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A brief review of Cherylline synthesis

Stanimir P Manolov a, Stoyanka N Atanasova a, Manjunath Ghate b & Iliyan I Ivanov a*

aDepartment of Organic Chemistry, University of Plovdiv, 24 Tzar Assen str., 4000 Plovdiv, Bulgaria
bDepartment of Pharmaceutical Chemistry, Institute of Pharmacy, Nirma University, Sarkhej-Gandhinagar Highway, Ahmedabad 382 481, India
E-mail: ivanov@uni-plovdiv.bg

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1,2,3,4-Tetrahydroisoquinolines are an important class of synthetic and natural compounds, which display a broad range of medicinal activities. The 1,2,3,4-tetrahydroisoquinoline system has attracted attention not only because of its biological activities, but also due to its presence as a basic framework in many naturally occurring products and drugs. Their skeletons are unique among the Amaryllidaceae alkaloids and they have long been alluring targets for synthetic chemists as witnessed by a number of articles dealing with biogenesis, isolation, characterization and synthesis. The alkaloid cherylline is an optically active naturally occurring, 4-phenyl-1,2,3,4-tetrahydroisoquinoline alkaloid, isolated from Crinum powelli, Amaryllidaceae plant. There are many ways for cherylline synthesis. In this short review is described the different methods for synthesis of the alkaloid cherylline.

Keywords: Amaryllidaceae alkaloids, Cherylline, Crinum, 4-aryl-1,2,3,4-tetrahydroisoquinolines, synthesis

Since antiquity several plants of the Amaryllidaceae family have been used in the treatment of illness related to cancer 1. The first recorded treatments specifically designed for cancerous conditions were prescribed by Hippocrates of Cos (ca. B.C. 460-370) (Ref 1). The “Father of medicine” and founder of the school of medicine bearing his name recommended application of narcissus oil (most likely from Narcissus poeticus L.) for the treatment of tumors of the uterus. Topical treatment prepared from Narcissus poeticus L. and Narcissus pseudonarcissus were prescribed by Gaius Plinius Secundus 2. Physician and prominent gynaecologist Soranos of Ephesus, who taught in Rome and Alexandria under Trajan and Hadrian, continued Hippocrates’ treatment for uterine cancer 3. In fact, historical use of plants from over 30 members of the Amaryllidaceae family in remedies for cancer is reported well into the 19th and 20th century, at which point individual congeners began to be isolated and tested for anti-tumor activity.

The Tropics are rich of Amaryllidaceae alkaloids as well as this class are widespread in South-Africa and Andean region. The Mediterranean area and some regions of Asia are also rich in Amaryllidaceae. The Amaryllidaceae alkaloids represent a large (so far over 300 alkaloids have been isolated) and still expanding group of biogenetically related isoquinoline alkaloids that are found exclusively in plants belonging to this family. In spite of their great variety of pharmacological and/or biological properties, only galanthamine is used therapeutically. The large variety of Amaryllidaceae alkaloids can be classified mainly into nine skeleton types 4, as shown in Figure 1.

These group of alkaloids are also prepared from two combined tyrosine derivatives. The reaction proceeds with loss of one carbon atom, to give a benzylphenylethylamine precursor – Norbelladine 9 (Figure 2). From this precursor, nine major skeletal groups can be prepared 4.

After oxidation of a Norbelladine-type precursor at C-7 followed by cyclisation at C-2′ 1-phenyltetrahydroisoquinolines could be afford. The same reaction proceeded to Cryptostyline I, which after oxidation at the benzyl position C-9 and cyclisation at C-6 afforded the 4-aryltetrahydroisoquinolines, as cherylline derivatives. Similar oxidation at position 2 and 2′ gives Nivalidine’s framework, but this may be is an artifact, derived from Galanthamine 5 (Figure 3).

1,2,3,4-Tetrahydroisoquinolines are a very important class of synthetic and natural compounds, which display a broad range of medicinal activities 6 such as antitumor 8, antibacterial 9, antiplasmodial 10, and β-adrenergic receptor antagonism 11. Tetrahydroisoquinoline-arylated at C-4 show prominent pharmaceutical activities.
Cherylline 1 is a naturally occurring 4-aryl-1,2,3,4-tetrahydroisoquinoline alkaloid which has one stereocenter in the molecule. That makes cherylline optically active. The alkaloid is isolated from *Crinum Powellii, Amaryllidaceae* plant. Cherylline occurs as the (-) or (S) enantiomer in nature (Figure 4). *Latifine* 3, *nomifensine* 4 and *dichlofensine* 5 are other representatives from the same 4-aryl-tetrahydroisoquinoline group. The required alkaloids are of interest because of their pharmacological activities. For instance, *nomifensine* 4 and *dichlofensine* 5 (Ref 15) show central nervous system activity and inhibit serotonin and dopamine uptake mechanisms (Figure 5).

Cherylline has a unique structure among Amaryllidaceae alkaloids. It’s biogenesis follows similar pathway to that operative in the creation of different...
alkaloids of this class, i.e. cyclisation preceded by oxidation of proper Norbelladine's derivatives\textsuperscript{16}.

**Methods for synthesis**

The cherylline skeleton synthesis can be achieved from the nature of the bond formed in the isoquinoline ring closure (Figure 6).

The bond C-C ‘a’ was gained by a Bischler-Napieralski reaction of $N$-formyl derivatives of phenethylamines\textsuperscript{17–19} or by cyclization of $\beta$-phenethylisocyanates\textsuperscript{20,21}.

The bond C-C ‘b’ was mostly formed by intramolecular Horner reaction\textsuperscript{22}.

The bond C-C ‘c’ was achieved by a variety of methods, such as photo-induced cyclisation of orthohalogenated $N$-acylbenzylamines\textsuperscript{23}, Friedel-Crafts type reactions\textsuperscript{24–30}, intramolecular coupling of quinonoid intermediates\textsuperscript{16,31–33} or palladium-catalyzed intramolecular cyclization of amide-enolates\textsuperscript{34}.

The C-N bonds ‘e’ or ‘d’ were formed mostly by $N$-alkylation\textsuperscript{13,35}.
C-C bond ‘a’ formation:

**Cyclization via Bischler-Napieralski reaction**

Brossi and Teitel reported the first racemic Cherylline synthesis. They use reaction sequences involving preparation of phenethylamine derivative and diphenolic intermediate by partial ether cleavage. Authors obtained benzophenone produced by condensation of phenol with veratric acid, which was transformed to the benzyloxy derivative. The next step involves reduction with sodium borohydride with subsequent treatment with thionyl chloride and fusion with cuprous cyanide. The catalytic hydrogenation using Raney cobalt gave phenethylamine via a number of intermediates. Monophenolic dihydroisoquinoline is yielded via Bischler-Napieralski cyclization of the N-formyl derivative, followed by debenzylation (Scheme I).

Thereafter, treatment of with HBr under controlled reaction conditions gave diphenol. Racemic cherylline is afforded after reduction with sodium borohydride of the quaternary salt, obtained from and methyl iodide.

The first total synthesis of cherylline and its unnatural isomer was reported from the same authors during March 1970. The diastereomeric salt was obtained after resolution of the (+)-phenethylamine with (-)-di-O-p-toluoyl-D-tartaric acid, the authors could obtain diastereomeric salt.

Authors converted both to crystalline hydro bromides which after reaction with methyl formate gave (+)-N-formyl derivative. Bischler-Napieralski cyclisation followed by debenzylation with HCl gave (-)-6,7-dimethoxydihydroisoquinoline. The next step involved selective O-demethylation of this using HBr for 6 hours at 100°C to obtain (-)-6-methoxy-7-hydroxy derivative which on treatment with methyl iodide gave the corresponding N-methyl(-)-quaternary salt. (-)-Cherylline was obtained after reduction with sodium borohydride by inversion of the Cotton effects. Using the same reaction sequences and (+)-phenethylamine as starting material afforded the unnatural isomer of cherylline to the authors.

![Scheme I](image1.png)

![Scheme II](image2.png)
Cyclization via Pictet-Spengler reaction

Kale et al. reported a synthesis of (+)-cherylline dimethyl ether 30. Michael-type addition, radical azidation of an aldehyde, Curtius rearrangement, and reduction of an isocyanate intermediate followed by Pictet-Spengler cyclisation are the key steps involved.

Veratrole was subjected to a Michael addition reaction with p-methoxycinnamitriile 25 in the presence of trifluoroacetic acid to give 3-(3,4-dimethoxyphenyl)-3-(4-methoxyphenyl)propanenitrile 26. Using DIBAL-H the authors successfully reduced a nitrile group in compound 26 to 3,4-dimethoxyphenyl-3-(4-methoxyphenyl)propanal 27. Radical azidation of aldehyde 27 with iodine azide generated in situ, gave an acyl azide and following Curtius rearrangement gave isocyanate 28. Direct reduction of the isocyanate 28 using lithium aluminium hydride in tetrahydrofuran gave N-methylamine 29. (+)-Cherylline dimethyl ether 30 could be obtained after Pictet–Spengler reaction of amine 29 with formaldehyde in acetic acid (Scheme III).

Kumar et al. reported a short way for the synthesis of (+)-latifine and (+)-cherylline dimethyl ethers. They use as key steps, Michael addition of p-methoxyphenyl magnesium bromide to the (E)-1,2-dimethoxy-3-(2-nitrovinyl)benzene, followed by reduction of the nitro intermediate obtained using the Pictet-Spengler cyclization and reductive N-methylation.

1, 2-Dimethoxy-4-(1-(4-methoxyphenyl)-2-nitroethyl)benzene 33 was obtained by the reaction of anisole with (E)-1,2-dimethoxy-4-(2-nitrovinyl)benzene 32 in presence of trifluoroacetic acid. After the subsequent reduction of the nitro group with iron under acidic conditions, they obtained 2-(3,4-dimethoxyphenyl)-2-(4-methoxyphenyl)ethanamine 34 (Scheme IV). Upon the Pictet-Spengler reaction and reductive N-methylation, the amine 34 could be transformed to (+)-cherylline dimethyl ether 30.

Kumar et al. reported synthesis of (+)-cherylline and latifine dimethyl ether. For constructing cherylline dimethyl ether 30 skeleton, the authors employed Michael addition reaction of veratrole to p-methoxynitrostyrene 35 in trifluoroacetic acid to give
Here the authors have again applied the procedure for reduction of nitro group with iron under acidic conditions at room temperature for obtaining 2-(3,4-dimethoxyphenyl)-2-(4-methoxyphenyl)ethylcarbamate intermediate 38, which on reduction by lithium aluminium hydride gave N-methyl amine 39 (Scheme V). After Pictet-Spengler reaction on amine 39 the authors could obtain (±)-cherylline dimethyl ether 30.

Alternative synthesis for obtaining of (±)-cherylline dimethyl ether was reported from Kurangi and co-workers. The synthetic approach involves only a few steps. The steps involved are acid-catalyzed Michael addition of veratrole to p-methoxycinnamic acid, Curtius rearrangement, reduction of the isocyanate intermediate and the final Pictet-Spangler cyclisation 40 (Scheme VI).

Vicario et al. reported a procedure for asymmetric synthesis of 4-aryl-1,2,3,4-tetrahydroisoquinoline 41. Recently the synthetic stereochemistry of isoquinoline alkaloids has been a field of increasing interest in the field of synthetic organic chemistry. The chiral non-racemic 4-substituted tetrahydroisoquinoline derivatives are significant, partly due to their biological properties and as naturally occurring alkaloids 42-48. They have developed a suitable and general enantioselective synthetic approach for obtaining 4-alkyl-1,2,3,4-tetrahydroisoquinolines using chiral arylketamine precursors as starting materials (Scheme VII), prepared using an asymmetric metalloenamine alkylation protocol starting from an imine derived from homoveratraldehyde and (R)-(−)-phenylglycinol methyl ether. This method is very interesting from a synthetic point of view taking into account the possibility of introducing any kind of alkyl chain at 4-position of the isoquinoline skeleton. The method can be used for synthesis of a wide range of naturally and unnaturally occurring isoquinoline derivatives.

Ruchirawat et al. reported a short route for synthesis of 4-aryltetrahydroisoquinolines using addition of Grignard reagents to nitro styrene derivatives 18 as the key step. Their approach begins with conjugate addition of the Grignard reagents to the appropriate nitro styrene derivative.
They have reported that by careful control of the exothermic reaction, 1,4-addition of Grignard reagent to nitrostyrene can occur smoothly. Authors have generated nitro compound 51 from reaction of nitrostyrene 50 with the Grignard reagent generated from 4-bromo-\(O\)-benzylphenol. The amine 52 could be obtained after the reduction of compound 51 with LAH. Reaction of the amine with formaldehyde and formic acid leads to the isoquinoline compound 53. For the final step, the authors have removed the benzyl protecting groups of \((\pm)-O,O\)-dibenzylcherylline via hydrogenolysis using 10% palladium on charcoal (Scheme VIII). The obtained yield of \((\pm)\)-cherylline is over 90%.

A novel method of building 4-aryl-1,2,3,4-tetrahydroisoquinolines is achieved via ether rearrangement methodology. The key steps used by Pailla and co-workers to achieve \((\pm)\)-cherylline and its monomethyl and dimethyl ethers are acid-catalyzed ether rearrangement and Pictet-Spengler cyclisation (Scheme IX).

**Synthesis of cherylline via isocyanate cyclization**

In 1988 Kataoka and co-workers reported synthesis of the alkaloids \((\pm)\)-cherylline and \((\pm)\)-latifine 12 by application of an isocyanate cyclisation reaction according to Tsuda’s two step procedure for constructing...
1,2,3,4-tetrahydroisoquinolinol-1-one and a regioselective cleavage reaction of aromatic methyl ethers with dimethyl sulphide in methanesulfonic acid.

Treatment of veratraldehyde 58 with dimethyl malonate in the presence of a catalytic amount of benzoic acid and piperidine with removal of water (Dean-Stark) gave the benzylidemalonalonate 59. Grignard 1,4-addition of \( p \)-methoxyphenyl magnesium bromide to the malonate 59 was accomplished by addition of the malonate to a solution of \( p \)-methoxyphenyl magnesium bromide and a small amount of copper iodide in ether, affording the diphylmethylmalonate 60. Alkaline hydrolysis of 60 followed by decarboxylation gave the acid 61. The requisite material 61 thus obtained for cyclisation was subjected to Tsuda’s two-step procedure, the first key point in their synthesis. The acid chloride derived from the acid 61 by treatment with oxalyl chloride was transformed into the acid azide by reaction with sodium azide. Heating (Curtius rearrangement) of the acid azide gave the corresponding isocyanate which was, without isolation, heated with phosphorus oxychloride at 90-95°C. After removal of the reagent, the resulting residue was treated with stannic chloride in methylene chloride, furnishing the tetrahydroisoquinoline 62. In this case, the pre-treatment of the isocyanate with phosphorus oxychloride was indispensable; otherwise the isoquinolone 62. Methylation of 62 gave the \( N \)-methyl-lactam 63, which was subjected to the second key reaction, a regioselective aromatic methoxyl group cleavage. Treatment of the \( N \)-methyl-lactam 63 with dimethyl sulphide in methanesulfonic acid at 60-65°C gave the phenolic lactam 64 (Scheme X) as a result of regioselective cleavage of methoxyl groups except for the methoxyl group at the \( para \)-position to carbonyl lactam. Confirmation of the positions of the phenolic hydroxyl groups was ultimately provided by the synthesis of (+)-cherylline.

### C-C bond “b” formation

**Synthesis of cherylline via Horner-Wadsworth-Emmons reaction**

Couture, A. et al., reported a new approach for synthesis of cherylline, using bond “b” formation. The strategy of the authors depended on the good nucleophilicity of phosphorylated \( \alpha \)-aminocarbanions and their sufficiency to generate inter and intramolecularly the N-C=C unit in a variety of open chain or annulated adducts. For constructing the \( o \)-aryldimethoxybenzoic acid derivative 65 (Scheme XI), dimethoxyphthalic anhydride, readily accessible by oxidation of \( m \)-meconine, was opened by Friedel-Crafts reaction with methoxybenzene.

Afterwards, the same authors coupled the acid 65 with \( N \)-diphenylphosphorylmethyl-\( N \)-methylamine. The authors report that the preliminary attempts to obtain the phosphorylated carboxamide 66 using Schotten-Baumann reaction between \( N \)-diphenylphosphorylmethyl-\( N \)-methylamine and carboxylic acid chloride deriving from 65 were unrewarding because of the difficulty associated with the acid chloride function.

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**Scheme X**

1) Dimethyl malonate, \( C_2H_5COOH \), \((CH_2)_2NH\); 2) \( p \)-OMe-\( C_6H_5MgBr\), Cul, \( CH_3COOH \); 3) 160-200°C, \( Na_2CO_3 \);

4) \((COCl)_2\), \( C_6H_6 \), \( CH_2COCH_3 \), \( NaN_3 \), \( SnCl_4 \); 5) \( NaH \), \( C_6H_6 \), reflux, MeI, \( CH_3COOH \); 6) DMS, MSA, 50°C;

7) \( LiAlH_4 \), THF, reflux, \( NH_2Cl \).
Treatment of acid 65 with different chlorinating agents led invariably to the 3-chloro-3-arylphthalide derivative. The choice of the diphenylphosphoryl function in the aminophosphorylated counterpart was dictated by the properties of diphenylphosphine oxides which are incontestably superior in many respects to phosphonates and phosphonium salts.

Two different conversions of compound 67 are reported. Preliminary reduction with diborane of the two carbonyl groups of 67 and following reduction of the enamine group of 1,2-dihydroisoquinoline under acidic conditions provides Cherylline dimethylether 30. Moreover, the catalytic hydrogenation of the diarylenamide C=C bond of 67 leads to N-methyl-3,4-dihydro-6,7-dimethoxy-4-(4-methoxyphenyl)-1-(2H)-isoquinoline which could be easily converted into (±)-cherylline employing the cleavage of aryl ether linkages, followed by subsequent reduction of the carboxamide group.

Synthesis of cherylline via lithiation of o-benzyl benzamides and cyclocondensation with DMF

Narasimhan and Patil describe a general synthesis of N-methyl-4-aryl-1,2,3,4-tetrahydroisoquinolines, which is an agonist for the dopamine receptor and methyl ether of cherylline 30, a rare phenolic isoquinoline alkaloid. They start with 3-aryl phthalides 68. On hydrogenolysis, the phthalides provided the ortho-benzyl benzoic acids. The N-methyl benzamides 69 of the acids, on lithiation with BuLi followed by treatment with dimethylformamide (DMF), gave the N-methyl-3-hydroxy-1,2,3,4-tetrahydroisoquinoline 70 (Scheme XII), which on dehydration and reduction or direct reduction furnished the target compounds 30.

Synthesis of cherylline via palladium-catalyzed reactions

Honda, Namiki and Satoh reported the synthesis of cherylline and latifine via palladium-catalyzed intramolecular δ-lactam formation of aryl halides and amide-enolates. The palladium-catalyzed coupling reaction of aryl or vinyl halides and enolates is an encouraging way for obtaining the carbon skeleton of polycyclic natural compounds. A number of modifications of this strategy were evolved to prove their versatility and utility in the synthesis of structurally interesting organic compounds. The lactam rings formation has already been reported by Hartwig and co-workers by this methodology to obtain the desired products (Figure 7).

Honda et al. concluded that the weak acidity of the methyl proton of an acetamide group to the instability of the generated enolate due to six-membered lactam formation.

The authors obtained amide 79 with a relatively strong acidic methylene group (Scheme XIII). Alcohol

![Scheme XI](image1)

![Scheme XII](image2)
75 was converted into amine using modified Cossy’s protocol. Amide derivative was obtained from the required amine with $p$-benzyloxyphenacyl chloride using the Schotten-Baumann reaction. Afterwards, the obtained amide was alkylated with methyl iodide to provide the corresponding amide 79 as a mixture of rotamers of the amide groups. A six-membered lactam 80 was synthesized in high yield in the next step with Pd-catalyzed intramolecular coupling reaction of 79 on refluxing dioxane.

The δ-lactam 80 was transformed into the natural product cherylline after reduction with borane-dimethyl sulfide (BMS) complex passing through di-0-benzyloxycherylline, which after hydrogenolysis over 10% palladium on carbon was converted to cherylline 10.

**C-C bond “c” formation**

**Synthesis via quinone methide intermediate**

Many compounds with quinone methide structure have been isolated. They have a vast array of applications as fungal metabolites, wood pigments, and insect pigments. Quinone methides have been implicated as intermediates in oxidative phosphorylation and also in the biosynthesis of chromans, lignin, and alkaloids.

Quinone methides are important compounds in biosynthesis and possess antitumor activity. Synthetic routes for obtaining and application of their derivatives are limited because intermediates $o$-quinone methides react as hetero-dienes in Diels-Alder reactions.

Besides para-derivatives are transition intermediates for the picropodophylline synthesis.

Raju et al. reported a novel C-C bond formation for the synthesis of 4-phenyl-1,2,3,4-tetrahydroisquinolines using *in situ* generated $p$-quinone methides.

The authors could obtain $N$-(4-benzyloxy-3,5-dimethylphenethyl)-$N$-tosyl-3,4-dimethoxybenzylamine 82 after the treatment of the substituted $N$-tosylated benzylamine 81 with NaH (Ref 61) followed by the addition of phenethyl bromide (Scheme XIV). After debenzylation of compound 82 with H$_2$/Pd-C the authors obtained $N$-(3,5-dimethyl-4-hydroxyphenet-
hyl)-N-tosyl-3,4-dimethoxybenzylamine, which, on oxidation with Ag₂O gave quinone methide 83 as a yellow viscous liquid. Lastly, 83 in dry DCM and ZnCl₂ with stirring at room temperature gave 4-(3,5-dimethyl-4-hydroxyphenyl)-N-tosyl-6,7-dimethoxy-1,2,3, 4-tetrahydroisoquinoline 84.

Synthesis of 4-aryl-1,2,3,4-tetrahydroisoquinolines and their derivatives of the alkaloid cherylline group via in situ generated p-quinone methides is also reported. 2,6-Disubstitution imparts enhancement of stability to a quinone methide. The nucleophile which is stable under the conditions used to generate the quinone methide, yet reactive enough to attack the carbon terminus is required after cyclisation. N-(3,5-Dimethyl-4-hydroxyphenethyl)-N-tosyl-3, 4-dimethoxybenzylamine is required to obtain the quinone methide and followed by cyclization to give the tetrahydroisoquinolines 84 (Scheme XIV).

Synthesis of (±)-cherylline via an aziridinium intermediate was reported by Kametani and co-workers in 1982 (Ref 34). In their previous investigations they reported synthesis of the 2-benzylisoquinoline alkaloids, sedaverine and corgoine, via a ring-opening reaction of quaternary aziridinium salts as a key step. The high reactivity of the aziridinium salts in this step arises from the release of the strain energy inherent in a small ring. In continuation of their work on the synthesis of various kinds of isoquinoline alkaloids using a quaternary aziridinium salt as a reactive intermediate, they have investigated the synthesis of 4-phenyl-1,2,3,4-tetrahydroisoquinoline alkaloid, (±)-cherylline.

A possible biosynthetic pathway for cherylline involves a cyclisation of a quinone methide, as shown (Scheme XV).

Their design for the synthesis of cherylline was based on facile ring opening of a quaternary aziridinium salt 85 to give a carbon-extended amine and cyclisation of a quinone methide 86, generated in situ during the above ring opening reaction, as shown in Scheme XVI.

David J. Hart and co-workers have reported the synthesis and chemistry for total synthesis of the Amaryllidaceae alkaloid cherylline using p-quinone methide ketals obtained from p-quinone monoketals and a-trimethylsilylamides or phosphoranes.

The synthesis of the alkaloid (±)-cherylline is summarized in Scheme XVII. The necessary α-silyl acetamide 89 was obtained by the treatment of the known benzylic amine with trimethylsilylketene. Thereafter, the amide 89 was treated with LDA and ketal 90. The lactam 92 was obtained after treatment of p-quinone methide ketal 91 with boron trifluoride etherate for several hours at room temperature. Hydrogenolysis of the benzyl protecting group afforded the
crystalline phenolic lactam 93. Tetrahydroisoquinoline 94 was obtained after reduction of lactam 93 with LiAlH₄. It was expected that delocalization of charge onto the ortho positions in the phenolate derived from 94 would intercept nucleophilic cleavage of the aryl ether linkage at C-6 relative to that at C-4'. Treatment of 94 with sodium ethyl mercaptide in DMF gave (±)-cherylline contaminated with 5-10% of the isomeric diphenol 95.

Kametani and co-workers reported total synthesis of (±)-cherylline and corgoine via quinonoid intermediates. The reaction for the synthesis of (±)-cherylline included acid catalysed cyclisation of N-(4′-benzyloxy-β-methoxyphenethyl)-3-benzyloxy-4-methoxy-N-methylbenzylamine 99 by intramolecular coupling of quinonoid intermediate 100 (Ref 32, Scheme XVIII).

4-Benzyloxy-α,β-dibromoethylbenzene 97, obtained by addition of bromine to 4-benzyloxy styrene 96, was transformed to 4-benzyloxy-β-methoxyphenethyl bromide 98. Fusion of the bromide 98 with 3-benzyloxy-4-methoxy-N-methylbenzylamine yielded the tertiary amine 99 (Scheme XIX) whose cyclisation followed by debenzylation gave (±)-cherylline.

Schwartz and Scott in 1971 reported synthesis of cherylline via cyclisation with previous oxidation of a suitable derivative of Norbelladine. The authors described total synthesis of the alkaloid cherylline via base-catalyzed cyclization of p-hydroxy-α-[(3-hydroxy-4-methoxybenzyl)methylamino]-methyl]benzyl alcohol 102, an intermediate of possible biogenetic importance.

Direct two-electron oxidation of O,N-dimethylNorbelladine 101 yielded a quinone methide intermediate which afterwards cyclised to cherylline. Alternatively, hydroxylation of 101 could give hydroxyl-O,N-dimethyl Norbelladine 102, which upon dehydration gave the same intermediate (Scheme XX).

Acid-catalyzed cyclizations

Hara and co-workers reported a facile synthesis of 4-phenyl-1,2,3,4-tetrahydroisoquinolines. The authors consider the key intermediate, N-benzyl-β-hydroxyphenethyamine derivatives, chosen by both Schwartz and Kametani.

They reported a new methodology for the formation of 104 using S₉₂ reaction of amines 105 with styrene oxides and an efficient synthesis of (±)-cherylline.

p-Benzylxystrene oxide 106 was quantitatively prepared from p-benzyloxybenzaldehyde by use of...
Kutsuma’s method. The reaction between 105 and 106 was attempted to give non-regioselectively, a mixture of the p-benzylxophenethylamine 104 and dibenzylamine 107 in the ratio of 1:1 (Scheme XXI). The fission between the α-carbon and the oxygen atoms was facilitated by an electron donating group at the para position.

To overcome the difficulty a by-pass was sought. Thus, treatment of the epoxide 106 with BF$_3$-Et$_2$O in MeOH at RT afforded solely the β-metoxyphenethyl alcohol 108 in excellent yield. Usual mesylation of 108 gave the mesylate 109 (Scheme XXII) quantitatively.

The reaction of 109 with the benzylmethylamine 110 proceeded nicely. Namely, heating of 110 and 109 together with Hüning’s base in a sealed tube at 120°C for 24 h gave the expected β-methoxyphenethylamine 111. Finally, refluxing of 111 with conc. HCl-benzene for 5 h gave (±)-cherylline (Scheme XXIII).

A facile and general synthesis of 4-aryl-1,2,3,4-tetrahydrossoquinolines by employment of styrene oxide as a crucial synthon could be established.

Cuevas and Snieckus reported a synthetic route for the synthesis of isoquinolines using α′-silylated benzamides which were converted into amide carbinols 114 and 115. These upon reduction with diborane and acid-catalyzed cyclization gave 116 and the dimethyl ether of the alkaloid cherylline 30 (Scheme XXIV).  

**Cyclization of ortho-halogenated n-acylbenzylamines**

In 1981 Kessar and co-workers reported a formal synthesis of (±)-cherylline via cyclization of ortho-halogenated N-acylbenzylamines. ortho-Halogenated N-alkyl-N-acylbenzylamines can be cyclised to
dihydroisoquinolines by reaction with KNH$_2$ in liquid NH$_3$ or lithium di-isopropylamide in tetrahydrofuran under photolytic and thermal conditions. This procedure has been employed to synthesize (±)-cherylline.

They have investigated the cyclisation of α-carbanions derived from ortho-halogenated N-alkyl-N-acylbenzyl and phenethyl amines as a route to heterocyclic systems, using different conditions: (i) KNH$_2$, in liq. NH$_3$, for 2 h; (ii) KNH$_2$, in liq. NH$_3$, under irradiation for 8 min; (iii) lithium di-isopropyl-amide in tetrahydrofuran under irradiation for 1.5 h. Remarkably, when these authors used LDA as a base, the cyclization proceeded smoothly under photolytic (iii) as well as thermal (iv) conditions. Irradiation of 117 in THF containing LDA (iii) gave the corresponding dihydroisoquinolone 118. It converted into (±)-cherylline (Scheme XXV).

Synthesis via hydroamination of enol carbamates

Jose Crecente-Campo reported an efficient and simple procedure for the synthesis of 4-phenyl-1,2,3,4-tetrahydroisoquinolones and 1-aryl-2,3,4,5-tetrahydro-3-benzoazepines. The approach uses easily available starting materials and requires just three steps. The hydroamination of an enol carbamate is the key step. They applied this general and direct method to the total synthesis of the natural alkaloid cherylline and to the biologically active 3-benzoazepines (Scheme XXVI).

Synthesis via regiocontrolled Polonovski type reaction

In 1984 Nomoto and co-workers reported a synthesis of (-)-cherylline 10 via a regiocontrolled Polonoski-type reaction as the key step. They have applied their previously developed ring transformation technique by using tetrahydro-6,12-methanodibenz[c.f]azocianes in the preparation of this natural alkaloid.

![Scheme XXIV](image-url)

![Scheme XXV](image-url)

![Scheme XXVI](image-url)
Nomoto reported a facile and efficient synthesis of 10 starting from 3,9-dibenzylxoy-2-methoxytetrahydro-6,12-methanodibenz[c]azocine 123 via a regiocontrolled Polonovski-type reaction as the key step.

Compound 123, prepared by the acid-catalysed double-cyclisation of the corresponding dibenzylamino-acetaldehyde dimethyl acetal 122, was resolved using 

\[ O,O'-dibenzoyl-L-(+)-tartaric acid \]

into (12S)-(-)-123 i.e. 124. Thus resolved, optically pure 124 under oxidation with \( m \)-chloroperbenzoic acid gave quantitatively the \( N \)-oxide which was subjected to the Polonovski-type reactions to afford the tetrahydro-isoquinoline aldehyde 126. The formyl group of 126 was removed with \( \text{RhCl(Ph}_3\text{P)}_3 \) in refluxing toluene to furnish 127 which was subsequently reduced with \( \text{LiAlH}_4 \) in tetrahydrofuran to \( N \)-methyl-1,2,3,4-tetrahydro derivative. Debenzylation with conc. HC\(_1\) in EtOH afforded (-)-cherylline 10 (Scheme XXVII).

Synthesis via oxazoline intermediate

Seijas and co-workers reported a strategy for the synthesis of 4-phenyl-1,2,3,4-tetrahydroisoquinolines. The main steps are nucleophilic substitution of the Grignard reagent in an ortho-methoxyphenyloxazoline and a 1,6-conjugate addition of a lithium amide to \( o \)-styrylphenyloxazoline.

They have found out a simple and powerful synthetic route to isoquinoline alkaloids. The approach is based on “c” and “e” bonds formation (Figure 6) mediated by nucleophilic additions - both of which rely on oxazoline chemistry - affording a simple and easy formation of “d” bond as the final step (Scheme XXVIII).

Synthesis of cherylline via Pummerer type cyclization

The synthesis of 4-phenyl-2-methyl-1,2,3,4-tetrahydroisoquinolines via Pummerer-type cyclization was described by Toda et al. in the year 2000.

The authors obtained the amide 135 after acylation of amine with acid chloride. The mixture of \( E/Z \) isomers with rotational isomerism of the amide group shows \( ^1H \) NMR spectra of 135. After an oxidation of sulfide 135 with sodium metaperiodate, a diastereomeric mixture of sulfoxides 136 is afforded. Thereafter, the solution of 136 was treated with TFAA for 10 min at room temperature, to afford 6,7-dimethoxy-2-methyl-4-phenyl-4-(phenylsulfanyl)-1,2,3,4-tetrahydroisoquinolin-3-one 138.

The authors noticed that Pummerer type cyclization depends very strongly on the solvent used in some cases. They carried out the reaction in several solvents and found that THF improved the cyclisation. These results shows that the cyclization of 136 proceeds under mild conditions. The proposed reaction intermediate 137, features the C=S bond in conjugation with the 2-aryl group. This is considered in the formation of intermediate 138, and, in turn, supports the intramolecular cyclisation reaction. The authors converted by conventional reductive steps 4-aryl-2-methyl-4-(phenylsulfanyl)-1,2,3,4-tetrahydroisoquinolin-3-ones 138 into 4-aryl-2-methyl-1,2,3,4-tetrahydroisoquinolines. Reductive elimination of the phenylsulfanyl group of 138 takes place on treatment with NaBH\(_4\)-NiCl\(_2\) in methanol-THF to give 2-methyl-4-phenyl-1,2,3,4-tetrahydroisoquinolin-3-one 139. Subsequent reduction of 139 with lithium aluminum hydride (LAH) furnished (±)-cherylline (Scheme XXIX).

C-N bond “d” formation

Synthesis of cherylline via intramolecular reductive amination

Stephane Lebrun and co-workers reported a synthesis of (+)-and (-)-cherylline. They devised a concise synthesis of compounds 10 and 11 which are enantiopure
antipodes of the alkaloid cherylline. The synthetic strategy relies upon the reduction of a diversely and polyprotected diarylamine bearing a chiral auxiliary. Separation of diastereopure intermediates, concomitant deprotections and intramolecular reductive amination complete the synthesis of the natural (S)-enantiomer and the unnatural (R)-configured antipode.

The authors report a synthetic approach that gives indiscriminate access to either (+) or (-)-cherylline and that involves for the first time, the formation of the carbon-carbon bond of the heterocyclic unit in the final step. Their synthetic route hinges upon the formation of the diastereomically pure diarylethylamines (1R,1′R)- and (1S,1′R)-140 obtained in the key step by reduction of the poly and diversely protected diarylenamine 141 equipped with a stereocontrolling appendage, i.e. the α-methylbenzylamine group (Scheme XXX).
When formulating this synthetic plan it was envisioned that the presence of this chiral auxiliary could significantly act on the level of diastereoselection at the tertiary carbon centre of \( 141 \) and consequently at the dibenzylic carbon centre embedded in the skeleton of the target natural product \( 10 \). Subsequent deprotection of \((1R,1′R)-\text{or} (1S,1′R)-140\) followed by regeneration of the hydroxyl phenolic functions on the environmentally different aromatic moieties and cyclization indeed should not affect the stereochemistry of the dibenzylic chiral centre and therefore should complete the synthesis of the target natural product in both pure enantiomeric forms.

The synthesis started with the assemblage of one of the major partners involved in the elaboration of \( 141 \), \textit{i.e.} the rather congested benzophenone derivative \( 142 \) (Scheme XXXI). Initially benzyl protected isovanillin \( 143 \) was regioselectively brominated to furnish the bromobenzaldehyde \( 144 \) which was converted into the acetal \( 145 \) in order to save the formyl functionality for subsequent manipulations. Bromine-lithium exchange was performed with \( t\)-BuLi at low temperature and quenching with \( 4\)-benzyloxybenzaldehyde delivered the unsymmetrically substituted dibenzyl alcohol. Oxidation under classical conditions furnished the desired diarylketone derivative \( 142 \) with a very satisfactory yield.

For the synthesis of the diarylenamine \( 141 \) equipped with the chiral auxiliary, the authors decided to adopt a synthetic method that has been mainly used for homologation of carbonyl compounds and for the generation of acyl anion equivalents. This method relies upon Horner reaction between the diarylketone \( 142 \) and the anion derived from the phosphorylated methylamine \( 148 \) bearing the stereocontrolling agent (Scheme XXXII). The mandatory chiral amine \( 148 \) was prepared beforehand by \( N\)-methylation of the secondary phosphorylated amine \( 147 \) obtained by treatment of the triazine \( 146 \) with diphenylphosphine oxide. With the rather unstable diarylenamine \( 141 \) in hand which anticipated that the bulky stereocontrolling agent, \textit{i.e.} the \( \alpha\)-methylbenzyl group, could influence the degree of asymmetric induction upon hydrogenation of the diarylmethylene unit namely through chirality transfer \textit{via} the transient species involved in the chemical process, \textit{i.e.} enammonium and immonium ions.

Rather disappointingly, only a modest diastereoselectivity was observed in this process by varying the nature of the reducing agent and the temperature. The best diastereoselection (major diastereoisomer \((1R,1′R)-149\)) were achieved with \( \text{NaBH}_3\text{CN} \) at \(-35^\circ\text{C}\).

Catalytic hydrogenation of diastereochemically pure \((1R,1′R)-140\) and \((1S,1′R)-140\) with \( \text{H}_2/\text{Pd-C} \) offered a triple advantage in effecting simultaneously the reduction of the carboxaldehyde group with concomitant removal of the chiral appendage and retrieval of the hydroxyl phenolic functions. This efficient process gave straightforward access to \((R)-150\) and \((S)-150\), direct candidates for the annulation reaction. The creation of the hetero-ring unit of the natural product could proceed uneventfully under acidic conditions to afford the target alkaloids \( 10 \) and \( 11 \).

**C-N bond “e” formation**

**Synthesis of cherylline via Horner-Wadsworth-Emmons reaction**

Couture and collaborators\(^ {22} \) reported a total synthesis of \((\pm)\)-cherylline and \((\pm)\)-latifine \( 12 \). Of central importance was the construction of the 4-arylisoquinolone template...
contiguously and differentially substituted by phenolic methyl-and benzyl-protected hydroxyl groups on the environmentally different aromatic moieties. Once prepared, sequential reduction of the carbonyl function and of the surviving N–C=C unit of the annulated compound 152 generated the tetrahydroisoquinoline ring system, and O-deprotection of the aromatic amines thus obtained completed the synthesis of the target natural products. For the assembly of the isoquinolone 152 equipped with a pendant aromatic unit at the 4-position of the heterocyclic nucleus, advantage has been taken of the remarkable nucleophilicity of the stabilized α-amino carbanions deriving from the phosphorylated o-aroylbenzamide derivative 151 and their ability to generate the N–C=C moiety inter-and intra-molecularly (Scheme XXXIII).

Other methods

The first report for cherylline synthesis was described by Brossi, Grethe and Teitel\textsuperscript{17,68} in the year 1969. They first reported isolation of cherylline from Crinum powelli. A facile synthesis of (±)-O,O-dimethyl-N-

\textsuperscript{152} dimethylcherylline was reported. The authors isolated the optically active alkaloid cherylline, from several species of Crinum, with 0.004% yield. They also synthesized cherylline using condensation of p-metoxyphenylmagnesium bromide with 2-benzyl-2,3-dihydro-6,7-dimetoxy-4(1H)-isoquinolone 153 which afforded carbinol. The carbinol was transformed using acid treatment and subsequent sodium borohydride reduction to the 4-phenyl-substituted tetrahydroisoquinoline. Thereafter, catalytic debenzylation afforded the secondary amine 154.
Reductive $N$-methylation of the obtained secondary amine provided $(\pm)$-O,O-dimethylcherylline hydrochloride, while resolution of 154 with dibenzoyl-$\alpha$-tartaric acid and L-tartaric acid gave the diastereoisomers with no methyl group at the N atom which, on reductive $N$-methylation of the corresponding secondary amines 155a and 156a, were transformed to the respective enantiomers 155b and 156b (Scheme XXXIV).

**Conclusion**

In conclusion, a variety of methods for the synthesis of cherylline and its derivatives are represented. Based upon interpretation of the literature data, it has been possible to collect methods for the synthesis of cherylline skeleton by the nature of the bond formation.

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