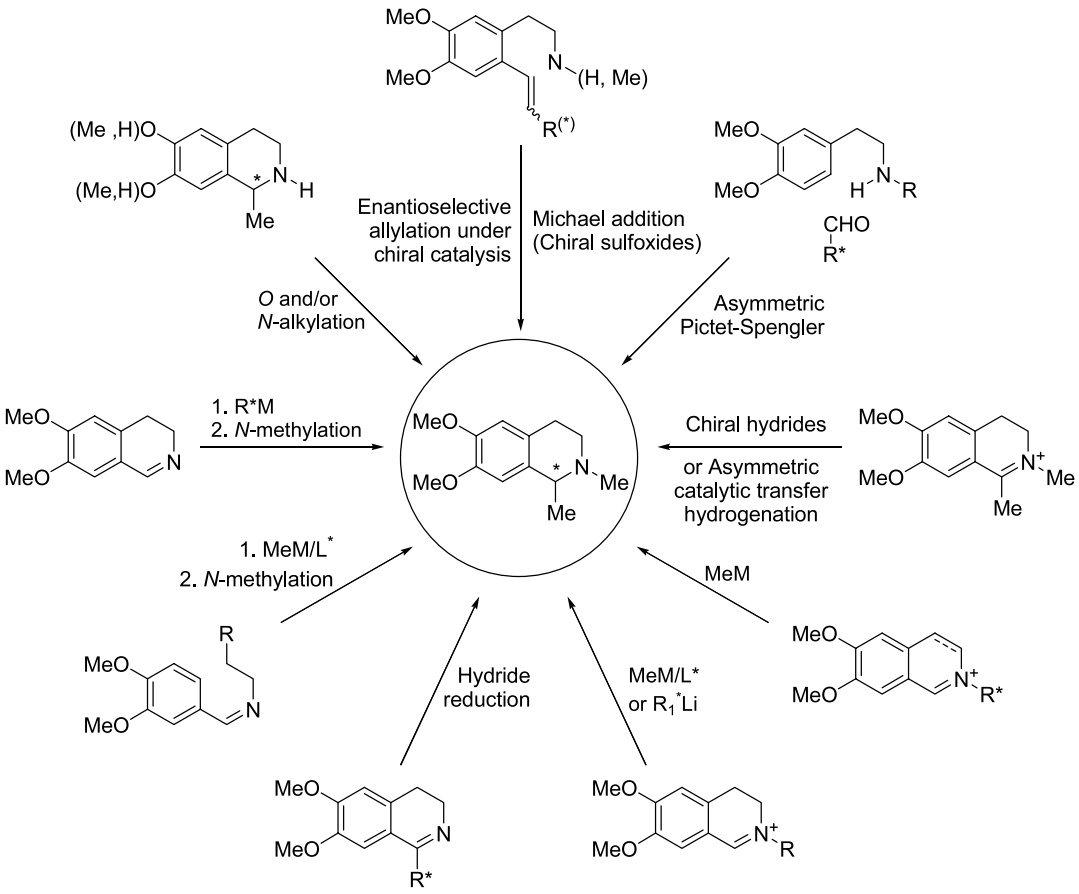
all possible methods of synthesizing enantiomerically pure compounds have been applied to the elaboration of chiral 1-substituted tetrahydroisoquinolines. These included resolution, catalytic and stoichiometric enantioselective reactions as well as the incorporation of components from the pool of chiral building blocks. Although this holds true for the elaboration of salsolidine (**8**),[7] a direct precursor of some syntheses of carnegine, many alternatives for the enantioselective elaboration of the latter still remain unexplored.

Carnegine has been prepared in chiral form by diastereoselective reduction of chiral iminium ions, enantioselective alkylation of imines with chiral organometallic reagents or with organometallics in the presence of chiral auxiliaries and by asymmetric modifications of the Pictet–Spengler condensation, as depicted in Scheme 2, among other routes. The body of current strategies for the enantioselective elaboration of 1-substituted tetrahydroisoquinolines have been recently compiled by Rozwadowska.[12]

The aim of this review is to highlight and discuss the most relevant strategies employed during the last 30 years for the total synthesis of carnegine and some of its precursors. Special emphasis was placed in those strategies leading to the natural product in optically active form, which started to appear in the literature less than 20 years ago. Brief details on the natural sources and probable biosynthesis of this alkaloid, as well as some details of its biological activity and interaction with biological systems, are also given.

2. Natural sources, isolation and structure elucidation

Carnegine was isolated from several Cactaceae, Chenopodiaceae and, more recently, from Boraginaceae. Among the first, sources of the natural product include *Carnegiea gigantea* (Engelm.) Br. & R., *Pachycereus pecten-aboriginum*, *P. pringlei*[13] and *Pachycereus weberi*. The first studies on carnegine were performed by Heyl in 1901,[14a] when the alkaloid, isolated from *P. pecten-aboriginum* was



Scheme 2.

termed pectenine; the same scientist isolated carnegine in 1928,[14b] while studying the alkaloids of *C. gigantea*, known as giant cactus or saguaro or the monarch of the Sonoran Desert.

This rare and endangered cactus which can reach 12 m high is native of the northern part of the Sonoran desert, where it is the predominant feature of its landscape; the fragrant, waxy white Saguaro Blossom was adopted as the floral emblem of the Arizona Territory of the United States, and officially confirmed as the state flower in 1931. Heyl prepared the hydrochloride, hydrobromide, chloroaurate and chloroplatinate salts of carnegine and also demonstrated that the natural product increases reflex excitability in frogs[14a] and is toxic to frogs and warm-blooded animals.

The structure of carnegine, the second most abundant alkaloid of *C. gigantea* after salsolidine, which accounts for approximately 50% of the total alkaloids, was shortly elucidated by Späth. This scientist first synthesized this natural product in 1929,[15a,b] by the Bischler Napieralski cyclization of *N*-acetyl homoveratrylamine with P_2O_5 in refluxing toluene, followed by MeI-mediated methylation and Sn/HCl reduction of the resulting methiodide. Späth also reported its presence in *P. pecten-aboriginum* and demonstrated its identity with pectenine through melting point determinations of the methiodide, hydrochloride, picrate and trinitro-*m*-cresolate derivatives[15c,d] and suggested to retain the name carnegine for the alkaloid as a consequence of the fact that pectenine was not as extensively studied as carnegine.

The alkaloid was also reported in *C. gigantea* by Bruhn and Lundström and by the McLaughlin group;[16] in the former case, carnegine was isolated as the inactive hydrochloride together with other three simple tetrahydroisoquinoline alkaloids shown in Figure 3: salsolidine (**8**), gigantine (**9**) and arizonine (**10**),[16a] while in the latter, the presence of 20 alkaloids including isosalsolidine (**11**), isonortehuanine (**12a**), isonorweberine (**12b**), isopachycereine (**12c**) and 13 new natural products were detected in *P. weberi* and additional confirmation of their structure was gained by mass-analyzed ion kinetic energy spectrometry (MIKES) analysis.[16d] These observations were confirmed by chromatography and, in many cases, by simple synthetic interconversions from known alkaloids. Particularly significant was the discovery of several alkaloids having the same molecular formula. Isomer distinctions such as these, which are difficult to make on pure compounds by mass spectrometry, were made by utilizing daughter spectra recorded successively during the evaporation of the material from the probe and/or from spectra recorded on different types of plant extracts.

Hodgkins et al.[17] also informed the isolation of carnegine in a reinvestigation of the alkaloids of *C. gigantea*, while Mata and McLaughlin isolated the natural product from the non-phenolic and phenolic extracts of the giant Mexican cereoid

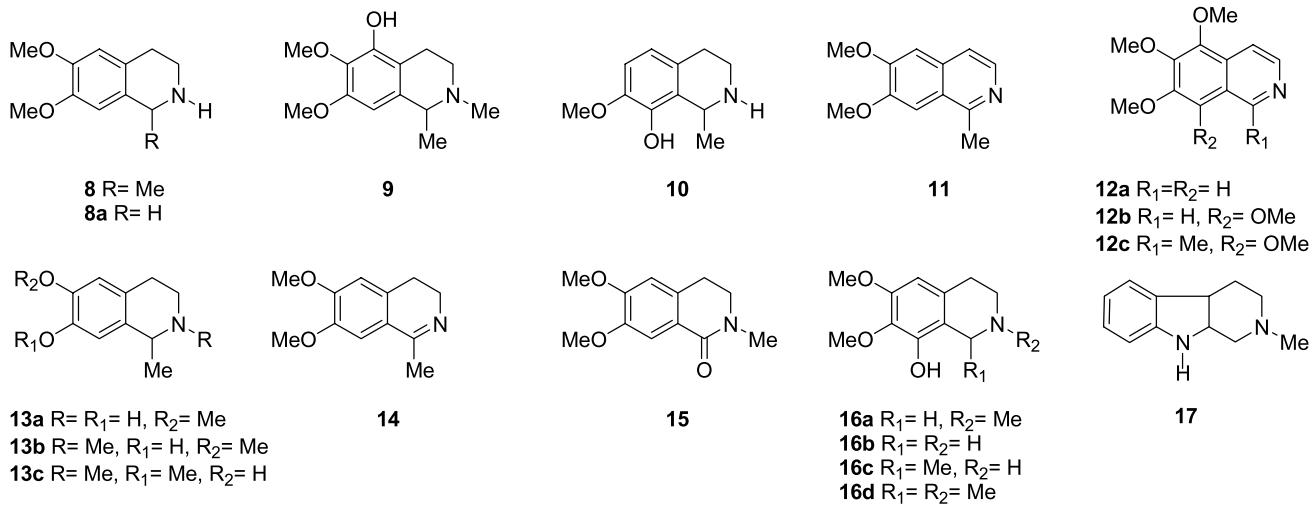


Figure 3.

cactus *P. weberi* (Coult.) Br. & R, together with seven other tetrahydroisoquinolines.[18]

Sources of carnegine among the Chenopodiaceae are *Hamada articulata* ssp. Scoparia,[19a] where it was found in its aerial parts together with isosalsoline (**13a**), **8**, dehydrosalsolidine (**14**), **11** and *N*-methylcorydaldine (**15**) and *Hamada scoparia* (pomel) Iljin,[19b] from where it was isolated together with isosalsoline (**13a**), *N*-methyl-isosalsoline (**13b**), *N*-methylcorydaldine (**15**), tryptamine, *N*-methyltryptamine, *N*-methyl-1,2,3,4-tetrahydro-β-carboline (**17**) and leptocladine. Other Chenopodeaceae sources are *Arthrocnemum glaucum*,[20] the aerial parts of which contain the natural product together with (−)-1-methyl-corypalline (**13b**, *N*-methylisosalsoline), *Haloxylon articulatum*[21] grown in Egypt, and *H. salicornicum*,[21] where it was found by El-Shazly et al. together with **8**, **13b** and tetrahydro-β-carboline **17**. In addition, the same group isolated (−)-carnegine from *Echium humile*, together with a series of pyrrolizidine alkaloids and also from *Arnebia decumbens*, being these the first records of the presence of carnegine among the Boraginaceae.[22] The recent discovery of carnegine in *Arnebia nobilis* further confirms that Boraginaceae are indeed a source of carnegine.[23]

By the use of GC-MS techniques, carnegine was also detected very recently in *Neobuxbaumia multiareolata*, *N. scoparia* and *N. tetetzo* (Cactaceae), together with anhalidine (**16a**) and salsolidine (**8**). The co-occurrence of these alkaloids in the three species of *Neobuxbaumia* studied has high chemotaxonomic value. It suggests that these species are closely related and since *Carnegiea* has all the alkaloids identified in the *Neobuxbaumia* species, plus others derived from the tetrahydroisoquinoline biosynthetic pathway, it can be speculated that *Carnegiea* is different from *Neobuxbaumia* and probably derived from it.[24]

Interestingly, in spite that some authors have isolated carnegine in optically active form from different Cactaceae, others found only racemic carnegine. Späth and Kesztler called the attention that many tetrahydro-isoquinolines isolated from cacti were obtained in racemic form and noted that some of them, particularly carnegine and those with free OH groups in certain positions readily racemized, especially in aqueous acidic solutions.[25]

In saguaro, gigantine (**9**) and carnegine are present in a 1:2 relationship, representing 1–2% of the dry weight of the cactus;[10] saguaro fruit has long been used by the Papago and Pima indians, who harvest the fruits and make syrup and a wine, used in their rain ceremonies. The group of Fogleman recently studied the successful utilization of necrotic cactus tissue by fly species (drosophilids) that are endemic to the Sonoran Desert. This plant–insect model represents an excellent context in which to investigate the chemical and molecular bases of interactions between insects and toxin-containing host plants. The scientists found that the cytochrome P450 monooxygenase system was implicated in plant utilization by *Drosophila nigrospiracula*, *D. mettleri*, and *D. Mojavensis* and that these insects adapt their metabolic pathways to better detoxify and tolerate the presence of cactus allelochemicals, which have been shown to be highly toxic to non-resident species. Total P450 levels, both basal and induced, were approximately 20 fold higher in adults than in larvae.[26] It was also evidenced that tolerance to carnegine can be induced and that there are very few—possibly only one—carnegine-metabolizing enzymes in *D. melanogaster*, a non-desert fly.

From the analytical chemistry point of view, the ^{13}C NMR spectrum of carnegine and other simple tetrahydroisoquinolines was analyzed and assigned[27] and the chiroptical properties of the natural product have been evaluated as part of the development of a semiempirical quadrant rule based on one-electron theory for the assignment of the absolute configuration of 1-methyl tetrahydroisoquinolines, independent of the substitution pattern of the benzene ring.[28] Physical data for the natural product have been compiled by Shamma et al.[3] and by others.[8,15d]In another publication, naturally occurring carnegine was proposed as a catalyst for the kinetic resolution of alkylphenyl carbinols with α-phenylethyl isocyanate.[29]

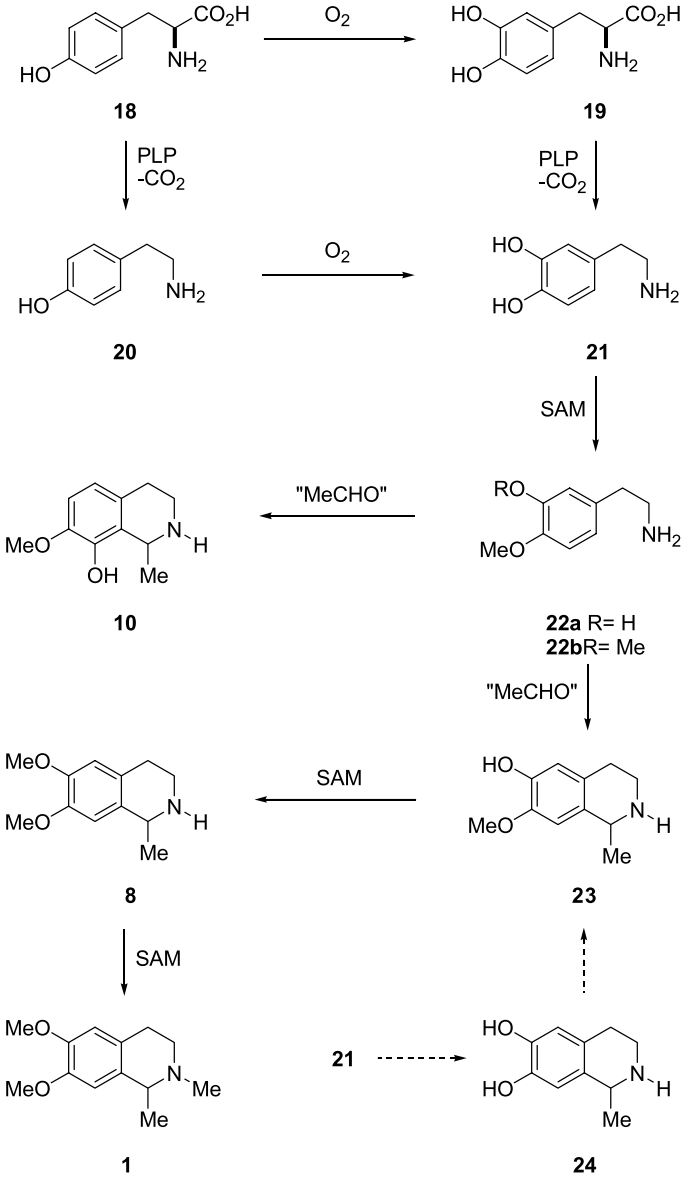
In addition, the fluorescence-inducing compound fluorescamine was introduced as visualization reagent for alkaloids in

TLC separations of carnegine and related substances,[30] while HPLC with UV detection was used to completely separate isomeric pairs of tetrahydro-isoquinolines and phenethylamines of Cactaceae, including carnegine.[31] Two interconnected stainless-steel columns (each 30 cm × 4.5 mm i.d.) were used, one packed with LiChrosorb Si 60 (10 μm) and the other with μPorasil (8 μm). Analyses were performed at a flow rate of 2 mL/min and a pressure of 1100 psi for one solvent system (acetonitrile–NH_3, 96:4) and flow rate of 1 mL/min at 900 psi for an alternative solvent mixture ($CHCl_3$–1% NH_3 in MeOH, 9:1). The isomeric pairs were separated by both solvent systems, and it was observed that the addition of alkali to the neutral solvent systems produced better separations with reduced tailing and faster elution.

In an analogous study, the gas–liquid chromatographic separation of 18 anhalonium alkaloids and related bases, including carnegine has been examined employing 1% methylsiloxane polymer containing about 5% phenyl substitution, as the liquid phase. It was observed that among the analytes *N*-monomethylation of primary and secondary amines, as well as *O*-methylation or *C*-monomethylation of the bases decrease the retention time, while introduction of hydroxyl, methoxyl, methylenedioxy group or an unsaturation, produced an increase in retentivity. These changes in retention time were attributed to the changes in polarity of amino and/or phenolic hydroxyl groups brought about by substitution in or adjacent to these groups.[32]

3. Biosynthesis of carnegine and its interaction with biological systems

Much of our current knowledge about the biosynthesis of cactus alkaloids is a result from thorough studies carried out on the Mexican peyote cactus *Lophophora williamsii*. The intense interest in the principal alkaloids of this plant anhalamine (**16b**), anhalonidine (**16c**) and pellotine (**16d**) is



Scheme 3.

a consequence of their pharmacological properties as hallucinogenic drugs.[33a] The biosynthetic path to carnegine was proposed by Agurell[16b] and also by Bruhn and Lundstrom.[16a] It follows the classical ideas set forth by Winterstein and Trier in 1910 for 1-benzyl-isoquinolines;[16f] however, some of its aspects are merely speculative or still remain unclear.

Being a simple tetrahydroisoquinoline alkaloid, carnegine is derived from tyrosine (**18**). Biosynthetic studies with ^{14}C-labeled amino acids and related compounds, including α-^{14}C-(±)-tyrosine (**18**), (±)-dopa (**19**), 3,4-dimethoxy-phenethylamine (**22b**), and methyl-^{14}C-labeled L-methionine, showed that in the cactus alternative routes operate from **18** via tyramine (**20**) or from **19** to dopamine (**21**),[33b,c] which is present in large amounts in the giant cactus.[34]

The labeled compounds were incorporated by *C. gigantea* plants into carnegine and the related alkaloid salsolidine (**8**), being the biosynthetic scheme similar to that of the peyote alkaloid pathway. Most probably, tetrahydroisoquinolines and phenolic phenethylamines are biosynthesized from 3-hydroxy-4-methoxy phenethylamine (**22a**), as shown in Scheme 3.

Precursor **22a** can be condensed with an acetaldehyde unit to furnish salsoline (**23**), a reaction that was demonstrated to occur in vivo, in *Echinocereus merkeri*,[35] as well as in vitro,[36] furnishing a 95:5 mixture of **23** and its isomer arizonine (**10**),[37] also found in cacti. Acetaldehyde is a chemical known to be present in *C. gigantea*;[38] however, the true cyclizing agent could be pyruvic acid, in which case a decarboxylation step would be necessary in order to get the 1-methyl tetrahydroisoquinolines.[39] Alternatively, acetaldehyde or its equivalent can condense with dopamine (**21**) to give salsolinol (**24**), which after *O*- and *N*-methylation would furnish **1**.

The presence of minor amounts of arizonine (**10**) in the *C. gigantea* extracts was regarded as an additional proof of the involvement of dopamine (**21**) or 3-hydroxy-4-methoxy-phenethylamine (**22a**) in the biosynthesis of carnegine and salsolidine.[40] Scheme 3 shows the proposed biosynthesis of some compounds found in *C. gigantea*, including carnegine.[41] *S*-adenosyl methionine (SAM) is involved in methylations, while pyridoxal phosphate (PLP) participates as a cofactor in decarboxylations.[33b]

On the other hand, Bahnmaier demonstrated the in vitro stereospecific *N*-methylation of salsolidine by amine-*N*-transferase A isolated from bovine liver. In this experiment, *S*-salsolidine was *N*-methylated by the enzyme, while the *R*-enantiomer remained essentially unchanged.[42] Interestingly, however, when (±)-salsolinol (**24**) was administered to Papaveraceae plants (*Corydalis pallida* var. Tenuis Yatabe and *C. incisa* Pers.) and their tissue-cultured cells the *O*- and *N*-mono and dimethylated derivatives were detected; the plants were incapable of producing carnegine, the *O*,*N*-trimethyl derivative of **24**.[43]

Interestingly enough, Stammel et al.[44] recently prepared highly specific and sensitive antibodies to salsolidine, which were able to distinguish a double bond between *C*1 and *N* and with less success, to recognize the absence of methyl groups on *C*1. However, in cross-reactivity tests, these antibodies were not capable of discriminating carnegine from salsolidine. The high cross-reactivity observed (99.1%) was explained as being a result of the strategy employed for the preparation of the immunogen consisting in coupling salsolidine to a carrier protein via the heteroatom of the natural product; besides carnegine, only heliamine (6,7-dimethoxy tetrahydroisoquinoline, **8a**) possessed appreciable cross reactivity (14.6%).

The pharmacological properties of carnegine have been investigated by the group of Furlanut. These Italian pharmacologists studied its acute toxicity as well as its effects on smooth muscle, isolated myocardial preparations and dog blood pressure and respiration.[45a] They observed that LD_{50} by intraperitoneal route in the mouse is approximately 15 mg/Kg, with its main toxic effects involving the central nervous system, as evidenced by strychnine-like tono-clonic convulsions. On isolated frog heart and guinea pig atria, the natural product produces a remarkable synusal bradycardia and on the latter model, the negative chronotropic effect is associated to a marked increase of the amplitude of the contractions; at lower concentration, however, carnegine can counteract the chronotropic effects of adrenaline and noradrenaline without affecting their inotropic properties.

In addition, in experiments with dogs, 0.5–2 mg/Kg carnegine demonstrated to possess hypotensive effect, with stimulation of the rate and amplitude of the respiration when 1–2 mg/Kg were given intravenously, while on smooth muscle preparations, the alkaloid elicited slight spasmolytic and vasodilator activities. It has also been demonstrated that, unlike other isoquinoline derivatives, carnegine has no effect on brain phosphodiesterase activity.[45b]

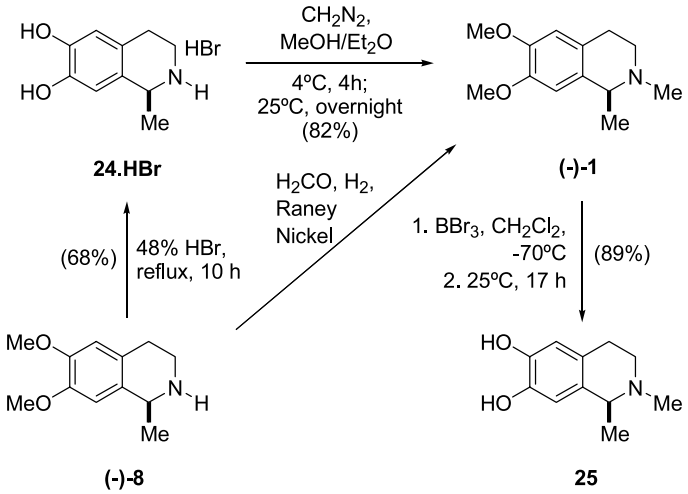
Finally, the effect of carnegine and other alkaloids on cellular metabolism employing the mouse ascites tumor cells model was examined by Schmitz. The natural product exhibited a threshold respiration inhibiting concentration of 80 μg/mL.[46] with the potency of carnegine being of the same order of magnitude as that of Cinchona alkaloids, physostigmine and strychnine.

4. Chemical synthesis of carnegine

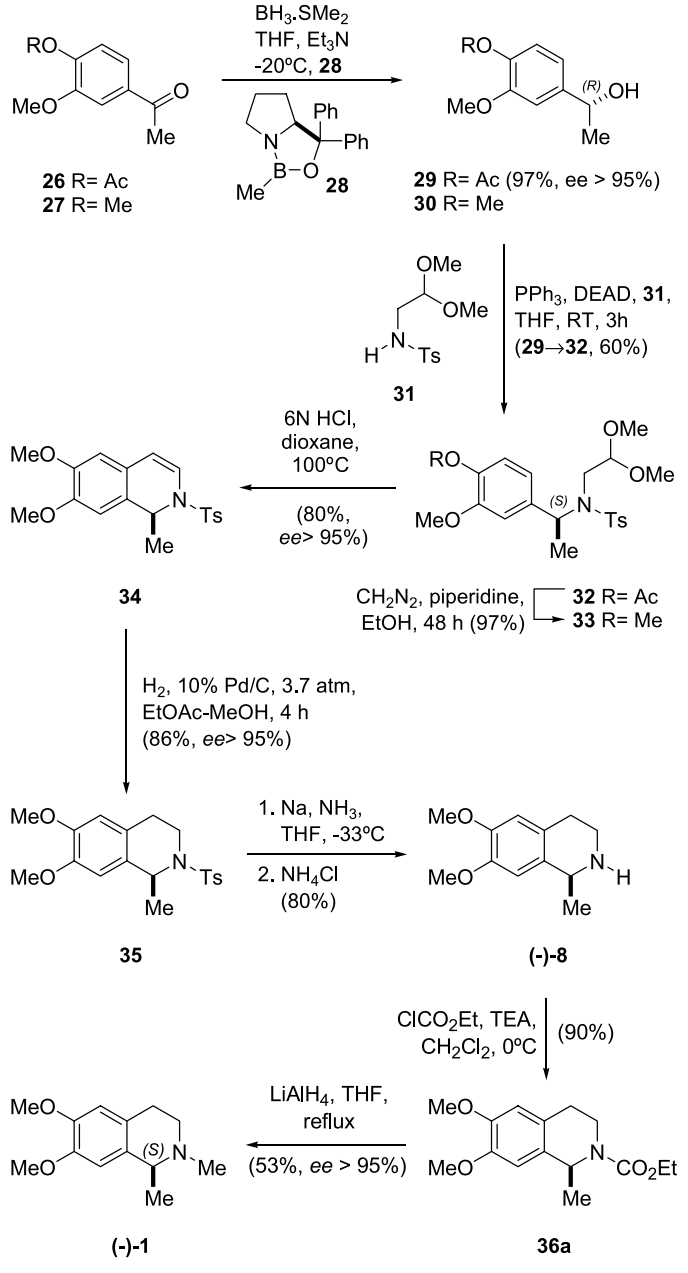
4.1. Alkylation reactions

4.1.1. *O*- and *N*-Alkylation of simple tetrahydroisoquinolines. This strategy constitutes the easiest access to the natural product, as it entails simple heteroatom alkylation procedures. Carnegine was elaborated by *N*-methylation of salsolidine (**8**),[7] *N*-methylation of dehydrosalsolidine with reduction of the resultant dihydroisoquinolinium derivative, as well as by *O*- and *N*-methylation of salsolinol (**24**). Synthesis of carnegine in optically active form following this alternative was carried out employing optically active tetrahydroisoquinoline precursors.

A simple synthesis of racemic carnegine was reported by



Scheme 4.



Scheme 5.

Japanese scientists, employing dehydrosalsolidine (**12**) as intermediate. This 1,2-dihydroisoquinoline was prepared by Bischler–Napieralski cyclization of *N*-acetyl homoveratrylamine or by cyclization of veratrylacetoxime, following the method of Sugasawa and Yoshikawa. For the elaboration of **1**, the methyl methosulfate derivative of **12** was prepared and catalytically reduced.[47] The reductive *N*-methylation of salsolidine to carnegine with the HCHO–HCO_2H system served to Orekhov et al. for correlation purposes.

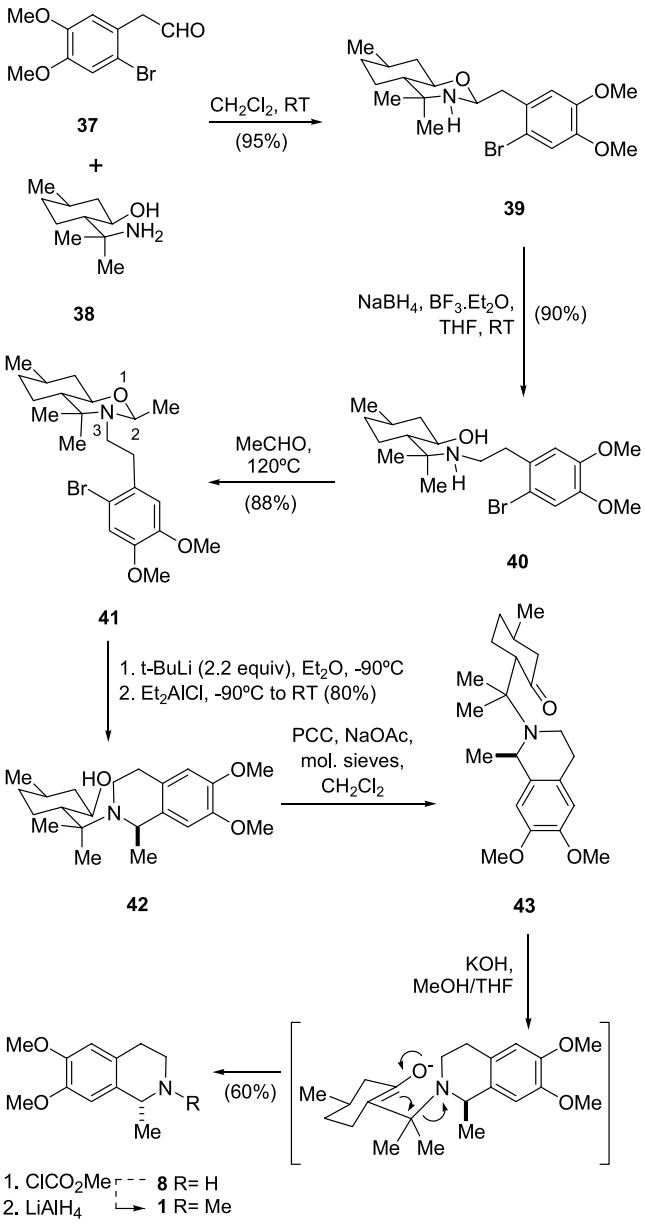
These authors characterized carnegine as its hydrochloride and picrate salts.[3b] The group of Brossi, while studying the concept of 'alkaloid formation in man', provided simple ways to access carnegine. In one example, the natural product was obtained from *S*-salsolinol hydrobromide (**24**·**HBr**), by *O*-and *N*-methylation of the latter in MeOH with excess ethereal diazomethane, as depicted in Scheme 4.[48] The research was part of their effort to ascertain that the configuration and optical purity of salsolinol, when prepared by demethylation of salsolidine, remains unchanged. These authors also prepared *S*-*N*-methylsalsolinol (**25**) in 89% yield, by selective *O*-demethylation of the thus obtained *S*-carnegine with boron tribromide.

The same procedure, when applied to *R*-carnegine hydrobromide, furnished the *R*-enantiomer of *N*-methylsalsolinol. In an alternative strategy, this group also prepared both enantiomers of **1** from the corresponding enantiomers of **8** by reductive *N*-methylation with formaldehyde and hydrogen under Raney nickel catalysis.[48] These compounds were tested as inhibitors of the monoaminooxidases (MAO) A and B, demonstrating stereoselective inhibition of the enzymes. The *R*-enantiomer was strikingly more potent than its enantiomer against MAO A (K_i=2 μM vs K_i=102 μM for *S*-**1**) and *R*-carnegine did not inhibit MAO B, while its enantiomer displayed only weak inhibition with K_i=1600 μM.[49]

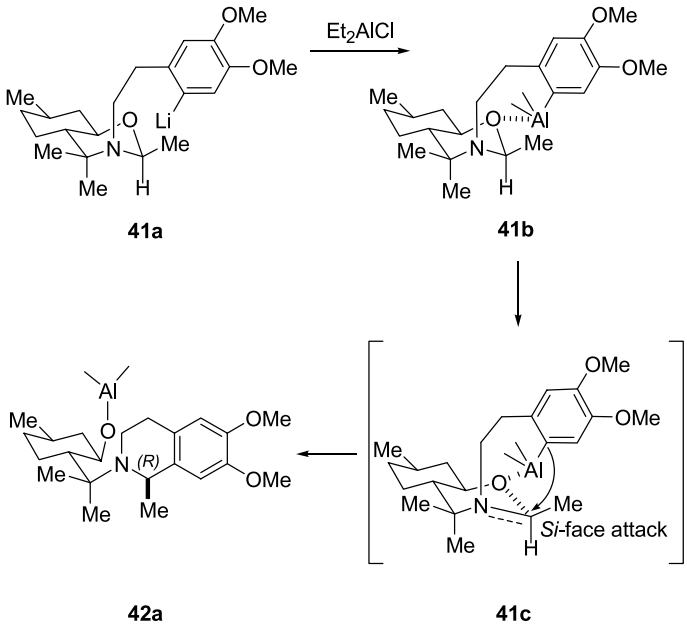
Ponzo and Kaufman[50] (Scheme 5) prepared *S*-carnegine from *S*-salsolidine in 48% overall yield by lithium aluminum hydride reduction of salsolidine-*N*-ethylcarbamate (**36a**). For the elaboration of salsolidine, these researchers coupled chiral alcohol **29** to sulfonamidoacetal **31** through a Mitsunobu sulfonamidation process, which proceeded with complete configurational inversion of the benzylic center. Acetate **26** derived from acetovanillone was used as starting material instead of acetophenone **27** a more straightforward precursor, because the Mitsunobu sulfonamidation of the more electron rich alcohol **30** yielded partially racemized sulfonamide **33**. The enantioselective elaboration of **29** and **30** was accomplished through CBS reductions with chiral oxazaborolidine **28**, a modern and highly improved version of the pioneering Itsuno's catalyst, developed by Corey's group.[51]

An extra step for the transformation of **32** into **33** consisting in an acetate to methyl ether transformation, was introduced.[52] Sulfonamidoacetal **33** was cyclized following Jackson's protocol, in a refluxing dioxane-6N HCl mixture and the resulting 1,2-dihydroisoquinoline **34** was submitted to catalytic hydrogenation providing *S*-**35**; subsequent removal of the sulfonyl moiety by means of a reductive desulfonylation with sodium in liquid ammonia furnished (−)-**8** in >95% ee, as determined by ^{1}H NMR spectrometry with chiral shift reagents. Reaction of salsolidine with ethyl chloroformate gave 90% the corresponding carbamate **36a**, which was finally reduced to (−)-**1** in 53% overall yield with lithium aluminum hydride in refluxing THF.

A total synthesis of salsolidine, leading to the *R*-enantiomer as shown in Scheme 6, was recently reported by a Spanish team, which also elaborated other 1-substituted tetrahydroisoquinolines.[53a] Their strategy consisted in the intramolecular attack of an appropriately substituted arylaluminum species to a chiral 1,3-perhydrobenzoxazine derived from (−)-8-aminomenthol (**38**) for the elaboration of the isoquinoline system. Subsequent *N*-methylation of the nitrogen after oxidative removal of the chiral auxiliary, completed the synthesis, serving compound **38** as chiral inductor and source of the nitrogen atom.



Scheme 6.



Scheme 7.

In this synthetic strategy, the aryl group was attached to the nitrogen of the *N*,*O*-acetal moiety of the 1,3-perhydrobenzoxazine through an ethylene tether. The elaboration of this synthetic intermediate was straightforward, by condensation of polysubstituted phenylacetaldehyde **37** with the chiral auxiliary, followed by reduction of the intermediate *N*,*O*-acetal **39** to amine **40**, which was transformed into 1,3-perhydrobenzoxazine **41** upon heating with acetaldehyde at 120 °C in a sealed tube.

Low temperature lithium–halogen exchange and transmetallation with diethylaluminum chloride provided an arylmetal (Scheme 7) which performed an intramolecular nucleophilic attack on *C*-2 of the *N*,*O*-heterocycle, forming the heterocyclic ring of the tetrahydroisoquinoline **42**.

A two-step efficient removal of the chiral auxiliary, leading to (+)-**8** culminated the synthesis; this was performed by PCC-mediated oxidation of chiral alcohol **42** to the corresponding ketone **43** followed by a retro-Michael process. These authors effected a final *N*-methylation of some of the synthesized chiral 1-substituted tetrahydroisoquinolines by reaction with methyl chloroformate, followed by lithium aluminum hydride reduction of the resulting carbamates.

In this sequence, the stereochemistry of the final product was determined beforehand by the stereochemical outcome of the reaction leading to the key perhydrobenzoxazine **41**, in which the methyl substituent is equatorially oriented.[53a]

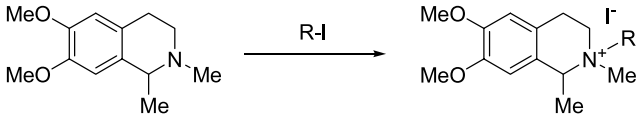
The key role of diethylaluminum chloride in the process leading to **42** was explained as shown in Scheme 7. The lithiated intermediate **41a** formed by lithium–halogen exchange of **41** with *tert*-butyl lithium is converted into the organoaluminum intermediate **41b** by transmetallation with Et_2AlCl; next, intramolecular transfer of the aryl group to the *si*-face of the incipient iminium ion from the aluminum atom, furnishes the aluminum species **42a**, which leads to **42** upon aqueous workup.

The stereochemical outcome of the intramolecular ring opening of the 1,3-perhydrobenzoxazine is similar to previous findings in related systems,[53b] while the stereodiscrimination is better for organoaluminum derivatives than for related organometallic species because of their comparative greater nucleophilic character.[54] The high selectivity observed is probably a consequence of the fact that transfer of the aryl group to the intermediate iminium moiety proceeds by synchronous intramolecular arylation in the early transition state **41c**, while the aluminum is still complexed to the oxygen atom of the chiral auxiliary. Employing the less nucleophilic and less reactive organomagnesium species, formation of minor amounts of the diastereomeric species resulting from attack to the *re*-face was observed.

It is worth mentioning that Battersby and Edwards also prepared carnegine methiodide, by *N*-methylation of the natural product with methyl iodide. A few years later, a Hungarian group studied the quaternarization of 1,2-disubstituted tetrahydroisoquinolines, finding that the transformation proceeds with moderate degrees of stereoselectivity, as shown in Table 1.[55a] Furthermore, the selectivity of the alkylation increased with the increase in the bulk of the new substituent; from NMR data it was concluded that all the major diastereomers of the mixtures (**44a**) have the same configuration and in these isomers, as expected the bulkier substituent on nitrogen and the *C*1-methyl group are *trans*-oriented.

In a related investigation, another group examined the quaternarization of *N*-methyl-6,7-dialkoxytetrahydroisoquinolines and the demethylation of the resulting quaternary salts, concluding that during both processes, methylation of the tetrahydroisoquinolines and demethylation of the

Table 1. Diastereoselective quaternarization of carnegine with different alkyl iodides



Entry No.	R	**44a** (%)	**44b** (%)	^{1}H NMR (δ-*N*–Me, **44a**)	^{1}H NMR (δ-*N*–Me, **44b**)
1	Me	100		3.53	
2	Et	70	30	3.38	3.28
3	*i*-Pr	75	25	3.42	3.33
4	*i*-Bu	75	25	3.42	3.33
5	Bn	100	0	3.29	3.12

tetrahydroisoquinolinium derivatives, the *C*1 substituent and the entering or leaving group are located preferentially *trans* in the respective transition states.[55b]

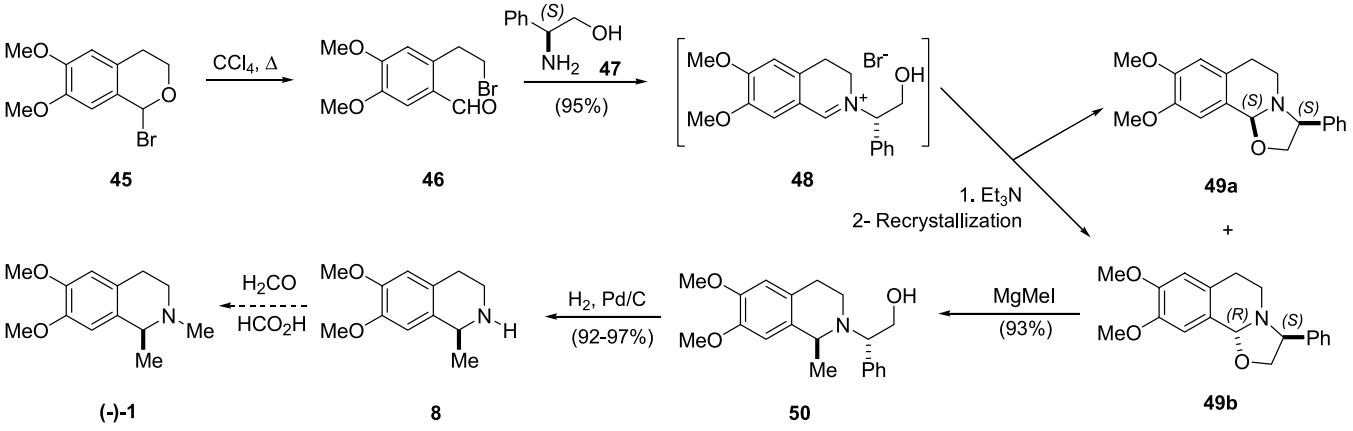
In a separate communication, it was also disclosed that experiments with the enantiomers of the *N*,*N*-dimethyl derivative (entry 1) demonstrated that it possesses ability to competitively inhibit acetylcholinesterase, being the potency of the *S*-enantiomer twice that of the *R*-enantiomer.[56a] These results reflect the stereochemical preferences of the neuromuscular junction towards nondepolarizing blocking agents. Other isoquinolines and isoquinolinium derivatives are known to behave similarly and the relationship between structure and curariform activity has been reviewed.[56b]

4.1.2. Alkylation of isoquinolinium derivatives. Addition of Grignard or organolithium reagents to isoquinolines or 3,4-dihydroisoquinolines is sluggish and sometimes there is no reaction unless external activation or strenuous conditions are employed; however, the transformation proceeds readily with synthetically useful yields if the heterocycles are activated as isoquinolinium or 3,4-dihydroisoquinolinium species, respectively. This key observation has been employed for the development of several syntheses of 1-substituted tetrahydro-isoquinolines, including salsolidine.[7] *N*-methylation of the latter by reductive alkylation or reduction of salsolidine carbamates constitute a direct access to carnegine. The use of chiral organometallic reagents, optically active ligands or chiral auxiliaries bound to the nitrogen offer the possibility of accessing the natural product in its optically active forms.

A Japanese team headed by Yamato[57] prepared optically active salsolidine and related 1-substituted tetrahydroisoquinolines as well as some *N*-methyl tetrahydroisoquinolines by *N*-methylation of chiral 1-substituted heterocycles. The tetrahydroisoquinolines were elaborated by diastereoselective methylation of a dihydroisoquinolinium-derived oxazolotetrahydroisoquinoline. This can be considered as an *N*,*O*-acetal, and was found to undergo facile nucleophilic substitution by organolithium and Grignard reagents.

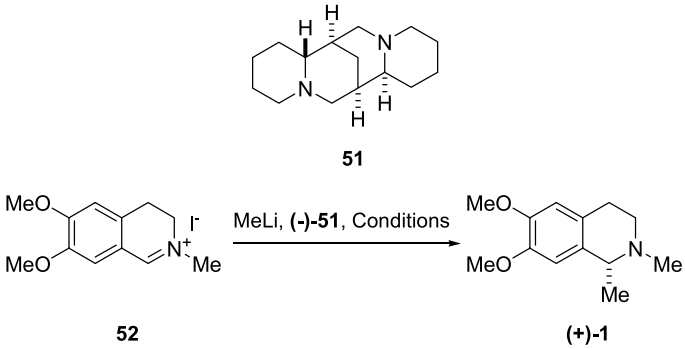
This group synthesized diastereomeric chiral oxazolo[2,3-a]-tetrahydroisoquinolines **49a** and **49b** (*de*=90%) in a highly selectively manner. This was done by base-assisted intramolecular cyclization of the 3,4-dihydroisoquinolinium salt **48** derived from *S*-phenylglycinol (*S*-**47**) and 1-bromoisochromane **45**, through the condensation of the chiral auxiliary with **46**, the open form of the isochromane.

Upon purification of the major diastereomer (**49a**) from the 19:1 mixture of tricyclic intermediates by crystallization, and subsequent ring opening of the oxazolidine ring by asymmetric methylation with MeMgI, compound **50** was



Scheme 8.

Table 2. Enantioselective addition of MeLi to methiodide **52** in the presence of 1 equiv of (−)-sparteine



Entry No.	Solvent	Temperature (°C)	Time (h)	Yield (%)
1	Et_2O	−76 to 10	24	67
2	Et_2O	−76	2.5	59
3	PhMe	−76 to 10	24	76
4	PhMe	−76	24	76

obtained in 93% yield (Scheme 8). Removal of the *N*-benzyl moiety was appropriately and efficiently carried out with Pd/C in acidic EtOH, furnishing (−)-**8**.

Both enantiomers of the chiral alcohol **47** were submitted to the same sequence of transformations, leading to both enantiomers of salsolidine. In this process, *S*-**47** afforded the 1*S* enantiomer of salsolidine (**8**), a precursor of carnegine. The same sequence was employed for the elaboration of other tetrahydroisoquinolines, which were reductively methylated with the formaldehyde-formic acid reagent (Eschweiler Clarke) to give the corresponding *N*-methyl derivatives.

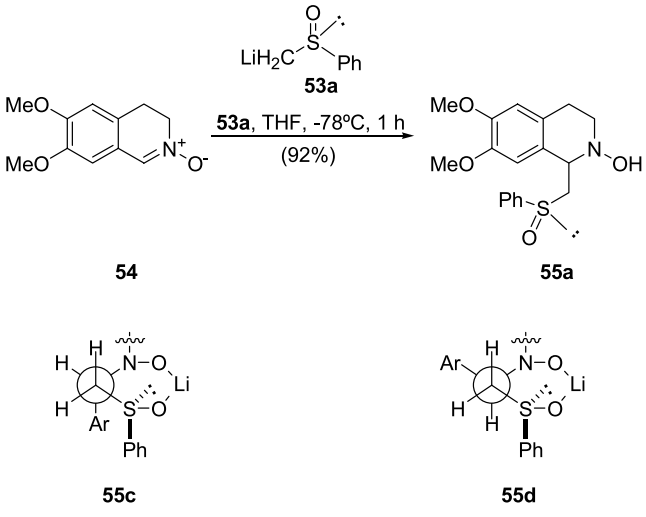
In more recent work, Chrzanowska and Sokolowska[58] provided an example of an interesting concept, the enantioselective alkylation of a dihydroisoquinolinium derivative in the presence of natural lupine alkaloid (−)-sparteine (**51**) as external ligand. In this case, no covalent bonds mediate between the ligand and the isoquinoline ring, thus shortening the synthetic sequence by avoiding the need of chemically removing the chiral inductor.

This inexpensive diamine is a natural product, which forms amine–organolithium complexes and acts as a bidentate ligand; it has also found use in asymmetric deprotonation and enantioselective addition of organolithium and Grignard reagents to carbonyl compounds.[59] The enantioselective addition of organometallic reagents to prochiral imines in the presence of a chiral ligands/catalysts has been recently reviewed.[60]

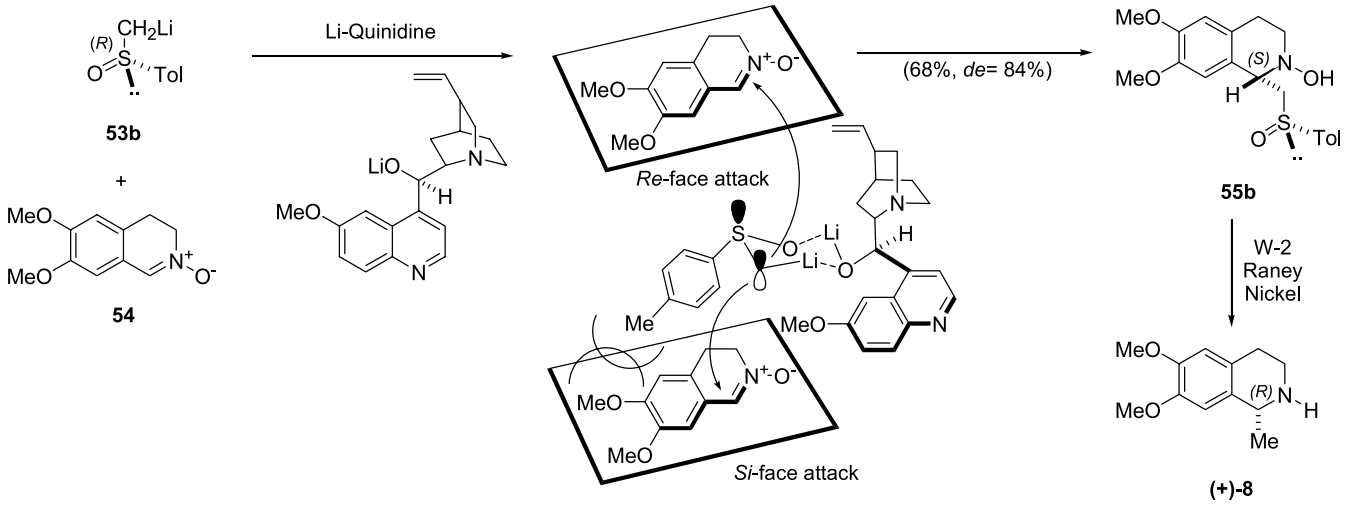
However, in spite that chemical yields of carnegine were reasonable (Table 2), optical yields were disappointingly low, being recorded values of 7%, at best and addition of the bulkier phenyllithium to **52** efficiently furnished the corresponding 1-phenyltetrahydroisoquinoline derivative, albeit in even lower ee. Interestingly enough, in mass spectrometry loss of the C-1 methyl with the formation of iminium derivatives such as **52** occurs readily and chemical ionization techniques have to be used in order to generate the molecular ion and deduce an accurate molecular weight. The recorded results indicated that in this system, enantioselection by organolithium addition to isoquinolinium salts is the opposite to that observed for the analogous reaction, carried out on the less reactive 3,4-dihydroisoquinolines; in addition, its performance is lower.

The electroreductive alkylation of dihydroisoquinolinium species such as **52** in DMF at −1.8 V vs the standard calomel electrode employing a lead cathode was demonstrated to furnish 1-substituted *N*-methyl tetrahydroisoquinolines; among them, racemic carnegine was produced in 35% yield by electroreductive methylation with methyl iodide.[61]

The ability of sulfur to stabilize negative charges on adjacent carbon atoms has been especially important in the development of new methods to form carbon–carbon bonds. The addition of methyl phenyl sulfoxide anion to nitrones, has been studied by Pyne and Hajipour.[62] This group added racemic organolithium derivative **53** to nitrone **54**,



Scheme 9.



Scheme 10.

observing the formation of a 86:14 mixture of diastereomeric hydroxylamines **55** in 92% yield, as shown in Scheme 9.

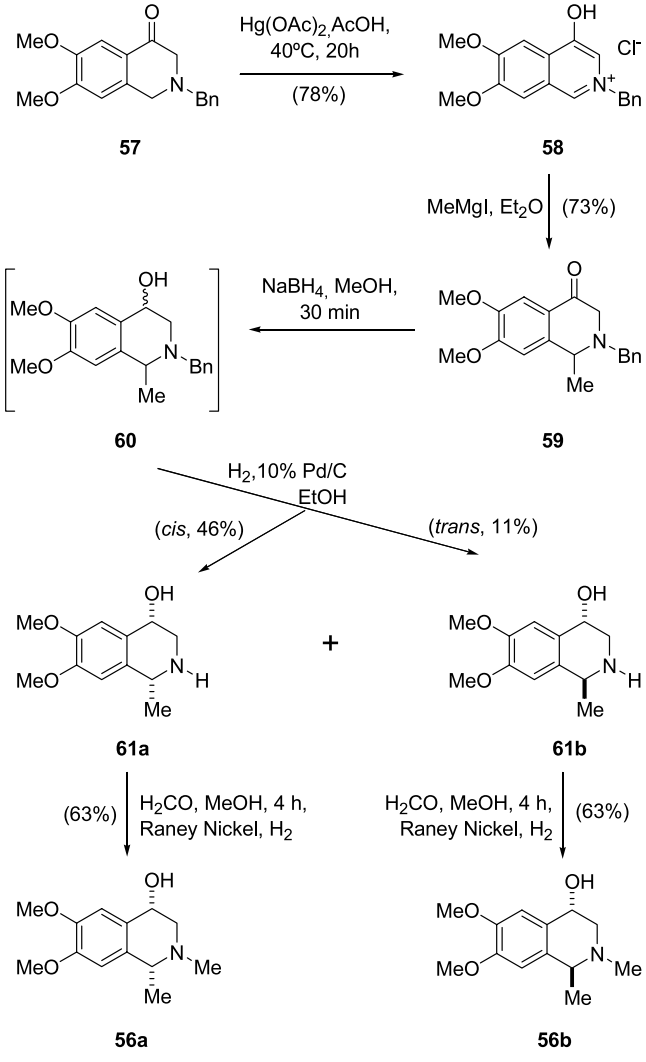
The election of the substrate is advantageous since nitrones offer enhanced reactivity over imines towards 1,2-addition of organometallic reagents.[63] By analogy with similar additions, a chelated chair-like transition state (**55c** vs **55d**) was proposed as the origin of the diastereoselection The diastereoselection observed with cyclic nitrone **54** was better than that observed in the cases of acyclic congeners, displaying less steric demand of the group bound to the nitrogen of the nitrone.

In a related synthesis, Murahashi et al.[64a] reacted nitrone **54** with *R*-(+)-methyl p-tolyl sulfoxide (**53b**) anion in the presence of lithium quinidine, accessing β-sulfinyl hydroxylamine **55b** in 68% yield and 84% *de*. Comparing with the results of Pyne, it is evident that the addition of quinidine was essential for attaining good diastereomeric excess of product. The reaction mechanism and the rationalization of the reaction course are shown in Scheme 10. Although the protocol was exploited for the elaboration of (+)-salsolidine (**8**), this transformation could in principle, be employed for accessing a variety of *N*-substituted tetrahydroisoquinoline derivatives,[63d] since several procedures for reduction of the hydroxylamine moiety are available.[64]

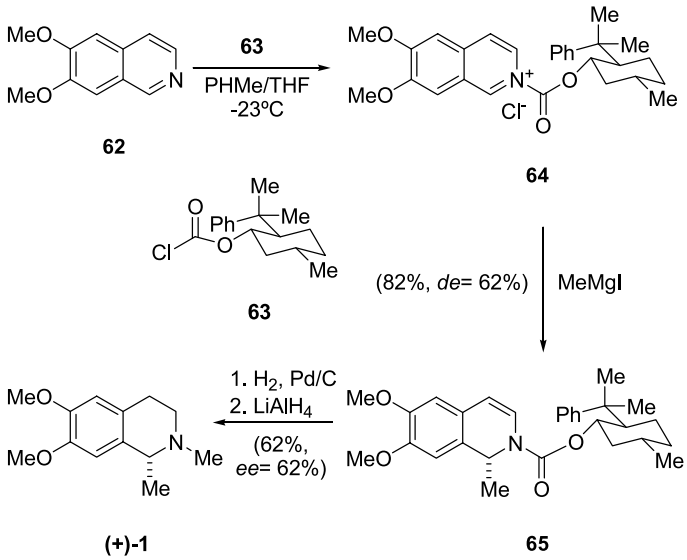
An interesting synthesis of the diastereomers of 4-hydroxycarnegine in racemic form was presented by Brossi et al. during their attempts to solve the problem of the identity of gigantine (**9**), proposed as **56**.[65]

To that end, isoquinolin-4-one **57** was oxidized with mercury(II) acetate to the isoquinolinium salt **58**, which was submitted to Grignard addition employing MeMgI. This furnished the corresponding isoquinolin-4-one **59**, which was reduced to a mixture of alcohols **60** with sodium borohydride and then subjected to Pd/C debenzylation, giving access to the separable diastereomeric tetrahydroisoquinolin-4-ols **61a** and **61b**.

Finally these were individually *N*-methylated with formaldehyde and hydrogen under Raney nickel catalysis, furnishing **56a** and **56b**, respectively, which proved to be different from the natural product (Scheme 11).



Scheme 11.



Scheme 12.

Another example of alkylation of an isoquinolinium derivative en route to carnegine was provided by Comins and Badawi.[66] These authors observed that, analogously to the pyridine series, isoquinolines react with chloroformates to form *N*-acyl isoquinolinium salts. In turn, these activated intermediates can be attacked by nucleophiles such as Grignard reagents to give 1,2-dihydroisoquinoline derivatives. Subsequent reduction of the double bond and the carbamate group generate 1,2-substituted tetrahydroisoquinolines in which the nitrogen atom supports a methyl group. In order to impart diastereofacial differentiation during the nucleophilic addition step, a homochiral chloroformate is required in this protocol. Thus, reaction of 6,7-dimethoxyisoquinoline **62**, easily accessible employing Jackson's isoquinoline synthesis[67a–c] and related procedures,[67d] with (−)-8-phenylmenthyl chloroformate **63**[68] in THF/toluene at −23 °C readily produced the corresponding *N*-acyl intermediate **64** (Scheme 12). Without isolation, this intermediate was reacted with methylmagnesium iodide to give 82% of a 78:22 mixture of diastereomers, in which **65** was predominant.

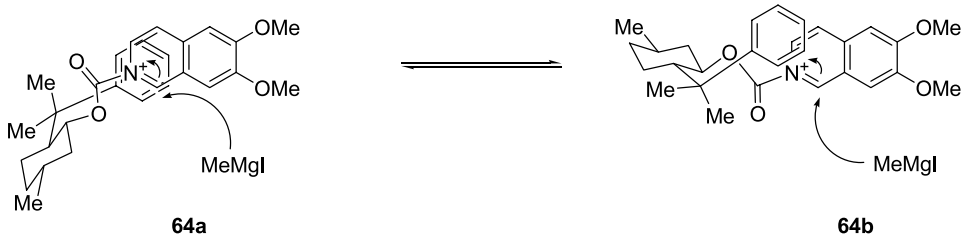
Temperature effects on the diastereomeric excess of product were observed, since a 83:17 mixture was obtained when the reaction was carried out at −78 °C; in this case, however, the yield dropped to 26%. Experiments with model isoquinolines demonstrated that under given solvent and temperature conditions, MeMgI was superior to MeMgCl, $MeTi(OiPr)_3$ and methylmagnesium 2,6-dimethylphenoxide, a bulky modified Grignard reagent, in terms of product yield and diastereomeric ratio.

When submitted to catalytic hydrogenation, a 81:19 mixture of **65** and its diastereomer afforded the corresponding tetrahydroisoquinolines in 95% yield. In turn, these were reduced with $LiAlH_4$ in refluxing THF, affording *R*-carnegine with an optical purity of 62%. Concomitantly, 71% of the valuable chiral alcohol (−)-8-phenylmenthol was also recovered.

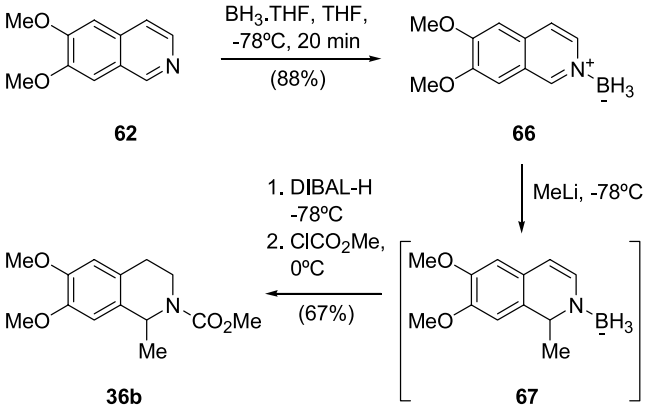
Since the energy difference between the two low energy reactive conformations **64a** and **64b** is very small, the observed diastereoselectivity of the reaction was explained as being a result of the π–π interaction between the phenyl ring of the chiral auxiliary and the electron deficient azomethine *C*=*N* bond, as shown in **64a**, which would stabilize the transition state (Scheme 13).[69]

Being 8-phenylmenthol readily accessible only as the (−)-enantiomer,[70] this process is highly suitable only for the synthesis of *R*-carnegine.

Finally, Minter[71] disclosed the elaboration of *N*-carboxymethyl salsolidine (**36a**),[50b] from isoquinoline **62** (backebergine) employing a very similar strategy, in which the nitrogen heterocycle was activated by formation of the zwitterionic complex with borane (**66**). The method is a one-pot procedure in which substituents are added sequentially as nucleophiles and electrophiles, accompanying the reduction of the heterocyclic ring. Alkylation of such complex with methyllithyium, followed by reduction with DIBAL-H of the 1,2-dihydroisoquinolineborane intermediate **67** and in situ acylation of the product with methyl



Scheme 13.

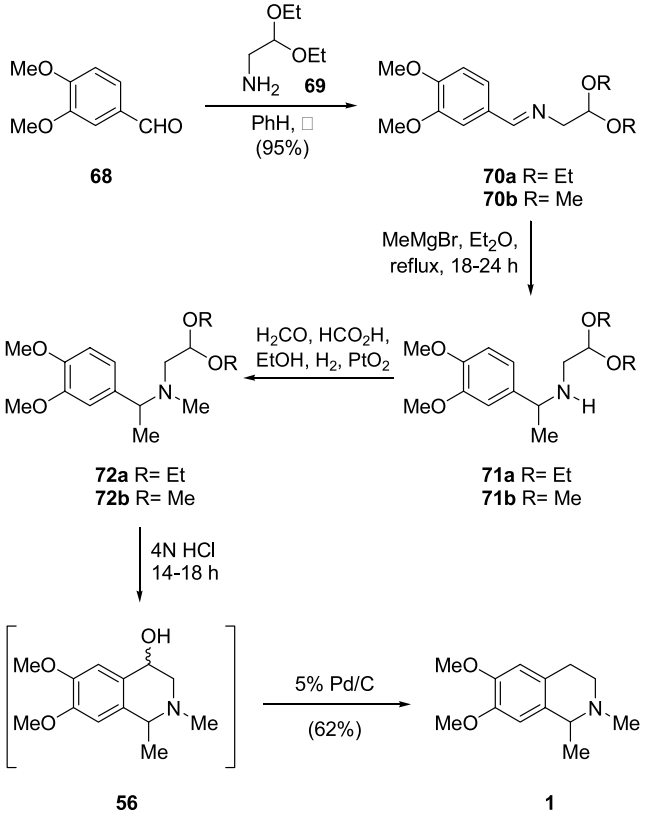


Scheme 14.

chloroformate gave the final product, as shown in Scheme 14. Tetrahydroisoquinoline **36b** is a precursor of carnegine (Scheme 5).

4.1.3. Alkylation of imines with organometallic reagents. Imines react with Grignard and organolithium reagents leading to the formation of new carbon–carbon bonds. Although the transformation is analogous to that involving organometallic addition to carbonyl compounds leading to alcohols, it has found less use than the latter because of the comparatively poorer reactivity of the nitrogen derivatives.

Nevertheless, the addition of organomagnesium and organolithium reagents to azomethines has been successfully employed as an entry to carnegine; both, 3,4-dihydroisoquinolines and Schiff base-type isoquinoline precursors served as suitable substrates. Enantioenriched carnegine emerged from protocols employing chiral auxiliaries or an optically active organometallic reagent.



Scheme 15.

In their modification of the classical Pomeranz–Fritsch isoquinoline synthesis leading to tetrahydroisoquinolines, the group of Bobbitt disclosed a synthesis of carnegine in racemic form, which resulted more practical and less laborious when compared with previous syntheses of carnegine.[72]

To that end, veratraldehyde **68** was condensed with aminoacetaldehyde diethylacetal (**69**) in 95% yield and the resulting Schiff base **70a**[73] was alkylated with methyl Grignard reagent, furnishing amine **71a**, as depicted in Scheme 15; in order to complete the transformation,[74a] the reaction mixture had to be heated to reflux in ether for 18–24 h, since Grignard reagents add sluggishly to Schiff bases like **70a**.[74b]

In turn, this was reacted with formaldehyde and acetic acid in ethanol, and the resulting intermediate was hydrogenated under platinum catalysis to furnish the *N*-methyl acetal **72a**. Final cyclization of **72a** in 4N HCl followed by catalytic hydrogenation with 5% Pd/C as catalyst provided carnegine in 62% yield, probably through the intermediacy of tetrahydroisoquinolin-4-ols **56**, like those elaborated by Brossi et al. (see Scheme 11).[73,74a]

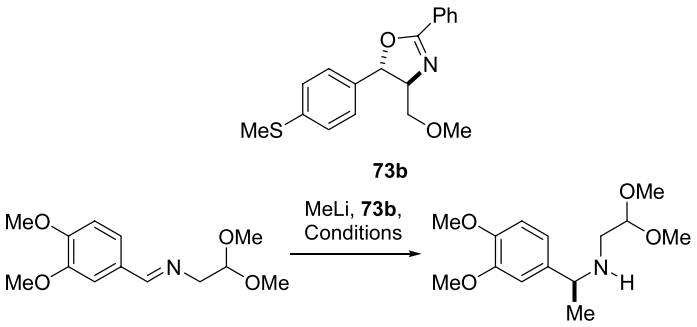
The oxidation of carnegine was studied;[75] the natural product withstood treatment with chromium trioxide-sulfuric acid during 1 h at 20 °C;[75b] however, when the oxidation was carried out at 60 °C in an acetic acid–acetic anhydride mixture, the 1,3,4-trioxo derivative was obtained, in a reaction entailing loss of the *C*1 methyl group.

A modern and chiral version of Bobbitt's group synthesis of carnegine was very recently provided by Gluszynska and Rozwadowska.[76] Table 3 summarizes the results of the optimization efforts towards the enantioselective addition of MeLi to imine **70b**, elaborated by condensation of **68** with aminoacetaldehyde dimethyl acetal.

These Polish scientists reported the enantioselective synthesis of this natural product and related alkaloids by enantioselective addition of methyllithium to imine **70a** in the presence of oxazolidine-type ligands **73a–d** (Fig. 4), which control the steric course of the reaction. The required ligands were obtained from (1*S*,2*S*)-2-amino-1-aryl-1,3-propanediols, inexpensive and widely available industrial waste products.[77] Noteworthy, the enantioselective addition of carbon nucleophiles to imines, not as intensively studied and not as widely used as the analogous reaction involving prochiral carbonyl compounds, has been recently reviewed.[78]

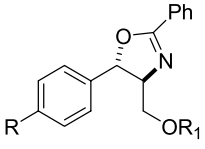
Incubation of a mixture of imine and ligand prior to MeLi addition produced some variation in yield and ee of the resulting product which was considered convenient; 2.5 equiv of MeLi and 2.5–3.5 h reaction time were judged as optimal for conducting the reaction and a non-coordinating medium such as toluene was found to be superior to the commonly used ethereal solvents.

Table 3. Addition of MeLi to imine **70b** in the presence of ligand **73b**



Entry	Reaction conditions			Product	
	Ligand (equiv)	Solvent	Temp (°C)	Yield (%)[a,b]	ee (%)[b,c]
1	0.1	PhMe	−65	43	7
2	0.5	PhMe	−65	55 (44)	23 (22)
3	1.0	PhMe	−65	78	28
4	2.0	PhMe	−65	85 (78)	37 (34)
5	2.6	PhMe	−65	85 (92)	38 (49)
6	2.6	PhMe	−42	85	33
7	2.6	PhMe	−42→20	81	15
8	2.6	PhMe	−90	(14)	(45)
9	3.0	PhMe	−65	(78)	(42)
10	2.6	THF	−65	NR	
11	2.6	Et_2O	−60	40 (40)	(14)
12	2.6	PhMe	0	56	8
13	2.6	PhMe	rt	(47)	(8)

[a] Chemical yields were established by NMR of crude reaction products.
[b] Numbers in parenthesis are chemical and optical yields of the addition product when 1 h of preliminary interaction of imine **70a** with ligand **73b** was produced.
[c] Enantiomeric excesses were determined in the presence of TADDOL.[79]



Compound	R_1	R_2
73a	SMe	H
73b	SMe	Me
73c	H	H
73d	H	Me

Figure 4.

It was also observed that the imine was essentially unreactive towards the organolithium reagent at low temperatures and in the absence of added ligand, and that enantioselectivity progressively increased from room temperature to −90 °C. Sub-stoichiometric amounts of ligand gave worse results than employing 1–2 equiv of oxazoline, while the best performance (ee=49%) was achieved in the presence of 2.6 equiv of ligand.

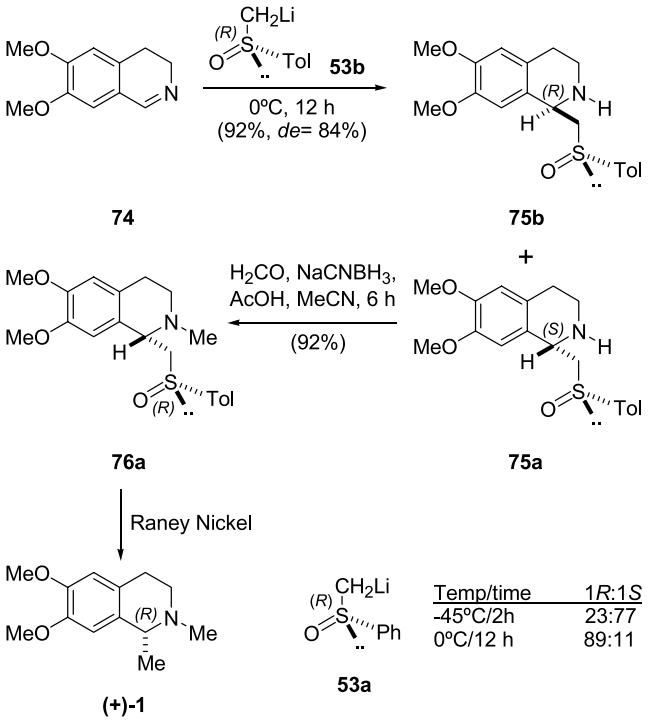
When the optimized conditions were applied to other ligands, lower asymmetric induction was observed; enantiomeric excesses were rather poor with **73a** and **73c** (1–9%), while **73d** allowed access to the addition product in 40% ee.

For the elaboration of carnegine, a protocol analogous to that of Bobbitt was followed (Scheme 14) and the resulting amine **71b** (ee=38%) was *N*-methylated with the H_2CO/AcOH–$NaBH_4$ system to furnish 86% of the corresponding *N*-methyl derivative. In turn, this was cyclized in 6N HCl during 2 days, after which Pd/C-catalyzed hydrogenolysis was carried out to furnish the natural product in 79% yield and 36% ee, that is, essentially without loss of optical purity. Interestingly, a related transformation, involving addition of methyllithium to *N*-methyl-6,7-dimethoxy-3,4-dihydroisoquinolinium iodide in the presence of sparteine proceeds with poor performance,[77] as discussed above.

Due to the acidic character of the a-protons of sulfoxides and sulfoximines, deprotonation is readily achieved with strong bases such as n-butyllithium, furnishing the corresponding α-metallated species. An attractive synthesis of (+)-**1** entailing the nucleophilic addition of a chiral α-sulfinyl carbanion compound[80] to an imine was reported by the group of Pyne.[80a] These Australian scientists added the versatile lithium carbanion of *R*-(+)-*p*-tolyl sulfoxide (**53b**) to 3,4-dihydroisoquinoline **74**, obtaining a mixture of diastereomeric sulfoxides **75a** and **75b**, which were characterized after chromatographic separation.

N-Methylation of **75a** by reductive alkylation of formaldehyde with sodium cyanoborohydride[81] to **76a** followed by reductive desulfurization with Raney nickel furnished the final product, as shown in Scheme 16. Chronologically speaking, this can be regarded as the first diastereoselective total synthesis of carnegine.[80a]

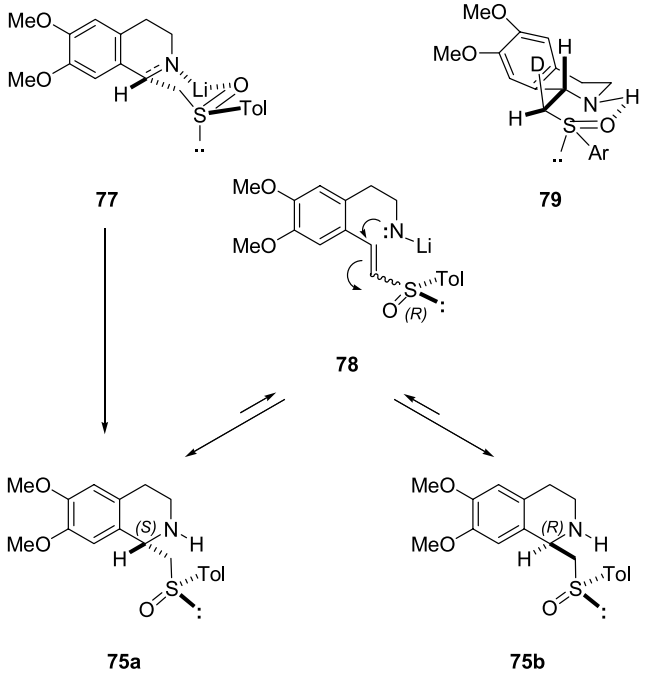
Appropriate temperature and reaction time were crucial to attain good chemical and optical yields. Experiments involving addition of phenylmethyl sulfoxide anion (**53a**)



Scheme 16.

to **74** demonstrated that better performance was achieved at room temperature than at −45 °C and that selectivity at the lower temperature was different than that observed at 0 °C.

Diastereoselectivity of the kinetically controlled addition of methyl-*p*-tolyl sulfoxide anion (**53b**) to imine **74** was rationalized by assuming a chair-like transition state **77**, as shown in Scheme 17, while diastereomer interconversion, leading to diminished diastereomeric excesses upon long reaction times, was proposed to occur through a retro Michael–Michael addition process involving vinylsulfoxides **78**.



Scheme 17.

Interestingly enough, quenching the addition reaction with D_2O lead to mono-deuterated species, which for the most abundant diastereomer **75a** probably exists in the intramolecular hydrogen-bonded form **79**, depicted in Scheme 17. A similar strategy consisting in a Mannich type reaction and based on the addition of the lithium anion of sulfoximines to complexes between 3,4-dihydroisoquinolines like **74** and $BF_3.Et_2O$ allowed the synthesis of more complex 1-susbtituted tetrahydro-isoquinolines;[80d] diastereoselectivities up to 95% were recorded for this approach.

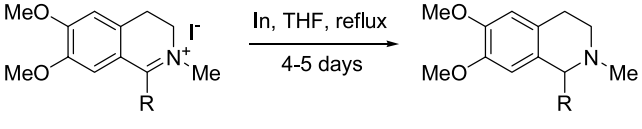
4.2. Reduction reactions

4.2.1. Reduction of dehydrosalsolidine methiodide. Reduction of 3,4-dihydroisoquinolinium derivatives has long been known to yield tetrahydroisoquinolines. For the purpose of accessing carnegine through this route, chemists have resorted to conventional reducing agents such as borohydrides, as well as novel reagents like indium metal. In addition, enantioselective transfer hydrogenation and chiral reducing agents have been employed for the preparation of optically active *N*-alkyl 1-substituted tetrahydroisoquinolines. To date, however, the use of this strategy for the elaboration of enantioenriched carnegine has met with rather poor success, being the best enantiomeric excesses recorded not more than 65%.

As part of their studies of the properties of indium metal as a reducing agent for use in organic synthesis, Moody et al. disclosed the efficient reduction of dehydrosalsolidine methiodide (**80**) with indium powder (1 g/mmol) in refluxing THF during 4–5 days, to provide 83% of carnegine. Notably, the reducing agent is stable towards water and air. The dehydrosalsolidine precursor **12** of the methiodide is easily available from 3,4-dimethoxyphenethylamine through the Bischler–Napieralski procedure.[82]

The full scope of the reaction, however, is still unclear because the related 1-pentenyl methiodide (**81**) was recovered unchanged after being submitted to the same treatment, and no tetrahydroisoquinoline **81a** could be isolated, as shown in Scheme 18.[83] The first ionization potential of indium (5.8 eV) is lower than that of reducing metals such as zinc (9.4 eV) and tin (7.3 eV) and close to that of alkali metals like sodium (5.1 eV), suggesting that the metal ought to participate in single electron transfer processes.

Interestingly enough, no radical intermediates could be intercepted during the reduction and no evidence of cyclized product derived from the pentenyl compound was observed.



80 R= Me
81 R= $(CH_2)_3CH=CH_2$

1 R= Me (83%)
81a R= $(CH_2)_3CH=CH_2$ (0%)

Scheme 18.

Moreover, dimeric products, which could have been formed by coupling of two heterocyclic rings, were not detected. This is in contrast with the facts that such coupling reactions are known to occur on treatment of isoquinolines and related heterocycles with zinc,[84] and that the effectiveness of indium in the aza-pinacol-type reductive coupling of imines to give 1,2-diamines has been demonstrated.[85]

Analogous syntheses of carnegine following similar protocols were previously disclosed by others. For studies on chemistry of 1-thienyl tetrahydroisoquinolines, Baker et al. also elaborated carnegine from **12**,[86] by methyl iodide methylation and reduction of **80** with sodium borohydride in aqueous ethanol. In an early synthesis of the natural product, Rozwadowska reported the use of 6,7-dimethoxy-2-ethoxycarbonyl-1,2-dihydroisoquinaldo nitrile, a Reissert compound produced by reaction of isoquinoline **62** with ethyl chloroformate and potassium cyanide, as an intermediate.[87a,c]

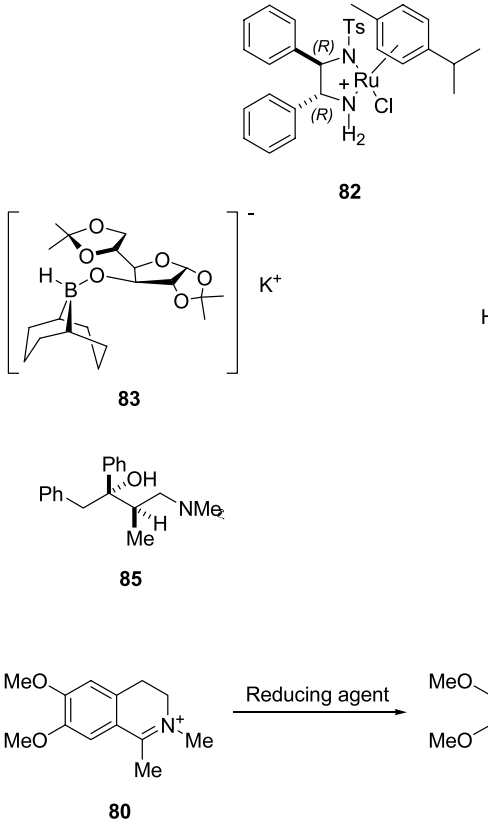
In the final step, 6,7-dimethoxy-1,2-dimethyl isoquinolinium iodide was reduced with sodium borohydride in MeOH, furnishing 60% of racemic carnegine.[87d] In addition, Späth's preparation of carnegine involved alkylation of **12** with methyl iodide, followed by Sn/HCl reduction of the resulting quaternary salt **80**.[10c]

On the other hand, and based on ruthenium neutral hydrocarbyl complex catalysts developed and popularized by the group of Noyori,[88] Blacker and Campbell recently disclosed a transfer hydrogenation process leading to carnegine;[89] employing the catalyst derived from bidentate ligand (*R*,*R*)-*N*-tosyl-1,2-diamino-1,2-diphenylethane. Carnegine was accessed in 63% ee and 72% yield when sodium isopropoxide-isopropanol was employed as hydrogen donor, while chemical yields of the natural product in excess of 98% were realized with little loss of optical purity when the advantageous triethylamine-formic acid azeotropic mixture in acetonitrile served as the hydrogen donor (Table 4, entries 1 and 2). These acceptable results were recorded with substrate/catalyst ratios of 400. Interestingly enough, Noyori previously demonstrated that these ruthenium catalysts perform better with the related imines; thus, salsolidine **8** was prepared from **12** in 99% yield and >95% ee.[88]

The use of chiral catalysts is one of the most attractive methods for performing asymmetric reactions, because compared to the stoichiometric use of chiral auxiliaries, a smaller amount of not always readily available chiral material is required. Therefore, large quantities of the resulting chiral materials are directly obtained, often with no need for further manipulation and little worry on recovery of the chiral auxiliary.

In addition, Cho and Han experienced the use of various chiral hydride reagents, such as K-glucoride (**83**),[90b] Itsuno's borane reagent (**84**)[90c] and Mosher's reagent,[90d] a complex prepared from aminoalcohol **85** (Darvon alcohol) and $LiAlH_4$ with the aim of enantioselectively reducing dihydrosalsolidine methiodide to carnegine.[90] Their results, consigned in Table 4 (entries 3–5), were slightly

Table 4. Synthesis of enantioenriched carnegine by enantioselective reduction of dehydrosalsolidine methiodide



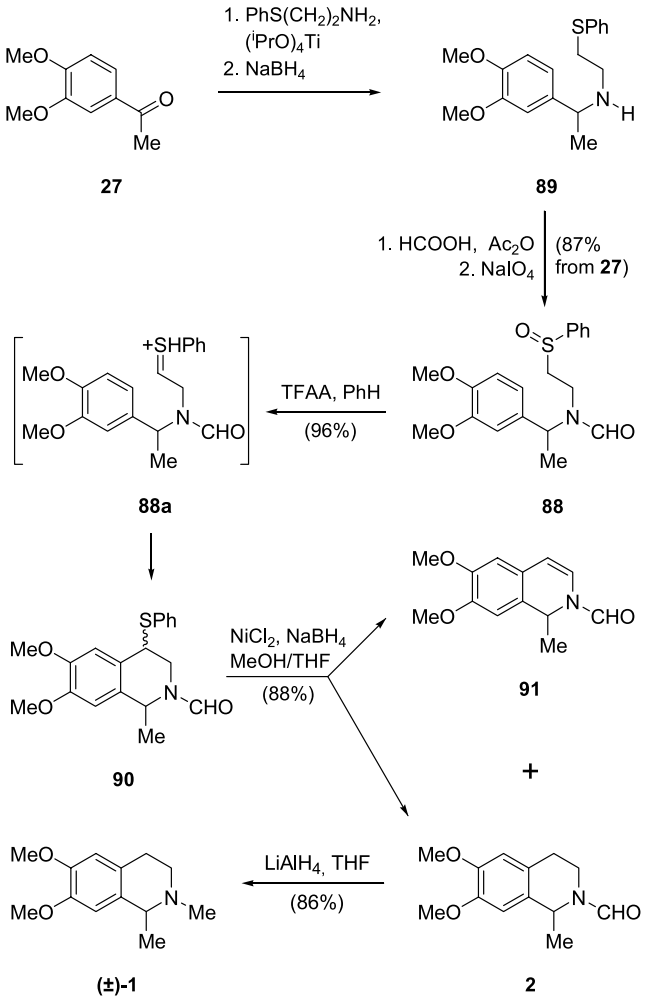
Entry No.	Reducing agent	ee, % (configuration)
1	Me_2CHOH, **82**	63
2	Et_3N, HCO_2H (2:5), **82**	≈ 60
3	K-Glucoride (**83**)	52.3 (*R*)
4	Itsuno's reagent (**84**)	17.8 (*R*)
5	Mosher' reagent (**85**)	66.4 (*S*)
6	Triacyloxyborohydride	11.9 (*R*)
7	Baker's yeast	No reaction

disappointing in terms of enantiomeric excess; since at best a 3:1 mixture of enantiomeric products was obtained.

Finally, Indian researchers informed that reduction of **80** with the chiral triacyloxy borohydride prepared from *S*-*N*-benzyloxycarbonyl proline (**86**) and sodium borohydride (3:1)[91a] provided 83% of carnegine slightly enriched in the dextrorotatory enantiomer (ee=11.9%).[91b] The same authors disclosed that submission of methiodide **80** to fermenting baker's yeast did not result in carnegine, being the substrate destroyed in the reaction medium, presumably by hydrolysis. Methods for the enantioselective reduction of the *C*=*N* function have been recently reviewed.[91c]

4.2.2. Reduction of imines, enamines and enamides. The reduction of imines and enamines serves as a convenient strategy for the installation of an 1-alkyl group in tetrahydroisoquinoline derivatives. This resource has been scarcely exploited in connection with the synthesis of carnegine.

The reductive amination of conveniently substituted



Scheme 19.

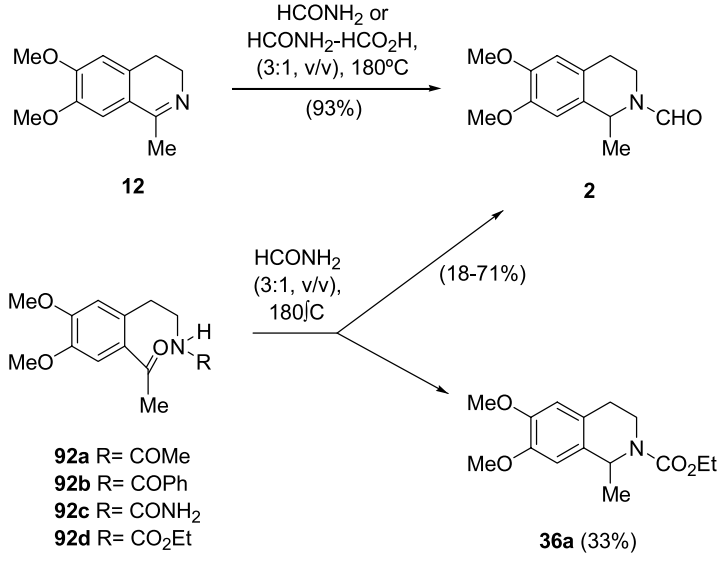
acetophenones is an acceptable alternative for the elaboration of 1-substituted tetrahydroisoquinolines.[92] In combination with the Pummerer sulfoxide rearrangement and an electrophilic aromatic cyclization reaction, this sequence proposed by Japanese scientists as a new modification of the Pomeranz–Fritsch isoquinoline synthesis constitute the key steps of another example of a Kametani type 5 synthetic strategy towards tetrahydroisoquinolines (Scheme 19).

This protocol has been developed only recently, as a special case of the Bobbitt sequence and it has been explored not as extensively as other classical cyclizations leading to tetrahydroisoquinoline derivatives. Initial work was done by the groups of Takano and Sano,[93] inspired in other sulfoxide-mediated electrophilic reactions[94] and has already resulted in the elaboration of several tetrahydroisoquinoline natural products, other polycyclic alkaloids, as well as biologically interesting tetrahydroisoquinolines.

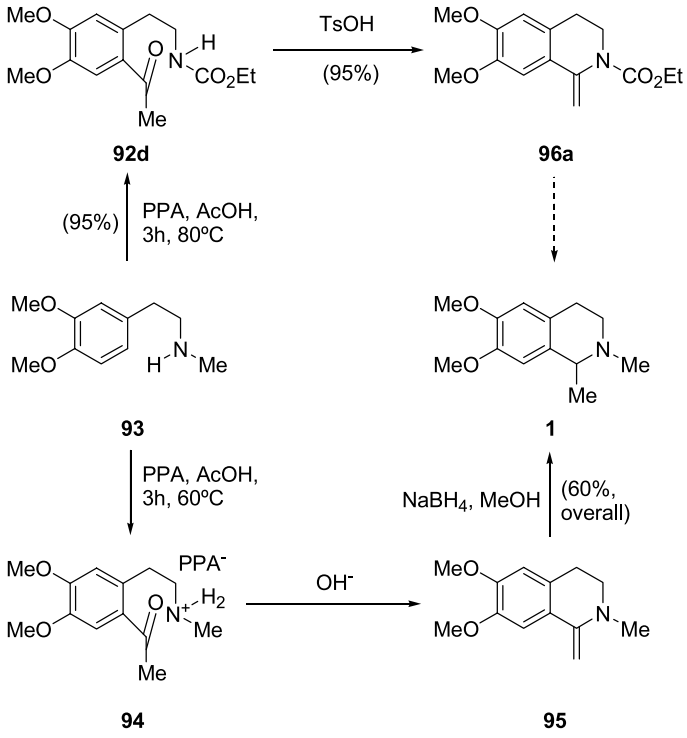
For the synthesis of (±)-carnegine, the required *N*-acyl-sulfoxide **88** was prepared in 87% overall yield from 3,4-dimethoxy acetophenone (**27**). Thus, reductive amination of the latter with 2-phenylthioethylamine under titanium isopropoxide promotion[95] in an EtOH–AcOH medium furnished **89**, which was acylated with mixed formyl-acetyl anhydride and then oxidized to the diastereomeric mixture of sulfoxides **88** with $NaIO_4$ in aqueous MeOH. Treatment of **88** with TFAA in benzene at room temperature for 18 h gave 96% of the cyclized product **90**,[94f] which was reductively desulfurized in 88% yield with the sodium borohydride–nickel chloride reagent, yielding a mixture of dihydroisoquinoline **91** and formyl tetrahydroisoquinoline **2**, which was subsequently reduced to the natural product in 86% yield by lithium aluminum hydride in THF.[96]

In a systematic study,[97] it was demonstrated that this type of cyclization is sensitive to the solvent and the nature of the *N*-acyl substituent. In CH_2Cl_2, a complex mixture of products is obtained and apparently, the formyl moiety as *N*-protecting group plays an important role in facilitating the intramolecular cyclization to take place.

Despite that to date only the elaboration of racemic carnegine has been reported following this route, the strategy has been adapted to large scale preparation of both enantiomers of



Scheme 20.



Scheme 21.

1-methyl tetrahydroisoquinoline[98] as well as of the four stereoisomers of 1,3-dimethyl-1,2,3,4-tetrahydroisoquinoline, which suggests its potential applicability to an enantioselective synthesis of carnegine. This route seems to be very attractive for preparing substrates for use in biological studies since isotope labeling at the $C-4$ position is possible by reductive elimination of the phenylthio group.

An alternative synthesis of racemic carnegine resorting to the reduction of the $C{=}N$ bond was provided by the group of Venkov. These Bulgarian scientists made use of the old finding that formamide can be used in the Leuckart-Wallach[99] reaction for the reductive amination of carbonyl compounds and for the reductive formylation of heterocycles, including methylisoquinolines.[100]

After heating of a mixture of **12** and formamide to 180 °C for 1–2 h, the *N*-formyl derivative **2** was obtained in 67% yield, as shown in Scheme 20.[101] Other *N*-formyl tetrahydroisoquinolines were accessed under similar conditions in yields ranging from 38 to 93%. Yields of **2** increased to 93% when 98% formic acid was added to formamide to form a 3:1 v/v mixture and the reaction was refluxed for 2 h. From analysis of the products it was proposed that the reaction probably proceeds with an initial reduction of the $C{=}N$ bond, followed by the *N*-formylation of the resulting tetrahydroisoquinoline.

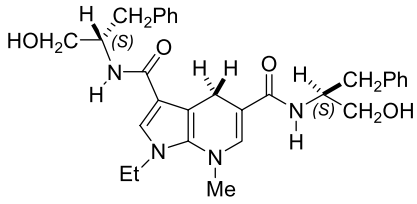
In a slight variation of their strategy, this group disclosed that heating to reflux during 3 h acetophenone derivatives[102a] **92a–d** in a 3:1 mixture of formamide and formic acid lead predominantly to *N*-formyltetrahydroisoquinoline **2**. However, in the case of **92d**, not possessing a good leaving group on nitrogen, the transamidation could not be made to reach completion leading to a mixture of **2** (18%) and carbamate **36** (33%).

In still another modification of their strategy, depicted in Scheme 21, the same group reported a two-step synthesis of carnegine. This involved the acid-catalyzed acylation of the conveniently substituted homoveratrylamine **93** with acetic acid to furnish acetophenone derivative **94**, which was not isolated, being instead submitted in situ to cyclization under basic conditions, to give enamine **95**.

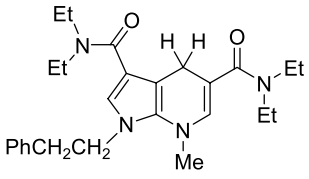
Conventional reduction of the enamine with sodium borohydride in methanol furnished 60% of the product.[103] These authors observed that the preferred acylation pattern of the aromatic ring of the homoveratrylamine precursor is general and takes place in good yields with many different carboxylic acids under polyphosphoric acid promotion. Following a somehow analogous strategy, the same group elaborated in good yield *N*-carboxyethyl enamine **96a**. This precursor of carnegine was prepared from the same starting material, the homoveratrylamine derivative **93** through acetophenone derivative **92d**.[104]

Bourguignon et al.[105] studied the biomimetic reduction of enamides with NADH models as hydride donors employing the chiral NADH mimic **97** (Fig. 5) derived from *S*-phenylalaninol, which reduces $C{=}O$ and $C{=}N$ bonds in the presence of $Mg(ClO_4)_2$. The biomimetic enantioselective reduction of the carnegine precursors **96b** and **96c** with NADH analog **97** was achieved, furnishing up to 95% yield of *N*-acetylsalsolidine (**36b**) in 87% optical yield. Addition of excess $Mg(ClO_4)_2$ to the reaction medium was critical, since the use of 1 equiv of the salt provided the product in only 32% ee.

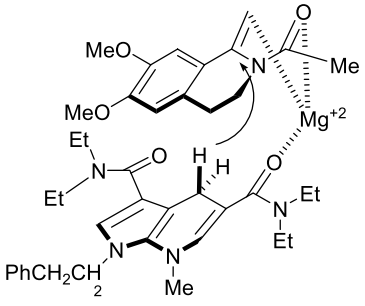
However, the related methyl carbamate **96a** was reduced to furnish 95% of (+)-**36b**, but in only 26% ee. Table 5 summarizes the variation of the enantiomeric excess of **36b** and **36c** with the concentration of $Mg(ClO_4)_2$ in the reaction



97



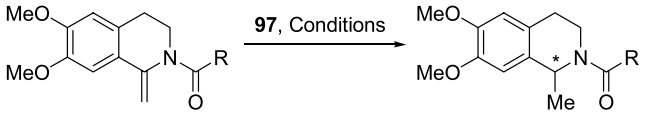
98



98a

Figure 5.

Table 5. Asymmetric reduction of enamides **96** and **96a** with NADH model **97**



96b R= OMe
96c R= Me

36b R= OMe
36c R= Me

$MgClO_4$ (equiv)	0.25	0.5	0.75	1	2	4	8
36c, ee(config)	13(*R*)	20(*R*)	25(*R*)	32(*R*)	51(*R*)	80(*R*)	87(*R*)
36b, ee %	—	—	0	+7	+13	+18	+26

medium. Curiously, inversion of selectivity depending upon the amount of $Mg(ClO_4)_2$ employed occurred during the reduction of methyl benzoyl formate to methyl mandelate. However, no such inversion was observed when reduction of 3,4-dihydroisoquinoline enamides was carried out.

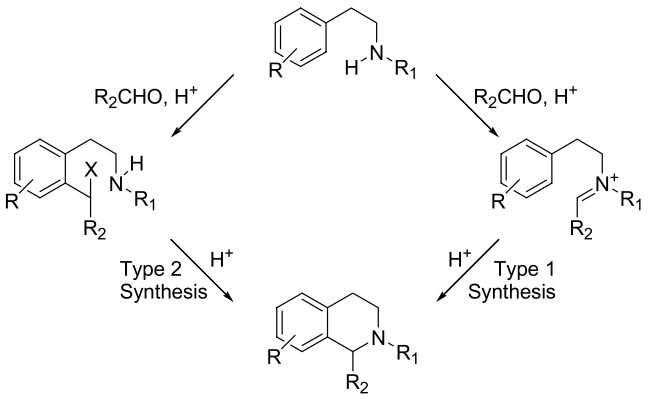
Use of non-chiral NADH models such as **98** to provide racemic **36c** have also been described by this group in earlier publications. A ternary complex model (**98a**) between the substrate, the NADH mimic **98** and Mg^{++} was assumed to be responsible for the hydride transfer; in the case of chiral NADH mimic **97**, the model correctly explains the preferential *si*-face hydrogen transfer to **96c**, leading to enantioenriched *R*-**36c**.

4.3. Cyclization reactions

4.3.1. Cyclizations employing the Pictet–Spengler reaction. The Pictet–Spengler reaction of β-phenethylamines with aldehydes is a well-known and widely used procedure for the synthesis of tetrahydroisoquinolines.[106d] The reaction is limited to phenethylamines without electron-withdrawing groups in their benzene rings. A variation of the Pictet–Spengler reaction, termed 'activated Pictet–Spengler'[106a–d] is carried out employing phenethylamines in which electron withdrawing groups, in the form of amides, carbamates and sulfonamides, are bound to the nitrogen. The *N*-acyliminium or *N*-sulfonyliminium intermediates formed enhance electrophilic reactivity often leading to more efficient cyclizations.[107b]

Although the Pictet–Spengler cyclization is usually regarded as a type 1 tetrahydroisoquinoline synthesis, two alternative mechanisms have been suggested as operative, especially in the case of the 'activated Pictet–Spengler' cyclization (Scheme 22).[107] One of them involves reaction of the aldehyde with the aromatic ring prior to cyclization by attack of the 'activated' nitrogen atom (type 2 synthesis), while the other comprises the formation of an iminium species between the aldehyde and the nitrogen moiety followed by nucleophilic attack by the aromatic ring to the iminium intermediate (type 1 synthesis).

Asymmetric versions of the Pictet–Spengler reaction



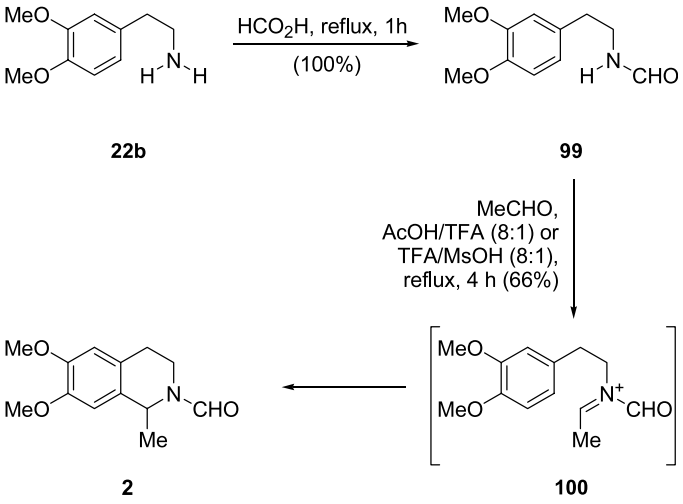
Scheme 22.

involve the presence of chirality either in the amine component or the aldehyde substrate.[106e] Thus, the use of chiral aldehydes may be exploited for the elaboration of enantioenriched tetrahydroisoquinolines.

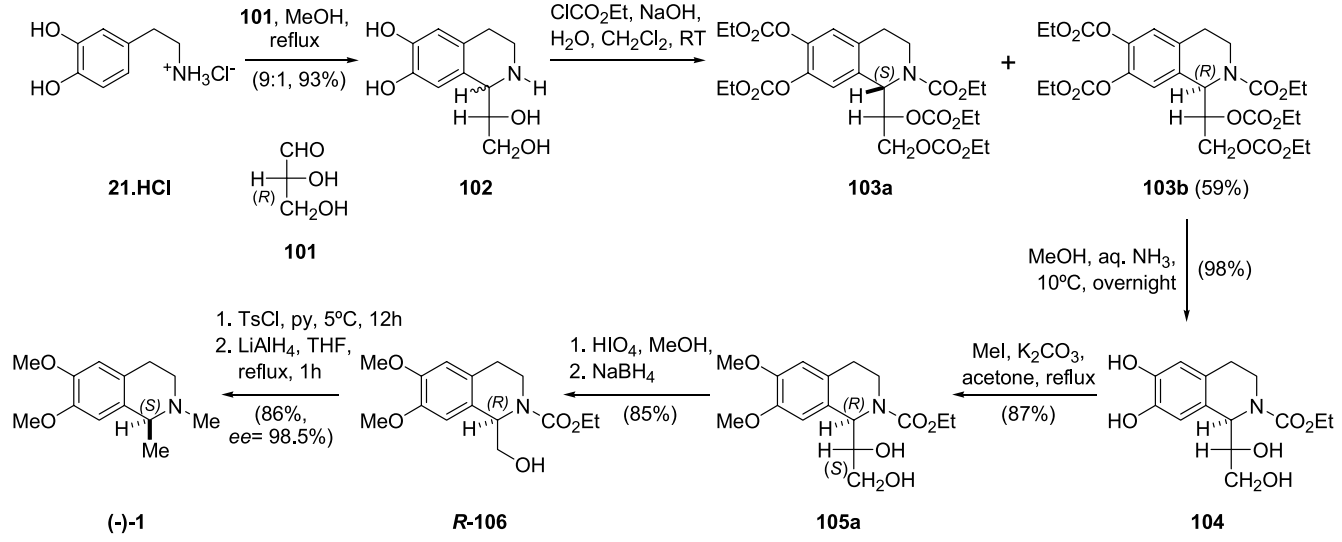
Venkov et al. developed an activated Pictet–Spengler protocol capable of providing 1-substituted *N*-formyl tetrahydroisoquinolines via *N*-formyliminium ions **100**.[108]

The synthetic strategy shown for carnegine in Scheme 23, consists in reacting an appropriately substituted *N*-formyl phenethylamine (**99**) with the required aldehyde (for carnegine, acetaldehyde) in the presence of an acid promoter (AcOH/TFA 8:1 or TFA/MsOH 8:1). The required *N*-formyl phenethylamine can be quantitatively prepared in situ by refluxing the phenethylamine **22b** with an excess of formic acid.

The use of optically active phenethylamine carbamates of less reactive nature was exploited by the group of Comins for the elaboration of substituted 1-benzyl tetrahydroisoquinolines. However, this chiral auxiliary mediated Pictet–Spengler reaction required more strenuous conditions and an enolether was employed as aldehyde surrogate.[109]



Scheme 23.

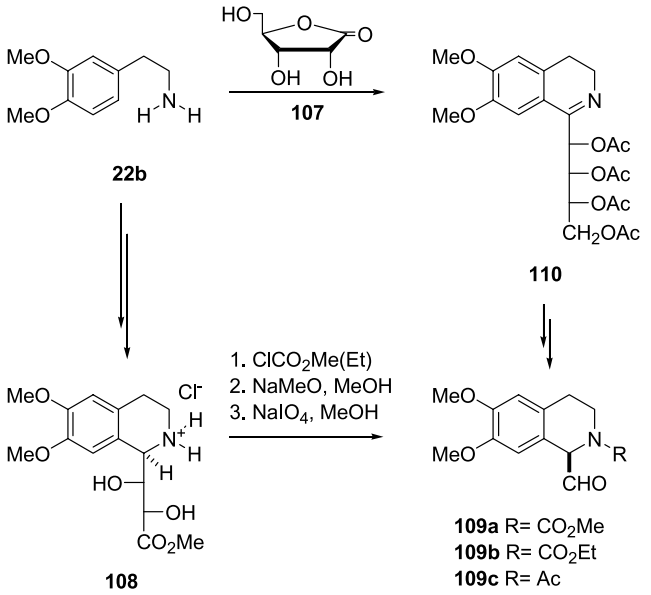


Scheme 24.

A Polish–Canadian group found that sugars and their derivatives could be used as the aldehyde part of the Pictet–Spengler condensation. The importance of this finding stems from the facts that carbohydrates are readily available in enantiomerically pure form and that sugar chirality is transferred to the newly generated asymmetric center. The suitability of this observation for the elaboration of optically active natural products was successfully tested in several occasions. Along these lines, Czarnocki et al. disclosed a total synthesis of (−)-carnegine which employs *R*-(+)-glyceraldehyde (**101**) and dopamine (**21**) as starting materials.[110]

Their synthesis, depicted in Scheme 24, commenced with the Pictet–Spengler condensation of dopamine hydrochloride and (+)-glyceraldehyde to furnish a 9:1 mixture of cyclized diols **102** in 93% yield; the mixture was treated with ethyl chloroformate and the resulting tetracarbonates **103** were chromatographically separated, affording 59% of the most abundant compound **103b**. Mild ammonolysis of **103b** lead to catechol **104** in 98% yield, which was submitted to a conventional Williamson etherification to give 87% of *R*,*S*-diol **105a**.

Next, periodic-acid mediated oxidative fission of the glycol moiety, followed by a reductive work-up provided 85% of carboxyethyl calycotomine (**106**). In turn, this product was reduced in 86% to carnegine via the tosylate of the primary alcohol, employing lithium aluminum hydride in refluxing THF. Analogously, compound **108**, prepared by cyclization of the corresponding phenethylamine **22b** with tartaric acid, has been employed for the elaboration of the versatile aldehydes **109a** and **109b** (Scheme 25). The use of ribonolactone (**107**) for the synthesis of **109c** via the highly unstable tetraacetate **110**, has also been disclosed.



Scheme 25.

The cyclization strategy in both cases was a Bischler–Napieralski reaction,[111w] followed by reduction of the cyclized product to a tetrahydroisoquinoline intermediate. Reduction was carried out directly on the 3,4-dihydroisoquinoline for the elaboration of **108**; however, due to the instability of **110**, the corresponding nitrone was prepared and then reduced. In addition, this group informed the elaboration of **109b** by Bischler–Napieralski reaction of **22b** with diethyl oxalate, followed by functional group transformations and chemical resolution, yielding **106**, which furnished the aldehyde after Swern oxidation.[110c]

Intramolecular radical cyclization reactions have emerged as powerful synthetic tools for the construction of carbocyclic and heterocyclic rings. With the aid of a properly placed chiral auxiliary, these can yield diastereoselective ring closures. An intramolecular aryl radical cyclization to an aldimine leading to **105b**, a diastereomer of glycol **105a** and somehow reminiscent of the outcome of a Pictet–Spengler condensation, was reported by Tomaszewski and Warkentin.[112a]

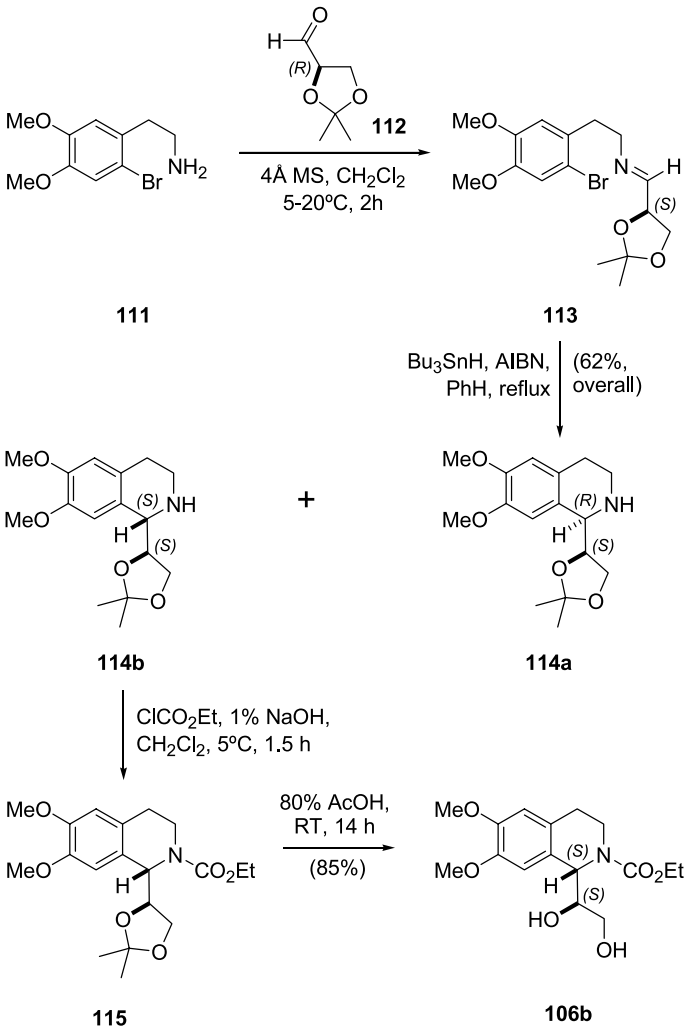
In this sequence depicted in Scheme 26, bromodopamine **111** was condensed with the acetonide of glyceraldehyde (**112**), furnishing imine **113**, which was cyclized with Bu_3SnH and AIBN furnishing 62% of a diastereomeric mixture of acetonides **114a** and **114b** (*de*=53%). This cyclization proceeded exclusively in a *6-endo* fashion and no products derived from the *5-exo* alternative pathway were observed.[112b] Protection of the amino group of the major diastereomer as the ethyl carbamate (**115**) and unmasking of the glycol, provided compound **105b**.

4.3.2. Cyclization of vinyl sulfoxides and sulfoximines. Nowadays, the sulfinyl group is widely used as an important tool in asymmetric synthesis. The sulfoxide moiety is very effective in diastereoselective auxiliary-induced reactions, being its effectiveness due to the steric as well as the stereoelectronic differences existing between the four different substituents of the sulfur atom, which are able to differentiate the diastereotopic faces of the proximal reaction center. Other influential factors contributing to the wide use of sulfoxides are their high configurational stability, the availability of an important array of efficient synthetic methods to obtain homochiral sulfoxides, as well as their synthetic versatility.[113]

The cyclization of vinyl sulfinyl derivatives leading to tetrahydroisoquinoline derivatives reported to date can be regarded as cases somehow reminiscing the Pictet–Spengler reaction in which either the nitrogen moiety or the aromatic part conclude the heterocyclic ring closure. An important difference with regards to the classical Pictet–Spengler condensation is that cyclization of vinyl sulfinyl entail a diastereoselective Michael addition.

This strategy employs the sulfinyl group as a removable stereocontrolling agent, as well as an activating moiety. The use of the stereogenic sulfur center of chiral sulfoxides to achieve enantioselective control in asymmetric synthesis and the participation of chiral sulfoxides in Michael addition reactions has many precedents.[113,114]

With regards to carnegine, Pyne et al. were the first in using organosulfur chemistry. However, this group reported two different procedures for the diastereoselective elaboration of carnegine derivatives based on the same general strategy.



Scheme 26.

This strategy relied on sulfur chirality for diastereoselection and on the Michael acceptor properties of the vinyl sulfur derivatives including their capability of adding amines, for tetrahydroisoquinoline ring formation.[115]

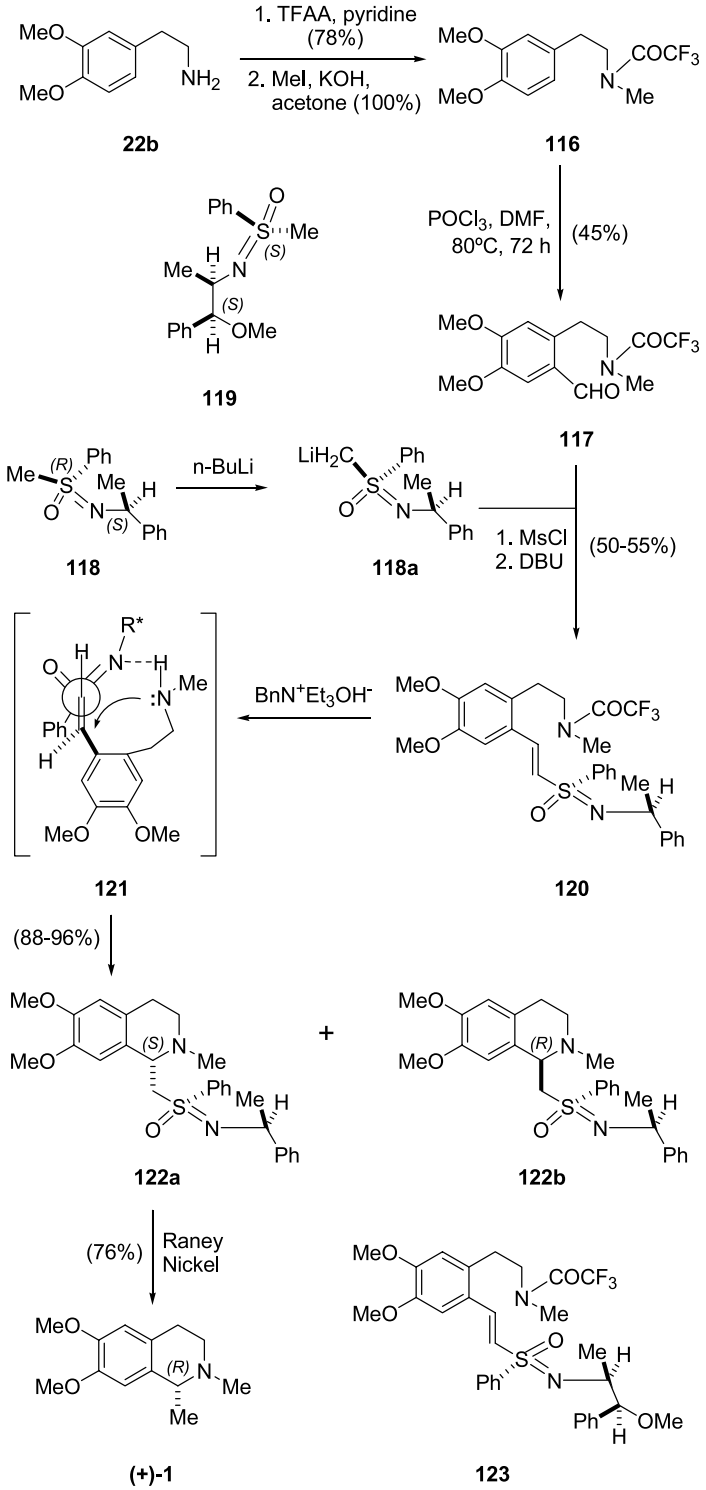
In the first approach, Pyne carried out one of the first successful intramolecular Michael addition to vinyl sulfoximines, employing chiral vinyl sulfoximines derived from compounds **118** and **119**, bearing opposite configurations on the heteoatom. To this end, these researchers appropriately acylated and *N*-alkylated 3,4-dimethoxyphenethylamine (**22b**), by successive treatment with trifluoroacetic anhydride and methyl iodide, accessing **116**, which was submitted to a Vilsmeier formylation providing 45% of aldehyde **117**,[116] as shown in Scheme 27.

Hydroxyalkylation of aldehyde **117** by addition of **118a**, the readily formed lithium anion of (R_S)-sulfoximine **118**,[115d] was followed by conventional mesylation of the resulting alcohol, and DBU-mediated mild elimination of the intermediate mesylate, furnishing the *E*-vinyl sulfoxymine **120** in good overall yield.

Next, uncovering of the nucleophilic nitrogen by basic hydrolysis of **120** triggered the expected Michael addition, giving a mixture of chromatographically separable cyclized products **122** in high yield, presumably through chelated intermediate **121**. Final reductive removal of the chiral auxiliary with Raney nickel furnished 76% of (+)-**1**. A similar sequence of reactions was carried out with **119**, leading to sulfoximine **123**.

In spite that cyclization yields were high, the diastereoselectivity obtained was only moderate, as shown in Table 6, being this the major drawback of the synthesis. Analysis of the reaction products derived from **120** and **123** indicated that the stereochemical course of this kinetically controlled cyclization seems to be governed by the chirality at the sulfur atom rather than by the chiral auxiliary ligand.

Solvent effects were also put in evidence; changing from CH_2Cl_2 to MeOH, a dramatic reduction in diastereoselectivity (from 48 to 16%) was observed. Interestingly, however, temperature had little effect on diastereoselectivity. Lithium anions of sulfoximines have also been employed for the elaboration of chiral 1-substituted tetrahydroisoquinoline derivatives by addition to Lewis

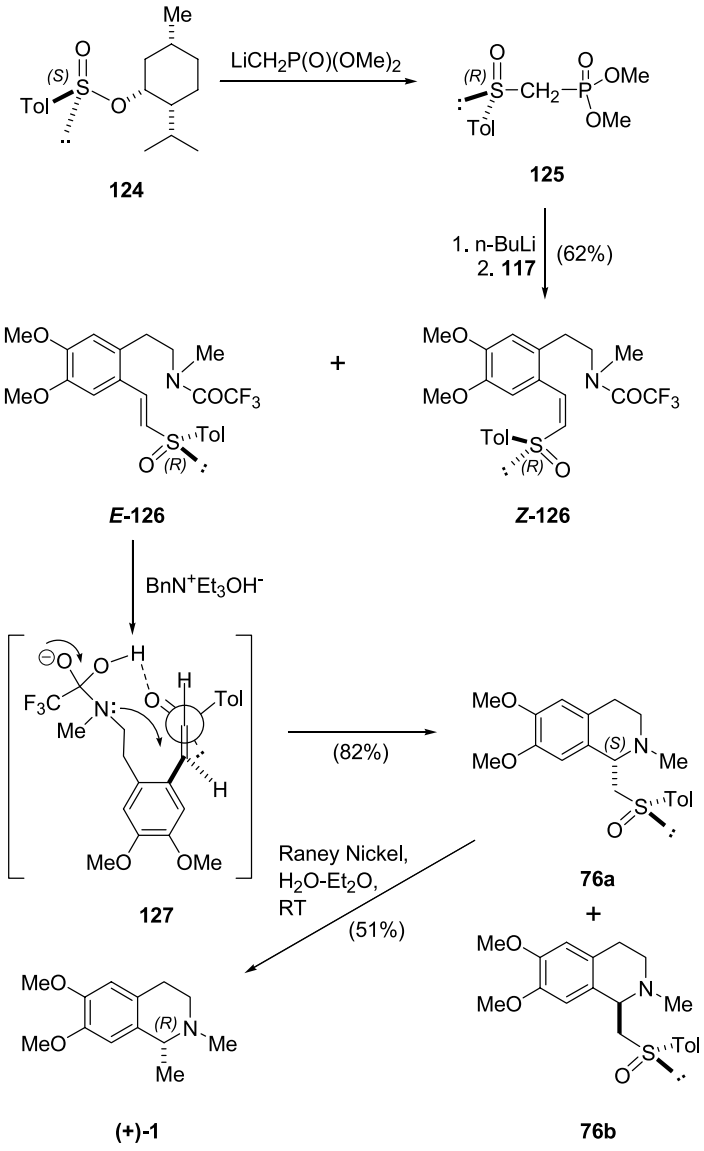


Scheme 27.

Table 6. Cyclization of sulfoximides **120** and **123**

Entry No.	Sulfoximine	Base	Solvent	Temperature (°C)	Diastereo-selection[a]
1	**120**	$BTEA^+OH^-$	CH_2Cl_2	0	26:74
2	**120**	$BTEA^+OH^-$	CH_2Cl_2	−40	28:72
3	**120**	$BTEA^+OH^-$	MeOH	0	58:42
4	**120**	LiOH	MeOH, H_2O	0	65:35
5	**123**	$BTEA^+OH^-$	CH_2Cl_2	0	71:29
6	**123**	$BTEA^+OH^-$	CH_2Cl_2	−40	68:32
7	**123**	$BTEA^+OH^-$	MeOH	0	54:46
8	**123**	LiOH	MeOH, H_2O	0	65:35

[a] Diastereomeric ratio between 1*S*- and 1*R*-tetrahydroisoquinoline derivatives.



Scheme 28.

acids activated 3,4-dihydroisoquinolines, such as **74**, resembling the strategy depicted in Scheme 16.

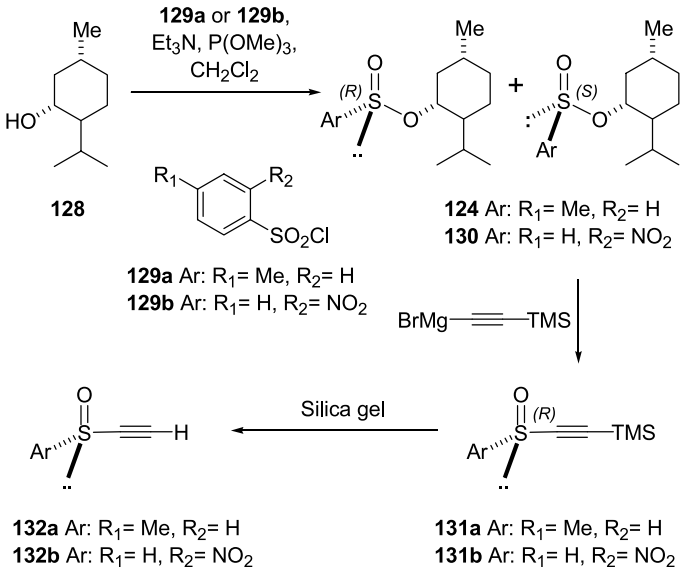
The second strategy devised by Pyne was based on properties of vinyl sulfoxides analogous to those of the vinylsulfoximides and relied on results of Stirling[115e] on the intermolecular addition of amines to chiral *Z*-vinyl sulfoxides, furnishing β-aminosulfoxides in 70% *de*. In order to synthesize the required sulfoxides, these researchers prepared **117** in 41% yield by submission of **116** to a Duff-type formylation with hexamethylene-tetraamine and trifluoroacetic acid.[115c]

In turn, this was submitted to a Wittig Horner olefination with the lithium salt of *R*-(dimethoxyphosphoryl)methyl aryl sulfoxide (**125**), yielding a mixture of separable *E*- and *Z*-vinyl sulfoxides **126** in 62% combined yield, as shown in Scheme 28. Compound **125** was prepared by *n*-BuLi treatment of the product arising from reaction of dimethoxyphosphoryl methyl lithium and Andersen's reagent (**124**).

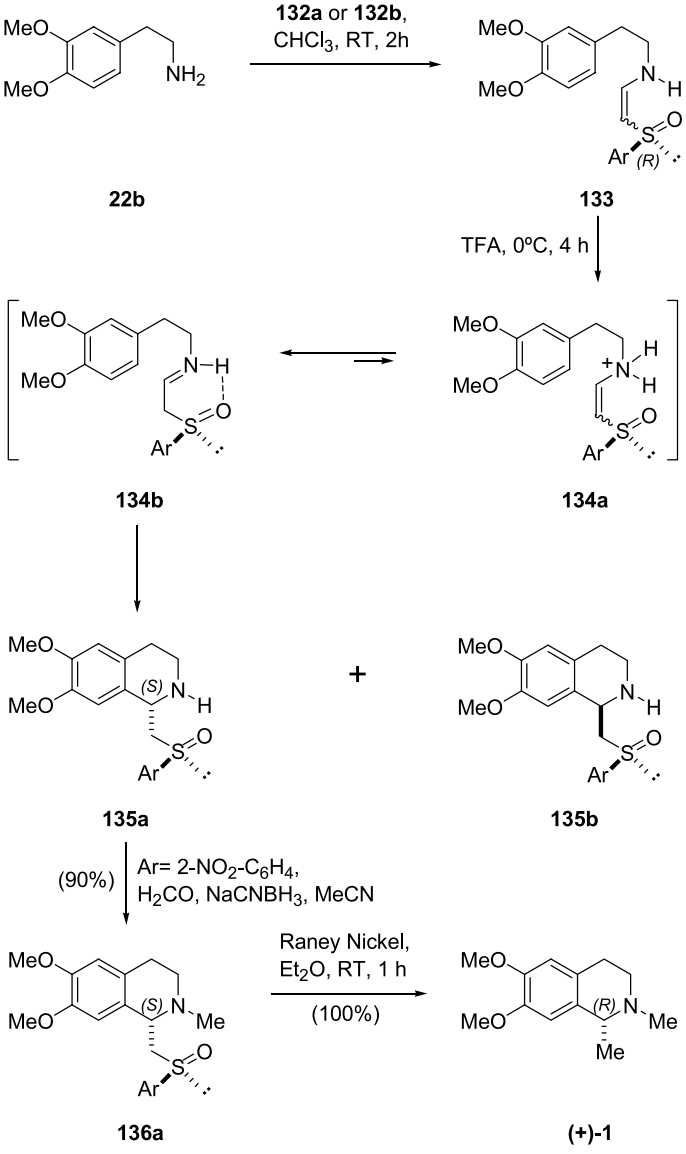
Cyclization of the vinyl sulfoxides was performed under basic conditions, leading to tetrahydroisoquinolines **76**. Interestingly, it was observed that the isomeric compounds **126** underwent cyclization in the opposite stereochemical

Table 7. Intramolecular diastereoselective Michael addition of vinyl sulfoxides **126**, leading to tetrahydroisoquinolines **76**

Entry No.	Sulfoxide	Base	Solvent	Temperature (°C)	Diastereo-selection
1	*E*-**126**	$BTEA^+OH^-$	CH_2Cl_2	−40	42:58
2	*E*-**126**	$BTEA^+OH^-$	MeOH	−40	38:62
3	*E*-**126**	LiOH	MeOH, H_2O	0	37:63
4	*Z*-**126**	$BTEA^+OH^-$	CH_2Cl_2	−40	83:17
5	*Z*-**126**	$BTEA^+OH^-$	MeOH	−40	84:16



Scheme 29.



Scheme 30.

Table 8. Diastereoselectivity of the cyclization of vinyl sulfoxides **135** to tetrahydroisoquinolines **135** in $CHCl_3$

Entry No.	Ar	Acid	Temperature (°C)	**135a/135b**	Yield (%)
1	2-NO_2–C_6H_4	TFA	−20	—	—
2	2-NO_2–C_6H_4	TFA	0	100:0	65
3	2-NO_2–C_6H_4	TFA	rt	100:0	35
4	2-NO_2–C_6H_4	$BF_3.Et_2O$	0	100:0	20
5	4-Me–C_6H_4	TFA	0	67:33	45

sense in this kinetically controlled process, as shown in Table 7. The most abundant of the diastereomeric tetrahydroisoquinolines was further elaborated into (+)-**1** by Raney nickel desulfurization.

This strategy was elaborated further by Pyne to enantioselectively provide *R*-(+)-canadine, a tetrahydroprotoberberine alkaloid.[117] By analogy with similar cyclizations, a chelated transition state **127** involving the cyclizing promoter and the starting vinyl sulfoxide can be proposed to rationalize the reaction outcome.

The group of Lee[118] prepared chiral acetylenic sulfoxides **132a** and **132b** by reaction of trimethylsilyl magnesium bromide with chiral menthyl sulfinates **124** and **130**, through the intermediacy of **131a** and **131b**. Anderson synthesis was employed for the elaboration of (−)-menthyl-*p*-toluenesulfinate (**124**) and the Sharpless' procedure[119] was used for the preparation of (−)-menthyl *o*-nitrobenzene sulfinate, both from natural menthol (**128**) and sulfonyl chlorides **129a** and **129b**, as depicted in Scheme 29.

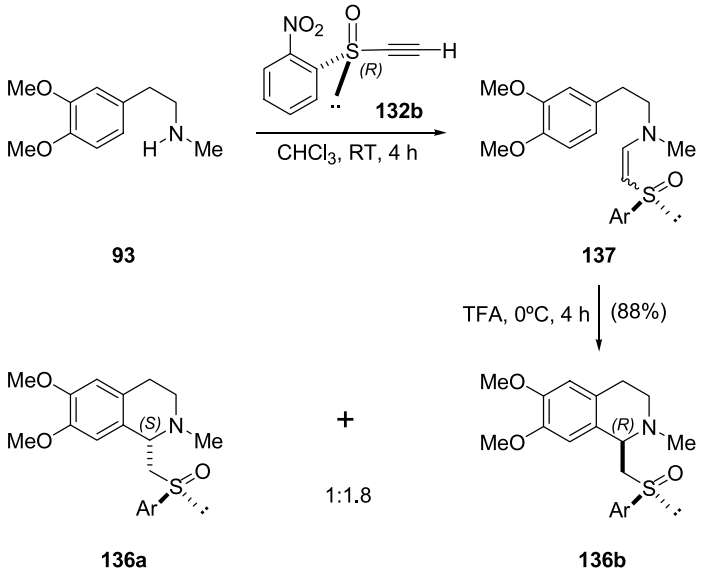
The acetylenic sulfoxides were submitted to a Michael addition with 3,4-dimethoxyphenethylamine (**22b**), furnishing vinyl sulfoxides **133**, which were cyclized in chloroform under TFA catalysis (Scheme 30). Several factors affecting the yield and diastereomeric ratio were detected. The type of acid and the temperature were found to be important, with the transformation having its best performance in the presence of TFA at 0 °C.

On the other hand, the substituent on the benzene ring of the starting aryl sulfoxide influenced the optical course of the cyclization; when *para*-toluenesulfinate was employed, a 4:1 mixture of diastereomers **135a** and **135b** (Ar=4-Me–C_6H_4) was realized; however, when the nitroderivative was used, exclusive formation of **135a** (Ar=2-NO_2–C_6H_4) was observed, as consigned in Table 8. This substituent effect on diastereoselectivity was rationalized assuming that under the influence of the acid, the protonated amine **134a** and the enamine **134b** are in equilibrium, with the latter as the predominant species. A hydrogen bond could be formed under these conditions, leading to a six-membered ring intermediate, which locks the conformation of the molecule.

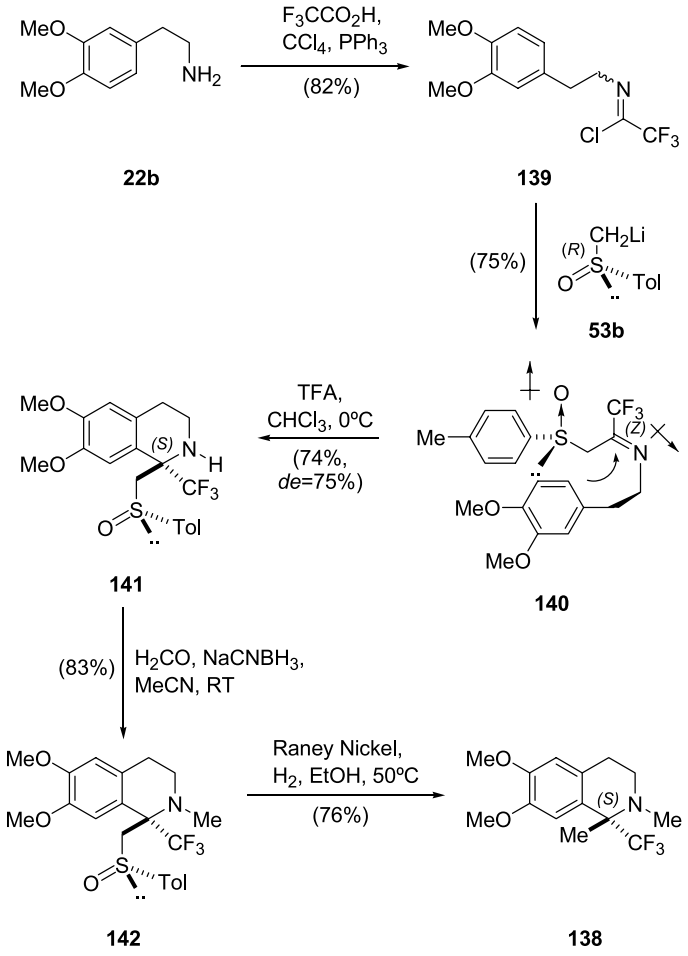
The higher diastereoselectivity observed with the nitro derivative was assigned to the differential stability of the transition states, involving hydrogen bond stabilization of the cyclizing intermediate by the presence of the electron withdrawing substituent in close proximity to the sulfoxide.

To complete the synthesis, sulfoxide **135a** was reductively *N*-methylated under conventional conditions and then desulfurized with Raney nickel in water-saturated ether. Interestingly enough, the resulting **136a** is analogous to **76a**, previously accessed by a slightly different route by Pyne et al.[115a,b]

An interesting feature of this sequence disclosed by the same group (Scheme 31),[120] is that employing *N*-methyl-3,4-dimethoxy phenethylamine (**93**) as starting amine and nitroderivative **132b** as chiral sulfoxide. Cyclization of intermediate vinylsulfoxide **137** proceeds with reverse diastereoselectivity, furnishing a 1.8:1 mixture of



Scheme 31.



Scheme 32.

diastereomers in favor of **136b**, less polar than its congener **136a**. Raney nickel desulfurization of the chiral auxiliary in the major diastereomer, as above, provides *S*-carnegine, being this a complementary and more convergent way of accessing the natural product.

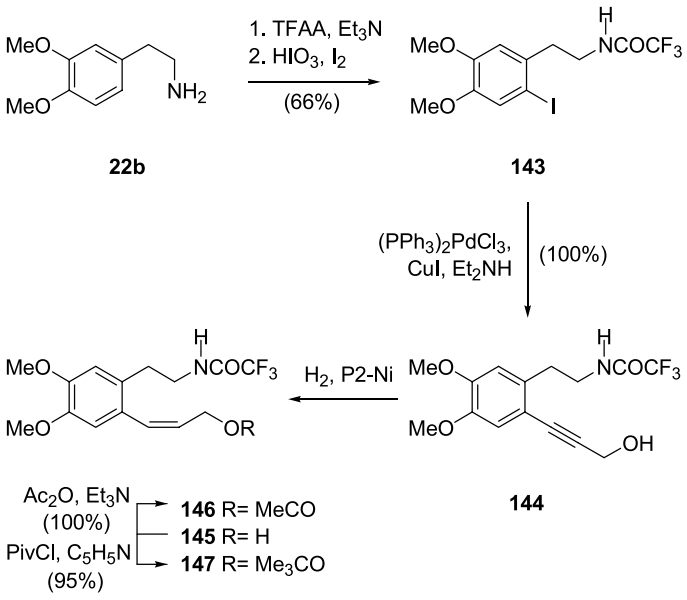
Notably enough, an extension of this cyclization reaction involving a stabilized sulfinylimine intermediate was recently employed for the elaboration of 1-trifluoromethyl carnegine (**138**).[121] The synthetic sequence, shown in Scheme 32, involved initial formation of trifluoroacetimidoyl chloride **139** by condensation of dimethoxy phenethylamine **22b** with trifluoroacetic acid in the presence of carbon tetrachloride and triphenylphosphine. Subsequent addition of *para*-toluenesulfonyl methyl anion **53b** to **139** furnished the required β-aminovinylsulfoxide **140**, which was submitted to trifluoroacetic acid in chloroform in order to assemble the crucial *C*–*C* bond by Pictet–Spengler cyclization of the electron reach aromatic moiety to the β-carbon of the chiral sulfoxide. This proceeded in 74% yield, furnishing a 6:1 mixture of diastereomers, in favor of the one possessing 1*S* configuration (**141**).

Opposite to similar processes discussed above, this cyclization is irreversible and no changes in diastereomeric ratio are observed by increasing the reaction time. *N*-methylation under reducing conditions of the major diastereomer to give **142**, followed by Raney-nickel desulfurization, furnished the final product **138**.

The good diastereoselectivity of this intramolecular Pictet–Spengler reaction was explained considering that, due to the *cis* geometry of the *C*=*N* bond of the substrate **140**, the electron-rich 3,4-dimethoxyphenyl group and the stereogenic *p*-tolylsulfinyl group should be spatially close to each other.

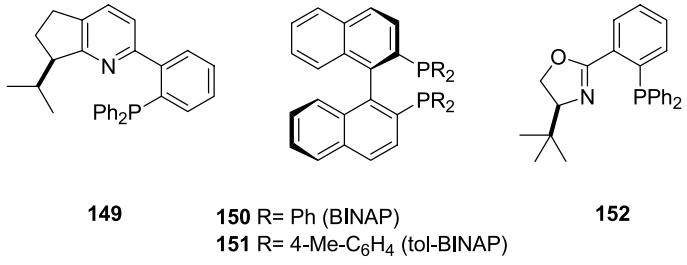
Thus, the sulfinyl auxiliary can exert a strong stereodirecting effect on the ring closure through a reactive conformation which minimizes the dipole–dipole interactions between the *S*=*O* and *C*=*N* bonds.[122] Then, attack of the 3,4-dimethoxyphenyl group is induced to occur from the less hindered *re* face of the stabilized carbocation on *C*1 formed via protonation of the imine nitrogen of **140** by TFA. Finally, it is worth mentioning that the use of chiral *N*-sulfinyl intermediates in a Pictet–Spengler reaction leading to the carnegine precursor (+)-salsolidine in > 98% ee was recently reported by Koomen et al.[123] This sequence involves a chiral sulfinyl-directed Pictet–Spengler condensation as the key step.

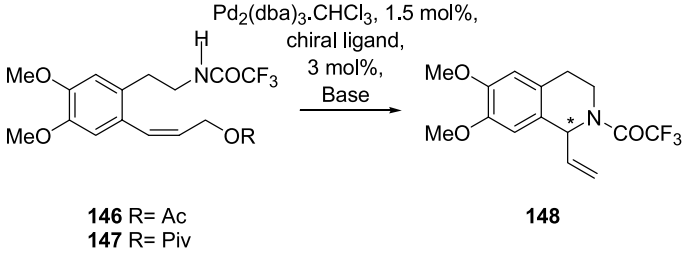
4.3.3. Catalytic asymmetric intramolecular allylic amination. Catalytic enantioselective synthesis of natural products is one of the most recent and elegant approaches



Scheme 33.

Table 9. Catalytic asymmetric intramolecular amination of olefins **146** and **147**





Entry No.	Olefin/ligand	Base	Solvent	Temperature (°C)	Time	Yield/ee (config.)
1	**146/149**	Cs_2CO_3	CH_2Cl_2	rt	4 h	90/39 (*R*)
2	**146/149**	Cs_2CO_3	DMF	rt	—	—
3	**146/149**	—	DMF	60	18 d	52/67 (*R*)
4	**146/150**	Cs_2CO_3	CH_2Cl_2	rt	4 d	83/53 (*S*)
5	**146/150**	—	DMF	60	18 h	82/23 (*R*)
6	**146/151**	Cs_2CO_3	CH_2Cl_2	rt	4 d	76/24 (*R*)
7	**146/151**	Cs_2CO_3	DMF	60	24 d	51/32 (*R*)
8	**146/152**	Cs_2CO_3	CH_2Cl_2	rt	3 d	58/12 (*R*)
9	**146/152**	—	DMF	60	13 d	42/23 (*R*)
10	**147/149**	Cs_2CO_3	CH_2Cl_2	rt	21 h	92/75 (*R*)
11	**147/149**	Cs_2CO_3	CH_2Cl_2	0	5 d	89/40 (*R*)
12	**147/149**	K_2CO_3	CH_2Cl_2	rt	12 d	89/88 (*R*)
13	**147/149**	Na_2CO_3	CH_2Cl_2	rt	23 d	49/88 (*R*)
14	**147/149**	Li_2CO_3	CH_2Cl_2	rt	—	—
15	**147/149**	—	DMF	60	23 d	58/82 (*R*)
16	**147/149**	—	DMF	60	3 h	76/79 (*R*)
17	**147/149**	—	DMF	100	3 h	78/77 (*R*)
18	**147/151**	Cs_2CO_3	CH_2Cl_2	rt	36 d	63/33 (*S*)

to the acquisition of natural products in chiral form and one of the most important innovations in organic synthesis. Almost all of the enantioselective syntheses of carnegine described above relied on diastereoselective reactions for the introduction of chirality at *C*1 and this implied the use of stoichiometric amounts of the chiral source. Furthermore, the asymmetric reduction of 1-alkylidene tetrahydroisoquinolines or the alkylation of imines, among them the 3,4-dihydroisoquinolines arising from Bischler–Napieralski cyclization demonstrated not to be efficient approaches for the elaboration of carnegine, since only moderate optical yields of the natural product were realized.

The use of transition metal complexes as catalysts for organic transformations is currently a subject of intense activity. Among the reasons to explain this interest are the possibility, offered by organometalic complexes, to carry out transformations which are difficult or not possible through the methods of 'classical' organic chemistry and the ability to control the selectivities associated with the transformation, that is, the distribution of products, through the use of appropriate ligands.

Very recently, however, Katsuki et al. disclosed a new palladium-catalyzed asymmetric intramolecular allylic amination, potentially very useful for the elaboration of various 1-substituted tetrahydroisoquinolines. Their strategy was explained in the form of a new total synthesis of carnegine.

The enantioselective synthesis of *R*-carnegine was employed in order to better evaluate the scope and limitations of the synthetic strategy. To that end, the known phenethylamine **22b** was protected as its trifluoroacetamide derivative under conventional conditions and then nuclearly iodinated furnishing **143** in 66% overall yield, with the iodic acid-iodine reagent.

Next, quantitative propargylation of **143** under palladium catalysis provided acetylene derivative **144**, which was partially and quantitatively reduced to *Z*-olefin **145** with the assistance of a nickel catalyst. Acetylation and pivaloylation of **145** afforded good yields of the corresponding esters **146** and **147**, as shown in Scheme 33.[124]

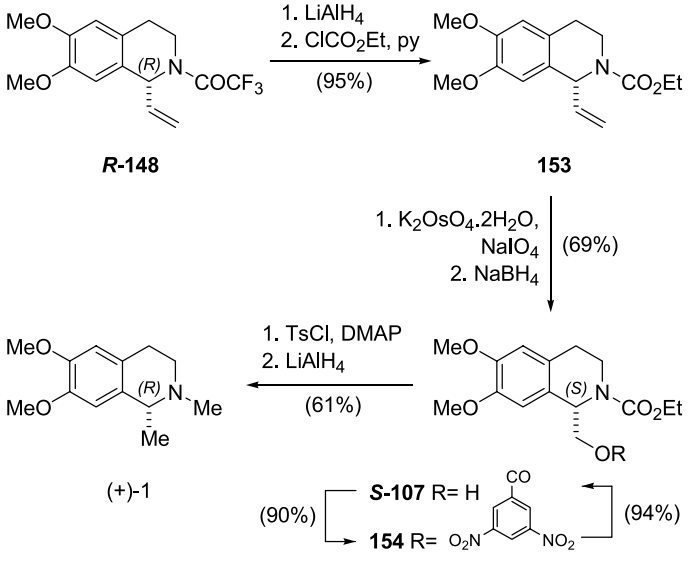
As depicted in Table 9, optimization experiments carried out towards the elaboration of tetrahydroisoquinoline **148** were run in different solvents with both esters, in the absence of base or employing alkaline carbonates with the aid of 1.5 mol% of $Pd_2(dba)_3.CHCl_3$ as palladium source and 3 mol% of ligands **149–152**.

It was observed that the bulkier ester **147** gave better enantiomeric excesses of product than its congener **146**, the most convenient conditions (89% yield, ee=88%) being achieved when potassium carbonate was employed as base, in the presence of pyridine derivative **149** as chiral ligand. On the other hand, chiral oxazoline **152** offered unexpectedly poor chemical and optical yields of product and BINAP derivatives **150** and **151** performed as poor ligands and exhibited inversion of the sense of asymmetric induction, depending on the reaction conditions (entries 4–7 and 18).

Culmination of the synthesis was carried out as depicted in Scheme 34, by changing the trifluoracetamide group of **148** into an ethyl carbamate (**153**) and producing the loss of the extra carbon atom by oxidative fision of the vinyl group employing the potassium osmate-sodium periodate reagent system, followed by a reductive step to calycotomine derivative *S*-**107**. Transformation of the *S*-**107** into the 3,5-dinitrobenzoate, followed by fractional crystallization increased the ee of the product to 98%, yielding back *S*-**107** upon basic alcoholysis (EtOH, K_2CO_3). Finally, conversion of the latter into the corresponding *para*-toluenesulfonate followed by lithium aluminum hydride reduction gave (+)-carnegine.[110b]

5. Conclusions

The various syntheses of carnegine published during the last thirty years are the result of investigations carried out by



Scheme 34.

different synthetic organic chemists around the world, and their steady efforts to devise novel and ingenious alternative solutions to this simple but important synthetic target.

The observed results in the synthesis of carnegine have accompanied the remarkable progress experienced by synthetic organic chemistry during the last 25 years, showing the evolution of reactions, reagents and synthetic strategies, from furnishing the product in low yields or in racemic form into elegant transformations which provide carnegine or related compounds in good chemical and optical yields.

While diastereoselective cyclization of vinyl sulfoxides and asymmetric Pictet–Spengler reactions appeared to be very promising strategies in the beginnings of the enantioselective synthesis of 1-substituted tetrahydroisoquinolines, moderate diastereoselectivities and the need of chromatographic separation of diastereomers remain as practical limitations associated with these type of strategies. On the other hand, the comparatively new catalytic enantioselective routes to the natural product rank among the major achievements in the synthesis of carnegine, being these results a consequence of the outstanding developments in catalysis which took place during the last couple of decades.

A significant group of the rosary of efficient synthetic procedures which have been explored and devised to accomplish some of the many syntheses of carnegine have already found important applications in the conquering of other interesting targets, including complex natural products, and providing a better understanding of our world. Not less important, they also constitute a fundamental part of a developing body of new and more sophisticated synthetic strategies or new synthetic tools, useful for accessing more demanding synthetic targets.

The continuous research and discovery of more practical and powerful catalysts, ligands, and other reagents, displaying more synthetic power and versatility are still formidable challenges for the synthetic organic chemists' community and therefore these are currently highly active areas of research. Consequently, it is expected that new, concise and more efficient diastereo- and enantioselective syntheses of carnegine will be conceived and carried out in the near future.

Acknowledgements

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