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# Bisindolyl Methane Alkaloids: Isolation, Bioactivity and Syntheses

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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, vibrindole, arundine and trisindole are found in marine bacteria, while the related compound, streptindole was obtained from *S. faecium* IB 37, found in human faeces. In recent years, these molecules, displaying wide range of biological properties such as antibacterial, antiviral, anti-oxidant, neurotoxic, etc., have attracted attention of several synthetic and natural product chemists. This review attempts to list all the BIM analogues reported from different natural sources until now along with their biological properties and synthesis.

## Key words

Bisindolyl methanes, Natural products, Isolation, Synthesis, Bioactive metabolites.

## Introduction

Bisindolyl methanes (BIMs) are a group of alkaloids which has a basic skeleton of two indole groups bridged by single carbon at 3 and 3' position. Based on the groups/substiuents attached to the bridging methyl carbon atom, they are called by different names (Figure 1). While most of these compounds are found commonly in both marine and terrestrial organisms, a few of them are reported exclusively from terrestrial or marine organisms only. Due to their wide applications in

medicinal chemistry, drug discovery and agrochemicals, the syntheses and isolation of BIMs have attracted attention of several chemists over last few years. Due to their symmetric structure, they are easy to synthesize from two molecules of indole and an aldehyde/ketone using acid or base catalyst. But for a large scale synthesis, the method should be environment - friendly and cost effective. Several syntheses of BIMs starting from harmful chemicals to environmentally benign green synthesis in aqueous medium are now known; although with widely varying reactivities depending upon the substituents on the aldehyde/ketone. Several Indole derivatives are known to display promising biological properties such as antibacterial, neurotoxic, antioxidant, antiviral, etc. A few of these compounds are used as pesticides while some serve as new drug leads for treatment of depression and anxiety.[1] Thus, brominated trisindole alkaloids isolated from a new Caledonian sponge exhibited cytotoxicity against KB cells.[2] Vinca alkaloids such as vinblastine, vincrstine, vindesine etc., are important anti-tumor indole alkaloids presently in clinical use.[3]

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

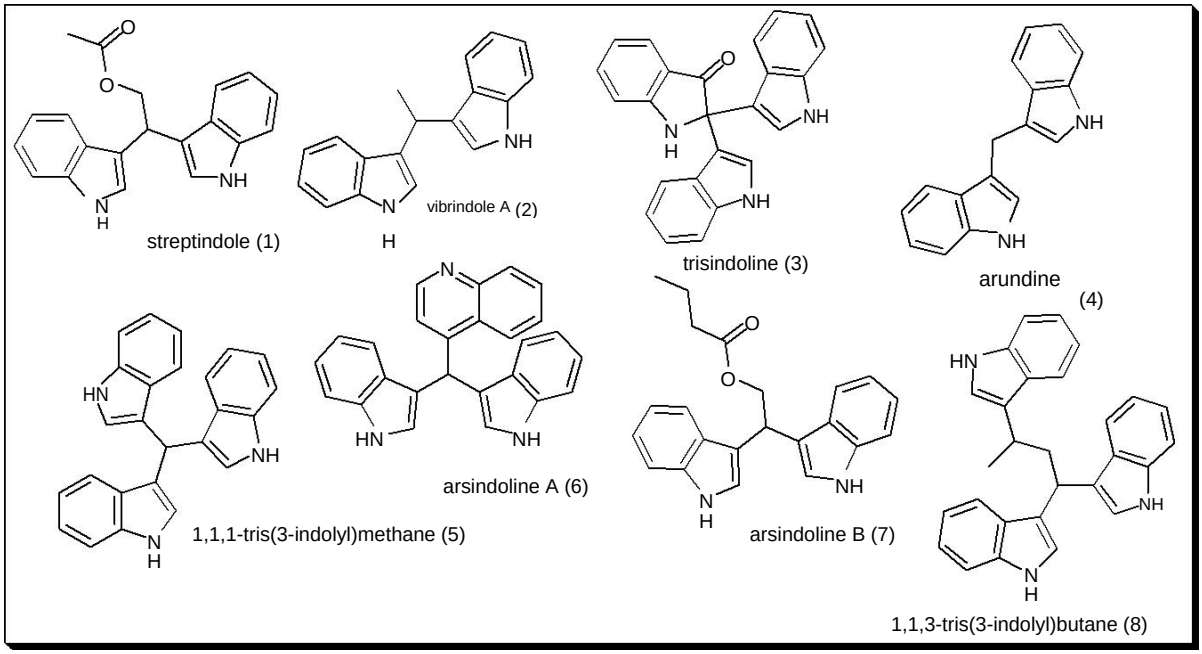


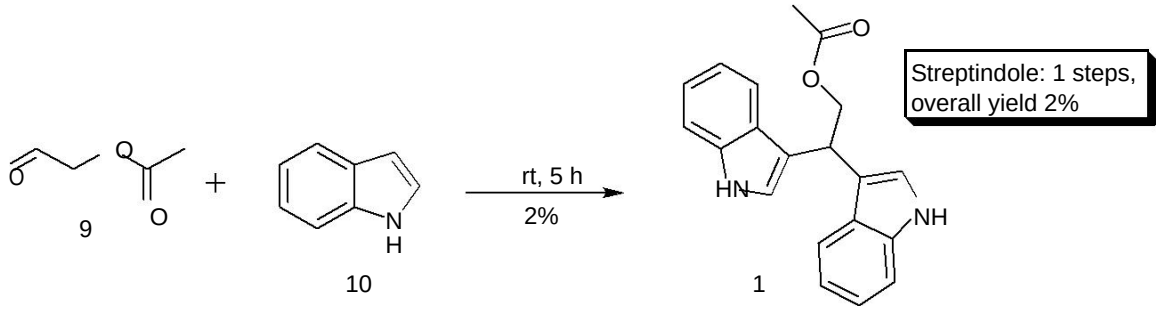

**Figure 1.** Structures of bis(indolyl) methane derivatives isolated from natural sources.

**Occurrence, Isolation, Structure elucidation and biological activities**

Streptindole **1**, isolated by T. Osawa *et al.* in 1983, is a genotoxic metabolite of human intestinal bacteria *S. faecium* IB 37.[6] The bacteria which is a predominant strain in human faeces was cultured in modified EG medium, and the compound was isolated from EtOAc fraction of the culture filtrate using prep 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

synthetic sample (Scheme 1). The synthetic protocol involves acetylation of glycoaldehyde at room temperature to furnish acetylated glycoaldehyde **9** which was treated with 2 equivalents of indole **10**

(253 mg) and stirred at room temperature for 5 h. The purified synthetic compound showed chromatographic behaviour and spectroscopic data identical to that of the natural product Streptindole **1**, reported earlier from the intestinal bacteria *B. Subtilis*, exhibiting DNA damaging and genotoxic properties. Streptindole **1** is structurally similar to the marine natural product arsindoline B **7** (Figure 1).

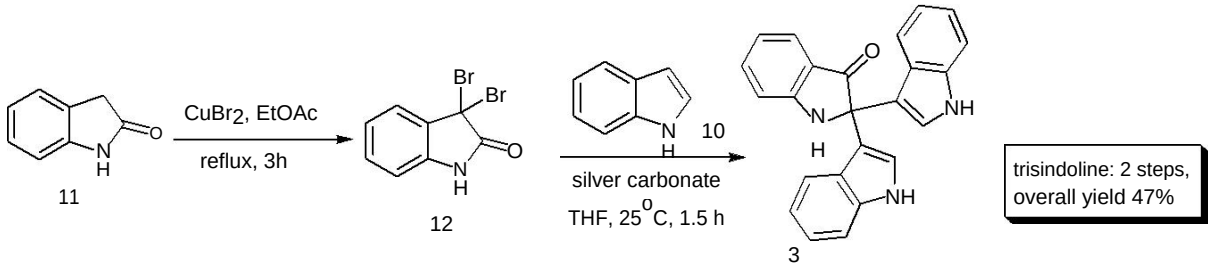



**Scheme 1** First synthesis of streptindole used for elucidation of structure obtained from natural source.

In 1994 R. Bell *et al.* described 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 onto petridish containing SLB agar. The culture medium was extracted with EtOAc and the extract was then purified using column chromatography (solvent: gradient PE-EtOAc mixture) to yield 12 fractions. Fractions displaying activity against *S. aureus* and *S. albus* were combined and further purified on a preparative HPLC column (C18, MeOH-$H_2O$ (3:1), 6mL/min), yielding 2,2-di(3-indolyl)-3-indolone (62.1 mg, Rt 13.3 min) as the major constituent. The target molecule, vibrindole A **2**, colorless oil eluted from the column much later (Rt = 44.7 min, 3.2 mg) (*m/z* 260.1370, $C_{18}H_{16}N_2$). The structure was also confirmed using different NMR techniques, *viz.*, $^{1}H$, $^{13}C$, HMQC and HMBC. Both the compounds displayed mild activity against *S. aureus* (11-mm zone of inhibition at 100µg/disc) while vibrindole A **2**, was also mildly active against two more strains, *S. albus* and *Bacilus subtilis* (11 & 7 mm) at same concentration level. Though vibrindole A **2** was isolated only in 1994, it was known as a synthetic product since 1963.[8,9,10]

In 1994, M. 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 *E. coli*, *B. subtilis* and *S. aureus*. Purification of the extract provided trisindoline **3** in 0.3% yield as a colourless amorphous powder (*m/z* 363, corresponding to the formula $C_{24}H_{17}N_3O$). Confirmation of the structure came from different 1D,

2D-NMR, techniques. The natural product was also synthesized subsequently (Scheme 2). Thus, oxindole **11**, upon refluxing with copper (II) bromide in ethyl acetate for 3 h yielded 3,3-dibromoxidole **12** which was then treated with indole **10** and silver carbonate in tetrahydrofuran at 25 $^{o}$C for 1.5 h 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). Few years later, trisindoline **3** was also reported from another marine bacterium *Vibrio parahaemolyticus bio249*[12] (North Sea) and the terrestrial plant *Isatis costata.*[13]




**Scheme 2** First synthesis of trisindoline **3** to support the data of isolated natural trisindoline.

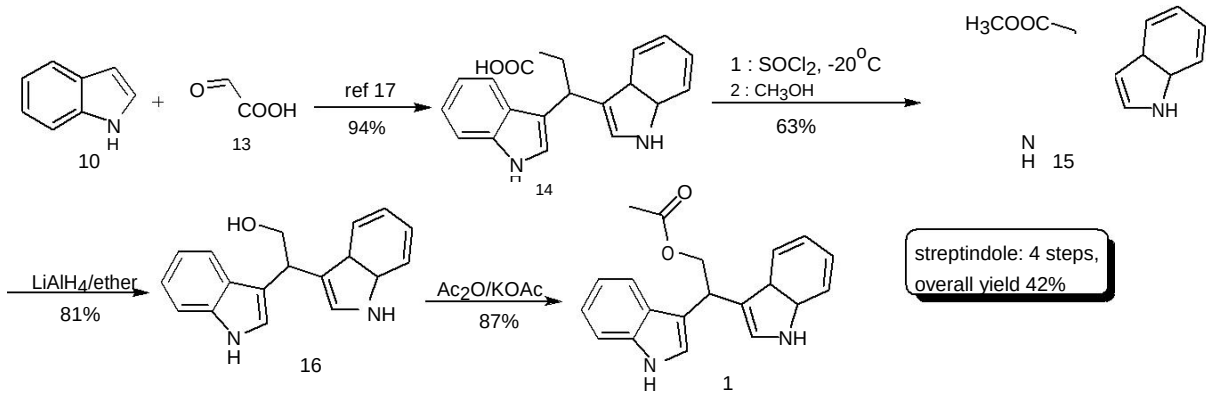
In 1994, Khuzhaev *et al.* first isolated arundine **4** (Figure 1) from the roots of arundodonax.[14] Nineteen years later (in 2013), H. Laatsch and co-workers isolated this metabolite along with a new compound 1,1,1-tris(3-indolyl)butane **5** (Figure 1) and several other known compounds from north sea bacterium *Vibrio parahaemolyticus* bio 249.[12] This was also the first report of occurrence of 3,3-bis(3-indolyl)butane-2-one, arundine **4** and 1,1,1-tris(3-indolyl)methane **8** 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 colour reaction with Ehrlich's reagent. The crude ethyl acetate extract of 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-di(3-indolyl)-3-indolone, paracine, p-hydroxyphenylethanol, phenyl actamide and thymine. The

compounds were inactive against a range of bacteria and fungi.

In 2010, Gu and co-workers isolated another indole alkaloids arsindoline A & B (**6**-**7**) (Figure 1) from a marine bacterial strain CB101 identified as *Aeromonas sp*. from the waters of Xiamen sea.[15] The EtOAc 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, 4-[di(1H-indol-3-yl)methyl]quinoline (arsindoline A **6**) and 2,2-di(1H-indol-3-yl)ethyl butanoate (arsindoline B **7**) as colourless amorphous powder alongwith 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).

**Synthetic Approaches towards Bisindolyl Methanes**

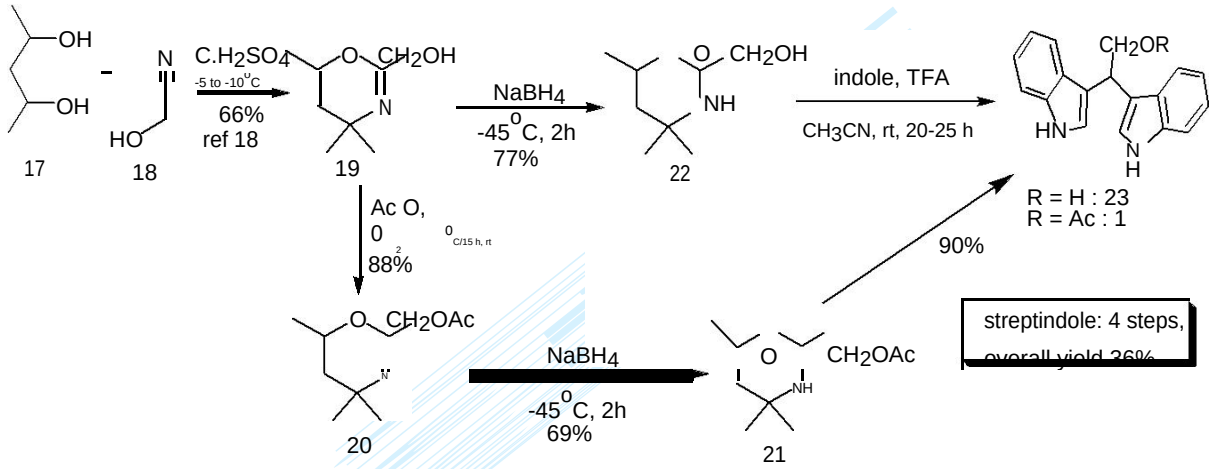
In an approach towards synthesis of bisindolyl methanes, Hogan and Sainsbury achieved total synthesis of streptindole **1** in 1984[16] (Scheme 3 ). Two indole rings were coupled together with glyoxylic acid **13** to give diindolylaceticacid[17] **14**, which is then converted into methyl ester **15**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




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

In 1988, Singh and Singh synthesized streptindole **1** and it's analogues by acid catalysed transfer of

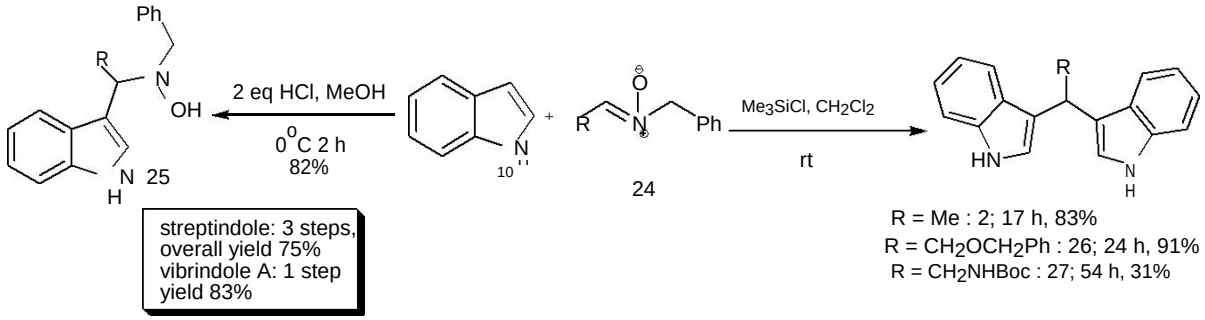
appropriate C-2 carbon units of oxazines **21, 22** to bisindoles as depicted in Scheme 4.[10] The synthetic approach involves Mayer's protocol[18] involving condensation of 1,3-diol **17** with hydroxy nitrile **18** to furnish oxazolidine **19**, which on acetylation followed by reduction gave dihydrooxazolidine acetate **21** and finally on condensation with indole and TFA delivered streptindole **1**. Alternatively, treatment of oxazine **22** with indole and TFA gave alcohol **23** which on acetylation furnished streptindole **1**. Thus, the total synthesis of streptindole **1** was achieved in 4 steps. Authors also highlighted the synthesis of various analogues of streptindole by varying the substituents on α-carbon of C-2 substituent of 5,6-dihydro-(4*H*)-1,3-oxazines **21, 22**.




**Scheme 4** Singh's approach for the synthesis of streptindole

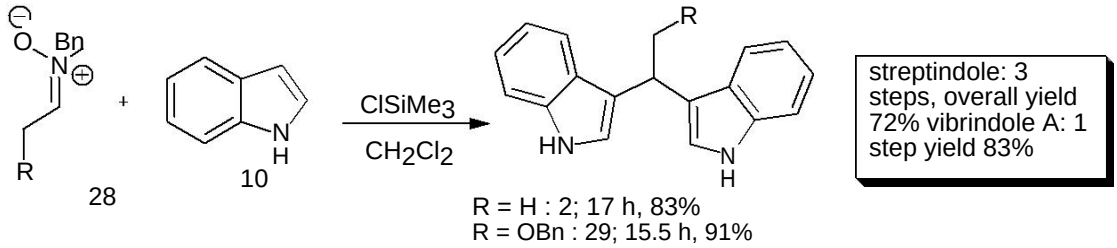
In 1997, Vallee and co-workers demonstrated the reaction of indoles **10** with nitrones **24** and generated the library of diindolyl alkanes (Scheme 5).[19] Three natural products containing 3,3'-diindolyl alkane skeleton has been prepared using this protocol. Among the various screened activation reagents, 1 eqv. of chloromethyl silane was found to be effective in reaction of indole **10** with nitrone **24** to deliver diindolyl alkane. However, this condensation reaction in presence of HCl/MeOH led to the formation of *N*-hydroxylamine **25**. Reaction of indole with various nitrones **24** gave BIM derivatives **2, 26, 27** in the presence of $Me_3SiCl$. Thus, vibrindole A **2** is prepared in 83% yield. Compound **26** on debenzylation followed by acetylation resulted in the formation of streptindole **1**. This resulted in synthesis of steptindole **1** in 3 steps with 75% overall yield. Bisindole derivative **27** on deprotection furnished amine which is a also natural product isolated

from California tunicate *Didemnum candidum*.




**Scheme 5** Vallee's earlier approach for the synthesis of streptindole and vibrindole

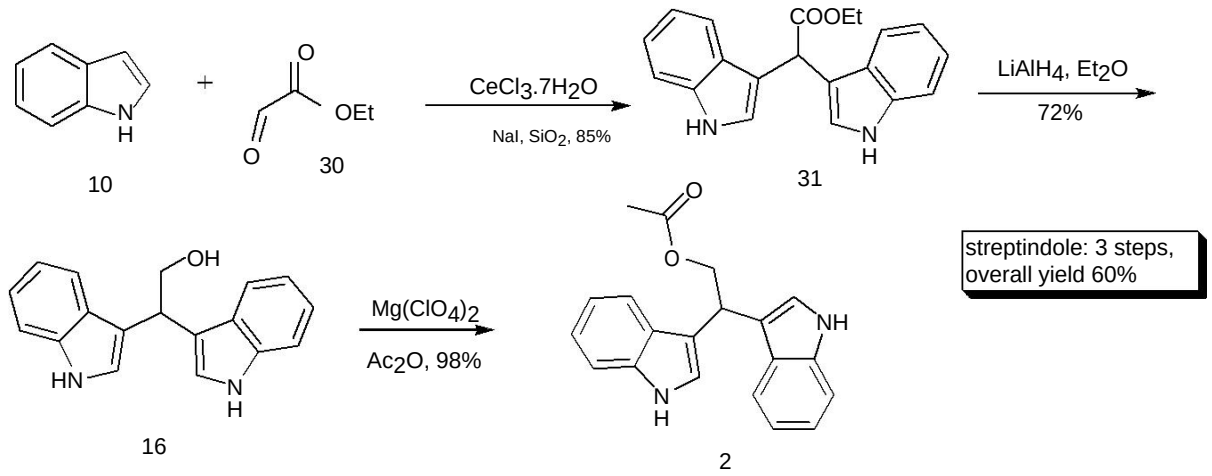
Three years later (in 2000), Vallee and co-workers also used nitrone chemistry for the synthesis of three bisindolyl methane natural products (scheme 6),[20] which represents the second article from their research group using nitrone chemistry. Like their previous work, authors had used $ClSiMe_3$ for the activation of nitrones **28** (R = H) to undergo electropilic substitution with indole **10** to give vibrinolle A **2**. Compound **29** was reduced to corresponding alcohol and the alcohol is acetylated to streptindole with 72% overall yield. Additionally, authors had reported the first time synthesis of 2,2-bis(6'-bromo-3'-indolyl)ethylamine which was isolated from the tunicate *Didemnum candidum*.




**Scheme 6** Vallee's second approach for the synthesis of streptindole and vibrindole

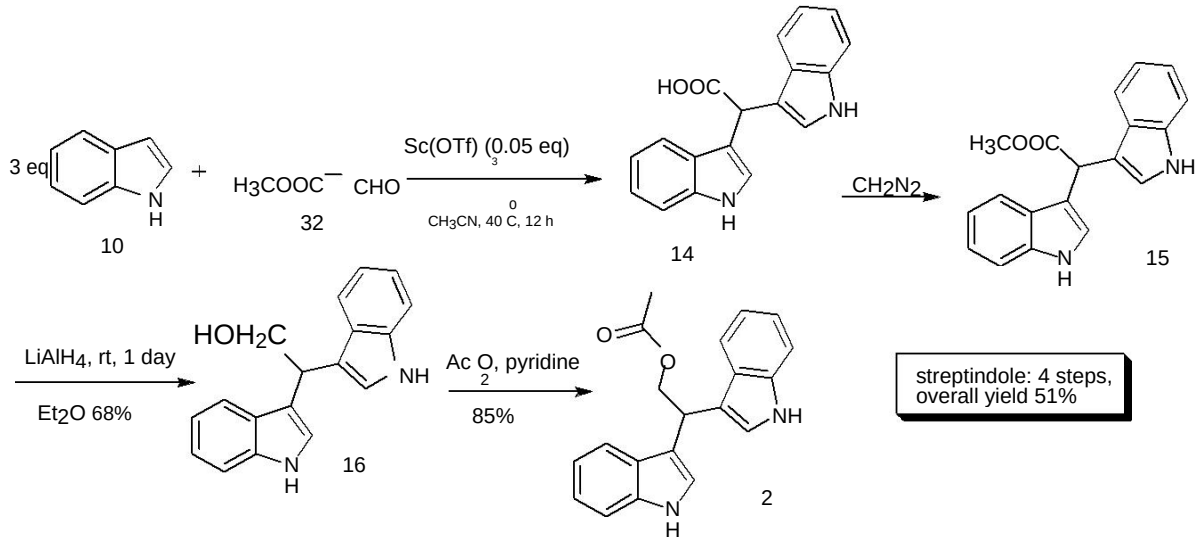
In 2004, Bartoli *et al.* had described an efficient route for construction of libraries of BIMs in high yield using solvent free condition using $CeCl_3.7H_2O$-NaI-$SiO_2$ as solvent free promoter in the key indole addition step (Scheme 7). Indole **10** is reacted with ethyl glyoxylate **30** in presence of $CeCl_3.7H_2O$-NaI-$SiO_2$ to give ethyl di-1H-indol-3yl-acetate **31**, which was then reduced into the corresponding alcohol **16**. Finally the alcohol **16** is *O*-acetylated using $Mg(ClO_4)$ as useful

alternative to metal triflate promoters to give streptindole **2**.[21]




**Scheme 7** Bartoli's approach for the synthesis of streptindole

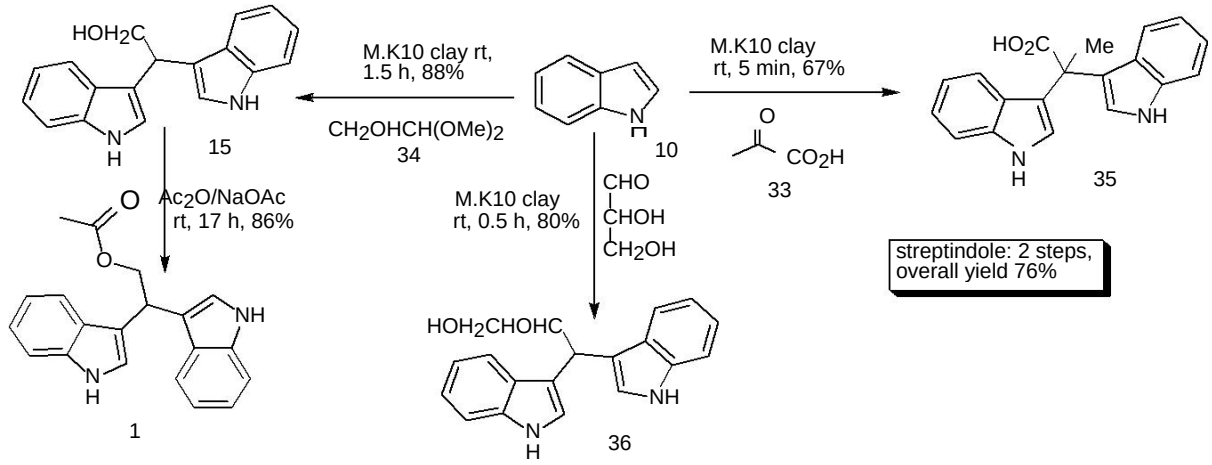
In 2005, Sato and Sato have demonstrated the utility of scandium(III)trifluoro- methanesulfonate [$Sc(OTf)_3$] for preparation of BIMs (Scheme 8) in good yield.[22] Further this method has been employed for the synthesis of streptindole **1**. Treatment of indole **10** with glyoxylic acid **32** in presence of $Sc(OTf)_3$ for 12 h gave bis(3'-indolyl)ethanoic acid **14** which on esterification using diazomethane followed by $LiAlH_4$ reduction give alcohol **16**. Subsequent acetylation under standard procedure gave the naturally occurring streptindole **1** in a total of 51% overall yield.




**Scheme 8**; Sato's approach for the synthesis of streptindole

Chakrabarty *et al.* used M.K10 clay (montmorillonite K10) under solvent free condition for the

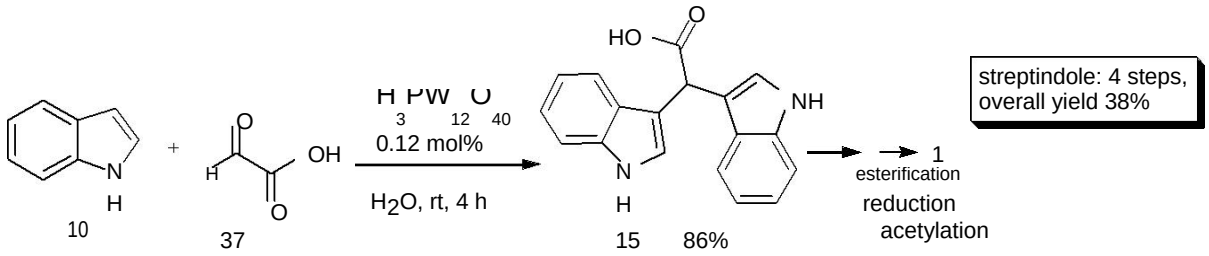
synthesis of three naturally occurring BIMs in 2006 (Scheme 9).[23] 3,3-bis(3'-indolyl)propane-1,2-diol **36** was synthesized by reaction of glycerol with indole **10** in 80% yield. Streptindole **1** was synthesized in two steps using M.K10 clay. Synthesis involves treatment of glycolaldehyde dimethyl acetal **34** with indole **10** in presence of M.K10 clay to give diindolylalkanol **15**, which on acetylation delivered streptindole **1** with 76% overall yield, Moreover, diindolylpropionic acid **35** was synthesized in single step by reacting indole **10** with pyruvic acid **33**. Overall, this approach is leading as efficient and concise method for the synthesis of streptindole **1** providing highest overall yield of 76% in 2 steps till date. The authors had previously reported the synthesis of vibrindole A in their previous communication which is included in the later section (vibrindole A synthesis) of this review.




**Scheme 9** Chakrabarty's approach for the synthesis of streptindole

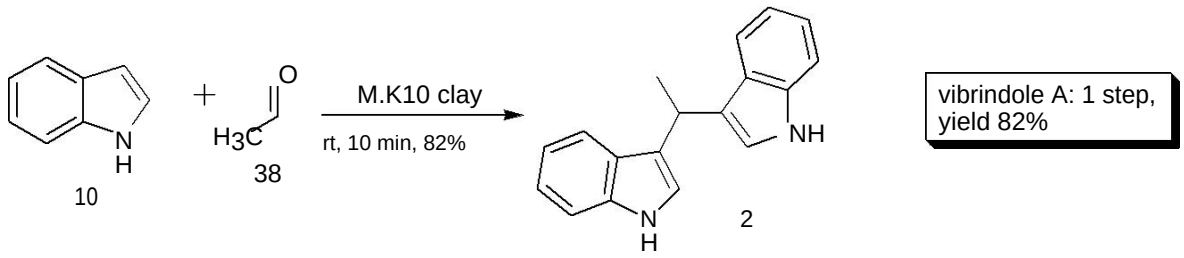
In 2007, Azizi *et al.* synthesized streptindole in water using heteropoly acid as catalyst.[24] Towards this end, authors have optimized reaction condition by using different acids and solvents. At first the reaction of indole with 2,4-dichlorobenzaldehyde catalysed by heteropoly acids in water and other solvents are investigated and identified water as optimal solvent for the reaction. Furthermore they tested the catalytic activity of different catalysts such as $HClO_4$, $WCl_6$, $ZnCl_2$ and obtained only moderate yield in water. In addition, reactivity of $H_3PMo_{12}O_{40}$ has been compared with $H_3PW_{12}O_{40}$ and found identical results for both the catalysts. Finally, $H_3PW_{12}O_{40}$ (0.12 mol%)

in water was chosen as optimum condition and applied for the synthesis of streptindole **1** (Scheme 10). Reaction of indole **10** with glyoxalic acid **37** in the presence of catalyst to give corresponding bis(indolyl)acetic acid **15**, which on esterification, reduction and acetylation gave streptindole **1** in 38% overall yield.




**Scheme 10** Azizi's approach for the synthesis of streptindole

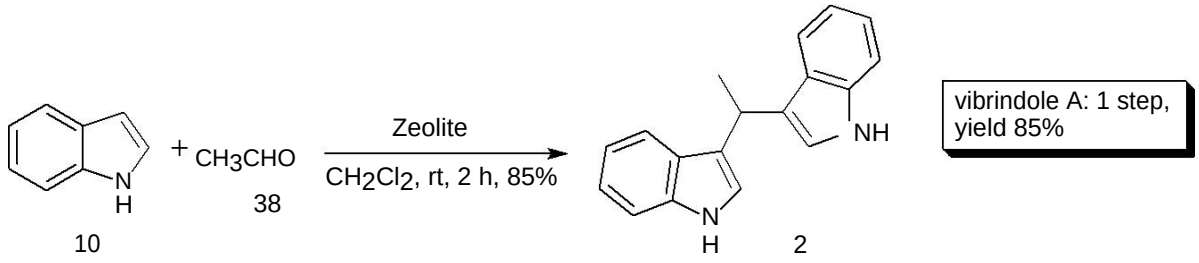
In next section, we had highlighted the synthetic approaches towards another BIM *i.e* vibrindole **2**. Chakrabarty and co-workers synthesized vibrindole using montmorillonite K10 clay (M.K10) as catalyst for the indole addition to acetaldehyde. [25] Moreover authors had also described synthesis of various substituted BIMs using this strategy. Treatment of indole **10** with acetaldehyde **38** under solvent free condition using M.K10 (2g/1mmole of indole) gave vibrindole **2** in 82% yield in 10 min reaction time (Scheme 11). The M. K10 clay was washed and dried at 110-120 $^{o}$C and reused without loss of catalytic activity. The simplicity of workup procedure and reusability of catalyst is highlight of this work.




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

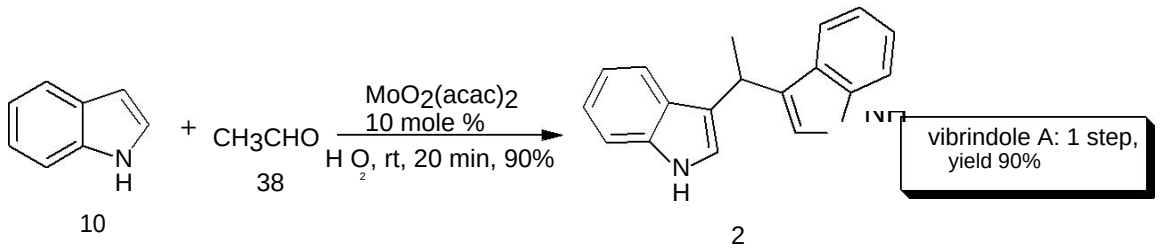
Karthik *et al.* synthesized vibrindole **2** using zeolite as the catalyst in 2005 (Scheme 12).[26] Reaction involves electrophilic substitution of indole **10** with acetaldehyde **38** at room temperature in DCM

to produce vibrindole **2** in 85% yield in 2 h reaction time. The catalyst is readily recyclable and can be reused five times without loss of activity. Also library of BIMs has been constructed by using indole and substituted aldehyde/ketone employing their protocol.




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

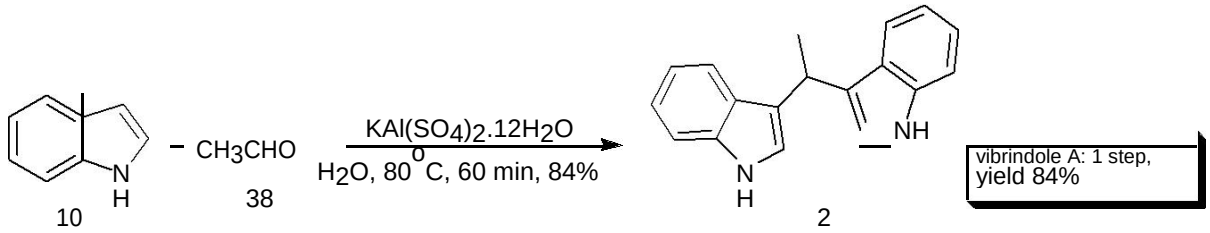
In 2007, Banerjee *et al.* synthesized vibrindole **2** in aqueous medium catalyzed by molbdenyl acetylacetonate (Scheme 13).[27] Reaction of indole **10** and acetaldehyde **38** in water and 10 mol % of $MoO_2(acac)_2$ at room temperature for 20 min gave vibrindole **2** in 90% yield. Moreover, the synthesis of related BIMs have been described using indole and various aldehyde and ketone in water medium catalysed by $MoO_2(acac)_2$.




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

In 2009, Kumar *et al.* demonstrated the synthesis of vibrindole **2** in aqueous medium using alum [$KAl(SO_4)_2.12H_2O$] as inexpensive and reusable catalyst.[28] Treatment of two equivalent of indole **10** with one equivalent of acetaldehyde **38** with 30 mol % alum in water at 80 $^{o}$C for 1h gave vibrindole **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 has been efficiently reused 5 times without any

further work up. A series of BIM analogues has been prepared by condensation of indole with various ketone in presence of alum.

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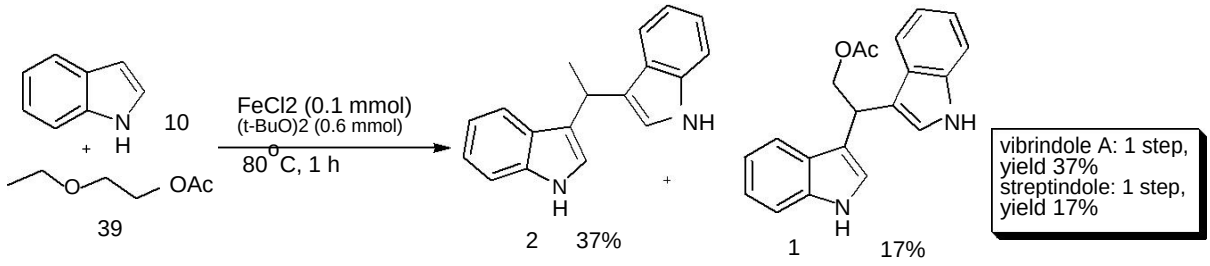
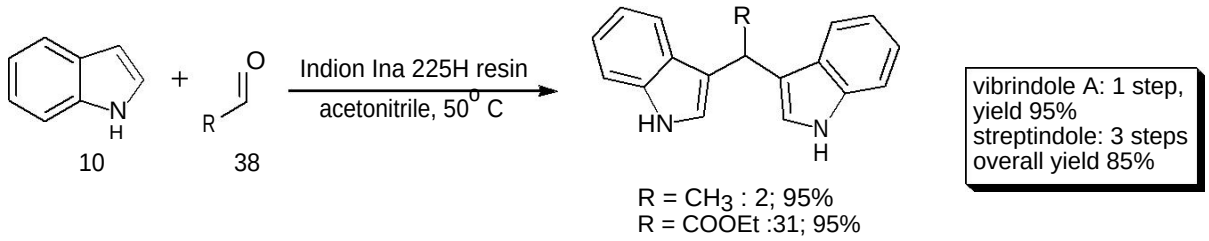
**Scheme 14** Kumar's approach for the synthesis of vibrindole A

In 2009, Guo *et al.* described the synthesis of both symmetrical and unsymmetric BIMs *via* catalytic oxidative coupling of the $sp^3$ C-H bond adjacent to an oxygen atom of both cyclic and non cyclic ethers **39** with $sp^2$ C-H bond in indole **10**. Evaluation of a series of catalysts and oxidants combination led to the identification of $FeCl_2$ and $(t\text{-BuO})_2$ as the best combination to provide target compounds in good yield.[29] Reaction of indole **10** with acetylated ether **39** in presence of Fe catalyst and $(t\text{-BuO})_2$ oxidant delivered mixture of two natural products vibrindole **2** and streptindole **1** which has been separated by using column chromatography (Scheme 15). Authors had demonstrated the synthesis of various analogues of symmetrical BIMs using this protocol. Interestingly, application towards unsymmetrical BIMs has been also highlighted. Towards this, when electron-withdrawing substituted indoles were used at 60 °C led to the formation of monoindolation products which was trapped by adding second indole at higher temperature resulted in the formation of unsymmetrical BIMs.



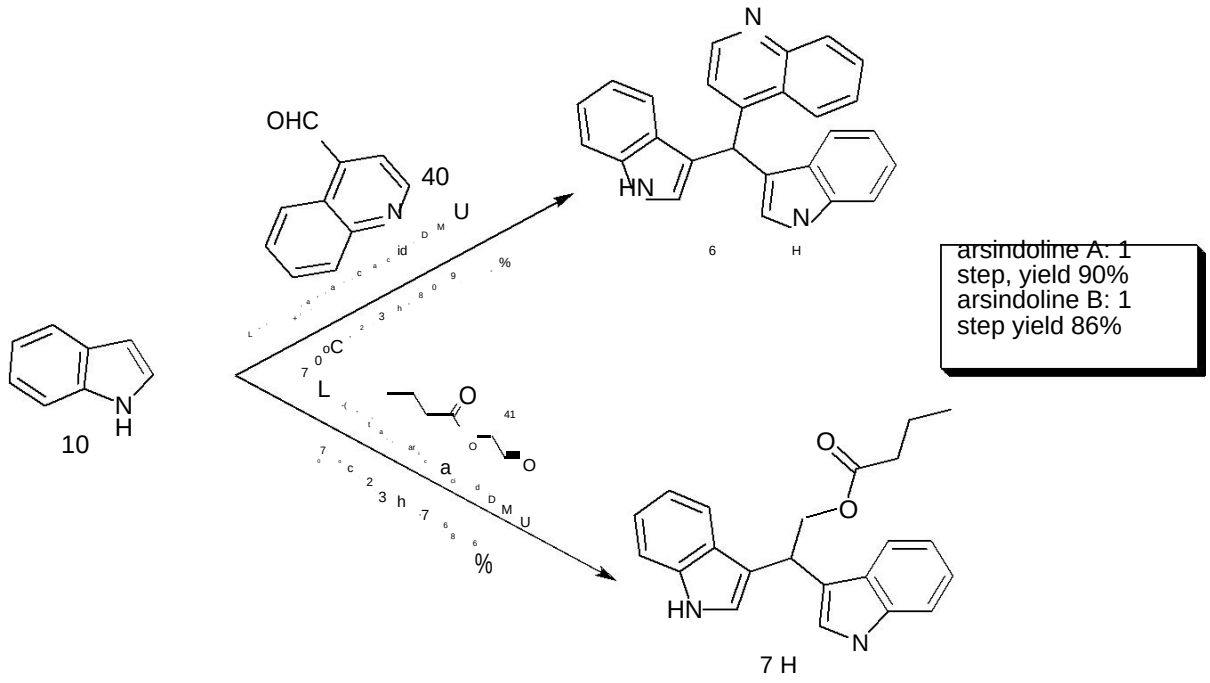

**Scheme 15** Guo's approach for the synthesis of vibrindole A and streptindole in one step

In 2012 Surasani *et al.* used Indion Ina 225H resin for the synthesis of vibrindole A **2** and streptindole **1** (Scheme 16). Indion Ina 225H heterogeneous catalyst has been identified as novel, selective, recyclable and echo-benign catalyst for electrophilic substitution of indole and various aldehyde to give BIMs in excellent yield.[30] Treatment of indole **10** with acetaldehyde **38** in the presence of Indion Ina 225H resin gave vibrindole **2**. Moreover, reduction of bis(indolyl)acetate **31** with ethyl glyoxalate gave ethyl(bis(indolyl) acetate **31** which on reduction using $BH_3$, followed by acetylation employing $FeF_3/Ac_2O$ gave streptindole **2** in 85% overall yield. This strategy represents the highest yield for streptindole in 3 steps till date.




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

In 2013, R. R. Jella and R. Nagarajan described the synthesis of arsindoline A **6** and B **7**, and their analogues using low melting mixture (Scheme 17).[31] They have used low melting mixture having organic acid as one of the melt components for the coupling of two molecules of indoles with various aldehydes and optimized the reaction using various low melting mixtures. L-(+)-tartaric acid-dimethyl urea has been identified as the best reaction medium in terms of reaction time and yield. L-(+)-tartaric acid-dimethyl urea (30:70) was heated to 70 $^{o}$C to obtain a clear melt, which was treated with indole (2mmol) and aldehyde (1 mmol ) for 2 h to construct arsindoline skeleton. Arsindoline A **6** was synthesized from quinoline-4-aldehyde **40** with 80-90% yield, whereas, arsindoline B **7** was synthesized from 2-oxoethyl butyrate **41** with 76-86% yield using their protocol.

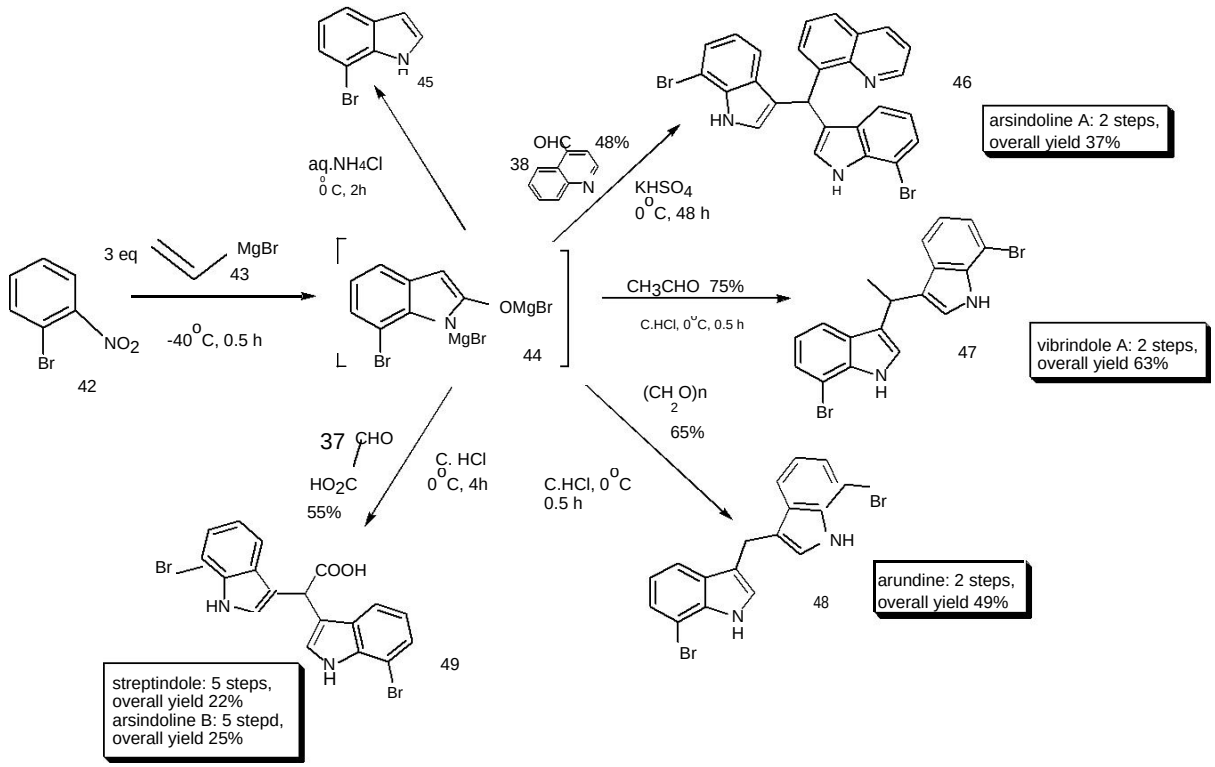



**Scheme 17** Jella's approach for the synthesis of arsindoline A and B

In 2013 Abe *et al.* reported the synthesis of five BIM natural products streptindole **1**, vibrindole **2**, arundine **4**, arsindoline A **6** and arsindoline B **7** by modifying Bartoli indole synthesis.[32] Reaction of 2-bromo nitrobenzene **42** with three equivalent of vinyl magnesium bromide gave the intermediate indole-*O*-MgBr **44**. This is used as an advanced intermediate for the synthesis of various natural BIMs. Usually intermediate **44** was quenched by aq. $NH_4Cl$ to form 7-bromo indole

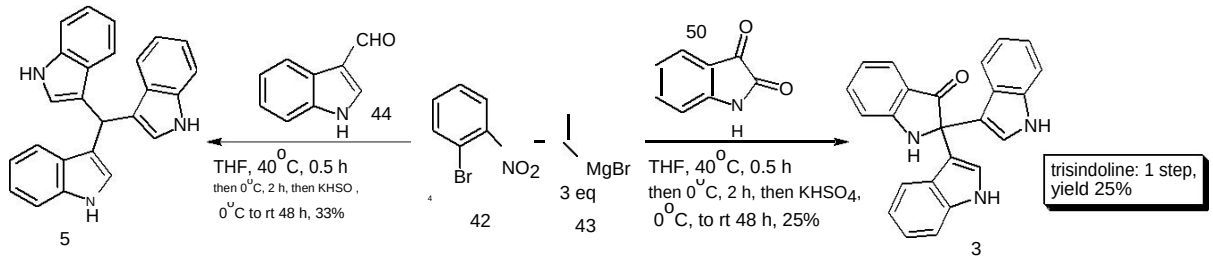
**45** in Bartoli indole synthesis. But addition of concentrated HCl instead of $NH_4Cl$ during quenching

led to the formation of bisindolyl methanes. Bisindolyl methane **47** was formed by the reaction between the intermediate and acetaldehyde which is generated by HCl from vinyl magnesium bromide. However, addition of aldehyde externally during the quenching step increases the yield of BIM formation. Reductive debromination of the intermediate compounds **46**, **47** and **48** (synthesized by using suitable quenching agent and aldehyde) using n-$Bu_3SnH$ in the presence of catalytic amount of AIBN in refluxing toluene gave arsindoline A, vibrindole and arundine respectively. Whereas, **49** on esterification, reduction, debromination and acylation using suitable reagent gave streptindole and arsindoline B.




**Scheme 18** Abe's synthesis of BIM natural products

Furthermore, Abe *et al.* used the same strategy for the synthesis of trisindoline **3** and tris(3-indolyl)methane **8** (Scheme 19). During the quenching step, utilization isatin **50** and indole-3-carboxaldehde **44** led to the formation of trisindole and tris(3-indolyl)methane 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.




**Scheme 19** Abe's synthesis of trisindoline

## Conclusions

BIMs are a family of alkaloids with simple structural skeleton possessing promising biological activities. The varieties of BIMs isolated from natural sources are increasing every year. However, the scarcity of natural products from natural sources led to the breakpoint in an exploration of natural products for biological studies. Corresponding to this fact, there is need to design a new, simple and an efficient protocols for the construction of this core structures. Among BIMs from natural sources, streptindole and vibrindole has been synthesized for many occasion with good yields. However arsindoline and arundine has been synthesized for couple of time. Most of the described methods utilizes catalyst for coupling of two indole ring. We belive that this review article will guide many researchers to construct libraries of BIM natural products of marine origin.

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