Synthesis P. J. Praveen et al. Short Review

Bis(indolyl)methane Alkaloids: Isolation, Bioactivity, and Syntheses

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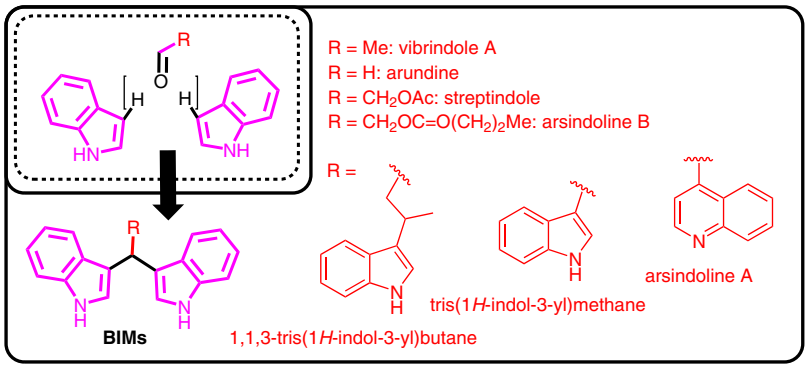

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Abstract Bis(indolyl)methane (BIM) alkaloids are an important group of bioactive natural products predominantly found in marine organisms. Thus, compounds like arsindoline A and B, vibrindole A, arundine, and trisindoline are found in marine bacteria, while the related compound, streptindole is obtained from *Streptococcus faecium* IB 37, found in human feces. In recent years, these molecules, which display a wide range of biological properties (antibacterial, antiviral, anti-oxidant, neurotoxic activity etc.), have attracted the attention of several synthetic and natural product chemists. This review lists selected bis(indolyl)methane analogues reported from different natural sources to date, together with their biological properties and synthesis.

Key words bis(indolyl)methanes, natural products, isolation, synthesis, bioactive metabolites

1 Introduction

Bis(indolyl)methanes (BIMs) are a group of alkaloids with a basic skeleton of two indol-3-yl groups bridged by single methyl carbon; they are differentiated by the groups/substituents attached to the bridging methyl carbon (Figure 1). While most bis(indolyl)methanes are found commonly in both marine and terrestrial organisms, a few of them are reported exclusively from either terrestrial or marine organisms. Due to their wide application in medicinal chemistry, drug discovery, and agrochemicals, the syntheses and isolation of bis(indolyl)methanes have attracted the attention of several chemists. Due to the symmetric structure of the BIM skeleton they are easy to synthesize from two molecules of indole and an aldehyde/ketone using an acid or base catalyst, but for large-scale synthesis the

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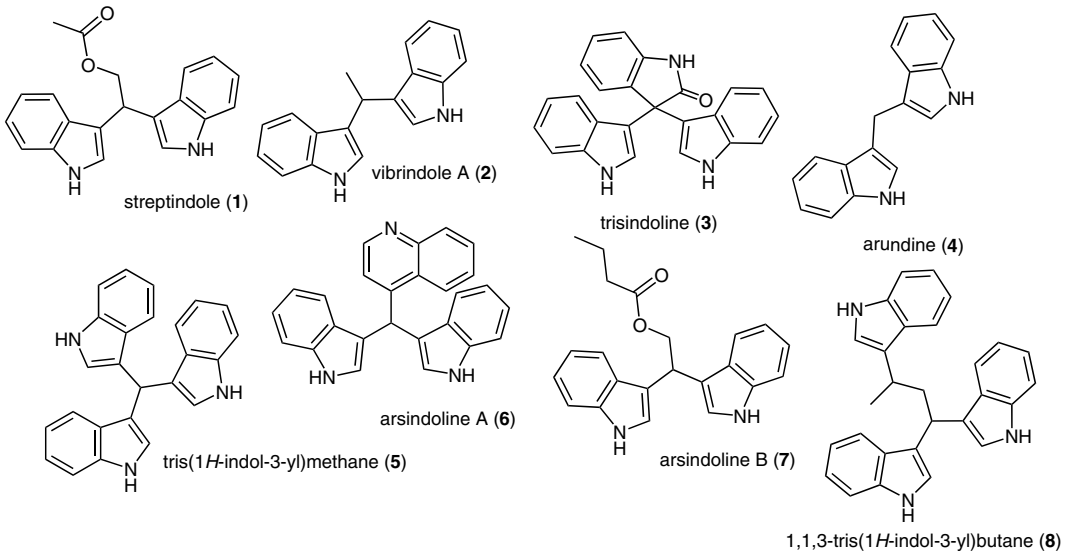


Figure 1 Structures of bis(indolyl)methane derivatives isolated from natural sources

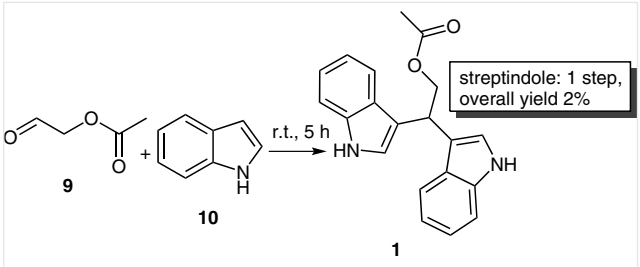
method should be environmentally friendly and cost effective. A number of syntheses of bis(indolyl)methanes, ranging from those using harmful chemicals to environmentally benign green synthesis in aqueous media, are now known; the reactivities vary widely depending upon the substituents on the aldehyde/ketone. Several indole derivatives are known to display promising biological properties, such as antibacterial, neurotoxic, antioxidant, antiviral activity etc. A few of these compounds are used as pesticides, while some have served as new drug leads for the treatment of depression and anxiety.[1] Brominated trisindole alkaloids isolated from a new Caledonian sponge exhibit cytotoxicity against KB cells.[2] Vinca alkaloids, such as vinblastine, vincristine, vindesine etc., are important antitumor indole alkaloids that are in clinical use at present.[3]

A recent review in Chinese by Haiwei and Zhengfeng on the synthesis of bis(indolyl)methanes summarizes the novel catalysts employed,[4] while a second review entitled 'Synthetic Approaches for Bis(indolyl)methanes' by Kaishap and Dohutia[5] highlights the different synthetic approaches towards building the basic skeleton of bis(indolyl)methanes. Unfortunately, both reviews omitted the structures and biological properties of natural alkaloids. It is interesting to note that, the majority of methods use two equivalents of indole and one equivalent of an aldehyde/ketone with different catalysts and solvents. In continuation of our interest in bioactive bisindole alkaloids, this article summarizes the isolation, structure determination, synthesis, and biological properties of the natural products **1**–**8**.

2 Occurrence, Isolation, Structure Elucidation, and Biological Activity

Streptindole (**1**), isolated by Osawa and Namiki in 1983, is a genotoxic metabolite of human intestinal bacteria *Streptococcus faecium* IB 37.[6] The bacteria, which is a predominant strain in human feces, was cultured in modified EG medium, and the compound was isolated from the ethyl acetate fraction of the culture filtrate using preparative HPLC (hexanes–EtOAc, 2:1). HRMS (*m*/*z* 318.1376) indicated its molecular formula to be $C_{18}H_{20}N_2O_2$ and the final structure was confirmed by matching spectral data with those of a synthetic sample (Scheme 1). The synthetic protocol involved acetylation of glycoaldehyde at room temperature to furnish acetylated glycoaldehyde **9**, which was treated with two equivalents of indole (**10**) (253 mg) and the mixture was stirred at room temperature for five hours. The purified synthetic compound showed chromatographic behavior and spectroscopic data identical to that of the natural product Streptindole (**1**), reported earlier from the intestinal bacteria *Bacillis subtilis*, exhibits DNA-damaging and genotoxic properties. Streptindole (**1**) is structurally similar to the marine natural product arsindoline B (**7**) (Figure 1).

In 1994, Bell and Carmeli described the isolation of vibrindole A (**2**) from the marine bacterium *Vibrio parahaemolyticus*, associated with the toxic mucus of the boxfish *Ostracion cubicus*.[7] They collected the white foamy mucus from a stressed fish and plated it onto a petri dish containing SLB agar. The culture medium was extracted with ethyl acetate and the extract was then purified using column chromatography (solvent: gradient petroleum ether–EtOAc



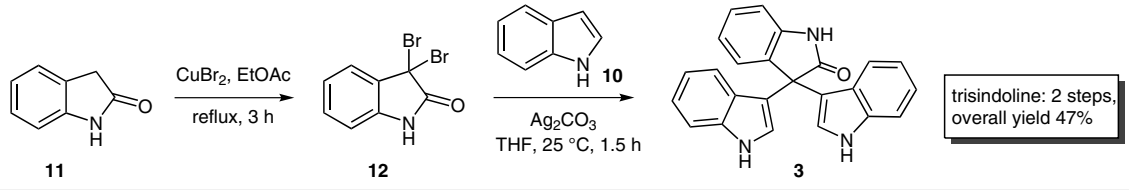
Scheme 1 First synthesis of streptindole used for elucidation of the structure of material obtained from a natural source

mixture) to yield 12 fractions. Fractions displaying activity against *Staphylococcus aureus* and *Staphylococcus albus* were combined and further purified on a preparative HPLC column (C18, MeOH–H_2O, 3:1, 6 mL/min), yielding trisindoline [2,2-bis(1*H*-indol-3-yl)-1,2-dihydro-3*H*-indol-3-one, **3**, 62.1 mg, t_R = 13.3 min) as the major constituent. The target molecule, vibrindole A (**2**) eluted from the column much later (t_R = 44.7 min, 3.2 mg) (*m*/*z* 260.1370, $C_{18}H_{16}N_2$) as a colorless oil. The structure was confirmed using different NMR techniques, namely, ^{1}H and ^{13}C NMR, HMQC, and HMBC. Both the compounds displayed mild activity against *S. aureus* (11-mm zone of inhibition at 100 µg/disc) while vibrindole A (**2**), was also mildly active against two more strains, *S. albus* and *B. subtilis* (11 and 7 mm) at the same concentration level. Though vibrindole A (**2**) was isolated from a natural source in 1994, it has been known as a synthetic product since 1963.[8–10]

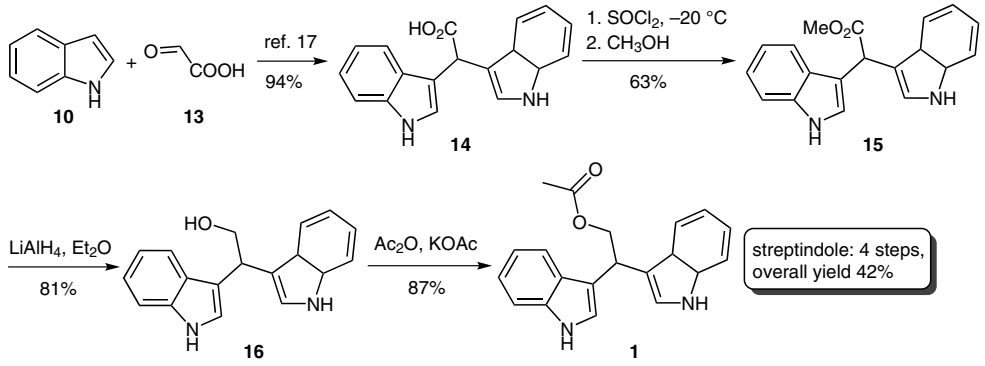
In 1994, Kobayashi et al. isolated trisindoline (**3**) (Figure 1), an antibiotic indole trimer,[3] from *Vibrio* sp. obtained from the marine sponge *Hyrtios altum*.[11] The ethyl acetate extract of the combined homogenized culture was active against *Escherichia coli*, *B. subtilis*, and *S. aureus*. Purification of the extract provided trisindoline (**3**) in 0.3% yield as a colorless amorphous powder (*m*/*z* 363, corresponding to the formula $C_{24}H_{17}N_3O$). Confirmation of the structure came from various 1D and 2D NMR techniques; the natural product was subsequently synthesized (Scheme 2). Thus, refluxing oxindole (**11**) with copper(II) bromide in ethyl acetate for three hours yielded 3,3-dibromoxindole (**12**), which was then treated with indole (**10**) and silver carbonate in tetrahydrofuran at 25 °C for 1.5 hours to furnish trisindoline (**3**) in 47% overall yield. The physical and spectroscopic data of the synthetic compound were identical to that of natural trisindoline (**3**). Trisindoline (**3**) exhibited promising activity against *E. coli*, *B. subtilis*, and *S. aureus* (zone of inhibition: 16, 17, and 10 mm, respectively, at 10 µg/disc concentration level). Trisindoline (**3**) was also isolated from another marine bacterium *Vibrio parahaemolyticus* Bio249[12] (North sea) and the terrestrial plant *Isatis costata*.[13]

In 1994, Khuzhaev et al. first isolated arundine (**4**) (Figure 1) from the roots of *Arundo donax*.[14] Nineteen years later (in 2013), Laatsch and co-workers isolated this metabolite along with a new compound 1,1,3-tris(1*H*-indol-3-yl)butane (**8**) (Figure 1) and several other known compounds from the North sea bacterium *Vibrio parahaemolyticus* Bio249.[12] This was also the first report of occurrence of 3,3-bis(1*H*-indol-3-yl)butane-2-one, arundine (**4**), and tris(1*H*-indol-3-yl)methane (**5**) from a microorganism. The strain Bio249 was initially isolated from a biofilm grown on a glass plate in the North Sea and later identified to be *Vibrio parahaemolyticus*. The bacteria failed to produce the antibiotic compounds in casein medium, instead producing several UV-absorbing indole derivatives, as indicated by their color reaction with Ehrlich's reagent. The crude ethyl acetate extract of the bulk culture was purified on silica gel and Sephadex LH-20 columns, yielding free indole, indole-3-carboxylic acid, indole-3-carbaldehyde, vibrindole A (**2**), trisindoline (**3**), arundine (**4**), 2,2-bis(1*H*-indol-3-yl)indol-3-one, paracine, 2-(4-hydroxyphenyl)ethanol, phenylacetamide, and thymine. The compounds were inactive against a range of bacteria and fungi.

In 2010, Gu and co-workers isolated indole alkaloids arsindoline A (**6**) and B (**7**) (Figure 1) from a marine bacterial strain CB101 identified as *Aeromonas* sp. from the waters of the Xiamen sea.[15] The ethyl acetate extract of the bacteria showed some cytotoxicity in vitro against the K562 cell line. The purification of the active fraction led to the isolation of two new indole alkaloids arsindoline A {4-[bis(1*H*-indol-3-yl)methyl]quinoline, **6**} and arsindoline B [2,2-bis(1*H*-indol-3-yl)ethyl butanoate, **7**] as a colorless amorphous powder together with six known indole alkaloids. The compounds were inactive against HL-60 and A-549 cell lines with arsindoline B (**7**) showing weak activity against A-549 cell lines (IC_{50} 22.6 µm).



Scheme 2 First synthesis of trisindoline (**3**) to support the data of the isolated natural product



Scheme 3 Hogan and Sainsbury's approach for the synthesis of streptindole

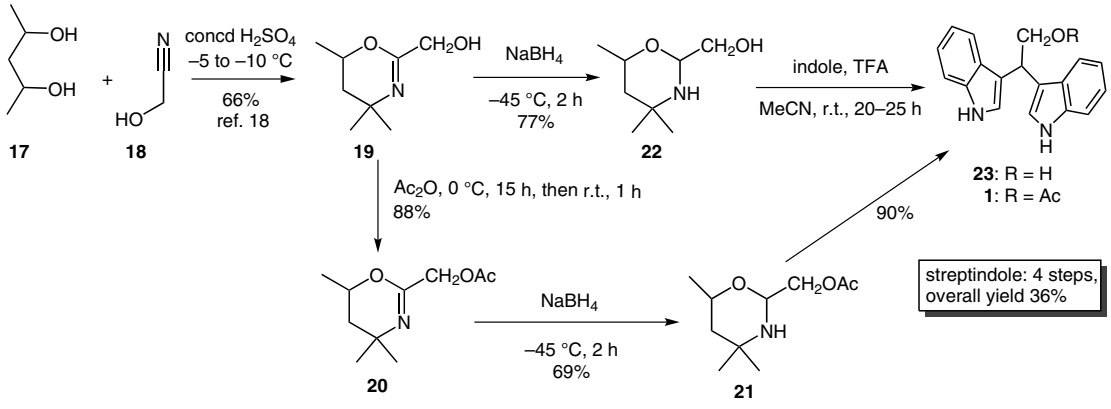
3 Synthetic Approaches towards Bis(indol-yl)methanes

In an approach towards the synthesis of bis(indol-yl)methanes, Hogan and Sainsbury achieved the total synthesis of streptindole (**1**) in 1984[16] (Scheme 3). Two indole rings were coupled together with glyoxylic acid (**13**) to give bis(1*H*-indol-3-yl)acetic acid (**14**),[17] which was converted into methyl ester **15** followed by reduction to the corresponding alcohol **16**. Finally the alcohol is O-acetylated to afford streptindole (**1**) in 42% overall yield.

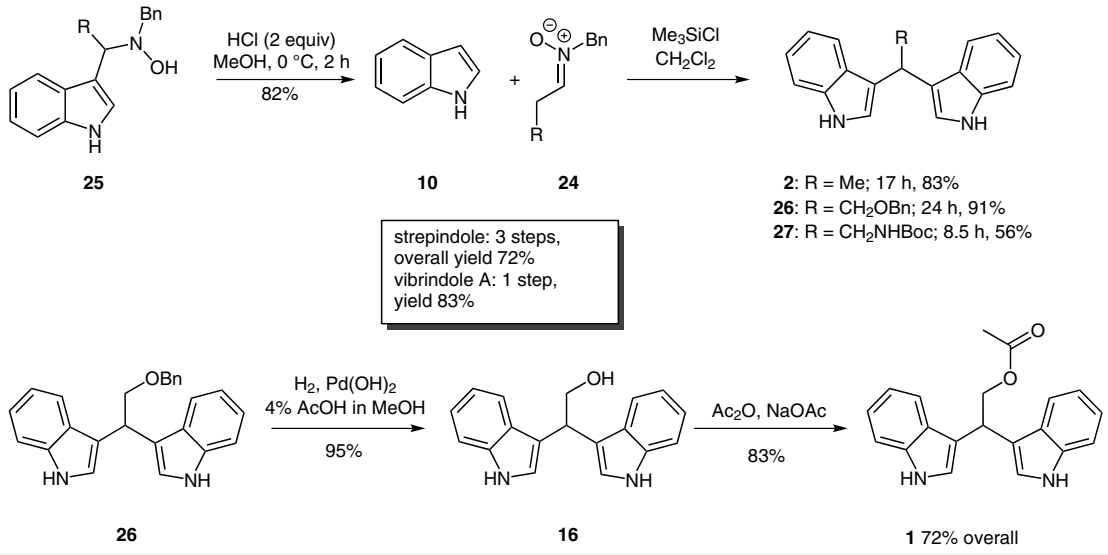
In 1988, Singh and Singh synthesized streptindole (**1**) and its analogues by acid-catalyzed transfer of the appropriate C2 carbon units of oxazines **21** or **22** to bisindoles as depicted in Scheme 4.[10] The synthetic approach includes Meyer's protocol[18] involving condensation of 1,3-diol **17** with hydroxy nitrile **18** to furnish oxazolidine **19**, which on acetylation followed by reduction gave dihydrooxazolidine acetate **21**, condensation with indole in trifluoroacetic acid finally delivered streptindole (**1**). Alternatively, treatment of oxazine **22** with indole and trifluoroacetic acid gave alcohol **23**, which on acetylation furnished streptindole (**1**). Thus, the total synthesis of streptindole (**1**) was achieved in four steps. The authors also highlighted the synthesis of various analogues of streptindole by varying the substituents on the α-carbon of the C2 substituent of 1,3-oxazines **21** and **22**.

Vallée and co-workers reacted indole (**10**) with various nitrones **24** and generated a number of bis(indolyl)alkanes (Scheme 5).[19,20] Three natural products containing the bis(indolyl)alkane skeleton were prepared using this protocol. Among the various screened activation reagents, the use of one equivalent of chlorotrimethylsilane was found to be the most effective; the reaction in the presence of hydrogen chloride in methanol led to the formation of *N*-hydroxylamine **25**. The reaction of indole **10** with various nitrones **24** gave bis(indolyl)methane derivatives **2**, **26**, and **27** in the presence of chlorotrimethylsilane; thus, vibrindole A (**2**) was prepared in 83% yield. Compound **26** on debenzylation followed by acetylation resulted in the formation of streptindole (**1**) in three steps with 72% overall yield.

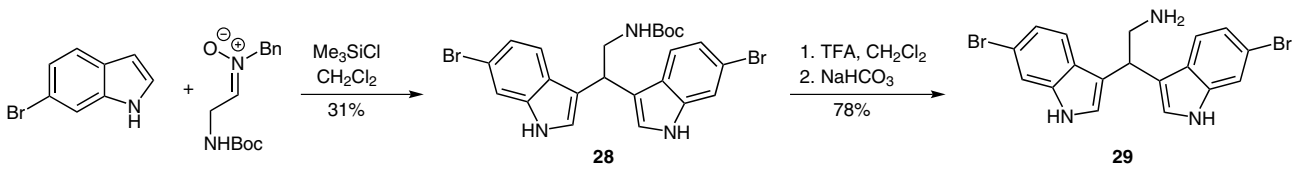
This versatile route was also used for the synthesis of substituted indole derivatives and furthermore, the hydroxylamine derivatives, such as **25**, could be reacted with a further molecule of an indole leading to the synthesis of unsymmetrical bis(indolyl)methanes. Vallée and co-workers



Scheme 4 Singh's approach for the synthesis of streptindole



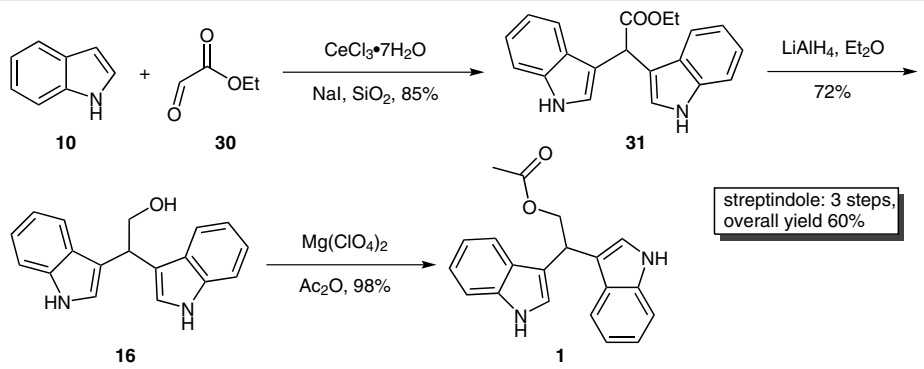
Scheme 5 Vallée's approach for the synthesis of streptindole and vibrindole A



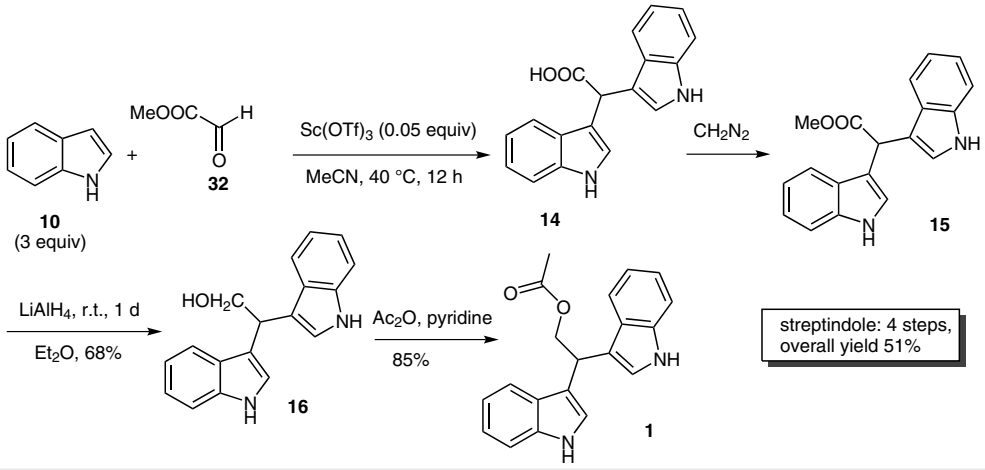
Scheme 6 Use of Vallée's approach for the synthesis of a 2,2-bis(6-bromo-1*H*-indol-3-yl)ethylamine

also performed the first synthesis of 2,2-bis(6-bromo-1*H*-indol-3-yl)ethylamine (**29**), which has been isolated from the tunicate *Didemnum candidum*. Reaction of 6-bromo-1*H*-indole with a Boc-amino-substituted nitrone gave the corresponding N-Boc-protected 2,2-bis(6-bromo-3-indolyl)ethylamine **28**; removal of the Boc protecting group gave 2,2-bis(6-bromo-1*H*-indol-3-yl)ethylamine (**29**) (Scheme 6).

In 2004, Bartoli et al. developed an efficient route for the construction of bis(indolyl)methanes in high yield under solvent-free conditions using cerium(III) chloride heptahydrate–sodium iodide–silica gel as a solvent-free promoter in the key indole addition step (Scheme 7). Indole (**10**) was reacted with ethyl glyoxylate (**30**) in the presence of cerium(III) chloride heptahydrate–sodium iodide–silica gel to give ethyl bis(1*H*-indol-3-yl)acetate (**31**); it was reduced to the corresponding alcohol **16**. Finally the alcohol **16** was O-acetylated using magnesium perchlorate as a useful alternative to metal triflate promoters to give streptindole (**1**).[21]



Scheme 7 Bartoli's approach for the synthesis of streptindole

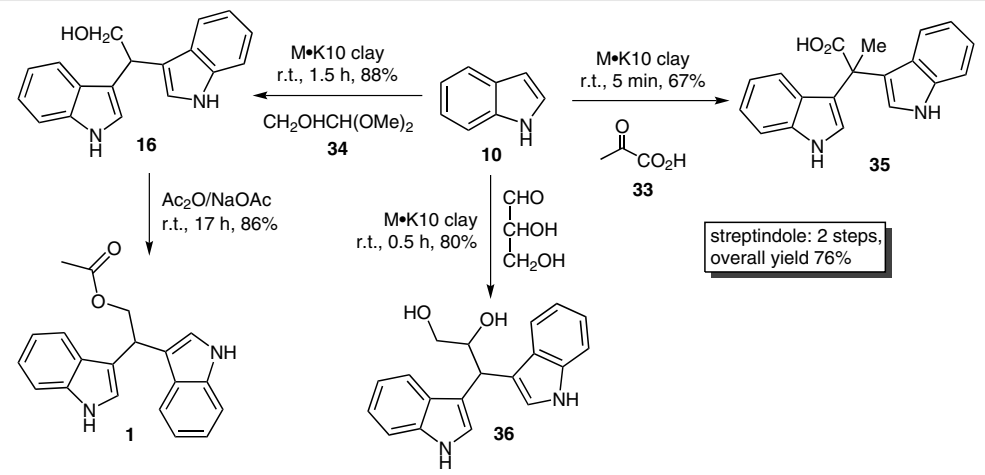


Scheme 8 Sato's approach for the synthesis of streptindole

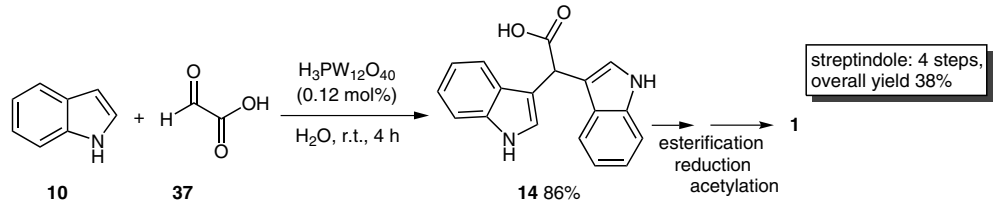
In 2005, Sato and Sato demonstrated the utility of scandium(III) triflate for preparation of bis(indolyl)methanes in good yield (Scheme 8);[22] this method was employed for the synthesis of streptindole (**1**). Treatment of indole (**10**) with glyoxylic acid (**32**) in the presence of scandium(III) triflate for 12 hours gave bis(1*H*-indol-3-yl)acetic acid (**14**), which was esterified using diazomethane and then reduced by lithium aluminum hydride to give alcohol **16**. Subsequent acetylation under standard conditions gave the naturally occurring streptindole (**1**) in 51% overall yield.

Chakrabarty et al. used montmorillonite K10 clay (MK10) under solvent-free conditions for the synthesis of three naturally occurring bis(indolyl)methanes (Scheme 9).[23] 3,3-Bis(1*H*-indol-3-yl)propane-1,2-diol (**36**) was synthesized by reaction of glycerol with indole (**10**) in 80% yield. Streptindole (**1**) was synthesized in two steps using montmorillonite K10 clay. The synthesis involves treatment of glycolaldehyde dimethyl acetal (**34**) with indole (**10**) in the presence of montmorillonite K10 clay to give bis(indolyl)alkanol **16**, which on acetylation delivered streptindole (**1**) in 76% overall yield. Moreover, 2,2-bis(indolyl)propanoic acid **35** was synthesized in a single step by the reaction of indole (**10**) with pyruvic acid (**33**). Overall, this approach is an efficient and concise method for the synthesis of streptindole (**1**) providing the highest overall yield to date of 76% in two steps.

In 2007, Azizi et al. synthesized streptindole (**1**) in water using heteropoly acid as a catalyst.[24] The reaction conditions were optimized using different acids and solvents. The reactions of indole with 2,4-dichlorobenzaldehyde catalyzed by heteropoly acids in water and other solvents were investigated and these identified water as the optimal solvent for the reaction. Furthermore they tested the catalytic activity of different catalysts (e.g., $HClO_4$, WCl_6, $ZnCl_2$) and obtained only moderate yields in water. In addition, the reactivity of $H_3PMo_{12}O_{40}$ was compared with that of



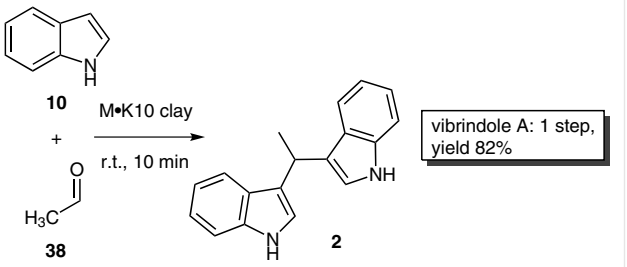
Scheme 9 Chakrabarty's approach for the synthesis of streptindole



Scheme 10 Azizi's approach for the synthesis of streptindole

$H_3PW_{12}O_{40}$ and identical results were found for both the catalysts. Finally, the optimum conditions were $H_3PW_{12}O_{40}$ (0.12 mol%) in water and these were applied to the synthesis of streptindole (**1**) (Scheme 10). Reaction of indole (**10**) with glyoxalic acid (**37**) in the presence of the catalyst gave corresponding bis(1*H*-indol-3-yl)acetic acid **14**, which on esterification, reduction, and acetylation gave streptindole (**1**) in 38% overall yield.

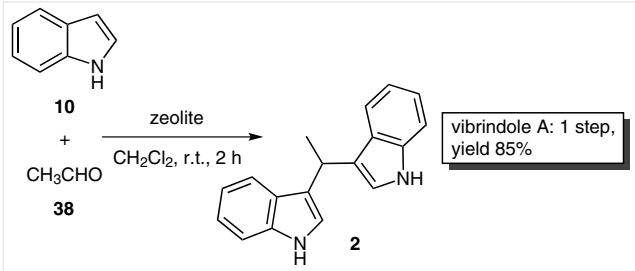
Chakrabarty and co-workers synthesized vibrindole A using montmorillonite K10 clay (MK10) as the catalyst for the addition of indole to acetaldehydes;[25] various substituted bis(indolyl)methanes were synthesized using this strategy. Treatment of indole (**10**) with acetaldehyde (**38**) under solvent-free conditions using montmorillonite K10 clay (2 g/1 mmol of indole) gave vibrindole A (**2**) in 82% yield with a reaction time of 10 minutes (Scheme 11). The montmorillonite K10 clay was washed and dried at 110–120 °C and reused without loss of catalytic activity. The simplicity of workup procedure and the reusability of catalyst are the highlights of this work.



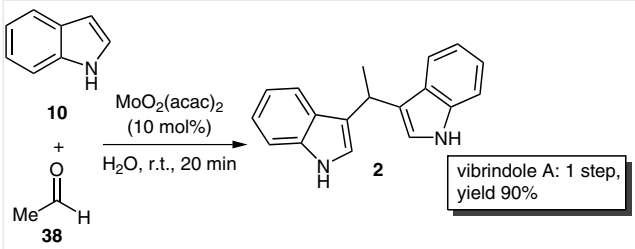
Scheme 11 Chakrabarty's approach for the synthesis of vibrindole A

Karthik et al. synthesized vibrindole A (**2**) using a zeolite catalyst (Scheme 12).[26] The reaction involves the electrophilic substitution of indole (**10**) with acetaldehyde (**38**) at room temperature in dichloromethane to produce vibrindole A (**2**) in 85% yield with a reaction time of two hours. The catalyst is readily recyclable and can be reused five times without loss of activity. A number of bis(indolyl)methanes were constructed by using indole and substituted aldehydes/ketones by this protocol.

In 2007, Banerjee et al. synthesized vibrindole A (**2**) in aqueous medium catalyzed by bis(acetylacetonato)dioxomolybdenum(VI) (Scheme 13).[27] Reaction of indole (**10**) and acetaldehyde (**38**) in water with 10 mol% bis(acetylacetonato)dioxomolybdenum(VI) at room temperature for 20 minutes gave vibrindole A (**2**) in 90% yield. Moreover, the synthesis of related bis(indolyl)methanes were described using indole and various aldehydes and ketones in water medium catalyzed by bis(acetylacetonato)dioxomolybdenum(VI).

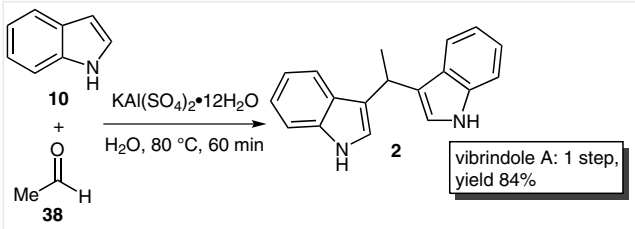


Scheme 12 Karthik's approach for the synthesis of vibrindole A

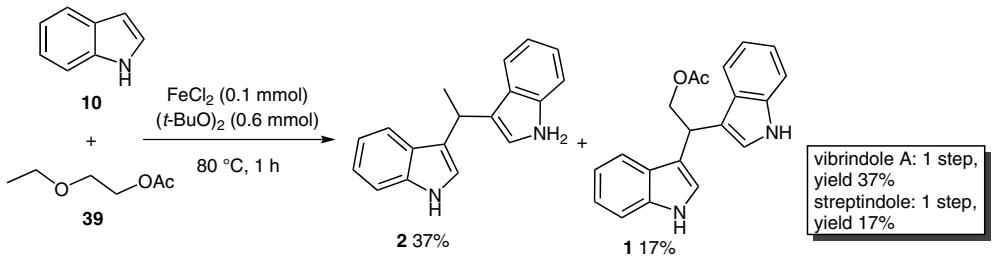


Scheme 13 Banerjee's approach for the synthesis of vibrindole A

In 2009, Kumar et al. demonstrated the synthesis of vibrindole A (**2**) in aqueous medium using alum $[KAl(SO_4)_2{\cdot}12\ H_2O]$ as an inexpensive and reusable catalyst.[28] Treatment of two equivalent of indole (**10**) with one equivalent of acetaldehyde (**38**) with 30 mol% alum in wa-



Scheme 14 Kumar's approach for the synthesis of vibrindole A

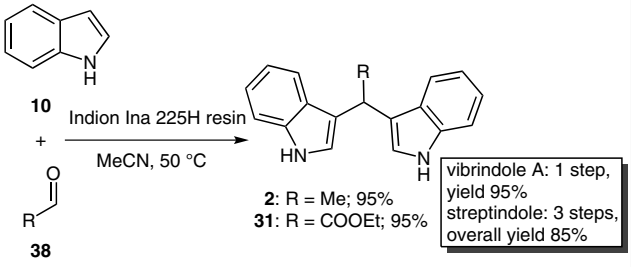


Scheme 15 Guo's approach for the synthesis of vibrindole A and streptindole in one step

ter at 80 °C for one hour gave vibrindole A (**2**) in 84% yield (Scheme 14). The workup procedure involves simple filtration, wherein precipitated product was collected as solid and the filtrate was concentrated under reduced pressure to recover the catalyst. The recovered catalyst was efficiently reused five times without any further workup. A series of bis(indolyl)methane analogues were prepared by condensation of indole with various ketones in the presence of alum.

In 2009, Guo et al. described the synthesis of both symmetrical and unsymmetrical bis(indolyl)methanes via catalytic oxidative coupling of the sp^3 C–H bond adjacent to an oxygen atom of both cyclic and noncyclic ethers **39** with the sp^2 C–H bond in indole (**10**). Evaluation of a series of catalyst and oxidant combinations led to the identification of iron(II) chloride and *tert*-butyl peroxide as the best combination to provide the target compounds in good yield.[29] Reaction of indole (**10**) with acetylated ether **39** in the presence of iron catalyst and *tert*-butyl peroxide oxidant delivered a mixture of two natural products, vibrindole A (**2**) and streptindole (**1**), which were separated by column chromatography (Scheme 15). Various analogues of symmetrical bis(indolyl)methanes were synthesized using this protocol. Interestingly, the application of this protocol to unsymmetrical bis(indolyl)methanes was also highlighted. When electron-withdrawing substituted indoles were used at 60 °C this led to the formation of monoindolation products that were trapped by the addition of a second indole at a higher temperature resulting in the formation of unsymmetrical bis(indolyl)methanes.

In 2012, Surasani et al. used Indion Ina 225H resin for the synthesis of vibrindole A (**2**) and streptindole (**1**)

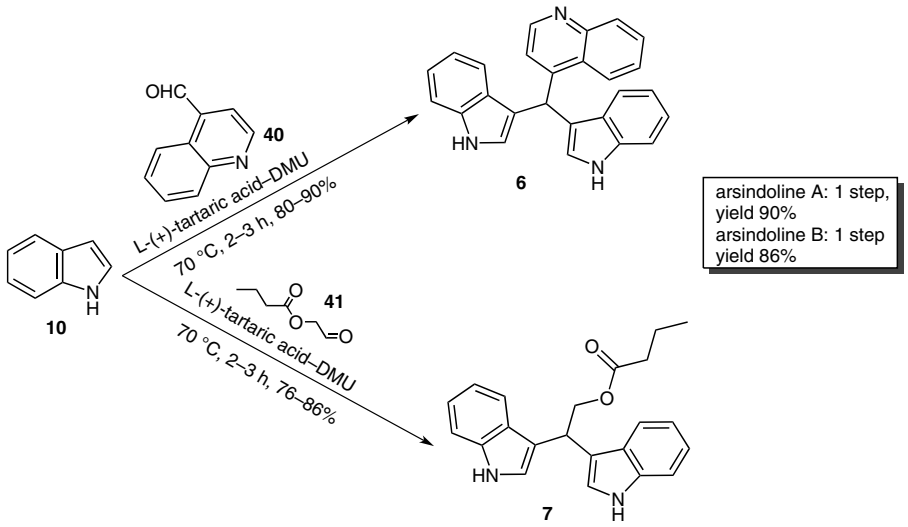


Scheme 16 Surasani's approach for the synthesis of vibrindole A

(Scheme 16). Indion Ina 225H heterogeneous catalyst has been identified as novel, selective, recyclable, and eco-benign catalyst for the electrophilic substitution of indole and various aldehydes to give bis(indolyl)methanes in excellent yields.[30] Treatment of indole (**10**) with acetaldehyde (**38**) in the presence of Indion Ina 225H resin gave vibrindole A (**2**). Moreover, reaction of indole (**10**) with ethyl glyoxalate gave ethyl bis(indolyl)acetate **31**, which on reduction using borane, followed by acetylation employing iron(III) fluoride–acetic anhydride gave streptindole (**1**) in 85% overall yield. This strategy represents the highest yield to date for the synthesis of streptindole in three steps .

In 2013, Jella and Nagarajan described the synthesis of arsindoline A (**6**) and B (**7**), and their analogues, using low melting mixtures (Scheme 17).[31] Low-melting mixtures having an organic acid as one of the melt components were used for the coupling of two molecules of indoles with various aldehydes; the conditions were optimized using various low-melting mixtures. L-(+)-Tartaric acid–dimethylurea (DMU) was the best reaction medium in terms of reaction time and yield. L-(+)-Tartaric acid–dimethylurea (30:70) was heated to 70 °C to obtain a clear melt, which was treated with indole (2 mmol) and aldehyde (1 mmol) for two hours to give the arsindoline skeleton. Arsindoline A (**6**) was synthesized from quinoline-4-carbaldehyde (**40**) in 80–90% yield, whereas, arsindoline B (**7**) was synthesized from 2-oxoethyl butanoate (**41**) in 76–86% yield using this protocol.

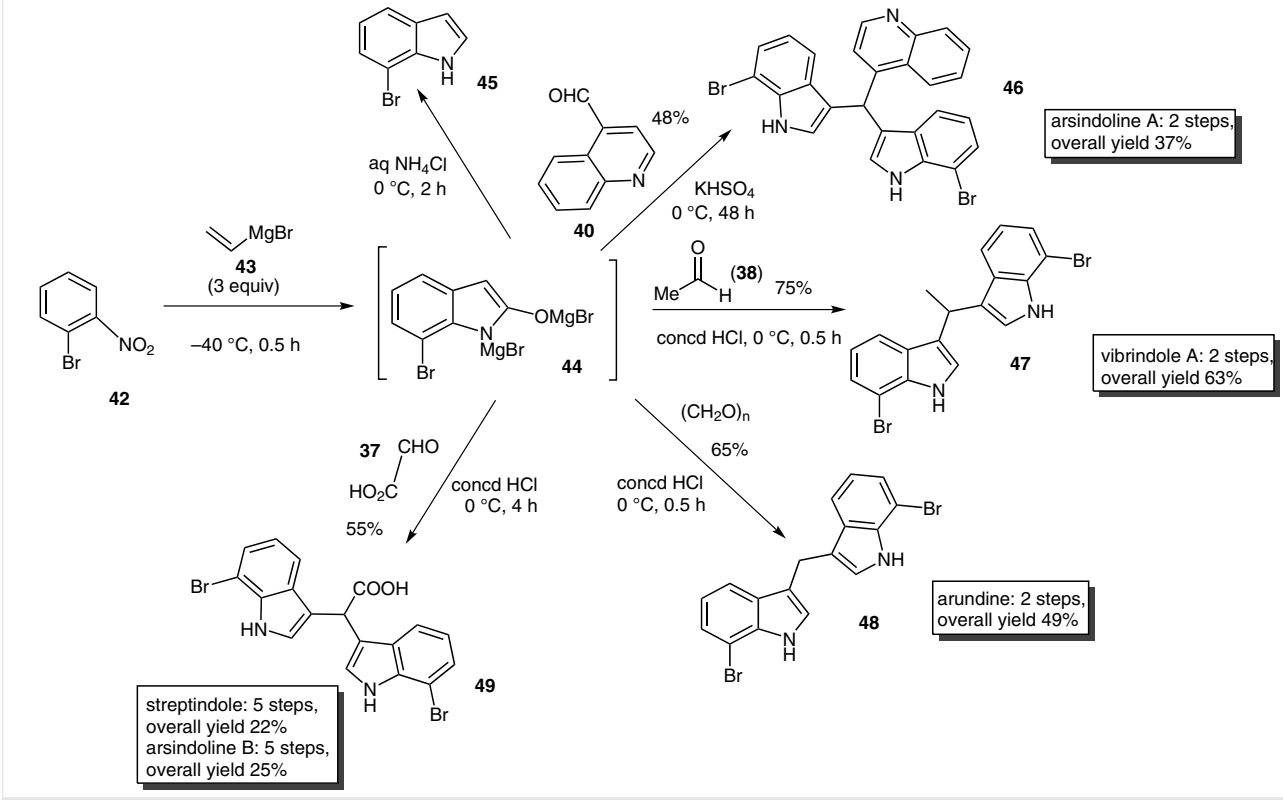
In 2013, Abe et al. reported the synthesis of five bis(indolyl)methane natural products streptindole (**1**), vibrindole A (**2**), arundine (**4**), arsindoline A (**6**), and arsindoline B (**7**) by modifying the Bartoli indole synthesis.[32] Reaction of 1-bromo-2-nitrobenzene (**42**) with three equivalents of vinylmagnesium bromide gave the intermediate indol-2-yloxymagnesium bromide **44**, which was used as an advanced intermediate for the synthesis of various natural bis(indolyl)methanes. Intermediate **44** was quenched by aqueous ammonium chloride to form 7-bromo-1*H*-indole (**45**) in the Bartoli indole synthesis, but the addition of concentrated hydrochloric acid instead of ammonium chloride during quenching led to the formation of bis(indolyl)methanes (Scheme 18). Bis(indolyl)methane **47** was formed by the reaction between intermediate **44** and acetaldehyde, generated by hydrochloric acid from vinylmagnesium bromide. However, the addition of an aldehyde during the



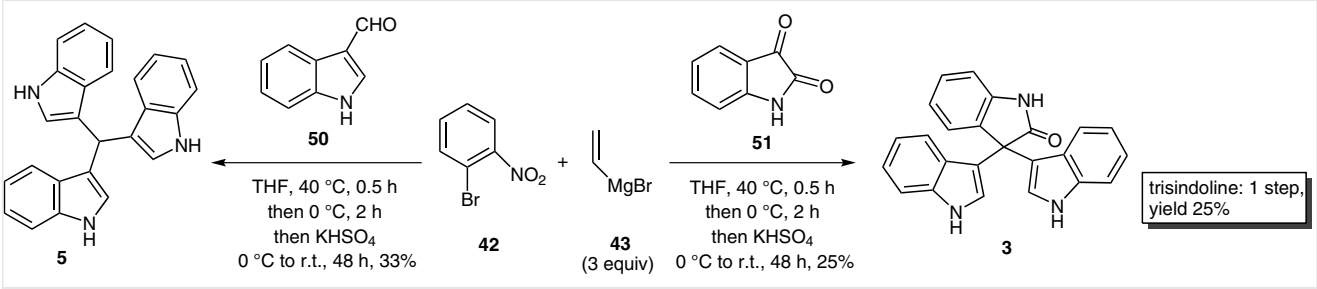
Scheme 17 Jella and Nagarajan's approach for the synthesis of arsindoline A and B

quenching step increases the yield of formation of the bis(indolyl)methane. Reductive debromination of the intermediate compounds **46**, **47**, and **48** (synthesized by using suitable quenching agent and aldehyde) using tributyltin hydride in the presence of a catalytic amount of 2,2′-azobis(isobutyronitrile) in refluxing toluene gave arsindoline A, vibrindole A, and arundine, respectively. Whereas, **49** on esterification, reduction, debromination, and acylation using a suitable reagent gave streptindole and arsindoline B.

Furthermore, Abe et al. used the same strategy for the synthesis of trisindoline (**3**) and tris(1*H*-indol-3-yl)methane (**5**) (Scheme 19). During the quenching step, the addi-



Scheme 18 Abe's synthesis of bis(indolyl)methane natural products



Scheme 19 Abe's synthesis of trisindoline

tion of isatin (**51**) or indole-3-carbaldehyde (**50**) led to the formation of trisindole **3** or tris(1*H*-indol-3-yl)methane (**5**), respectively. It is exciting to note that, during this reaction an unexpected debromination at the 7-position of the indole ring was observed, so the second step debromination was not required for the synthesis of the natural products. Recently, BIM-inspired skeletons have also been constructed and exploited for structural–activity relationship studies.[33,34] We also acknowledge that several published works on the topic that deserved to be cited may have been excluded, as this review deals with only selected natural BIMs.

4 Conclusions

Bis(indolyl)methanes are a family of alkaloids with a simple structural skeleton that possess promising biological activity. The varieties of bis(indolyl)methanes isolated from natural sources are increasing every year. However, the scarcity of natural products from natural sources led to a decrease in the exploration of natural products for biological studies. Corresponding to this fact, there is a need to design a new, simple, and efficient protocols for the construction of this core structures. Among bis(indolyl)methanes from natural sources, streptindole and vibrindole A have been synthesized by many routes with good yields. However, the synthesis of arsindoline and arundine is much less explored. The majority of the described methods utilize a catalyst to couple two indole rings. We believe that this review article will guide many researchers to construct libraries of bis(indolyl)methane natural products of marine origin.

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