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REVIEW

The biology and total syntheses of bisbenzylisoquinoline alkaloids

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This mini-review provides a concise overview of the biosynthetic pathway and pharmacology of the bisbenzylisoquinoline alkaloid (bisBIA) natural poducts. Additional emphasis is given to the methodologies in the total syntheses of both the simpler acyclic diaryl ether dimers and their macrocyclic counterparts bearing two diaryl ether linkages.

1. Introduction and classification

The benzylisoquinoline alkaloids (BIAs) represent a family of over 2500 plant natural products that have been used for centuries as analgesics and wound disinfectants.[1] Some of the active and biosynthetically-related members, have been exploited in modern medicine, for example, morphine for pain, colchicine for gout, and noscapine for cough and cancer.[2] In recent years, the pursuit of bisbenzylisoquinoline alkaloids (bisBIAs), molecules comprising two BIA motifs, is gaining traction. Isolated from the *Berberidaceae*, *Ranunculaceae*, *Lauraceae* and *Menispermaceae* plant families, these compounds can modulate diverse biological functions.[3,4] With varied and rich pharmacology and chemistry, the majority of these alkaloids arise from the condensation of two coclaurine units (**1** or **2**) while some can arise from the condensation of a coclaurine with reticuline (**3**, Figure 1).[5,6] Based on these distinctions, bisBIAs are often divided into three major classes: bisreticulines, coclaurine-reticulines, and biscoclaurines.[7]

In all instances, the two benzylisoquinoline moieties are linked via biphenyl, diphenyl ether, or benzyl phenyl ether bonds.[7] Aromatic rings with hydroxy, methoxy or methylenedioxy substituents and two chiral centers make up the key features of bisBIAs. Therefore, a high degree of variation is observed depending on the number of ether linkages, the sites on the two units at which the linkage originates, the nature of substitution of the nitrogen atoms, and the degree of unsaturation with regard to the heterocycles.

Currently, over five hundred bisBIAs are known and have since been the subject of several review articles detailing their

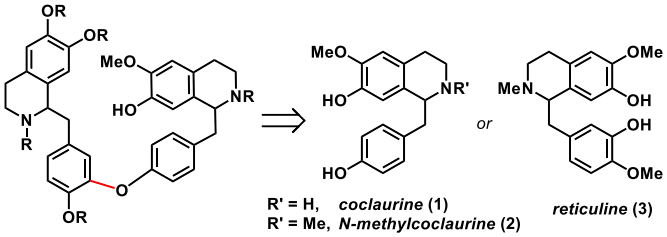

Figure 1. Coclaurine (**1** and **2**) and/or reticuline (**3**) are the biosynthetic building blocks of the majority of bisBIAs.

their botanical sources as well as spectral and physical data.[1-8] This review highlights the biosynthesis and medicinal implications of bisBIAs. Further attention is given to the prevailing synthesis strategies for preparing these alkaloids.

2. Biosynthesis

BisBIAs come from a highly conserved biosynthetic pathway.[8] Catalyzed by tyrosine decarboxylase, the biosynthesis begins with the conversion of amino acid (*S*)-tyrosine (**4**) into 4-hydroxyphenylacetaldehyde (**5**) and dopamine (**6**, Figure 2).[8,9] A Pictet–Spengler transformation facilitated by the enzyme norcoclaurine synthase combines arylacetaldehyde **5** with dopamine (**6**) to generate (*S*)-norcoclaurine. After two successive enzymatic *O*- and *N*-methylation steps, the core intermediate *N*-methylcoclaurine (**2**) is attained that ultimately gives rise to an array of BIAs.

For simple bisBIA derivatives, two *N*-methylcoclaurine units are oxidatively dimerized via the P450 enzyme CYP80A1.[8,10] More complex cyclic bisBIAs are produced following a series of downstream biosynthetic modifications that lead to the introduction of additional functionality. Even so, and as noted by Weber and Opatz, the observed structural diversity of bisBIAs is not entirely substantiated by our current understanding of their biosynthesis.[8] For example, the

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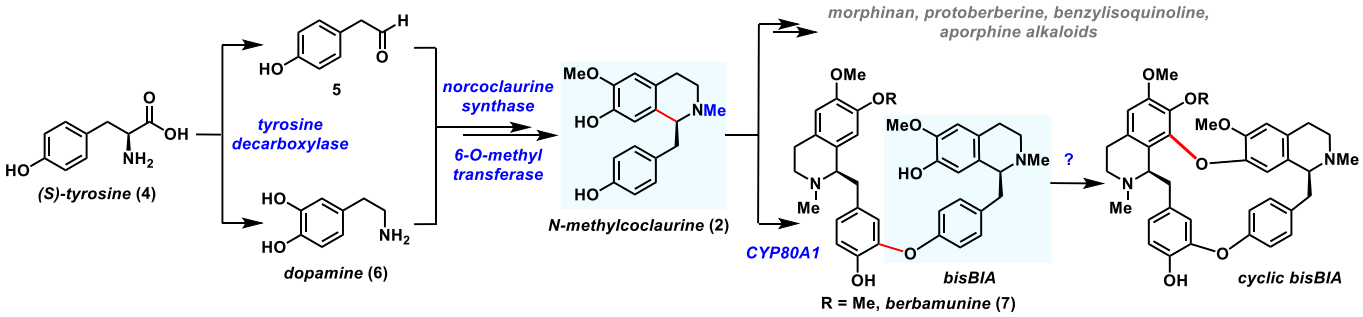


Figure 2. Current understanding of the bisBIA biosynthetic pathway.

enzyme(s) responsible for the formation of sterically encumbered, electron-rich diaryl ether bonds of cyclic bisBIAs such as tetrandrine (**8**) and berbamine (**9**) from berbamunine (**7**) has not been identified.[11,12]

3. Biological activity

Bisbenzylisoquinoline alkaloids have drawn significant attention due to their potent anti-inflammatory, antiviral, antitumor, analgesic and antiplasmodial properties.[6] Formulations containing these alkaloids have been used for centuries as traditional medicines in India, China, sub-Saharan Africa and Southeast Asia.[13] Some active members even have the ability to immobilize skeletal muscle, hence their pronounced use as arrow poisons in South America.[14]

While a detailed analysis of the pharmacology is beyond the scope of this review, the quantity of publications concerning the bioactivities of bisBIAs has largely increased. Several extensive studies have examined the antimicrobial and anti-allergenic characteristics of bisBIAs. The antiparasitic influence of twenty unique bisBIAs against *Trypanosoma brucei* and *Leishmania donovani* was explored by Camacho and co-workers.[15] Comparably, these alkaloids exhibited heightened synergistic effects with the antibiotic cefazolin on methicillin-resistant *Staphylococcus aureus* strains.[16]

More recent findings have identified bisBIAs as inhibitors of calcium influx in glial cells and neurons, combatting neuroinflammation and neuroapoptosis.[17] Another example by Medeiros et al. reported that the alkaloid curine (**10**) induced vasorelaxation via direct inhibition of L-type voltage-gated calcium current in rat aorta smooth muscle cells, triggering an intracellular decrease in transient calcium stores (Figure 3).[18]

Of particular interest is the potential of these natural products as latent agents against the novel and highly pathogenic SARS-CoV-2, which is the fundamental cause of coronavirus disease 2019 (COVID-19). Plants of the *Menispermaceae* family are repeatedly used for the treatment of malaria as well as dengue fever and a number of isolated alkaloids exert comparable antiviral consequences.[19,20] He et al. identified nine bisBIAs as potent *in vitro* SARS-CoV-2 entry inhibitors.[21] Tetrandrine (**8**) dramatically blocked viral S and N protein expression as well as human coronavirus OC43 (HCoV-OC43) replication in MRC-5 human lung cells.[22] Likewise, the approved bisBIA drug cepharanthine (**11**) was shown to inhibit SARS-CoV-2 replication with minimal toxicity at a half maximal effective concentration (EC_{50}) of 0.35 μM (Figure 3).[23,24] While the mechanism of action of cepharanthine (**11**) is multifaceted, the antiviral activity not only relies on suppression of nuclear factor-κB (NF-κB) signaling pathways but also induction of plasma membrane rigidity to hamper entry of the pathogen into the cell.[23] These activities highlight a new role for bisBIAs in the prevention and treatment of SARS-CoV-2 infection. Though many bisBIAs have yet to be biologically evaluated, some demonstrate potential as drug candidates and merit special emphasis: tetrandrine (**8**), berbamine (**9**), neferine (**12**), and dauricine (**13**, Figure 3).

3.1 Tetrandrine

First isolated by Kondo and Tano in 1928, tetrandrine (**8**) is the major bisBIA found in the roots of *Stephania tetrandra* (*Menispermaceae*), a climbing plant used in traditional Chinese and Japanese medicine (Figure 3).[25] Beyond its traditional use for remedying autoimmune disorders, hypertension and cardiovascular diseases, the pharmacological effects of tetrandrine have been the focus of various studies since the late-1990s. The immunologic and vasodilatory properties of tetrandrine have been well evaluated, particularly as a latent therapeutic to treat drug-resistant autoimmune diseases and prevent excess fibrosis in patients with severe conjunctival inflammation.[26,27]

The labs of Xu[28] and Huang[29] described the antiproliferative nature of tetrandrine (**8**) on human T and liver cancer cells, respectively, by inhibition of NF-κB and calcium/calmodulin-dependent protein kinase II, both of which are critical regulators of not only innate immunity, but also cancer-related inflammation. It was even found to upregulate *in vitro* expression and activation of initiator and effector caspases in glucocorticoid-resistant Jurkat T-cells, contributing to the apoptosis-inducing effect in T cell acute lymphoblastic leukemia (T-ALL).[26,30]

Recently, the alkaloid has been recognized as an antagonist of two-pore channels (TPC), or voltage-dependent calcium channels located on lysosomal membranes, which have been

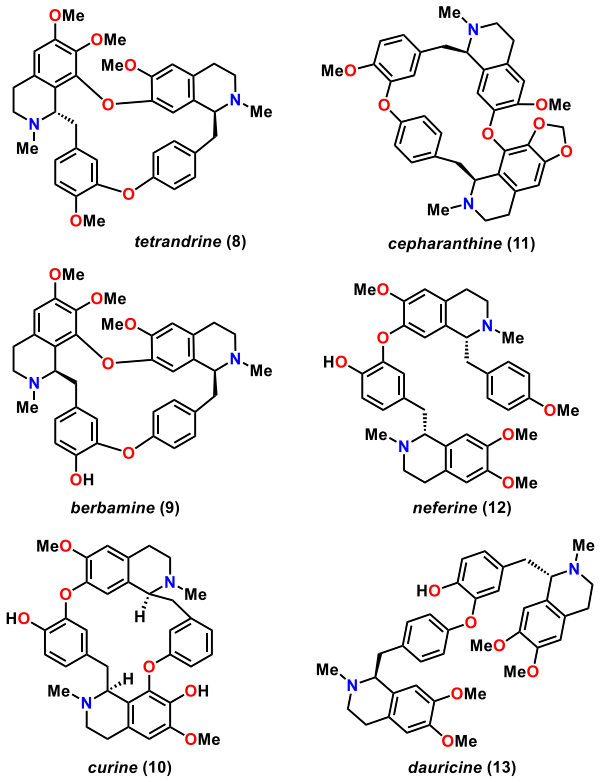


Figure 3. Selected bioactive bisBIAs.

implicated in the pathogenesis of cancer and Ebola virus infection.[31] Sakurai et al. determined that *in vivo* and *in vitro* Ebola virus entry can be hindered by disrupting TPC channels using submicromolar concentrations of tetrandrine (**8**).[32] The alkaloid also reduced tumor metastasis through inhibition of TPC1 and TPC2 *in vivo* and *in vitro*.[33]

An additional pharmacological target of tetrandrine (**8**) is P-glycoprotein (Pgp), a ubiquitous membrane transporter with the ability to efflux drug molecules out of cancer cells, which reduces the efficacy of chemotherapies.[34] Overexpression of Pgp in cancer cells is a crucial factor of multi-drug resistance toward a variety of antitumor agents. Among a series of bisBIAs, tetrandrine was identified as an effective modulator of Pgp activity.[26,35] Named CBT-1, this alkaloid is being developed by CBA Research Inc. as an adjunctive therapy to chemotherapy in various cancer types with multiple drug resistance, including sarcoma, non-Hodgkin's lymphoma, acute myelogenous leukemia, and multiple myeloma.[36] Prior phase I trials with CBT-1 defined the tolerable dose range and side effects when administered with doxorubicin.[37] The most recent clinical study is currently investigating the combination of doxorubicin and CBT-1 for the treatment of unresectable, metastatic sarcoma in patients who previously progressed with doxorubicin.[38] A thorough discussion of the synergistic, apoptotic, and autophagic consequences of tetrandrine on multiple cancers, both *in vitro* and *in vivo*, is included in a comprehensive review by Luan et al.[35]

From a toxicity perspective, oxidative metabolism involving the 12-*O*-methoxy group of tetrandrine (**8**) leads to the generation of a highly reactive quinone methide intermediate suspected to be responsible for massive pulmonary edema and hemorrhage in mice models.[39] Likewise, continuous administration of the alkaloid caused a marked pathological change in the liver tissues of dogs.[40]

3.2 Berbamine

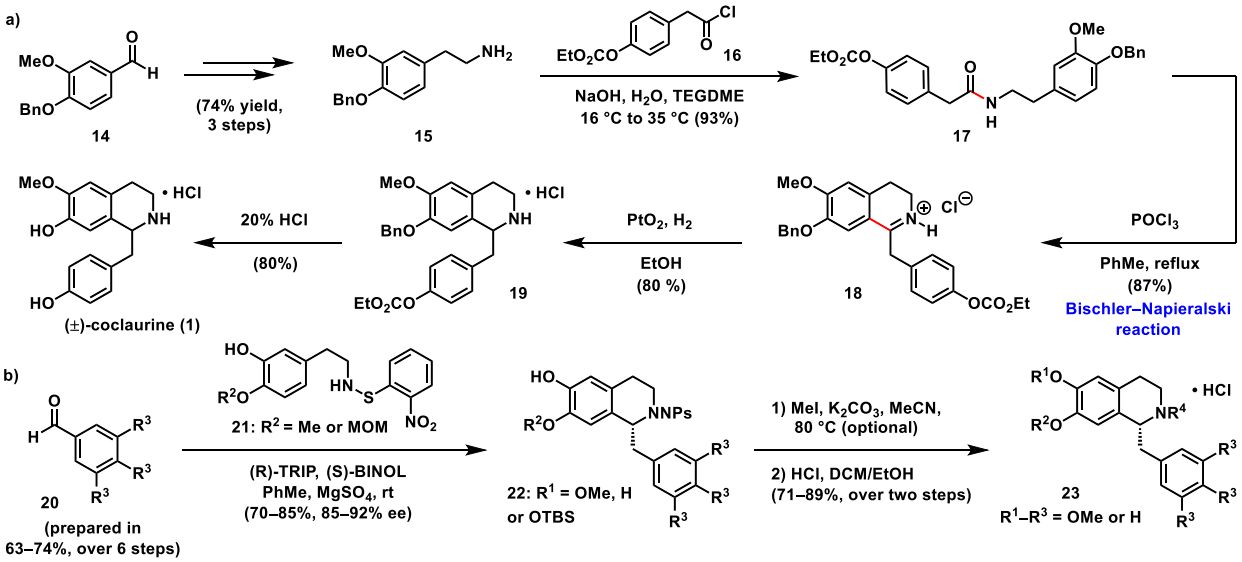
Berbamine (**9**) is a cyclic bisBIA isolated from the traditional Chinese herbal medicine *Berberis amurensis* (Figure 3).[5] There is a well-documented history of its usage in clinical practice for treating inflammation, cancer, and autoimmune diseases.[6] A simple keyword search in scientific databases returns about five hundred publications on berbamine's pharmaceutical assessment spanning from 1969 to present day. Numerous findings have disclosed its inhibitory effects toward a variety of cancer cell lines, specifically advanced melanoma, ovarian cancer, and chronic myeloid leukemia.[41] Its antiproliferative qualities are frequently associated with the inactivation of critical pro-tumorigenic pathways, such as p53, Fas signals, and Ca^{2+}/calmodulin-dependent protein kinase II γ.[42]

Interestingly, recent studies uncovered an unforeseen synergy of berbamine (**9**) with an assortment of targeted therapies. Zhao et al.[43], Hu et al.[44] and Jia et al.[45] demonstrated that berbamine improved the efficacy of sorafenib, gefitinib and paclitaxel, respectively, on advanced hepatocellular carcinoma (HCC), pancreatic cancer and glioma cells through suppression of STAT3 signaling pathway and reactive oxygen species (ROS)-dependent phospho-Akt protein expression.

3.3 Neferine and dauricine

Neferine (**12**) and dauricine (**13**) are the primary bioactive components obtained from the seed embryo of *Nelumbo nucifera* (lotus) and the roots of *Menispermum dauricum* (Asian moonseed), respectively (Figure 3).[6,39] Both compounds display antiviral, antioxidant, antidepressant, antiarrhythmic and anti-cancer actions.[39]

Neferine (**12**) has neuroprotective capabilities and can function as a ROS mediated autophagy inducer (Figure 3).[46,47] Its anti-diabetic implications were disclosed by Li and co-workers.[48] Their study revealed that compared to untreated diabetic mice, an evident reduction in the blood pressure, body weight, fasting blood sugar glucose, insulin, triglycerides and total cholesterol was seen in type II diabetic mice upon neferine treatment. Additionally, the alkaloid not only bolstered the anti-tumor effects of chemotherapeutic agents, but also reversed multiple drug resistance in *in vitro* as well as *in vivo* models of cancer by decreasing epithelial-mesenchymal transition (EMT), a process associated with chemoresistance and tumor invasion.[46,49,50] In a recent investigation, neferine reduced the viability of human prostate cancer (PCa) cells and their stem cells in a time- and dose-dependent manner by upregulating cleaved PARP, apoptotic caspase-3, and downregulating the expression of anti-apoptotic protein Bcl-2. Intriguingly, neferine also elevated the expression of several tumor suppressor genes and downregulated cyclin-dependent kinase 4 (CDK-4) expression, leading to cell cycle arrest at the G_1 phase.[51]



Scheme 1. a) Total synthesis of (±)-coclaurine (1) and b) Hiemstra's strategy to access ten benzyltetrahydroisoquinolines (**23**).

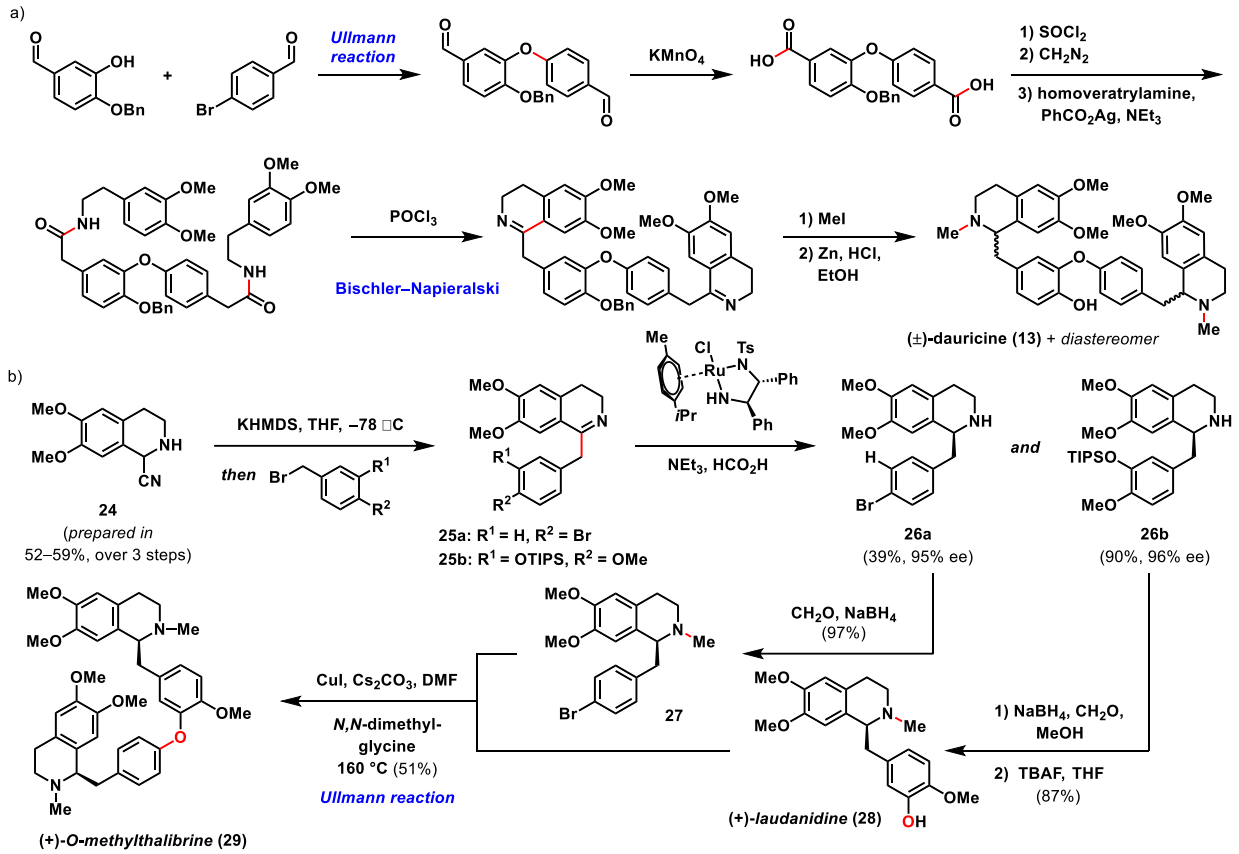
Dauricine (**13**) exerts similar pharmacological attributes with clinical potential. Its cardiovascular, anti-inflammatory, membrane modulating, anti-platelet aggregation and neurological effects are well-documented (Figure 3).[5,6] Outlined by Wang et al., dauricine (**13**) significantly minimizes the *in vitro* secretion level of amyloid beta (Aβ) and Cu^{2+}-induced ROS in human β-amyloid precursor protein (APPsw) cells.[52] Hence, it is suggested that the alkaloid could rescue neurons from oxidative stress-induced apoptosis and possibly relieve acute oxidative damage in Alzheimer's disease (AD) models. The therapeutic capacity of dauricine against lipopolysaccharide (LPS)-induced inflammatory bone loss is more recently demonstrated by Park and co-workers via its action on osteoclasts (OC).[53] Yet, the adverse cytotoxicity of the alkaloid in liver, kidney and lung-derived cell lines is often overlooked.[54]

4. Total syntheses of bisBIAs

4.1 Synthesis of coclaurine and its derivatives

Besides being structural fragments and precursors, the synthesis of coclaurine (**1**) and its derivatives is imperative in accessing the dimeric bisBIAs. The original strategy of assembling coclaurine involved the condensation of 4-benzyloxy-3-methoxyphenylethylamine (**15**) with (4-ethoxycarbonyloxyphenyl)acetyl chloride (**16**), Bischler–Napieralski cyclization of the resultant amide (**17**) to afford the hydrochloride salt of dihydroisoquinoline **18**, PtO_2-mediated reduction of the imine, and deprotection by acid hydrolysis (Scheme 1a).[55] An Arndt–Eistert reaction between amine (**15**) and 4-methylsulphonyloxydiazoketone has also been employed to synthesize amide **17** en-route to coclaurine (**1**).[56] The above sequence has since been adapted and modified in later syntheses of related tetrahydroisoquinolines. For example, *N*-methylcoclaurine (**2**) was obtained through a $LiAlH_4$-mediated reduction of the urethane derivative of dibenzylcoclaurine followed by hydrogenolysis.[57] The Bischler–Napieralski reaction and a Noyori-type reduction is another representative synthesis sequence often applied in the construction of these isoquinoline scaffolds.

Contemporary synthetic methods have been aimed at utilizing *N*-acyl Pictet–Spengler reactions rather than the conventional Bischler–Napieralski protocols to provide the tetrahydroisoquinolines directly, thus enhancing step-economy. In 2015, Hiemstra and co-workers reported an enantio- and regioselective Pictet–Spengler condensation between aryl acetaldehydes (**20**) and *o*-nitrophenylsulfenyl (Nps)-substituted arylethylamines (**21**) using (*R*)-TRIP as the chiral catalyst (Scheme 1b).[58] This method provided access to several 1-benzyl-1,2,3,4-tetrahydroisoquinolines with up to 92% enantiomeric excess. With this organocatalyzed Pictet–Spengler reaction, the Hiemstra group accomplished the synthesis of ten biologically relevant tetrahydroisoquinoline alkaloids, including (*R*)-coclaurine, (*R*)-reticuline, (*R*)-norprotosinomenine, and other variants. Illustrated in Scheme **2**, the steps subsequent to the key (*R*)-TRIP-catalyzed Pictet–Spengler reaction are high yielding and straightforward. *O*-Methylation of the resulting tetrahydroisoquinolines (**22**) using MeI and K_2CO_3 followed by acid-mediated cleavage of the MOM, TBS, and Nps groups gave the alkaloids (**23**) as their hydrochloride salts in 71–89% overall yield with the ee's being mostly preserved. The *N*-methyl derivatives were fashioned from the unprotected alkaloids via reductive amination with $NaCNBH_3$ and formaldehyde.



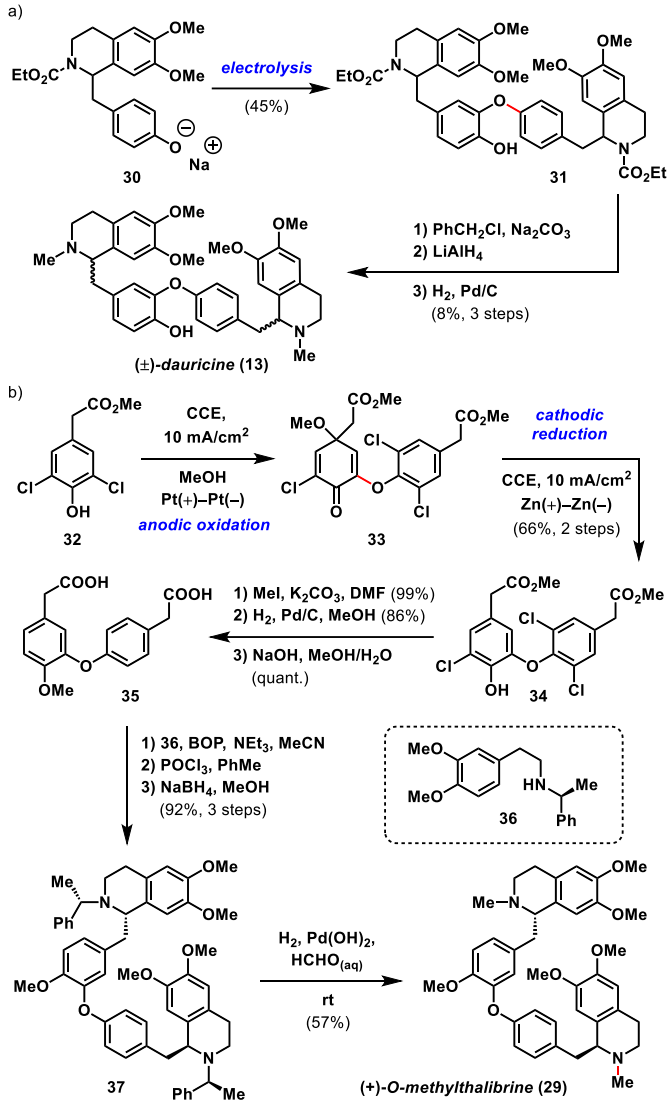
Scheme 2. Total synthesis of a) (±)-dauricine (**13**, no yields reported) and b) (+)-*O*-methylthalibrine (**29**).

4.2 Synthesis of acyclic bisBIAs

There exists two fundamental synthetic approaches to bisBIAs.[8] One is to form diaryl ether bonds for tail-to-tail or head-to-tail connected bisBIAs, to which are subsequently elaborated to isoquinoline fragments (see Scheme 2). The second method is to prefunctionalize both benzylisoquinoline units and then merge them via diaryl ether bonds. Nearly all syntheses of acyclic and cyclic bisBIAs to-date rely on the classical intra- and intermolecular copper-catalysed Ullmann reaction to generate mono- and (bis)ether linkages, respectively, despite its lack of efficiency: long reaction times, high temperatures, stoichiometric amount of copper salts, and low yields. Variations of the reaction utilizing nickel and palladium have relatively broadened the substrate scope and rendered the reaction conditions milder. Namely, modern alternatives such as the Chan–Evans–Lam reaction[59] and Buchwald–Hartwig coupling[60] have been explored to assemble the diaryl ether linkages. However, yields remain inconsistent for C–O bond formation, especially in the context of bisBIAs.

One of the early pioneering efforts in the synthesis of the acyclic bisBIA series was in 1955, when a scheme was devised for constructing *O*-methyldauricine via Ullmann coupling between (–)-armepavine and (–)-3-bromo-*O*-methylarmepavine, which was achieved in 24% yield.[61] A similar approach was opted by Kametani and Fukumoto nearly one decade later for the first total synthesis of (±)-dauricine (**13**) and its diastereomer using both the Arndt–Eistert homologation and Bischler–Napieralski reactions (Scheme 2a).[62] Other early synthetic iterations of magnolamine, daurinoline, magnoline and berbamunine were obtained through reaction sequences analogous to Scheme 2a, all of which integrated Ullmann couplings as the key step with yields ranging from 4–20%.[63] A comparable tactic was chosen by Nishimura et al. for the synthesis of nelumboferine and three unnatural stereoisomers of neferine and *O*-methylneferine.[64] Ullmann coupling of the tetrahydroisoquinoline units with copper(I) bromide and Cs_2CO_3 in pyridine gave the respective dimers in 34–45% yields.

Modular strategies have been developed for the enantioselective synthesis of bisBIAs. Both benzylisoquinoline units in the total synthesis of (+)-*O*-methylthalibrine (**29**) arose from 1,2,3,4-tetrahydroisoquinoline-1-carbonitrile (**24**), which was deprotonated with KHMDS and alkylated to provide 3,4-dihydroisoquinolines **25a** and **25b** (Scheme 2b).[65] Noyori transfer hydrogenation, reductive *N*-methylation with $NaBH_4$ and formaldehyde afforded bromobenzylisoquinoline **27** and (+)-laudanidine (**28**) as the precursors for the final Ullmann coupling, which delivered bisBIA **29** in 51% yield. This protocol was exploited for the asymmetric synthesis of bisbenzylisoquinoline derivative (+)-tetramethyl-magnolamine



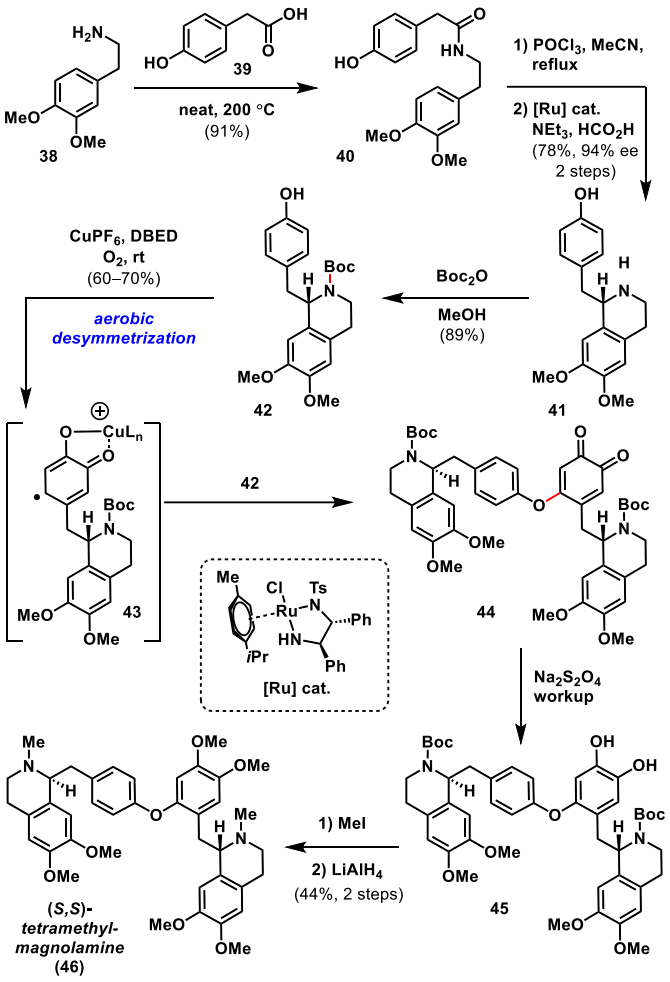
Scheme 3. Electrochemical methods to synthesize a) (±)-dauricine (**13**) and b) (+)-O-methylthalibrine (**29**). BOP = benzotriazol-1-yloxytris(dimethylamino)phosphonium hexafluorophosphate. CCE = constant current electrolysis.

as well as benzylisoquinolines (+)-laudanosine and (+)-armepavine.

Although Ullmann cross-coupling reactions have been extensively applied in aryl ether syntheses, oxidative C–O bond forming reactions have been considered as green and cost-effective surrogates. The first preparation of a naturally occurring bisBIA using an electrolytic oxidation was described in 1971 by Bobbitt and Hallcher.[66] When the sodium salt of (±)-*N*-carbethoxy-*N*-norarmepavine (**30**) was subjected to electrolysis using tetramethylammonium perchlorate as the electrolyte, a graphite anode together with a platinum cathode, a carbon–oxygen (**31**) linked dimer was obtained (Scheme 3a). Subsequent *O*-benzylation, reduction, and catalytic debenzylation, furnished a racemic and diastereomeric mixture of dauricine (**13**).

To install the diaryl ether moieties of bisBIAs at an early stage, Nishiyama and co-workers broadly surveyed electrolytic phenol couplings.[67] Following an extensive screening of electrochemical constraints and reactants, the conditions for the anodic oxidation of phenol **32** and ensuing cathodic reduction of dimer **33** were developed for the preparation of (+)-*O*-methylthalibrine (**29**) and its derivatives (Scheme 3b). *O*-methylation and dehalogenation of dimer **34** yielded diacid **35.** The phenylacetic acid moieties were then coupled to phenylethylamine derivative **36** bearing a chiral auxiliary to achieve two simultaneous asymmetric Bischler–Napieralski reactions. Substitution of the auxiliaries with methyl groups afforded (+)-*O*-methylthalibrine (**29**) in an overall yield of 29%.

A recent total synthesis of (*S,S*)-tetramethylmagnolamine (**46**) featured a unique instance of catalytic aerobic desymmetrization that took advantage of the alkaloid's inherent pseudosymmetry (Scheme 4).[68] The synthesis commenced with the preparation of Boc-protected tetrahydroisoquinoline **42** via amidation of homoveratrylamine (**38**) and 4-hydroxyphenylacetic acid (**39**). The Bischler–Napieralski cyclization of the accompanying amide (**40**) permitted an asymmetric Noyori hydrogenation to deliver free amine **41** in 70% yield with 94% ee. Upon protection of the amine (**41**) with Boc_2O, the strategic aerobic oxidative coupling was realized by treatment with O_2 and a catalyst system



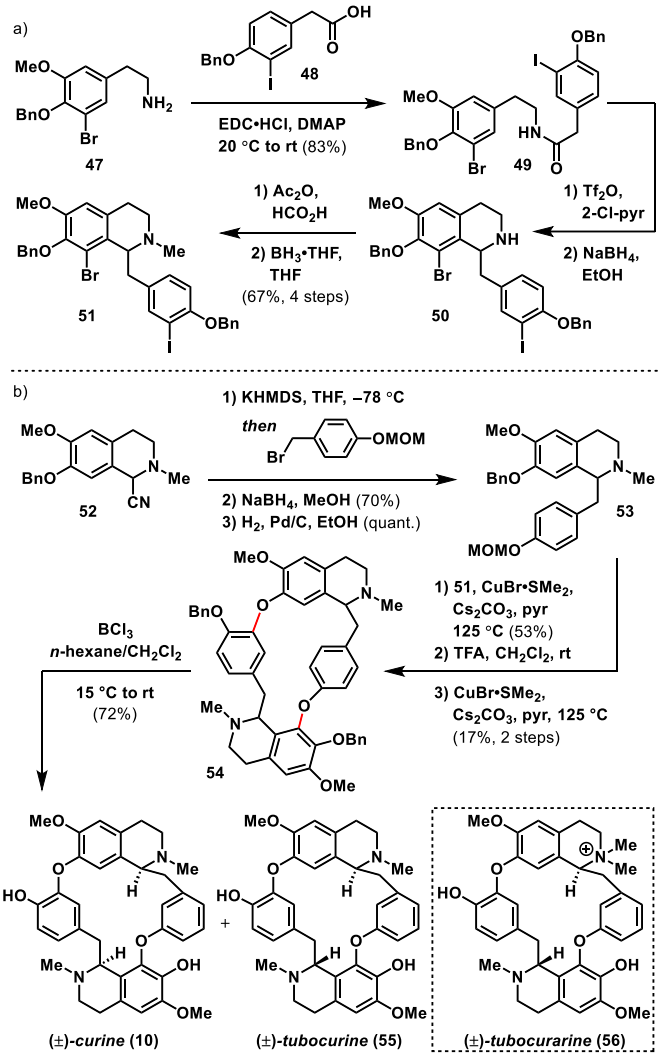
Scheme 4. Huang and Lumb's synthesis of (*S,S*)-tetramethylmagnolamine (**46**). DBED = *N,*N'-di-*tert*-butylethylenediamine.

comprised of $CuPF_6$ and *N,*N'-di-*tert*-butylethylenediamine (DBED). Reductive workup then gave rise to the corresponding catechol derivative (**45**). Methylation of **45** and reduction of the *N*-Boc groups supplied the dimeric alkaloid (**46**) over seven steps in 21% overall yield. A prior synthesis of **46** by Blank and Opatz required sixteen steps in 14% overall yield and employs a conventional Ullmann coupling to form the key diaryl ether.[65]

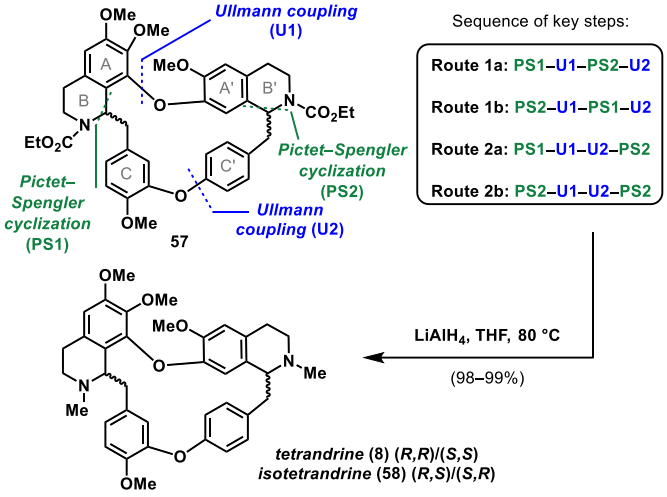
4.3 Synthesis of cyclic bisBIAs

Cyclic bisbenzylisoquinoline alkaloids constitute the more prominent yet challenging class of this natural product family, especially in the context of establishing the appropriate diaryl ether linkages. In 2017, Opatz and co-workers accomplished the racemic synthesis of (±)-curine (**10**) and (±)-tubocurine (**55**) based on two sequential Ullmann-type condensations (Scheme 5).[8,69] Preparation of the dihalogenated building block (**51**) began with an amide coupling of phenylethylamine **47** and phenylacetic acid **48** (Scheme 5a). The Bischler–Napieralski reaction of amide **49** mediated by 2-chloropyridine and triflic anhydride generated an imine, which was subsequently reduced to amine **50**. *N*-methylation of the amine (**50**) provided the dihalide (**51**).

Analogous to the protocol shown in Scheme **2b**, the second MOM-protected benzylisoquinoline moiety (**53**) was synthesized from aminonitrile **52** over three steps via an umpolung, alkylation-reduction sequence (Scheme 5b). The rather risky double C–O couplings of precursors **51** and **53** were performed under the reported Ullmann reaction conditions in Scheme **5b**. Finally, removal of the benzyl groups delivered (±)-curine (**10**) and (±)-tubocurine (**55**) in a 2:1 diastereomeric ratio. The total synthesis of **55** also embodied the formal synthesis of (±)-tubocurarine (**56**).



Scheme 5. Opatz's synthesis of (±)-curine (**10**) and (±)-tubocurine (**55**), and formal total synthesis of (±)-tubocurarine (**56**).



Scheme 6. Bracher's modular total synthesis of (±)-tetrandrine (**8**) and isotetrandrine (**58**). Conditions for vital Ullmann couplings: CuBr•SMe_2, Cs_2CO_3, pyridine, 110 °C; Pictet–Spengler reactions: TFA, CH_2Cl_2.

The aforementioned dual Ullmann reaction was similarly presented in a modular twelve-step synthesis to racemic tetrandrine (**8**) and its diastereomer isotetrandrine (**58**), Scheme 6).[70] Presented in four distinct routes, each strategy incorporated *N*-acyl Pictet–Spengler reactions to access the 1-benzyltetrahydroisoquinoline units and copper-mediated Ullmann-type couplings for C–O bond formation. The first route provided the macrocyclic skeleton (**57**) using two alternating intermolecular Pictet–Spengler cyclizations and an intramolecular diaryl ether coupling. In the second route, an intramolecular *N*-acyl Pictet–Spengler condensation constructed the final alkaloid precursor (**57**). An additional variant for the above routes was also devised, whereby either of the aromatic ring systems (A–C or A'–C') could be assembled at the outset. The final step of all four variants was an $LiAlH_4$-reduction of both carbamates in macrocycle **57** to obtain racemic mixtures of (*R,R*)/(*S,S*) tetrandrine (**8**) and (*S,R*)/(*R,S*) isotetrandrine (**58**) in 3–19% overall yields. The authors computationally analyzed the observed diastereomeric outcome of the key Pictet–Spengler cyclizations, which revealed that the stereochemistry at the C-1 stereocenter of the macrocycle helps to control the formation of the second chiral center of tetrandrine (**8**).

Conclusions

Existing approaches for the total synthesis of bisBIAs underscore limitations in the current state-of-the-art. Not only do the unique structures of bisBIAs serve as inspiration for the development of practical synthetic protocols, but the therapeutic properties of these compounds are also compelling and have spurred numerous efforts in analog synthesis. With continual interest in the function of bisBIAs, advancing synthetic strategies for practical access to enantioenriched bisBIA frameworks is warranted.

Author Contributions

VKN and KGMK wrote the mini-review.

Conflicts of interest

There are no conflicts to declare.

Acknowledgements

The acknowledgements come at the end of an article after the conclusions and before the notes and references.

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