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Synthesis of novel non-isoprenoid phenolic acids and 3-alkylpyridines*

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Abstract: A new strategy has been developed for the synthesis of naturally occurring 6-alkenyl phenolic acids and 3-alkylpyridine alkaloids of biological importance. This strategy makes use of the proper substituted aryl or pyridyl sulfone as the potent intermediate. A carbanion was generated from the sulfone by treating it with NaH in dimethylformamide (DMF) at –5 °C and was used for alkylation reaction with alkyl/alkenyl bromide in DMF at 0 °C to give product, which, on reduction with sodium-amalgam, yielded the desired natural product. Using this methodology, we have synthesized 11 natural 6-alkyl/alkenyl salicylic acids, which were known to possess strong antimicrobial activities against many pathogens and had also shown molluscicidal activity against the snail *Biomphalaria glabrata*. This methodology was also extended to synthesize two natural 3-alkylpyridine alkaloids that were known to possess strong cytotoxic activity against P-388 murine leukemia cells with IC_{50} values of 1–2.3 μg/ml. Taking leads from these natural products, we have also synthesized a number of related compounds in order to find a potential drug candidate for the future. This paper presents the highlights of the work done on the synthesis of these two classes of compounds.

INTRODUCTION

The biologically active natural products isolated from different sources serve as the lead compounds for the discovery of new drugs. This is why the importance of plants and marine sponges has been appreciated from time to time as natural resources in pharmaceutical research. A number of compounds have been isolated from both these sources recently, which contained a lipophilic moiety in the form of an alkyl/alkenyl chain, attached to either benzene or heterocyclic skeleton. For example, anacardic acids (6-alkylsalicylic acids) are important constituents of cashew nut shell oil, while 3-alkylpyridines are that of marine sponges. Both of these classes of compounds are biologically important and hence require a good method for their construction. The present study deals with the development of a simple general method for the synthesis of 6-alkyl/alkenyl salicylic acids and 3-alkylpyridines exploiting sulfone chemistry.

NON-ISOPRENOID PHENOLIC ACIDS

The non-isoprenoid phenolic acids commonly known as anacardic acids are widely distributed in plants such as *Anacardium occidentale*, *Anacardium gigantium*, *Pentaspadon officinalis*, and *Pistachia vera*

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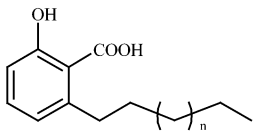
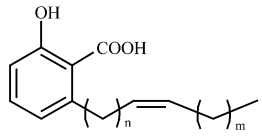
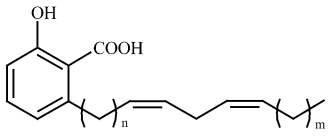
[1,2]. A series of new 6-*n*-alkenyl salicylic acids have been reported from *Spondias mombin* L. [3], the leaves of which are used as antimicrobial agents in folklore medicine for various purposes. These non-isoprenoid phenolic acids have shown antifeedant and antitumor activities besides inhibiting the prostaglandin synthesis [4–6]. Some of these compounds (**6**, **7**, **8**, **10**) have also shown pronounced antibacterial activities against *Bascillus cereus*, *Streptococcus pyogenes*, and *Mycobacterium fortuitum* and antiviral activities against *Coxsackie* B_2 and *Herpes simplex* type-1 viruses and had also molluscicidal activities against the snail *Biomphalaria glabrata*, an intermediate host in the Schistosome life cycle [3].



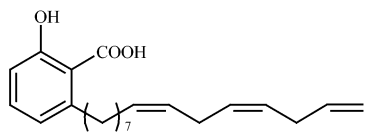
1 n = 6
2 n = 12
3 n = 14



4 n = 7, m = 3 **7** n = 11, m = 5
5 n = 7, m = 5 **8** n = 14, m = 4
6 n = 9, m = 5



9 n = 7, m = 2
10 n = 7, m = 4



11

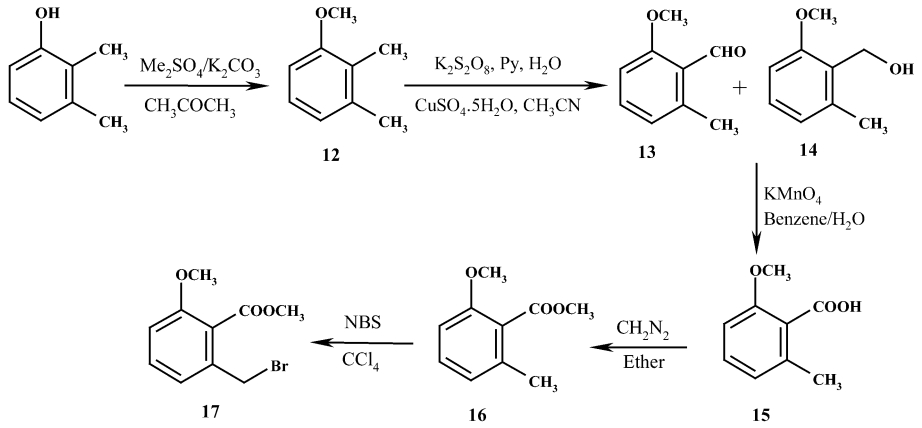
Salicylic acid, which is the basic unit present in these molecules, is also known to exhibit weak antimicrobial activity, and an addition of a long non-isoprenoid alkyl/alkenyl side chain results in its increased activity mainly against gram-positive bacteria [7]. To date, 18 compounds containing different alkyl/alkenyl side chains at C-6 position in salicylic acid have been isolated from various species and were found to be active. The maximum antibacterial activity was found against the cariogenic bacteria cl. Sp. *Propionibacterium acnes*, *Streptococcus mutans*, and *Brevibacterium ammoniagenes* when the alkyl/alkenyl chain in these compounds contained 12 carbon atoms [8].

Synthetic efforts have been made in the past [9–11] to obtain some of these phenolic acids, but in poor yields only. Since the methods described earlier were cumbersome and gave phenolic acids in poor yields, we have developed a general and economical method for the synthesis of these natural products in order to confirm their constitution and to obtain them in good amounts to assay them further.

Various synthetic strategies using different reactions were, therefore, envisaged to obtain these compounds in good yield, but none was successful. For example, 3-nitrophthalic anhydride when alkylated with dialkyl cadmium reagent gave an isomeric compound identified as 2-acyl-3-nitrobenzoic acid in place of the desired intermediate 2-acyl-6-nitrobenzoic acid. In another attempt, alkylation of 4-methoxyphthalide under different conditions also failed to give anticipated intermediate, 2-methoxy-6-acyl-benzylalcohol.

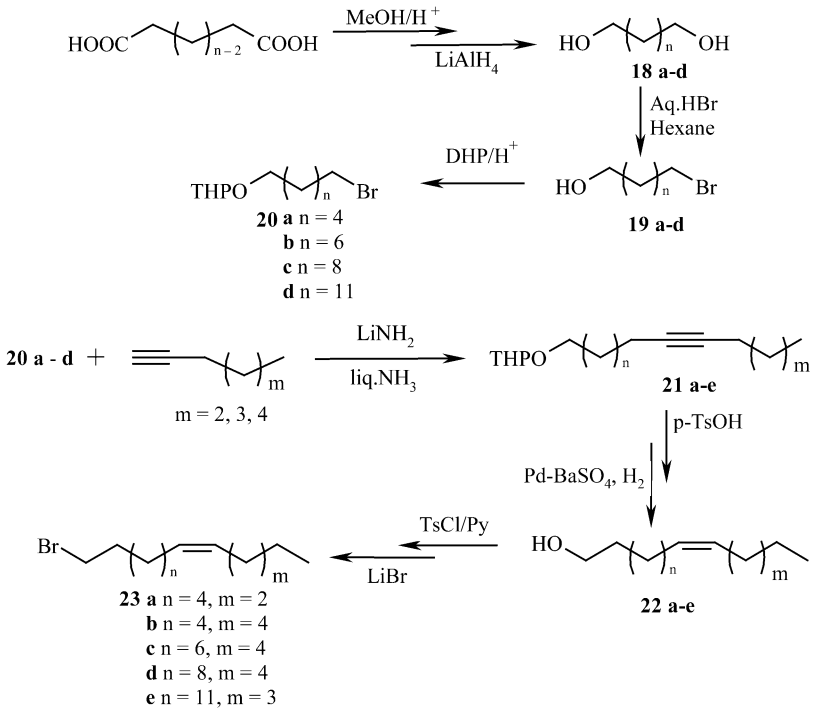
Finally, on the basis of retrosynthetic analysis, we identified two important synthons viz. methyl 6-bromomethyl-2-methoxybenzoate (**17**) and an alkyl/alkenyl bromide to construct our target molecule.

The benzoate **17** was prepared starting from the commercially available 2,3-dimethylphenol, which, on methylation followed by persulfate oxidation of the resulting methylether **12**, gave an oil that contained a mixture of aldehyde **13** and alcohol **14** [12]. This mixture was oxidized to 6-methyl-2-methoxybenzoic acid (**15**) using aq. $KMnO_4$. **15** on esterification with diazomethane followed by bromination using NBS gave methyl 6-bromomethyl-2-methoxybenzoate (**17**) in 60 % overall yield.



Scheme 1

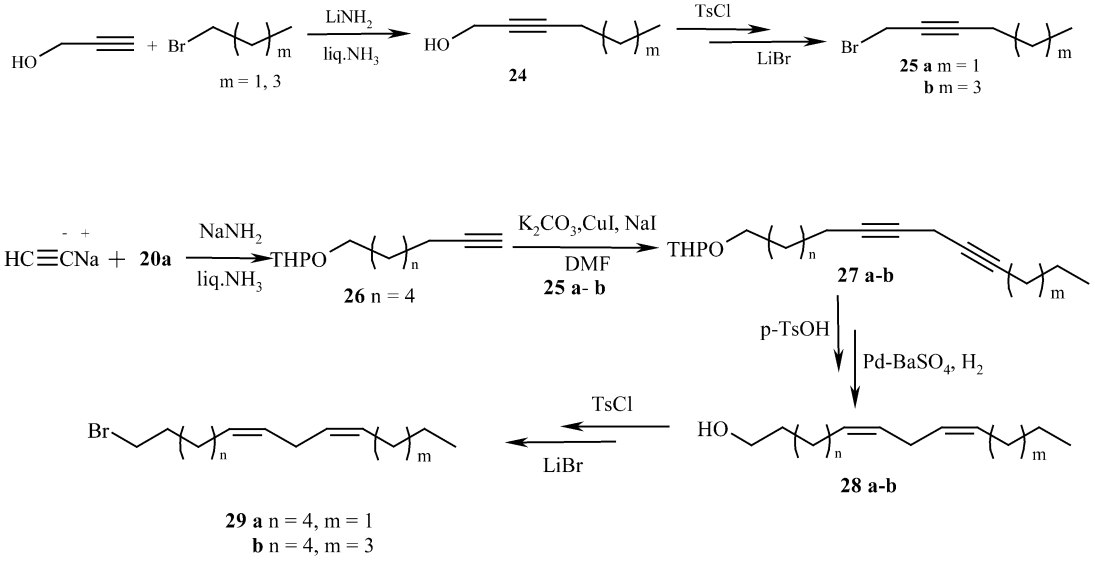
The lipophilic part of the target molecule required various alkenyl bromides **23a–e**, which have been synthesized using the synthetic strategy as underlined in Scheme 2. For example, 1-bromo-7*Z*-dodecene was synthesized starting from 1-[(tetrahydro-2*H*-pyran-2yl)oxy]-6-bromohexane (**20a**) and 1-hexyne; **20a** required for the synthesis was prepared from hexane-1,6-dioic acid via its diester. The diester was reduced using $LiAlH_4$ to the corresponding diol **18a**, which, on monobromination using aq. HBr, gave 6-bromohexanol. **19a** was then protected as a tetrahydropyranyl ether **20a** using DHP in the presence of HCl.



Scheme 2

The coupling of **20a** with 1-hexyne in the presence of a strong base ($LiNH_2$ in liq. NH_3) gave 1-[(tetrahydro-2*H*-pyran-2yl)oxy]-7-dodecyne (**21a**), which, on hydrolysis with *p*-TsOH in aq. methanol followed by reduction in the presence of a Lindlar catalyst, gave 7*Z*-dodecenol (**22a**). The geometry of the double bond was found to be *Z* only from its ^{1}H NMR spectrum. This was indirectly supported by IR, which showed the absence of a characteristic absorption at 960 cm^{-1} for its *E*-isomer. Finally, **22a** was converted into bromide **23a** via its tosylate using LiBr under anhydrous conditions [13]. Using the above set of reactions, alkenyl bromides **23b–e** were also prepared.

Further alkadienyl bromides viz. 1-bromo-7*Z*,10*Z*-tetradecadiene (**29a**) and 1-bromo-7*Z*,10*Z*-hexadecadiene (**29b**) required for the synthesis of natural products **9** and **10** were prepared using the synthetic strategy as outlined in Scheme 3; **29a** was synthesized starting from 1-bromo-2-hexyne (**25a**) and 1-[(tetrahydro-2*H*-pyran-2yl)oxy]-7-octyne (**26**). **25a** was prepared from 2-hexynol, while **26** was obtained by monoalkylation of sodium acetylide with **20a**. The bromoalkyne **25** thus obtained was purified by fractional distillation under reduced pressure and characterized by its ^{1}H NMR spectrum, which showed a characteristic peak at δ 2.10 (s, 1H, –C≡CH). Its IR spectrum also showed the presence of absorption band at 2165 cm^{-1}, confirming, thereby, the presence of monosubstituted acetylenic group.

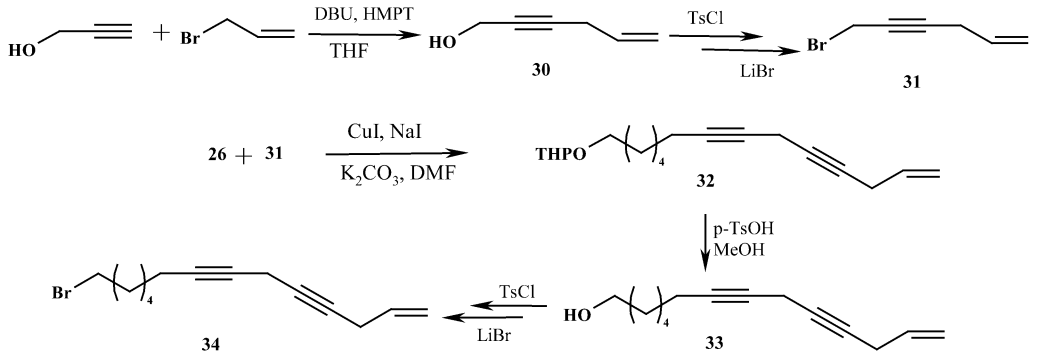


Scheme 3

The purified bromoalkyne **25a** was then coupled with **26** in the presence of K_2CO_3 in DMF using a mixture of CuI and NaI as catalyst to obtain 1-[(tetrahydro-2*H*-pyran-2yl)oxy]-7,10-tetradecadiyne (**27a**). This was followed by reduction using H_2 in presence of Lindlar catalyst to give 7*Z*,10*Z*-tetradecadienol (**28a**), which was finally converted into bromide **29a** via its tosylate.

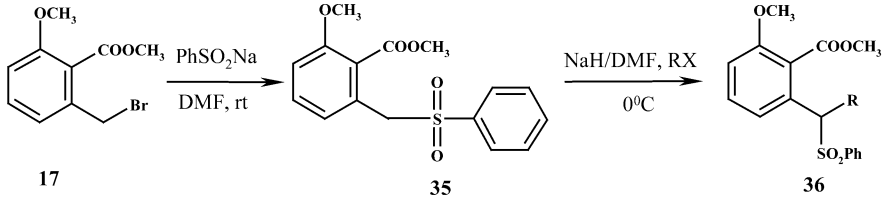
Besides alkenyl and alkadienyl bromides **23a–e** and **29a–b**, we also required 1-bromo-tetradec-13-en-7,10-dyne (**34**) for the synthesis of natural product **11**. It was synthesized starting from **26** and 1-bromo-hex-5-en-2-yne (**31**) following the steps shown in Scheme 4. Bromohexenyne **31** required was, however, prepared starting from hex-5-en-2-ynol (**30**), which in turn was obtained by coupling propargyl alcohol with allyl bromide in the presence of DBU and HMPT.

After synthesizing both the required aromatic and aliphatic synthons, our next goal was to put them together using a simple and convenient reaction involving C–C bond formation, in order to get the desired phenolic acids in good yield. Our initial efforts of coupling the Grignard derivative of either of the synthon with the other bromide failed to give alkyl or alkenyl salicylic acids in good yield.



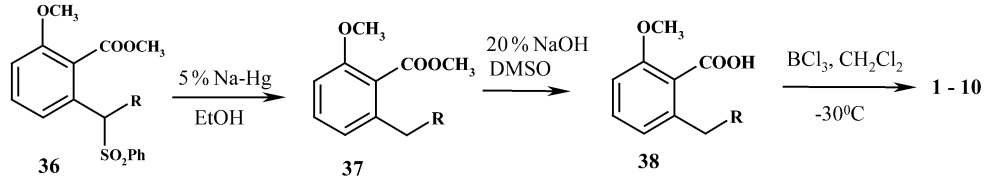
Scheme 4

Therefore, we turned around to the sulfone chemistry and converted **17** into methyl 2-methoxy-6-(phenylsulfonylmethyl)benzoate (**35**) using sodium benzenesulfinate in DMF at room temperature (Scheme 5). Treatment of sulfone **35** separately with LDA and *n*-BuLi at –78 °C gave a brown enolate, which on quenching with alkyl/alkenyl bromide gave the desired product, methyl 2-methoxy-6-(1-phenylsulfonyl alkyl/alkenyl)benzoate (**36**) in 10–15 % yield only. But when the sulfone **35** was treated with sodium hydride, we got a yellow enolate, which, on quenching with alkyl/alkenyl bromide, gave the alkylated product in 75 % yield. These alkylated compounds were fully characterized by their ^{1}H NMR spectrum, which showed a characteristic double doublet for –C**H**(SO_2Ph) at δ 5.20 (1H, J = 4.66 and 4.70 Hz).

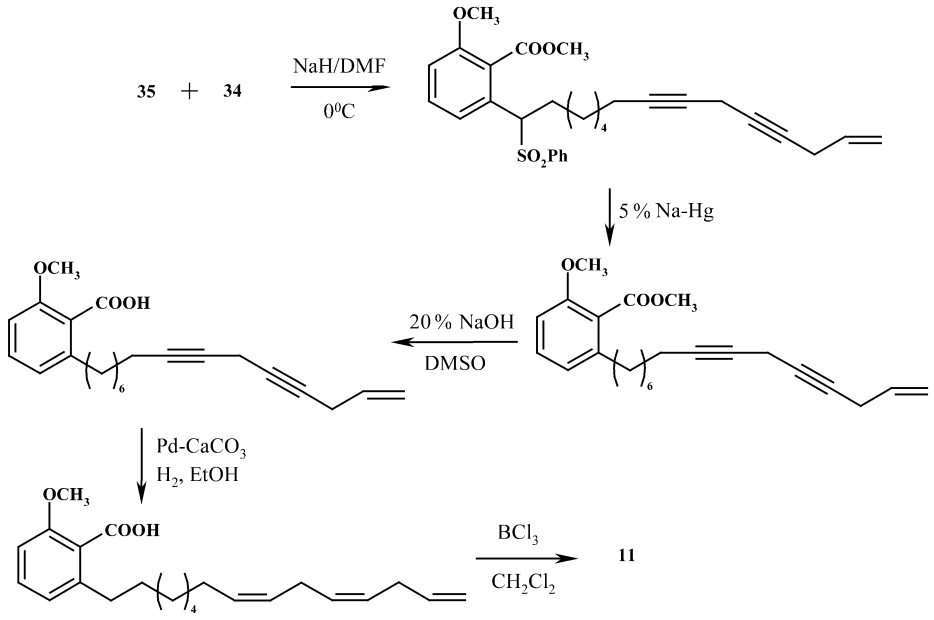


Scheme 5

The benzene sulfonyl group was then removed by reduction with 5 % Na–Hg in absolute ethanol to obtain the corresponding ester **37**, which was hydrolyzed to get the methoxy acid **38**. On demethylation using 1 M solution of BCl_3 in CH_2Cl_2 at –30 °C under nitrogen, this gave corresponding 2-hydroxy-6-alkyl/alkenyl benzoic acids (**1**–**10**) (Scheme 6). All of these hydroxy acids gave green color with alcoholic $FeCl_3$ solution, indicating that demethylation had occurred. Using the above strategy of hooking the aliphatic moiety with an aromatic moiety, we have also synthesized another natural product 2-hydroxy-6-(8*Z*,11*Z*,14-*Z*-pentadecatrienyl)benzoic acid, isolated from *Anacardium occidentale* (Scheme 7).



Scheme 6



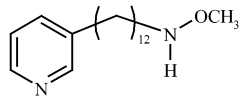
Scheme 7

Thus, in all, we have synthesized 11 natural products, namely, 2-hydroxy-6-undecylbenzoic acid (**1**), 2-hydroxy-6-heptadecylbenzoic acid (**2**), 2-hydroxy-6-nondecylbenzoic acid (**3**), 2-hydroxy-6-(8*Z*-tridecenyl)benzoic acid (**4**), 2-hydroxy-6-(8*Z*-pentadecenyl)benzoic acid (**5**), 2-hydroxy-6-(10*Z*-heptadecenyl)benzoic acid (**6**), 2-hydroxy-6-(12*Z*-nondecenyl)benzoic acid (**7**), 2-hydroxy-6-(12*Z*-15*Z*-heneicosadienyl)benzoic acid (**8**), 2-hydroxy-6-(8*Z*,11*Z*-pentadecadienyl) benzoic acid (**9**), 2-hydroxy-6-(8*Z*,11*Z*-heptadecadienyl)benzoic acid (**10**), and 2-hydroxy-6-(8*Z*,11*Z*,14-pentadecatrienyl)benzoic acid (**11**). All of these hydroxy acids and their intermediates have been fully characterized on the basis of their detailed spectral studies, and the data recorded were comparable to those reported for the corresponding natural products in the literature, thus confirming their structures.

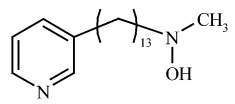
3-ALKYLPYRIDINES

In continuation to our interest on the synthesis of biologically active compounds that contain a lipophilic chain, we have recently come across some naturally occurring 3-alkylpyridine alkaloids which contained *O*- or *N*-methyl hydroxylamine groups. These have been reported to occur in marine sponges and were found to show biological activities such as cytotoxic and antimicrobial [14]. Lipophilic extracts of two sponges namely *Xestospongia* (family *Petrosiidae*) and *Amphimedon* (family *Niphatidae*) were also found to be toxic against P-388 murine leukemia cells at IC_{50} values of 1–2.3 μg/ml [14].

In view of these biological activities, we undertook the synthesis of two such new cytotoxic alkaloids Hachijodines **A** and **E** isolated from *Xestospongia* and *Amphimedon*, respectively, in order to confirm their assigned constitution and to take leads from them to develop more potent molecules as drug candidates for the future. Moreover, no detailed studies have been reported on the synthesis of such type of compounds, which contain either *N*- or *O*-methylhydroxylamine group at the end of the alkyl chain. However, few methods known for the synthesis of simple 3-alkylpyridines are cumbersome as they involve many steps and give the alkaloid in overall very poor yield [15].

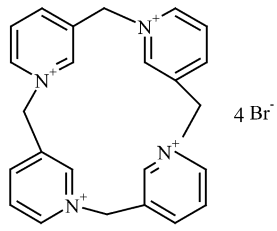


39
Hachijodine - A



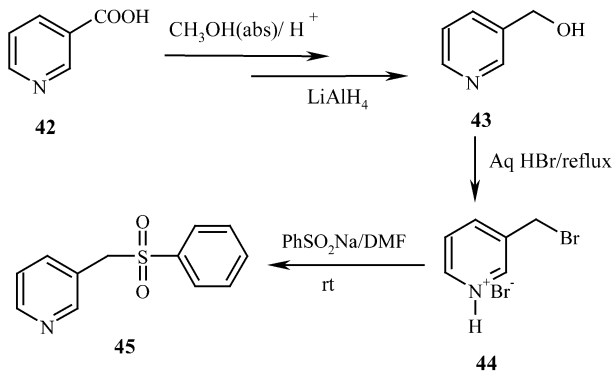
40
Hachijodine - E

Therefore, we envisaged the synthesis of these pyridine alkaloids using a hitherto unknown sulfone **45** as intermediate and carrying out similar alkylation reaction as described earlier in the synthesis of phenolic acids. The starting material initially chosen for the synthesis was β-picoline, which we envisaged to convert into sulfone **45** via its bromide. But all of our efforts to convert it into 3-bromomethyl pyridine failed, as every time a sticky substance identified as the tetramer **41** was obtained.



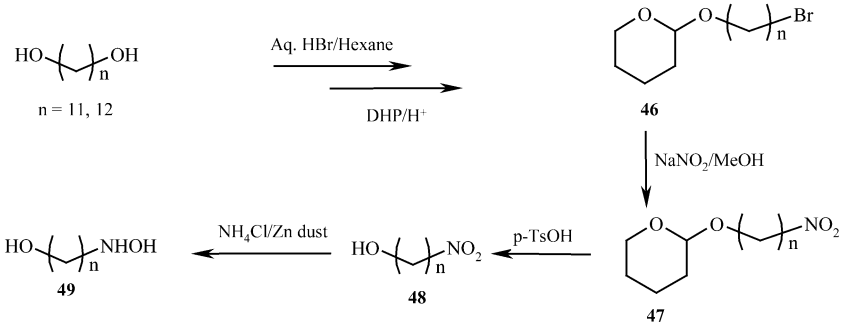
41

Therefore, we changed the route and prepared bromide starting from nicotinic acid in good yield using a series of reactions as outlined in Scheme 8; **44** on stirring with sodium benzenesulfinate in DMF gave the required sulfone **45**, which was fully characterized using elemental analysis, ^{1}H NMR and ^{13}C NMR spectroscopy.



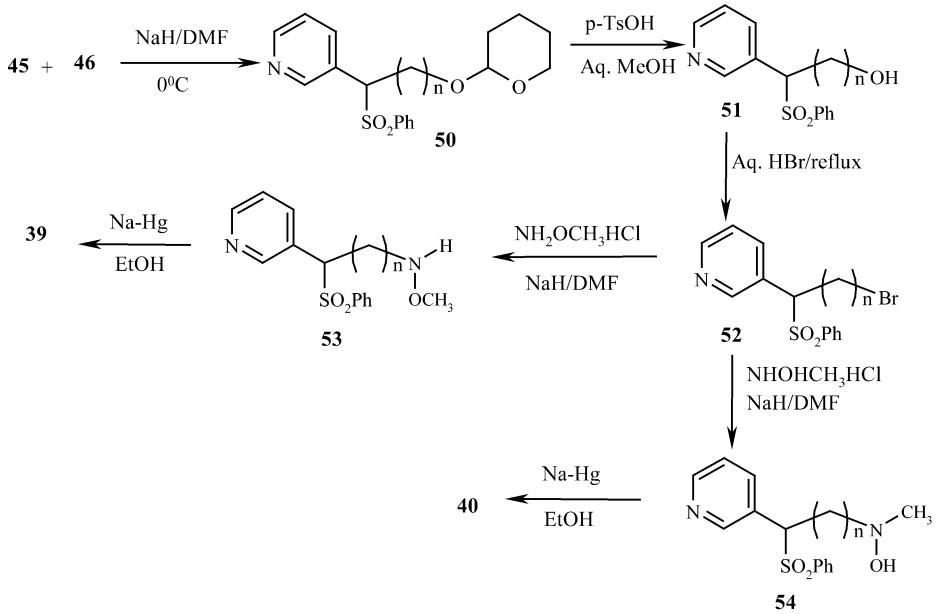
Scheme 8

The lipophilic part of the alkaloids **39** and **40** contained a unique alkyl chain, which is substituted with *O*- and *N*-methylhydroxylamine group, respectively, at the end. Therefore, we thought of synthesizing this part so that it could be coupled with the sulfone **45** to give the desired pyridine alkaloids after desulfonation. For this purpose, the common intermediate envisaged was bromoalkylhydroxylamine, which, on selective O- and N-methylation at the hydroxylamine moiety, would give the desired aliphatic part for final coupling. Hence, **49** required for the preparation of bromoalkylhydroxylamine was obtained from nitroalkanol **48** by reduction with Zn dust under neutral conditions. The nitroalkanol, however, was obtained from alkane diol in four steps (Scheme 9).



Scheme 9

N-Hydroxyalkylhydroxylamine (**49**) was then subjected to selective methylation using different reagents and conditions, but in vain. Therefore, we changed our strategy (Scheme 10) and first alkylated sulfone **45** with **46** as described earlier to obtain **50**, which, on hydrolysis followed by bromination, gave bromosulfone **52**.



Scheme 10

Treatment of **52** separately with methoxylamine hydrochloride and *N*-methyl hydroxylamine hydrochloride under alkaline conditions gave **53** and **54**, respectively. These were then reduced separately using sodium amalgam in ethanol to obtain the desired compounds **39** and **40**, respectively, which were found to be identical in all respect with Hachijodine **A** and **E** isolated from *Xestospongia* and *Amphimedon*, thereby confirming their constitutions.

We thus have successfully designed and developed a general strategy for the synthesis of an important class of pyridine alkaloids using sulfone as potent intermediate. Efforts are still on to find a reagent and suitable conditions for selective O- and N-alkylation at the hydroxylamine moiety, which so far is not reported in literature. This will certainly help in replacing the commercially available expensive materials like *N*-methylhydroxylamine hydrochloride and methoxylamine hydrochloride in the future for such synthesis.

CONCLUSION

Hooking a lipophilic chain containing carbon to an aromatic moiety has always been of immense interest as it can be used in designing the synthesis of a large number of biologically active natural products. Sulfone chemistry has been fully exploited here to do this job. From a proper substituted aryl or pyridyl sulfone, we were able to generate a stabilized α-carbanion and utilized it successfully to form a carbon–carbon bond with the alkyl/alkenyl group from the corresponding halides. This has resulted in hooking a lipophilic moiety to an aromatic or a heterocyclic system. Using this methodology, we have been able to synthesize 11 naturally occurring 6-alkyl/alkenyl phenolic acids along with two natural 3-alkylpyridine alkaloids. Taking leads from these compounds and using the above mentioned strategy, we have also synthesized a large number of related compounds of biological importance in order to discover new potential drug candidates for the future.

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