New Synthetic Methodologies by Using *in situ* Generated Iodonium Ion and by Trapping of *o*-Quinone Methide Intermediate with Various Nucleophiles

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DOCTOR OF PHILOSOPHY

by

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Dedicated to

My Parents

INDIAN INSTITUTE OF TECHNOLOGY GUWAHATI

Department of Chemistry

STATEMENT

I do hereby declare that the matter embodied in this thesis entitled "*New Synthetic Methodologies by Using in situ Generated Iodonium Ion and by Trapping of o-Quinone Methide Intermediate with Various Nucleophiles*" is the result of investigations carried out by me under the supervison of Prof. A. T. Khan in the Department of Chemistry, Indian Institute of Technology Guwahati, India.

In keeping with the general practice of reporting scientific observations, due acknowledgements have been made wherever the work described is based on the findings of other investigators.

IIT Guwahati
21st January 2012

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Professor of Chemistry

CERTIFICATE

This is to certify that Mr. Shahzad Ali has been working in my research group since 1st January 2007 as a regular registered Ph. D. student. I am forwarding his thesis entitled "*New Synthetic Methodologies by Using in situ Generated Iodonium Ion and by Trapping of o-Quinone Methide Intermediate with Various Nucleophiles*" being submitted for the Ph. D. (Science) Degree of this Institute. I certify that he has fulfilled all the requirements according to the rules of this Institute regarding the investigations embodied in his thesis and this work has not been submitted elsewhere for a degree.

IIT Guwahati
21st January 2012

Prof. A. T. Khan
(Thesis Supervisor)

ACKNOWLEDGMENT

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Last but not least, I would like to thank family members such as my parents, brother, sisters, and wife. My parents, for all of their encouragement, understanding and dedication to my education, it would not been possible to reach at this point in my life.

Shahzad Ali

CONTENTS

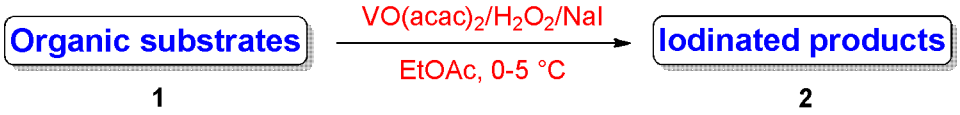
SUMMARY OF THE THESIS

The thesis entitled "**New Synthetic Methodologies by Using *in situ* Generated Iodonium Ion and by Trapping of *o*-Quinone Methide Intermediate with Various Nucleophiles**" has been divided mainly into two parts viz. **Part A** and **Part B**.

Part A has been subdivided into three chapters.

Chapter 1 outlines the brief review of literature of peroxovanadium complexes for generation of halonium ion from the halide ion and some of their synthetic application in organic synthesis.

Chapter 2 deals with the iodination of various organic substrates such as 1,3-dicarbonyl compounds, electron rich aromatic substrates such as amines and phenols using *in situ* generated iodonium ion by employing peroxovanadium complexes. The same iodination reaction was further extended for heterocyclic system such as pyrazoles. This is shown in graphical presentation as below.



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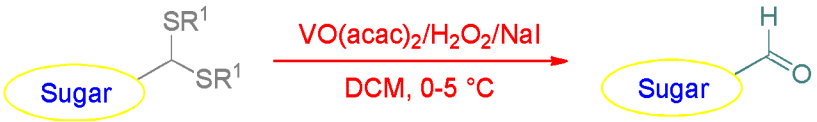
Chapter 3 describes the cleavage of dithioacetals of sugars into the corresponding open chain aldehyde sugar derivatives using *in situ* generated iodonium ion involving peroxovanadium complexes which is presented in the graphical presentation as below.

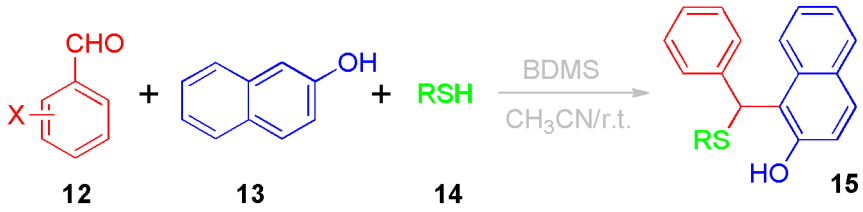


3 4

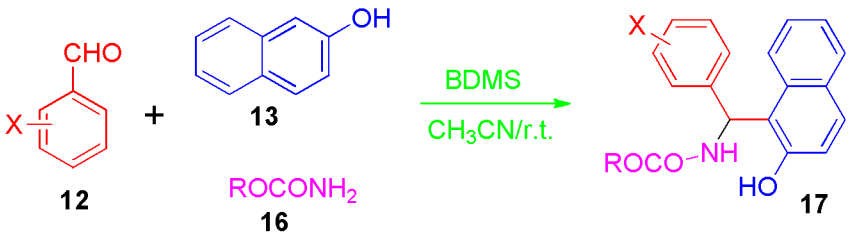
In **Part B** of the dissertation contains four chapters.

Chapter 1 elaborates the brief review on *o*-quinone methides and some of their useful application in natural and non-natural product synthesis.

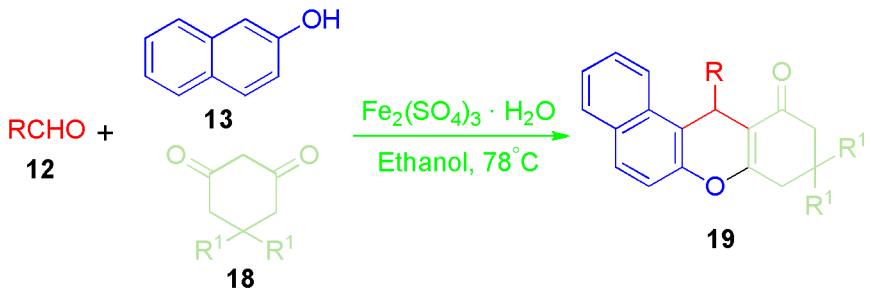
Chapter 2 gives the synthesis of 1-[(alkylthio)(phenyl)methyl]-naphthalene-2-ol using bromodimethylsulfonium bromide as pre-catalyst starting from aromatic aldehyde, 2-naphthol and various thiols. Here we have demonstrated that *o*-naphthoquinone methide intermediate can be generated *in situ* which can be trapped with various thiols, which act as nucleophile, which is given below in the form of graphical presentation.



Chapter 3 describes the synthesis of N-protected 1-amino-alkyl-2-naphthols by trapping of *in situ* generated *o*-naphthaquinone methides with nitrogen nucleophiles such as various carbamates and butyl amine using bromodimethylsulfonium bromide as pre-catalyst. The scheme is shown in the graphical representation.



Chapter 4 delineates the synthesis of 8,9,10,12-tetrahydrobenzo[a]xanthen-11-one derivatives by capturing *in situ* generated *o*-quinone methides with cyclic 1,3-diketones catalyzed by ferric sulfate hydrate, which is given below.



GENERAL REMARKS

The present investigations were carried out in the Department of Chemistry, Indian Institute of Technology Guwahati, Guwahati -781 039, Assam, from January 1, 2007 to January 21, 2012 as a Ph.D. student under the supervision of Prof. Abu T. Khan.

The analytical samples were routinely dried *in vacuo* at 50 °C for 8 hours. In TLC experiments, silica gel G (SRL) or silica gel GF 254 (SRL) were employed as adsorbent or precoated TLC plates (0.2 mm layer thickness of silica gel 60 F-254) were used. The spots were detected by staining with iodine vapors or under UV light or charring with 10% conc. H_2SO_4 in MeOH or MOSTAIN solution (by dissolving 20 g ammonium heptamolybdate and 0.4 g cerium(IV) sulphate in 400 mL 10% H_2SO_4 solution). Column chromatography was carried out with silica gel (60-120 mesh, Merck, SRL or Qualigen), for purifications of reaction mixture. After purification, the solvent was usually removed in rotavapor using Buechi R-114V instrument. Melting points were determined on a Büchi melting point apparatus and are uncorrected. Optical rotations were measured with a Perkin-Elmer 243 polarimeter at 25 ºC temperature. IR spectra were recorded on Perkin-Elmer 281 IR spectrophotometer. ^1H and ^{13}C NMR spectra were recorded on Varian 400 spectrometer TMS as internal reference; chemical shifts (δ scale) are reported in parts per million (ppm). ^1H NMR Spectra are reported in the order: multiplicity, no of protons and coupling constant (J value) in hertz (Hz); signals were characterized as s (singlet), d (doublet), t (triplet), m (multiplet), brs (broad singlet), dq (doublet of quartet) and ddt (doublet of doublet of triplet). HRMS spectra were recorded using WATERS MS system, Q-TOF premier and data analyzed using Mass Lynx 4.1. Elemental analyses were carried out using Perkin-Elmer 2400 Series II CHNS/O analyzer at the Department of Chemistry, Indian Institute of Technology, Guwahati. Crystal data were collected with Bruker Smart Apex-II CCD diffractometer using graphite monochromated MoKα radiation (λ = 0.71073 Å) at 298 K.

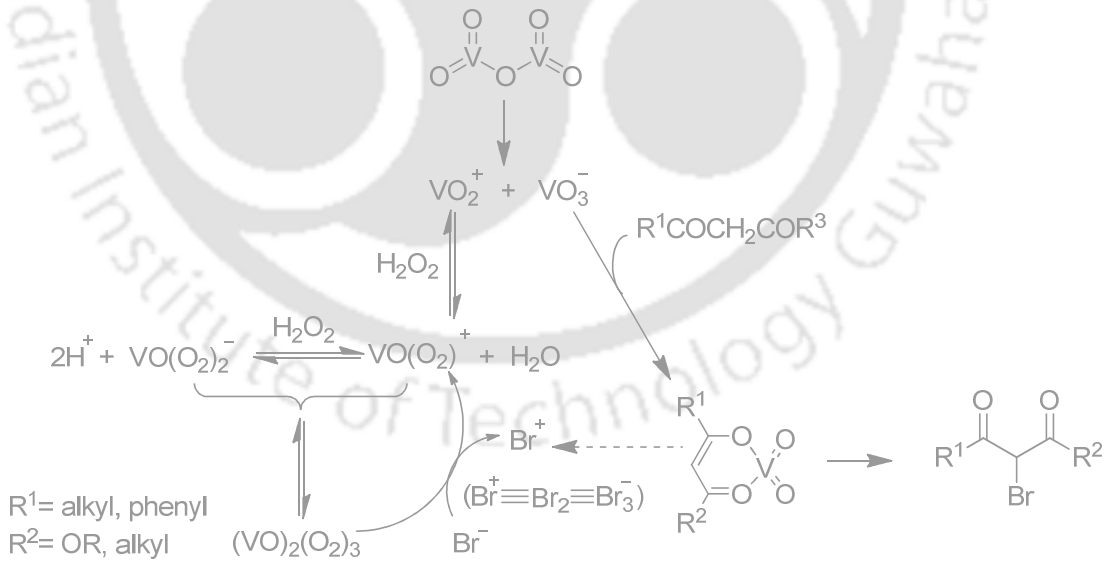
ABBREVIATIONS

Ac	acetyl
BDMS	bromodimethylsulfonium bromide
Boc	*t*-butoxycarbonyl
Bn	benzyl
BNBTS	N,N'-dibromo-N,N'-1,2-ethanediyl*bis*(*p*-toluenesulfonamide)
Bu	butyl
CAN	cerium(IV)ammonium nitrate
CCDC	cambridge crystallographic data centre
CetTMATB	cetyl trimethylammonium tribromide
DCE	1,1-dichloroethane
DCM	dichloromethane
DMS	dimethylsulfide
DMSO	dimethylsulfoxide
Et	ethyl
HTIB	[hydroxy(tosyloxy)iodo]benzene
IR	infrared
MCR	multicomponent reaction
Me	methyl
MHz	mega hertz
MP	melting point
MW	microwave
NMR	nuclear magnetic resonance
NIS	N-iodosuccinimide
o-QM	*ortho*-quinone methide
ORTEP	oak ridge thermal ellipsoid program
Ph	phenyl
POV	peroxovanadium
Ppm	parts per million
Pr	propyl
p-TSA	*p*-toluenesulfonic acid
r.t.	room temperature

SBA-15	santa barbara amorphous material
SDS	sodium dodecylsulfate
TBAF	tetrabutylammonium fluoride
TBATB	tetrabutylammonium tribromide
TBHP	tertiary-butylhydroperoxide
TBS	*t*-butyldimethylsilyl
Tf	trifluoromethanesulfonyl
TFA	trifluoroacetic acid
THF	tetrahydrofuran
TLC	thin layer chromatography
TMADCl	tetramethylammonium dichloroiodate
TMS	trimethylsilyl
Ts	*p*-toluenesulfonyl

PART A

Brief review on peroxovanadium metal complexes for oxidation of halide ion to halonium ion and their application with special emphasis on iodination reactions



CHAPTER 1

Introduction: Naturally occurring organohalogen compounds are widely distributed in nature, which has been compiled recently by Gribble.[1] Some of the naturally occurring organohalogen compounds exhibit interesting biological activity such as cytoxicity towards four different human tumor cell lines,[2] Na,K-ATPase inhibitory activity[2] and antihistamine activity[3] (Figure 1).

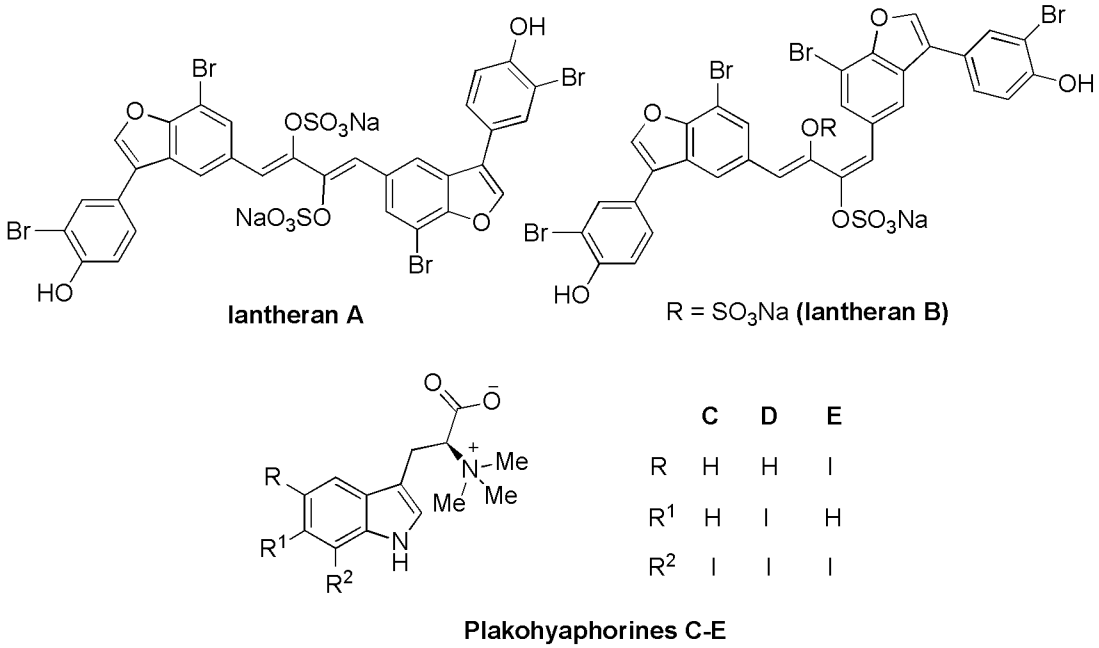


Figure 1: Some naturally occurring halogenated natural products.

In addition, some of the brominated and iodinated important are already known as valuable drug molecules (Figure 2) for the treatment of various diseases such as polycythemia vera -- a condition in which the bone marrow produces excess red blood cells, tranquilizer and muscle relaxant, causing behavioral disorders in older people.

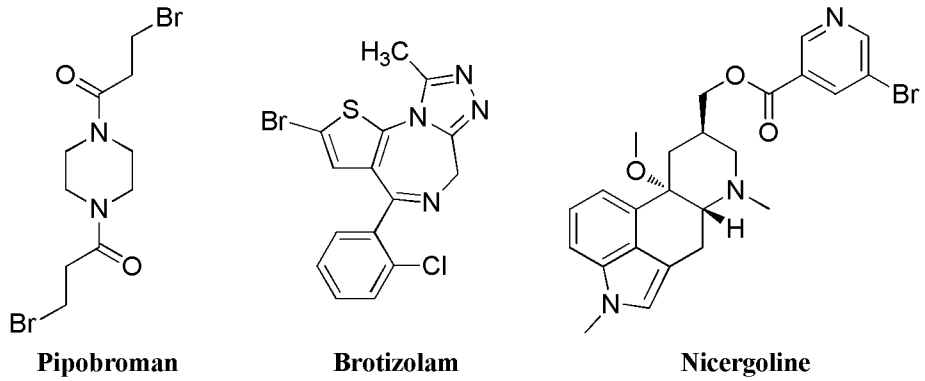


Figure 2: Examples of some halogenated organic compounds used as drugs.

Organohalogen compounds particularly bromo- and iodo compounds serve as synthetic precursors for Wurtz reaction,[4] Sonogashira[5] and Suzuki coupling reactions[6] as well as

for the preparation of organolithium and Grignard reagents,[7] and Wittig reagents,[8] which are extensively used in *C-C* bond forming reactions in organic synthesis.

The use of molecular halogens for direct halogenation reaction has some drawbacks such as difficult to handle as chlorine is a gas and bromine is a corrosive liquid. In addition, molecular iodine is less reactive for direct iodination reaction.

For a long time, the scientists were curious to know how halogenated organic compounds were formed in nature. In the meantime, there was a major breakthrough when haloperoxidases enzymes were isolated from marine plant and animal kingdom, which might be responsible for the formation of organohalogen compounds in the marine plants and micro-organisms.[9,10] This interest led to very detailed study of reaction mechanisms, kinetics and bio-mimicking studies of haloperoxidases.[11] Among the various haloperoxidase enzymes, the structure of the bromoperoxidase has been determined through X-ray crystallographic study.[12]

Di Furia *et al.* proposed that the enzyme bromoperoxidases contain vanadium metal which may react with hydrogen peroxide present in the sea water to generate reactive peoxovanadium species leading to the oxidation of bromide ion (Br^-) to bromonium ion (Br^+).[13] This *in situ* generated reactive bromonium ion is the main source of organic bromination reaction of various substrates to form bromoorganics in nature. In addition to vanadium based haloperoxidases, iron based haloperoxidases are also present in the nature, which function in a similar fashion to generate the oxidised form of halonium ion. The halonium ion generated reacts with the substrate to produce the haloorganic compounds. Taking cues from nature, the chemists were interested in knowing the form of oxidized species for bromonium ion that may exist in the solution. Di Furia *et al.* proposed that it can either exist as Br_2 or HOBr in solution based on isolating the brominated products from the reaction with alkenes.[14,15] Later on, Butler *et al.* further proposed that Br_3^- may also be one of the alternate oxidized species, which could be present in the solution.[16]

$$HOBr \equiv Br_2 \equiv Br_3^-$$

Figure 3: An equilibrium of different species of bromine equivalent exist in solution.

Using these studies as motivation, over the decade greener synthetic procedures have been developed in our lab and by others to address the lacuna in the bromination of the organic substrates. The push towards green chemistry and the trend towards bio-

inspired catalysts have led to the indirect applications of metal peroxo complexes, one such complex being peroxovandates (POV). These metal-peroxo complexes are strong oxidants, which have been proven by the conversion of aldehyde to esters[17] and benzylalcohol to benzylaldehyde.[18] These provide direct evidence that POVs are better oxidant than hydrogen peroxide itself. As expected, peroxometal complexes can oxidize Br^- to Br^+ ion which we have used as reagents for bromination of the organic substrates. During such an endeavor, we conceived that the soft non-metallic electrophilic property of bromonium ion can be exploited to develop new methodologies where catalytic amount of bromonium ion produced can replace the function of metallic electrophiles such as Hg, Cd, Ag.

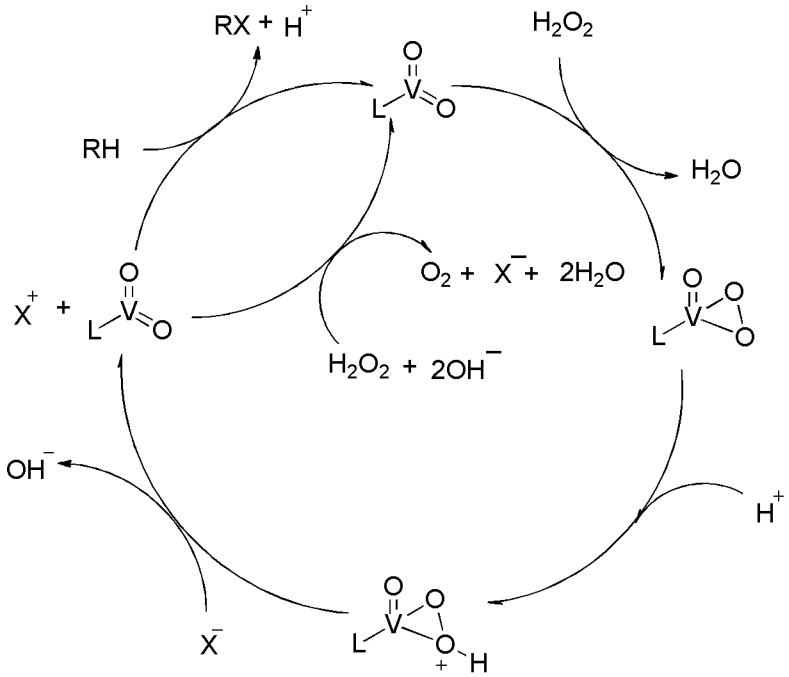
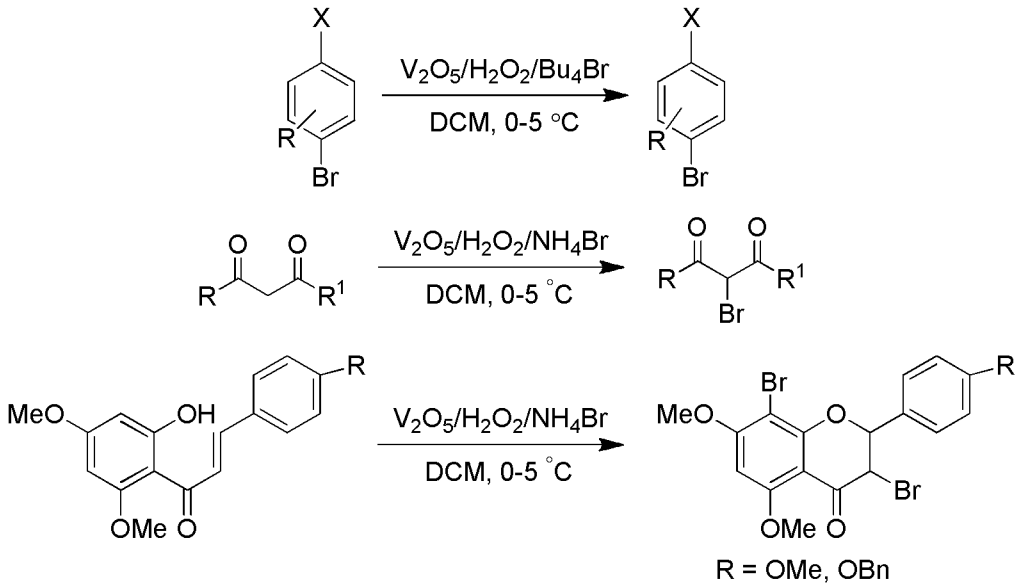


Figure 4: A general catalytic cycle of the vanadium peroxo complex.

The general catalytic cycle of the POV in organic reactions has been well-established which is shown in Figure 4 and may be summed up in the following manner: the formation of a POV species, generation of Br^+ species, and in the final step Br^+ reacts with the organic substrate. H_2O_2 coordinates with the vanadium (IV) species to form the POV species. The bromide ion now reacts with the complex, generating an oxidized Br^+ species which can exist in equilibrium as shown in Figure 3. In the third step, the Br^+ reacts with the organic compound to form bromoorganics. The other possible mechanism is that *in situ* generated Br^+ ion reacts with H_2O_2 to regenerate the Br^- ion. Thus, the net reaction involves the metal ion which forms the peroxo complex and it

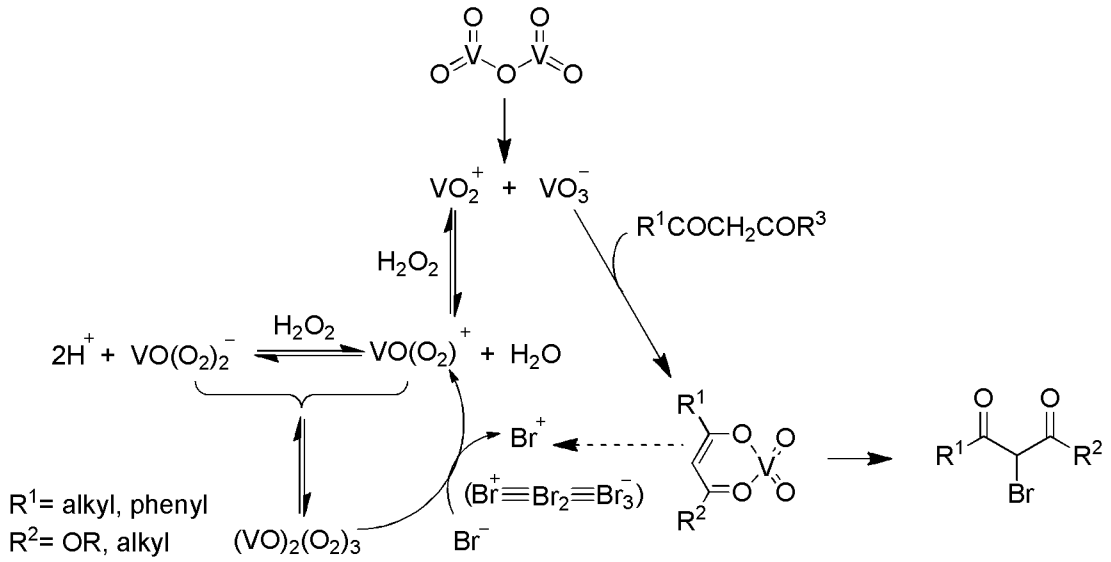
oxidizes bromide ion (Br^-) to bromonium ion (Br^+) in association with hydrogen peroxide (H_2O_2). The catalytic cycle explained above is bio-mimicking of the vanadium haloperoxidase enzyme. There was no direct evidence for the use of tribromide (Br_3^-) ion in the reactions; even though the ion was proposed earlier as a feasible source for the bromonium ion in aqueous media. Later on, Chaudhuri and co-workers were able to isolate the solid organic ammonium tribromides depending upon the quaternary ammonium salt.[19] This is a direct evidence for the existence of tribromide ion in aqueous solution which is in equilibrium with other brominating species (Br_2 and HOBr) as shown earlier in Figure 3.

The *in situ* generated Br^+ ion has been demonstrated for bromination of aromatic substrates,[20] α-bromination of 1,3-dicarbonyl compounds[21] and synthesis of 3-bromo flavanones,[22] which is shown in Scheme 1.



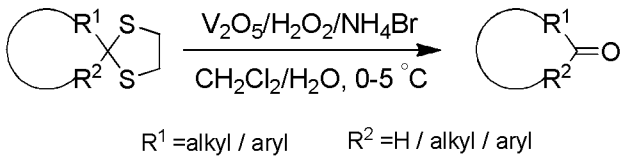
Scheme 1

The formation of selective mono α-brominated product can be explained using a combination of vanadium pentoxide, hydrogen peroxide and ammonium bromide as follows: The V_2O_5 dissociates into VO_2^+ and VO_3^- species in solution, the species VO_2^+ assists for the formation of POV complexes, which oxidizes Br^- to Br^+. On the other hand, the species VO_3^- stabilizes the enolic form of 1,3-dicarbonyl compounds and this results in selective monobromination to yield α-bromo-1,3-dicarbonyl compounds as shown below.



Scheme 2

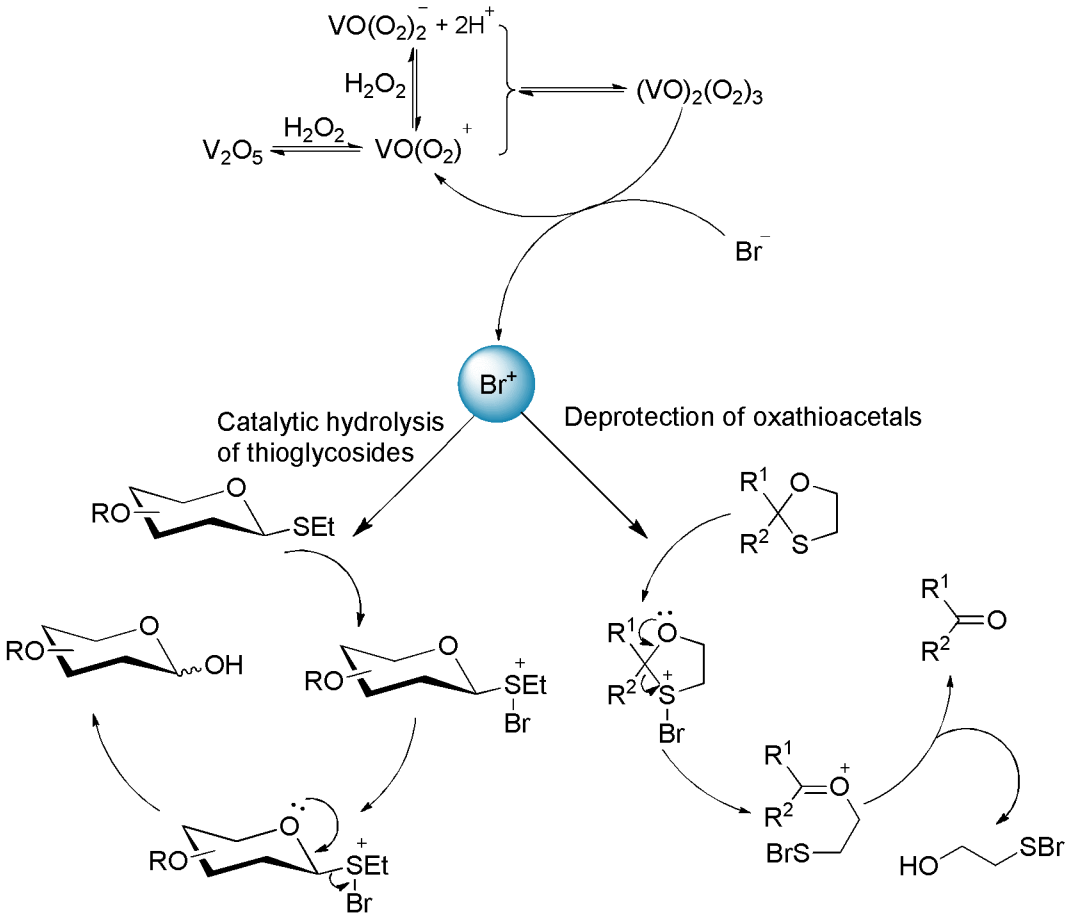
Similarly, catalytically generated bromonium (Br^+) ion acts as a soft non-metallic electrophile and promotes in the removal of sulfur based protecting group. By using bromonium ion we have demonstrated the cleavage of dithioacetals,[23] oxathioacetals[24] into the corresponding carbonyl compounds and hydrolysis of 1-thioglycoside into the corresponding 1-hydroxy sugars[25] which is shown in Scheme 3 and 4.



Scheme 3

From taking cues of the above successful results, we realized that *in situ* generated iodonium ion may also be used for iodination of various organic substrates by involving POV catalyzed oxidation of iodide ion, which is similar to bio-mimicking of iodoperoxidase enzymes. The second aim of my research plan is to explore *in situ* generated iodonium ion assisted cleavage of dithioacetals of sugars into the corresponding open chain aldehyde sugars.

Among various halogenated organic compounds, organoiodine compounds are valuable precursors used in the carbon-carbon, carbon-nitrogen and carbon-sulfur bond formation because iodine atom is an excellent leaving group.[26-28]

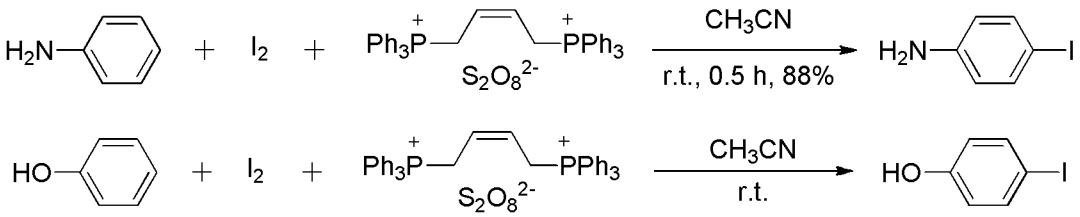


Scheme 4

As a result, we were interested to know, what are the existing methods available in the literature for iodination of various organic substrates?

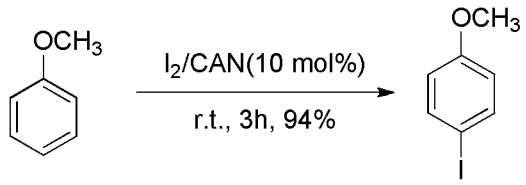
Iodination of aromatic substrates:

Conventionally, electrophilic iodination of organic compounds is usually achieved by using elemental iodine in presence of bis(tetra-n-butylammonium) peroxidisulfate[29] or hydrogen peroxide,[30] or other oxidants.[31] Badri *et al* reported[32] selective iodination of various aromatic compounds using iodine and 1,4-bis(triphenylphosphonium)-2-butene peroxodisulfate, as depicted in Scheme 5.



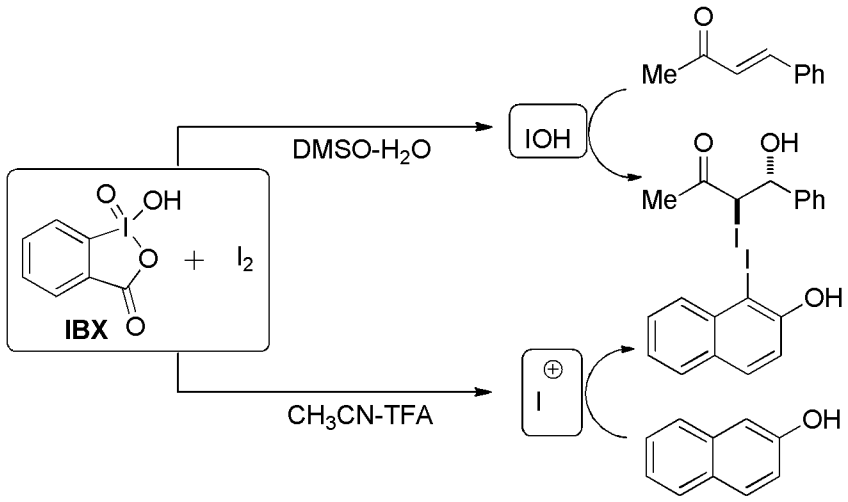
Scheme 5

Likewise, Das *et al* reported[33] regioselective iodination of activated aromatics with iodine and catalytic amount of cerium ammonium nitrate (CAN), as shown in Scheme 6.



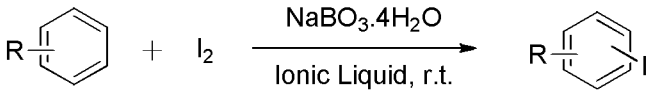
Scheme 6

Moorthy and his co-workers demonstrated eletrophilic aromatic iodination of organic compounds and iodohydroxylation of olefins using IBX-I_2, which is depicted in Scheme 7.[34]



Scheme 7

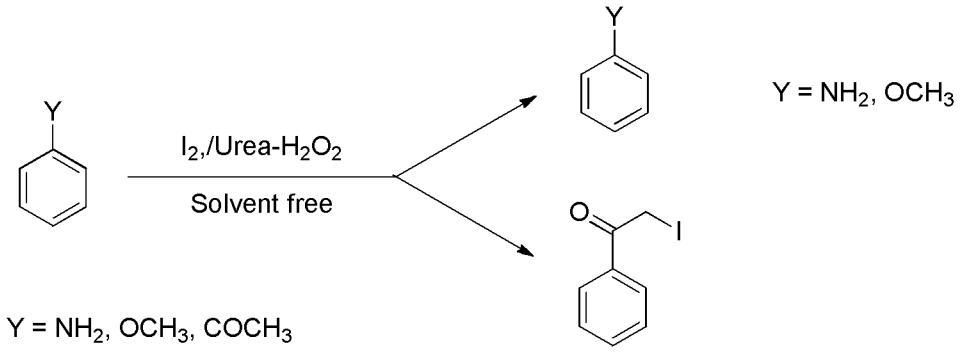
The regioselective iodination of arenes using a combination of iodine/sodium borate/ionic liquid was described by Bhilare *et al*[35], which is represented in Scheme 8.



R = NH_2, OH, OMe, NMe_2

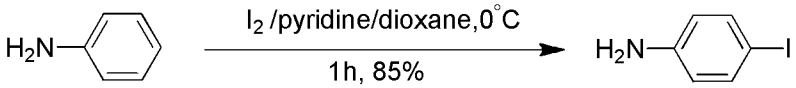
Scheme 8

Stavber *et al* reported[36] iodination of organic molecules using iodine, urea and hydrogen peroxide combination as depicted in Scheme 9.



Scheme 9

Odobel and his co-workers demonstrated the regioselective iodination[37] of aniline or its derivatives by using a combination of iodine and pyridine in dioxane at 85 °C, which is depicted in Scheme 10.

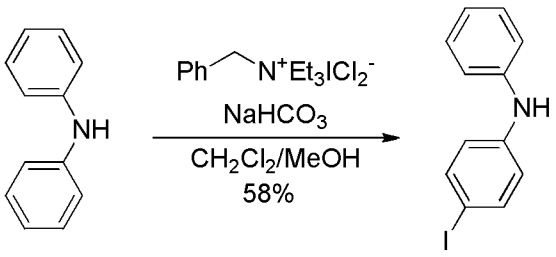


Scheme 10

The iodination of organic substrates using molecular iodine has some demerits such as low electrophilicity of I_2 and thus low reactivity towards majority of organic compounds, while the second demerit is the release of HI during the iodination process, which is responsible for the rupture of carbon-iodine bonds.

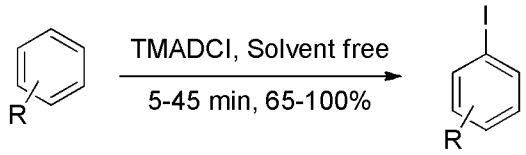
Similarly, iodination can also be performed by employing sodium iodide and hydrogen peroxide in acidic medium.[38] Zupan and his co-workers recently reviewed the iodination of organic compounds using elemental iodine and iodides.[39]

Many other electrophilic iodinating reagents have also been developed over the years, namely N-iodosuccinimide[40] or N-I compounds[41] or interhalogen compounds such as iodochloride (ICl).[42] In 2001, Tour et al reported [43] regioselective iodination of various substituted anilines by employing a combination of benzyltriethylammonium dichloroiodate and sodium bicarbonate as shown in Scheme 11.



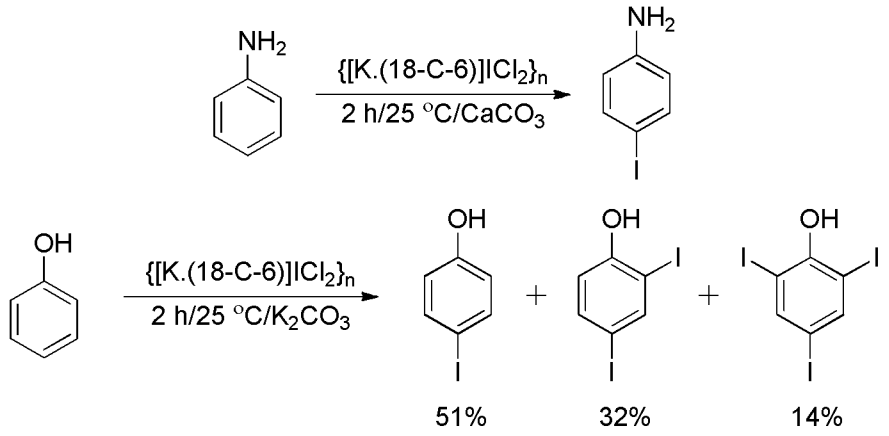
Scheme 11

Subsequently, Hajipour *et al* extended the above protocol[44] for regioselective iodination of various aromatic substrates at room temperature involving tetramethylammonium dichloroiodate (TMADCI) as iodinating reagent as shown in Scheme 12.



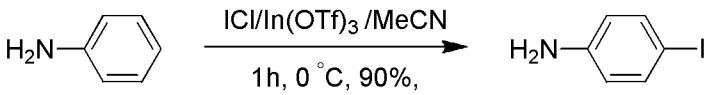
Scheme 12

Recently, Burdette reported[45] iodination of electron rich aromatic substrates such as aniline and phenol with 18-crown-6 supported ICl_2^- . In case of phenol, a mixture of products was isolated using the above reaction conditions, which is shown in Scheme 13.



Scheme 13

The direct iodination of various aromatic compounds by employing interhalogen compound such as iodochloride in presence of indium triflate was reported by Ellervik and his co-workers[46] as shown in Scheme 14.



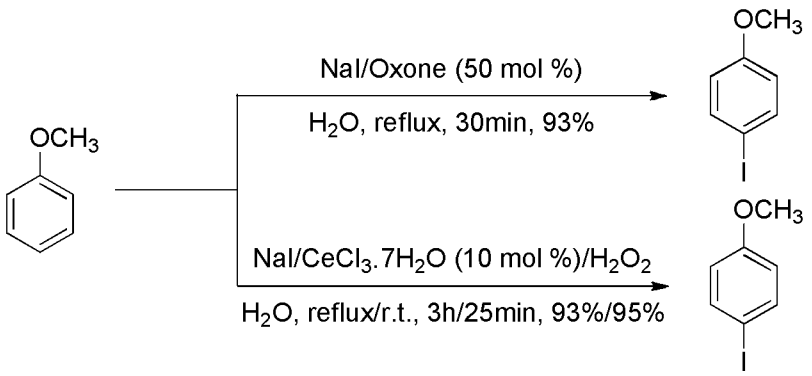
Scheme 14

Though all of these reagents are excellent iodinating reagents, each one of them has some demerits. Protocols for their preparation are often chemical and energy consuming processes, while many of them are not only expensive but also produce a considerable amount of waste material after iodine transfer. Keeping in mind the green

trends in modern organic chemistry, there is still a requirement to reduce these inconveniences as far as possible. Therefore, iodide anion (I^-) or elemental iodine (I_2) seem to be a more logical and suitable choice.

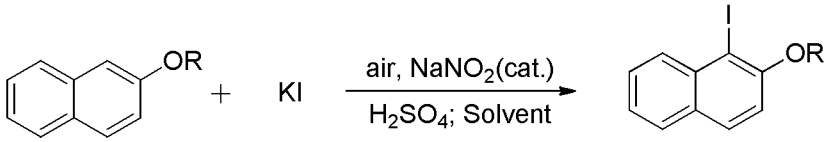
Oxidative iodination is the only choice when iodide ion is used as the source of an iodonium ion for the electrophilic transfer into organic molecule; that is, I^- is first oxidized to iodonium ion (I^+), which further reacts with an organic molecule for obtaining the desired iodinated products.

By following the above approach, Firouzabadi *et al* reported the direct halogenation of organic compounds using a combination of oxone with sodium iodide[47] in water under reflux conditions. The same research group has further demonstrated[48] oxidative mono-iodination of organic compounds by employing a combination of sodium iodide, cerium chloride hepta hydrate and H_2O_2 (Scheme 15). The major demerits of the present protocol are firstly, oxone is explosive in nature and secondly, cerium salts are expensive.



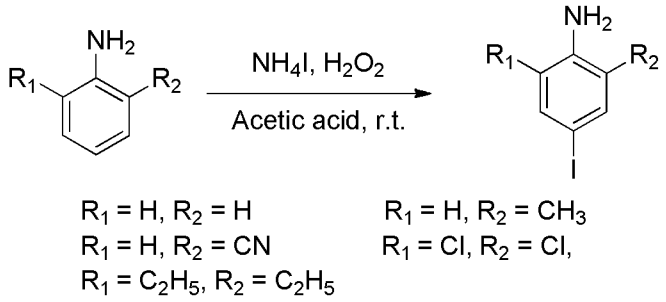
Scheme 15

Stavber *et al* has demonstrated[49] aerobic oxidative iodination of aromatic compounds using a combination of $KI/NaNO_2/air/H_2SO_4$ as shown in Scheme 16.



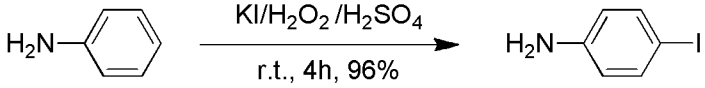
Scheme 16

Narender *et al* reported[50] the iodination of organic compounds using ammonium iodide and hydrogen peroxide, as shown in Scheme 17.



Scheme 17

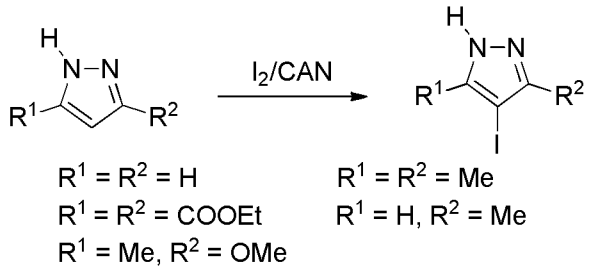
The similar approach was further extended by Iskra *et al*[51] for iodination of arenes using potassium iodide instead of ammonium iodide, hydrogen peroxide and sulphuric acid at room temperature (Scheme 18).



Scheme 18

Iodination of heterocyclic substrates are quite interesting as they serve as valuable building blocks in organic synthesis. Among various heterocyclic compounds, the iodination of pyrazole derivatives are quite difficult in presence of strong co-oxidant. Hence, iodination of pyrazole is usually done by oxidative iodination using iodine and lead(IV) acetate. But the main demerit is that lead is a heavy metal and is highly toxic. As per our knowledge, nobody has reported the *in situ* generated iodination of heterocyclic system. Therefore, there is a further scope for studying the iodination of various organic substrates using a combination of $VO(acac)_2/H_2O_2/NaI$.

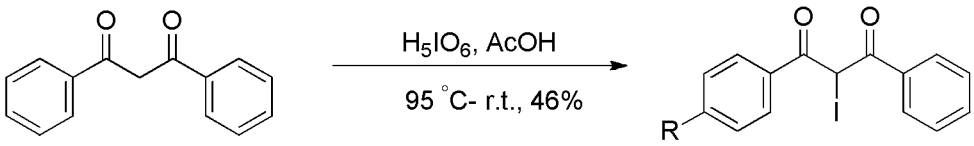
Rodriguez-Franco *et al* reported[52] the regioselective iodination of pyrazoles using elemental iodine in the presence of ceric ammonium nitrate (CAN) as the *in situ* oxidant to prepare 4-iodopyrazoles, which is displayed in Scheme 19. The iodination of various pyrazole derivatives was also achieved by using iodobenzene diacetate (or polymer supported iodobenzene diacetate) with iodine to obtain 4-iodopyrazoles.[53] The 4-iodo-3,5-dimethyl pyrazoles have also been synthesized[54] by reaction of 3,5-dimethyl pyrazoles with N-iodosuccinimide under ultrasound irradiation.



Scheme 19

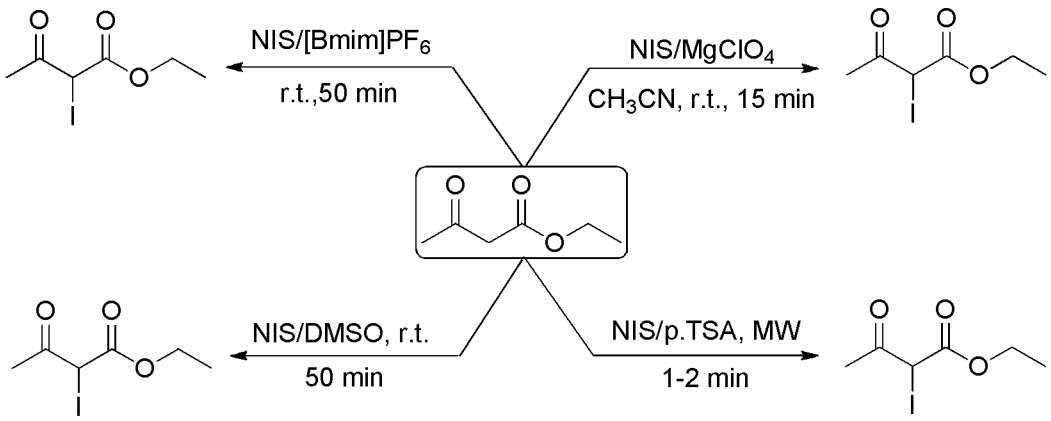
Iodination of 1,3-dicarbonyl compounds:

Iodination of 1,3-dicarbonyl compounds was first reported[55] by Fatiadi as shown in the Scheme 20.



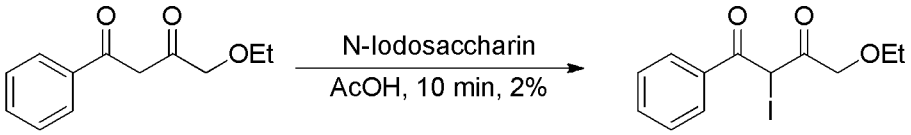
Scheme 20

Later on, Yang and his co-worker demonstrated α-iodination of β-ketoester and mono α-substituted β-ketoester[56] with N-iodosuccinimide in the presence of magnesium percholorate in good yields as shown in Scheme 21. Similar transformations were also performed[57] by Lee *et al* using N-iodosuccinimide in combination with *p*-TSA under microwave irradiation which is displayed below. Meshram *et al* further demonstrated[58] the 2-halogenation of 1,3-ketoesters and cyclic ketones using NIS in ionic liquid. Sreedhar *et al* also reported[59] the iodination of ketones, 1,3-diketones, β-ketoesters by employing NIS in DMSO at room temperature as depicted in Scheme 21. The only demerit of these methods is that N-iodosuccinimide is a very expensive reagent.



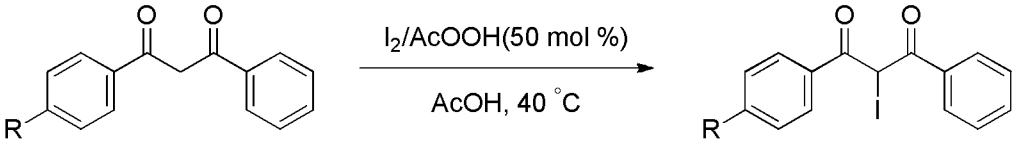
Scheme 21

Dolenc demonstrated[60] the iodination of enol acetates and 1,3-diones using N-Iodosaccharin as shown in Scheme 22.



Scheme 22

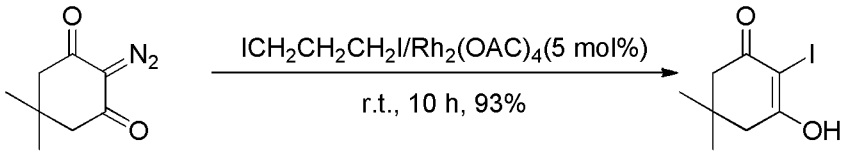
Urasaki *et al* reported[61] iodination of dibenzoylmethanes using a combination of iodine and periodic acid in acetic acid at 40 °C, which is depicted in Scheme 23.



R = MeO, Me, H, Cl, NO_2

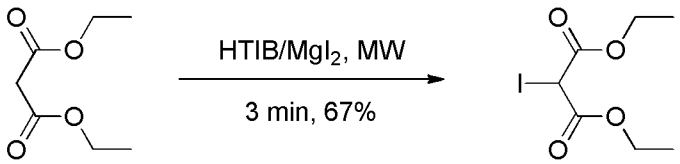
Scheme 23

Lee and his co-workers demonstrated[62] the preparation of β-substituted α-iodoenones from diazodicarbonyl compounds, which is shown in Scheme 24.



Scheme 24

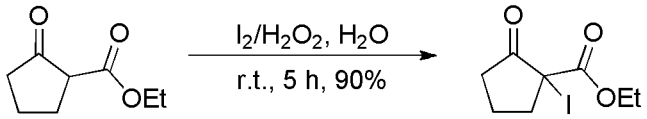
Lee et al reported[63] the microwave induced α-iodination of 1,3-dicarbonyl compounds and ketones with Koser's reagent (HTIB) [hydroxyl(tosyloxy)iodo]benzene as shown below.



HTIB - Hydroxy(tosyloxy)iodobenzene

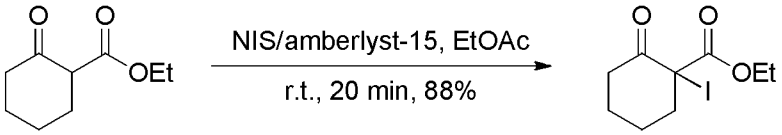
Scheme 25

Jereb et al demonstrated[64] the iodofunctionalistion of several types of organic molecules including some 1,3-dicarbonyl compounds, which is shown in Scheme 26.



Scheme 26

Meshram et al described[65] the iodination of various 1,3-dicarbonyl compounds using NIS and amberlyst-15 at room temperature as depicted below in Scheme 27.



Scheme 27

From all the above literature, it reveals that there is still scope to develop a new methodology for iodination of various organic substrates by generating iodonium ions from the oxidation of various iodide salts by employing peroxometal complexes.

The regioselective iodination of phenol and 1,3-dicarbonyl compounds are difficult, hence further research has to be carried out to find a suitable condition for the iodination of the above mentioned compounds . Therefore, in the end, we have conceived that POV mediated iodination is a good and safer alternative in comparison to all the other known ways.

Cleavage of dithioacetals derivatives of sugars:

Aldehydo-sugar derivatives are important building blocks in carbohydrate chemistry for the synthesis of *C*-disaccharides,[66] *C*-arylglycosides[67] and natural products.[68-70] For examples, acyclic aldehydo derivatives of D-glucose, D-xylose, L-arabinose are used for the syntheses of valieneamine,[68] *C*-disaccharide,[66] (+)-phorboxazole A: a potent cytostatic agent[69] and anemoclemoside B1[70] respectively as depicted in Figure 5.

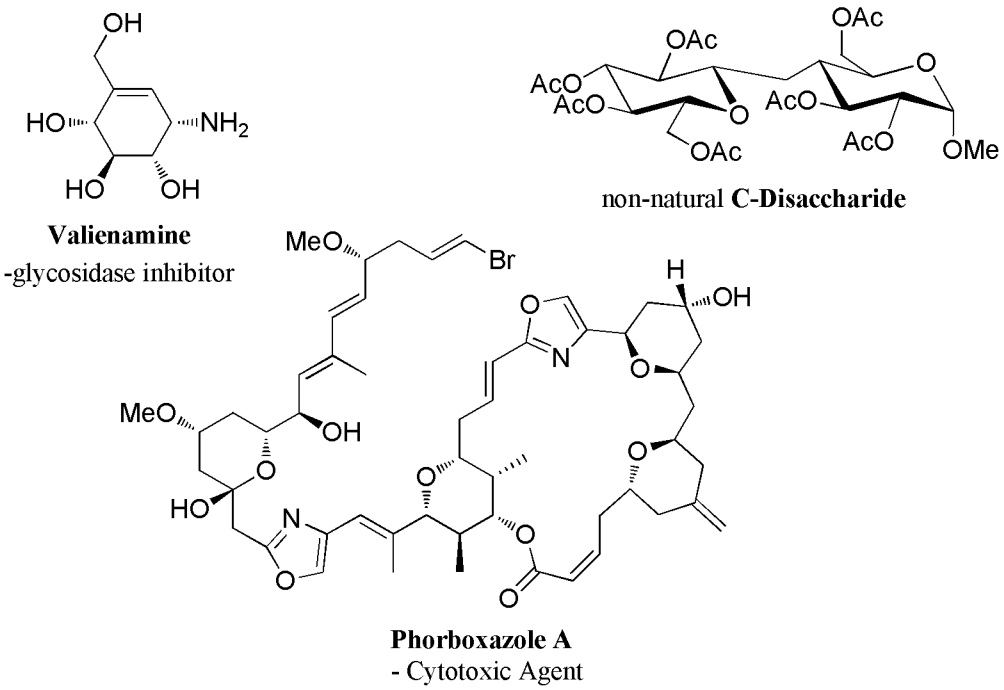
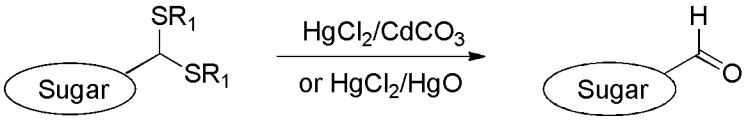


Figure 5. Biological active compounds synthesized from acyclic aldosugar derivative.

Conventionally, mercury(II) chloride and cadium carbonate[71-73] or mercury(II) chloride and mercuric oxide[74-76] are found to be the most suitable combination for deprotection of dithioacetal derivatives of sugar as shown in Scheme 28.



Scheme 28

This method is based on using a heavy metal(s) as soft electrophile, which is highly toxic and the additional difficulty is in the work up procedure to remove the mercuric oxide.

Different methods have been reported for the deprotection of dithioacetals by using $I_2/NaHCO_3$,[77] $MeI/CdCO_3$,[78] $NaNO_2/AcCl$,[79] CetTMATB or TBATB,[80] N-iodosaccharin,[81] $V_2O_5/H_2O_2/NH_4Br$,[82] and $(NH_4)_6Mo_7O_{24}.4H_2O/H_2O_2/NH_4Br$.[83] However, these methods have some limitations such as low yield, incompatibility with acidic functional groups and are also less common for preparation of aldehydo-sugar derivatives.

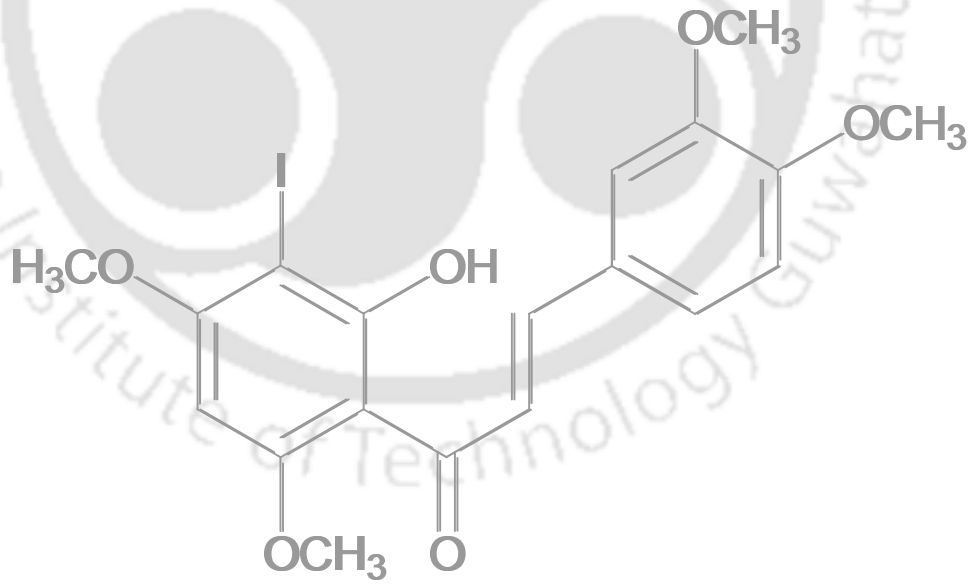
On the basis of brief review presented above, the following problems require some serious attention:

(a) The iodination of various organic substrates can be achieved by various reagents. Some of these reagents are expensive; require harsh reaction conditions, etc. Hence, an alternative has to be devised which is not only environmentally benign method but also efficient and practical.

(b) To prepare open chain aldehyde sugars from dithioacetals are difficult to achieve. The methods for the preparation of open chain aldehyde sugars from dithioacetals is usually achieved using heavy metal such as mercury salts till today, which is highly toxic and is not environmentally benign. Therefore, iodonium ion assisted cleavage of dithioacetal of sugars will add a new methodology in carbohydrate chemistry.

PART A

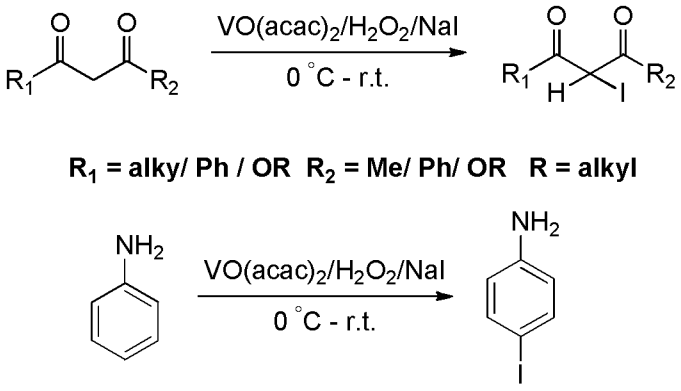
Iodination of organic substrates using *in situ* generated iodonium ion



The importance of halogenated compounds and probable pathways of how these compounds are formed in nature have been discussed in the previous chapter. In addition, various methods of iodination that are known in the literature, the demerits of the existing methods of iodination and future scope are also highlighted there. Over the years, numerous methods have been developed for halogenation reactions, which are already mentioned in the reference section of Part A. A few years ago, we have demonstrated peroxovanadium complexes (POV) are useful oxidants for oxidation of bromide ion into reactive bromonium ion.[20-25] By trapping the reactive bromonium ion, we have synthesized many brominated organic compounds. Similarly, we have shown the cleavage of sulfur based protecting groups namely dithioacetals, oxothioacetals and thioglycoside.[23-25] For achieving all these successful results, we have mainly used vanadium pentoxide and hydrogen peroxide for the source of POV complexes and ammonium bromide as the source of bromonium ion. As a matter of fact, we have successfully demonstrated the usefulness of *in situ* generated bromonium ion in various organic transformations. Subsequently, we are also interested whether similar transformations are feasible by involving iodonium ion or not. Keeping this goal in mind, we tried for iodination of 1,3-dicarbonyl compounds using a combination of V_2O_5 or $NH_4VO_3/H_2O_2/NaI$ and the results are shown in Table 1.The low yield may be due to formation of monoperoxo, diperoxo and triperoxocomplexes, which oxidizes iodide ion so vigorously to iodine or iodine equivalent that escapes from the reaction flask. Therefore, we thought that vanadyl acetylacetonate may be other alternative reagent instead of either vanadium pentoxide or NH_4VO_3.

We have found in the literature that vanadyl acetylcaetonate is an effective and important catalyst for the selective epoxidation of allylic alcohols.[84] Later on, Frerie et al demonstrated[85] that vanadyl acetylacetonate anchored onto amine-functionalized clays for epoxidation of geraniol. It can also be used for oxidation of cyclohexane[86] into cyclohexanol and cyclohexanone, and asymmetric oxidation of sulfides.[87,88] The efficacy of the combination of vanadyl acetylacetonate and *tert*-butylhydroperoxide (TBHP) has been further exploited for the selective conversion of *bis*-homoallylic alcohols into functionalized *cis*-THFs by catalytic olefin epoxidation followed by epoxide ring opening.[89] Very recently, West et al have shown the usefulness of vanadyl acetylacetonate for Meyer-schuster rearrangement.[90]

In this chapter, α-iodination of 1,3-dicarbonyl compounds, various aromatic compounds and iodination of pyrazoles using a combination of $VO(acac)_2/H_2O_2/NaI$ is described as shown in Scheme 29.



Scheme 29. Selective iodination of various organic compounds.

For the present study, the catalyst vanadyl acetylacetonate was prepared according to the literature procedure.[91] Initially, we have chosen benzoyl acetone (**1a**) as a model substrate for optimization in terms of yield and reaction time. Several reactions were examined using different amounts of $VO(acac)_2$ and NaI. The best yield of iodinated product **2a** was obtained using the combination of substrate:$VO(acac)_2$:H_2O_2:NaI (1.0:0.2:4.4:2.0 equiv), respectively (Table 1, entry 7). After screening of various solvent systems such as CH_2Cl_2, EtOAc, CH_3CN, CH_3OH and CH_3COCH_3, it was observed that ethyl acetate was the best solvent for this transformation. It is obvious that $VO(acac)_2$ plays an important role in the formation of the product and the results are summarized in Table 1.

After completion of the reaction, the product **2a** was characterized by recording ^1H and ^{13}C NMR spectra and by elemental analysis. In the NMR spectrum, -CHI proton appears at δ 5.97 ppm and ^{13}C signal for –CHI appears at δ 32.82 ppm. In the starting material these signal appeared at δ ~4.1 ppm and δ ~53 ppm (in the keto form), respectively. The ^1H and ^{13}C NMR spectra are given in Figure 6 in the experimental section of Chapter 2 on page number 30. Subsequently, the 1,3-dicarbonyl compounds such as dibenzoylmethane (**1b**) was subjected to iodination under similar reaction conditions and furnished **2b** in 90% yield as shown in Table 2 (entry 2).

Table 1: Optimisation of the reaction conditions for the selective α-iodination of benzoyl acetone[a]

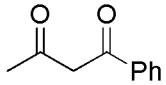
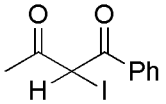
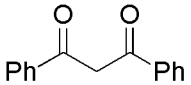
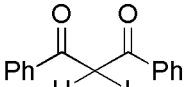
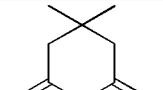
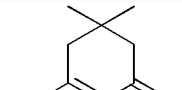
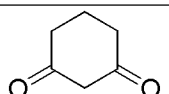
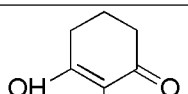
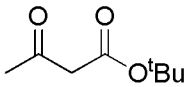
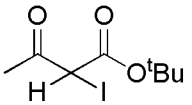
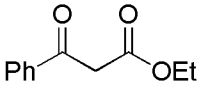
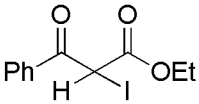
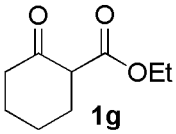
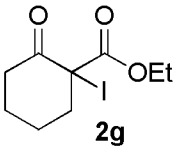
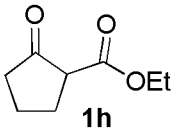
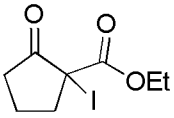
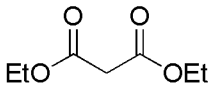
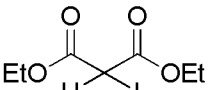
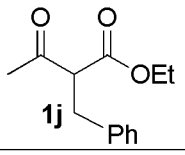
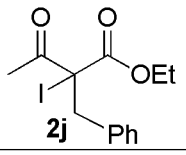
Entry	Catalyst	Amount used in mol%	NaI (equiv.)	Solvent	Time/ min.	Yield[b] /%
1	V_2O_5	20	2.0	EtOAc	25	38
2	NH_4VO_3	20	2.0	EtOAc	15	20
3	$VO(acac)_2$	10	2.0	EtOAc	30	59
4	$VO(acac)_2$	15	2.0	EtOAc	25	75
5	$VO(acac)_2$	20	1.5	EtOAc	25	73
6	$VO(acac)_2$	20	1.7	EtOAc	25	81
7	**$VO(acac)_2$**	**20**	**2.0**	**EtOAc**	**25**	**91**
8	$VO(acac)_2$	20	2.2	EtOAc	25	90
9	$VO(acac)_2$	20	2.0	CH_2Cl_2	25	66
10	$VO(acac)_2$	20	2.0	CH_3CN	25	69
11	$VO(acac)_2$	20	2.0	CH_3OH	10	65
12	$VO(acac)_2$	20	2.0	$CH_3CO\ CH_3$	35	72

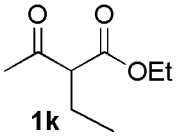
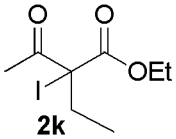
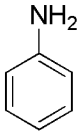
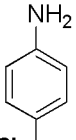
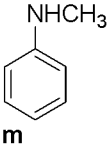
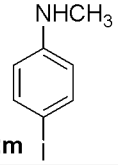
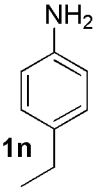
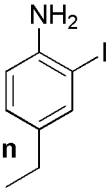
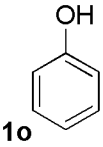
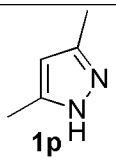
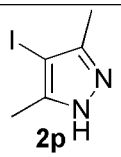
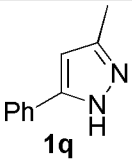
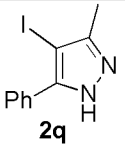
[a]All the reactions were carried out with 1 mmol scale. [b]Isolated yield

These successful results further motivated us to study the iodination reaction with cyclic 1,3-diketones such as dimedone (**1c**) and 1,3-cyclohexanedione (**1d**) using the same combination under similar reaction conditions. The iodinated products **2c** and **2d** were obtained in fairly good yield.

Next, we wanted to study the efficacy of the present protocol with β-keto esters. Likewise,various β-esters (**1e-k)** were smoothly converted into the corresponding mono α-iodinated product **2e-k** in good yields (entries 5-11) under identical condition, which is indicated in the Table 2.

Table 2: Iodination of 1,3-dicarbonyl compounds, aromatic amines, phenol and pyrazoles using $VO(acac)_2/H_2O_2/NaI$

Entry	Substrate (**a**)	Products (**b**)	NaI (eq.)	Time/h Or [min]	Yield[a] (%)
1	 **1a**	 **2a**	2.0	[25]	91
2	 **1b**	 **2b**	2.0	3.5	90
3	 **1c**	 **2c**	2.0	instant	67
4	 **1d**	 **2d**	2.0	instant	62
5	 **1e**	 **2e**	2.0	11.5	87
6	 **1f**	 **2f**	2.5	24	92
7	 **1g**	 **2g**	2.0	1	73
8	 **1h**	 **2h**	2.0	1	90
9	 **1i**	 **2i**	2.5	26	80
10	 **1j**	 **2j**	2.0	16	75

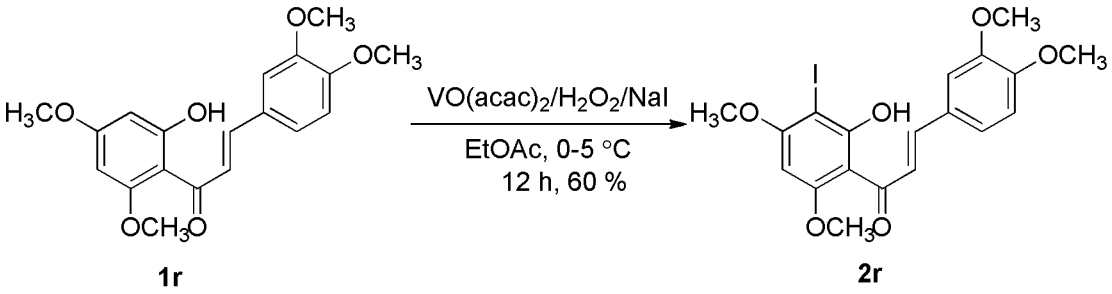
11	 **1k**	 **2k**	2.0	13	79
12	 **1l**	 **2l**	2.0	8.0	85
13	 **1m**	 **2m**	2.0	8.0	87
14	 **1n**	 **2n**	2.0	8.0	84
15	 **1o**	Mixture of products	2.0	1.0	-
16	 **1p**	 **2p**	2.0	1.0	90
17	 **1q**	 **2q**	2.0	6.5	92

[a] Isolated Yield

The same protocol was further extended with electron-rich aromatic substrates such as aniline, N-methylaniline and 4-ethylaniline. The regioselective monoiodinated products **2l-n** were obtained in good yields under identical reaction condition. The ^{1}H and ^{13}C NMR spectra of compound **2l** are given in Figure 7 in the experimental section of Chapter 2 on page number 31. However, phenol does not provide regioselective iodinated product like aniline and its derivatives under similar reaction conditions.

To extend the scope and general applicability of this protocol, pyrazole derivatives (**1p** and **1q)** were also iodinated easily and gave the desired product **2p** and **2q** in very good yields as shown in the Table 2.

To verify competitive iodination in the aromatic ring and olefinic double bond, we have carried out a iodination reaction with (*E*)-1-(2-hydroxy-4,6-dimethoxyphenyl)-3-(3,4-dimethoxyphenyl)prop-2-en-1-one (**1r**) under similar reaction condition which is shown in Scheme 30. From the observation, it reveals aromatic ring iodination is preferred over olefinic double bond.

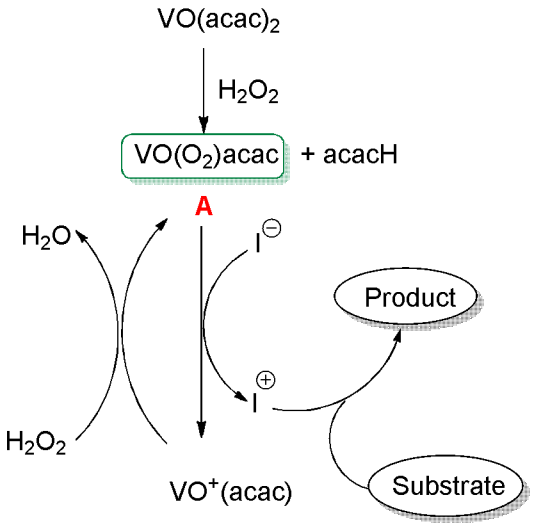


1r **2r**

Scheme 30

All these products were characterized by recording ^{1}H- and ^{13}C NMR spectra and elemental analysis.

A plausible mechanism for the formation of product is depicted in Scheme 31. It is known that $VO(acac)_2$ undergoes hydrolysis in two steps in acidic aqueous solution where the first ring is removed instantly while the removal of the second ring is 150 times slower.[92,93]



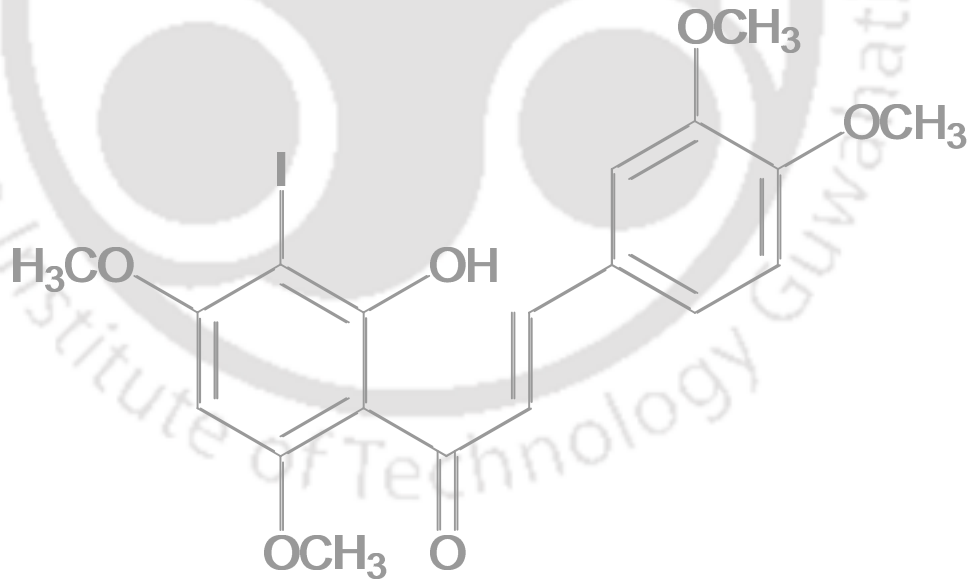
Scheme 31. A plausible mechanism for iodination of various organic substrates

Based on this concept we have put forward a mechanism, the interaction of vanadyl acetylacetonate with hydrogen peroxide can generate mono peroxo complex of vanadium(V) **A** by replacing one unit of acetylacetonate, which can oxidize iodide ion to iodonium ion. Then *in situ* generated iodonium ion was successfully trapped by various organic substrates to provide iodinated product. In the above combination vanadyl acetylacetonate acts as a catalyst, hydrogen peroxide and sodium iodide as the sources of active oxygen and iodoniun ion, respectively. All these chemicals are environmentally benign.

In conclusion we have demonstrated an important and efficient method for the mono-iodination of 1,3-dicarbonyl compounds and pyrazoles by using a combination of $VO(acac)_2$/ H_2O_2/NaI. Moreover, these reagents are environmentally acceptable. Notably, the ester functionality does not undergo hydrolysis under the reaction conditions although the medium is acidic. The catalyst plays a dual role in the formation of peroxo complexes which oxidizes the iodide ion to iodonium ion and promotion of the enol formation by chelating with the two carbonyl groups of the 1,3-dicarbonyl compounds. Good yield, high selectivity, use of cost effective reagents, mild and environmentally benign reaction conditions are some major advantages of this protocol.

PART A

Iodination of organic substrates using *in situ* generated iodonium ion



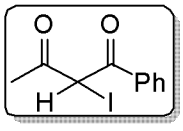
Preparation of VO(acac)$_2$:

To an aqueous suspension of vanadium pentoxide (5 g, 27.49 mmol) in 20 mL of water taken in a 500 mL beaker, 30% hydrogen peroxide (38 mL, 330 mmol) was added dropwise in an ice-cold condition and stirred till a clear dark solution was formed. To the dark brown colored solution, distilled acetylacetone (20 mL, 192.5 mmol) was added dropwise very carefully with continuous stirring. Vigorous effervescence took place after 15 min. Stirring for a period of 30 min led to a precipitation of a brown colored microcrystalline compound. The reaction mixture was heated at 70 °C for 15 min under stirring. The precipitate turned olive green with shiny crystalline appearance with the solution also turning green. The solution was concentrated by heating on a steam bath for 30 min and then placed in an ice-water bath for 15 min. The compound was filtered through Whatman No. 42 filter paper, washed with acetone and dried in vacuo over fused CaCl2. Yield: 11.7 g (80%).

Typical Procedure for iodination:

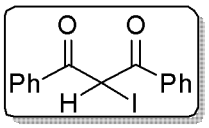
$VO(acac)_2$ (53 mg, 0.2 mmol) was taken in 2 mL of water at ice- bath temperature (0-5 °C). Then H_2O_2 (0.5 mL, 4.4 mmol) was added slowly into it and kept for stirring at the same temperature. The solution becomes yellow after 10 min. and the substrate was added into it by dissolving in 3 mL of ethylacetate followed by NaI (300 mg, 2.0 mmol) solution, by taking into 2 mL of water, was added. The solution becomes dark brown instantly. Finally, the reaction mixture was extracted with ethylacetate (3 × 25 mL) and the organic layer was washed with 10% sodium thiosulfate solution. Finally, the organic layer was washed with water and dried over sodium sulfate. The solvent was evaporated under vacuum and pure product was obtained.

2-Iodo-1-phenylbutane-1,3-dione (2a)



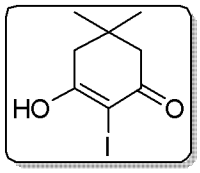
Nature: Yellow oil; **IR (KBr):** 3388, 3066, 1687, 1599, 1448, 1355, 1221, 1185, 1124, 1018 cm^{-1}; **^{1}H NMR (400 MHz, $CDCl_3$):** δ 2.56 (s, 3H), 5.97 (s, 1H), 7.51 (t, *J* = 7.6 Hz, 2H), 7.64 (t, *J* = 7.6 Hz, 1H), 7.98 (d, *J* = 7.6 Hz, 2H); **^{13}C NMR (100 Hz, $CDCl_3$):** δ 27.2, 32.8, 129.3 (2C), 129.35 (2C), 133.7, 134.6, 191.3, 199.0; **Anal Calcd.** $C_{10}H_9IO_2$ (288.08): requires C, 41.69; H, 3.15%. Found C, 41.51; H, 3.06%

2-Iodo-1,3-diphenylpropane-1,3-dione (2b)



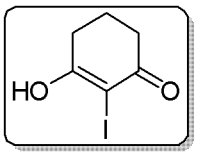
Nature: White solid; mp 107–108 °C. **IR (KBr):** 2957, 1688, 1662, 1594, 1446, 1289, 1240, 1182, 994, 979 cm^{-1}; **^{1}H NMR (400 MHz, $CDCl_3$):** δ 6.95 (s, 1H), 7.48 (t, *J* = 8.0 Hz, 4H), 7.61 (t, *J* = 7.6 Hz, 2H), 8.00 (d, *J* = 7.6 Hz, 4H); **^{13}C NMR (100 MHz, $CDCl_3$):** δ 34.1, 129.3 (4C), 129.5 (4C), 133.4 (2C), 134.4 (2C), 190.3 (2C); **Anal Calcd.** $C_{15}H_{11}IO_2$ (350.15): requires C, 51.45; H, 3.17%. Found C, 51.32; H, 3.09%

3-Hydroxy-2-iodo-5,5-dimethylcyclohex-2-enone (2c)



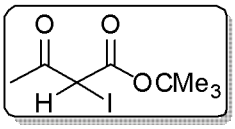
Nature: White solid; mp 154–155 °C. (Lit.[5c]166-167 ^{0}C); **IR (KBr):** 3448, 1624, 1574, 1317, 1000 cm^{-1}; **^{1}H NMR (400 MHz, $CDCl_3$):** δ 1.15 (s, 6H), 2.48 (s, 4H); **^{13}C NMR (100 MHz, DMSO):** δ 27.5 (2C), 32.3, 46.6 (2C), 76.7, 184.5 (2C); **Anal Calcd.** $C_8H_{11}IO_2$ (266.08): requires C, 36.11; H, 4.17%. Found C, 36.01; H, 4.06%

3-Hydroxy-2-iodocyclohex-2-enone (2d)



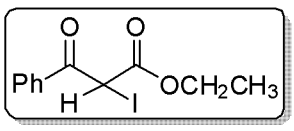
Nature: White solid; mp 138–139 °C; **IR (KBr):** 3105, 1645, 1580, 1368, 1315, 1190, 1144, 1066, 956 cm^{-1}; **^{1}H NMR (400 MHz, $CDCl_3$+DMSO):** δ 1.97 (quint, *J* = 6.0 Hz, 2H), 2.61 (t, *J* = 6.0 Hz, 4H); **^{13}C NMR (100 MHz, DMSO):** δ 20.9, 33.3 (2C), 78.6, 185.6 (2C); **Anal Calcd.** $C_6H_7IO_2$ (238.02): requires C, 30.28; H, 2.96%. Found C, 30.16; H, 2.88%

Tert-butyl 2-iodo-3-oxobutanoate (2e)



Nature: Yellow oil; **IR (KBr):** 2981, 1731, 1639, 1371, 1251, 1154 cm^{-1}; **^{1}H NMR (400 MHz, $CDCl_3$):** δ 1.48 (s, 9H), 2.51 (s, 3H), 4.94 (s, 1H); **^{13}C NMR (100 MHz, $CDCl_3$):** δ 26.3, 27.8 (3C), 28.2, 84.3, 165.7, 197.9; **Anal Calcd.** $C_8H_{13}IO_3$ (284.09): requires C, 33.82; H, 4.61%. Found C, 33.74; H, 4.53%

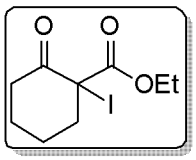
Ethyl 2-iodo-3-oxo-3-phenylpropanoate (2f)



Nature: Yellow oil; **IR (KBr):** 2931, 1675, 1272, 1002 cm^{-1}; **^{1}H NMR (400 MHz, $CDCl_3$):** δ 1.22 (t, *J* = 7.2 Hz, 3H), 4.24 (q, *J* = 7.2 Hz, 2H), 5.92 (s, 1H), 7.46 (t, *J* = 7.6 Hz, 2H), 7.57 (t, *J* = 7.6, 1H), 7.96 (d, *J* = 7.6 Hz, 2H); **^{13}C NMR (100 MHz, $CDCl_3$):** δ 14.0, 24.2,

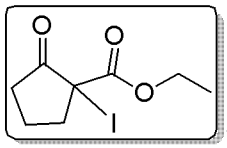
63.5, 129.1 (2C), 129.3 (2C), 133.1, 134.3, 166.7, 189.4; **Anal Calcd.** $C_{11}H_{11}IO_3$ (318.10): requires C, 41.53; H, 3.49%. Found C, 41.42; H, 3.39%

Ethyl 1-iodo-2-oxocyclohexanecarboxylate (2g)



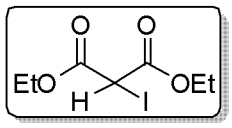
Nature: Yellow oil; **IR (KBr):** 2941, 2868, 1722, 1449, 1235, 1122, 1092, 1018 cm^{-1}; **^{1}H NMR (400 MHz, $CDCl_3$):** δ 1.28 (t, *J* = 7.2 Hz, 3H), 1.67–1.74 (m, 2H), 1.75–1.80 (m, 1H), 1.94–1.98 (m, 1H), 2.25–2.32 (m, 1H), 2.47-2.54 (m, 1H), 2.91–2.96 (m, 2H), 4.27 (q, *J* = 7.2 Hz, 2H); **^{13}C NMR (100 MHz, $CDCl_3$):** δ 13.9, 24.8, 27.3, 38.3, 43.3, 53.3, 63.1, 169.5, 200.0; **Anal Calcd.** $C_9H_{13}IO_3$ (296.10): requires C, 36.51; H, 4.43%.Found C, 36.38; H, 4.33%

Ethyl 1-iodo-2-oxocyclopentanecarboxylate (2h)



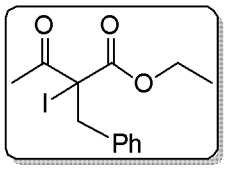
Nature: Yellow oil; **IR (KBr):** 2973, 1745, 1256, 1180, 1132, 1020 cm^{-1}**^{1}H NMR (400 MHz, $CDCl_3$):** δ 1.29 (t, *J* = 7.2 Hz, 3H), 2.07–2.14 (m, 2H), 2.35–2.53 (m, 4H), 4.26 (dq, *J* = 7.2 , 0.6 Hz, 2H); **^{13}C NMR (100 MHz, $CDCl_3$):** δ 14.0, 20.0, 35.1, 40.3, 43.6, 63.3, 168.1, 207.1.

Diethyl 2-iodomalonate (2i)



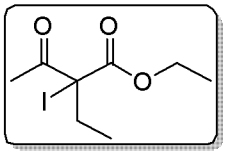
Nature: Yellow oil; **IR (KBr):** 2984, 1745, 1630, 1372, 1300, 1236, 1136, 1099, 1024 cm^{-1}; **^{1}H NMR (400 MHz, $CDCl_3$):** δ 1.30 (t, *J* = 7.2 Hz, 6H), 4.32 (q, *J* = 7.2 Hz, 4H), 4.80 (s, 1H); **^{13}C NMR (100 MHz, $CDCl_3$):** δ 14.0 (2C), 63.5 (2C), 90.4, 168.4 (2C); **Anal Calcd.** $C_7H_{11}IO_4$ (286.06): requires C, 29.39; H, 3.88%. Found C, 29.23; H, 3.71%.

Ethyl 2-benzyl-2-iodo-3-oxobutanoate (2j)



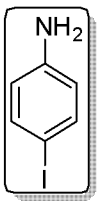
Nature: Yellow oil; **IR (KBr):** 2978, 1711, 1356, 1309, 1236, 1187, 1083, 1015 cm^{-1}; **^{1}H NMR (400 MHz, $CDCl_3$):** δ 1.20 (t, *J* = 7.6 Hz, 3H), 2.47 (s, 3H), 3.54 (d, *J* = 14.4 Hz, 1H), 3.67 (d, *J* = 14.4 Hz, 1H), 4.17 (q, *J* = 7.2 Hz, 2H) 7.17–7.26 (m, 5H); **^{13}C NMR (100 MHz, $CDCl_3$):** δ 13.9, 26.9, 44.4, 54.5, 63.4, 127.6, 128.4 (2C), 130.4 (2C), 136.4, 168.4, 198.2; **Anal Calcd.** $C_{13}H_{15}IO_3$ (346.16): requires C, 45.11; H, 4.37%. Found C, 45.01; H, 4.26%

Ethyl 2-ethyl-2-iodo-3-oxobutanoate (2k)



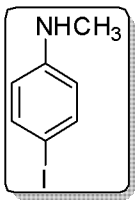
Nature: Yellow oil; **IR (KBr):** 3418, 2979, 2044, 1714, 1457, 1358, 1229, 1122, 1022 cm^{-1}; **^{1}H NMR (400 MHz, $CDCl_3$):** δ 0.96 (t, *J* = 7.2 Hz, 3H), 1.28 (t, *J* = 7.6 Hz, 3H), 2.17 (q, *J* = 7.2 Hz, 2H), 2.45 (s, 3H), 4.25 (q, *J* = 7.2 Hz, 2H); **^{13}C NMR (100 MHz, $CDCl_3$):** δ 12.3, 14.0, 26.0, 32.5, 56.5, 63.3, 168.8, 198.2; **Anal Calcd.** $C_8H_{13}IO_3$ (284.09): requires C, 33.82; H, 4.61%. Found C, 33.69; H, 4.53%

4-iodo aniline (2l)



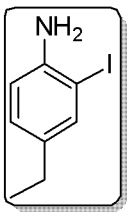
Nature: White solid, mp 60-62 °C; **IR (KBr, cm^{-1}):** 3405 (-NH_2), 3297 (-NH_2); **^{1}H NMR (400 MHz, $CDCl_3$):** *δ* 3.68 (brs, 2H), 6.47 (d, *J* = 8.4 Hz, 2H), 7.41 (d, *J* = 8.4 Hz, 2H); **^{13}C NMR (100 MHz, $CDCl_3$):** *δ* 79.5, 117.5 (2C), 138.1 (2C), 146.2; **Anal Calcd.** C_6H_6NI (219.02): requires C, 32.90; H, 2.76; N, 6.40%. Found C, 32.71; H, 2.55; N, 6.26%.

4-iodo N-methylaniline (2m)



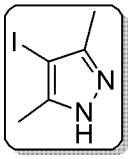
Nature: Colorless Liquid; **IR (KBr, cm^{-1}):** 3422 (-NH_2); **^{1}H NMR (400 MHz, $CDCl_3$):** *δ* 2.72 (s, 3H), 3.67 (brs, 1H), 6.31 (d, *J* = 8.4 Hz, 2H), 7.35 (d, *J* = 8.8 Hz, 2H). **^{13}C NMR (100 MHz, $CDCl_3$):** *δ* 30.7, 77.9, 114.8 (2C), 137.9 (2C), 149.0; **Anal Calcd.** C_7H_8NI (233.05): requires C, 36.08; H, 3.46; N, 6.01%. Found C, 36.26; H, 3.54; N, 6.14%.

4-ethyl-2-iodoaniline (2n)



Nature: Colorless Liquid; **IR (KBr, cm^{-1}):** 3398 (-NH_2), 3299 (-NH_2); **^{1}H NMR (400 MHz, $CDCl_3$):** *δ* 1.17 (t, *J* = 7.6 Hz, 3H), 2.50 (q, *J* = 7.6 Hz, 2H), 3.96 (brs, 2H), 6.69 (d, *J* = 8.4 Hz, 1H), 6.98 (dd, J_1 = 2.0, J_2 = 8. 0 Hz, 1H). 7.48 (d, *J* = 1.6 Hz, 1H). **^{13}C NMR (100 MHz, $CDCl_3$):** *δ* 16.0, 27.6, 84.5, 114.9, 129.0, 136.2, 138.1, 144.6; **Anal Calcd.** $C_8H_{10}NI$ (247.08): requires C, 38.89; H, 4.08; N, 5.67%. Found C, 38.71; H, 3.99; N, 5.54%.

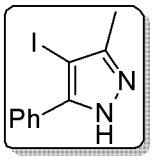
4-Iodo-3,5-dimethyl-1H-pyrazole (2p)



Nature: White solid, mp 138–140 °C (Lit.[15b]134-136 ^{0}C); **IR (KBr):** 3165, 3067, 3030, 2917, 2830, 1577, 1412, 1305, 1164, 1077, 1034 cm^{-1}; **^{1}H NMR (400 MHz, $CDCl_3$):** δ 2.24 (s, 6H), 4.27 (s, 1H); **^{13}C NMR (100**

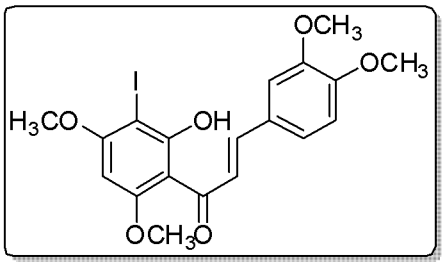
MHz, $CDCl_3$): δ 13.1 (2C), 62.7, 146.5 (2C); **Anal Calcd.** $C_5H_7IN_2$ (222.02): requires C, 27.05; H, 3.18; N, 12.62%. Found C, 26.92; H, 3.11; N, 12.46%

4-Iodo-3-methyl-5-phenyl-1H-pyrazole (2q)



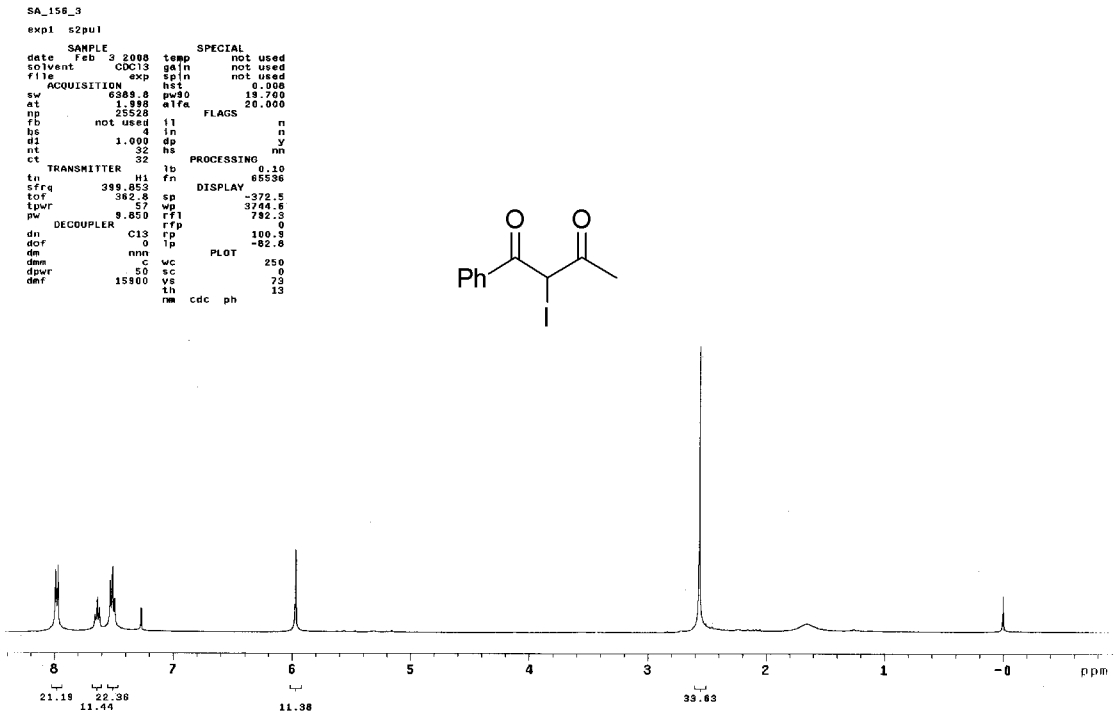
Nature: White solid, mp 117–120 ºC (Lit.[15b]113-115 ^{0}C); **IR (KBr):** 3173, 3067, 2929, 1567, 1448, 1291, 1269, 1179, 1116, 1045, 967, 915 cm^{-1}; **^{1}H NMR (400 MHz, $CDCl_3$):** δ 2.26 (s, 3H), 7.39–7.46 (m, 3H), 7.70–7.73 (m, 2H); **^{13}C NMR (100 MHz, $CDCl_3$):** δ 12.7, 60.6, 128.4 (2C), 128.6 (2C), 128.7, 131.9, 146.4, 149.8; **Anal Calcd.** $C_{10}H_9IN_2$ (284.10): requires C, 42.28; H, 3.19; N, 9.86%. Found C, 42.17; H, 3.08, N, 9.69%

(E)-1-(2-hydroxy-3-iodo-4,6-dimethoxyphenyl)-3-(3,4-dimethoxyphenyl)prop-2-en-1-one (2r)



Nature: Yellow solid, mp 152 °C; **IR (KBr, cm^{-1}):** 3445 (-OH), 1624 (-C=O); **^{1}H NMR (400 MHz, $CDCl_3$):** *δ* 3.94 (s, 3H), 3.95 (s, 3H), 3.98 (s, 3H), 4.00 (s, 3H), 6.05 (s, 1H), 6.90 (d, *J* = 8.0 Hz, 1H), 7.12 (s, 1H), 7.22 (d, *J* = 8.4 Hz, 1H). 7.75 (d, *J* = 15.2 Hz, 1H), 7.81 (d, *J* = 15.6 1H), **^{13}C NMR (100 MHz, $CDCl_3$):** *δ* 56.1, 56.2, 56.3, 56.6, 87.2, 91.4, 106.9, 110.7, 111.4, 123.0, 124.8, 128.5, 143.8, 149.3, 151.5, 163.8, 164.3, 165.8, 192.4; **Anal Calcd.** $C_{19}H_{19}IO_6$ (470.26): requires C, 48.53; H, 4.07%. Found C, 48.71; H, 4.18%.

^{1}H NMR (400 MHz, $CDCl_3$): *2-iodo-1-phenylbutane-1,3-dione* **(2a)**



^{13}C NMR (100 MHz, $CDCl_3$): *2-iodo-1-phenylbutane-1,3-dione* **(2a)**

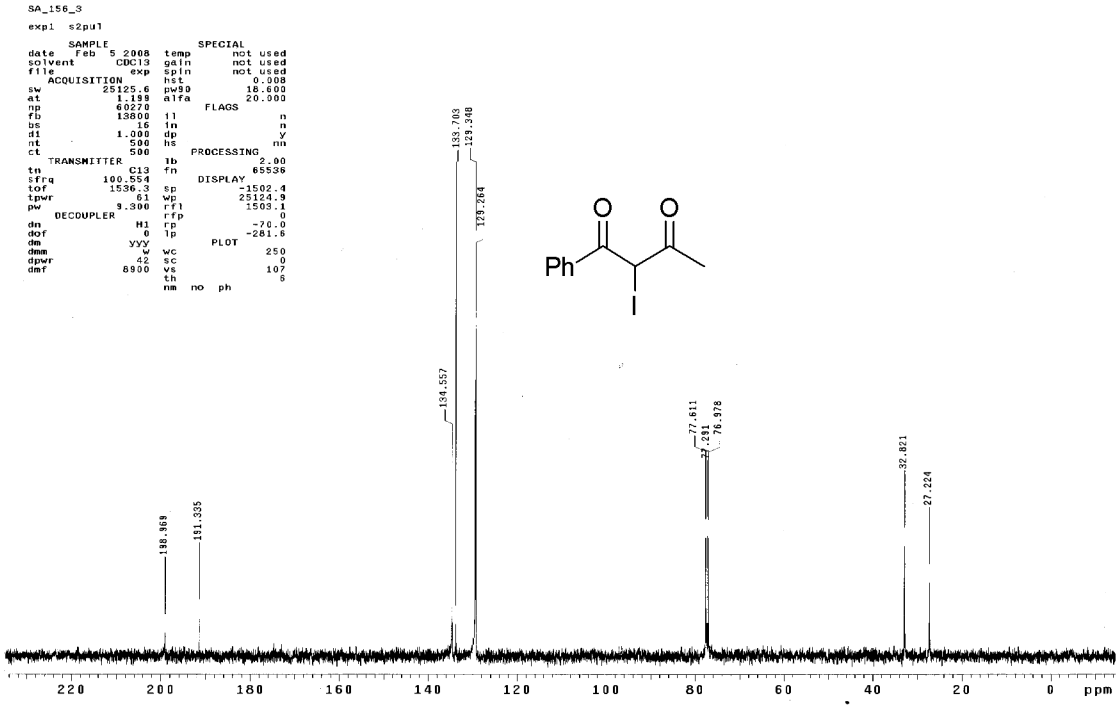
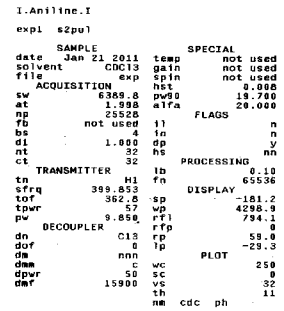
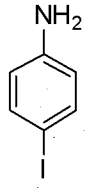
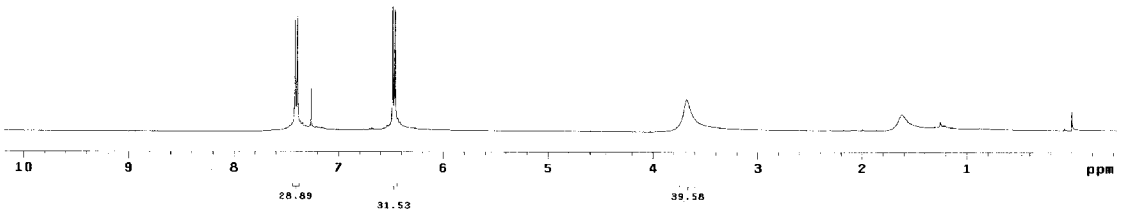


Figure 6

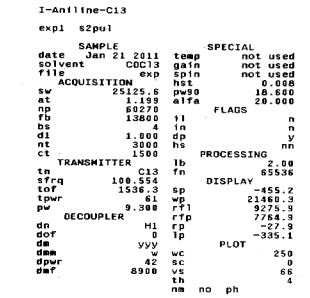
^{1}H NMR (400 MHz, CDCl$_3$): *4-iodoaniline* **(2l)**

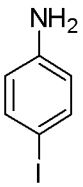






^{13}C NMR (100 MHz, CDCl$_3$): *4-iodoaniline* **(2l)**





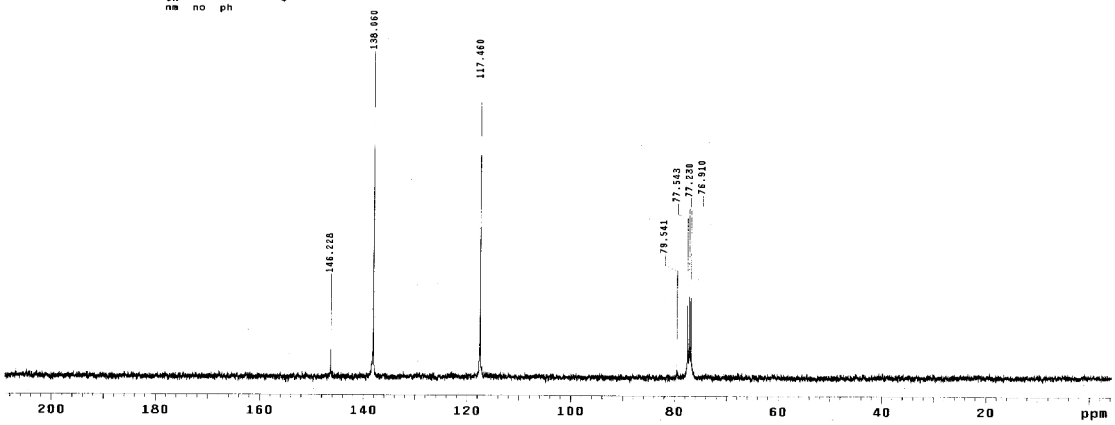
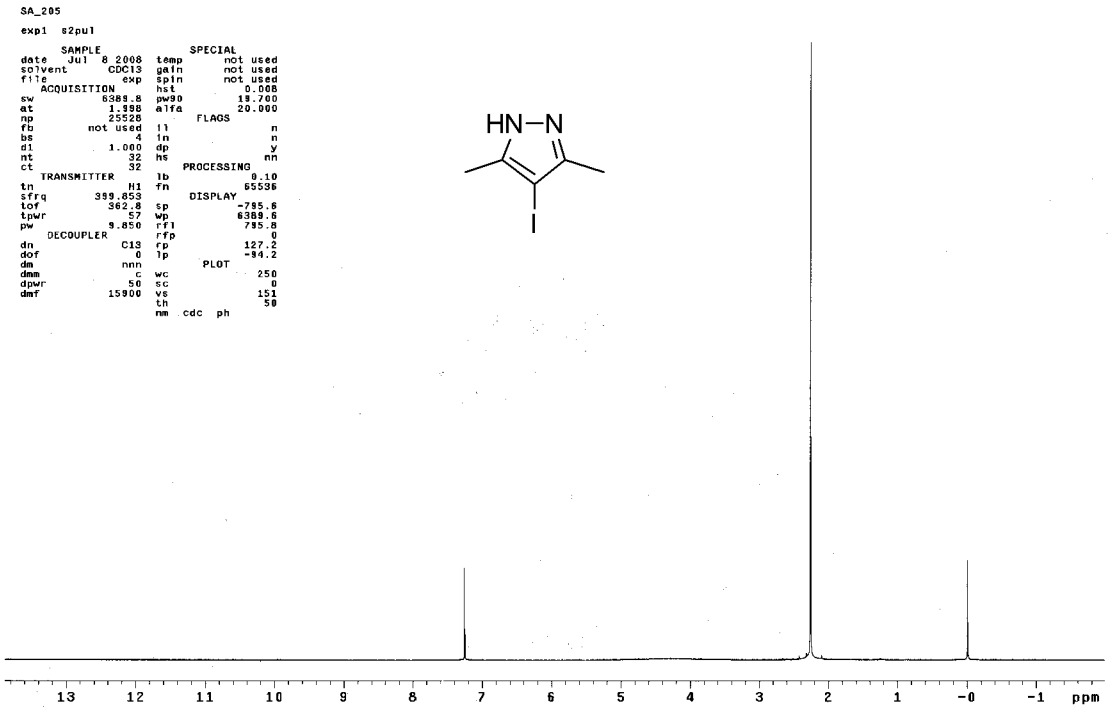


Figure 7

^{1}H NMR (400 MHz, $CDCl_3$): 4-iodo-3,5-dimethyl-1H-pyrazole **(2p)**



^{13}C NMR (100 MHz, $CDCl_3$): 4-iodo-3,5-dimethyl-1H-pyrazole **(2p)**

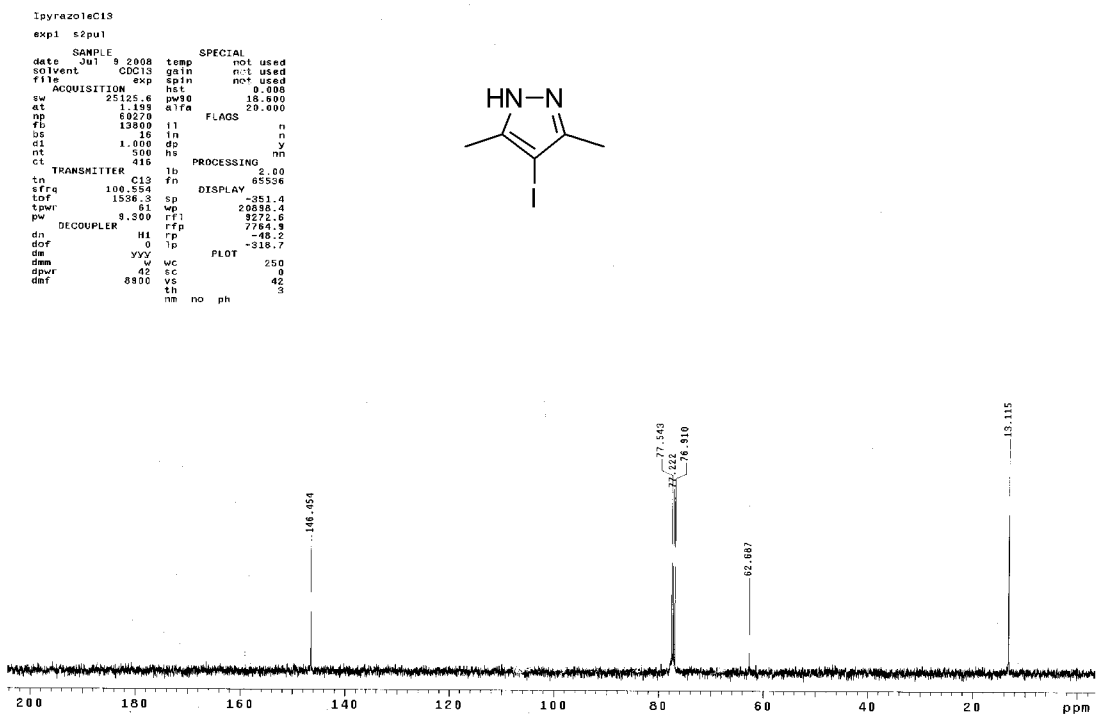
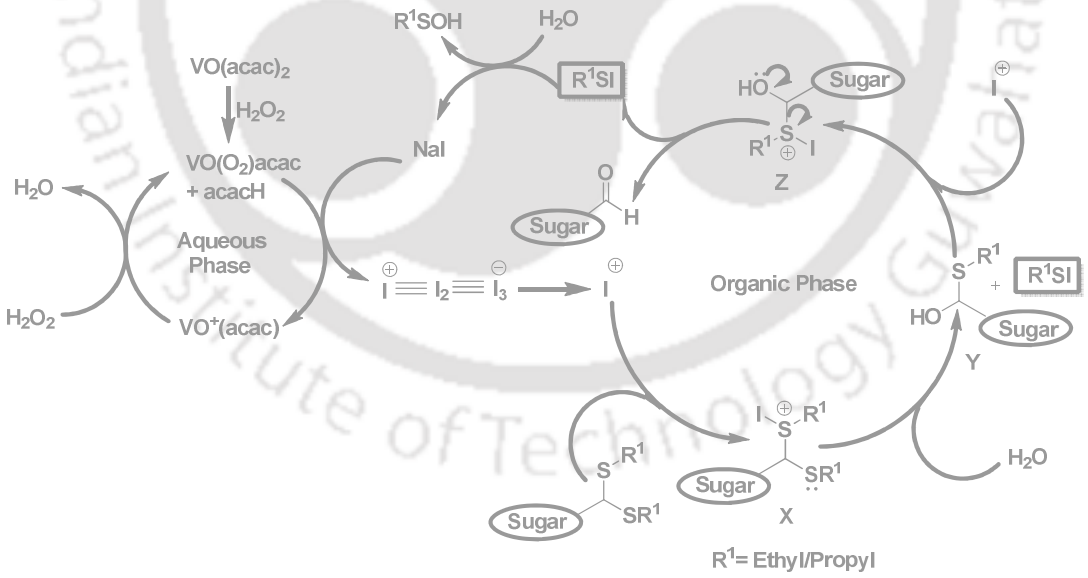


Figure 8

PART A

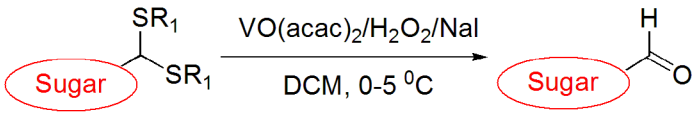
Cleavage of dithioacetals of sugars into the corresponding open chain aldehyde sugar derivatives using iodonium ion



POV mediated oxidation of iodide ion into iodonium ion has been described for the iodination of various organic substrates; which is described in Chapter 2 of Part A. From our earlier experience, it was noted that dithioacetals can be cleaved easily by using *in situ* generated bromonium ion. Therefore, the same knowledge can be extended further for the cleavage of dithioacetals of sugars to access open chain aldehyde sugars. Our group has developed various synthetic methodologies by using *in situ* generated halonium ion.[20-22] From our previous experiences, we have perceived that iodonium ion is a soft electrophile and would be suitable for similar kind transformation.

In this Chapter, the successful results of deprotection of dithioacetals of sugars into corresponding open chain aldehyde sugars have been elaborated using a combination of $VO(acac)_2/H_2O_2/NaI$ is reported as shown in Scheme 32.

In this combination vanadyl acetylacetonate acts as a catalyst, hydrogen peroxide and sodium iodide as the sources of active oxygen and iodoniun ion, respectively. All these chemicals are environmentally benign.



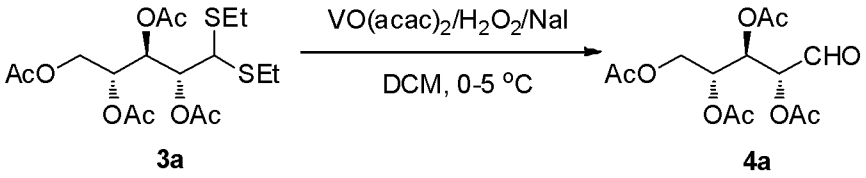
Scheme 32. Cleavage of dithioacetal of sugars derivatives

As per our requirement for the present study, various dithioacetals derivatives were prepared by following the literature procedure[94] and all these products were acetylated using standard procedure for characterization and handling purpose for future study. The detailed procedures for preparing these starting materials have been given in the experimental section.

As per our desire, D-ribose diethyl dithioacetal (**3a**) was initially chosen as a model substrate. The reaction condition for cleavage of sugar derivative (**3a**) was optimized in terms of yield and reaction time. Several reactions were examined using different amounts of $VO(acac)_2$, H_2O_2 and NaI. The best yield of **4a** was obtained using the combination of **3a**/$VO(acac)_2$/NaI/H_2O_2 in 1.0, 0.2, 1.0 and 10 equiv., respectively (Table 3, entry 4). After screening of solvents such as DCM, EtOAc, CH_3CN and

EtOH, dichloromethane (DCM) was the best solvent for this transformation and the results are summarized in Table 1. It is obvious that $VO(acac)_2$ plays an important role in the formation of the product (Table 3, entry 1). The product **4a** was confirmed by recording ^1H NMR and ^{13}C NMR spectra which is given in Figure 12. In the H NMR spectrum the disappearance of the signals at δ 1.24-1.25 and 2.58–2.76 due to the presence of SCH_2CH_3 group and appearance of new peak at δ 9.53 singlet due to the formation of -CHO group clearly indicates the cleavage of dithioacetals groups. Similarly, in the ^{13}C NMR spectrum disappearance of signals at δ 14.1, 14.3, 25.07, 25.13 and appearance of new signal at 193.2 due to aldehydic carbon clealy supports the formation of open chain aldehydic sugar derivatives.

Table 3: Optimization of the reaction conditions[a]



3a **4a**

Scheme 33

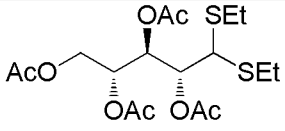
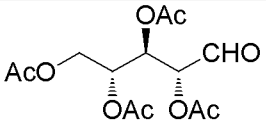
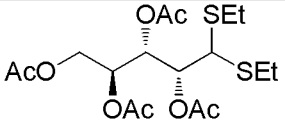
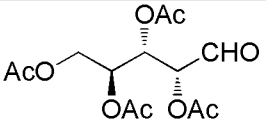
Entry	$VO(acac)_2$ (mol%)	Solvent	30% H_2O_2 mL (mmol)	NaI (mmol)	Time (h)	Yield[b] (%)
1	No Catalyst	DCM	1.2 (10)	1	5	NR[c]
2	10	DCM	1.2 (10)	1	5	32
3	15	DCM	1.2 (10)	1	5	50
4	20	DCM	1.2 (10)	1	3	68
5	25	DCM	1.2 (10)	1	3	65
6	20	DCM	1.2 (10)	0.5	3	39
7	20	DCM	0.6	1	3	50

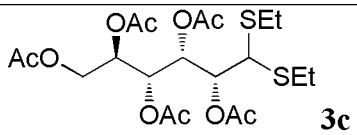
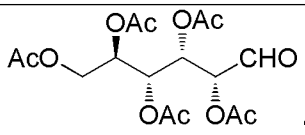
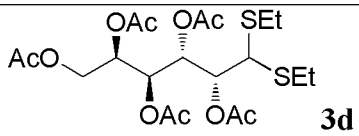
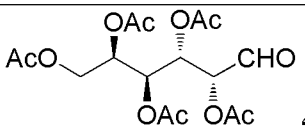
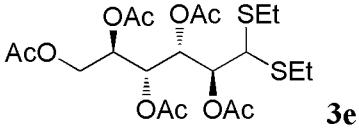
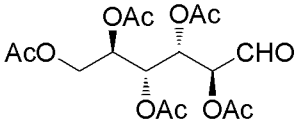
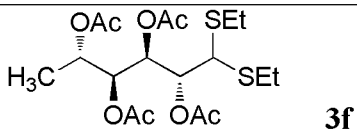
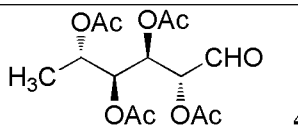
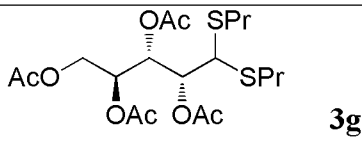
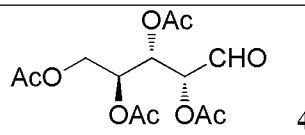
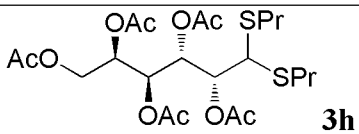
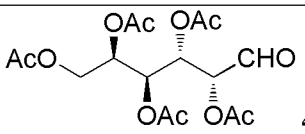
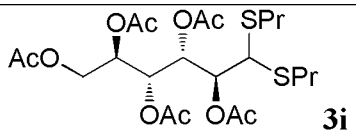
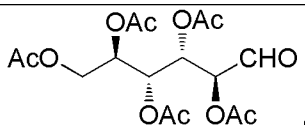
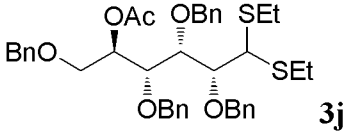
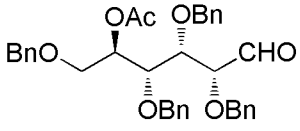
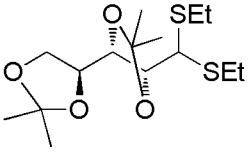
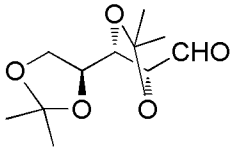
			(5)			
8	20	DCM	2.2 (20)	1	3	64
9	20	CH_3CN	1.2 (10)	1	3	6
10	20	EtOAc	1.2 (10)	1	3	10
11	20	EtOH	1.2 (10)	1	3	NR[c]

[a] Reaction was carried out using 1 mmol of 2,3,4,5-tetra-*O*-acetyl-D-ribose diethyl dithioacetal.[b] Isolated yield.[c] No Reaction.

The present protocol was examined for the deprotection of tetra-*O*-acetylated diethyldithioacetal of L-arabinose (**3b**) to give the desired product **4b** in 76 % of yield. By following the above procedures, various diethyl dithioacetal derivatives of different aldohexose such as D-glucose (**3c**), D-galactose (**3d**), D-mannose (**3e**) and L-rhamnose (**3f**) were cleaved to corresponding aldehydo-sugars **4c-4f** in good yields which are mentioned in Table 4. in the experimental section. The scope of this method was further verified for the deprotection of dipropyldithioacetal derivatives of sugars such as L-arabinose (**3g**), D-galactose (**3g**), D-mannose (**3i**) and obtained the desired products **4b**, **4d** and **4e** in good yields. It is important to mention that the reaction time required for cleavage of diethyl dithioacetal is less as compared to dipropyldithioacetal.

Table 4: Deprotection of dithioacetals of sugar[a]

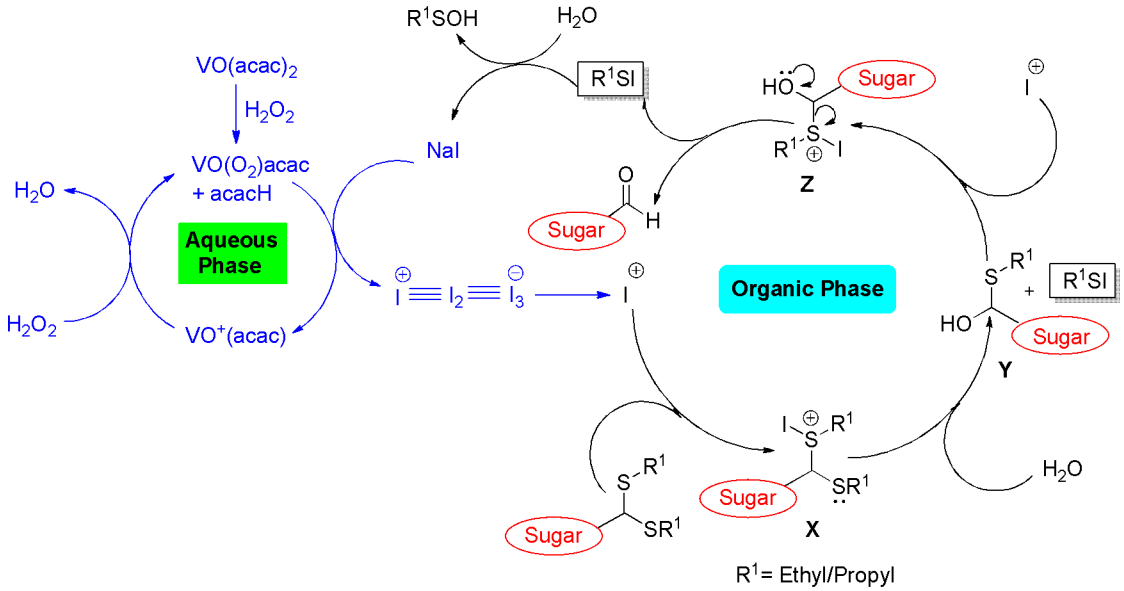
Entry	Substrate	Product	Time (h)	Yield[b] (%)
1	 **3a**	 **4a**	3	68
2	 **3b**	 **4b**	3	76

3	 **3c**	 **4c**	3	64
4	 **3d**	 **4d**	2.5	92
5	 **3e**	 **4e**	3	70
6	 **3f**	 **4f**	3.5	75
7	 **3g**	 **4b**	4.5	73
8	 **3h**	 **4d**	4.5	86
9	 **3i**	 **4e**	5	68
10	 **3j**	 **4j**	4	88
11	 **3k**	 **4k**	2.5	66

[a] The reaction was performed using 0.2 mmol $VO(acac)_2$, 10 mmol H_2O_2 and 1 mmol NaI. [b] Isolated yields.

We have extended our protocol for the substrate having other sensitive functional group such as acetals and benzyl groups. For this study, we performed the reaction of compounds **3j** and **3k**, which gave aldehydo-product **4j** and **4k** in good yields. From these observations, we have noted that our protocol is compatible with other functional groups in the substrates.

Finally we turned our attention towards a plausible mechanism for this transformation. Initially, the treatment of vanadyl acetylacetonate with hydrogen peroxide can generate mono peroxo complex of vanadium(V) by replacing one unit of acetylacetonate, which can oxidize iodide ion to iodonium ion (which might exist as I_2 and/or I_3^- in the solution). Thus *in situ* generated iodonium ion (I^+) react with sulphur to generate species (**X**) which on hydrolysis to give intermediate (**Y**). Further, attack on nucleophilic sulphur atom of intermediate (**Z**) with another I^+ followed by lone pair migration leading to the formation of desired product as shown in Scheme 34.

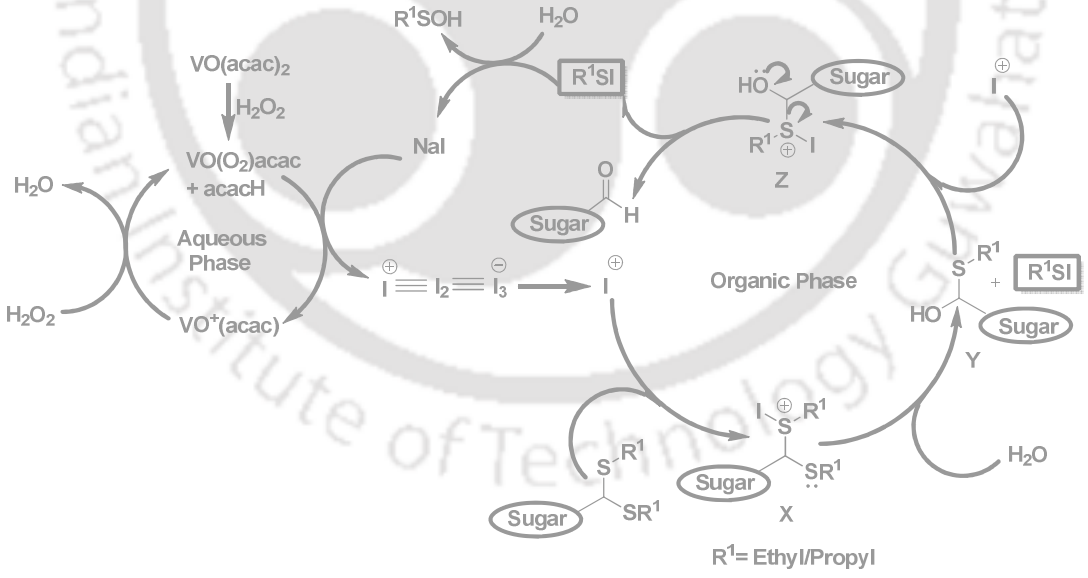


Scheme 34: Cleavage of dithioacetals into the corresponding aldehydes sugar

In conclusion, a simple and efficient protocol has been devised for the preparation of various aldehydo-sugars from cleavage of corresponding sugars dithioacetal using a combination of $VO(acac)_2$, H_2O_2 and NaI. Short reaction time, benign reaction conditions, and good yields are the main features. The reaction can be applied to a large number of sugars dithioacetals. Moreover, other protecting groups such as acetyl, benzyl and isopropylidene are unaffected during the experimental conditions.

PART A

Cleavage of dithioacetals of sugars into the corresponding open chain aldehyde sugar derivatives using iodonium ion



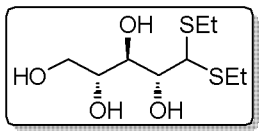
General procedure for preparation of dialkyl dithioacetal

To an ice cold stirring suspension of sugar (20.0 mmol) in thiol (10 mL), BDMS (0.134 g, 0.6 mmol) was added in two portions after an interval of 10 minutes. The reaction mixture was allowed to continue for stirring. After completion of reaction, the excess thiol was removed by short-path distillation, which was reused for next set of reaction. The crude residue was recrystallized in hot water or other solvents system, which are mentioned with each compounds.

General experimental protocol for per-O-acetylation of dialkyl dithioacetal of sugars

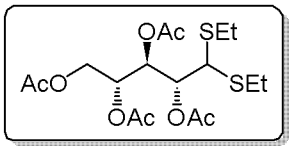
A suspension of dialkyl dithioacetal (2.0 mmol) in Ac_2O (0.94 mL, 10.0 mmol) was placed in an ice bath for stirring. To the cold suspension of the reaction mixture was added $HClO_4$–SiO_2 (50 mg) and stirring was continued further. After completion of the reaction (monitored by TLC), the reaction mixture was passed through a celite pad and washed with toluene. The crude reaction mixture was further co-evaporated with toluene (2 x 10 mL) to remove traces of acetic acid and the crude product was purified by column chromatography on silica gel using 3:1 hexane-EtOAc to furnish pure per-*O*-acetyl of dialkyl dithioacetals.

D-Ribose diethyl dithioacetal



Nature: Creamy solid; M.p. 78–80 °C (recrystallized from water); $[\alpha]_D^{25}$ –38.2 (*c* 1.0, H_2O).

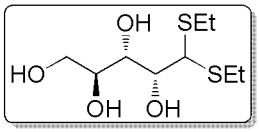
***2,3,4,5-Tetra-O-acetyl-D-ribose diethyl dithioacetal* (3a)**



Nature: Colorless solid; M.p. 47–48 °C (recrystallized from ethanol); $[\alpha]_D^{25}$ +29.6 (*c* 1.0, MeOH); **IR** (KBr): 2971, 1749, 1372, 1220, 1049 cm^{-1}; **^{1}H NMR** (400 MHz, $CDCl_3$): δ 1.24 (t, 3H, *J* = 7.6 Hz, SCH_2CH_3), 1.25 (t, 3H, *J* = 7.2 Hz, SCH_2CH_3), 2.04 (s, 3H, $COCH_3$), 2.07 (s, 6H, 2 × $COCH_3$), 2.15 (s, 3H, $COCH_3$), 2.58–2.76 (m, 4H, 2 × SCH_2CH_3), 3.95 (d, 1H, *J* = 6.0 Hz, H-1), 4.13 (dd, 1H, *J* = 7.6 Hz, *J* = 12.0 Hz, H-5), 4.42 (dd, 1H, *J* = 2.8 Hz, *J* = 12.0 Hz, H-5'), 5.32 (t, 1H, *J* = 6.0 Hz, H-2), 5.37–5.40 (m, 1H, H-4), 5.64 (dd, 1H, *J* = 4.0 Hz, *J* = 6.0 Hz, H-3); **^{13}C NMR** (100 MHz, $CDCl_3$): δ 14.1, 14.3, 20.7,

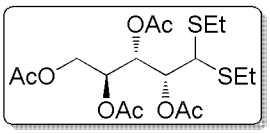
20.8 (2C), 20.9, 25.07, 25.13, 51.6, 62.2, 69.8, 71.2, 72.1, 169.3, 169.7, 169.9, 170.7; **Anal. Calcd** for $C_{17}H_{28}O_8S_2$ (424.53): C, 48.10; H, 6.65; S, 15.11. Found: C, 48.03; H, 6.56; S, 14.92.

L-Arabinose diethyl dithioacetal



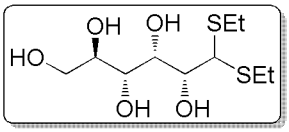
Nature: White solid; M.p. 124–126 °C; $[\alpha]_D^{25}$ –8.4 (*c* 1.0, H_2O).

***2,3,4,5-Tetra-O-acetyl-L-arabinose diethyl dithioacetal* (3b)**



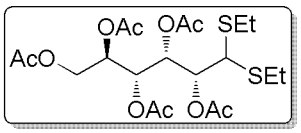
Nature: Colorless crystalline solid; M.p. 84 °C; $[\alpha]_D^{25}$ –34 (*c* 1.0, MeOH); **IR** (KBr): 2968, 1738, 1371, 1229, 1032 cm^{-1}; **^{1}H NMR** (400 MHz, $CDCl_3$): δ 1.21 (t, 3H, *J* = 7.6 Hz, SCH_2CH_3), 1.23 (t, 3H, *J* = 7.6 Hz, SCH_2CH_3), 2.03 (s, 3H, $COCH_3$), 2.04 (s, 3H, $COCH_3$), 2.10 (s, 3H, $COCH_3$), 2.11 (s, 3H, $COCH_3$), 2.58–2.76 (m, 4H, 2 × SCH_2CH_3), 3.89 (d, 1H, *J* = 8.0 Hz, H-1), 4.03 (dd, 1H, *J* = 5.6 Hz, *J* = 12.4 Hz, H-5), 4.26 (dd, 1H, *J* = 2.8 Hz, *J* = 12.4 Hz, H-5'), 5.09–5.13 (m, 1H, H-4), 5.27 (dd, 1H, *J* = 2.8 Hz, *J* = 8.0 Hz, H-2), 5.72 (dd, 1H, *J* = 2.8 Hz, *J* = 8.0 Hz, H-3); **^{13}C NMR** (100 MHz, $CDCl_3$): δ 14.2, 14.5, 20.9 (2C), 21.06, 21.12, 25.0 (2C), 51.9, 62.3, 69.0, 69.7, 70.9, 169.7, 170.1, 170.2, 170.9; **Anal. Calcd** for $C_{17}H_{28}O_8S_2$ (424.54): C, 48.10; H, 6.65; S, 15.11. Found: C, 48.00; H, 6.44; S, 14.95.

D-Glucose diethyl dithioacetal



Nature: White solid; M.p. 125–126 °C (recrystallized from hot water); $[\alpha]_D^{25}$ –28 (*c* 1.0, H_2O).

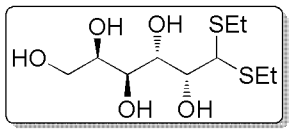
***2,3,4,5,6-Penta-O-acetyl-D-glucose diethyl dithioacetal* (3c)**



Nature: White syrup; $[\alpha]_D^{25}$ +13.6 (*c* 1.0, $CHCl_3$); **IR** (KBr): 2969, 1750, 1372, 1226, 1069, 1031 cm^{-1}; **^{1}H NMR** (400 MHz, $CDCl_3$): δ 1.20 (t, 3H, *J* = 7.6 Hz, SCH_2CH_3), 1.30 (t, 3H, *J* = 8.0 Hz, SCH_2CH_3), 2.01 (s, 3H, $COCH_3$), 2.03 (s, 3H, $COCH_3$), 2.05 (s, 3H, $COCH_3$), 2.06 (s, 3H, $COCH_3$), 2.12 (s, 3H, $COCH_3$), 2.48–2.80 (m, 4H, 2 × SCH_2CH_3), 4.04 (d, 1H, *J* = 4.0 Hz, H-1), 4.10 (dd, 1H, *J* = 4.8 Hz, *J* = 12.4 Hz, H-6),

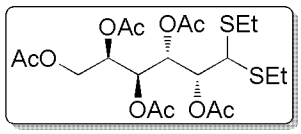
4.21 (dd, 1H, J = 2.8 Hz, J = 12.4 Hz, H-6'), 5.02–5.05 (m, 1H, H-5), 5.26 (dd, 1H, J = 4.0 Hz, J = 7.2 Hz, H-2), 5.40 (dd, 1H, J = 2.8 Hz, J = 8.4 Hz, H-4), 5.73 (dd, 1H, J = 2.8 Hz, J = 7.2 Hz, H-3); **^{13}C NMR** (100 MHz, $CDCl_3$): δ 14.3, 14.5, 20.5, 20.6, 20.7, 20.8 (2C), 24.8, 25.6, 50.6, 61.4, 68.3, 68.4, 70.0, 72.1, 169.6, 169.8, 169.9, 170.2, 170.5; **Anal. Calcd** for $C_{20}H_{32}O_{10}S_2$ (496.60): C, 48.37; H, 6.49; S, 12.91. Found: C, 48.29; H, 6.43; S, 12.82.

D-Galactose diethyl dithioacetal



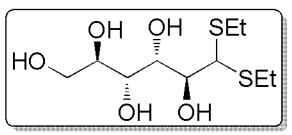
Nature: White needles; M.p. 142–143 °C (recrystallized from methanol); $[\alpha]_D^{25}$ –3.6 (*c* 1.0, H_2O).

***2,3,4,5,6-Penta-O-acetyl-D-galactose diethyl dithioacetal* (3d)**



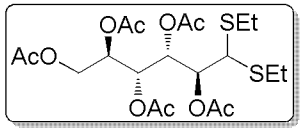
Nature: Colorless solid; M.p. 78–80 °C (recrystallized from ethanol); $[\alpha]_D^{25}$ +11.6 (*c* 1.0, MeOH); **IR** (KBr): 2977, 1747, 1372, 1220, 1025 cm^{-1}; **^{1}H NMR** (400 MHz, $CDCl_3$): δ 1.19 (t, 3H, J = 7.2 Hz, SCH_2CH_3), 1.22 (t, 3 H, J = 7.2 Hz, SCH_2CH_3), 1.99 (s, 3H, $COCH_3$), 2.08 (s, 6H, 2 x $COCH_3$), 2.09 (s, 3H, $COCH_3$), 2.09 (s, 3H, $COCH_3$), 2.54–2.67 (m, 4H, 2 × SCH_2CH_3), 3.80 (d, 1H, J = 6.8 Hz, H-1), 3.83 (dd, 1H, J = 7.2 Hz, J = 12.0 Hz, H-6), 4.26 (dd, 1H, J = 5.2 Hz, J = 12.0 Hz, H-6'), 5.14 (dd, 1H, J = 1.6 Hz, J = 8.0 Hz, H-2), 5.16–5.19 (m, 1H, H-5), 5.22 (dd, 1H, J = 2.0 Hz, J = 9.6 Hz, H-4), 5.75 (dd, 1H, J = 1.6 Hz, J = 9.6 Hz, H-3); **^{13}C NMR** (100 MHz, $CDCl_3$): δ 14.2, 14.4, 20.8 (2C), 20.9, 21.1, 25.1, 25.4, 28.9, 52.0, 62.3, 67.9, 68.1, 68.4, 70.5, 169.6, 169.9, 170.3, 170.5, 170.6; **Anal. Calcd** for $C_{20}H_{32}O_{10}S_2$ (496.60): C, 48.37; H, 6.49; S, 12.91. Found: C, 48.29; H, 6.41; S, 12.79.

D-Mannose diethyl dithioacetal



Nature: White solid; M.p. 135–136 °C (recrystallized from water); $[\alpha]_D^{25}$ +25.2 (*c* 1.0, H_2O).

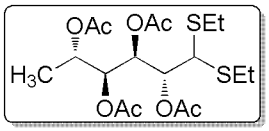
***2,3,4,5,6-Penta-O-acetyl-D-mannose diethyl dithioacetal* (3e)**



Nature: White syrupy; $[\alpha]_D^{25}$ +30 (*c* 0.35, MeOH); **IR** (KBr): 2971, 1749, 1371, 1218, 1047 cm^{-1}; **^{1}H NMR** (400 MHz,

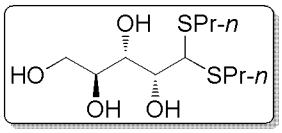
$CDCl_3$): δ 1.24 (t, 3H, J = 7.6 Hz, SCH_2CH_3), 1.28 (t, 3H, J = 7.2 Hz, SCH_2CH_3), 2.06 (s, 3H, $COCH_3$), 2.08 (s, 3H, $COCH_3$), 2.09 (s, 6H, 2 × $COCH_3$), 2.10 (s, 3H, $COCH_3$), 2.60–2.76 (m, 4H, 2 × SCH_2CH_3), 3.90 (d, 1H, J = 5.6 Hz, H-1), 4.08 (dd, 1H, J = 5.2 Hz, J = 12.4 Hz, H-6), 4.22 (dd, 1H, J = 2.8 Hz, J = 12.4 Hz, H-6'), 5.06–5.09 (m, 1H, H-5), 5.29 (dd, 1H, J = 5.6 Hz, J = 7.2 Hz, H-2), 5.50 (dd, 1H, J = 2.0 Hz, J = 9.2 Hz, H-4), 5.75 (dd, 1H, J = 1.6 Hz, J = 7.2 Hz, H-3); **^{13}C NMR** (100 MHz, $CDCl_3$): δ 14.3, 14.4, 20.9, 21.0 (2C), 21.03 (2C), 25.3, 25.6, 51.5, 62.0, 67.4, 68.2, 69.2, 71.2, 169.9, 170.1 (2C), 170.7, 170.8; **Anal. Calcd** for $C_{20}H_{32}O_{10}S_2$ (496.60): C, 48.37; H, 6.49; S, 12.91. Found: C, 48.30; H, 6.41; S, 12.82.

***2,3,4,5-Tetra-O-acetyl-L-rhamnose diethyl dithioacetal* (3f)**



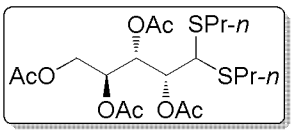
Nature: Syrupy; $[\alpha]_D^{25}$ –44.6 (*c* 1.0, MeOH); **IR** (KBr): 2974, 1751, 1371, 1224, 1069 cm^{-1}; **^{1}H NMR** (400 MHz, $CDCl_3$): δ 1.16 (d, 3H, J = 6.4 Hz, CH_3), 1.22 (t, 3H, J = 7.2 Hz, SCH_2CH_3), 1.23 (t, 3H, J = 7.6 Hz, SCH_2CH_3), 2.03 (s, 3H, $COCH_3$), 2.06 (s, 3H, $COCH_3$), 2.07 (s, 3H, $COCH_3$), 2.08 (s, 3H, $COCH_3$), 2.58–2.72 (m, 4H, 2 × SCH_2CH_3), 3.83 (d, 1H, J = 4.4 Hz, H-1), 4.85–4.92 (m, 1H, H-5), 5.23 (dd, 1H, J = 1.6 Hz, J = 8.4 Hz, H-4), 5.28 (dd, 1H, J = 4.4 Hz, J = 7.6 Hz, H-2), 5.78 (dd, 1H, J = 1.6 Hz, J = 7.6 Hz, H-3); **^{13}C NMR** (100 MHz, $CDCl_3$): δ 14.1, 14.3, 16.5, 20.9, 21.0 (2C), 21.2, 25.3, 25.6, 51.5, 67.2, 69.0, 71.0, 71.1, 169.6, 169.9, 170.1, 170.4; **Anal. Calcd** for $C_{18}H_{30}O_8S_2$ (438.56): C, 49.30; H, 6.89; S, 14.62. Found: C, 49.21; H, 6.80; S, 14.49.

L-Arabinose dipropyl dithioacetal



Nature: White needles; M.p. 138–139 °C (recrystallized from water/ethanol/ethyl acetate: 3:1:1); $[\alpha]_D^{25}$ +13.3 (*c* 1.0, MeOH).

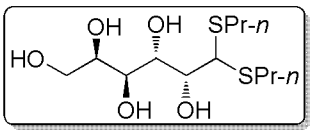
***2,3,4,5-Tetra-O-acetyl-L-arabinose dipropyl dithioacetal* (3g)**



Nature: Syrupy; $[\alpha]_D^{25}$ –35 (*c* 1.0, MeOH); **IR (KBr):** 2964, 1749, 1372, 1217, 1044 cm^{-1}; **^{1}H NMR (400 MHz, $CDCl_3$):** δ 0.96–1.01 (m, 6H, 2 × $SCH_2CH_2CH_3$), 1.56–1.63 (m, 4H, 2 × SCH_2CH_2), 2.05 (s, 3H, $COCH_3$), 2.06 (s, 3H, $COCH_3$), 2.11 (s, 3H, $COCH_3$), 2.12 (s,

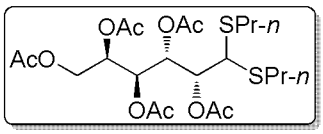
3H, COCH_3), 2.50–2.74 (m, 4H, 2 × SCH_2CH_2), 3.86 (d, 1H, J = 8.4 Hz, H-1), 4.01 (dd, 1H, J = 6.0 Hz, J = 12.4 Hz, H-5), 4.27 (dd, 1H, J = 3.2 Hz, J = 12.4 Hz, H-5'), 5.10–5.13 (m, 1H, H-4), 5.26 (dd, 1H, J = 2.8 Hz, J = 8.4 Hz, H-2), 5.74 (dd, 1H, J = 2.8 Hz, J = 8.0 Hz, H-3); **^{13}C NMR (100 MHz, CDCl$_3$):** δ 13.6, 13.8, 20.9 (2C), 21.0, 21.1, 22.5, 22.7, 32.9, 33.0, 52.4, 62.3, 68.9, 69.6, 70.9, 169.7, 170.0, 170.2, 170.8; **Anal. Calcd** for $C_{19}H_{32}O_8S_2$ (452.59): C, 50.42; H, 7.13; S, 14.17. Found: C, 50.31; H, 7.00; S, 14.06.

D-Galactose dipropyl dithioacetal



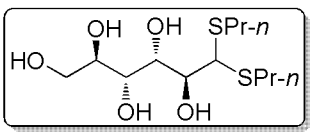
Nature: White needles; M.p. 151–154 ºC (recrystallized from water/ ethanol/ethyl acetate: 3:1:1); $[\alpha]_D^{25}$ +10.8 (*c* 1.0, MeOH).

***2,3,4,5,6-Penta-O-acetyl-D-galactose dipropyl dithioacetal* (3h)**



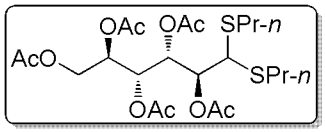
Nature: Syrupy; $[\alpha]_D^{25}$ +6.6° (*c* 0.80, MeOH); **IR (KBr):** 2961, 1750, 1371, 1215, 1030 cm^{-1}; **^{1}H NMR (400 MHz, CDCl$_3$):** δ 0.98 (t, 3H, J = 7.2 Hz, SCH$_2$CH$_2$CH_3), 0.99 (t, 3H, J = 7.6 Hz, SCH$_2$CH$_2$CH_3), 1.52–1.64 (m, 4H, 2 × SCH$_2$CH_2), 2.02 (s, 3H, COCH_3), 2.10 (s, 3H, COCH_3), 2.11 (s, 6H, 2 × COCH_3), 2.13 (s, 3H, COCH_3), 2.60–2.70 (m, 4H, 2 × SCH_2CH$_2$), 3.79 (d, 1H, J = 8.4 Hz, H-1), 3.84 (dd, 1H, J = 7.2 Hz, J = 12.0 Hz, H-6), 4.28 (dd, 1H, J = 5.2 Hz, J = 12.0 Hz, H-6'), 5.15 (dd, 1H, J = 2.0 Hz, J = 8.4 Hz, H-2), 5.17–5.20 (m, 1H, H-5), 5.24 (d, 1H, J = 2.0 Hz, J = 9.6 Hz, H-4), 5.79 (dd, 1H, J = 2.0 Hz, J = 9.6 Hz, H-3); **^{13}C NMR (100 MHz, CDCl$_3$):** δ 13.7, 13.8, 20.9 (2C), 21.0, 21.2, 22.6 (2C), 22.7, 33.1, 33.6, 52.7, 62.4, 68.0, 68.2, 68.5, 70.7, 169.7, 170.1, 170.4, 170.6, 170.7; **Anal. Calcd** for $C_{22}H_{36}O_{10}S_2$ (524.65): C, 50.37; H, 6.92; S, 12.22. Found: C, 50.26; H, 6.85; S, 12.13.

D-Mannose dipropyl dithioacetal



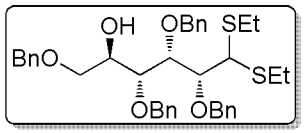
Nature: White reddish needles; M.p. 130–132 ºC (recrystallized from water/ethanol/ethyl acetate: 3:1:1); $[\alpha]_D^{25}$ +4.3 (*c* 1.0, MeOH).

2,3,4,5,6-Penta-O-acetyl-D-mannose dipropyl dithioacetal **(3i)**



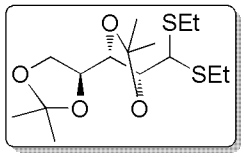
Nature: Syrupy; $[\alpha]_D^{25}$ +26.1 (*c* 1.2, MeOH); **IR (KBr):** 2964, 1750, 1372, 1218, 1052 cm^{-1}; **^{1}H NMR (400 MHz, $CDCl_3$):** δ 0.98 (t, 3H, *J* = 7.6 Hz, $SCH_2CH_2CH_3$), 1.01 (t, 3H, *J* = 7.6, $SCH_2CH_2CH_3$), 1.54–1.66 (m, 4H, 2 × SCH_2CH_2), 2.05 (s, 3H, $COCH_3$), 2.07 (s, 6H, 2 × $COCH_3$), 2.08 (s, 3H, $COCH_3$), 2.10 (s, 3H, $COCH_3$), 2.53–2.62 (m, 2H, SCH_2CH_2), 2.64–2.72 (m, 2H, SCH_2CH_2), 3.87 (d, 1H, *J* = 6.0 Hz, H-1), 4.08 (dd, 1H, *J* = 5.2 Hz, *J* = 12.8 Hz, H-6), 4.20 (dd, 1H, *J* = 2.4 Hz, *J* = 12.8 Hz, H-6'), 5.05–5.09 (m, 1H, H-5), 5.28 (dd, 1H, *J* = 6.0 Hz, *J* = 7.2 Hz, H-2), 5.50 (dd, 1H, *J* = 1.6 Hz, *J* = 9.2 Hz, H-4), 5.74 (dd, 1H, *J* = 1.6 Hz, *J* = 7.2 Hz, H-3); **^{13}C NMR (100 MHz, $CDCl_3$):** δ 13.7 (2C), 20.9 (2C), 21.0 (2C), 22.5, 22.6 (2C), 33.2, 33.5, 52.1, 62.0, 67.4, 68.2, 69.2, 71.4, 169.9 (2C), 170.1 (2C), 170.8; **Anal. Calcd** for $C_{22}H_{36}O_{10}S_2$ (524.65): C, 50.37; H, 6.92; S, 12.22. Found: C, 50.29; H, 6.80; S, 11.97.

2,3,4,6-Tetra-O-benzyl-D-glucose diethyl dithioacetal **(3k)**



Nature: White syrup; $[\alpha]_D^{25}$ +27 (*c* 1.0, MeOH); **IR (KBr):** 3492, 2925, 1454, 1100, 697 cm^{-1}; **^{1}H NMR (400 MHz, $CDCl_3$):** δ 1.17 (t, 3H, *J* = 7.6 Hz, SCH_2CH_3), 1.18 (t, 3H, *J* = 7.2 Hz, SCH_2CH_3), 2.50–2.60 (m, 2H, SCH_2CH_3), 2.66 (q, 2H, *J* = 7.6 Hz, SCH_2CH_3), 3.08 (d, 1H, *J* = 5.2 Hz, OH), 3.61 (dd, 1H, *J* = 5.6 Hz, *J* = 10.0 Hz, H-6), 3.66 (dd, 1H, *J* = 4.0 Hz, *J* = 10.0 Hz, H-6'), 3.71 (dd, 1H, *J* = 3.6 Hz, *J* = 6.8 Hz, H-4), 3.93 (d, 1H, *J* = 4.0 Hz, H-1), 4.03–4.15 (m, 1H, H-5), 4.14 (dd, 1H, *J* = 4.0 Hz, *J* = 6.8 Hz, H-2), 4.27 (dd, 1H, *J* = 3.6 Hz, 6.8 Hz, H-3), 4.49–4.59 (m, 4H, 2 × CH_2), 4.67 (d, 1H, *J* = 11.6 Hz, *CH*H), 4.79 (d, 1H, *J* = 11.6, CH*H*), 4.80 (d, 1H, *J* = 11.2, *CH*H), 4.89 (d, 1H, *J* = 11.2 Hz, CH*H*), 7.23–7.38 (m, 20H, Ar*H*); **^{13}C NMR (100 MHz, $CDCl_3$):** δ 14.6 (2C), 25.5, 25.7, 54.0, 71.1, 71.6, 73.0, 73.7, 75.1, 75.5, 77.5, 80.3, 82.9, 127.6, 127.9, 127.96, 128.0 (4C), 128.03 (4C), 128.2, 128.3, 128.4, 128.6 (6C), 138.1, 138.4 (2C), 138.7; **Anal. Calcd** for $C_{38}H_{46}O_5S_2$ (646.28): C, 70.55; H, 7.17; S, 9.91. Found: C, 70.46; H, 7.03; S, 9.82.

***2,3:4,5-Di-O-isopropylidene-L-arabinose diethyldithioacetal* (3l)**

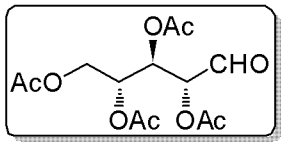


Nature: Colorless oil; $[\alpha]_D^{25}$ –80.8° (*c* 1.0, MeOH); **IR (KBr):** 2986, 2931, 1455, 1372, 1219, 1064, 847 cm^{-1}; **^{1}H NMR (400 MHz, $CDCl_3$):** δ 1.23 (t, 3H, *J* = 7.6 Hz, SCH_2CH_3), 1.26 (t, 3H, *J* = 7.6 Hz, SCH_2CH_3), 1.31 (s, 3H, CH_3), 1.35 (s, 3H, CH_3), 1.39 (s, 3H, CH_3), 1.42 (s, 3H, CH_3), 2.66–2.78 (m, 4H, 2 × SCH_2CH_3), 3.94 (dd, 1H, *J* = 4.4 Hz, *J* = 8.4 Hz, H-5), 4.01 (d, 1H, *J* = 2.4 Hz, H-1), 4.03 (t, 1H, *J* = 4.8 Hz, H-3), 4.06–4.12 (m, 2H, H-4 and H-5'), 4.11 (dd, 1H, *J* = 2.8 Hz, *J* = 4.8 Hz, H-2); **^{13}C NMR (100 MHz, $CDCl_3$):** δ 14.4, 14.5, 25.0, 25.2, 25.3, 26.8, 27.2, 27.4, 52.4, 67.8, 77.2, 79.2, 84.6, 109.8, 110.2; **Anal. Calcd** for $C_{15}H_{28}O_4S_2$ (336.51): C, 53.54; H, 8.39; S, 19.06. Found: C, 53.31; H, 8.30; S, 18.86.

General experimental procedure for cleavage of dithioacetals

To a stirred solution of $VO(acac)_2$ (0.053 g, 0.2 mmol) in water (1 mL), was added 30% H_2O_2 solution (1.2 mL, 10 mmol) at 0–5 °C. After 20 min solution turns yellow from bluish green. NaI (0.149 g, 1 mmol) was added into it by dissolving in water (1 mL). The color changes from yellow to dark brown. Then the substrate (1 mmol) in dichloromethane (2 mL) was added instantly into it. The reaction was monitored by the TLC until the complete consumption of the starting material. The reaction mixture was extracted with ethyl acetate (3 × 25 mL) and the organic layer was washed with 10% sodium thiosulfate solution to remove excess iodine. Finally, the organic layer was washed with water and dried over anhydrous sodium sulfate. The solvent was evaporated under vacuum and the crude product was purified through a column chromatography using ethyl acetate: hexane (20: 80).

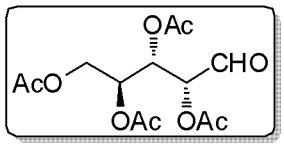
***2,3,4,5-Tetra-O-acetyl-aldehydo-D-ribose* (4a)**



Nature: White solid; M.P. 96-97 °C; $[\alpha]_D^{25}$ -12.4° (*c* 1.0, MeOH); **IR (KBr):** 1748 (CO) cm^{-1}; **^{1}H NMR (400 MHz, $CDCl_3$):** δ 2.0 (s, 3H), 2.05 (s, 3H), 2.08 (s, 3H), 2.18 (s, 3H), 4.15 (dd, *J* = 4.4 Hz, *J* = 12.8 Hz, 1H), 4.34 (dd, *J* = 2.0 Hz, *J* = 8.4 Hz, 1H), 5.26-5.31 (m, 1H), 5.44 (d, *J* = 2.0 Hz, 1H), 5.60 (dd, *J* = 2.4 Hz, *J* = 9.2 Hz, 1H), 9.53 (s, 1H); **^{13}C NMR (100 Hz, $CDCl_3$):** δ 20.4, 20.7 (3C), 61.4, 68.3, 68.4, 76.7, 169.1, 169.5,

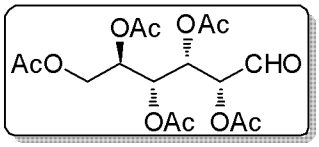
169.8, 170.6, 193.2. **Anal. Calcd** for $C_{13}H_{18}O_9$ (318.28): C, 49.06; H, 5.70. Found C, 48.93; H, 5.61.

***2,3,4,5-Tetra-O-acetyl-aldehydo- L-arabinose* (4b)**



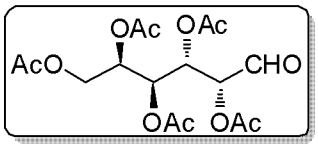
Nature: White solid; M.P. 115-116 °C; $[\alpha]_D^{25}$ –60.0° (*c* 2.0, $CHCl_3$); **IR (KBr):** 1749 (CO) cm^{-1}; **^{1}H NMR (400 MHz, $CDCl_3$):** δ 2.07 (s, 3H), 2.07 (s, 3H), 2.07 (s, 3H), 2.08 (s, 3H), 4.16-4.20 (m, 1H), 4.31 (dd, *J* = 2.4 Hz, *J* = 12.4 Hz, 1H), 5.24-5.28 (m, 1H), 5.38 (d, *J* = 2.0 Hz, 1H), 5.68 (dd, *J* = 2.4 Hz, *J* = 9.2 Hz, 1H), 9.73 (s, 1H); **^{13}C NMR (100 Hz, $CDCl_3$):** δ 20.5, 20.7, 20.9 (2C), 61.7, 67.4, 68.2, 76.1, 169.8, 169.9, 170.9 (2C), 194.1. **Anal. Calcd** for $C_{13}H_{18}O_9$ (318.28): C, 49.06; H, 5.70. Found C, 48.94; H, 5.61.

***2,3,4,5,6-Penta-O-acetyl-aldehydo-D-glucose* (4c)**



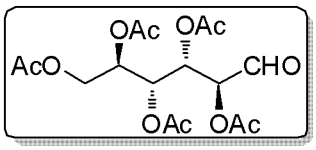
Nature: White solid; mp 118-119 °C, $[\alpha]_D^{25}$ +4.2° (*c* 2.0, $CHCl_3$); **IR (KBr):** 1749 (CO) cm^{-1}; **^{1}H NMR (400 MHz, $CDCl_3$):** δ 2.04 (s, 9H), 2.10 (s, 3H), 2.18 (s, 3H), 4.07 (dd, *J* = 5.2 Hz, *J* = 12.4 Hz, 1H), 4.25 (dd, *J* = 2.8 Hz, *J* = 12.8 Hz, 1H), 5.08-5.13 (m, 1H), 5.25 (d, *J* = 5.2 Hz, 1H), 5.48 (dd, *J* = 3.6 Hz, *J* = 7.6 Hz, 1H), 5.57 (dd, *J* = 3.6 Hz, *J* = 4.8 Hz, 1H), 9.50 (s, 1H); **^{13}C NMR (100 Hz, $CDCl_3$):** δ 20.4, 20.5, 20.6, 20.77, 20.83, 61.8, 68.3, 68.4, 68.6, 75.2, 169.4, 169.6, 169.8, 169.9, 170.7, 194.0. **Anal. Calcd** for $C_{16}H_{22}O_{11}$ (390.34): C, 49.23; H, 5.68. Found C, 49.11; H, 5.60.

***2,3,4,5,6-Penta-O-acetyl-aldehydo-D-galactose* (4d)**



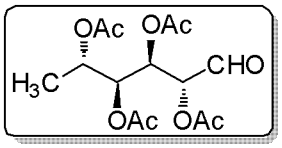
Nature: White solid; mp 105-110 °C, $[\alpha]_D^{25}$ –6.0° (*c* 2.0, $CHCl_3$); **IR (KBr):** 1750 (CO) cm^{-1}; ^{1}H **NMR (400 MHz, $CDCl_3$):** δ 2.04 (s, 3H), 2.05 (s, 3H), 2.11 (s, 3H), 2.12 (s, 3H), 2.22 (s, 3H), 3.90 (dd, *J* = 3.6 Hz, *J* = 11.2 Hz, 1H), 4.28 (dd, *J* = 5.2 Hz, *J* = 11.6 Hz, 1H), 5.29 (d, *J* = 15.6 Hz, 1H), 5.37 (t, *J* = 5.6 Hz, 1H), 5.47 (d, *J* = 10.0 Hz, 1H), 5.65 (d, *J* = 9.6 Hz, 1H), 9.46 (s, 1H); **^{13}C NMR (100 Hz, $CDCl_3$):** δ 20.6, 20.8 (4C), 62.1, 66.4, 67.7 (2C), 75.9, 170.3, 170.5, 170.8 (3C), 193.9. **Anal. Calcd** for $C_{16}H_{22}O_{11}$ (390.34): C, 49.23; H, 5.68. Found C, 49.09; H, 5.58.

***2,3,4,5,6-Penta-O-acetyl-aldehydo-D-mannose* (4e)**



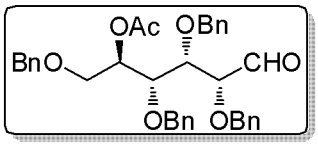
Nature: Syrup; $[\alpha]_D^{25}$ +23.6° (*c* 1.0, CH_2Cl_2); **IR (KBr):** 1749 (CO) cm^{-1}; **^{1}H NMR (400 MHz, $CDCl_3$):** δ 2.05 (s, 3H), 2.06 (s, 3H), 2.09 (s, 3H), 2.11 (s, 3H), 2.17 (s, 3H), 4.09-4.14 (m, 1H), 4.21 (dd, *J* = 2.8 Hz, *J* = 10.0 Hz, 1H), 5.03 (dd, *J* = 0.8 Hz, *J* = 7.6 Hz, 1H), 5.12-5.17 (m, 1H), 5.45-5.50 (m, 2H), 9.41 (s, 1H); **^{13}C NMR (100 Hz, $CDCl_3$):** δ 20.4, 20.5, 20.6, 20.7, 20.8, 61.8, 67.4, 67.6, 67.8, 74.3, 169.66, 169.7, 169.8, 170.0, 170.6, 195.4. **Anal. Calcd** for $C_{16}H_{22}O_{11}$ (390.34): C, 49.23; H, 5.68. Found C, 49.33; H, 5.74.

***2,3,4,5-Tetra-O-acetyl-aldehydo-L-rhamnose* (4f)**



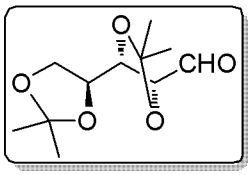
Nature: Syrup; $[\alpha]_D^{25}$ -33°(*c* 0.06, CH_2Cl_2); **IR (KBr):** 1748 (CO) cm^{-1}; **^{1}H NMR (400 MHz, $CDCl_3$):** δ 1.04 (d, *J* = 6.4 Hz, 3H), 1.87 (s, 3H), 1.91 (s, 3H), 1.93 (s, 3H), 1.97 (s, 3H), 4.78-4.88 (m, 2H), 5.07-5.13 (m, 1H), 5.36 (d, *J* = 8.0 Hz, 1H), 9.35 (s, 1H); **^{13}C NMR (100 Hz, $CDCl_3$):** δ 16.6, 20.5, 20.7, 20.8, 21.0, 66.8, 67.4, 71.4, 74.3, 170.0, 170.1 (2C), 170.3, 195.5. **Anal. Calcd** for $C_{14}H_{20}O_9$ (332.30): C, 50.60; H, 6.07. Found C, 50.46; H, 6.00.

***5-O-Acetyl-2,3,4,6-tetra-O-benzyl- aldehydo- D-glucose* (4j)**



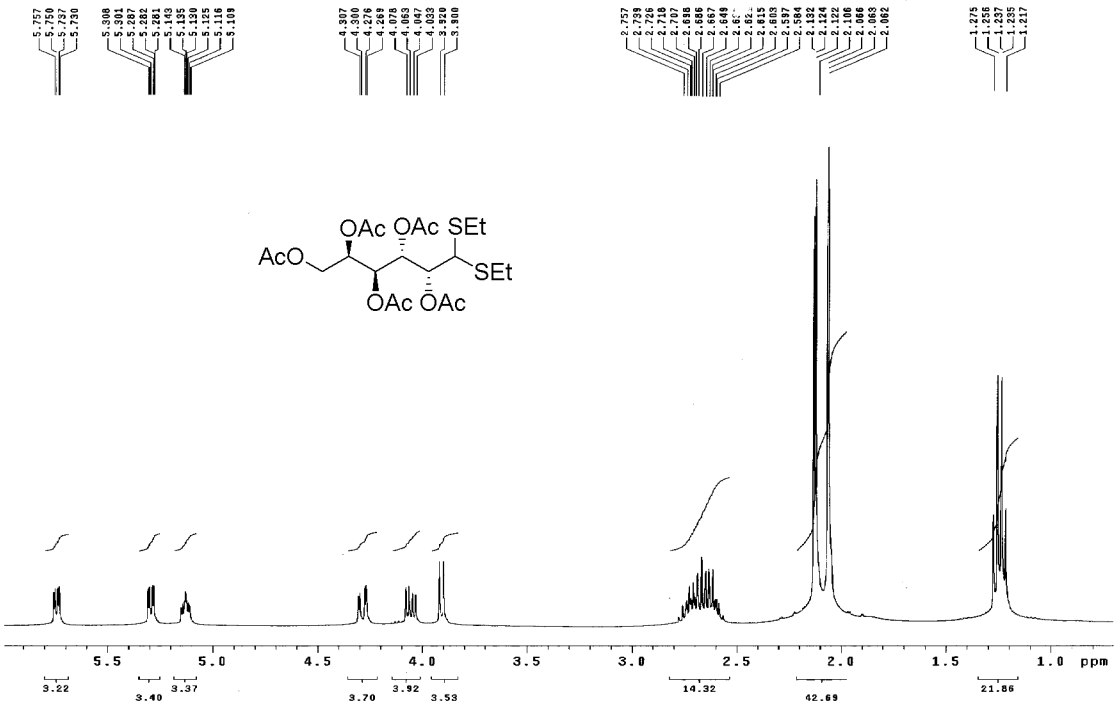
Nature: Syrup; **IR (KBr):** 1735 (CO) cm^{-1}; **^{1}H NMR (400 MHz, $CDCl_3$):** δ 1.90 (s, 3H), 3.62 (dd, *J* = 4.8 Hz, *J* = 11.2 Hz, 1H), 3.74 (dd, *J* = 3.2 Hz, *J* = 11.2 Hz, 1H), 3.81-3.85 (m, 2H), 3.95-3.97 (m, 1H), 4.30-4.44 (m, 7H), 4.71 (d, *J* = 11.6 Hz, 1H), 5.11 (d, *J* = 3.2 Hz, 1H), 7.07-7.23 (m, 20H), 9.59 (s, 1H); **^{13}C NMR (100 Hz, $CDCl_3$):** δ 21.2, 68.1, 72.5, 73.1, 73.2, 73.7, 74.0, 76.7, 79.7, 80.3, 127.7 (2C), 127.9 (2C), 128.1 (2C), 128.2 (2C), 128.3 (2C), 128.4 (3C), 128.43 (3C), 128.5 (4C), 137.1, 137.2, 137.6, 137.8, 170.0, 200.1. **Anal. Calcd** for $C_{36}H_{38}O_7$ (582.68): C, 74.21; H, 6.57. Found C, 74.09; H, 6.48.

2,3:4,5-Di-O-isopropylidene-aldehydo-L-arabinose **(4k)**



Nature: Syrup; $[\alpha]_D^{25}$ +10°(*c* 0.25, CH_2Cl_2); **IR (KBr):** 1739 (CO) cm^{-1}; **^{1}H NMR (400 MHz, $CDCl_3$):** δ 1.33 (s, 3H), 1.36 (s, 3H), 1.40 (s, 3H), 1.45 (s, 3H), 3.94-4.15 (m, 4H), 4.39 (dd, *J* = 0.8 Hz, *J* = 6.0 Hz, 1H), 9.73 (s, 1H); **^{13}C NMR (100 Hz, $CDCl_3$):** δ 25.3, 26.4, 26.9, 27.2, 67.2, 76.65, 77.9, 83.5, 110.2, 112.1, 200.1. **Anal. Calcd** for $C_{11}H_{18}O_5$ (230.26): C, 57.38; H, 7.88. Found C, 57.51; H, 7.97.

^{1}H NMR (400 MHz, $CDCl_3$): *2,3,4,5-Tetra-O-acetyl-L-arabinose diethyl dithioacetal* ***(3b)***



^{13}C NMR (100 MHz, $CDCl_3$): *2,3,4,5-Tetra-O-acetyl-L-arabinose diethyl dithioacetal* ***(3b)***

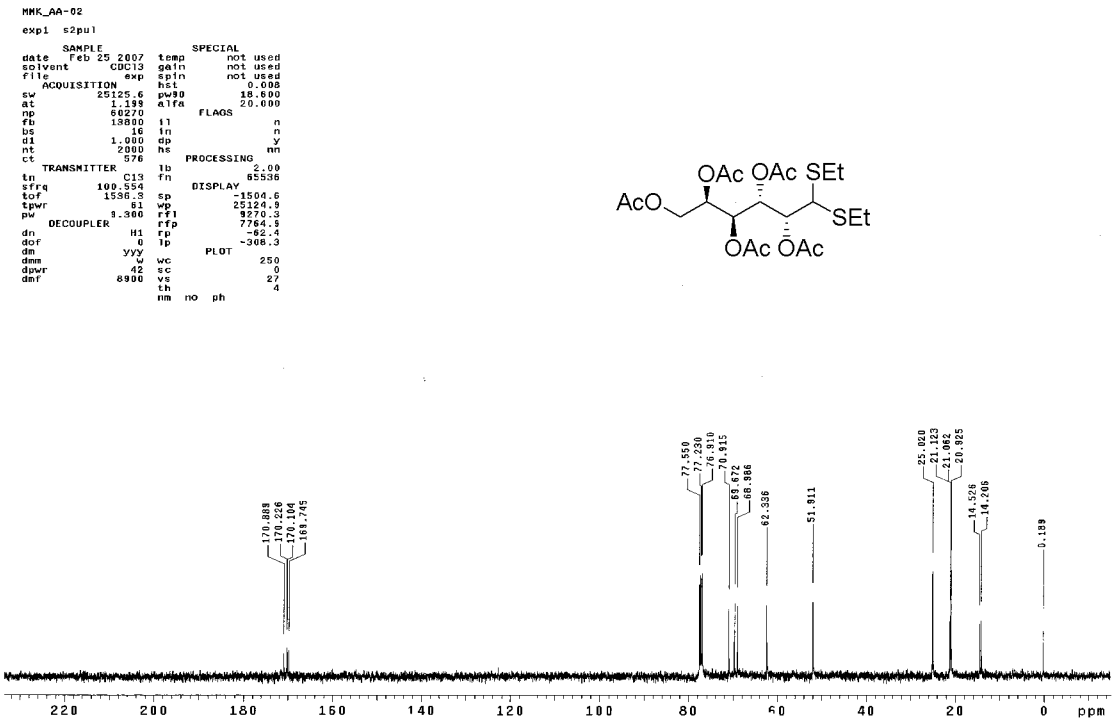
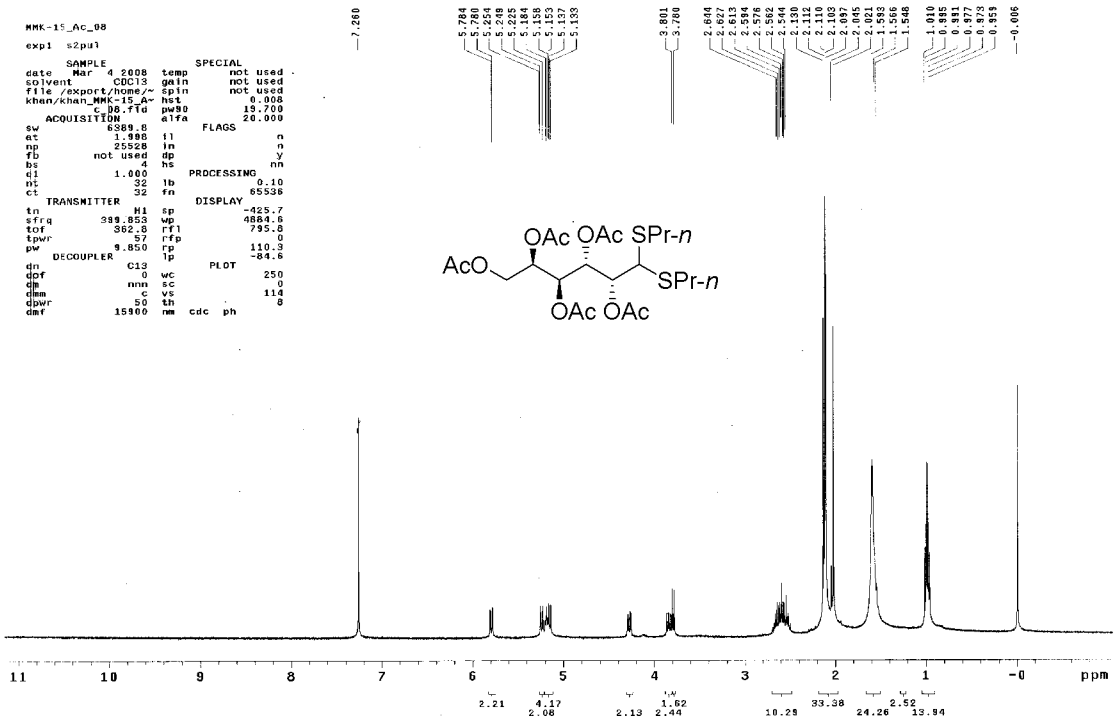


Figure 9

^{1}H NMR (400 MHz, CDCl$_3$): *2,3,4,5,6-Penta-O-acetyl-D-galactose dipropyl dithioacetal* ***(3h)***



^{13}C NMR (100 MHz, CDCl$_3$): *2,3,4,5,6-Penta-O-acetyl-D-galactose dipropyl dithioacetal* ***(3h)***

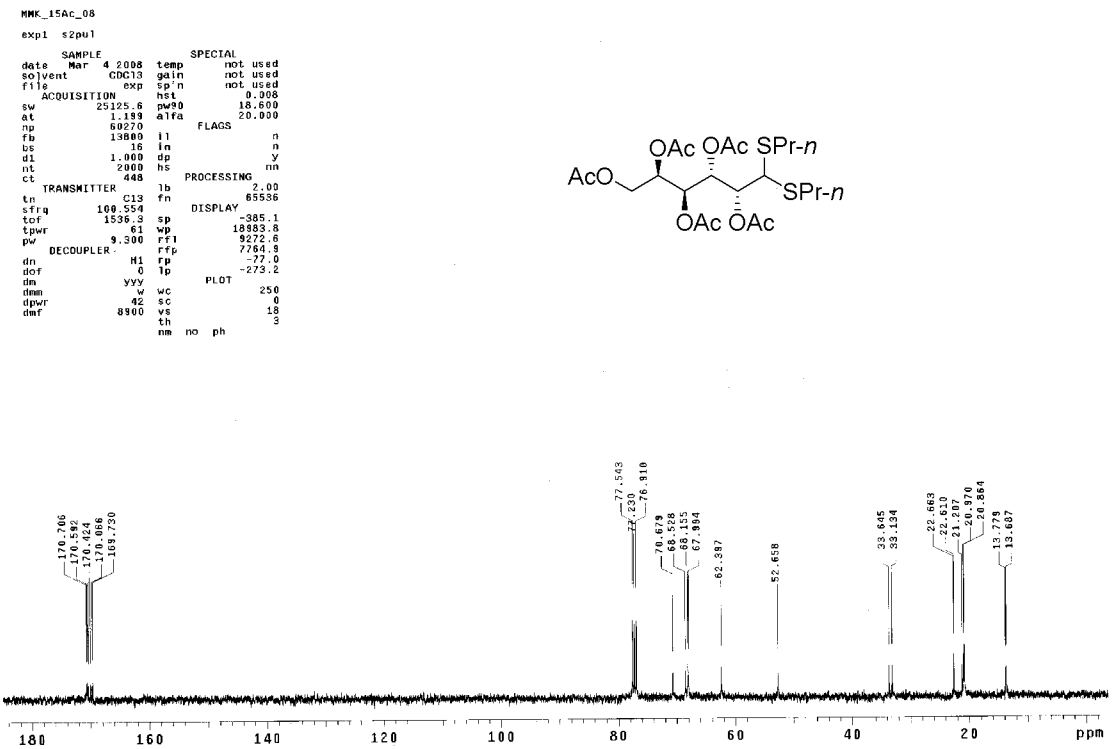
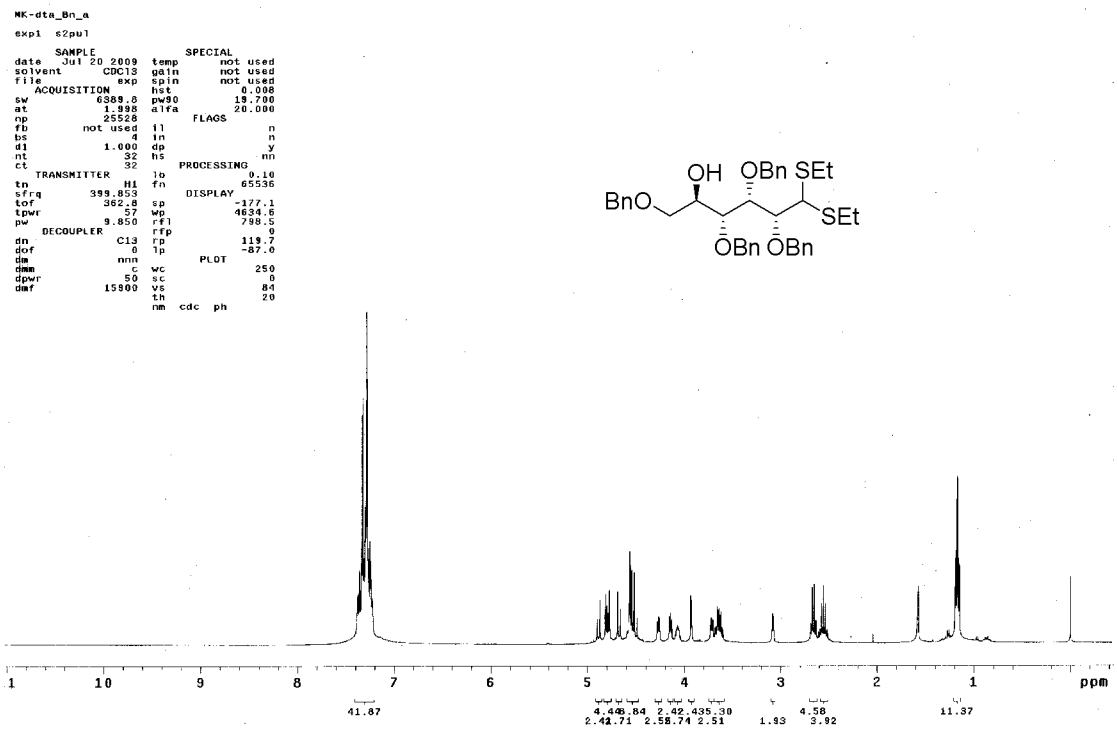


Figure 10

^{1}H NMR (400 MHz, CDCl$_3$): *2,3,4,6-Tetra-O-benzyl-D-glucose diethyl dithioacetal* ***(3j)***



^{13}C NMR (100 MHz, CDCl$_3$): *2,3,4,6-Tetra-O-benzyl-D-glucose diethyl dithioacetal* ***(3j)***

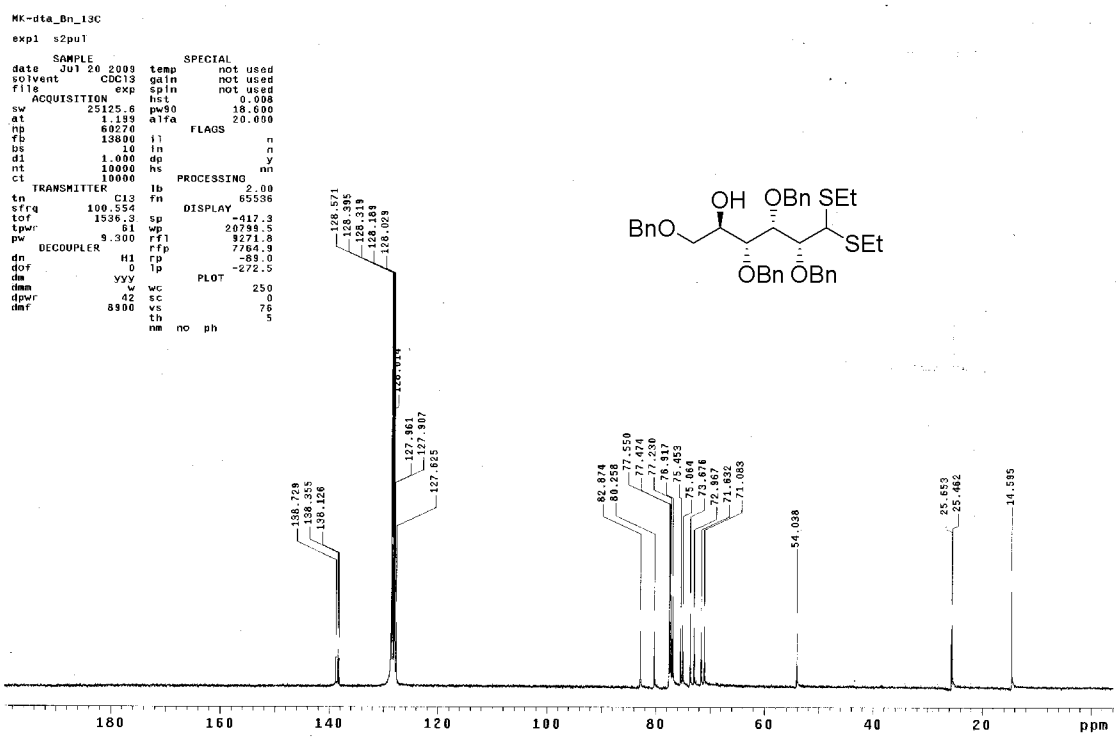
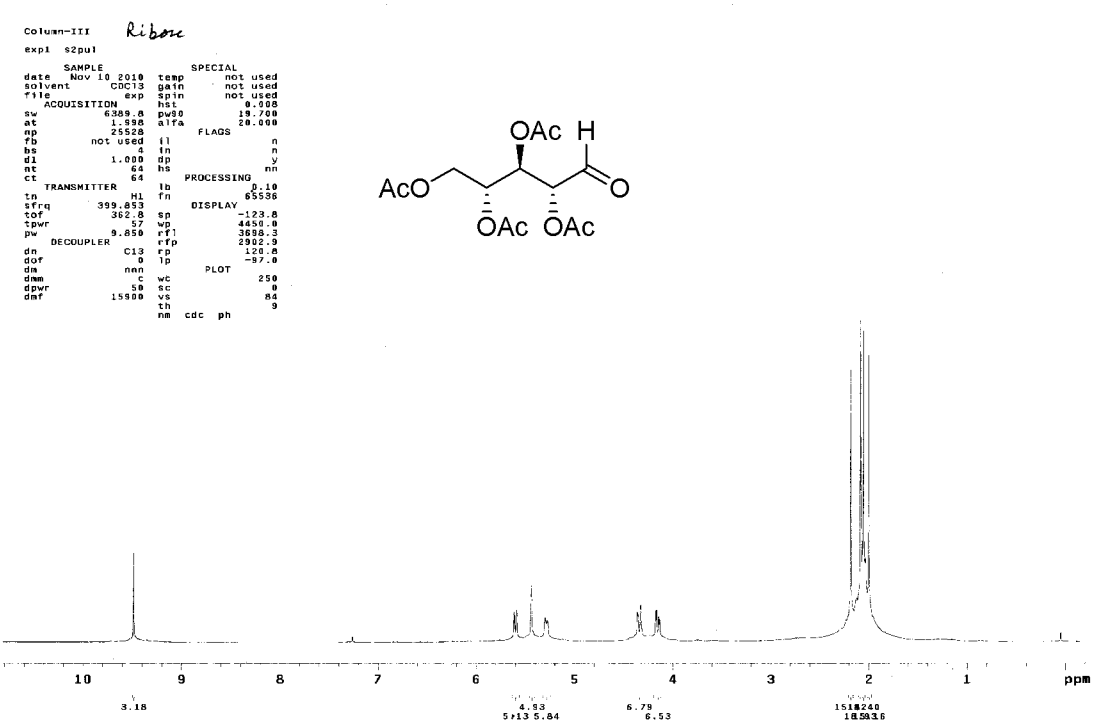


Figure 11

^{1}H NMR (400 MHz, CDCl$_3$): *2,3,4,5-Tetra-O-acetyl-aldehydo-D-ribose* ***(4a)***



^{13}C NMR (100 MHz, CDCl$_3$): *2,3,4,5-Tetra-O-acetyl-aldehydo-D-ribose* ***(4a)***

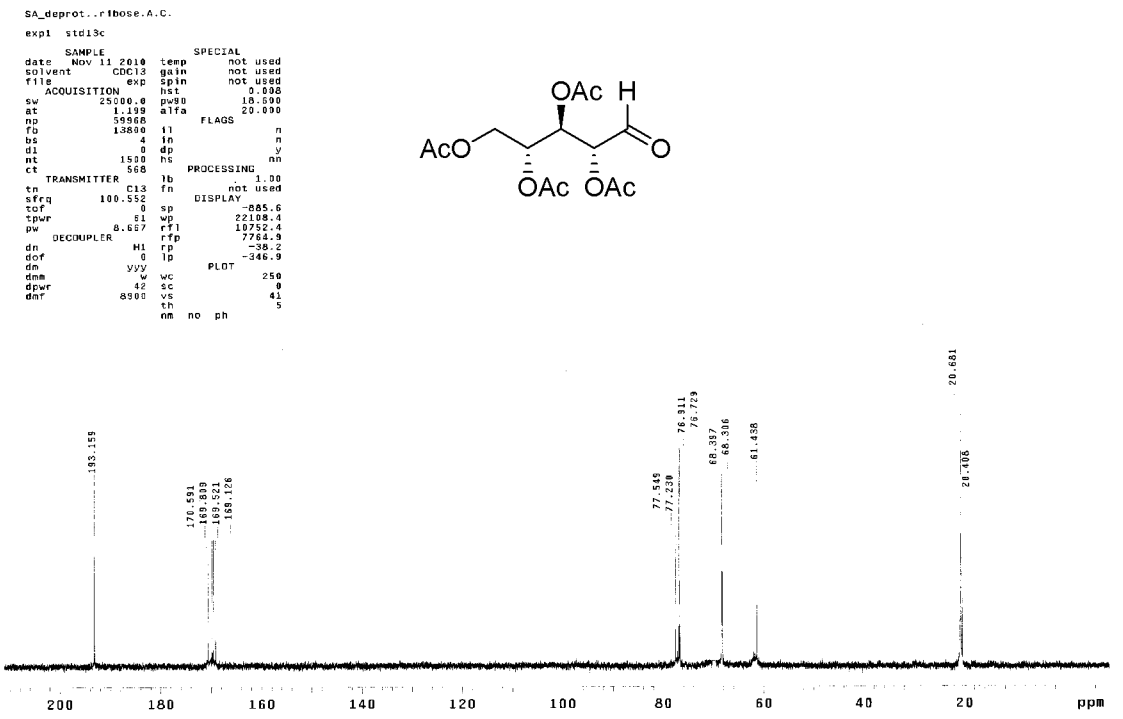
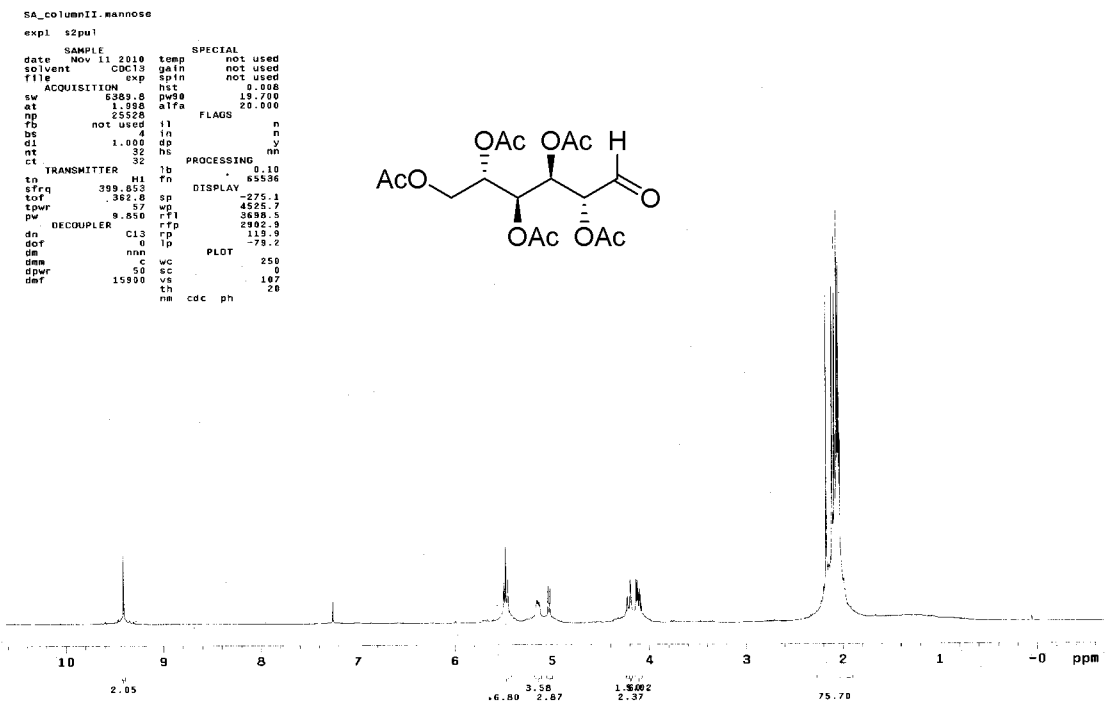


Figure 12

^{1}H NMR (400 MHz, CDCl$_3$): *2,3,4,5,6-Penta-O-acetyl-aldehydo-D-mannose* ***(4e)***



^{13}C NMR (100 MHz, CDCl$_3$): *2,3,4,5,6-Penta-O-acetyl-aldehydo-D-mannose* ***(4e)***

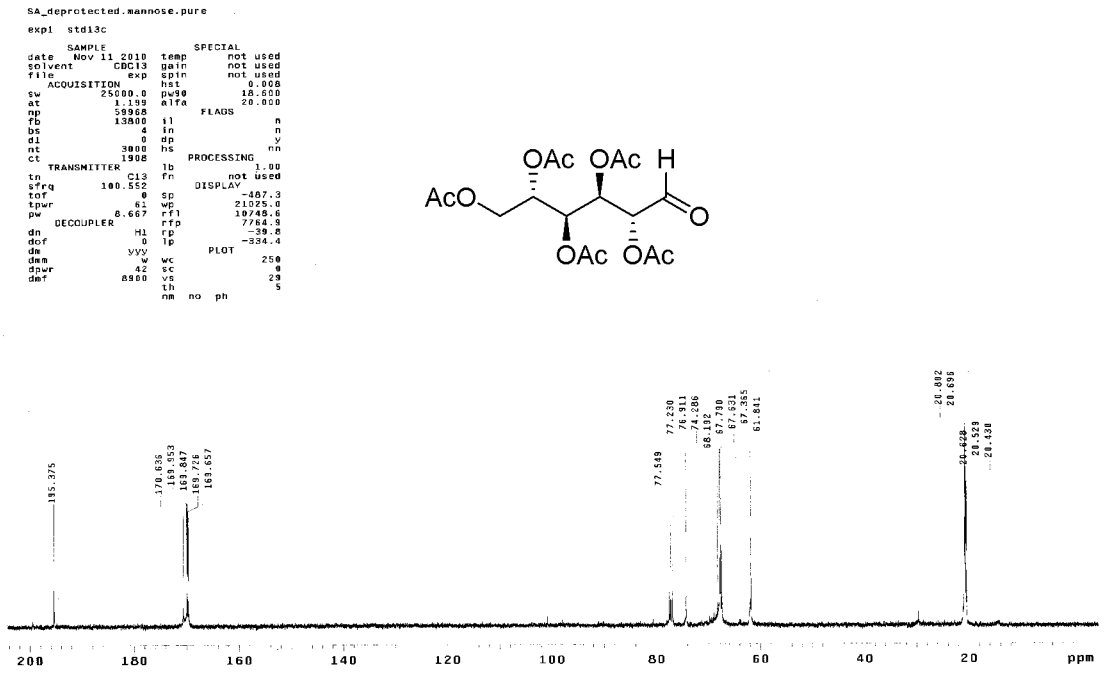


Figure 13

1. Gribble, G. W. *Progress in the Chemistry of Organic Natural Products. Naturally Occurring Organohalogen compounds – a comprehensive update*, Springer: New York, 2010.

2. Gribble, G. W. *Progress in the Chemistry of Organic Natural Products. Naturally Occurring Organohalogen compounds – a comprehensive update*, Springer: New York, 2010, p 218 and pp-226-227.

3. Borelli, F.; Campagnuolo, C.; Capasso, R.; Fattorusso, E.; Taglialatela-Scafati, O. *Eur. J. Org. Chem.* **2004**, 3227.

4. Kürti, L.; Czakó, B. *Strategic Applications of Named Reactions in Organic Synthesis,* Elsevier:Amsterdam, 2005, pp 498-499.

5. Kürti, L.; Czakó, B. *Strategic Applications of Named Reactions in Organic Synthesis,* Elsevier:Amsterdam, Netherland, 2005, p 424-425 and 448.

6. Li, J. J.; Gribble, G. W. *Palladium in Heterocyclic Chemistry*, 2nd Ed. Elsevier: Oxford, UK, 2007.

7. Kürti, L.; Czakó, B. *Strategic Applications of Named Reactions in Organic Synthesis,* Elsevier:Amsterdam, 2005, p 36 and 38.

8. Kolodiazhnyi, O. I. *Phosphorus Ylides*, Wiley-VCH: Weinheim, 1999.

9. Butler, A.; Walker, J. V. *Chem. Rev.* **1993**, *93*, 1937.

10. Butler, A.; Carter-Franklin, J. N. *Nat. Prod. Rep*. **2004**, *21*, 180.

11. Carter-Franklin, J. N.; Butler, A. *J. Am. Chem. Soc.* **2004**, *126*, 15060.

12. Weyland, M.; Hecht, H.; Kiesz, M.; Liaud, M. F.; Vitler, H.; Schomburg, D. *J. Mol. Biol.* **1999**, *293*, 595.

13. Conte, V.; Di Furia, F.; Moro, S. *Tetrahedron Lett.* **1994**, *35*, 7429.

14. Conte, V.; Di Furia, F.; Moro, S.; Rabbolini, S. *J. Mol. Cat. A: Chemical* **1996**, *113,* 175.

15. Andersson, M.; Conte, V.; Di Furia, F.; Moro, S. *Tetrahedron Lett.* **1995**, *36*, 2675.

16. Clague, M. J.; Butler, A. *J. Am. Chem. Soc.* **1995**, *117*, 3475

17. Gopinath, R.; Patel, B. K. *Org. Lett.* **2000**, *2*, 577.

18. Li, C.; Zheng, P.; Li, J.; Zhang, H.; Cui, Y.; Shao, Q.; Ji, X.; Zhang, J.; Zhao, P.; Xu, Y. *Angew. Chem. Int. Ed.* **2003**, *42,* 5063.

19. Chaudhuri, M. K.; Khan, A. T.; Patel, B. K.; Dey, D.; Kharmawophlang, W.; Lakshmiprabha, T. R.; Mandal, G. C. *Tetrahedron Lett.* **1998**, *39*, 8163.

20. Bora, U.; Bose, G.; Chaudhuri, M. K.; Dhar, S. S.; Gopinath, R.; Khan, A. T.; Patel, B. K. *Org. Lett.* **2000**, *2*, 247.

21. Khan, A. T.; Goswami, P.; Choudhury, L. H. *Tetrahedron Lett.* **2006**, *47*, 2751.

22. Khan, A. T.; Goswami, P. *Tetrahedron Lett.* **2005**, *46*, 4937.

23. Mondal, E.; Bose, G.; Sahu, P. R.; Khan, A. T. *Chem. Lett.* **2001**, *11*, 1158.

24. Mondal, E.; Sahu, P. R.; Bose, G.; Khan, A. T. *J. Chem. Soc., Perkin Trans. I* **2002**, 1026.

25. Bujar Barua, P. M.; Sahu, P. R.; Mondal, E.; Bose, G.; Khan, A. T. *Synlett* **2002**, 81.

26. Diederich, F.; Stang, P. J. *Metal-Catalyzed Cross-Coupling Reactions*; Wiley-VCH: Weinheim, **1998**.

27. Hassan, J.; Sevignon, M.; Gozzi, C.; Schulz, E.; Lemaire, M. *Chem. Rev.* **2002**, *102*, 1359.

28. Bellina, F.; Carpita, A.; Rossi, R. *Synthesis* **2004**, 2419.

29. Whang, J. P.; Yang, S. G.; Kim, Y. H.; *Chem. Commun*. **1997**, 1355.

30. Jereb, M.; Zupan, M.; Stavber, S.; *Chem. Commun*. **2004**, 2614.

31. Iskra, J.; Stavber, S.; Zupan, M. *Tetrahedron Lett.* **2007**, *49*, 893

32. Badri, R.; Gorjizadeh, M.; *Chin. Chem. Lett.* **2009**, *20*, 1439.

33. Das, B.; Krishnaiah, M.; Venkateswarlu, K.; Reddy, V. S. *Tetrahedron Lett.* **2007**, *48*, 81.

34. Moorthy, J. N.; Senapati, K., Kumar, S.; *J. Org. Chem.* **2009**, *74*, 6287.

35. Bhilare, S. V.; Deorukhkar, A. R.; Darvatkar, N. B.; Salunkhe, M. M. *Synth. Commun.* **2008**, *38*, 2881.

36. Pavlinac, J.; Zupan, M.; Stavber, S. *Org. Biomol. Chem.* **2007**, *5*, 699.

37. Monnereau, C.; Blart, E.; Odobel, F. *Tetrahedron Lett*. **2005**, *46*, 5421.

38. Barluenga, J.; Marco-Arias, M.; Gonzalez-Bobes, F.; Ballesteros, A.; Gonzalez, J. M. *Chem. Eur. J.* **2004**, *10*, 1677.

39. Stavber, S.; Jereb, M.; Zupan, M. *Synthesis* **2008**, 1487.

40. Virgil, S. C. In *Encyclopedia of Reagents for Organic Synthesis*, Vol. 4; Paquetttte, L. A., Ed.; Wiley: Chichester, **1995**, 2845.

41. Hanson, J. R. *J. Chem. Res.* **2006**, 277; and references therein.

42. Šket, B.; Zupet, P.; Zupan, M. *J. Chem. Soc., Perkin Trans. I* 1989, 2279.

43. Kosynkin, D. V.; Tour, J. M. *Org. Lett.* **2001**, *3*, 991.

44. Hajipour, A. R.; Arbabian, M.; Ruoho, A. E. *J. Org. Chem.* **2002**, *67*, 8622.

45. Mbatia, H. W.; Ulloa, O. A.; Kennedy, D. P.; Incarvito, C. D.; Burdette, S. C. *Org. Biomol. Chem.* **2011**, *9*, 2987.

46. Johnsson, R.; Meijer, A; Ellervik, U. *Tetrahedron* **2005**, *61*, 11657.

47. Firouzabadi, H.; Iranpoor, N.; Kazemi, S. *Can. J. Chem.* **2009**, *87*, 1675.

48. Firouzabadi, H.; Iranpoor, N.; Kazemi, S.; Ghaderi, A.; Garzen, A. *Adv. Synth. Catal.* **2009**, *351*, 1925.

49. Stavber, G.; Iskra, J.; Zupan, M.; stavber, S. *Adv. Synth. Catal.* **2008**, *350*, 2921.

50. Narender, N.; Reddy, K. S. K.; Mohan, K. V. V. K.; Kulkarni, S. J. *Tetrahedron Lett.* **2007**, *48*, 6124.

51. Iskra, J.; Stavber, S.; Zupan, M. *Synthesis* **2004**, *11*, 1869.

52. Rodriguez-Franco, M. I.; Dorronsoro, I.; Hernadez-Higueras, A. I.; Antequera, G. *Tetrahedron Lett.* **2001**, *42*, 863.

53. Cheng, D.-P.; Chen, Z.-C.; Zheng, Q.-G. *Synth. Commun.* **2003**, *33*, 2671.

54. Stefani, H. A.; Pereira, C. M. P.; Almeida, R. B.; Braga, R. C.; Guzen, K. P.; Cella, R. *Tetrahedron Lett.* **2005**, *46*, 6833.

55. Fatiadi, A. J. *Chem. Commun*. **1970**, 11.

56. Yang, D.; Yan, Y.; Lui, B. *J. Org. Chem.* **2002**, *67,* 7429.

57. Lee, J. C.; Bae, Y. H. *Synlett* **2003**, 507.

58. Meshram, H. M.; Reddy, P. N.; Vishnu, P.; Sadashiv, K.; Yadav, J. S. *Tetrahedron Lett*. **2006**, *47,* 991.

59. Sreedhar, B.; Reddy, P. S.; Madhavi, M. *Synth. Commun.* **2007**, *37*, 4149.

60. Dolenc, D. *Synth. Commun.* **2003**, *33*, 2917.

61. Urasaki, I.; Ogata, Y. *J. Chem. Soc. Perkin 1* **1975,** 1285.

62. Lee, Y. R.; Cho, B. S.; Kwon, H. J. *Tetrahedron* **2003**, *59*, 9333.

63. Lee, J. C. ; Park, J. Y. ; Yoon, S. Y. ; Bae, Y. H. ; Lee, S. J. *Tetrahedron Lett.* **2004**, *45,* 191.

64. Jereb, M.; Zupan, M.; Stavber, S.; *Chem. Commun*. **2004,** *22,* 2614.

65. Meshram, H. M.; Reddy, P. N.; Sadashiv, K.; Yadav, J. S. *Tetrahedron Lett.* **2005**, *46,* 623.

66. Khan, A. T.; Sharma, P.; Schmidt, R. R. *J. Carbohydr. Chem*. **1995**, *14*, 1353.

67. Khan, A. T.; Ahmed, W.; Schmidt, R. R. *Carbohydr. Res*. **1996**, *280*, 277.

68. Chang, Y. K.; Lee, B. Y.; Kim, D. J.; Lee, G. S.; Jeon, H. B.; Kim, K. S. *J. Org. Chem.* **2005**, *70*, 3299.

69. Pattenden, G.; González, M. A.; Little, P. B.; Millan, D. S.; Plowright, A. T.; Tornos, J. A.; Ye, T. *Org. Biomol. Chem.* **2003**, *1*, 4173.

70. Sun, J.; Han, X.; Yu, B. *Org. Lett.* **2005**, *7*, 1935.

71. Roberts, J. C.; Nagasawa, H. T.; Zera, R. T.; Fricke, R. F.; Goon, D. J. W. *J. Med. Chem.* **1987**, *30*, 1891.

72. Wolfrom, M. L. *J. Am. Chem. Soc.* **1929**, *51*, 2188.

73. Wolfrom, M. L.; Newlin, M. R.; Stahly, E. E. *J. Am. Chem. Soc.* **1931**, *53*, 4379.

74. Tang, C. J.; Wu, Y. *Tetrahedron* **2007**, *63*, 4887.

75. Sambaiah, T.; Fanwick, P. E.; Cushman, M. *J. Org. Chem.* **2001**, *66*, 4405.

76. Eitelman, S. J.; Horton, D. *Carbohydr. Res.* **2006,** *341*, 2658.

77. Ohlsson, J.; Magnusson, G. *Carbohydr. Res.* **2001**, *331*, 91.

78. Lichtenthaler, F. W.; Lorenz, K.; Ma, W. Y. *Tetrahedron Lett*. **1987**, *28*, 47.

79. Khan, A. T.; Mondal, E.; Sahu, P. R. *Synlett.* **2003**, *3*, 377.

80. Mondal, E.; Bose, G.; Khan, A. T. *Synlett.* **2001**, *6*, 785.

81. Mandal, P. K.; Mishra, A. K. *Synlett.* **2007**, 1207.

82. Mondal, E.; Bose, G.; Sahu, P. R.; Khan, A. T. *Chem. Lett.* **2001**, *11*, 1158.

83. Khan, A. T.; Barua, J.; Mondal, E.; Bose, G. *Indian J. Chem., Sect. B* **2001**, *40*, 1039.

84. Carley, S.; Brimble, M. A. *Org. Lett.* **2009**, *11*, 563.

85. Pereira, C.; Silva, A. R.; Carvalho, A. P.; Pires, J.; Freire, C. *J. Mol. Catal. A: Chemical* **2008**, *283*, 5214.

86. Poukutsa, A.; Kubaj, J.; Zaborovskyi, A.; Maksym, D. Muzart, J.; Sobkowiak, A. *App. Catal. A: General* **2010**, *390*, 190.

87. Liu, H.; Wang, M.; Wang, Y.; Sun, H.; Sun, L. *Catal. Commun.* **2009**, *11*, 294.

88. Wang, Y.; Wang, M.; Wang, Y.; Wang, X.;Wang, L.; Sun, L. *J. Catal.* **2010**, *273*, 177.

89. Blanc, A.; Toste, F. D. *Angew. Chem. Int. Ed.*, **2006**, *45*, 2096.

90. Rieder, C. J.; Winberg, K. J.; West, F. G. *J. Org. Chem.* **2011**,

91. Kantam, M. L.; Neelam, B.; Reddy, C. V.; Chaudhuri, M. K.; Dehury, S. K. *Catal. Lett*., **2006**, *95*, 19.

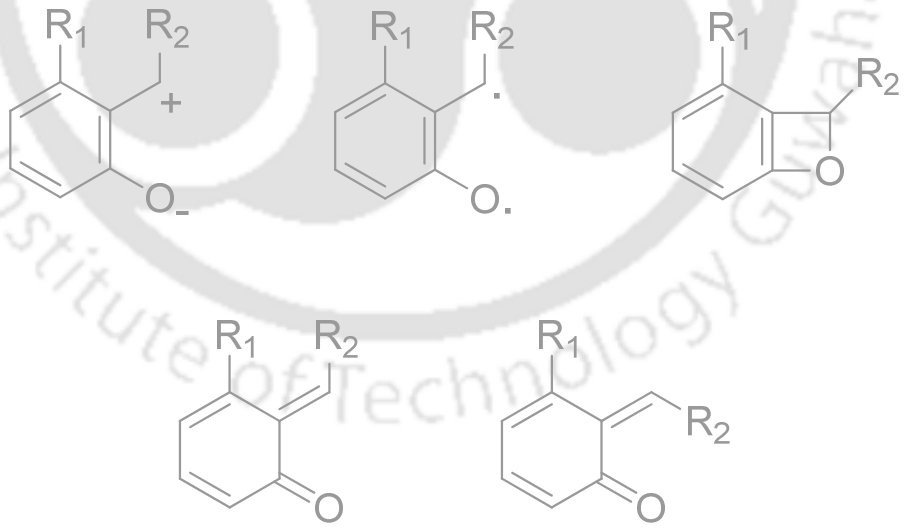
92. J. Hartung, and M. Greb, *J. Organomet.* Chem., **2002**, *661*, 67.

93. M. M. Faul, and B. E. Huff, *Chem. Rev.*, **2000**, *100*, 2407.

94. Khan, A. T.; Khan. M. M. *Carbohydr. Res.* **2010**, *345*, 2139.

PART B

Brief review on *o*-quinone methide intermediates and some of their synthetic application in organic synthesis.



CHAPTER 1

Introduction: *Ortho*-quinone methides (*o*-QMs) are one of the important synthetic intermediates that are widely implicated in many biological processes.[1] They are widely used in organic synthesis,[2-5] materials chemistry,[6] and in biological chemistry.[7] The parent *ortho*-quinone methide (**1**) is composed of a cyclohexadiene core unit in conjugation with a carbonyl group and an exocyclic methylene group, attached to each other which is shown in Figure 1. It is correlated with *ortho*-quinone (**2**), which has two carbonyl groups, and *ortho*-quinone dimethide (**3**), which has two methylene groups. *ortho*-Quinone methides are highly polarized and reactive species as compared to the structures **2** and **3**, which has two identical groups.[6,7]

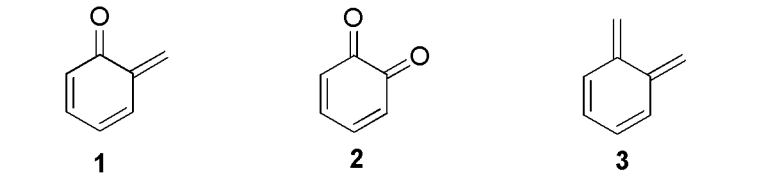


Figure 1: Structural differences between *o*-QM, *o*-quinone, and *o*-quinone dimethide

Gardner and his co-workers reported the reactive intermediate *o*-quinone methide spectroscopically at -100 °C in condensed phase because it is an extremely transient reactive species.[8] The substituted *o*-QMs might be represented in five possible structural forms which is shown in Figure 2. Among all these structures, structure **4** is aromatic as well as exhibits charge separation. As a matter of fact, the predominant reactivity mode of *ortho*-quinone methide intermediate is well understood, in which nucleophiles preferably attack at the exocyclic carbon atom while electrophiles at the oxygen terminal.

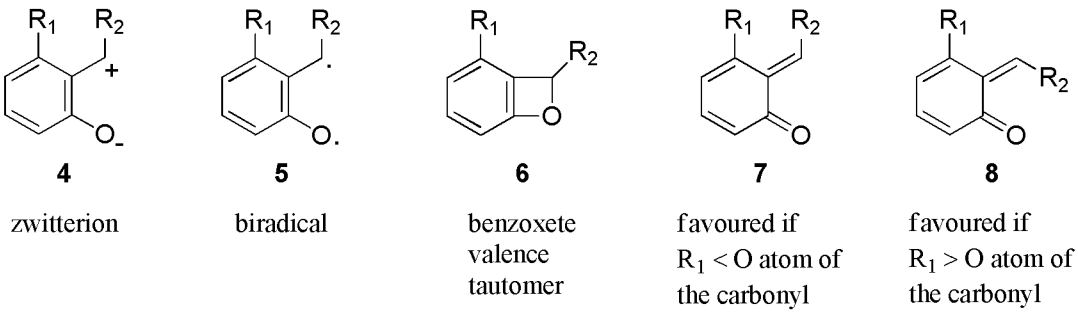
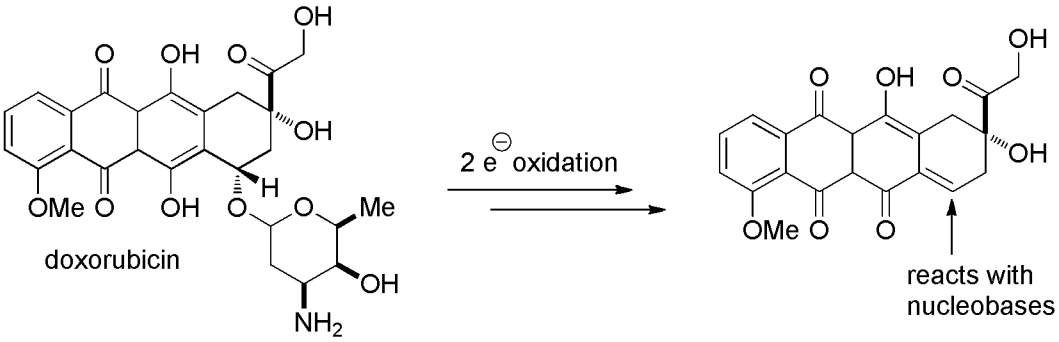


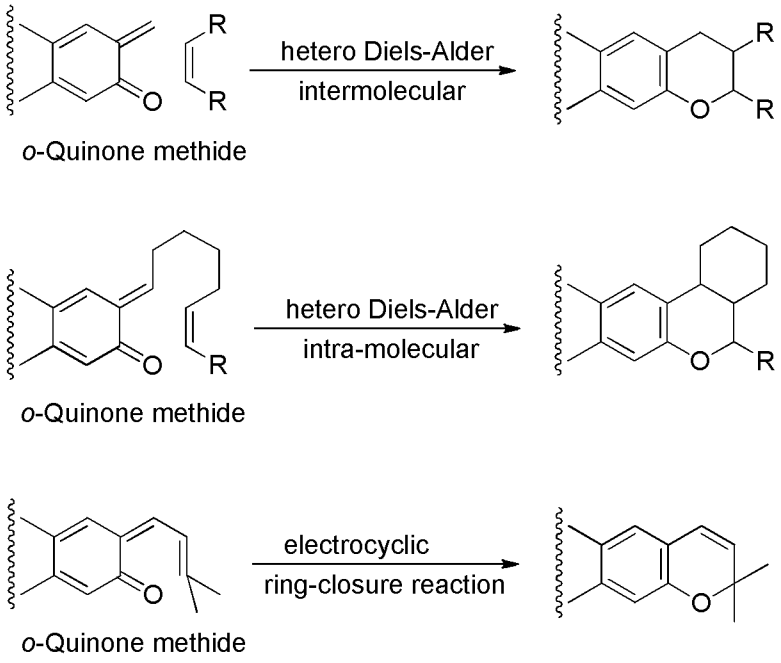
Figure 2: Some plausible structural representation of *o*-quinone methide

The therapeutic benefits of vitamins E and K as well as the anticancer property of natural products such as the anthracycline antibiotics result due to the formation of *o*-QM species *in vivo,* as shown Scheme 1.[9]



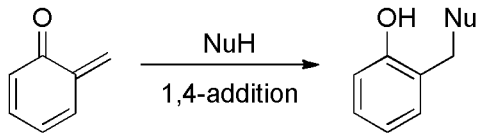
Scheme 1

These are highly versatile reactive intermediate and they serve as either Michael acceptors or hetero-dienes in cycloaddition reactions. The construction of chromenes and chromanes are easily accessible by employing [4+2] cycloaddition reactions with various dienophiles via inter- and intra-molecular hetero-Diels-Alder reaction or electrocyclic ring closure reactions, which is presented in Scheme 2.[10]



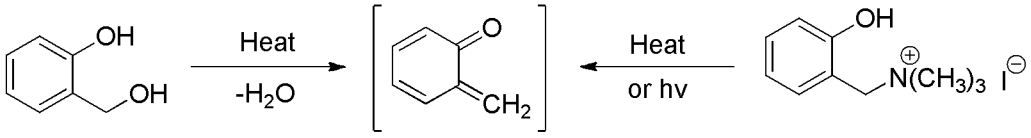
Scheme 2

Similarly, they can undergo 1,4-conjugate addition reactions with various nucleophiles[11,12] as shown in Scheme 3.



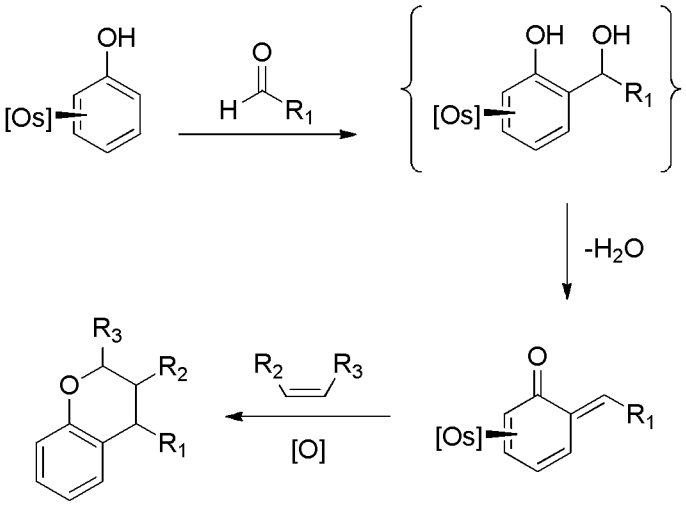
Scheme 3

The most common methods for their generation is either from *o*-hydroxy benzyl alcohols[13] by dehydration or from (2-hydroxybenzyl)trimethylammonium iodide[14] by pyrolysis/photolysis which is shown in Scheme 4.



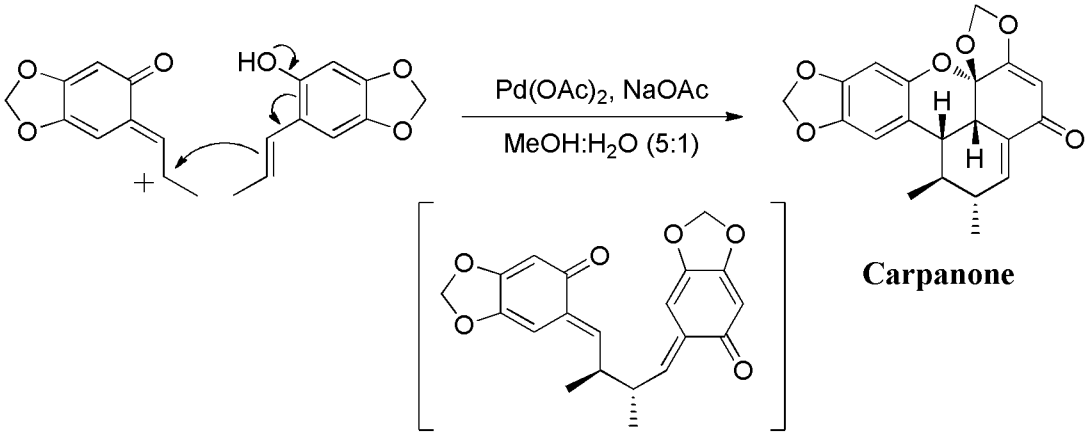
Scheme 4

Two independent research groups demonstrated that the reactive *o*-QMs can be stabilized by coordination with a transition metal.[5,15] They have proposed that metal stabilized hydroxy benzyl alcohol may undergo dehydration and the resulting ephemeral *o*-QMs may react with a dienophile to form the chroman ring system in presence of an oxidant, as given in Scheme 5.



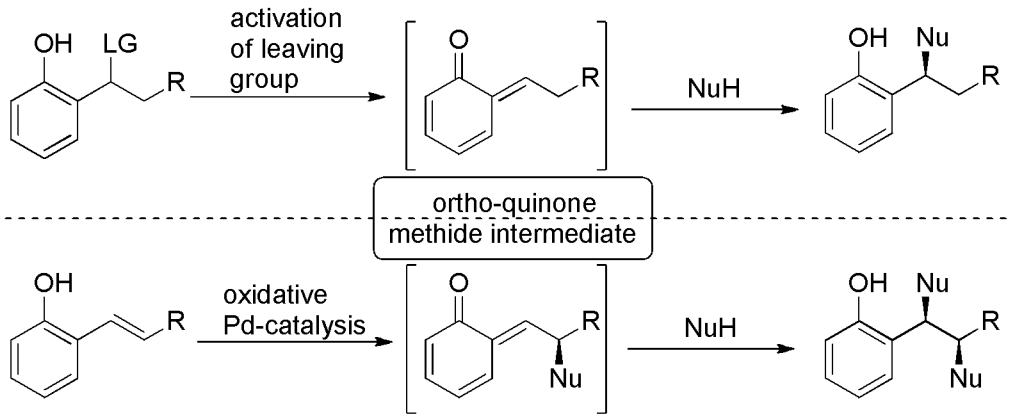
Scheme 5

In 1971, Chapman and co-workers shown[16] an elegant synthesis of the natural product carpanone starting from vinyl phenols using stoichiometric $Pd(OAc)_2$. The formation of the final product is going through *o*-quinone methide intermediate as shown in Scheme 6.



Scheme 6

Sigman *et al* presented[17] the synthetic utility of *o*-quinone methide intermediates for conjugative two nucleophilic addition reactions for asymmetric synthesis as shown in Scheme 7. They have proposed that the *o*-quinone methide intermediate is stabilized by palladium which is finally trapped with diverse range of nucleophiles for generation of new organic compounds.

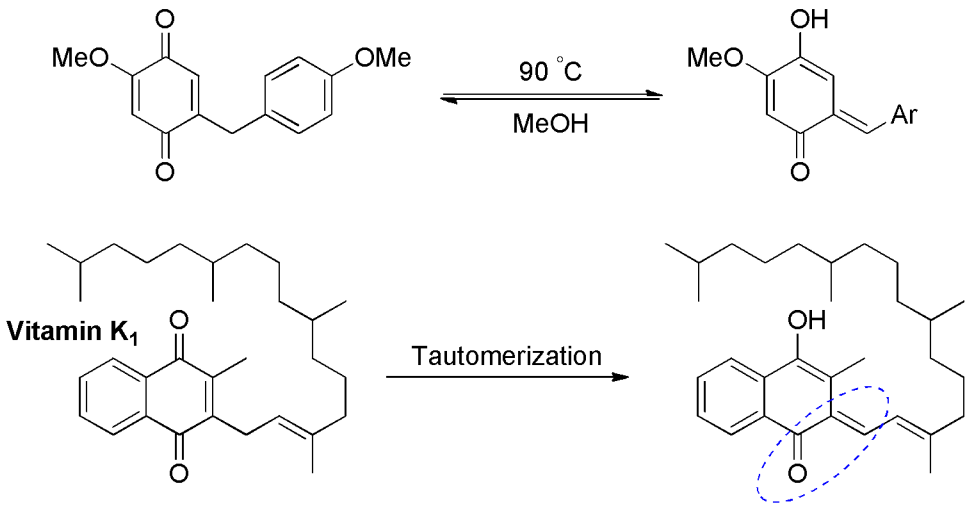


Scheme 7

Various methods for their generation: Various starting materials have been used for the generation of *o*-quinone methide intermediate in organic synthesis. Some of the representative examples are mentioned below:

I. Initiation by tautomerization

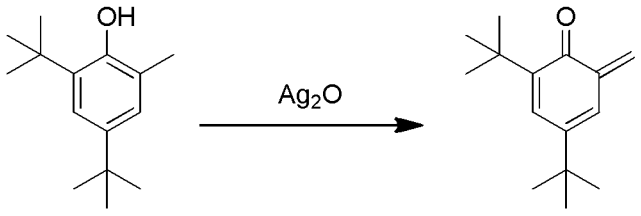
Jurd first reported[18] that an *o*-QM intermediate can be generated from α-substituted *p*-quinone having an allylic proton adjacent to the quinone ring by tautomerization, which has been used in organic synthesis as shown in Scheme 8. The classic biological example of this method of generation is vitamin K, which plays an important role in promoting blood coagulation via its redox cycle that involves the *o*-QM tautomer as shown in Scheme 8.[19]



Scheme 8

II. Oxidative Initiation

Waters first shown[20] the generation of *o*-QMs from 2,4-di-tert-butyl-6-methylphenol using chemical oxidants such as silver(I) oxide as shown in Scheme 9.

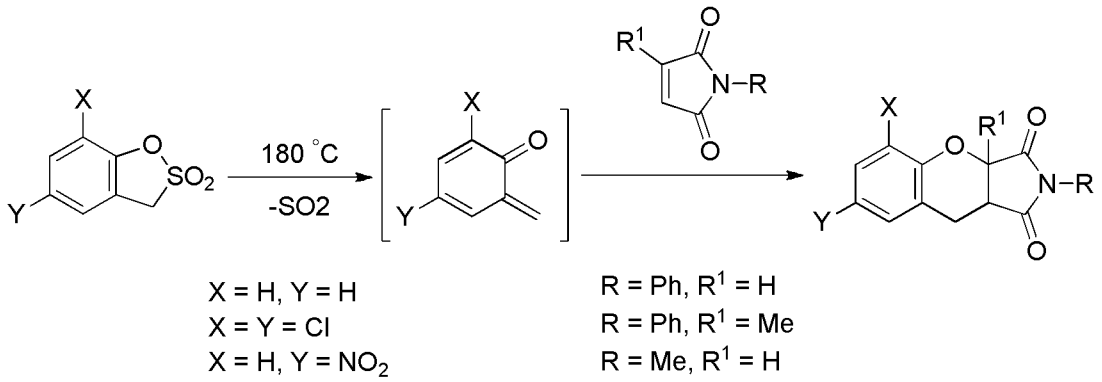


Scheme 9

III. Thermal initiation

Wojciechowski and his co-worker recently demonstrated[21] the generation of *o*-QMs from benzosultones by thermal extrusion of sulfur dioxide, which has been used for [4+2] cycloaddition reaction for the synthesis of new heterocyclic entities as shown in

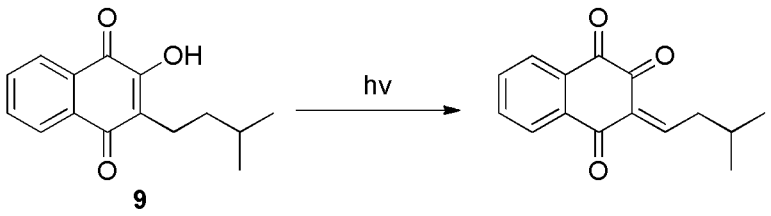
Scheme 10.



Scheme 10

IV. Photochemical initiation

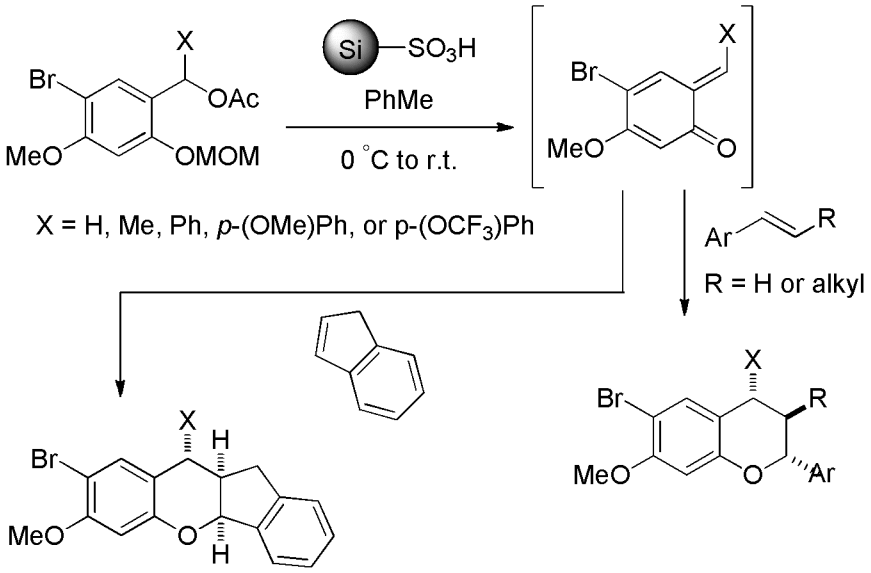
Photochemical excitation drastically reduces the temperature required for *o*-QM generation for many of the precursors. Ettlinger,[22] Creed,[23] and Leary[24] independently investigated the photochemistry of Tocoquinone **9** to gain insight into the role that this compound plays in photobiology. The above compound **9** on irradiation with UV light produces the *o*-QM intermediate species, which in turn undergo further reaction such as oxidation with oxygen, as shown in Scheme 11.



Scheme 11

V. Acid facilitation

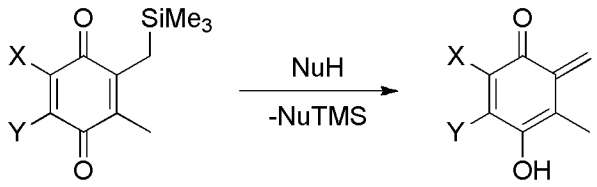
Ploypradith *et al* shown[25] the synthesis of 2-arylchroman by treating the MOM protected benzyl acetate derivative using *p*-TsOH immobilized in silica gel (PTS-Si) in toluene under mild conditions. They have proposed that the reaction is passing through *o*-QM intermediate in presence of acid, as shown in Scheme 12.



Scheme 12

VI. Base facilitation

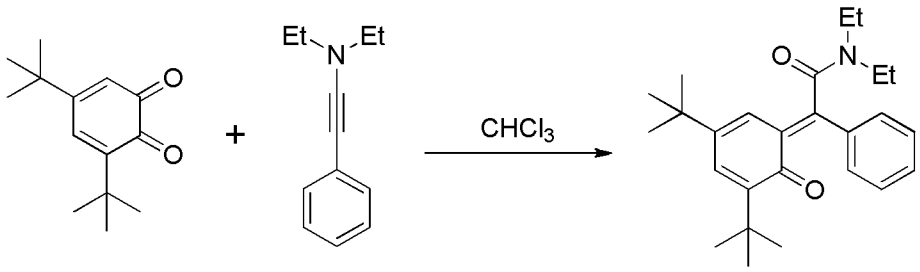
Moore *et al* has demonstrated[26] the generation of *o*-QM intermediate by cleavage of trimethyl silyl groups 2,3-disubstituted-5-methyl-6-((trimethylsilyl)methyl)cyclohexa-2,5-diene-1,4-dione through base initiation, as shown in Scheme 13.



Scheme 13

VII. Olefination of *o*-quinones

Bos and his co-worker have first isolated[27] the stable *o*-quinone methide, as shown in Scheme 14 by the condensation of *o*-quinone with an ynamine at room temperature.

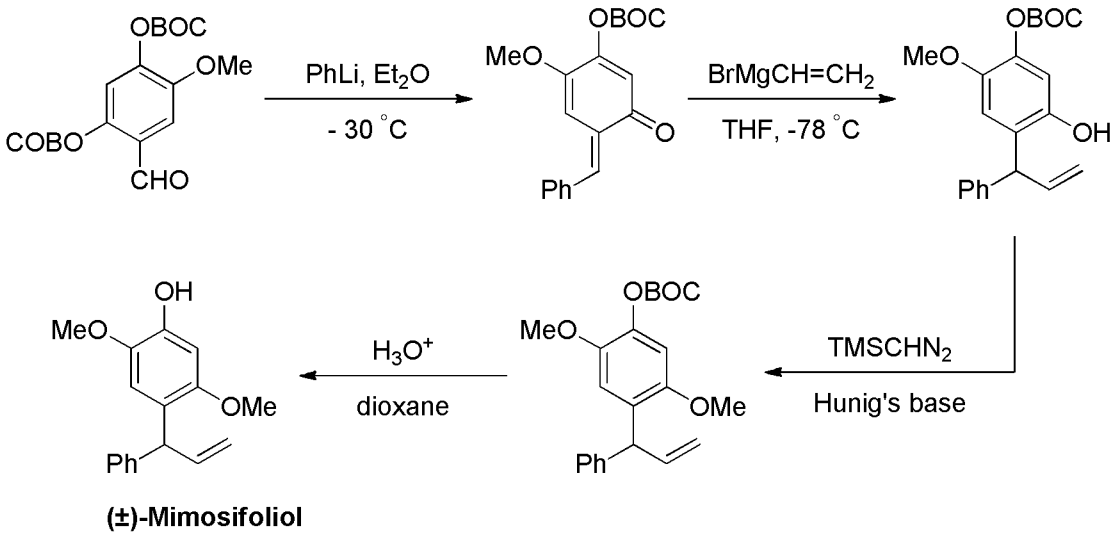


Scheme 14

The stability of *o*-QM intermediate is due to double conjugation and steric congestion, which in turn preventing dimerization. As a result, it can be isolated easily.

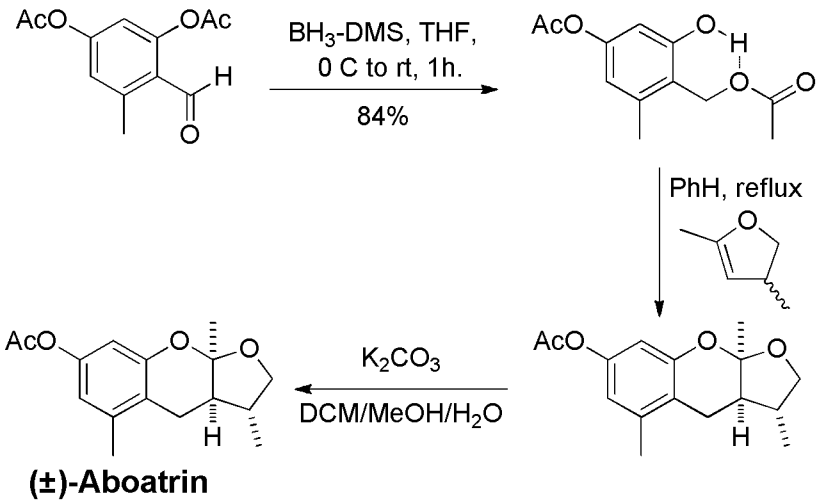
Synthetic application of *o*-QMs towards natural product synthesis:

Pettus *et al* elaborated[28] the total synthesis of (±)-Mimosifoliol involving *o*-quinone methide intermediate followed by nucleophilic addition of vinyl magnesium bromide, as shown in Scheme 15.



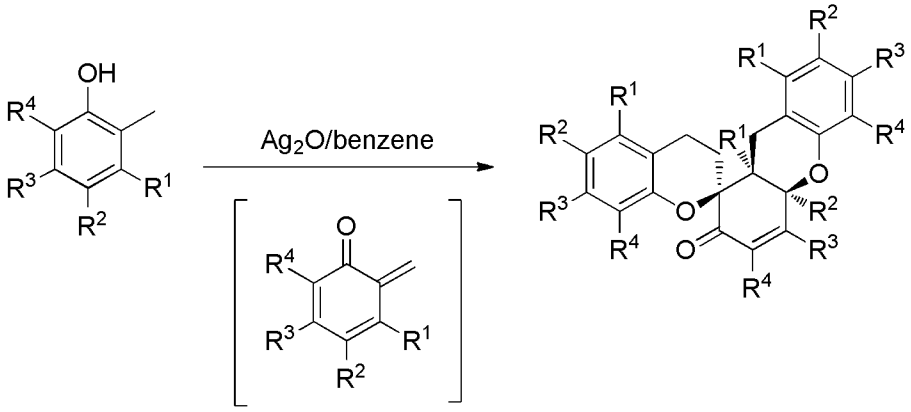
Scheme 15

Baldwin and his co-worker have shown[29] the biomimetic synthesis of (±)-Alboatrin from *o*-methyleneacetoxy-phenols by employing *in situ* generated *o*-QM intermediate followed by [4+2] cycloaddition reaction, as shown in Scheme 16.



Scheme 16

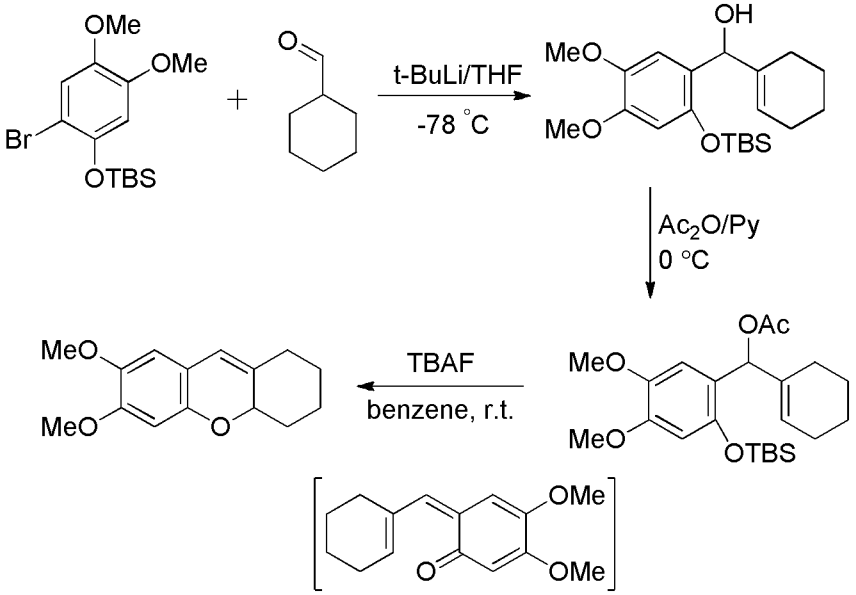
Lei *et al* shrewdly demonstrated[30] biomimetic syntheses of novel trimeric natural products, (±)-Schefflone and Tocopherol trimmers starting from highly substituted 6-methylphenol through oxidative initiation of *o*-QM as shown in Scheme 17.



Scheme 17

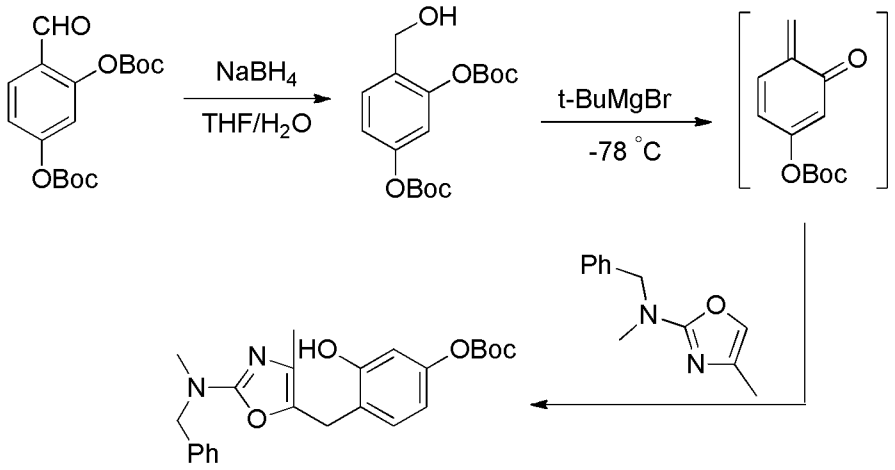
Non-natural product synthesis:

Barrero *et al* have demonstrated[31] a simpler rout for the synthesis of bioactive puupehedione derivatives by generating *o*-quinone methide intermediate via fluoride induced desilylation of silyl derivatives of *o*-hydroxy benzyliodide followed by electrocyclic ring closure reaction as shown in Scheme 18.



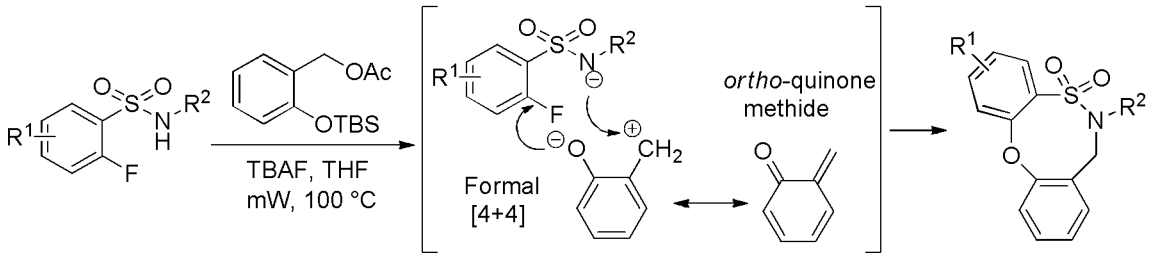
Scheme 18

Pettus *et al* have shown[32] unusual reactions between various electron rich oxazoles and *in situ* generated *o*-QM intermediates for accessing some interesting adduct, as depicted in Scheme 19.



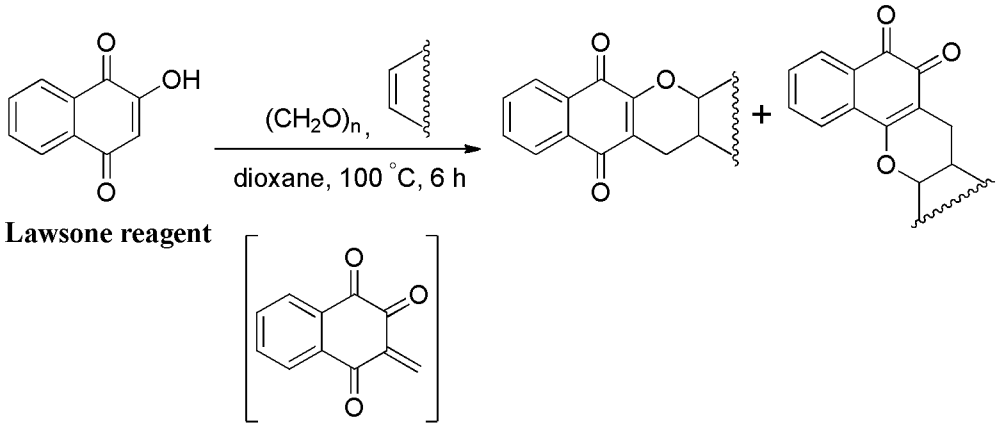
Scheme 19

We have discussed that the *o*-quinone methide intermediate **1** may exist as one of the possible structures as **4**, which is given in Figure **2**. Hanson and his co-workers have shown[33] [4+4] complementary ambiphile pairing reaction, a new pathway, for the synthesis of eight membered sultams from *in situ* generated *o*-QM intermediate and *o*-fluorobenzenesulfonamides. From this reaction, it is a direct evidence that *o*-quinone methide intermediate might possibly exist as structure **4**, as shown in Scheme 20.



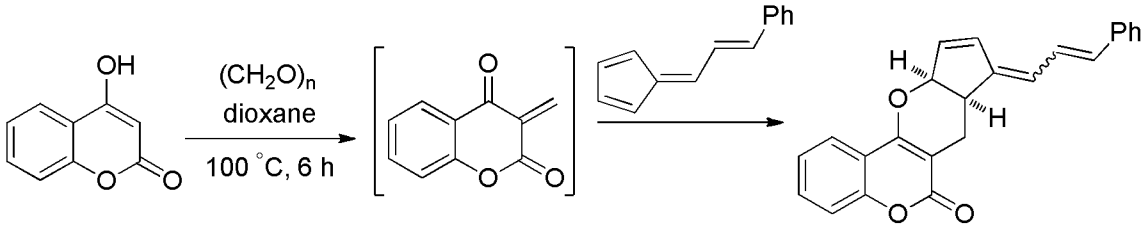
Scheme 20

Nair and Treesa described[34] a new, general three component reaction for the synthesis of a wide variety of derivatives α- and β –lapachone and other heterocyclic compounds. The reaction involve the Knoevenagel condensation between lawsone reagent and paraformaldehyde leading to the *o*-QM intermediate which reacts *in situ* with several olefins to generate products in moderate to good yields, as shown in Scheme 21.



Scheme 21

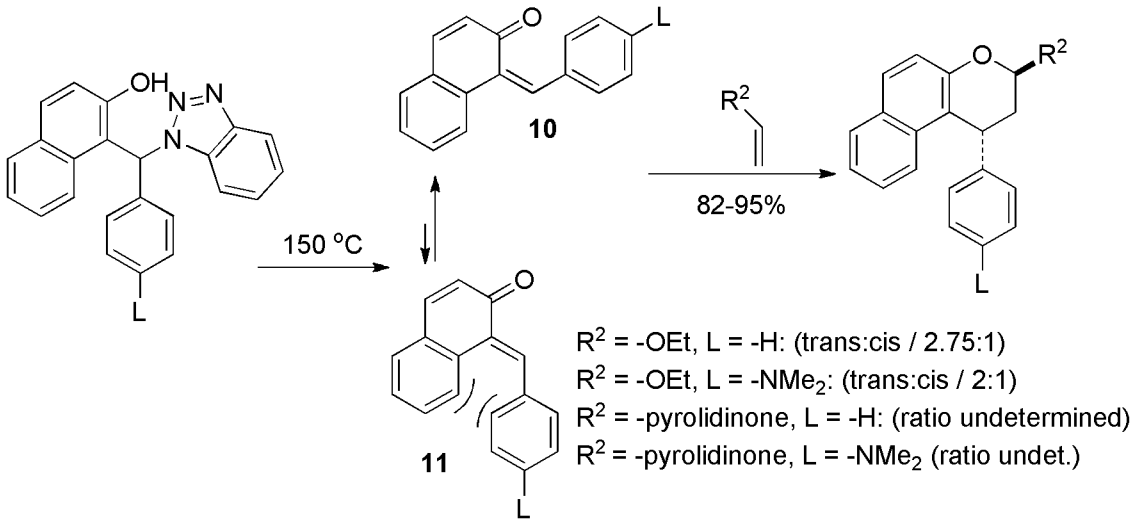
The same group further extended[35] these three component methodology for the preparation of pyranopyrone derivatives as shown in Scheme 22.



Scheme 22

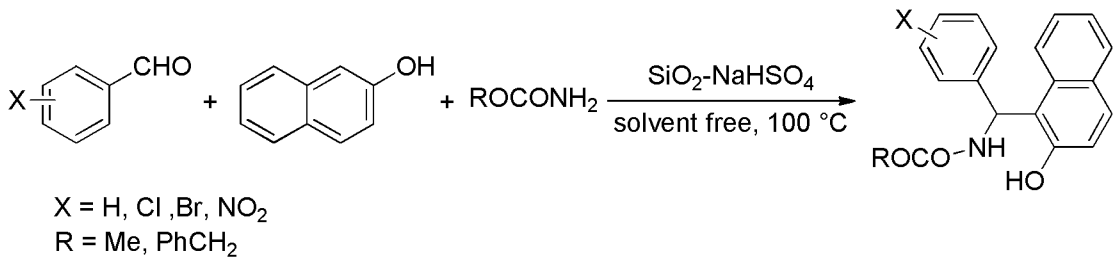
From the remarkable contributions of Pettus *et al* and by others as well as from literature reveal *o*-quinone methide intermediates are valuable synthons, which may be generated from various starting materials in various ways, for the synthesis of natural and non-natural products. Therefore, we perceived that 2-naphthol and aromatic aldehyde can generate *in situ o*-naphthoquinone methide intermediate analogue to *o*-QM which can be trapped with various nucleophiles such as nitrogen, sulfur and carbon nucleophiles in organic synthesis. We became interested whether *ortho*-naphthoquinone methide intermediate is known or not in the literature. It was noticed that Katritzky and his co-worker demonstrated[36] the preparation of *o*-naphthoquinone methide intermediate from *o*-(α-(benzotriazol-1-yl)alkyl)-2-naphthols. He has also verified the synthesis of 2,3-dihydro-1H-naphtho[2,1-b]pyrans through [4+2] cycloaddition reaction between *in situ* generated *ortho*-naphthoquinone methide intermediate and electron rich olefins namely ethyl vinyl ether and 1-vinyl-2-pyrrolidinone, as shown in Scheme 23. He also proposed that *in situ* generated *ortho*-

naphthoquinone methide intermediate may exist in two possible structures **10** and **11**, as shown in Scheme 23. Out of which, the structure **10** is more preferable because of the steric repulsion between phenyl ring and B ring of naphthalene. The only demerit of this method is the cumbersome preparation of the starting material *o*-(α-(benzotriazol-1-yl)alkyl)-2-naphthols for the generation of *ortho*-naphthoquinone methide intermediate.



Scheme 23

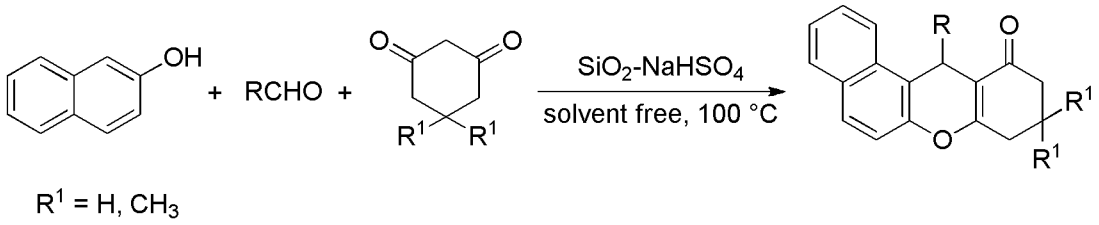
Shaterian *et al* demonstrated the synthesis of N-protected 1-aminoalkyl-2-naphthol derivatives by generating *o*-naphthoquinone methide starting from 2-naphthol and aldehyde using various catalyst such as silica supported $NaHSO_4$,[37] silica supported $HClO_4$,[38] silica supported poly phosphoric acid[39] under different reaction conditions which are shown in Scheme 24.



Scheme 24

Recently, Hajra *et al* have shown the synthesis of the same compound involving three component reactions using ionic liquid as catalyst.[40]

Das *et al* reported[41] the synthesis of unsymmetrical 12-aryl-xanthen-11-one derivatives starting from 2-naphthol, aromatic aldehydes and dimedone using silica supported $NaHSO_4$ under reflux conditions. They have proposed that the formation of the product is going through *o*-naphthoquinone methide intermediate, which is shown in Scheme 25.



Scheme 25

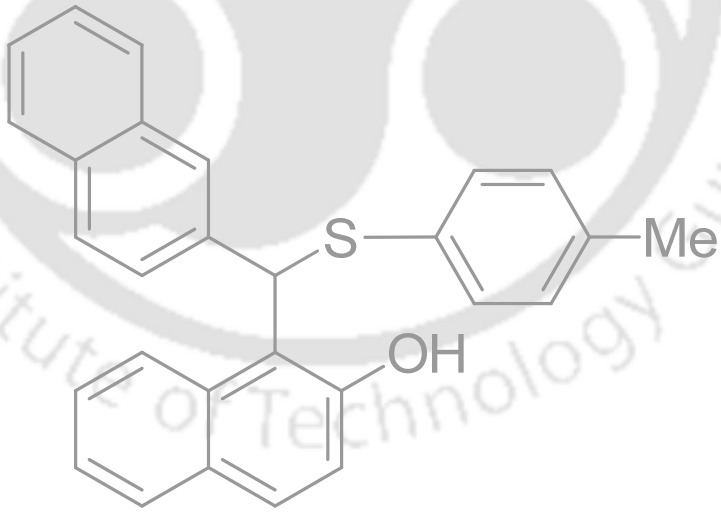
Over the years, numerous catalysts have been developed by others such as strontium triflate,[42] $InCl_3$,[43] *p*-TSA/[bmim]BF_4,[44] TBAF,[45] I_2,[46] proline triflate,[47] CAN,[48] BNBTS,[49] *p*-TSA with ultrasound[50] and caro's acid in silica gel,[51] NH_4Cl,[52] Cu/SiO_2,[53] I_2/MW,[54] p-TSA/[bmim]BF_4.[55]

Though all these methods are quite useful, still there is a further scope to develop a methodology which might work under mild reaction condition.

In Part B of this dissertation, we would like to address the successful results for the trapping of *o*-naphthoquinone methide intermediate with thiols, carbamates and cyclic 1,3-diketones for the synthesis of 1-[(alkylthio)(phenyl)methyl]naphthalene-2-ol derivatives, 1-carbamato-alkyl-2-naphthols and unsymmetrical 12-aryl-xanthen-11-one derivatives.

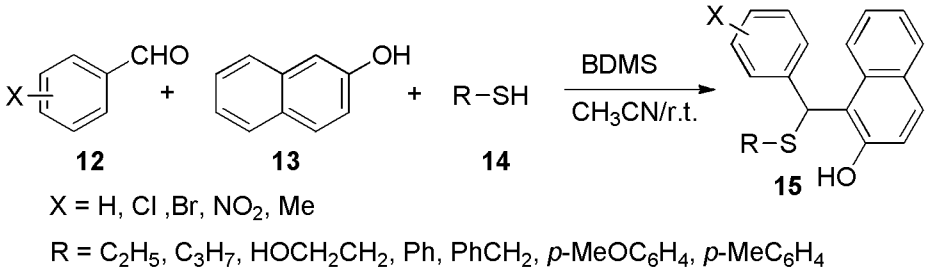
PART B

Synthesis of 1-[(alkylthio)(phenyl) methyl]-naphthalene-2-ol by trapping *o*-naphthoquinone methide with thiols



In the Chapter 1 of the Part B, we have highlighted the importance of *o*-quinone methide intermediates for the synthesis of natural and non-natural products. In addition, we have shown how these intermediates are prepared and successively utilized either for cycloaddition reactions or nucleophilic addition reactions for the synthesis of new organic molecules. In the objective, we have aimed that the *in situ* generated *o*-naphthoquinone methide intermediate, which is analogue of *o*-quinone methide, will be exploited for nucleophilic addition reactions for accomplishing new organic entities. Previously, our group has shown that bromodimethylsulfonium bromide (BDMS) is a unique brominating reagent for organic bromination as well as pre-catalyst for various organic transformations.[56,57] In the continuation of our previous work, we wanted to examine the catalytic activity of BDMS for the development of new synthetic method in multi-component reactions. We have expected that 2-naphthol and aromatic aldehyde can easily generate *o*-naphthoquinone methide intermediate in presence of a suitable acid catalyst, which can act as Michael acceptor and it can react with various thiols leading to the formation of 1-[(alkylthio)(phenyl)methyl]naphthalene-2-ol derivatives. Over the years, numerous reagents have been developed for thia-Michael reaction such as Cinchona alkaloid-squareamide,[58] $[LNi_2(CH_3CN)(THF)](ClO_4)_3$,[59] $InCl_3$,[60] silica nanoparticles,[61] (IMesPr)AuCl,[62] [Ru(acetone)(R,R-BIPHOP-F)Cp][SbF_6],[63] cinchona alkaloid-derived urea,[64] NEt_3,[65] SDS/$NaHCO_3$,[66] Co/SBA-15,[67] $VO(OTf)_2$,[68] silica-alumina supported NEt_3.[69] A few years ago, we have also demonstrated acid catalyzed thia-Michael reaction[70] for the preparation of sulfur containing compounds and aza-Michael reaction[71] using BDMS as pre-catalyst. Therefore, we presumed that BDMS might be a suitable pre-catalyst for the formation of *in situ* generated *o*-naphthoquinone methide followed by Michael addition reaction. As per our requirement, we have prepared BDMS by following the literature procedure.[56] Then, we have investigated the reaction of 2-naphthol, benzaldehyde and ethanethiol in the presence of 5 mol % BDMS, which is mentioned in optimization Table 1 (Entry 2). The product **15a** was fully characterized by recording IR, ^{1}H NMR, ^{13}C NMR spectra and by elemental analysis. The signals appears in the ^{1}H NMR spectrum at δ 1.22 (t, J = 7.6 Hz, 3H), 2.45-2.59 (m, 2H), 6.33 (s, 1H), 7.22 (d, J = 9.2 Hz, 2H), 7.27 (t, J = 8.0 Hz, 2H), 7.32 (d, J = 7.6 Hz, 1H), 7.38-7.44 (m, 3H), 7.78 (d, J = 7.6 Hz, 2H), 7.86 (d, J = 7.2 Hz, 1H), 9.08 (s, 1H, OH). The signals at δ 1.22

correspond to $SCH_2\underline{CH_3}$ and 2.45-2.59 for $S\underline{CH_2}CH_3$ group, 6.33 for methine proton and 9.08 for OH group clearly indicates the formation of the desired product. Similarly, the various peaks obtained in the ^{13}C NMR spectrum are at δ 14.4, 26.8, 46.3, 113.5, 120.3, 121.8, 123.3, 127.2, 127.8, 128.4 (2C), 129.0 (2C), 129.2, 129.5, 130.5, 133.4, 138.6, 155.4 and the characteristic peak at δ 14.4, 26.8, 46.3 and 155.4 resulting due to the formation of product, which are coming from all the reactants.



Scheme 26. Synthesis of 1-[(alkylthio)(phenyl)methyl]naphthalene-2-ol.

After getting the desired product, we tried to optimize the reaction condition using different amount of catalyst and solvent system. For this purpose, benzaldehyde, 2-naphthol and ethanethiol were chosen as the model substrates. The reaction conditions were optimized for the synthesis of the 1-[(ethylthio)(phenyl)methyl]naphthalene-2-ol in terms of the yield and reaction time. Several reactions were scrutinized using different catalysts and various solvents such as CH_3CN, DCM and EtOH. The optimal amount of the reactants such as benzaldehyde, 2-naphthol, thiol and BDMS was found to be 1.0, 1.0, 1.1 and 0.1 equivalent, respectively (Table 1, entry 3). We have noted that no product is formed in the absence of the catalyst. From this observation, it is clear that BDMS has significant role for the formation of the product.

The reaction was also studied in presence of other catalysts namely acetic acid, ferric sulfate, silica supported-perchloric acid and HBr-CH_3COOH. The best suited catalyst for the reaction is BDMS. When 10 mol% of BDMS was used, the reaction proceeded smoothly and the maximum yield was obtained 74% (Table 1, entry 3). Moreover, the yield was found to be affected by the amount of BDMS added. When 5 mol % and 15 mol % of BDMS were used, the yield was 35% and 75%, respectively (Table 1, entries 2 and 4). It was noted that 10 mol% of BDMS was sufficient enough to carry out the reaction. Similarly, the role of solvent in this reaction was studied. Accordingly, the reaction was carried out with various solvent systems such as acetonitrile,

dichloromethane and ethanol. It was found that acetonitrile is the most suitable solvent for this reaction. The product was fully characterized by recording IR, ^{1}H NMR, ^{13}C NMR and elemental analysis.

Table 1: Optimization for reaction conditions[a]

Entry	Catalyst	Solvent	Amount of catalyst (mol%)	Time (hours)	Yield[b] (%)
1	No catalyst	Acetonitrile	0	6.0	0
2	BDMS	Acetonitrile	5	6.0	35
3	BDMS	Acetonitrile	10	6.0	74
4	BDMS	Acetonitrile	15	6.0	75
5	$Fe_2(SO_4)_3H_2O$	Acetonitrile	10	12.0	0
6	CH_3COOH	Acetonitrile	10	12.0	0
7	SiO_2-$HClO_4$	Acetonitrile	10	6.0	60
8	HBr-CH_3COOH	Acetonitrile	10	6.0	64
9	BDMS	DCM	10	6.0	71
10	BDMS	Ethanol	10	6.0	20

[a]All the reactions were carried out with 1 mmol scale. [b]Isolated yield.

Having established the optimum reaction condition, the scope of this domino thia-Michael condensation reaction was explored with various thiols. Thus, several thiols were treated with a variety of aromatic aldehydes bearing different substituents such as NO_2, Br, Cl, and Me group at different positions in the aromatic ring of the aldehyde and 2-naphthol in presence of 10 mol% BDMS at room temperature in acetonitrile and the successful result is shown in Scheme 2 and the yield, and reaction time are summarized in Table 2. Almost all the reactions worked well with a variety of aromatic aldehydes including those bearing electron-withdrawing and electron-donating groups such as NO_2, Br, Cl and Me with ethanethiol, *n*-propanethiol, 2-mercaptoethanol, *p*-thiocresol, *p*-methoxythiophenol, benzylthiol and thiophenol. The desired compounds were obtained in good to high yields within short reaction time (Table 2, Compound **15a**, **15b**, **15d-h**, **15j-4o**, and **15q**). It was shown that the aromatic aldehydes with electron-withdrawing groups reacted faster as compared to the aromatic aldehydes bearing electron-donating groups as would be expected. With thiophenol, *p*-

chlorobenzaldehyde gives low yield 30% (Table 2, **15i**) due to low electrophilicity of C-atom of aldehyde group in comparison to arylaldehyde bearing nitro group at para position (62% yield, Table 2, compound **15f**). Similarly, the reaction of thiophenol, benzaldehyde and *2*-naphthol provides only 21% yield due to less nucleophilicity of the thiophenol. From these observations, it is quite clear that both electrophilicity of the aldehydic carbon and nucleophilicity of thiols play crucial role for the formation of products. Furthermore, when *o*-nitrobenzaldehyde along with ethanethiol was taken, then the desired product was obtained in low yield (20%) due to steric hindrance of nitro group at the *ortho*-position (Table 2, compound **15p**). In addition, when *o*-chlorobenzaldehyde along with ethanethiol was used, then no desired product was obtained (Table 2, entry 18). All these products were characterized by recording melting point, IR, ^{1}H NMR, ^{13}C NMR spectra and elemental analysis. The ^{1}H NMR and ^{13}C NMR spectra of compound **15b** and **15d** are shown in the experimental section in Figure 3 and 4, respectively.

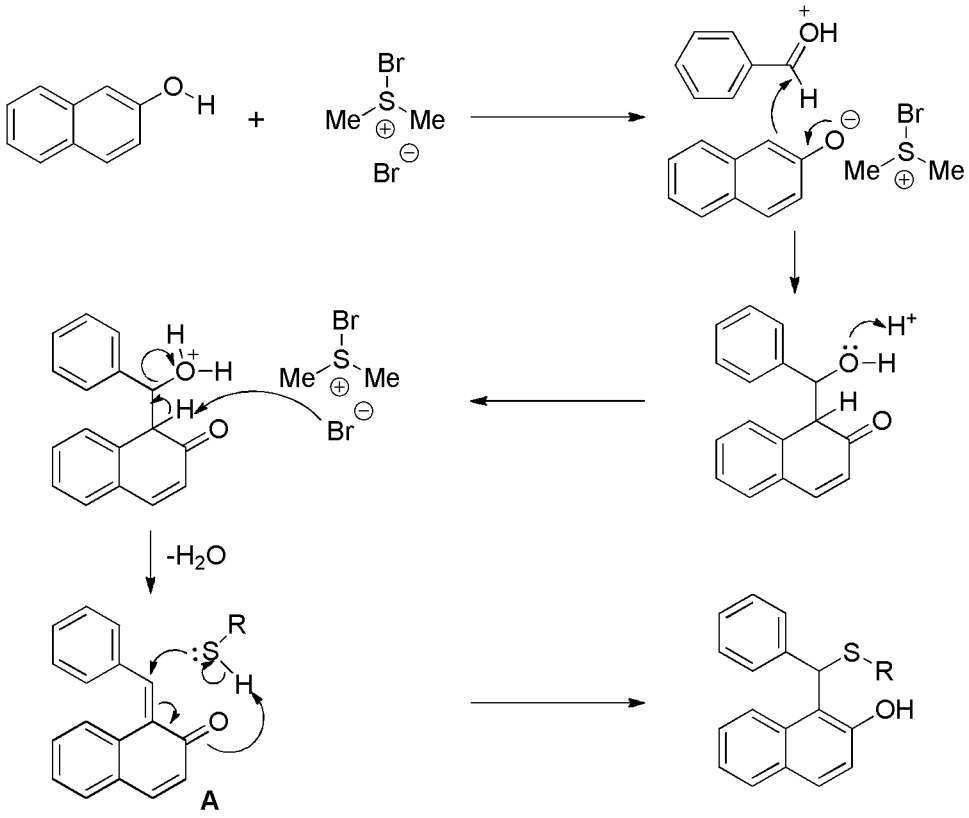
Table 2: Synthesis of 1-[(alkylthio)(phenyl)methyl]naphthalene-2-ol

Entry	Aldehydes	Thiols	Compd. No.	Time (h)	Yield[a] (%)
1	Benzaldehyde	Ethanethiol	**15a**	6	74
2	Benzaldehyde	n-Propanethiol	**15b**	6	73
3	Benzaldehyde	Thiophenol	**15c**	8	21
4	*p*-Nitrobenzaldehyde	Ethanethiol	**15d**	5	77
5	*p*-Nitrobenzaldehyde	*n*-Propanethiol	**15e**	5	78
6	*p*-Nitrobenzaldehyde	Thiophenol	**15f**	7	62
7	*p*-Chlorobenzaldehyde	*n*-Propanethiol	**15g**	6	81
8	*p*-Chlorobenzaldehyde	Benzylthiol	**15h**	6	71
9	*p*-Chlorobenzaldehyde	Thiophenol	**15i**	8	30
10	*p*-Bromobenzaldehyde	*n*-Propanethiol	**15j**	6	80
11	*p*-Bromobenzaldehyde	*p*-Methoxythiophenol	**15k**	5	72
12	*p*-Methylbenzaldehyde	Ethanethiol	**15l**	6	59
13	*m*-Nitrobenzaldehyde	Ethanethiol	**15m**	5	77
14	*m*-Nitrobenzaldehyde	Mercaptoethanol	**15n**	5	65
15	*m*-Bromobenzaldehyde	*p*-Thiocresol	**15o**	5	70

16	*o*-Nitrobenzaldehyde	Ethanethiol	**15p**	6	20
17	2-Naphthaldehyde	*p*-Thiocresol	**15q**	6	73
18	*o*-Chlorobenzaldehyde	Ethanethiol	-	7	-

[a] Isolated Yield.

The formation of the 1-[(alkylthio)(phenyl)methyl]naphthalene-2-ol products can be explained as follows: It has been anticipated that bromodimethylsulfonium bromide may react with 2-naphthol to generate dry HBr in the reaction medium. The *in situ* generated dry HBr catalyzes Knoevenagel condensation between aromatic aldehydes and 2-naphthol to generate reactive *ortho*-naphthoquinone methide intermediate **A** similar to *o*-QMs as shown in Scheme 27. Then the intermediate **A** instantly reacts with thiol to give the desired thia-Michael product.



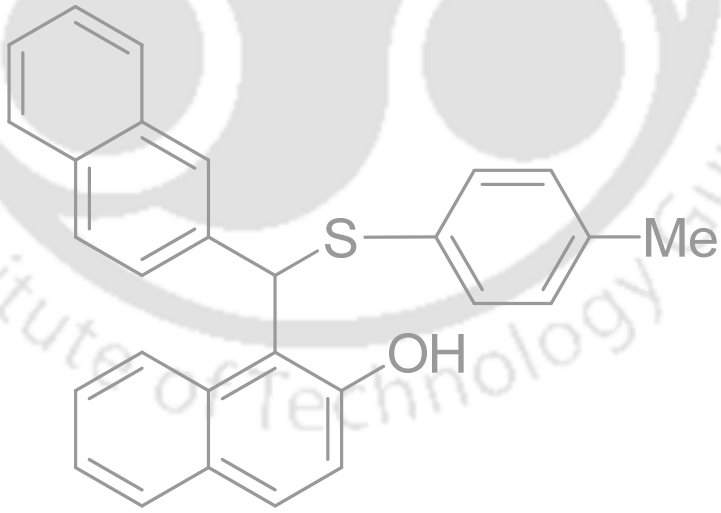
Scheme 27: Proposed plausible mechanism for the formation of product.

In conclusion, we have demonstrated the synthesis of 1-[(alkylthio) (phenyl) methyl] naphthalene-2-ol starting from aromatic aldehyde, 2-naphthol and various thiols in presence of readily available catalyst BDMS. In this method, we have shown that *o*-naphthoquinone methide intermediate can be generated in the reaction medium which

can be trapped by various sulfur nucleophiles. In addition, the reaction condition is very mild and produces a fairly good yield. Furthermore, we have demonstrated the capturing of the *o*-quinone methide intermediate with sulfur nucleophiles. The similar avenue may be further utilized for thia-Michael reaction with other *in situ* generated *o*-quinone methide intermediate.

PART B

Synthesis of 1-[(alkylthio)(phenyl) methyl]-naphthalene-2-ol by trapping *o*-naphthoquinone methide with thiols



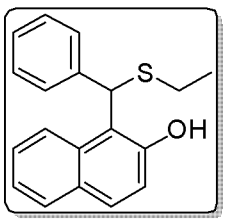
Preparation of bromodimethylsulfonium bromide (BDMS)[56]

Dimethyl sulfide (1.83 mL, 25 mmol) was dissolved in 5 mL of dry dichloromethane in a 150 mL standard joint conical flask. Then, 1.3 mL of bromine (25 mL) dissolved in 5 mL of dry dichloromethane was added slowly to the above solution at ice bath temperature over a period of 5 minute. During the addition, light orange crystals of bromodimethylsulfonium bromide begin to separate out. After the complete addition of bromine, the crystals of bromodimethylsulfonium bromide were collected by filtration. The solid material was then washed with dry hexane and dried under vaccum. The yellow crystalline product was obtained 4.3 g in 77% yield, M.P. 80 °C

Typical Procedure for the preparation of 1-[(alkylthio) (phenyl) methyl] naphthalene-2-ol

To a mixture of aldehyde (1 mmol) and 2-naphthol (1 mmol) in 3 mL of acetonitrile was added BDMS (0.1 mmol) and kept for stirring at room temperature. Then the corresponding thiol (1.1 mmol) was added into it. The reaction mixture was stirred at room temperature and the progress of the reaction was monitored by TLC. After completion of the reaction, ethyl acetate (25 mL) was added into it and the organic layer was washed with 10 mL of water. The water layer was further extracted using ethyl acetate (2 x 25 mL). The combined organic layer dried over anhydrous sodium sulfate and it was concentrated under rotary evaporator. The crude mixture was purified through silica gel column chromatography and the desired product was obtained by eluting with ethyl acetate and hexane (1:99) mixture.

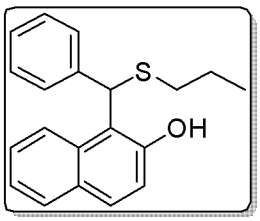
1-((ethylthio)(phenyl)methyl)naphthalen-2-ol (15a):



Nature: Pale yellow semi-solid; **IR (KBr, cm^{-1}):** 3429 (OH); **^{1}H NMR (400 MHz, $CDCl_3$):** δ 1.22 (t, *J* = 7.6 Hz, 3H), 2.45-2.59 (m, 2H), 6.33 (s, 1H), 7.22 (d, *J* = 9.2 Hz, 2H), 7.27 (t, *J* = 8.0 Hz, 2H), 7.32 (d, *J* = 7.6 Hz, 1H), 7.38-7.44 (m, 3H), 7.78 (d, *J* = 7.6 Hz, 2H), 7.86 (d, *J* = 7.2 Hz, 1H), 9.08 (s, 1H, OH); **^{13}C NMR (100 MHz, $CDCl_3$):** δ 14.4,

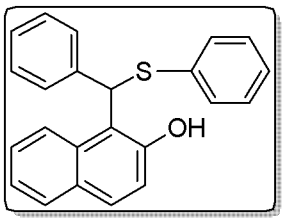
26.8, 46.3, 113.5, 120.3, 121.8, 123.3, 127.2, 127.8, 128.4 (2C), 129.0 (2C), 129.2, 129.5, 130.5, 133.4, 138.6, 155.4; **Anal Calcd.** $C_{19}H_{18}OS$ (294.41): requires C, 77.51; H, 6.16%. Found C, 77.41; H, 6.22%.

1-(phenyl(propylthio)methyl)naphthalen-2-ol (15b):



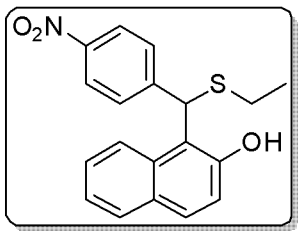
Nature: Pale yellow semi-solid; **IR (KBr, cm^{-1}):** 3439 (OH); **^{1}H NMR (400 MHz, $CDCl_3$):** δ 0.93 (t, *J* = 8.0 Hz, 3H), 1.55-1.64 (m, 2H), 2.39-2.46 (m, 1H), 2.52-2.58 (m, 1H), 6.28 (s, 1H), 7.22 (d, *J* = 8.0 Hz, 2H), 7.26-7.33 (m, 3H), 7.39-7.43 (m, 3H), 7.79 (d, *J* = 8.4 Hz, 2H), 7.85 (d, *J* = 8.4 Hz, 1H), 9.14 (s, 1H, OH); **^{13}C NMR (100 MHz, $CDCl_3$):** δ 13.5, 22.4, 34.6, 46.7, 113.6, 120.3, 121.8, 123.3, 127.2, 127.8, 128.3 (2C), 128.9 (2C), 129.2, 129.5, 130.4, 133.4, 138.8, 155.3; **Anal Calcd.** $C_{20}H_{20}OS$ (308.44): requires C, 77.88; H, 6.54%. Found C, 77.78; H, 6.49%.

1-(phenyl(phenylthio)methyl)naphthalen-2-ol (15c):



Nature: Pale Yellow semisolid; **IR (KBr, cm^{-1}):** 3445 (-OH); **^{1}H NMR (400 MHz, $CDCl_3$):** δ 6.62 (s, 1H), 7.10-7.16 (m, 4H), 7.23-7.36 (m, 7H), 7.51 (dd, J_1 = 1.2 Hz, J_2 = 6.4 Hz, 2H), 7.69-7.73 (m, 2H), 7.80 (d, *J* = 8.8 Hz, 1H), 8.25 (s, 1H, OH) ppm; **^{13}C NMR (100 Hz, $CDCl_3$):** δ 50.6, 115.4, 119.8, 122.3, 123.3, 127.0, 127.7, 127.9, 128.5 (2C), 129.0 (3C), 129.1 (2C), 129.5, 130.4, 131.0 (2C), 132.9, 134.1, 138.5, 154.1 ppm; **Anal Calcd.** $C_{23}H_{18}OS$ (342.45): requires C, 80.67; H, 5.30%. Found C, 80.49; H, 5.21%.

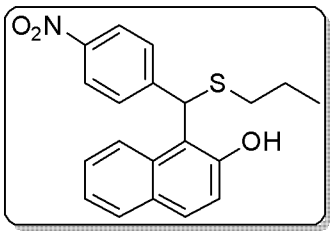
1-((ethylthio)(4-nitrophenyl)methyl)naphthalen-2-ol (15d):



Nature: Pale yellow solid. M.P. 127-129 ^{0}C; **IR (KBr, cm^{-1}):** 3432 (OH), 1514 (NO_2), 1346 (NO_2); **^{1}H NMR (400 MHz, $CDCl_3$):** δ 1.25 (t, *J* = 7.6 Hz, 3H), 2.49-2.65 (m, 2H), 6.36 (s, 1H), 7.22 (d, *J* = 8.8 Hz, 1H), 7.33 (t, *J* = 7.6 Hz, 1H), 7.43 (t, *J* = 8.0 Hz, 1H), 7.57 (d, *J* = 8.4 Hz, 2H), 7.77-7.83 (m, 3H), 8.11 (d, *J* = 8.8 Hz, 2H), 8.61 (s, 1H, OH); **^{13}C NMR (100 MHz, $CDCl_3$):** δ 14.4, 27.1, 45.4, 113.2, 120.1, 121.7, 123.7, 124.0 (2C), 127.5, 129.4 (3C), 129.6,

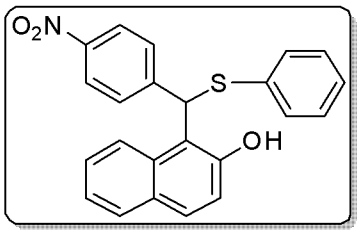
131.0, 133.0, 146.6, 147.3, 154.9; **Anal Calcd.** $C_{19}H_{17}NO_3S$ (339.41): requires C, 67.24; H, 5.05; N, 4.13%. Found C, 67.12; H, 4.97; N, 4.05%.

1-((4-nitrophenyl)(propylthio)methyl)naphthalen-2-ol (15e):



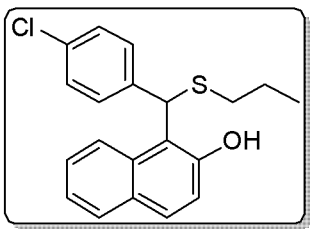
Nature: Pale yellow semi-solid; **IR (KBr, cm^{-1}):** 3437 (OH), 1518 (NO_2), 1346 (NO_2); **^{1}H NMR (400 MHz, $CDCl_3$):** δ 0.95 (t, *J* = 7.6 Hz, 3H), 1.58-1.65 (m, 2H), 2.44-2.51 (m, 1H), 2.57-2.63 (m, 1H), 6.32 (s, 1H), 7.23 (d, *J* = 8.4 Hz, 1H), 7.35 (t, *J* = 7.2 Hz, 1H), 7.44 (t, *J* = 9.2 Hz, 1H), 7.58 (d, *J* = 8.4 Hz, 2H), 7.77 (d, *J* = 8.4 Hz, 1H), 7.82 (d, *J* = 8.0 Hz, 1H), 7.83 (d, *J* = 9.2 Hz, 1H), 8.13 (d, *J* = 8.8 Hz, 2H), 8.71 (s, 1H, OH); **^{13}C NMR (100 MHz, $CDCl_3$):** δ 13.6, 22.5, 35.0, 45.9, 113.4, 120.2, 121.7, 123.8, 124.1 (2C), 127.6, 129.5 (3C), 129.7, 131.1, 133.1, 146.8, 147.4, 155.1; **Anal Calcd.** $C_{20}H_{19}NO_3S$ (353.43): requires C, 67.97; H, 5.42; N, 3.96%. Found C, 67.84; H, 5.31; N, 3.87%.

1-((4-nitrophenyl)(phenylthio)methyl)naphthalen-2-ol (15f):



Nature: Pale yellow semi-solid; **IR (KBr, cm^{-1}):** 3437 (OH), 1515 (NO_2), 1345 (NO_2); **^{1}H NMR (400 MHz, $CDCl_3$):** δ 6.68 (s, 1H), 7.05 (t, *J* = 7.2 Hz, 1H), 7.10-7.18 (m, 5H), 7.29 (d, *J* = 7.6 Hz, 2H), 7.56 (d, *J* = 8.8 Hz, 2H), 7.60-7.64 (m, 3H), 7.95 (d, *J* = 8.8 Hz, 2H), 9.52 (s, 1H, OH); **^{13}C NMR (100 MHz, $CDCl_3$):** δ 49.0, 116.8, 118.6, 123.1, 123.5, 123.6 (2C), 126.9, 127.5, 129.0 (2C), 129.1 (3C), 129.6, 130.5, 130.7 (2C), 132.2, 134.7, 146.6, 147.8, 152.3; **Anal Calcd.** $C_{23}H_{17}NO_3S$ (387.45): requires C, 71.30; H,4.42; N, 3.62%. Found C, 71.19; H, 4.33; N, 3.51%.

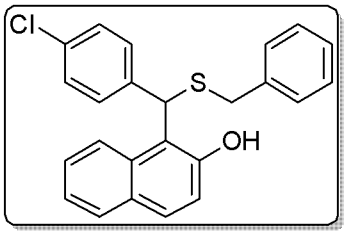
1-((4-chlorophenyl)(propylthio)methyl)naphthalen-2-ol (15g):



Nature: Pale yellow solid, M.P. 88-91 ^{0}C; **IR (KBr, cm^{-1}):** 3436 (OH); **^{1}H NMR (400 MHz, $CDCl_3$):** δ 0.85 (t, *J* = 7.2 Hz, 3H), 1.46-1.56 (m, 2H), 2.31-2.38 (m, 1H), 2.43-2.50 (m, 1H), 6.15 (s, 1H), 7.15 (t, *J* = 8.4 Hz, 3H), 7.23-7.27 (m,

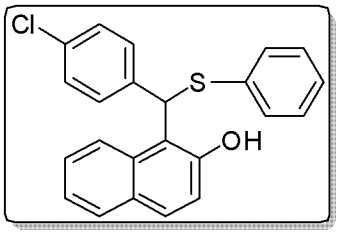
3H), 7.35 (t, *J* = 7.6 Hz, 1H), 7.68-7.73 (m, 3H), 8.94 (s, 1H, OH); **^{13}C NMR (100 MHz, $CDCl_3$):** δ 13.5, 22.4, 34.7, 45.9, 113.3, 120.3, 121.6, 123.5, 127.3, 129.1 (2C), 129.3, 129.5, 129.8 (2C), 130.7, 133.2, 133.6, 137.3, 155.3; **Anal Calcd.** $C_{20}H_{19}ClOS$ (342.88): requires C, 70.06; H, 5.59%. Found C, 69.93; H, 5.49%.

1-((benzylthio)(4-chlorophenyl)methyl)naphthalen-2-ol (15h):



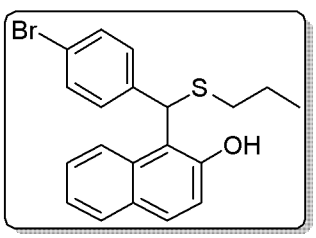
Nature: Pale yellow semi-solid; **IR (KBr, cm^{-1}):** 3430 (OH); **^{1}H NMR (400 MHz, $CDCl_3$):** δ 3.51 (d, *J* = 13.2 Hz, 1H), 3.61 (d, *J* = 13.6 Hz, 1H), 5.85 (s, 1H), 6.90 (d, *J* = 6.8 Hz, 2H), 7.07-7.23 (m, 9H), 7.37 (d, *J* = 8.4 Hz, 2H), 7.71 (t, *J* = 8.8 Hz, 2H), 8.81 (s, 1H, OH); **^{13}C NMR (100 MHz, $CDCl_3$):** δ 37.0, 45.2, 112.8, 120.2, 121.9, 123.5, 127.1, 127.6, 128.8 (2C), 129.0 (2C), 129.1, 129.2 (2C), 129.5, 129.9 (2C), 130.8, 133.1, 133.6, 136.5, 136.8, 155.3; **Anal Calcd.** $C_{24}H_{19}ClOS$ (390.93): requires C, 73.74; H, 4.90%. Found C, 73.61; H, 4.99%.

1-((4-chlorophenyl)(phenylthio)methyl)naphthalen-2-ol (15i):



Nature: Pale yellow semi-solid; **IR (KBr, cm^{-1}):** 3450 (OH); **^{1}H NMR (400 MHz, $CDCl_3$):** δ 6.56 (s, 1H), 7.12-7.15 (m, 3H), 7.24-7.29 (m, 3H), 7.32-7.38 (m, 4H), 7.42 (d, *J* = 8.4 Hz, 2H), 7.71 (d, *J* = 8.8 Hz, 1H), 7.72 (d, *J* = 8.0 Hz, 1H), 7.74 (d, *J* = 8.0 Hz, 1H), 8.04 (s, 1H, OH); **^{13}C NMR (100 MHz, $CDCl_3$):** δ 50.0, 115.2, 119.9, 122.2, 123.5, 127.2, 128.0, 129.2 (3C), 129.3 (2C), 129.6, 129.9 (3C), 130.6, 131.2 (2C), 132.8, 133.7, 137.2, 154.0; **Anal Calcd.** $C_{23}H_{17}ClOS$ (376.90): requires C, 73.29; H, 4.55%. Found C, 73.09; H, 4.46%.

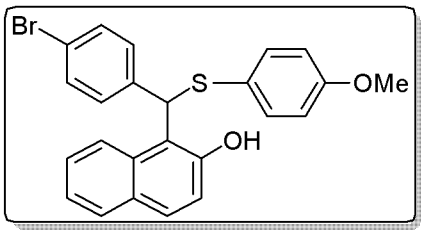
1-((4-bromophenyl)(propylthio)methyl)naphthalen-2-ol (15j):



Nature: Pale yellow solid, M.P. 96-99 °C; **IR (KBr, cm^{-1}):** 3423 (OH); **^{1}H NMR (400 MHz, $CDCl_3$):** δ 0.93 (t, *J* = 7.2 Hz, 3H), 1.54-1.64 (m, 2H), 2.39-2.45 (m, 1H), 2.51-2.58

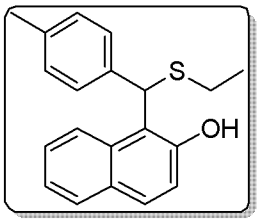
(m, 1H), 6.21 (s, 1H), 7.21 (d, J = 8.8 Hz, 1H), 7.27 (d, J = 9.2 Hz, 2H), 7.33 (t, J = 7.6 Hz, 1H), 7.39 (d, J = 8.8 Hz, 2H), 7.43 (d, J = 6.8 Hz, 1H), 7.80 (d, J = 8.8 Hz, 3H), 9.01 (s, 1H, OH); **^{13}C NMR (100 MHz, $CDCl_3$):** δ 13.6, 22.4, 34.8, 46.0, 113.2, 120.4, 121.6, 121.8, 123.5, 127.3, 129.3, 129.5, 130.1 (2C), 130.7, 132.1 (2C), 133.3, 137.9, 155.3; **IR (KBr, cm^{-1}):** 3423 (OH); **Anal Calcd.** $C_{20}H_{19}BrOS$ (387.33): requires C, 62.02; H, 4.94%. Found C, 61.93; H, 4.99%.

1-((4-bromophenyl)((4-methoxyphenyl)thio)methyl)naphthalen-2-ol (15k):



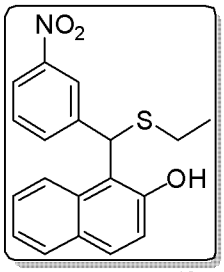
Nature: Pale yellow semi-solid; **IR (KBr, cm^{-1}):** 3437 (OH); **^{1}H NMR (400 MHz, $CDCl_3$):** δ 3.61 (s, 3H), 6.39 (s, 1H), 6.62 (d, J = 8.8 Hz, 2H), 7.16 (d, J = 8.8 Hz, 1H), 7.23 (t, J = 8.0 Hz, 1H), 7.29-7.35 (m, 5H), 7.37-7.40 (m, 2H), 7.66-7.71 (m, 3H), 8.38 (s, 1H, OH); **^{13}C NMR (100 MHz, $CDCl_3$):** δ 51.8, 55.3, 114.8 (2C), 115.0, 119.8, 121.7, 122.1, 123.36, 123.45, 127.0, 129.0, 129.5, 130.2 (2C), 130.5, 132.0 (2C), 132.9, 134.7 (2C), 137.7, 154.0, 160.0; **Anal Calcd.** $C_{24}H_{19}BrO_2S$ (451.38): requires C, 63.86; H, 4.24%. Found C, 63.93; H, 4.30%.

1-((ethylthio)(p-tolyl)methyl)naphthalen-2-ol (15l):



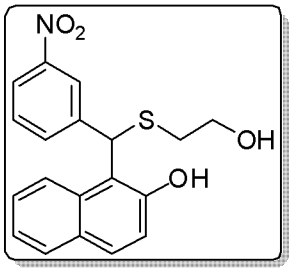
Nature: Pale yellow semi-solid; **IR (KBr, cm^{-1}):** 3417 (OH); **^{1}H NMR (400 MHz, $CDCl_3$):** δ 1.18 (t, J = 7.6 Hz, 3H), 2.24 (s, 3H), 2.40-2.55 (m, 2H), 6.28 (s, 1H), 7.05 (d, J = 8.0 Hz, 2H), 7.20 (d, J = 8.8 Hz, 1H), 7.27 (t, J = 8.8 Hz, 1H), 7.28 (d, J = 7.6 Hz, 2H), 7.38 (t, J = 8.4 Hz, 1H), 7.75 (d, J = 8.8 Hz, 2H), 7.84 (d, J = 8.8 Hz, 1H), 9.09 (s, 1H, OH); **^{13}C NMR (100 MHz, $CDCl_3$):** δ 14.3, 21.2, 26.7, 46.0, 113.7, 120.2, 121.8, 123.2, 127.1, 128.2 (2C), 129.1, 129.4, 129.6 (2C), 130.3, 133.3, 135.6, 137.5, 155.3; **Anal Calcd.** $C_{20}H_{20}OS$ (308.44): requires C, 77.88; H, 6.54%. Found C, 77.79; H, 6.46%.

1-((ethylthio)(3-nitrophenyl)methyl)naphthalen-2-ol (15m):



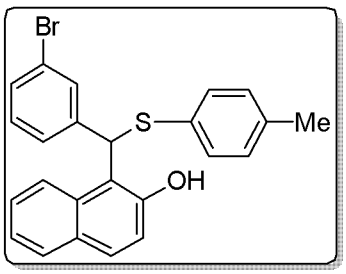
Nature: Pale yellow semi-solid; **IR (KBr, cm^{-1}):** 3445 (OH), 1527 (NO_2), 1349 (NO_2); **^{1}H NMR (400 MHz, $CDCl_3$):** δ 1.25 (t, *J* = 7.2 Hz, 3H), 2.50-2.65 (m, 2H), 6.37 (s, 1H), 7.24 (d, *J* = 8.8 Hz, 1H), 7.35 (d, *J* = 7.2 Hz, 1H), 7.40-7.47 (m, 2H), 7.67 (d, *J* = 8.0 Hz, 1H), 7.78-7.84 (m, 3H), 8.09 (d, *J* = 8.4 Hz, 1H), 8.35 (s, 1H), 9.30 (s, 1H, OH); **^{13}C NMR (100 MHz, $CDCl_3$):** δ 14.4, 27.1, 45.3, 115.0, 120.3, 121.5, 122.8, 123.6, 123.7, 127.5, 129.4, 129.7, 129.9, 130.1, 133.0, 134.5, 141.2, 148.7, 155.2; **Anal Calcd.** $C_{19}H_{17}NO_3S$ (339.41): requires C, 67.24; H, 5.05, N, 4.13%. Found C, 67.12; H, 5.14, N, 4.21%.

1-(((2-hydroxyethyl)thio)(3-nitrophenyl)methyl)naphthalen-2-ol (15n):



Nature: Pale yellow solid, M.P. 142-145 ^{0}C; **IR (KBr, cm^{-1}):** 3531 (OH), 1531 (NO_2), 1351 (NO_2); **^{1}H NMR (400 MHz, $CDCl_3$):** δ 2.31 (brs, 1H), 2.75 (q, *J* = 5.6 Hz, 2H), 3.81 (s, 2H), 6.50 (s, 1H), 7.20 (d, *J* = 8.8 Hz, 1H), 7.32 (t, *J* = 8.0 Hz, 1H), 7.39 (t, *J* = 9.2 Hz, 1H), 7.41 (t, *J* = 8.0 Hz, 1H), 7.68 (d, *J* = 8.0 Hz, 1H), 7.74 (d, *J* = 8.4 Hz, 1H), 7.79 (d, *J* = 8.4 Hz, 2H), 8.08 (d, *J* = 8.0 Hz, 1H), 8.39 (s, 1H), 9.80 (s, 1H, OH); **^{13}C NMR (100 MHz, CD_3OD):** δ 36.3, 45.0, 62.4, 118.6, 119.3, 122.3, 123.7, 123.8, 125.8, 126.8, 129.9, 130.2, 131.0, 133.1, 135.3, 145.6, 149.4, 154.1; **Anal Calcd.** $C_{19}H_{17}NO_4S$ (355.41): requires C, 64.21; H, 4.82, N, 3.94%. Found C, 64.12; H, 4.71, N, 3.81%.

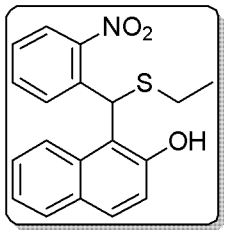
1-((3-bromophenyl)(p-tolylthio)methyl)naphthalen-2-ol (15o):



Nature: Pale yellow semi-solid; **IR (KBr, cm^{-1}):** 3436 (OH); **^{1}H NMR (400 MHz, $CDCl_3$):** δ 2.20 (s, 3H), 6.57 (s, 1H), 6.97 (d, *J* = 8.0 Hz, 2H), 7.16 (t, *J* = 8.0 Hz, 1H), 7.21 (d, *J* = 8.8 Hz, 1H), 7.31 (t, *J* = 7.2 Hz, 1H), 7.35 (d, *J* = 8.0 Hz, 2H), 7.38-7.43 (m, 2H), 7.46 (d, *J* = 7.6 Hz, 1H), 7.73-7.77 (m, 3H), 7.80 (d, *J* = 8.8 Hz, 1H), 8.32 (s, 1H, OH); **^{13}C NMR (100 MHz, $CDCl_3$):** δ 21.1, 50.7, 115.0, 119.7, 122.2, 122.9, 123.4, 127.1 (2C), 129.0,

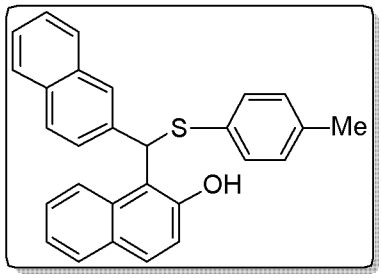
129.5, 130.0 (2C), 130.4, 130.5, 130.9, 131.5 (2C), 131.8 (2C), 132.8, 138.3, 141.2, 153.9; **Anal Calcd.** $C_{24}H_{19}BrOS$ (435.38): requires C, 66.21; H, 4.40%. Found C, 66.12; H, 4.34%.

1-((ethylthio)(2-nitrophenyl)methyl)naphthalen-2-ol (15p):



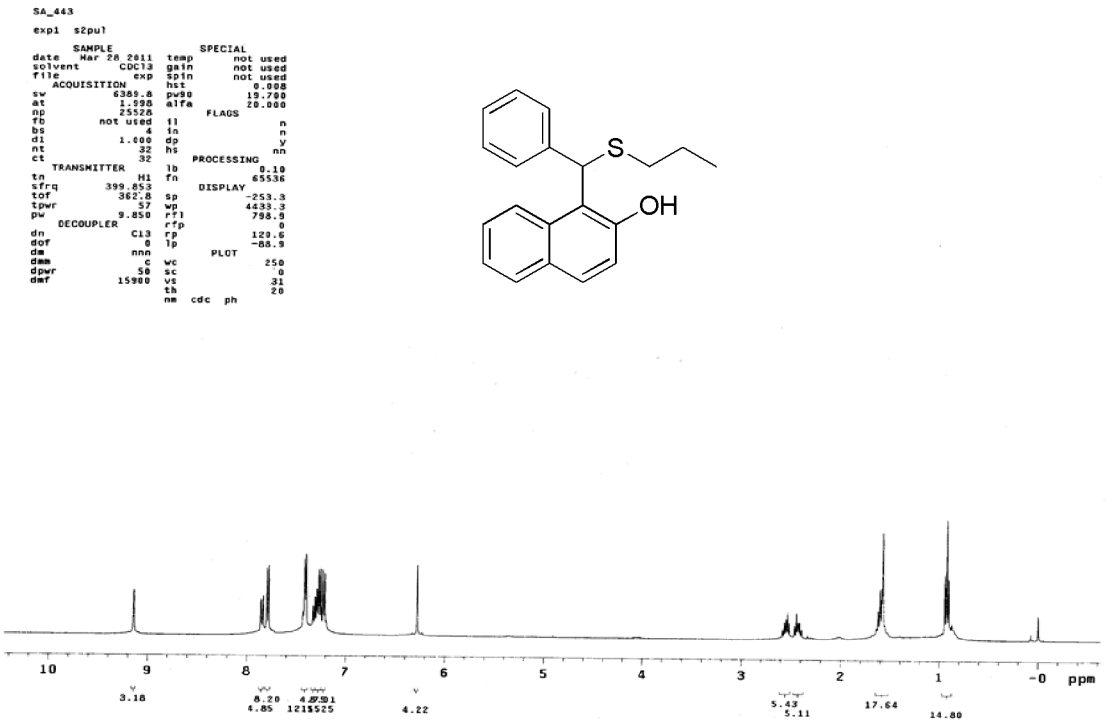
Nature: Pale yellow semi-solid; **IR (KBr, cm^{-1}):** 3433 (OH), 1528 (NO_2), 1353 (NO_2); **^{1}H NMR (400 MHz, $CDCl_3$):** δ 1.25 (s, *J* = 7.6 Hz, 3H), 2.56-2.64 (m, 2H), 7.23 (s, 1H), 7.25 (d, *J* = 9.2 Hz, 1H), 7.28 (dd, J_1 = 3.6 Hz, J_2 = 5.6 Hz, 1H), 7.34 (t, *J* = 6.8 Hz, 1H), 7.38 (dd, J_1 = 3.6 Hz, J_2 = 6.4 Hz, 2H), 7.46 (t, *J* = 7.6 Hz, 1H), 7.80 (d, *J* = 8.0 Hz, 1H), 7.84 (d, *J* = 9.2 Hz, 1H), 7.91 (d, *J* = 8.4 Hz, 1H), 7.95 (dd, J_1 = 3.6 Hz, J_2 = 5.6 Hz, 1H), 9.55 (s, 1H, OH); **^{13}C NMR (100 MHz, $CDCl_3$):** δ 13.9, 27.7, 41.4, 111.4, 120.5, 121.9, 123.7, 125.7, 127.8, 129.0, 129.2, 129.6, 130.6, 131.2, 133.0, 133.5, 133.6, 149.1, 156.5; **Anal Calcd.** $C_{19}H_{17}NO_3S$ (339.41): requires C, 67.24; H, 5.05, N, 4.13%. Found C, 67.12; H, 5.14, N, 4.19%.

1-(naphthalen-2-yl(p-tolylthio)methyl)naphthalen-2-ol (15q):



Nature: White solid, M.P. 117-120 ^{0}C; **IR (KBr, cm^{-1}):** 3434 (OH); **^{1}H NMR (400 MHz, $CDCl_3$):** δ 2.20 (s, 3H), 6.68 (s, 1H), 6.95 (d, *J* = 7.6 Hz, 2H), 7.21 (d, *J* = 9.2 Hz, 1H), 7.26 (t, *J* = 7.6 Hz, 1H), 7.32 (d, *J* = 8.0 Hz, 2H), 7.33 (t, *J* = 7.6 Hz, 1H), 7.41-7.46 (m, 2H), 7.67 (dd, J_1 = 2.0 Hz, J_2 = 8.8 Hz, 1H), 7.72-7.76 (m, 3H), 7.77-7.82 (m, 3H), 7.87 (s, 1H), 8.51 (s, 1H, OH); **^{13}C NMR (100 MHz, $CDCl_3$):** δ 21.2, 51.9, 115.0, 120.2, 122.2, 123.3, 126.4 (2C), 126.7, 127.1, 127.4, 127.7, 128.3, 128.9, 129.0, 129.5, 130.0 (2C), 130.5, 131.7 (3C), 133.0, 133.1, 133.6, 135.9, 138.2, 154.6; **Anal Calcd.** $C_{28}H_{22}OS$ (406.54): requires C, 82.72; H, 5.45%. Found C, 82.82; H, 5.54%.

^{1}H NMR (400 MHz, $CDCl_3$):** 1-(phenyl(propylthio)methyl)naphthalen-2-ol **(15b)



^{13}C NMR (100 MHz, $CDCl_3$):** 1-(phenyl(propylthio)methyl)naphthalen-2-ol **(15b)

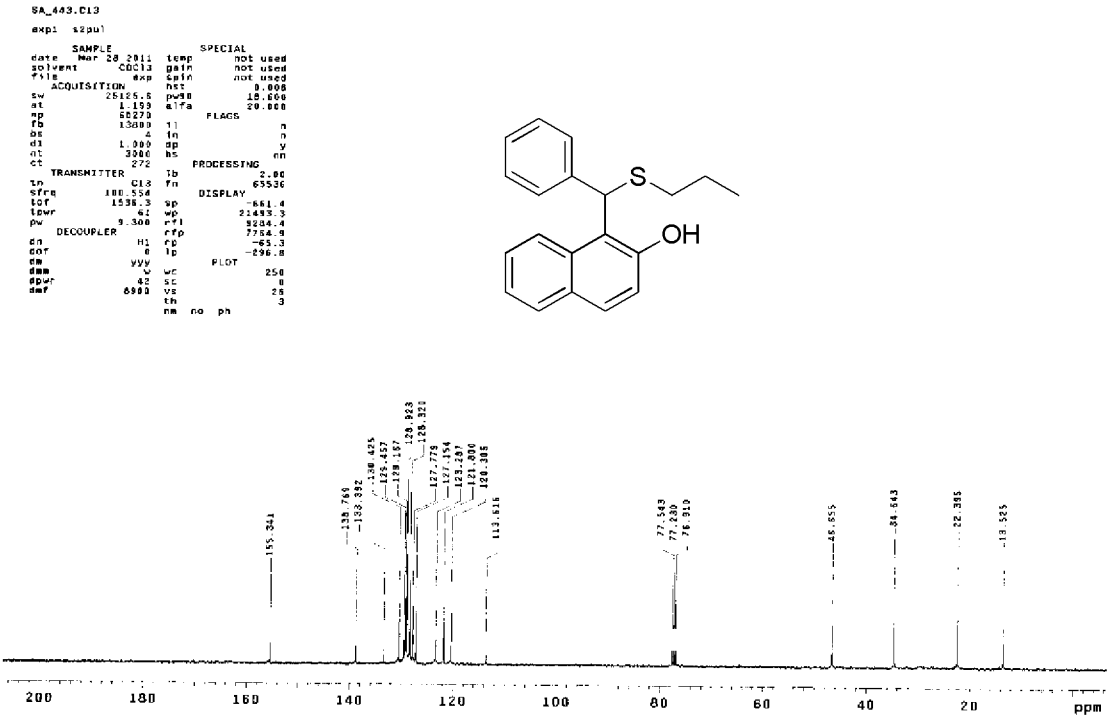
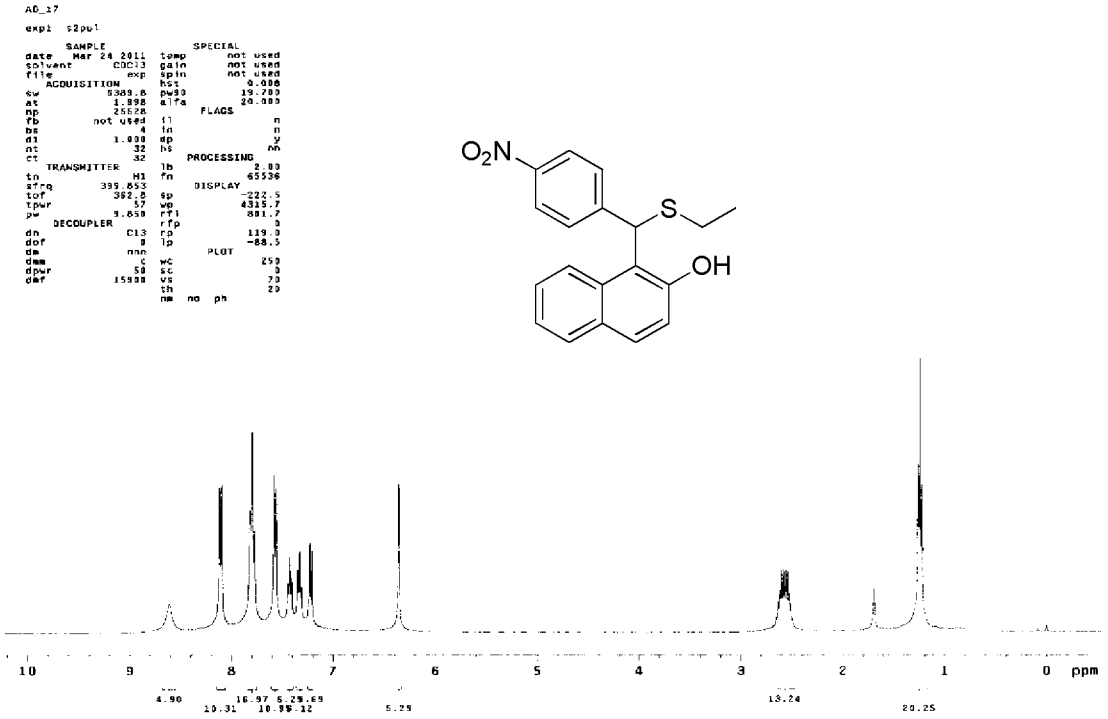


Figure 3

^{1}H NMR (400 MHz, $CDCl_3$): *1-((ethylthio)(4-nitrophenyl)methyl)naphthalen-2-ol* ***(15d)***



^{13}C NMR (100 MHz, $CDCl_3$): *1-((ethylthio)(4-nitrophenyl)methyl)naphthalen-2-ol* ***(15d)***

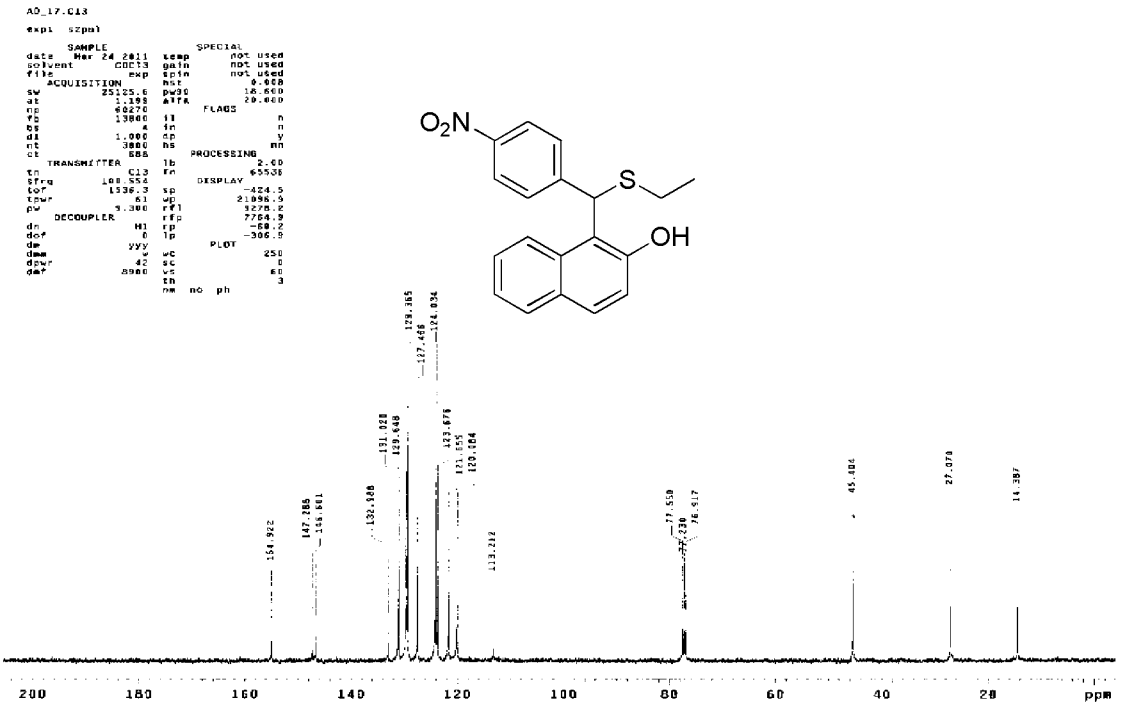
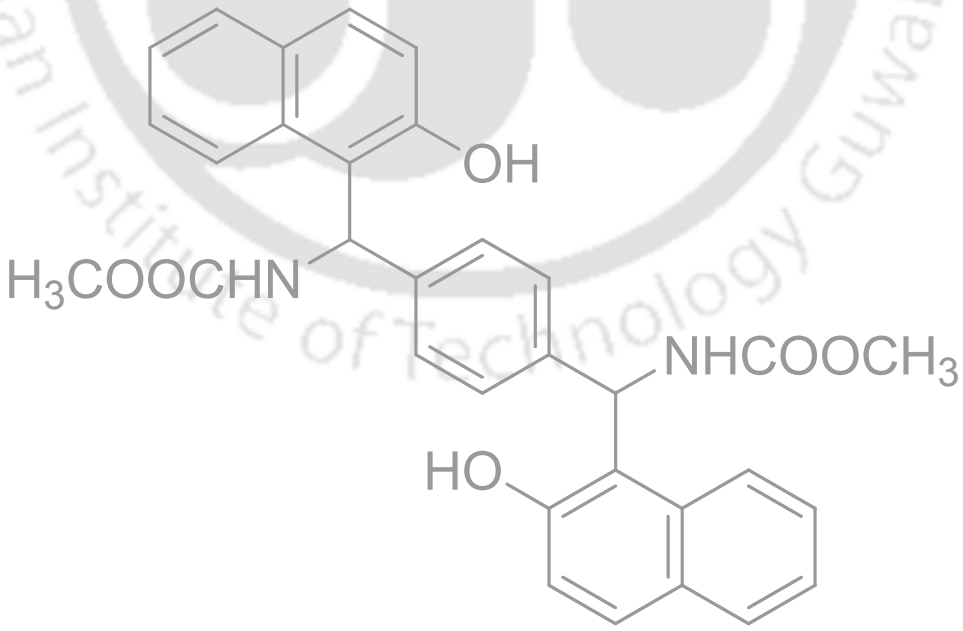


Figure 4

PART B

Synthesis of *N*-protected 1-amino-alkyl-2-naphthols through capturing of *in situ* generated *o*-naphthoquinone



In the previous Chapter 2, we have shown that 2-naphthol and aromatic aldehyde can provide transient species *o*-naphthoquinone methide intermediate in presence of bromodimethylsulfonium bromide (BDMS) and finally it was trapped with various sulfur nucleophiles such as thiols. On basis of our experimental findings, we realized that the same *o*-naphthoquinone methide intermediate might be captured with nitrogen containing nucleophiles to obtain new class of compounds through aza-Michael reaction. Likewise 1-[(alkylthio)(phenyl) methyl]-naphthalene-2-ol, 1-carbamato-alkyl-2-naphthols can be easily accessible using 2-naphthol, aromatic aldehyde and carbamate derivatives in presence of BDMS, which acts as pre-catalyst.

The importance of carbamate derivatives and their method of preparation and their biological importance have been reviewed recently.[72] Some of the carbamates act as valuable drugs, which is shown in Figure 5.

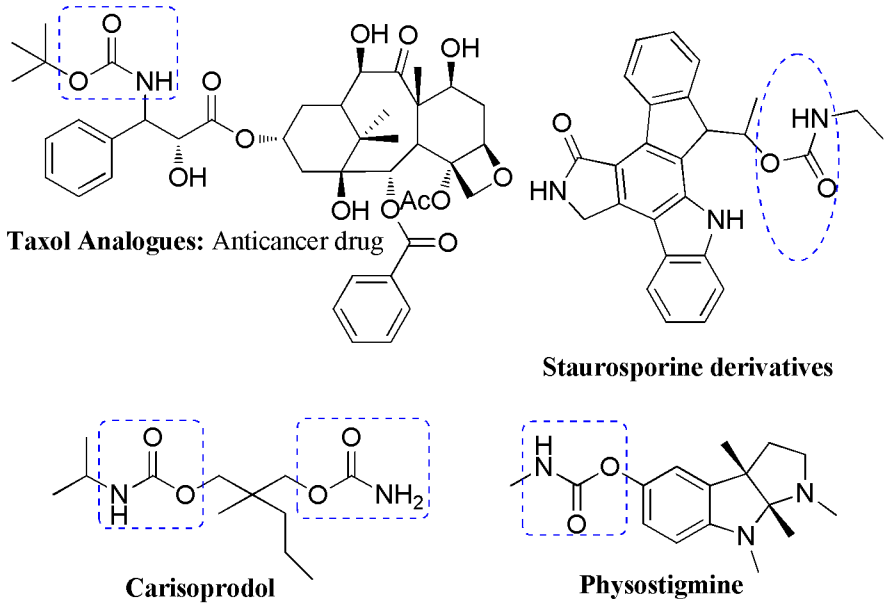
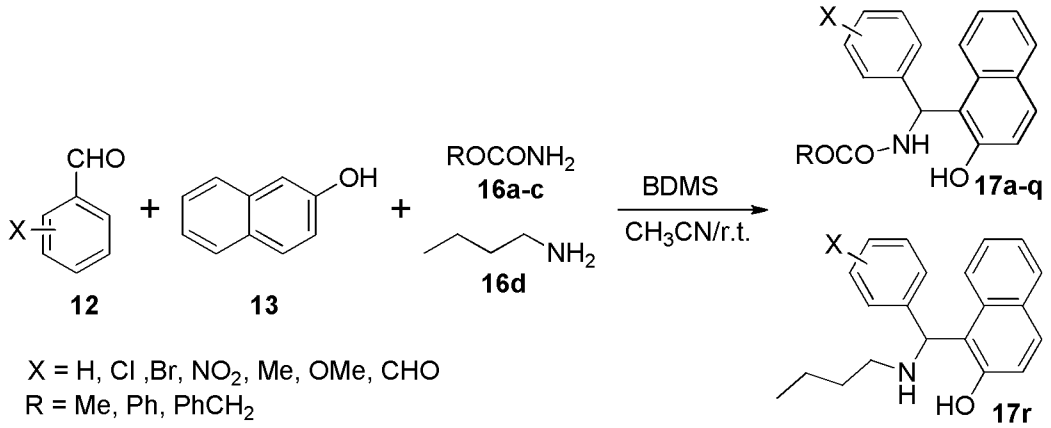


Figure 5

The synthesis of 1-carbamato-alkyl-2-naphthols has been reported through similar approach by using various catalysts, which is already mentioned in Chapter 1 of Part B. Though these synthetic methods are quite useful but some of these methods are associated with certain drawbacks such as the reaction has to be carried out at high temperature, provide lower yields and are not applicable on a broad range of substrates. Therefore, there is a further scope to develop a new methodology, which might even proceed under mild, environmentally benign, and clean reaction conditions.

With this aim in mind, we carried out the reaction benzaldehyde, 2-naphthol and methyl carbamate in presence of 5 mol% of BDMS. As expected, we have isolated the product 1-methyl N-[(2-hydroxynaphthalen-1-yl)(phenyl)methyl]carbamate (**17a**), which was also characterized by ^{1}H NMR, ^{13}C NMR spectra and by elemental analysis. The product shows ^{1}H NMR values at δ 3.56 (s, 3H), 6.84 (d, J = 9.2 Hz, 1H), 7.15-7.29 (m, 7H), 7.38 (t, J = 7.6 Hz, 1H), 7.65 (d, J = 8.8 Hz, 1H), 7.76 (d, J = 8.8 Hz, 1H), 7.80 (d, J = 8.0 Hz, 1H), 7.90 (d, J = 8.4 Hz, 1H), 10.14 (s, 1H, OH) ppm. The characteristic signals at δ 3.56, 6.84 and 10.14 clearly indicate for the formation of methyl N-[(2-hydroxynaphthalen-1-yl)(phenyl)methyl] carbamate. Similarly, in ^{13}C NMR spectrum gives signals at δ 50.5, 51.8, 118.6, 119.0, 122.7, 123.2, 126.2 (2C), 126.6, 126.7, 128.3 (2C), 128.5, 128.8, 129.5, 132.2, 142.5, 153.0, 156.8. Out of which, the signals at δ 50.5, 51.8 and 156.8 due to the presence of Ar<u>C</u>H, O<u>C</u>H$_3$ and =<u>C</u>-OH which can come only from the three starting materials. This clearly confirms that the desired product is formed. The spectral data were also compared with earlier reported data[37] and found to be in good agreement with them. ^{1}H NMR and ^{13}C NMR spectra of compound **17a** are given in experimental section in Figure 7. After getting the desired product, we optimized the amount of catalyst as well as the suitable solvent required for the above transformation. For this purpose, we have performed several trial reactions using a mixture of 2-naphthol, benzaldehyde and methyl carbamate as a model reaction which is mentioned in the optimization Table 3.



Scheme 28: Synthesis of *N*-protected 1-aminoalkyl-2-naphthols

It was found that the reaction takes relatively longer time (2.5 h) in presence of 5 mol% BDMS as compared to 10 mol% of catalyst and also provide lower yield. During the screening of different solvents, it was noticed that acetonitrile was found to be better

solvent as compared to the other solvents like DCM, ethyl acetate and ethanol in terms of reaction time and yields. Similarly, various other catalysts were also examined like HBr-CH_3COOH, $Fe_2(SO_4)_3.xH_2O$, $FeCl_3.6H_2O$ and CH_3COOH for the same reaction. Among them, BDMS has been found to be the best catalyst in terms of yield for the desired product. The optimized reaction conditions were found using 10 mol% of BDMS in acetonitrile at room temperature.

Table 3. Optimization for the reaction conditions[a]

Entry	Catalyst	Solvent	Catalyst (mol%)	Time (h)	Yield[b] (%)
1	No catalyst	CH_3CN	0	24	11
2	BDMS	CH_3CN	5	2.5	57
3	BDMS	CH_3CN	10	1.5	77
4	BDMS	CH_3CN	15	1.5	78
5	BDMS	-	10	1.5	58
6	BDMS	DCM	10	2	71
7	BDMS	EtOAc	10	2	70
8	BDMS	C_2H_5OH	10	4	55
9	HBr-MeCOOH	CH_3CN	10	2.0	68
10	$Fe_2(SO_4)_3.H_2O$	CH_3CN	10	24	15
11	$FeCl_3.6H_2O$	CH_3CN	10	24	50
12	CH_3COOH	CH_3CN	10	24	12

[a]The reactions were carried out using benzaldehyde (1 mmol), 2-naphthol (1 mmol) and methyl carbamate (1.2 mmol) scale. [b]Isolated yields.

After optimizing the reaction condition, we have performed the reaction of 4-chlorobenzaldehyde with 2-naphthol and methyl carbamate using 10 mol% BDMS and the desired product (**17b**) was obtained in 88% yield.

The generality of the present protocol is verified by carrying out the reaction with various aromatic aldehydes having substituents Cl, Br, NO_2, Me, OMe at different positions in the aromatic ring with 2-naphthol and methyl carbamate under identical reaction condition, which is presented in Scheme 28. The successful results are summarized in Table 4.

The reaction worked well with a variety of aromatic aldehydes having electron-withdrawing and electron-donating groups with methyl carbamate and the desired

compounds were obtained in good to high yields within a short reaction of time (**17a-k**). It was noticed that the aromatic aldehydes having electron withdrawing groups in the aromatic ring reacted faster as compared to the aromatic aldehyde bearing electron donating groups. However, aliphatic aldehydes did not give the desired product as *o*-naphthoquinone methide intermediate was formed in lesser amount. Interestingly, 1,4-disubstituted aromatic aldehyde such as terephthaldehyde reacted with 2-naphthol and methyl carbamate gave bis-product (**17k**) in good yield under similar experimental conditions.

The scope of the present protocol was further examined by performing the reactions with other carbamates derivatives such as phenyl and benzyl carbamates along with various aromatic aldehydes. The desired products (**17l-q**) were obtained in good yields. It was noted that lower yields were obtained in case of phenyl carbamate as compared to methyl carbamate due to lesser nucleophilicity of its N atom (**17l-o**).

Further, the reaction was studied with benzaldehyde, 2-naphthol and *n*-butylamine under identical reaction condition and the desired product (**17r**) was obtained in 65% yield. However, the similar reaction proved to be a failure in case of aniline instead of *n*-butylamine, which may be due to less basicity of aniline as compared to aliphatic amine. All the products were characterized by recording IR, ^{1}H and ^{13}C NMR spectra and elemental analysis, which was compared with the reported spectroscopic data.[37] ^{1}H NMR and ^{13}C NMR spectra of compound **17d** is given in Figure **8** in experimental section. Finally, the structure of phenyl N-[(2-hydroxynaphthalen-1-yl)(phenyl)methyl] carbamate was further confirmed by X-ray crystallographic analysis, which is given in the ORTEP diagram in Figure 6.

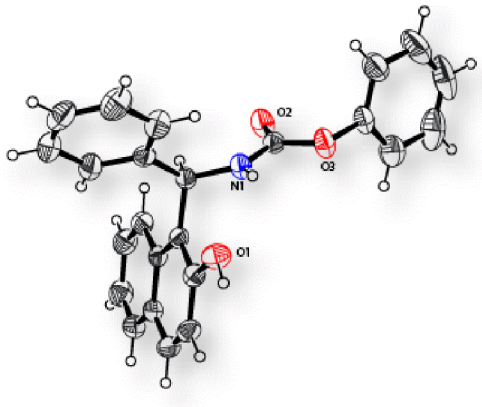


Figure 6: Crystal structure of Phenyl N-[(2-hydroxynaphthalen-1-yl)(phenyl)methyl] carbamate (CCDC No. 824332)

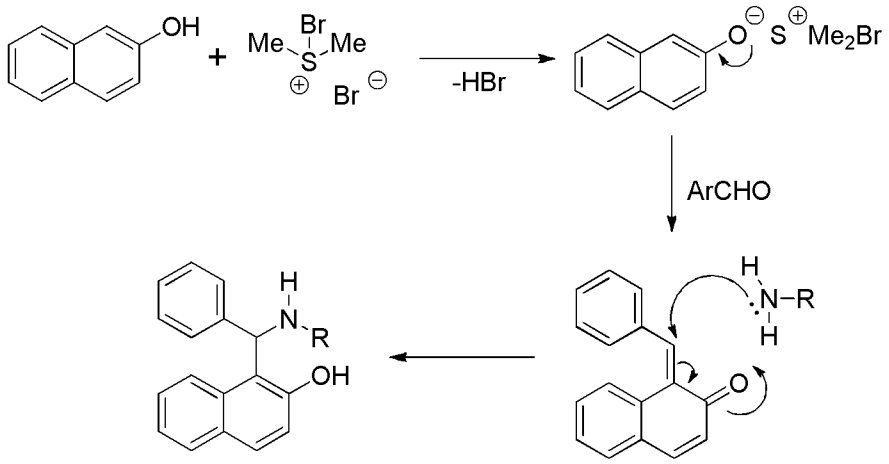
Table 4: Synthesis of *N*-protected 1-aminoalkyl-2-naphthols using BDMS as catalyst

Entry	Aldehyde	Compd. **16**	Product **17**	Reaction Time min/[h]	Yield[a] (%)
1	C_6H_5CHO	$MeOCONH_2$	**17a**	[1.5]	77
2	4-ClPhCHO	$MeOCONH_2$	**17b**	45	88
3	4-BrPhCHO	$MeOCONH_2$	**17c**	40	87
4	$4\text{-}NO_2PhCHO$	$MeOCONH_2$	**17d**	30	90
5	4-MePhCHO	$MeOCONH_2$	**17e**	[6]	50
6	$4\text{-}MeOC_6H_4CHO$	$MeOCONH_2$	**17f**	[6]	51
7	3-ClPhCHO	$MeOCONH_2$	**17g**	45	75
8	$3\text{-}NO_2PhCHO$	$MeOCONH_2$	**17h**	35	86
9	2-ClPhCHO	$MeOCONH_2$	**17i**	50	73
10	$2\text{-}NO_2PhCHO$	$MeOCONH_2$	**17j**	30	62
11	OHCPhCHO	$MeOCONH_2$	**17k**	[1]	82
12	PhCHO	$PhOCONH_2$	**17l**	[10]	60
13	$4\text{-}NO_2PhCH$	$PhOCONH_2$	**17m**	[5]	76
14	4-ClPhCHO	$PhOCONH_2$	**17n**	[8.5]	63
15	4-BrPhCHO	$PhOCONH_2$	**17o**	[8]	65
16	PhCHO	$BnOCONH_2$	**17p**	[5]	71
17	3-ClPhCHO	$BnOCONH_2$	**17q**	[4]	76
18	PhCHO	*n*-$BuNH_2$	**17r**	[5]	65

[a]Isolated yields

The formation of the product can be explained as follows like earlier discussed in Chapter 2 of Part B. The first step is the formation of *o*-naphthoquinone intermediate in

presence of dry HBr, which is similar to Knoevenagel type reaction. In the second step the nitrogen containing nucleophiles such as substituted carbamate and amine reacted instantly with transient species *o*-naphthaquinone intermediate like aza-Michael reaction to give the final product (Scheme 29).



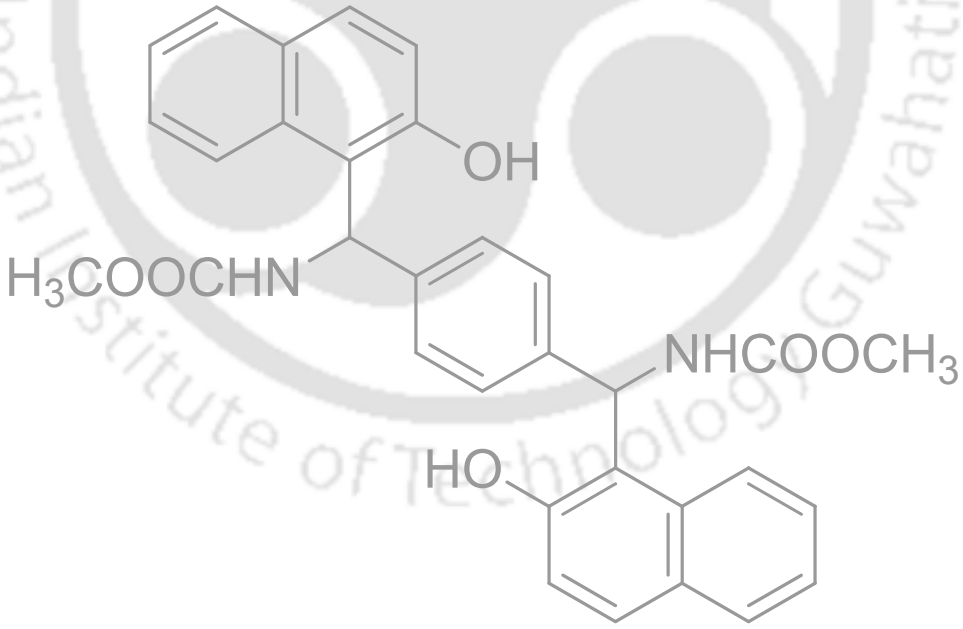
Scheme 29: Proposed mechanism for preparation of N-protected 1-aminoalkyl-2-naphthol

We thought that the hydrolysis of the final product can give 1-aminoalkyl-2-naphthol derivatives after hydrolysis using a suitable reagent. However, the reaction was not successful either in presence of various mineral acids such as HCl, H_2SO_4, HBr-CH_3COOH or alkali solution i.e. aqueous NaOH solution.

In conclusion, we have achieved the synthesis of *N*-protected 1-aminoalkyl-2-naphthol derivatives from aromatic aldehydes, 2-naphthol and methyl/phenyl/benzyl carbamates in acetonitrile in presence of 10 mol% BDMS at room temperature. The present protocol is quite effective for a wide variety of aromatic aldehydes and carbamates. The mild and efficient reaction conditions, good yields and metal-free catalyst are some of the advantages of the present method, which provides a better and practical alternative to the existing protocols. These products can be hydrolyzed using a suitable reagent, which is under investigation. The hydrolyzed product 1-aminomethyl-2-naphthol derivatives may exhibit some pharmacological properties.

PART B

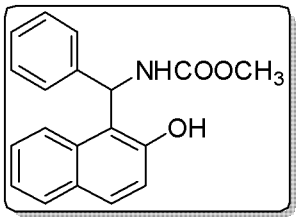
Synthesis of *N*-protected 1-amino-alkyl-2-naphthols through capturing of *in situ* generated *o*-naphthoquinone



General Procedure for preparation of N-protected 1-amino-alkyl-2-naphthols

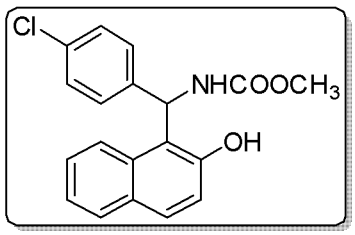
Into a 25 mL of round-bottom flask was dissolved aldehyde (2 mmol), 2-naphthol (2 mmol), and carbamate derivative (2.4 mmol) in 4 mL of acetonitrile. Then the catalyst bromodimethylsulfonium bromide (10 mol%) was added into the above reaction mixture and it was kept for stirring at room temperature until the reaction was complete which was monitored by TLC. The solid precipitate was appeared at the end of the reaction which was filtered off through a Buchner funnel. The product was washed with 5 mL of a mixture of ethanol and hexane (20:80) for removing unreacted aldehyde and 2-naphthol. The pure product was obtained after recrystallization from ethanol.

Methyl N-[(2-hydroxynaphthalen-1-yl)(phenyl)methyl]carbamate (17a):



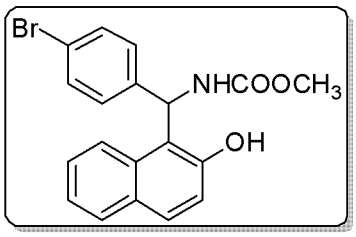
Nature: Colorless solid; M.P. 222-224 °C; **IR (KBr, cm^{-1}):** 3422 (-OH), 3201 (-NH), 1677(-CO); **^{1}H NMR (400 MHz, DMSO-d$_6$):** δ 3.56 (s, 3H), 6.84 (d, *J* = 9.2 Hz, 1H), 7.15-7.29 (m, 7H), 7.38 (t, *J* = 7.6 Hz, 1H), 7.65 (brs, 1H), 7.76 (d, *J* = 8.8 Hz, 1H), 7.80 (d, *J* = 8.0 Hz, 1H), 7.90 (d, *J* = 8.4 Hz, 1H), 10.14 (s, 1H, OH) ; **^{13}C NMR (100 Hz, DMSO-d$_6$):** δ 50.5, 51.8, 118.6, 119.0, 122.7, 123.2, 126.2 (2C), 126.6, 126.7, 128.3 (2C), 128.5, 128.8, 129.5, 132.2, 142.5, 153.0, 156.8; **Anal. Calcd.** For $C_{19}H_{17}NO_3$ (307.34): C, 74.25; H, 5.58; N, 4.56%. Found C, 74.01; H, 5.48; N, 4.42%

Methyl N-[(4-chlorophenyl)(2-hydroxynaphthalen-1-yl)methyl]carbamate (17b):



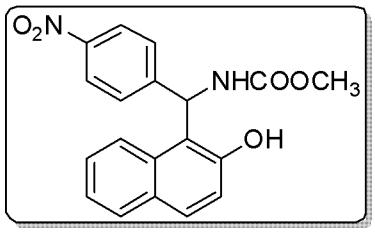
Nature: Colorless solid; M.P. 203-205 °C; **IR (KBr, cm^{-1}):** 3421 (-OH), 3227 (-NH), 1685 (-CO); **^{1}H NMR (400 MHz, DMSO-d$_6$):** δ 3.56 (s, 3H), 6.81 (d, *J* = 8.8 Hz, 1H), 7.19 (d, J = 8.0 Hz, 3H), 7.26 (t, *J* = 7.6 Hz, 1H), 7.30 (d, J = 8.0 Hz, 2H), 7.39 (t, *J* = 7.6 Hz, 1H), 7.70 (bs, 1H), 7.77 (d, *J* = 9.2 Hz, 1H), 7.80 (d, *J* = 8.0 Hz, 1H), 7.86 (bs, 1H), 10.18 (s, 1H, OH); **^{13}C NMR (100 MHz, DMSO-d$_6$):** δ 50.6, 52.4, 119.1 (2C), 123.3, 123.5, 127.3, 128.6 (2C), 128.7 (2C), 129.1, 129.3, 130.2, 131.6, 132.6, 142.1, 153.6, 157.3; **Anal. Calcd.** for $C_{19}H_{16}ClNO_3$ (341.79): C, 66.77; H, 4.72; N, 4.10%. Found C, 66.42; H, 4.68; N, 4.00%.

Methyl N-[(4-bromophenyl)(2-hydroxynaphthalen-1-yl)methyl]carbamate (17c):



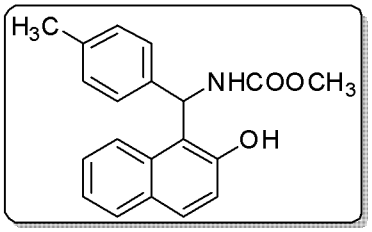
Nature: Colorless solid; M. P. 201-203 °C; **IR (KBr, cm^{-1}):** 3420 (-OH), 3207 (-NH), 1683 (-CO); **^{1}H NMR (400 MHz, DMSO-d_6):** δ 3.57 (s, 3H), 6.83 (d, *J* = 8.4 Hz, 1H), 7.17 (d, *J* = 8.4, 2H), 7.22 (d, *J* = 8.4 Hz, 1H), 7.27 (t, *J* = 7.6 Hz, 1H), 7.39 (t, *J* = 7.6 Hz, 1H), 7.46 (d, *J* = 8.4 Hz, 2H), 7.72 (bs, 1H), 7.77 (d, J = 8.8 Hz, 1H), 7.80 (d, J = 8.0 Hz, 1H), 7.88 (bs, 1H), 10.19 (s, 1H, OH); **^{13}C NMR (100 MHz, DMSO-d_6):** δ 49.9, 51.8, 118.4 (2C), 119.5, 122.6, 123.1, 126.7, 128.4 (2C), 128.7, 129.6, 131.0 (3C), 132.0, 142.0, 153.0, 156.7; **Anal. Calcd.** For $C_{19}H_{16}BrNO_3$ (386.24): C, 59.08; H, 4.18; N, 3.63%. Found C, 58.89; H, 4.12; N, 3.51%.

Methyl N-[(2-hydroxynaphthalen-1-yl)(4-nitrophenyl)methyl]carbamate (17d):



Nature: Pale yellow solid; M. P. 212-214 °C; **IR (KBr, cm^{-1}):** 3395 (-OH), 3326 (-NH), 1686 (-CO), 1517 (NO_2), 1345 (NO_2); **^{1}H NMR (400 MHz, DMSO-d_6):** δ = 3.59 (s, 3H), 6.93 (d, *J* = 8.4 Hz, 1H), 7.20 (d, *J* = 8.8 Hz, 1H), 7.29 (t, *J* = 7.6 Hz, 1H), 7.40 (t, *J* = 8.0 Hz, 1H), 7.45 (d, *J* = 8.8 Hz, 2H), 7.81 (t, *J* = 9.2 Hz, 2H), 7.87 (bs, 2H), 8.15 (d, *J* = 8.8 Hz, 2H), 10. 22 (s, 1H, OH); **^{13}C NMR (100 MHz, DMSO-d_6):** δ 50.2, 51.9, 118.0, 118.4, 122.7, 122.9, 123.4 (2C), 126.9, 127.2 (2C), 128.4, 128.7, 130.0, 132.0, 146.1, 150.8, 153.2, 156.8; **Anal. Calcd.** for $C_{19}H_{16}N_2O_5$ (352.34): C, 64.77; H, 4.58; N, 7.95%. Found C, 64.52; H, 4.51; N, 7.81%

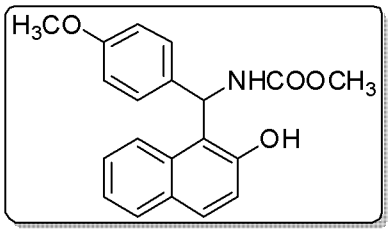
Methyl N-[(2-hydroxynaphthalen-1-yl)(4-methylphenyl)methyl]carbamate (17e):



Nature: Colorless solid; M. P. 183-185 °C; **IR (KBr, cm^{-1}):** 3423 (-OH), 3248 (-NH), 1683 (-CO); **^{1}H NMR (400 MHz, DMSO-d_6):** δ 2.22 (s, 3H), 3.57 (s, 3H), 6.85 (d, *J* = 8.4 Hz, 1H), 7.05 (d, *J* = 8.0 Hz, 2H), 7.12 (d, *J* = 8.0 Hz, 2H), 7.23 (d, *J* = 9.2 Hz, 1H), 7.26 (t, *J* = 7.6 Hz, 1H), 7.38 (t, *J* = 6.4 Hz, 1H), 7.67 (bs, 1H), 7.76 (d, *J* = 8.8 Hz, 1H), 7.80 (d, *J* = 8.0 Hz, 1H), 7.91 (bs, 1H), 10.16 (s, 1H, OH); **^{13}C NMR (100 MHz, DMSO-d_6):** δ

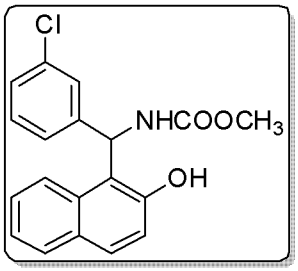
20.6, 50.3, 51.7, 118.5, 119.0, 122.6, 123.2, 126.1 (2C), 126.6, 128.5, 128.7, 128.8 (2C), 129.3, 132.1, 135.5, 139.4, 152.9, 156.7; **Anal. Calcd.** for $C_{20}H_{19}NO_3$ (321.37): C, 74.75; H, 5.96; N, 4.36%. Found C, 74.52; H, 5.91; N, 4.26%.

Methyl N-[(2-hydroxynaphthalen-1-yl)(4-methoxyphenyl)methyl]carbamate (17f):



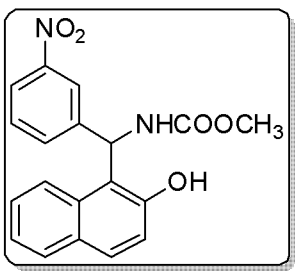
Nature: Colorless solid; M. P. 188-189 °C; **IR (KBr, cm^{-1}):** 3391 (-OH), 3260 (-NH), 1691 (-CO); **^{1}H NMR (400 MHz, CDCl$_3$):** δ 3.69 (s, 3H), 3.74 (s, 3H), 6.85 (d, *J* = 8.4 Hz, 1H), 7.05 (d, *J* = 8.0 Hz, 2H), 7.12 (d, *J* = 8.0 Hz, 2H), 7.23 (d, *J* = 9.2 Hz, 1H), 7.26 (t, *J* = 7.6 Hz, 1H), 7.38 (t, *J* = 6.4 Hz, 1H), 7.67 (bs, 1H), 7.76 (d, *J* = 8.8 Hz, 1H), 7.80 (d, *J* = 8.0 Hz, 1H), 7.91 (bs, 1H); **^{13}C NMR (100 MHz, DMSO-d$_6$):** δ 50.3, 51.7, 55.0, 113.6 (2C), 118.6, 119.1, 122.6, 122.9, 126.6, 127.4 (2C), 128.5, 128.6, 129.3, 132.1, 134.3, 152.9, 156.6, 158.0; **Anal. Calcd.** for $C_{20}H_{19}NO_4$ (337.37): C, 71.20; H, 5.68; N, 4.15%. Found C, 71.01; H, 5.60; N, 4.02%.

Methyl N-[(3-chlorophenyl)(2-hydroxynaphthalen-1-yl)methyl]carbamate (17g):



Nature: Colorless Solid, M. P. 199-200 °C; **IR (KBr, cm^{-1}):** 3417 (-OH), 3294 (-NH), 1689 (-CO); **^{1}H NMR (400 MHz, DMSO-d$_6$):** δ 3.56 (s, 3H), 6.87 (d, *J* = 8.8 Hz, 1H), 7.13 (d, *J* = 7.2 Hz, 1H), 7.20-7.28 (m, 5H), 7.40 (t, *J* = 7.6 Hz, 1H), 7.78 (t, *J* = 9.2 Hz, 3H), 7.92 (d, *J* = 6.0 Hz, 1H), 10.22 (s, 1H, OH); **^{13}C NMR (100 MHz, DMSO-d$_6$):** δ 50.1, 51.8, 118.3, 118.5, 122.7, 123.0, 124.9, 125.8, 126.5, 126.8, 128.4, 128.7, 129.7, 130.1, 132.0, 133.0, 145.2, 153.1, 156.7; **Anal. Calcd.** for $C_{19}H_{16}ClNO_3$ (341.79): C, 66.77; H, 4.72; N, 4.10%. Found C, 66.58; H, 4.67; N, 4.01%.

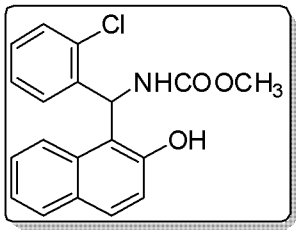
Methyl N-[(2-hydroxynaphthalen-1-yl)(3-nitrophenyl)methyl]carbamate (17h):



Nature: Pale yellow solid; M. P. 250-251 °C; **IR (KBr, cm^{-1}):** 3388 (-OH), 3291 (-NH), 1685 (-CO), 1523 (NO_2), 1345 (NO_2); **^{1}H NMR (400 MHz, DMSO-d$_6$):** δ 3.66 (s, 3H), 6.97 (d, *J* = 8.4 Hz, 1H), 7.23 (d, *J* = 9.2 Hz, 1H), 7.29 (t, *J* = 7.2 Hz, 1H), 7.43 (t, *J* = 7.6 Hz, 1H), 7.55 (t, *J* = 8.0 Hz, 1H),

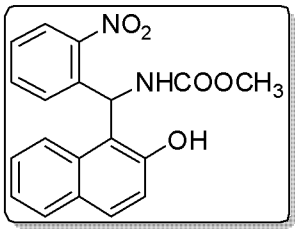
7.63 (d, *J* = 8.0 Hz, 1H), 7.82 (t, *J* = 6.8 Hz, 2H), 7.96 (d, *J* = 6.8 Hz, 2H), 8.06 (d, *J* = 8.0 Hz, 1H), 8.12 (s, 1H), 10.29 (bs, 1H, OH); **^{13}C NMR (100 MHz, DMSO-d$_6$):** δ 50.1, 51.9, 118.0, 118.5, 120.6 (2C), 121.6, 122.8, 127.0, 128.4, 128.8, 129.8, 130.0, 132.0, 132.9, 145.1, 147.8, 153.2, 156.8; **Anal. Calcd.** for $C_{19}H_{16}N_2O_5$ (352.34): C, 64.77; H, 4.58; N, 7.95%. Found C, 64.80; H, 4.51; N, 7.77%.

Methyl N-[(2-chlorophenyl)(2-hydroxynaphthalen-1-yl)methyl]carbamate (17i):



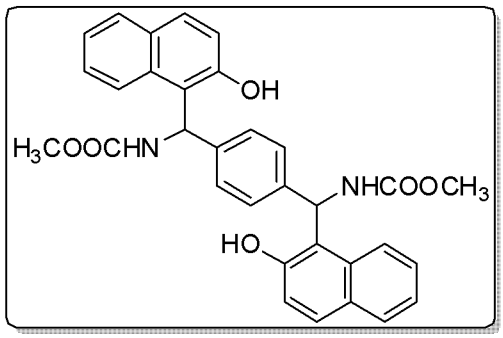
Nature: Colorless solid; M. P. 237-238 °C; **IR (KBr, cm^{-1}):** 3431 (-OH), 3217 (-NH), 1689 (-CO); **^{1}H NMR (400 MHz, DMSO-d$_6$):** δ 3.54 (s, 3H), 6.89 (d, *J* = 8.4 Hz, 1H), 7.14 (d, *J* = 8.8 Hz, 1H), 7.20-7.27 (m, 3H), 7.35-7.42 (m, 2H), 7.49-7.51 (m, 1H), 7.74 (d, *J* = 8.8 Hz, 1H), 7.78 (d, *J* = 8.0 Hz, 1H), 7.86 (d, *J* = 8.4 Hz, 1H), 8.02 (d, *J* = 8.8 Hz, 1H), 9.96 (bs, 1H, OH); **^{13}C NMR (100 MHz, DMSO-d$_6$):** δ 49.8, 51.6, 117.0, 118.6, 122.4, 123.0, 126.4, 126.6, 128.3, 128.5, 128.7, 129.4, 129.6, 130.0, 132.6, 132.7, 139.4, 153.6, 156.2; **Anal. Calcd.** for $C_{19}H_{16}NO_3$ (341.79): C, 66.77; H, 4.72; N, 4.10%. Found C, 66.58; H, 4.80; N, 4.79%.

Methyl N-[(2-hydroxynaphthalen-1-yl)(2-nitrophenyl)methyl]carbamate (17j):



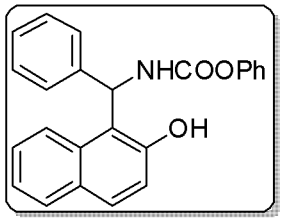
Nature: Pale yellow solid; M. P. 234-236 °C; **IR (KBr, cm^{-1}):** 3398 (-OH), 3298 (-NH), 1694 (-CO), 1529 (NO_2), 1335 (NO_2); **^{1}H NMR (400 MHz, DMSO-d$_6$):** δ 3.57 (s, 3H), 7.09 (d, *J* = 8.8 Hz, 1H), 7.28 (d, J = 7.2 Hz, 1H), 7.31 (d, J = 8.0 Hz, 1H), 7.42-7.49 (m, 2H), 7.60-7.66 (m, 2H), 7.73 (d, *J* = 8.8 Hz, 1H), 7.76 (d, *J* = 7.2 Hz, 1H), 7.80 (d, *J* = 8.0 Hz, 1H), 7.94 (d, *J* = 8.8 Hz, 1H), 7.99 (d, 1H), 9.88 (s, 1H, OH); **^{13}C NMR (100 MHz, DMSO-d$_6$):** δ 47.9, 51.8, 116.2, 118.5, 122.6, 122.7, 124.2, 126.7, 127.9, 128.2, 128.6, 129.1, 130.1, 132.3, 133.0, 136.5, 148.7, 153.8, 156.6; **Anal. Calcd.** for $C_{19}H_{16}N_2O_5$ (352.34): requires C, 64.77; H, 4.58; N, 7.95%. Found C, 64.71; H, 4.52; N, 7.85%.

Bis product (17k)



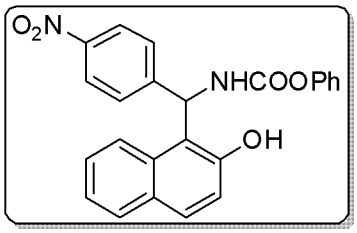
Nature: Colorless solid; M. P. 271-273 °C; **IR (KBr, cm^{-1}):** 3411 (-OH), 3204 (-NH), 1695 (-CO); **^{1}H NMR (400 MHz, DMSO-d$_6$):** δ 3.54 (s, 6H), 6.78 (d, *J* = 7.6 Hz, 2H), 7.12 (s, 4H), 7.16-7.20 (m, 2H), 7.25 (t, *J* = 7.2 Hz, 2H), 7.36 (bs, 2H), 7.65 (bs, 2H), 7.74 (d, *J* = 8.8 Hz, 2H), 7.78 (d, *J* = 8.0 Hz, 2H), 7.89 (bs, 2H), 10.12 (s, 2H, OH); **^{13}C NMR (100 MHz, DMSO-d$_6$):** δ 50.3 (2C), 51.7 (2C), 118.5 (2C), 118.8 (2C), 122.6 (2C), 123.1 (2C), 126.0 (4C), 126.6 (2C), 128.4 (2C), 128.6 (2C), 129.3 (2C), 132.1 (2C), 140.5 (2C), 152.9 (2C), 156.5 (2C); **Anal. Calcd.** for $C_{32}H_{28}N_2O_6$ (536.57): requires C, 71.63; H, 5.26; N, 5.22%. Found C, 71.43; H, 5.21; N, 5.08%.

Phenyl N-[(2-hydroxynaphthalen-1-yl)(phenyl)methyl]carbamate (17l):



Nature: Colorless solid; M. P. 153-155 °C; **IR (KBr, cm^{-1}):** 3376 (-OH & -NH), 1711 (-CO); **^{1}H NMR (400 MHz, DMSO):** δ 6.92 (d, *J* = 8.4 Hz, 1H), 7.12 (d, *J* = 7.6 Hz, 2H), 7.18 (t, *J* = 6.8 Hz, 2H), 7.25 (d, *J* = 8.8 Hz, 2H), 7.26-7.29 (bs, 4H), 7.35 (t, *J* = 8.0 Hz, 3H), 7.80 (t, *J* = 9.2 Hz, 2H), 7.91 (d, *J* = 8.0 Hz, 1H), 8.33 (d, *J* = 6.8 Hz, 1H), 10.18 (s, 1H, OH); **^{13}C NMR (100 MHz, DMSO):** δ 50.67, 118.5, 121.9 (2C), 122.6, 123.2, 125.1, 126.2 (2C), 126.6 (2C), 128.3 (2C), 128.5, 128.7, 129.3 (2C), 129.6, 132.1, 142.0, 151.1, 153.1, 154.5; **Anal. Calcd.** for $C_{24}H_{19}NO_3$ (369.41): C, 78.03; H, 5.18; N, 3.79. Found C, 77.84; H, 5.11; N, 3.63%.

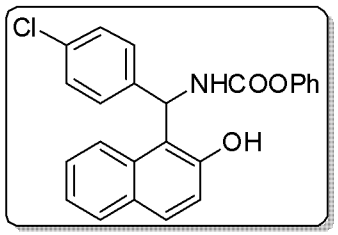
Phenyl N-[(2-hydroxynaphthalen-1-yl)(4-nitrophenyl)methyl]carbamate (17m):



Nature: Pale yellow solid; M.P. 192-194 °C; **IR (KBr, cm^{-1}):** 3318 (-OH & -NH), 1701 (-CO), 1516 (NO_2), 1346 (NO_2); **^{1}H NMR (400 MHz, DMSO-d$_6$):** δ 7.00 (d, *J* = 8.4 Hz, 1H), 7.16 (d, *J* = 7.6 Hz, 2H), 7.20 (d, *J* = 8.4 Hz, 1H), 7.24 (d, *J* = 8.8 Hz, 1H), 7.30 (t, *J* = 7.6 Hz, 1H), 7.38 (t, *J* = 7.6 Hz, 2H), 7.42 (d, *J* = 8.4 Hz, 1H), 7.55 (d, *J* = 8.8 Hz, 2H), 7.83 (d,

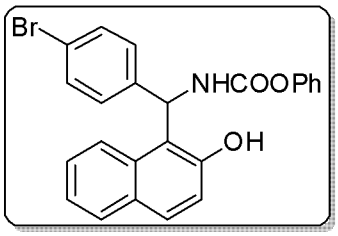
J = 8.8 Hz, 1H), 7.84 (d, *J* = 7.6 Hz, 1H), 7.89 (bs, 1H), 8.18 (d, *J* = 8.8 Hz, 2H), 8.58 (d, *J* = 6.8 Hz, 1H), 10. 29 (s, 1H, OH); **^{13}C NMR (100 MHz, DMSO-d$_6$):** δ 50.4, 117.5, 118.4, 121.9 (2C), 122.7, 123.0, 123.5 (2C), 125.3, 126.9, 127.3 (2C), 128.5, 128.8, 129.4 (2C), 130.2, 132.0, 146.2, 150.3, 151.0, 153.3, 154.7; **Anal. Calcd.** $C_{24}H_{18}N_2O_5$ (414.41): C, 69.56; H, 4.38; N, 6.76%. Found C, 69.38; H, 4.30; N, 6.58%.

Phenyl N-[(4-chlorophenyl)(2-hydroxynaphthalen-1-yl)methyl]carbamate (17n):



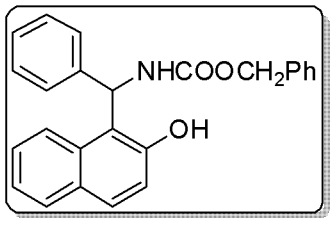
Nature: Colorless solid; M.P. 174-175 °C; **IR (KBr, cm^{-1}):** 3419 (-OH), 3226 (-NH), 1698 (-CO); **^{1}H NMR (400 MHz, DMSO):** δ 6.92 (d, *J* = 8.4 Hz, 1H), 7.14 (d, *J* = 8.4 Hz, 2H), 7.20 (d, *J* = 7.2 Hz, 1H), 7.28 (d, *J* = 9.2 Hz, 2H), 7.30-7.42 (m, 7H), 7.82 (t, *J* = 8.4 Hz, 2H), 7.91 (d, *J* = 6.8 Hz, 1H), 8.4 (bs, 1H), 10.27 (s, 1H, OH); **^{13}C NMR (100 MHz, DMSO):** δ 50.2, 118.0, 118.5, 121.9 (2C), 122.7, 123.1, 125.2, 126.7, 128.1 (2C), 128.2 (2C), 128.5, 128.7, 129.3 (2C), 129.8, 131.2, 132.0, 141.1, 151.1, 153.2, 154.5; **Anal. Calcd.** for $C_{24}H_{18}ClNO_3$ (403.86): C, 71.38; H, 4.49; N, 3.47%. Found C, 71.19; H, 4.40; N, 3.36%.

Phenyl N-[(4-bromophenyl)(2-hydroxynaphthalen-1-yl)methyl]carbamate (17o):



Nature: Colorless solid; M.P. 170-172 °C; **IR (KBr, cm^{-1}):** 3419 (-OH), 3203 (-NH), 1698 (-CO); **^{1}H NMR (400 MHz, DMSO):** δ 6.89 (d, *J* = 7.6 Hz, 1H), 7.12 (d, *J* = 7.2 Hz, 1H), 7.19 (t, *J* = 7.2 Hz, 1H), 7.21-7.42 (m, 8H), 7.48 (d, *J* = 6.8 Hz, 2H), 7.81 (t, *J* = 7.6 Hz, 2H), 7.90 (bs, 1H), 8.35 (bs, 1H), 10.32 (s, 1H, OH); **^{13}C NMR (100 MHz, DMSO):** δ 50.4, 118.1, 118.6, 119.8, 122.0 (2C), 122.9, 123.1, 125.4, 126.9, 128.5 (2C), 128.6, 128.9, 129.5 (2C), 130.0, 131.3 (2C), 132.1, 141.6, 151.1, 153.3, 154.7; **Anal. Calcd.** for $C_{24}H_{18}BrNO_3$ (448.31): C, 64.30; H, 4.05; N, 3.12%. Found C, 64.12; H, 3.96; N, 3.01%.

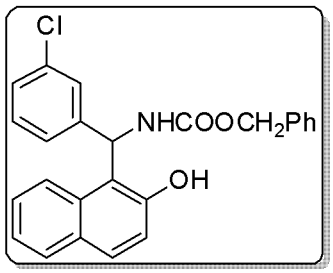
Benzyl N-[(2-hydroxynaphthalen-1-yl)(phenyl)methyl]carbamate (17p):



Nature: Colorless solid; M.P. 186-187 °C; **IR (KBr, cm^{-1}):** 3423 (-OH), 3201 (-NH), 1676 (-CO); **^{1}H NMR (400 MHz, DMSO-d$_6$):** δ 5.05 (d, *J* = 12.8 Hz, 1H), 5.11 (d, *J* =

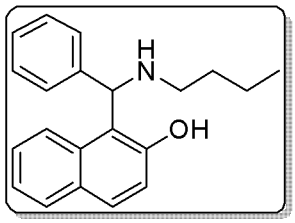
12.4 Hz, 1H), 6.93 (d, J = 8.4 Hz, 1H), 7.17 (bs, 1H), 7.21-7.41 (m, 12H), 7.79 (t, J = 9.6 Hz, 2H), 7.85 (bs, 1H), 7.92 (bs, 1H), 10.20 (s, 1H, OH); **^{13}C NMR (100 MHz, DMSO-d$_6$):** δ 50.4, 65.8, 118.5, 118.9, 122.6, 123.2, 126.1 (3C), 126.5, 126.6, 127.9 (2C), 128.2 (3C), 128.5 (2C), 128.7, 129.5, 132.1, 137.1, 142.4, 153.0, 156.2; **Anal. Calcd.** for $C_{25}H_{21}NO_3$ (383.44): C, 78.31; H, 5.52; N, 3.65%. Found C, 78.05; H, 5.60; N, 3.51%.

Benzyl N-[(3-chlorophenyl)(2-hydroxynaphthalen-1-yl)methyl]carbamate (17q):



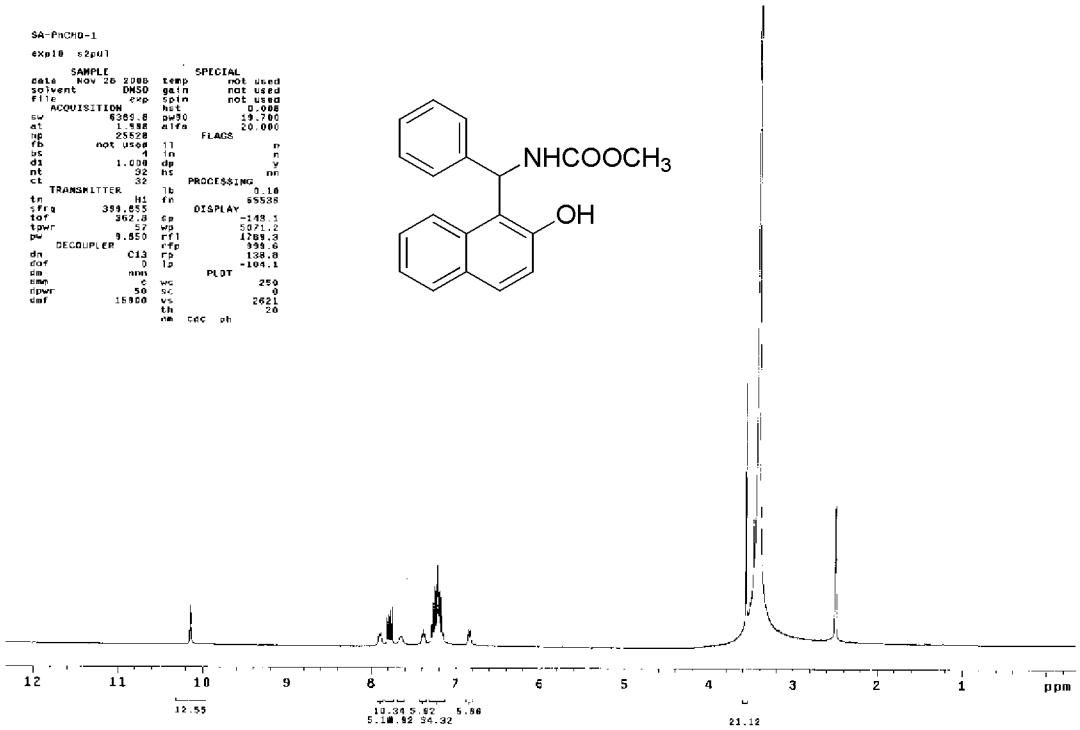
Nature: Colorless solid; M.P. 185-187 °C; **IR (KBr, cm^{-1}):** 3412 (-OH), 3324 (-NH), 1682 (-CO); **^{1}H NMR (400 MHz, DMSO-d$_6$):** δ 5.05 (d, J = 12.4 Hz, 1H), 5.11 (d, J = 12.4 Hz, 1H), 6.93 (d, J = 8.0 Hz, 1H), 7.16 (d, J = 6.8 Hz, 1H), 7.21-7.42 (m, 11H), 7.80 (t, J = 9.2 Hz, 2H), 7.94 (bs, 2H), 10.26 (s, 1H, OH); **^{13}C NMR(100 MHz, DMSO-d$_6$):** δ 50.1, 65.9, 118.3, 118.5, 122.7, 123.0, 124.9, 125.8, 126.5, 126.8, 127.9 (2C), 128.0, 128.5 (3C), 128.7, 129.8, 130.1, 132.0, 133.0, 137.0, 145.2, 153.1, 156.2; **Anal. Calcd.** for $C_{25}H_{20}ClNO_3$ (417.88): C, 71.85; H, 4.82; N, 3.35%. Found C, 71.66; H, 4.74; N, 3.22%.

1-[(butylamino)(phenyl)methyl]naphthalen-2-ol (17r):



Nature: Colorless solid; M.P. °C; **IR (KBr, cm^{-1}):** 3436 (-OH), 3313 (-NH); **^{1}H NMR (400 MHz, DMSO-d$_6$):** δ 0.82 (t, J = 7.2 Hz, 3H), 1.25-1.29 (m, 2H), 1.47-1.54 (m, 2H), 2.55 (dt, J_1 = 12.0 Hz, J_2 = 6.0 Hz, 1H), 2.69 (dt, J_1 = 12.0 Hz, J_2 = 6.0 Hz, 1H), 5.69 (s, 1H), 7.03 (d, J = 8.8 Hz, 2H), 7.20 (t, J = 7.2 Hz, 2H), 7.28 (t, J = 7.2 Hz, 2H), 7.34 (t, J = 7.2 Hz, 1H), 7.50 (d, J = 7.6 Hz, 2H), 7.69 (d, J = 9.2 Hz, 1H), 7.73 (d, J = 8.0 Hz, 1H), 7.84 (d, J = 8.4 Hz, 1H); **^{13}C NMR (100 MHz, DMSO-d$_6$):** δ 14.0, 20.2, 30.9, 48.1, 62.8, 115.0, 120.1, 121.5, 122.3, 126.0, 127.8, 128.0 (2C), 128.1, 128.8 (3C), 129.3, 132.4, 142.2, 157.0; **Anal. Calcd.** for $C_{21}H_{23}NO$ (305.41): C, 82.58; H, 7.59; N, 4.59%. Found C, 82.39; H, 7.65; N, 4.46%.

^{1}H NMR (400 MHz, $CDCl_3$): *Methyl (2-hydroxynaphthalen-1-yl)(phenyl)methylcarbamate* ***(17a)***



^{13}C NMR (100 MHz, $CDCl_3$): *Methyl (2-hydroxynaphthalen-1-yl)(phenyl)methylcarbamate* ***(17a)***

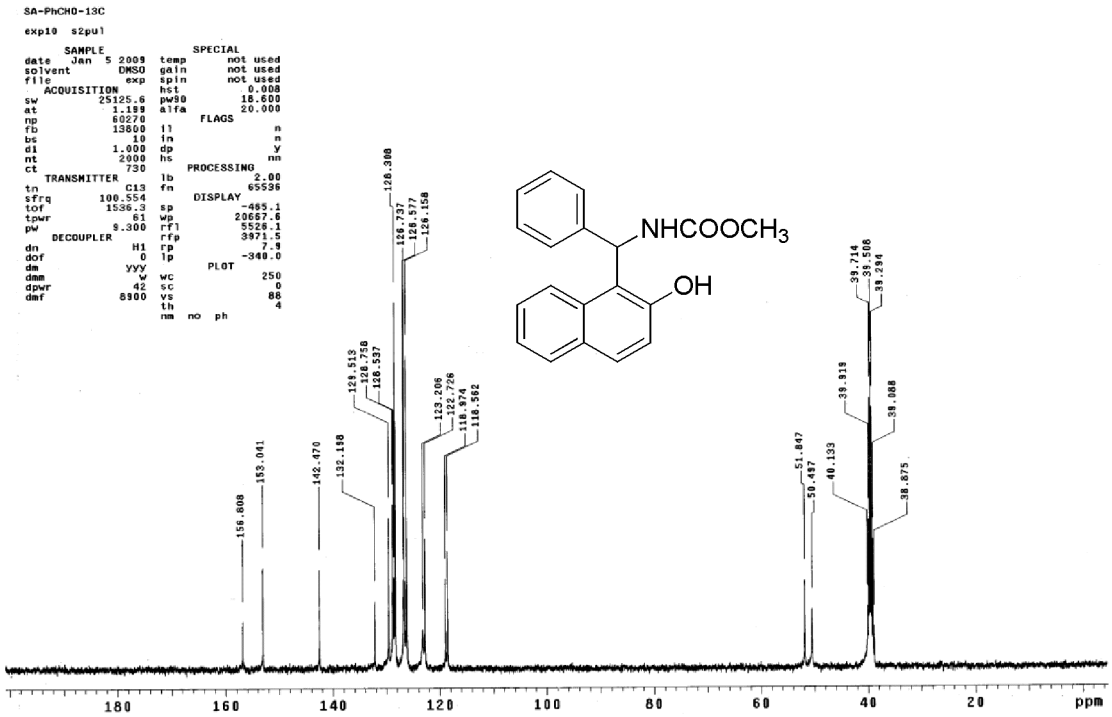
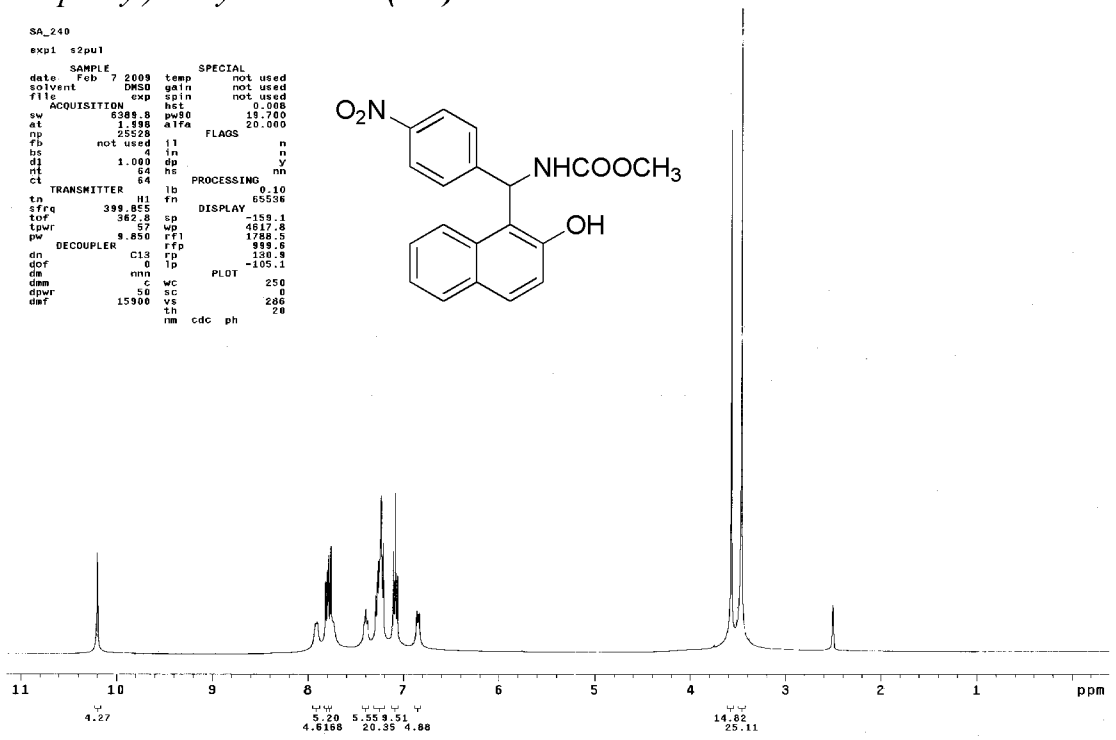


Figure 7

^{1}H NMR (400 MHz, $CDCl_3$): *Methyl (2-hydroxynaphthalen-1-yl)(4-nitrophenyl)methylcarbamate* ***(17d)***



^{13}C NMR (100 MHz, $CDCl_3$): *Methyl ((2-hydroxynaphthalen-1-yl)(4-nitrophenyl)methyl)carbamate* ***(17d)***

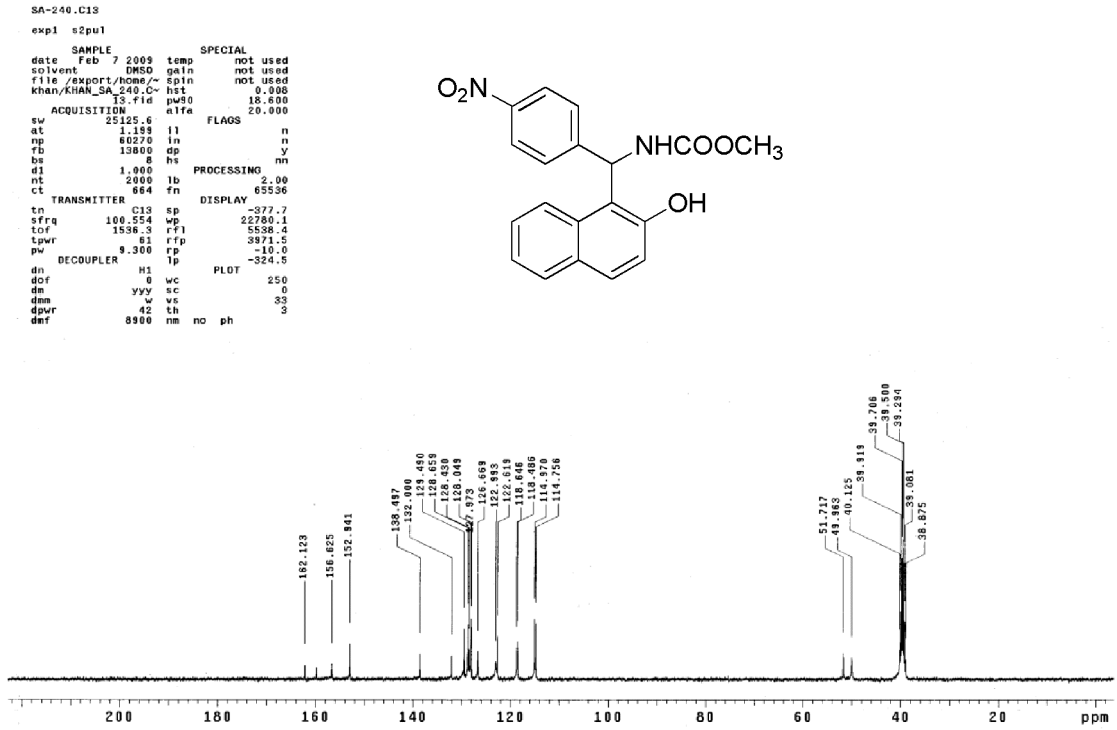
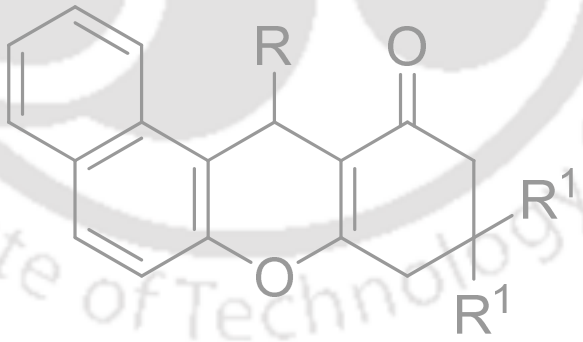


Figure 8

PART B

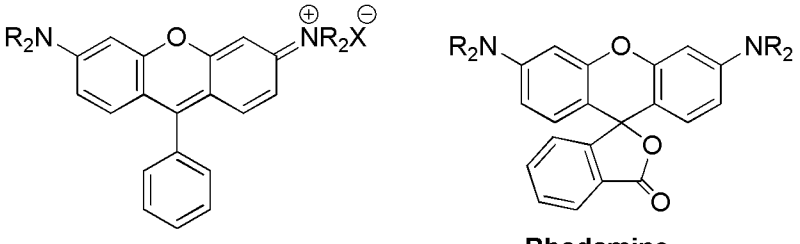
Synthesis of unsymmetrical xanthene derivatives by trapping of *o*-naphthoquinone methide with cyclic 1,3-dikeones



The usefulness and trapping of *o*-naphthoquinone methide intermediate, which is generated *in situ* from 2-naphthol and aromatic aldehyde, has been demonstrated for the synthesis of 1-[(alkylthio)(phenyl) methyl]-naphthalene-2-ol and N-protected 1-amino-alkyl-2-naphthols. In the Chapter 2 and 3 of Part B, we have shown that *in situ* generated *o*-naphthoquinone methide intermediate is a useful Michael acceptor, which reacts with sulfur and nitrogen containing nucleophiles. It is also well established from the literature that it may react with dimedone or 1,3-cyclohexadione to synthesize xanthenes derivatives as they have inherent ability to act C-nucleophile.

The synthesis of tetrahydrobenzo[a]xanthen-11-ones derivatives has been reported by employing various catalysts, which is already mentioned in Chapter 1 of Part B. Some of these synthetic methods are quite useful and provided good yields but they have some demerits such as long reaction time, harsh reaction conditions and often require of expensive catalysts. Furthermore, the synthesis has been usually carried out in solvent leading to complex isolation and recovery of final products. Consequently, there is a scope of further improvement towards lower reaction time & improved yields.

Xanthenes and their derivatives have attracted considerable attention over the years due to their diverse biological properties such as antiviral,[73] anti-inflammatory[74] and antibacterial activities[75] as well as their use as dyes[76] and fluorescent materials[77] (Fig. 9).



Rosamine Rhodamine

Figure 9

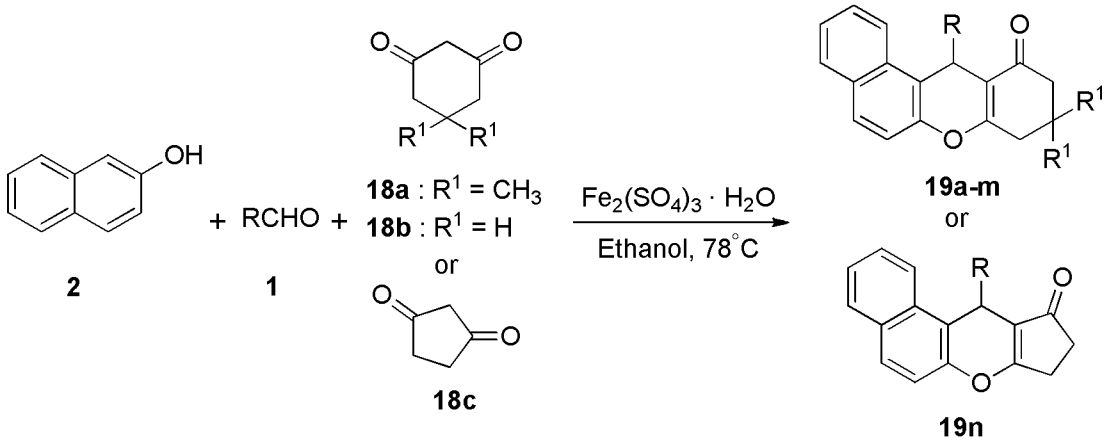
These compounds have also been utilized as antagonist for the paralyzing action of zoxazolamine[78] and in photodynamic therapy (PDT).[79,80]

Iron is an abundant, cheap and benign element which exists in nature, and one of its salt e.g. ferric sulfate hydrate has been used recently in many organic reactions. Because of its specific catalytic properties, it has been used in various organic transformations such as the preparation of acylals from aldehydes,[81] per-*O*-acylation of

sugars,[82] *O*-glycosylation using glycols,[83] esterifcation of free fatty acids in waste cooking oils,[84] conversion of waste cooking oil to biodiesel[85] and multi-component reaction.[86] It has received considerable attention due to its low toxicity, cost effectiveness, air and water compatibility, ease of handling, good reactivity and experimental simplicity. In this Chapter, we would like to discuss ferric sulfate as an effective catalyst for the synthesis of unsymmetrical xanthene derivatives involving one-pot three-component reaction starting from aldehydes, 2-naphthol and 1,3-cyclic dicarbonyl compounds at room temperature.

To optimize the reaction conditions, the reaction of benzaldehyde (1 equiv), 2-naphthol (1 equiv), and dimedone (1.1) was refluxed in the presence of $Fe_2(SO_4)_3.xH_2O$ in ethanol. The best result was obtained by carrying out the reaction using 15 mol % of $Fe_2(SO_4)_3.xH_2O$ (Table 5). From this observation, it is clear that $Fe_2(SO_4)_3.xH_2O$ plays an important role in the formation of the product.

The reaction was investigated in presence of three other catalysts namely $SnCl_2.2H_2O$, $NiCl_2.6H_2O$ and TBATB. The best suited catalyst for this reaction is ferric sulfate hydrate. When 15 mol % $Fe_2(SO_4)_3.H_2O$ was used, the reaction proceeded smoothly and yield was 75% (Table 5, entry 4). Moreover, we found that the conversion was obviously affected by the amount of $Fe_2(SO_4)_3.H_2O$ loaded. When 0 mol %, 10 mol %, and 20 mol % of $Fe_2(SO_4)_3 \cdot H_2O$ were used, the yield was 0%, 21%, 45% and 76% respectively (Table 5, entries 1-3 and 5). Therefore, 15 mol % of $Fe_2(SO_4)_3 \cdot H_2O$ was sufficient to carry out the reaction, and further increasing the amount of $Fe_2(SO_4)_3.H_2O$ did not increase the yield.



Scheme 30: $Fe_2(SO_4)_3.H_2O$ catalyzed condensation of aldehyde, 2-naphthol and 1,3-dicarbonyl compounds.

The role of solvent in this reaction was studied carrying out reaction in various solvents such ethanol, acetonitrile, 1,2-dichloroethane and water. It was found that ethanol is the most suitable solvent for this reaction.

Table 5:-Optimization for reaction conditions

Entry	Catalyst	Catalyst amount(mol%)	Solvent	Time (h)	Yield[a] (%)
1	No Catalyst	0	Ethanol	7	0
2	$Fe_2(SO_4)_3.xH_2O$	5	Ethanol	7	21
3	$Fe_2(SO_4)_3.xH_2O$	10	Ethanol	7	45
4	$Fe_2(SO_4)_3.xH_2O$	15	Ethanol	7	75
5	$Fe_2(SO_4)_3.xH_2O$	20	Ethanol	7	76
6	$SnCl_2.2H_2O$	15	Ethanol	7	59
7	$NiCl_2.6H_2O$	15	Ethanol	7	50
8	TBATB	15	Ethanol	7	65
9	$Fe_2(SO_4)_3.xH_2O$	15	DCE	7	70
10	$Fe_2(SO_4)_3.xH_2O$	15	Acetonitrile		68
11	$Fe_2(SO_4)_3.xH_2O$	15	Water	7	5
12	$Fe_2(SO_4)_3.xH_2O$	15	No solvent	7	50

[a]Isolated yield

Among various solvents, acetonitrile, dichloroethane and water gave relatively low yields. The reaction could be carried out under solvent-free conditions and gave low yield. Finally, when ethanol was used, the yield increased to 75% better than any other solvents checked here (Table 5). The product **19a** was characterized by recording melting point, IR, ^{1}H and ^{13}C NMR, and elemental analysis. In ^{1}H NMR spectrum, it shows signals at δ 0.96 (s, 3H), 1.11 (s, 3H), 2.24 (d, J = 16.4 Hz, 1H), 2.30 (d, J = 16.4 Hz, 1H), 2.56 (s, 2H), 5.71 (s, 1H), 7.04 (t, J = 8.0 Hz , 1H), 7.16 (t, J = 7.8 Hz, 2H), 7.31-7.44 (m, 4H), 7.42 (t, J = 6.8 Hz, 1H), 7.76 (t, J = 8.0 Hz, 2H), and 7.99 (d, J = 8.4 Hz, 1H) ppm. The signals at 0.96, 1.11, 2.24, 2.30, 2.56 and 5.71 clearly indicate the formation of 9,10-dihydro-9,9-dimethyl-12-phenyl-8H-benzo[a]xanthen-11(12H)-one. Similarly, ^{13}C NMR spectrum shows peaks at δ 27.2, 29.4, 32.3, 34.8, 41.5, 51.0, 114.4, 117.2, 117.8, 123.8, 125.0, 126.4, 127.1, 128.4 (2C), 128.5, 128.6 (2C), 129.0,

131.5, 131.6, 144.9, 147.9, 164.0, and 197.0 ppm. The spectral data were compared with earlier reported data and found to be in good agreement.[41,42]

The scope, generality and efficacy of the protocol were further examined for the synthesis of a wide variety of substituted tetrahydrobenzo[a]xanthen-11-ones by employing various aryl/alkyl aldehydes, 2-naphthol, and dimedone/1,3-cyclohexadione. In order to study the generality of this procedure, a series of aldehydes and 1,3-dicarbonyl compounds were used (Scheme 28, Table 6). In all the cases, aromatic aldehydes substituted with either electron-donating or electron-withdrawing groups underwent the reaction smoothly and provided the desired products in good yields. It also be concluded that the aldehydes bearing electron- withdrawing groups required shorter time and high yields (Table 6). The ^{1}H NMR and ^{13}C NMR Spectra of compounds **19a** and **19b** are given in Figure 10 and 11 in the experimental section, respectively.

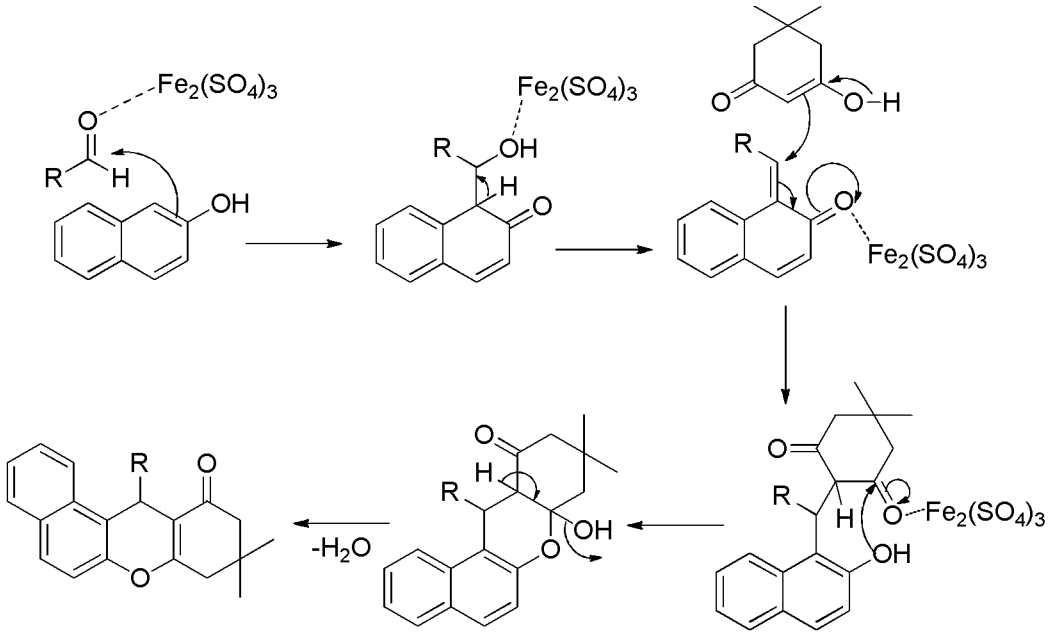
Table 6: $Fe_2(SO_4)_3 \cdot xH_2O$ catalyzed condensation of aldehyde, 2-naphthol and 1,3-dicarbonyl compounds

Entry	Aldehyde	1,3-Dicarbonyl compound	Product	Time/h	Yield/%[a]
1	PhCHO	**18a**	**19a**	6.0	77
2	*p*-$NO_2C_6H_4CHO$	**18a**	**19b**	4.0	89
3	*m*-$NO_2C_6H_4CHO$	**18a**	**19c**	4.0	87
4	*p*-ClC_6H_4CHO	**18a**	**19d**	4.5	88
5	*p*-BrC_6H_4CHO	**18a**	**19e**	4.5	87
6	*p*-$MeOC_6H_4CHO$	**18a**	**19f**	7.0	65
7	*p*-MeC_6H_4CHO	**18a**	**19g**	7.0	71
8	*p*-HOC_6H_4CHO	**18a**	**19h**	7.0	63
9	$CH_3(CH_2)_2CHO$	**18a**	**19i**	7.0	66
10	PhCHO	**18b**	**19j**	6.0	75
11	*p*-$NO_2C_6H_4CHO$	**18b**	**19k**	4.0	86

12	*p*-ClC_6H_4CHO	**18b**	**19l**	4.5	85
13	p.MeC_6H_4CHO	**18b**	**19m**	7.0	70
14	PhCHO	**18c**	**19n**	6.0	73

[a]Isolated yield

The probable mechanism is shown in Scheme 29. In 2-naphthol the electron density at the benzylic C-1 position is higher than at the C-3 position due to conjugation with aromatic ring. Therefore, the formation of *ortho*-quinone methides from 2-naphthol and aldehyde involving aforementioned two positions is favored.

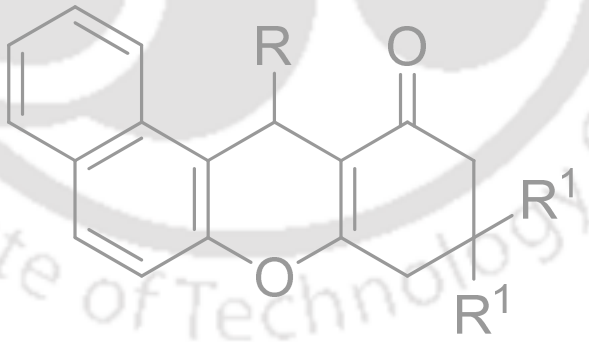


Scheme 31: Probable mechanism for the formation of final product

In conclusion, we have described an efficient and mild method for the preparation of 8,9,10,12-tetrahydrobenzo[a]xanthen-11-ones. This reaction efficiently catalyzed by the ferric sulfate hydrate. Unlike other existing methods, the advantages of this method include the use of cheap catalyst, high yields, simple work up, and easy isolation procedure.

PART B

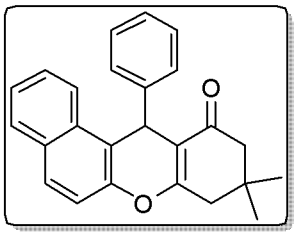
Synthesis of unsymmetrical xanthene derivatives by trapping of *o*-naphthoquinone methide with cyclic 1,3-dikeones



Typical procedure for the preparation of xanthenes derivatives

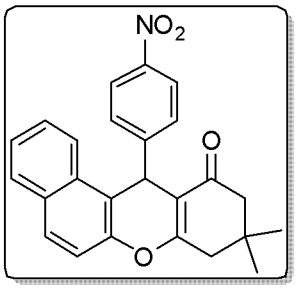
To a mixture of aldehyde (1.0 mmol), 2-naphthol (1.0 mmol), and cyclic 1,3-dicarbonyl compounds (1.1 mmol), ferric sulfate hydrate (0.15 mmol) was added in ethanol (3 ml). The mixture was stirred at 78°C. The reaction was monitored by TLC. After completion of the reaction, water was added and the product was extracted with ethylacetate (3*25 ml). The organic layer was dried over Na_2SO_4.and evaporated, and the crude product was purified by column chromatography (ethyl acetate/hexane, 1:20) to provide the pure product.

9,10-dihydro-9,9-dimethyl-12-phenyl-8*H*-benzo[a]xanthen-11(12*H*)-one (19a)



Nature: White solid; M.P. 156-158 ^{0}C; **IR (KBr, cm^{-1}):** 1650 (-CO); **^{1}H NMR (400 MHz, $CDCl_3$):** δ 0.96 (s, 3H), 1.11 (s, 3H), 2.24 (d, *J* = 16.4 Hz, 1H), 2.30 (d, *J* = 16.4 Hz, 1H), 2.56 (s, 2H), 5.71 (s, 1H), 7.04 (t, *J* = 8.0 Hz , 1H), 7.16 (t, *J* = 7.8 Hz, 2H), 7.31-7.44 (m, 4H), 7.42 (t, *J* = 6.8 Hz, 1H), 7.76 (t, *J* = 8.0 Hz, 2H) 7.99 (d, *J* = 8.4 Hz, 1H) ppm; **^{13}C NMR (100 Hz, $CDCl_3$):** δ 27.2, 29.4, 32.3, 34.8, 41.5, 51.0, 114.4, 117.2, 117.8, 123.8, 125.0, 126.4, 127.1, 128.4 (2C), 128.5, 128.6 (2C), 129.0, 131.5, 131.6, 144.9, 147.9, 164.0, 197.0 ppm; **Anal. Calcd.** for $C_{25}H_{22}O_2$ (354.44): C, 84.72; H, 6.26%. Found C, 84.61; H, 6.19%.

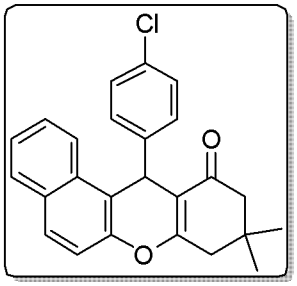
9,10-dihydro-9,9-dimethyl-12-(4-nitrophenyl)-8*H*-benzo[a]xanthen-11(12*H*)-one (19b)



Nature: Pale yellow solid; M.P. 182-183 ^{0}C; **IR (KBr, cm^{-1}):** 1646 (-CO), 1516 (-NO_2), 1345 (-NO_2); **^{1}H NMR (400 MHz, $CDCl_3$):** δ 0.95 (s, 3H), 1.13 (s, 3H), 2.23 (d, *J* = 16.4 Hz, 1H), 2.34 (d, *J* = 16.4 Hz, 1H), 2.60 (s, 2H), 5.82 (s, 1H), 7.36 (d, *J* = 8.8 Hz , 1H), 7.39-7.47 (m, 2H), 7.52 (d, *J* = 8.8 Hz, 2H), 7.81 (d, *J* = 8.8 Hz, 1H), 7.82 (d, *J* = 8.8 Hz, 1H), 7.83 (d, *J* = 8.0 Hz, 1H), 8.04 (d, *J* = 8.4 Hz, 2H) ppm; **^{13}C NMR (100 Hz, $CDCl_3$):** δ 27.2, 29.5, 32.4, 35.0, 41.5, 50.9, 113.1, 116.2, 117.3, 123.3, 123.8 (2C), 125.4, 127.5, 128.8, 129.5 (2C), 129.8, 131.2, 131.7, 146.5, 147.9, 152.1, 164.8, 196.9 ppm; **Anal. Calcd.**

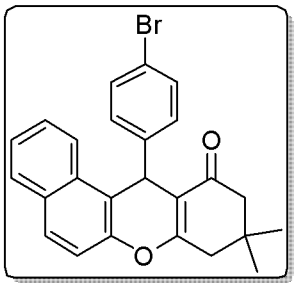
for $C_{25}H_{21}NO_4$ (399.44): C, 75.17; H, 5.30, N, 3.51%. Found C, 74.97; H, 5.21; N 3.39%.

12-(4-chlorophenyl)-9,10-dihydro-9,9-dimethyl-8*H*-benzo[a]xanthen-11(12*H*)-one (19c)



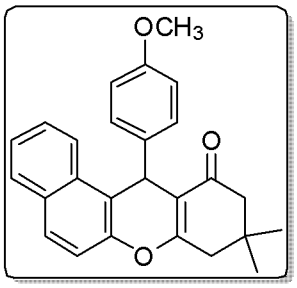
Nature: White solid; M.P. 178-179 ^{0}C; **IR (KBr, cm^{-1}):** 1647 (-CO); **^{1}H NMR (400 MHz, $CDCl_3$):** δ 0.97 (s, 3H), 1.12 (s, 3H), 2.24 (d, *J* = 16.4 Hz, 1H), 2.32 (d, *J* = 16.4 Hz, 1H), 2.57 (s, 2H), 5.68 (s, 1H), 7.13 (d, *J* = 8.4 Hz , 2H), 7.27 (d, *J* = 8.4 Hz , 2H), 7.33 (d, *J* = 8.8 Hz , 1H), 7.37-7.46 (m, 2H), 7.78 (d, *J* = 8.8 Hz, 1H), 7.79 (d, *J* = 8.8 Hz, 1H), 7.90 (d, *J* = 8.0 Hz, 1H) ppm; **^{13}C NMR (100 Hz, $CDCl_3$):** δ 27.3, 29.5, 32.5, 34.4, 41.6, 51.1, 114.0, 117.2, 123.7, 125.2, 127.3, 128.6 (3C), 128.7, 129.3, 130.0 (2C), 131.4, 131.7, 132.1, 143.4, 147.9, 164.3, 197.1 ppm; **Anal. Calcd.** for $C_{25}H_{21}ClO_2$ (388.89): requires C, 77.21; H, 5.44%. Found C, 77.01; H, 5.35%

12-(4-bromophenyl)-9,10-dihydro-9,9-dimethyl-8*H*-benzo[a]xanthen-11(12*H*)-one (19d)



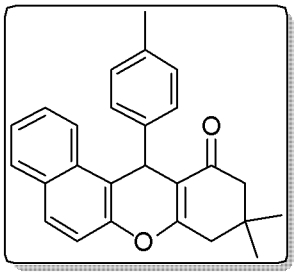
Nature: White solid; M.P. 191-193 ^{0}C; **IR (KBr, cm^{-1}):** 1643 (-CO); **^{1}H NMR (400 MHz, $CDCl_3$):** δ 0.96 (s, 3H), 1.12 (s, 3H), 2.24 (d, *J* = 16.4 Hz, 1H), 2.31 (d, *J* = 16.4 Hz, 1H), 2.56 (s, 2H), 5.67 (s, 1H), 7.21 (d, *J* = 8.4 Hz, 2H), 7.28 (d, *J* = 8.4 Hz, 2H), 7.32 (d, *J* = 9.2 Hz, 1H), 7.38 (t, *J* = 8.0 Hz, 1H), 7.44 (t, *J* = 8.0 Hz, 1H), 7.77 (d, *J* = 8.4 Hz, 1H), 7.79 (d, *J* = 8.0 Hz, 1H), 7.90 (d, *J* = 8.4 Hz, 1H) ppm; **^{13}C NMR (100 Hz, $CDCl_3$):** δ 27.2, 29.5, 32.4, 34.4, 41.5, 51.0, 113.8, 117.1, 117.2, 120.3, 123.6, 125.2, 127.3, 128.6, 129.3, 130.3 (2C), 131.3, 131.5 (2C), 131.6, 143.9, 147.8, 164.2, 197.0 ppm; **Anal. Calcd.** for $C_{25}H_{21}BrO_2$ (433.34): C, 69.29; H, 4.88%. Found C, 69.02; H, 4.77%

9,10-dihydro-12-(4-methoxyphenyl)-9,9-dimethyl-8*H*-benzo[a]xanthen-11(12*H*)-one (19e)



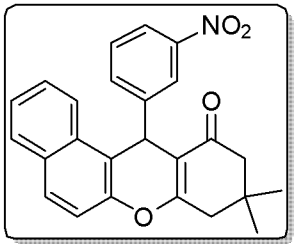
Nature: White solid; M.P. 206-208 ^{0}C; **IR (KBr, cm^{-1}):** 1646 (-CO); **^{1}H NMR (400 MHz, $CDCl_3$):** δ 0.97 (s, 3H), 1.12 (s, 3H), 2.24 (d, *J* = 16.0 Hz, 1H), 2.31 (d, *J* = 16.4 Hz, 1H), 2.56 (s, 2H), 3.69 (s, 3H), 5.66 (s, 1H), 6.70 (d, *J* = 8.8 Hz , 2H), 7.25 (d, *J* = 8.8 Hz , 2H), 7.31 (d, *J* = 9.2 Hz , 1H), 7.37 (dt, *J* = 1.2 Hz, *J* = 6.8 Hz, 1H), 7.43 (dt, *J* = 1.2 Hz, *J* = 6.8 Hz, 1H), 7.76 (t, *J* = 9.6 Hz, 2H), 7.99 (d, *J* = 9.2 Hz, 1H) ppm; **^{13}C NMR (100 Hz, $CDCl_3$):** δ 27.3, 29.5, 32.4, 34.0, 41.5, 51.1, 55.2, 113.8 (2C), 114.6, 117.2, 118.1, 123.9, 125.0, 127.1, 128.6, 128.9, 129.5 (2C), 131.6, 131.7, 137.3, 147.9, 157.9, 163.9, 197.2; **Anal. Calcd.** for $C_{26}H_{24}O_3$ (384.47): requires C, 81.22; H, 6.29%. Found C, 81.01; H, 6.20%

9,10-dihydro-9,9-dimethyl-12-p-tolyl-8*H*-benzo[a]xanthen-11(12*H*)-one (19f)



Nature: White solid; M.P. 180-181 ^{0}C; **IR (KBr, cm^{-1}):** 1647 (-CO); **^{1}H NMR (400 MHz, $CDCl_3$):** δ 0.97 (s, 3H), 1.11 (s, 3H), 2.19 (s, 3H), 2.23 (d, *J* = 16.4 Hz, 1H), 2.30 (d, *J* = 16.0 Hz, 1H), 2.56 (s, 2H), 5.66 (s, 1H), 6.97 (d, *J* = 8.0 Hz , 2H), 7.22 (d, *J* = 8.0 Hz , 2H), 7.31 (d, *J* = 9.2 Hz , 1H), 7.35 (t, *J* = 7.6 Hz 1H), 7.42 (t, *J* = 7.6 Hz, 1H), 7.75 (t, *J* = 9.2 Hz, 2H), 8.00 (d, *J* = 8.4 Hz, 1H); **^{13}C NMR (100 Hz, $CDCl_3$):** δ 21.1, 27.4, 29.4, 32.4, 34.4, 41.5, 51.0, 114.5, 117.2, 118.0, 123.8, 125.0, 127.1, 128.4 (2C), 128.5, 128.9, 129.1 (2C), 131.5, 131.6, 135.8, 142.0, 147.8, 163.9, 197.1; **Anal. Calcd.** for $C_{26}H_{24}O_2$ (368.47): C, 84.75; H, 6.57%. Found C, 84.54; H, 6.48%.

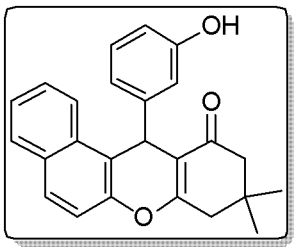
9,10-dihydro-9,9-dimethyl-12-(3-nitrophenyl)-8*H*-benzo[a]xanthen-11(12*H*)-one (19g)



Nature: Pale yellow solid; M.P. 172-173 ^{0}C; **IR (KBr, cm^{-1}):** 1649 (-CO), 1530 (-NO_2), 1348 (-NO_2); **^{1}H NMR (400 MHz, $CDCl_3$):** δ 0.96 (s, 3H), 1.13 (s, 3H), 2.24 (d, *J* = 16.4 Hz, 1H), 2.33 (d, *J* = 16.0 Hz, 1H), 2.61 (s, 2H), 5.82 (s, 1H), 7.37 (d, J = 8.8 Hz, 1H), 7.38 (d, *J* = 8.0 Hz, 1H), 7.41 (d, *J* = 7.6 Hz, 1H), 7.50 (t, *J* = 8.0

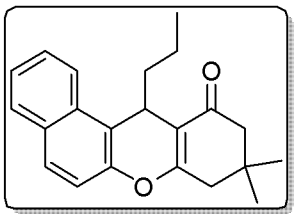
Hz, 1H), 7.79-7.83 (m, 3H), 7.86 (d, *J* = 8.4 Hz , 1H), 7.93-7.95 (m, 1H), 8.12 (s, 1H) ppm; **^{13}C NMR (100 Hz, $CDCl_3$):** δ 27.3, 29.4, 32.5, 34.9, 41.5, 51.0, 113.3, 116.2, 117.4, 121.7, 123.3, 123.4, 125.4, 127.5, 128.9, 129.2, 129.8, 131.1, 131.8, 135.0, 147.0, 148.0, 148.5, 164.7, 197.0; **Anal. Calcd.** for $C_{25}H_{21}NO_4$ (399.44): C, 75.17; H, 5.30; N, 3.51%. Found C, 74.93; H, 5.22; N, 3.37%.

9,10-dihydro-12-(3-hydroxyphenyl)-9,9-dimethyl-8*H*-benzo[a]xanthen-11(12*H*)-one (19h)



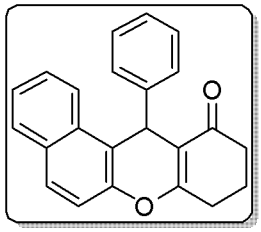
Nature: White solid; M.P. 244-246 ^{0}C; **IR (KBr, cm^{-1}):** 3410 (-OH), 1640 (-CO); **^{1}H NMR (400 MHz, $CDCl_3$):** δ 0.97 (s, 3H), 1.11 (s, 3H), 2.29 (d, *J* = 16.4 Hz, 1H), 2.34 (d, *J* = 16.4 Hz, 1H), 2.57 (s, 2H), 5.71 (s, 1H), 6.56 (dq, *J* = 0.8 Hz, *J* = 2.4 Hz, *J* = 8.0 Hz, 1H), 6.76 (dt, *J* = 1.2 Hz, *J* = 8.0 Hz, 1H), 7.01 (t, *J* = 8.0 Hz, 1H), 7.06 (t, *J* = 2.0 Hz, 1H), 7.32 (d, *J* = 8.8 Hz, 1H), 7.35-7.44 (m, 2H), 7.76 (d *J* = 8.4 Hz, 1H), 7.78 (d, *J* = 9.2 Hz, 1H), 7.99 (d, *J* = 8.4 Hz, 1H); **^{13}C NMR (100 Hz, $CDCl_3$ + DMSO-d_6):** δ 27.2, 29.1, 32.2, 34.5, 41.3, 50.8, 113.6, 114.0, 115.7 (2C), 117.1, 117.7, 119.8, 123.7, 124.8, 126.9, 128.3, 128.7, 129.0, 131.3, 146.1, 147.6, 156.8, 164.0, 197.1; **Anal. Calcd.** for $C_{25}H_{22}O_3$ (370.44): C, 81.06; H, 5.99%. Found C, 80.80; H, 5.90%.

9,10-dihydro-9,9-dimethyl-12-propyl-8*H*-benzo[a]xanthen-11(12*H*)-one (19i)



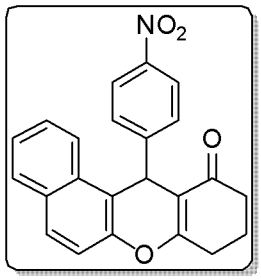
Nature: Viscous liquid; **IR (KBr, cm^{-1}):** 1651 (-CO); **^{1}H NMR(400 MHz, $CDCl_3$):** δ 0.72 (t, *J* = 7.2 Hz, 3H), 0.83-0.97 (m, 2H), 1.15 (s, 3H), 1.19 (s, 3H), 1.72-1.78 (m, 2H), 2.34 (d, *J* = 16.4 Hz, 1H), 2. 39 (d, *J* = 16.4 Hz, 1H), 2.52 (d, *J* = 17.6 Hz, 1H), 2.57 (d, *J* = 17.6 Hz, 1H), 4.72 (t, *J* = 4.4 Hz, 1H), 7.20 (d, *J* = 8.4 Hz , 1H), 7.44 (dt, *J* = 1.6 Hz, *J* = 8.4 Hz, 1H), 7.55 (dt, *J* = 1.6 Hz, *J* = 8.4 Hz, 1H), 7.70 (d, *J* = 8.8 Hz, 1H), 7.82 (d, *J* = 8.0 Hz, 1H), 8.10 (d, *J* = 8.0 Hz, 1H); **^{13}C NMR (100 Hz, $CDCl_3$):** δ 14.2, 18.4, 27.4, 28.0, 29.7, 32.2, 37.5, 41.4, 51.1, 112.8, 116.9, 118.5, 123.3, 124.9, 126.8, 128.0, 128.6, 131.3, 131.5, 148.5, 166.2, 197.6; **Anal. Calcd.** for $C_{22}H_{24}O_2$ (320.42): C, 82.46; H, 7.55%. Found C, 82.17; H, 7.7.49%.

9,10-dihydro-12-phenyl-8*H*-benzo[a]xanthen-11(12*H*)-one (19j)



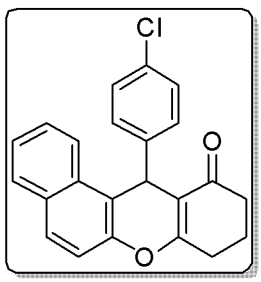
Nature: White solid; M.P. 198-200 ^{0}C; **IR (KBr, cm^{-1}):** 1665 (-CO); **^{1}H NMR (400 MHz, $CDCl_3$):** δ 1.97-2.09 (m, 2H), 2.34-2.48 (m, 2H), 2.63-2.77 (m, 2H), 5.74 (s, 1H), 7.06 (t, *J* = 7.6 Hz, 1H), 7.17 (d, *J* = 7.6 Hz, 2H), 7.33 (d, *J* = 8.8 Hz, 3H), 7.36 (d, *J* = 8.0 Hz, 1H), 7.42 (d, *J* = 8.4 Hz, 1H), 7.77 (d, *J* = 6.8 Hz, 2H) 7.96 (d, *J* = 8.4 Hz, 1H) ppm; **^{13}C NMR (100 Hz, $CDCl_3$):** δ 20.4, 27.8, 34.8, 37.2, 115.6, 117.1, 117.8, 123.8, 125.0, 126.4, 127.1, 128.4 (2C), 128.5, 128.6 (2C), 129.0, 131.5, 131.6, 145.2, 147.9, 165.8, 197.3 ppm; **Anal. Calcd.** for $C_{23}H_{18}O_2$ (326.39): C, 84.64; H, 5.56%. Found C, 84.46; H, 5.47%.

9,10-dihydro-12-(4-nitrophenyl)-8*H*-benzo[a]xanthen-11(12*H*)-one (19k)



Nature: Pale yellow solid; M.P. 242-244 ^{0}C; **IR (KBr, cm^{-1}):** 1650 (-CO), 1518 (-NO_2), 1350 (-NO_2); **^{1}H NMR (400 MHz, $CDCl_3$):** δ 1.93-2.03 (m, 1H), 2.04-2.12 (m, 1H), 2.36-2.49 (m, 2H), 2.66-2.81 (m, 2H), 5.84 (s, 1H), 7.37 (d, *J* = 8.8 Hz, 1H), 7.42 (t, *J* = 8.8 Hz, 2H), 7.51 (d, *J* = 8.0 Hz, 2H), 7.81 (d, *J* = 7.6 Hz, 2H), 7.82 (d, *J* = 8.8 Hz, 1H), 8.04 (d, *J* = 8.0 Hz, 2H) ppm; **^{13}C NMR (100 Hz, $CDCl_3$):** δ 20.3, 27.9, 34.9, 37.1, 114.3, 116.1, 117.2, 123.3, 123.8 (2C), 125.4, 127.5, 128.8, 129.6 (2C), 129.8, 131.1, 131.7, 146.4, 147.9, 152.3, 166.5, 197.1 ppm; **Anal. Calcd.** for $C_{23}H_{17}NO_4$ (371.39): C, 74.38; H, 4.61; N, 3.77%. Found C, 74.12; H, 4.53; N, 3.64%.

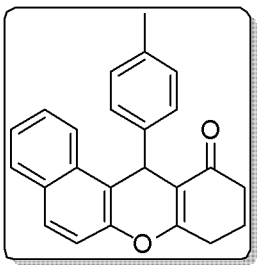
12-(4-chlorophenyl)-9,10-dihydro-8*H*-benzo[a]xanthen-11(12*H*)-one (19l)



Nature: White solid; M.P. 211-212 ^{0}C; **IR (KBr, cm^{-1}):** 1647 (-CO); **^{1}H NMR (400 MHz, $CDCl_3$):** δ 1.93-2.09 (m, 2H), 2.34-2.50 (m, 2H), 2.63-2.78 (m, 2H), 5.71 (s, 1H), 7.13 (d, *J* = 8.4 Hz, 2H), 7.26 (d, *J* = 8.0 Hz, 2H), 7.33 (d, *J* = 8.8 Hz, 1H), 7.38 (t, *J* = 7.6 Hz, 1H), 7.43 (t, *J* = 6.8 Hz, 1H), 7.77 (d, *J* = 8.8 Hz, 1H), 7.79 (d, *J* = 8.0 Hz, 1H),7.88 (d, *J* = 8.4 Hz, 1H) ppm; **^{13}C NMR (100 Hz, $CDCl_3$):** δ 20.4, 27.9, 34.3, 37.1, 115.2, 117.1, 117.2, 123.6, 125.2, 127.3, 128.5 (2C), 128.6 (2C), 129.3, 130.0, 131.3, 131.6, 132.1, 143.7, 147.9, 166.0,

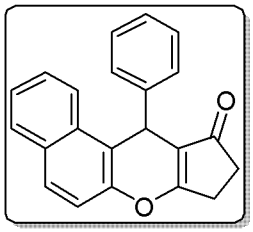
197.3 ppm; **Anal. Calcd.** for $C_{23}H_{17}ClO_2$ (360.83): C, 76.56; H, 4.75%. Found C, 76.39; H, 4.67%.

9,10-dihydro-12-p-tolyl-8*H*-benzo[a]xanthen-11(12*H*)-one (19m)



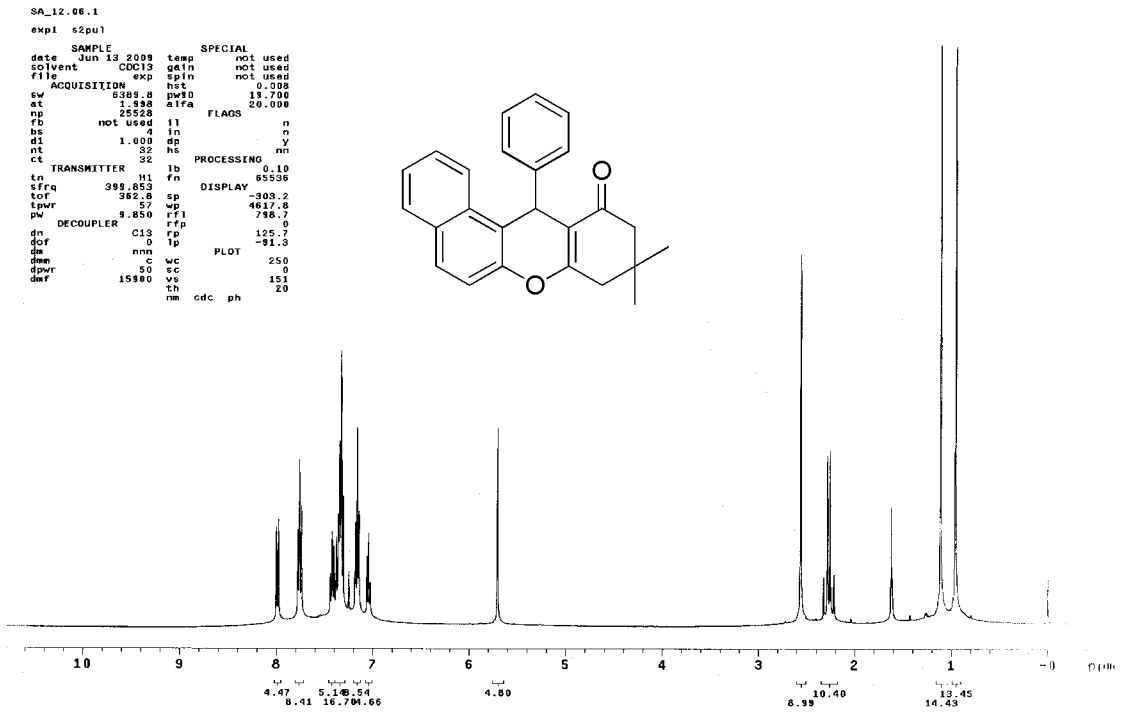
Nature: White solid; M.P. 214-216 ^{0}C; **IR (KBr, cm^{-1}):** 1649 (-CO); **^{1}H NMR (400 MHz, $CDCl_3$):** δ 1.92-2.07 (m, 2H), 2.20 (s, 3H), 2.32-2.48 (m, 2H), 2.60-2.76 (m, 2H), 5.70 (s, 1H), 6.97 (d, *J* = 8.0 Hz, 2H), 7.22 (d, *J* = 8.0 Hz, 2H), 7.32 (d, *J* = 8.8 Hz, 1H), 7.35 (t, *J* = 8.0 Hz, 1H), 7.41 (t, *J* = 8.4 Hz, 1H), 7.75 (t, *J* = 7.2 Hz, 2H), 7.96 (t, *J* = 8.4 Hz, 1H) ppm; **^{13}C NMR (100 Hz, $CDCl_3$):** δ 20.4, 21.1, 27.8, 34.3, 37.2, 115.8, 117.1, 118.0, 123.8, 125.0, 127.1, 128.5 (3C), 128.9, 129.1 (2C), 131.5, 131.6, 135.9, 142.3, 147.8, 165.6, 197.3 ppm; **Anal. Calcd.** for $C_{24}H_{20}O_2$ (340.41): C, 84.68; H, 5.92%. Found C, 84.53; H, 5.84%.

11-phenyl-8,9-dihydrobenzo[f]cyclopenta[b]chromen-10(11*H*)-one (19n)



Nature: White solid; M.P. 248-250 ^{0}C; **IR (KBr, cm^{-1}):** 1662 (-CO);**^{1}H NMR (400 MHz, $CDCl_3$):** δ 2.49-2.52 (m, 2H), 2.77-2.81 (m, 2H), 5.58 (s, 1H), 7.09 (m, 1H), 7.18-7.22 (m, 2H), 7.26-7.28 (m, 2H), 7.37-7.41 (m, 3H), 7.76-7.84 (m, 3H) ppm; **^{13}C NMR (100 Hz, $CDCl_3$):** δ 25.4, 33.9, 36.9, 116.2, 117.5, 118.9, 124.3, 125.3, 126.7, 127.3, 128.3 (2C), 128.5, 128.6 (2C), 129.7, 131.8, 131.9, 143.7, 149.3, 177.3, 202.6 ppm; **Anal. Calcd.** for $C_{22}H_{16}O_2$ (312.36): C, 84.59; H, 5.16%. Found C, 84.38; H, 5.07%.

^{1}H NMR (400 MHz, CDCl3): *9,10-dihydro-9,9-dimethyl-12-phenyl-8H-benzo[a]xanthen-11(12H)-one* ***(19a)***



^{13}C NMR (100 MHz, CDCl$_3$): *9,10-dihydro-9,9-dimethyl-12-phenyl-8H-benzo[a]xanthen-11(12H)-one* ***(19a)***

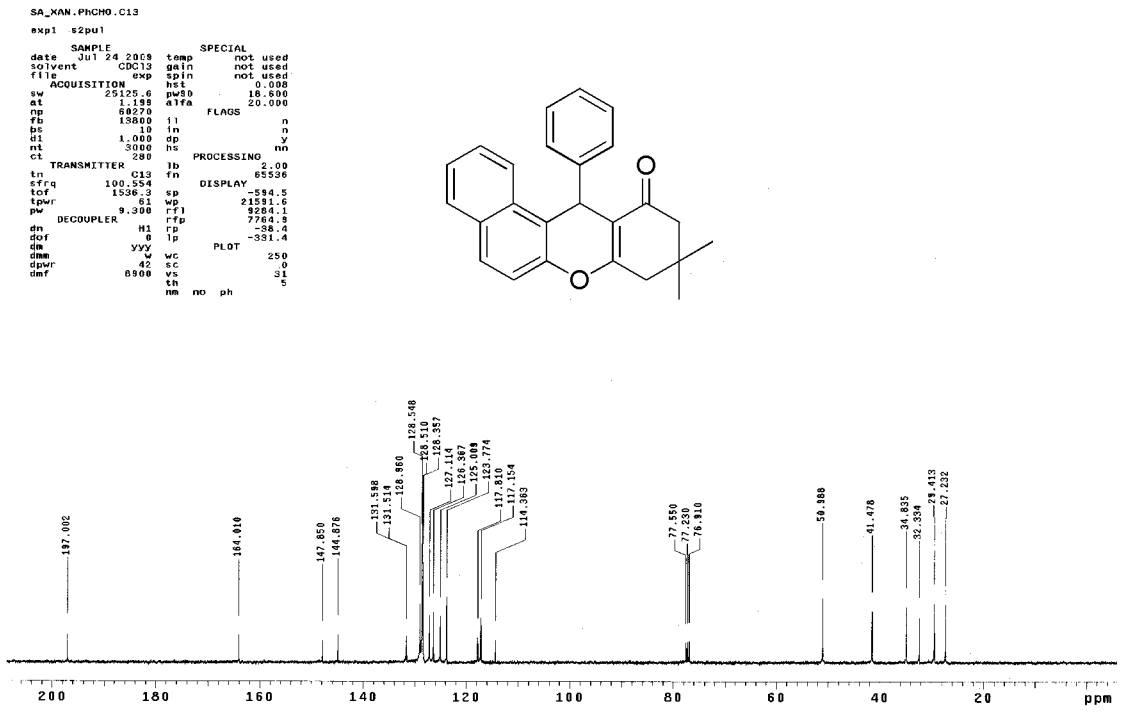
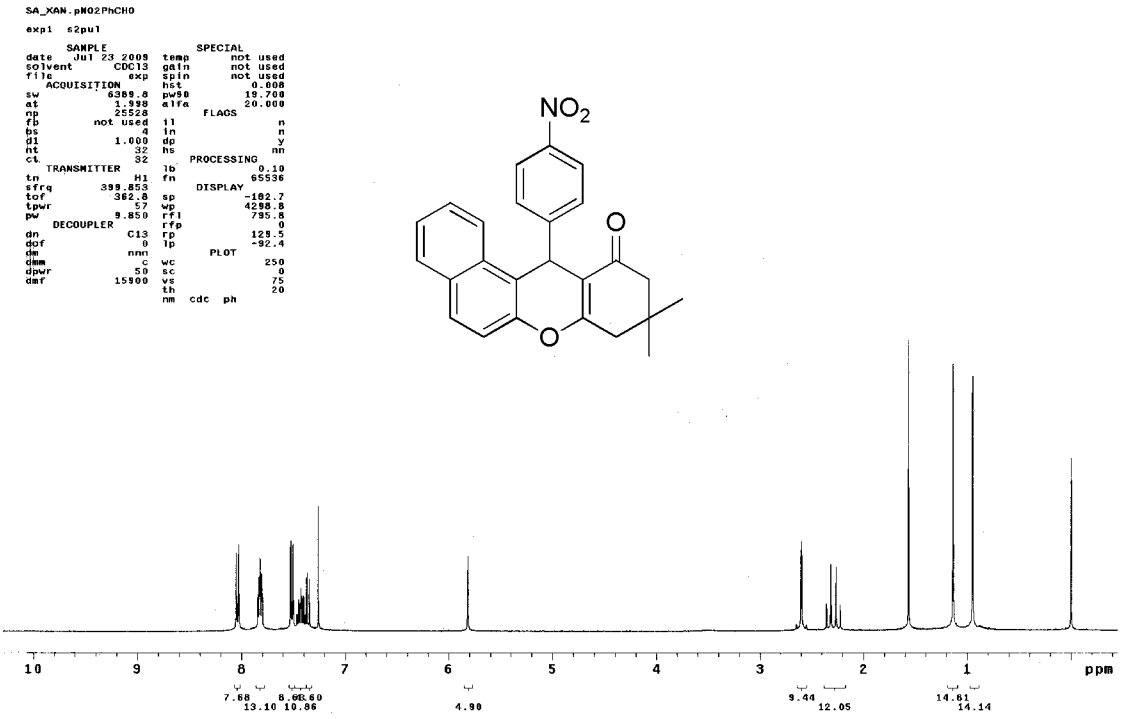


Figure 10

^{1}H NMR (400 MHz, $CDCl_3$): *9,10-dihydro-9,9-dimethyl-12-(4-nitrophenyl)-8H-benzo[a]xanthen-11(12H)-one* ***(19b)***



^{13}C NMR (100 MHz, $CDCl_3$): *9,10-dihydro-9,9-dimethyl-12-(4-nitrophenyl)-8H-benzo[a]xanthen-11(12H)-one* ***(19b)***

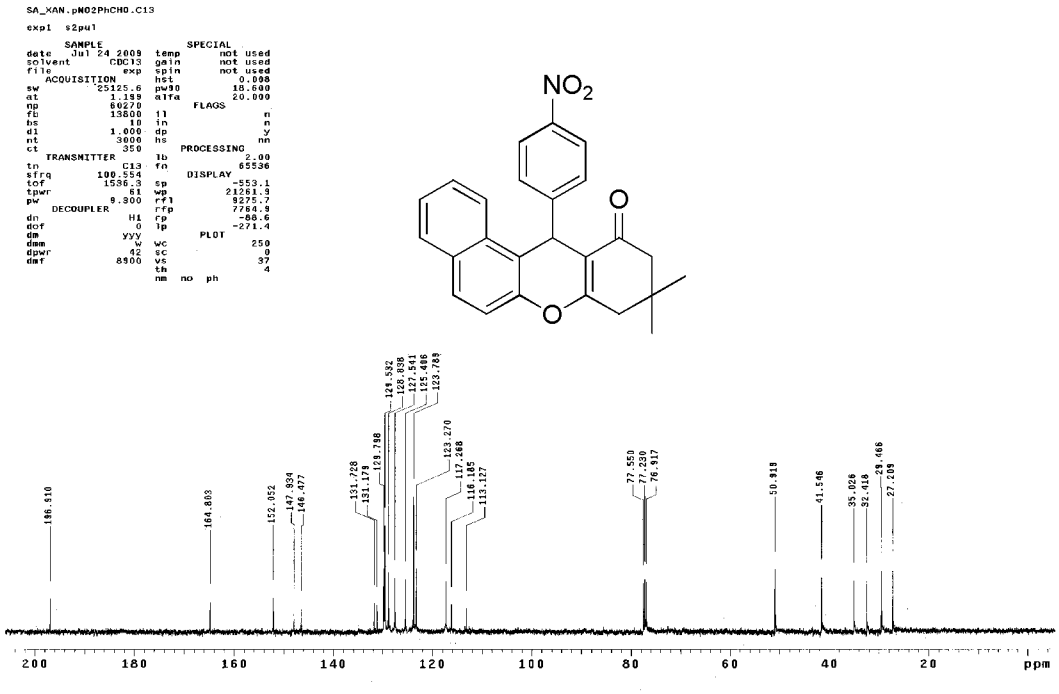


Figure 11

1. Rokita, S. E., Ed. *Quinone Methides, Wiley Series of Reactive Intermediates in Chemistry and Biology*; John Wiley & Sons, Inc.: New York, 2009; Vol 1 and references therein.

2. Rosenau, T.; Habicher, W. D. *Tetrahedron Lett.* **1997**, *38*, 5959.

3. Van De Water, R. W.; Pettus, T. R. R. *Tetrahedron* **2002**, *58*, 5367.

4. Pettus, T. R. R.; Selenski, C. In *Science of Synthesis*; Griwsbeck, A. G., Ed. Houben-Weyl: New York, 2006; Chapter 12 pp 831-899.

5. Amouri, H.; Le Bras, J. *Acc. Chem. Res.* **2002**, *35*, 501.

6. Rosenau, T.; Boehmdorfer, S. *Wiley Series of Reactive Intermediates in Chemistry and Biology* **2009**, *1*, 163.

7. Wolkenberg, S. E.; Boger, D. L. *Chem. Rev.* **2002**, *102*, 2477.

8. Brandon, R. L.; Sarrafizadeh, H.; Gardner, P. D. *J. Am. Chem. Soc.* **1959**, *51*, 5515.

9. Chaires, J. V.; Dattagupta, N.; Crothers, D. M. *Biochemistry* **1982**, *21*, 3933.

10. Ferreira, S. B.; Da Siliva, F. C.; Pinto, A. C.; Gonzaga, D. T. G.; Ferreira, V. F. *J. Heterocycl. Chem.* **2009**, *46*, 1080.

11. Angle, S. R.; Yang, W. *J. Am. Chem. Soc.* **1990**, *112*, 4524.

12. Angle, S. R.; Rainier, J. D.; Woytowicz, C. *J. Org. Chem.* **1997**, *62*, 5884.

13. Merijan, A.; Gardner, P. D. *J. Org. Chem.* **1965**, *30*, 3965.

14. Modica, M.; Zanaletti, R.; Freccero, M.; Mella, M. *J. Org. Chem.* **2001**, *66*, 41.

15. Stokes, S. M., Ding, F.; Smith, P. L.; M. Keane, J. M.; Kopach, M. E.; Jervis, R.; Sabat, M.; Harman, W. D. *Organometallics* **2003**, *22*, 4170

16. Chapman, O. L.; Engel, M. R.; Springer, J. P.; Clardy, J. C. *J. Am. Chem. Soc.* **1971**, *93*, 6696.

17. Pathak, T. P.; Sigman, M. S. *J. Org. Chem.* **2011**, *76*, 9210.

18. Jurd, L.; Wong, R. Y. *Aust. J. Chem.* **1980**, *33*, 137 and references therein.

19. Takahashi, O. *Arch. Toxicol.* **1988**, *62*, 325.

20. Moore, R. F.; Waters, W. A. *J. Chem. Soc.* **1954**, 243.

21. Wojciechowski, K.; Dolatowska, K. *Tetrahedron*, **2005**, *61*, 8419.

22. Ettlinger, M. G. *J. Am. Chem. Soc.* **1950**, *72*, 3666.

23. Creed, D.; Werbin, H.; Daniel, T. Tetrahedron Lett. **1981**, *22*, 2039.

24. Leary, G. *J. Chem. Soc. (A)* **1971**, 2248.

25. Batsomboon, P.; Phakhodee, W.; Ruchirawat, S.; Ploypradith, P. *J. Org. Chem.* **2009**, *74*, 4009.

26. Karabelas, K.; Moore, H. W. *J. Am. Chem. Soc.* **1990**, *112*, 5372 and references therein.

27. Verboom, W.; Bos, H. J. T. *Tetrahedron Lett.* **1978**, *19*, 1229.

28. Tuttle, K.; Rodriguez, A. A.; Pettus, T. R. R. *Synlett* **2003**, 2234.

29. Rodriguez, R.; Adlington, R. M.; Moses, J. E.; Cowley, A.; Baldwin, J. E. *Org. Lett.* **2004**, *6,* 3617.

30. Liao, D.; Li, H.; Lei, X. *Org. Lett.* Online from November 2, **2011.**

31. Barrero, A. F.; del Moral J. F. Q.; Herrador, M. M.; Arteaga, P.; Cortes, M.; Benites, J.; Rosellon, A.; *Tetrahedron*, **2006**, *62*, 6012-017.

32. Lindsey, C. C.; Pettus, T. R. R. *Tetrahedron Lett.* **2006**, *47*, 201-204.

33. Samarakoon, T. B.; Hur, M. Y.; Kurtz, R. D.; Hanson, P. R.; *Org. Lett.* **2010**, *12,* 2182.

34. Nair, V.; Tressa, P. M. *Tetrahedron Lett.* **2001**, *42*, 4549.

35. Nair, V.; Jayan, C. N.; Radhakrishnan, K. V. *Tetrahedron* **2001**, 57, 5807.

36. Katritzky, A. R.; Z.; Lan, X. *Synthesis* **1992**, 763.

37. Shaterian, H. R.; Hosseinian, A.; Ghashang, M. *Tetrahedron Lett.* **2008**, *49,* 5804.

38. Shaterian, H. R.; Hosseinian, A.; Ghashang, M. *Synth. Commun.* **2009**, *39,* 2560.

39. Shaterian, H. R.; Hosseinian, A.; Ghashang, M. *Chin. J. Chem.* **2009**, *27,* 821.

40. Kundu, D.; Majee, A.; Hajra, A. *Catal. Commun.* **2010**, *11*, 1157.

41. Das, B.; Laxminarayana, K.; Krishnaiah, M.; Srinivas, Y. *Synlett* **2007**, 3107.

42. Li, J.; Tang, W.; Lu, L.; Su, W. *Tetrahedron Lett* **2008**, *49*, 7117.

43. Nandi, G. C.; Samai, S.; Kumar, R.; Singh, M. S. *Tetrahedron* **2009,** *65,* 7129.

44. Khurana, J. M.; Magoo, D. *Tetrahedron Lett* **2009**, *50*, 4777.

45. Gao, S.; Tsai, C. H.; Yao, C. F. *Synlett* **2009**, 949.

46. Wang, R.-Z.; Zhang, L.-F.; Cui, Z.-S. *Synth Commun* **2009**, *39*, 2101.

47. Li, J.; Lu, L.; Su, W. *Tetrahedron Lett.* **2010**, *51*, 2434.

48. Kumar, A.; Sharma, S.; Maurya, R. A.; Sarkar, J.; *J. Comb. Chem.* **2010**, *12*, 20.

49. Ghorbani-Vaghei, R.; Malaekehpoor, S. M. *Org. Prep. Proced. Int.* **2010**, *42*, 494.

50. Li, J.; Li, J.; Fang, J.; Su, W. *Synth. Commun.* **2010**, *40*, 1029.

51. Karimi, N.; Oskooie, H. A.; Heravi, M. M.; Tahershamsi, L. *Synth. Commun.* **2011**, *41*, 307.

52. Foroughifar, N.; Mobinikhaledi, A.; Moghanian, H.; Mozafari, R.; Esfahani, H. R. M. *Synth. Commun.* **2011**, *41*, 2663.

53. Oskooie, H. A.; Heravi, M. M.; Karimi, N.; Kohansal, G, *Synth. Commun.* **2011**, *41*, 2763.

54. Sun, X. J.; Zhou, J. F.; Zhao, P. S. *J. Heterocycl. Chem.* **2011**, *48*, 1347.

55. Khurana, J. M.; Nand, Bhaskara, Sneha *J. Heterocycl. Chem.* **2011**, *48*, 1388.

56. Choudhury, L. H.; Parvin, T.; Khan, A. T. *Tetrahedron* **2009**, *65*, 9513 and references cited therein.

57. Khan, A. T.; Khan, M. M. *Carbohydr. Res.* **2010**, *345*, 2139.

58. Dai, L.; Wang, S.-X.; Chen, F.-E.; *Adv. Synth. Catal.* **2010**, *352*, 2137.

59. Lee, W.-Z.; Tseng H.-S.; Wang, T.-L.; Tsai, H.-L.; Kuo, T.-S. *Organometallics*, **2010**, *29*, 2874.

60. Dia, R.-M.; Belaqziz, R.; Romane, A.; Antoniotti, S.; Dunach, E. *Tetrahedron Lett.* **2010**, *51*, 2164.

61. Banerjee, S.; Das, J.; Alvarez, R. P.; Santra, S. *New J. Chem.*, **2010**, *34*, 302.

62. Corma, A.; Gonzalez-Arellano, C.; Iglesias, M.; Sanchez, F. *App. Catal. A General* **2010**, *375*, 49.

63. Badoiu, A.; Bernardinelli, G.; Besnard, C.; Kundig, E. P. *Org. Biomol. Chem.*, **2010**, *8*, 193; 64. Rana, N. K.; Selvakumar, S.; Singh, V. K. *J. Org. Chem*. **2010**, *75*, 2089.

65. O'Byrne, A.; Murray, C.; Keegan, D.; Palacio, C.; Evans, P.; Morgan, B. S. *Org. Biomol. Chem.* **2010**, *8*, 539.

66. Firouzabadi, H.; Iranpoor, N.; Abbasi, M. *Adv. Synth. Catal.* **2009**, *351*, 755.

67. Rajabi, F.; Razavi, S.; Luque, R. *Green Chem.* **2010**, *12*, 786.

68. Chen, C.-T.; Lin, Y.-D.; Liu, C.-Y. *Tetrahedron* **2009**, *65*, 10470.

69. Motokura, K.; Tanaka, S.; Tada, M.; Iwasawa, Y. *Chem. Eur. J.*, **2009**, *15*, 10871. And references cited therein.

70. Khan, A. T.; Ghosh, S.; Choudhury, L. H. *Eur. J. Org. Chem.* **2006**, 2226.

71. Khan, A. T.; Parvin, T.; Gazi, S.; Choudhury, L. H. *Tetrahedron Lett.* **2007**, *48*, 3805.

72. Chaturvedi, D. *Tetrahedron* **2012**, *68*, 15

73. Lambert, R. W.; Martin, J. A.; Merrett, J. H.; Parkes, K. E. B.; Thomas, G. J. PCT Int. Appl. WO 9, 706, 178, **1997**.

74. Poupelin, J. P.; Saint-Ruf, G.; Foussard-Blanpin, O.; Narcisse, G.; Uchida Ernouf, G.; Lacroix, R. *Eur. J. Med. Chem.* **1978**, *13*, 67.

75. Hideo, T.; Teruomi, J. Jpn. Patent 56, 005, 480, 1981.

76. Banerjee, A.; Mukherjee, A. K. Stain Technol 1981, 56, 83.

77. Knight, C. G.; Stephens, T. *Biochem. J.* **1989**, *258*, 683.

78. Buu-Hoi, N. P.; Saint-Ruf, G.; De, A.; Hieu, H. T. *Bull. Chim. Ther.* **1972**, *7*, 83.

79. Ion, R.-M. *Prog. Catal.* **1997**, *6*, 55.

80. Ion, R.-M.; Planner, A.; Wiktorowicz, K.; Frackowiak, D. *Acta. Biochim. Pol.* **1998**, *45*, 833.

81. Zhang, X.; Li, L.; Zhang, G. *Green Chem* **2003**, *5*, 646.

82. Shi, L.; Zhang, G.; Pan, F. *Tetrahedron* **2008**, *64*, 2572.

83. Zhang, G.; Liu, Q.; Shi, L.; Wang, J. *Tetrahedron* **2008**, *64*, 339.

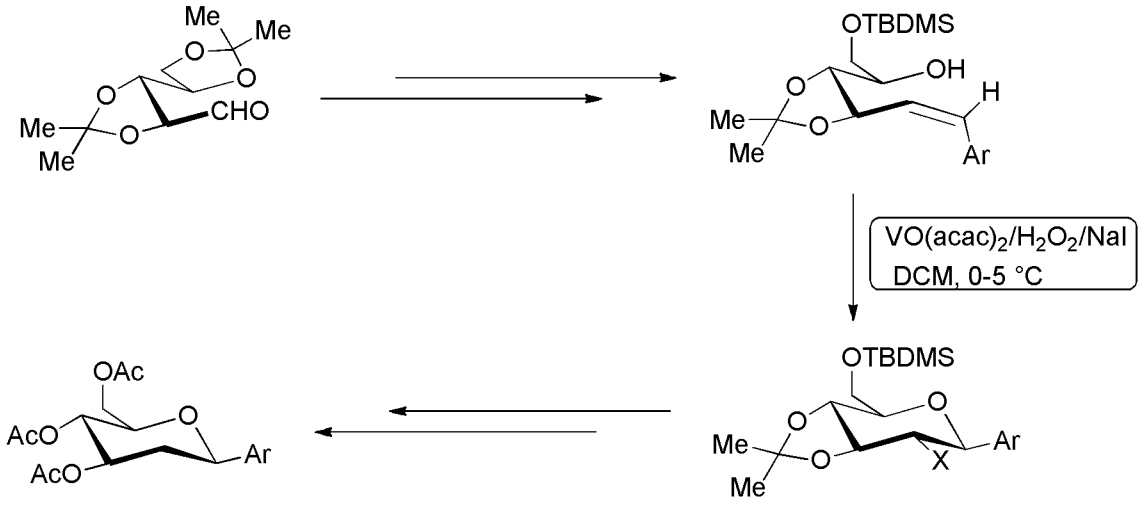
84. Gan, S.; Ng, H. K.; Ooi, C. W.; Motala, N.O.; Ismail M. A. F. *Bioresour Technol* **2010**, *101*, 7338.

85. Patil, P.; Deng, S.; Rhodes, J. I.; Lammers, P. J. *Fuel* **2010**, *89*, 360.

86. Khan, A. T.; Das, D. K.; Khan, M. M. *Tetrahedron Lett.* **2011**, *52*, 4539.

Conclusion and future perspective

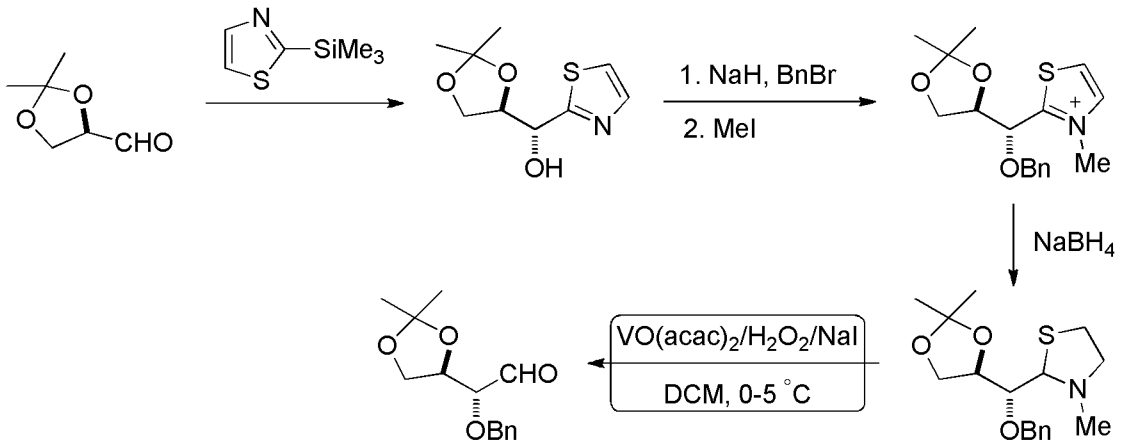
We have shown that vanadyl acetylacetonate, hydrogen peroxide and sodium iodide is a good combination for oxidizing iodide ion into iodonium ion in the solution. This *in situ* generated iodonium ion exploited for direct iodination of various organic substrates namely 1,3-dicarbonyl compounds, electron rich aromatic compounds and heterocyclic compounds such as pyrazole derivatives. Alternatively, the reactive iodonium ion can act as soft non-metallic electrophile for cleavage of dithioacetals of sugar derivatives into the corresponding open chain aldehyde sugar derivatives. All these successful results are elaborated in the Part A of the dissertation. The future scope can be extended further for the synthesis of 2-deoxy-*C*-aryl glycoside synthesis which is shown in the retro-synthetic analysis as shown below.



Scheme 1: Retro-synthetic analysis for the synthesis of 2-deoxy-*C*-aryl glycoside

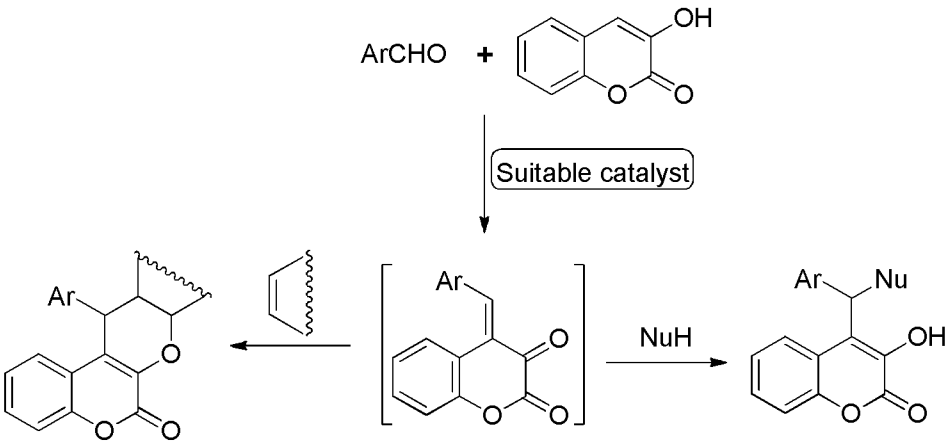
In the above synthetic plan the key cyclisation step will be carried out with *in situ* generated iodonium ion. After completing the model studies, it will be implemented towards target oriented synthesis.

Similarly, the iodonium ion can be utilised for the cleavage of thiazolyl group, which is used as mask aldehyde functionality. This protecting group is used for preparing higher sugar derivatives from the lower sugar derivatives as shown in Scheme 2.



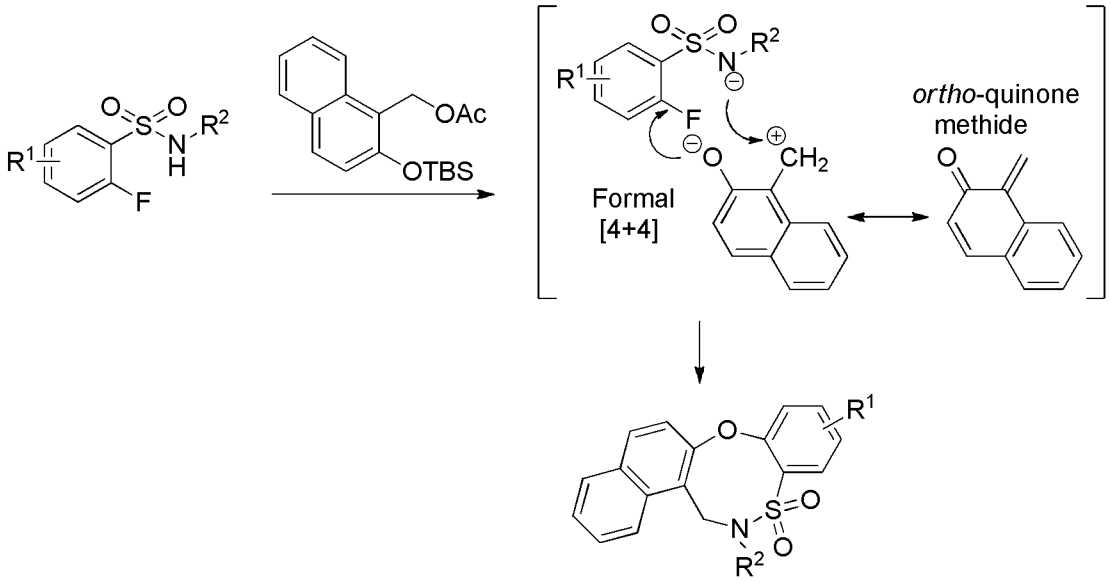
Scheme 2

In part B of the thesis, we have demonstrated that 2-naphthol and aromatic aldehyde can generate *ortho*-naphthoquinone methide analogue to *ortho*-quinone methide intermediate in presence of bromodimethysulfonium bromide and ferric sulphate. This reactive intermediate has been utilised for synthesis of various organic compound by capturing with various nucleophiles. We would like to study whether it can be used for cycloaddition reaction for generating new class of compounds. In addition, other compound will be searched for generating *ortho*-quinone methide intermediate, which will be used for nucleophile addition and cycloaddition reaction, as shown in Scheme 3.



Scheme 3

In addition, [4 + 4] ambiphile pairing reaction will be investigated by generating *in situ* *o*-naphthoquinone methide intermediate as shown in Scheme 4.



Scheme 4

LIST OF PUBLICATIONS OF THE AUTHOR

1. *Selective and effective oxone-catalysed α-iodination of ketones and 1,3-dicarbonyl compounds in the solid state*
Goswami, P.; Ali, Shahzad, Khan, M. M.; and Khan, A. T. *ARKIVOC* **2007** (*xv*) 82-89.

2. *New three-component condensation reaction: synthesis of 1-[(alkylthio)(phenyl)methyl] naphthalene-2-ol catalyzed by bromodimethylsulfonium bromide (BDMS)*
Khan, A. T.; Ali, Shahzad; Dar, A. J.; Lal, M. *Tetrahedron Lett.* **2011**, *52*, 5157.

3. *One-pot three-component reaction for the synthesis of pyran annulated heterocyclic compounds using DMAP as a catalyst*
Khan, A. T.; Lal, M.; Ali, Shahzad, Khan, M. M. *Tetrahedron Lett.* **2011**, *52*, 5327

4. *$VO(acac)_2/H_2O_2/NaI$: A mild and efficient combination for the cleavage of dithioacetal derivatives of sugars*
Khan, A. T.; Ali, Shahzad; Sidick Basha, R.; Khan, M. M.; Lal, M. *Carbohydr. Res.* **2011**, *346*, 2629

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Note

$VO(acac)_2/H_2O_2/NaI$: a mild and efficient combination for the cleavage of dithioacetal derivatives of sugars

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ABSTRACT

A wide variety of dithioacetal derivatives of sugars can be cleaved easily into the corresponding open-chain aldehydo sugars using an efficient combination of $VO(acac)_2/H_2O_2/NaI$ at 0–5 °C. Some of the salient features of this protocol are mild reaction conditions, good yields, short reaction times, easy work-up procedures, and non-involvement of toxic chemicals.

Aldehydo sugar derivatives are important building blocks in carbohydrate chemistry for the synthesis of C-disaccharides,[1] C-arylglycosides,[2] and natural products.[3–5] For examples, acyclic aldehydo derivatives of D-glucose, D-xylose, and L-arabinose are used for the syntheses of valieneamine (**1**),[3] a synthetic C-disaccharide **2**,[1] and (+)-phorboxazole A (**3**), a potent cytostatic agent[4] (Fig. 1), as well as anemoclemoside B1.[5]

Conventionally, mercury(II) chloride and cadmium carbonate[6–8] or mercury(II) chloride and mercuric oxide[9–11] are found to be the most suitable combination for deprotection of dithioacetal derivatives of sugars. This method is based on using a heavy metal(s) as soft electrophiles that are highly toxic and the additional difficulty is in the work-up procedure to remove mercuric oxide.

Different methods have been reported for the deprotection of dithioacetals by using $I_2/NaHCO_3$,[12] $MeI/CdCO_3$,[13] $NaNO_2/AcCl$,[14] CetTMATB or TBATB,[15] *N*-iodosaccharin,[16] $V_2O_5/H_2O_2/NH_4Br$,[17] and $(NH_4)_6Mo_7O_{24}{\cdot}4H_2O/H_2O_2/NH_4Br$.[18] However, these methods have some limitations such as low yields and incompatibility with acidic functional groups. These latter methods are less commonly used for preparation of aldehydo sugar derivatives. Therefore, there is a need to explore a compatible method that is environmentally benign and applicable to a number of dithioacetals of sugars. Our group has developed various synthetic methodologies by using in situ generated halonium ions.[19–21] From our previous experience, we perceived that the iodonium ion is a soft electrophile and would be suitable for this transformation.

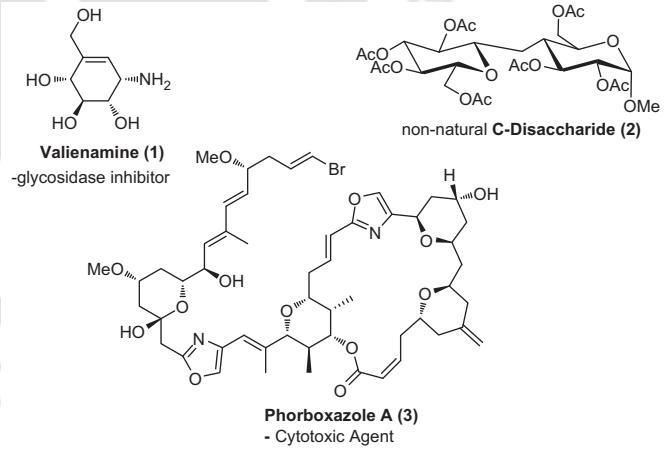

Figure 1. Biological active compounds synthesized from acyclic aldehydo sugar derivatives.

Vanadyl acetylacetonate is an effective and important catalyst for the selective epoxidation of allylic alcohols.[22] Because of its efficacy, a combination of vanadyl acetylacetonate and *tert*-butylhydroperoxide (TBHP) is used for the selective conversion of bishomoallylic alcohols into functionalized *cis*-THFs.[23] In this communication, the deprotection of dithioacetals of sugars using a combination of $VO(acac)_2/H_2O_2/NaI$ is reported as shown in Scheme 1.

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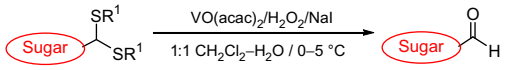


Scheme 1. Cleavage of dithioacetals of sugars.

In the above combination, vanadyl acetylacetonate acts as a catalyst, with hydrogen peroxide and sodium iodide as the sources of active oxygen and iodoniun ion, respectively. All of these chemicals are environmentally benign and acceptable.

Vanadyl acetylacetonate was prepared by following the literature procedure,[24] D-ribose diethyl dithioacetal (**4**) was initially chosen as a model substrate. The reaction conditions for the cleavage of sugar derivative **4** were optimized in terms of yield and reaction time. Several reactions were examined using different amounts of $VO(acac)_2$, H_2O_2, and NaI. The best yield of **15** was obtained using the combination of **4**/$VO(acac)_2$/NaI/H_2O_2 in 1.0, 0.2, 1.0, and 10 equiv, respectively (Table 1, entry 4). After screening of solvents such as CH_2Cl_2, EtOAc, CH_3CN, and EtOH, dichloromethane was the best solvent for this transformation, and the results are summarized in Table 1. It is obvious that $VO(acac)_2$ plays an important role in the formation of the product (Table 1, entry 1).

This protocol was examined for the deprotection of the tetra-*O*-acetyl diethyl dithioacetal of L-arabinose **5** to give the desired product **16** in 76% of yield. Various diethyl dithioacetal derivatives of different aldohexoses such as D-glucose (**6**), D-galactose (**7**), D-mannose (**8**), and L-rhamnose (**9**) were cleaved to the corresponding aldehydo sugars **17**–**20** in good yields under similar reaction conditions (Table 2). The scope of this method was further verified for the deprotection of the dipropyl dithioacetal derivatives of sugars such as L-arabinose (**10**), D-galactose (**11**), and D-mannose (**12**), and the desired products **16**, **18,** and **19** were obtained in good yields. It is important to mention that the reaction time required for the cleavage of a diethyl dithioacetal is less as compared to the dipropyl dithioacetal (entries 7–9 in Table 2).

We have extended our protocol for substrates having other sensitive functional groups such as acetals and benzyl groups. For this study, we performed the reaction on compounds **13** and **14** which gave the aldehydo products **21** and **22** in good yields. From these observations, we have noted that our protocol is compatible with other functional groups in the substrates.

Finally we turned our attention toward a plausible mechanism for this transformation. Initially, the treatment of vanadyl acetylacetonate with hydrogen peroxide can generate the mono peroxo complex of vanadium(V) by replacing one unit of acetylacetonate, which can oxidize the iodide ion to the iodonium ion (which might exist as I_2 and/or I_3^- in the solution). Thus in situ generated iodonium ion (I^+) can react with sulfur to generate species **1a**, which on hydrolysis gives intermediate **1b**. Further, attack on the nucleophilic sulfur atom of intermediate (**1b**) with another I^+ ion leads to the formation of the desired product as shown in Scheme 2. The by-product R^1SI may undergo hydrolysis into R^1SOH and iodide ion. The iodide ion can participate in the same catalytic cycle as indicated in Scheme 2.

In conclusion, a simple and efficient protocol has been devised for the preparation of various aldehydo sugars from the cleavage of the corresponding sugar dithioacetals using a combination of $VO(acac)_2$, H_2O_2, and NaI. Short reaction times, benign reaction conditions, and good yields are the main features. The reaction can be applied to a large number of sugars dithioacetals. Moreover, other protecting groups such as acetyl, benzyl, and isopropylidene are unaffected during the experimental conditions.

1. Experimental

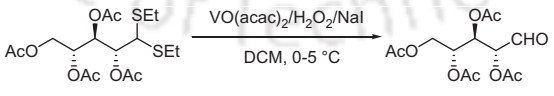
1.1. General methods

Starting materials such as vanadyl acetylacetonate[24] and monosaccharide derivatives[25] were prepared by the literature procedures, and other reagents were purchased from commercial suppliers. Residual solvent was removed under high vacuum. Analytical thin-layer chromatography was performed on precoated TLC plates (0.2 mm layer thickness of Silica Gel 60 F-254). Spots were visualized by spraying 10% H_2SO_4 in MeOH. Column chromatography was carried out using silica gel (60–120 mesh, E. Merck or Qualigen). Melting points were determined on a Büchi melting point apparatus and are uncorrected. Optical rotations were measured with a Perkin–Elmer 243 polarimeter at 25 °C temperature. IR spectra were recorded on a Perkin–Elmer Spectrum One FTIR spectrometer. ^1H and ^{13}C NMR spectra were recorded on a Varian (400 MHz) spectrometer using TMS as the internal reference. Chemical shifts were reported in parts per million (ppm). ^1H NMR data are reported in the order of chemical shift, multiplicity (s = singlet, d = doublet, t = triplet, dd = doublet of doublet, m = multiplet), coupling constant in hertz (Hz), and number of protons. Elemental analyses were performed on a Perkin–Elmer CHNS/O-2400 analyzer.

1.2. General experimental procedure

To a stirred solution of $VO(acac)_2$ (0.053 g, 0.2 mmol) in water (1 mL), was added 30% H_2O_2 solution (1.2 mL, 10 mmol) at

Table 1
Optimization of the reaction conditions[a]

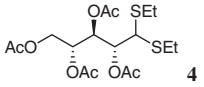
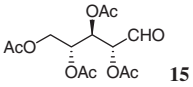
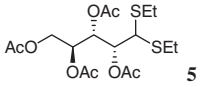
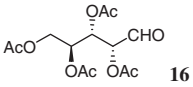
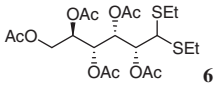
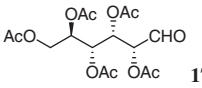
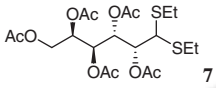
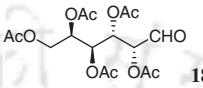
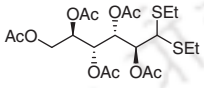
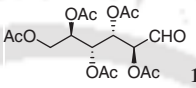
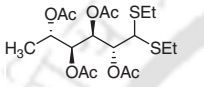
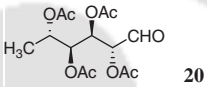
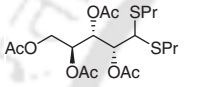
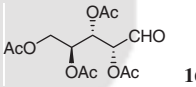
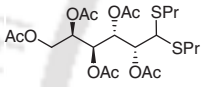
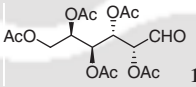
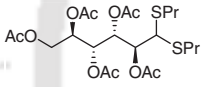
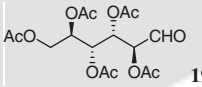
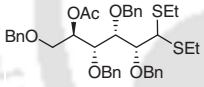
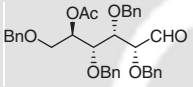
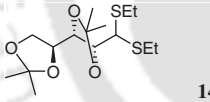
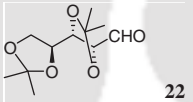


4 15

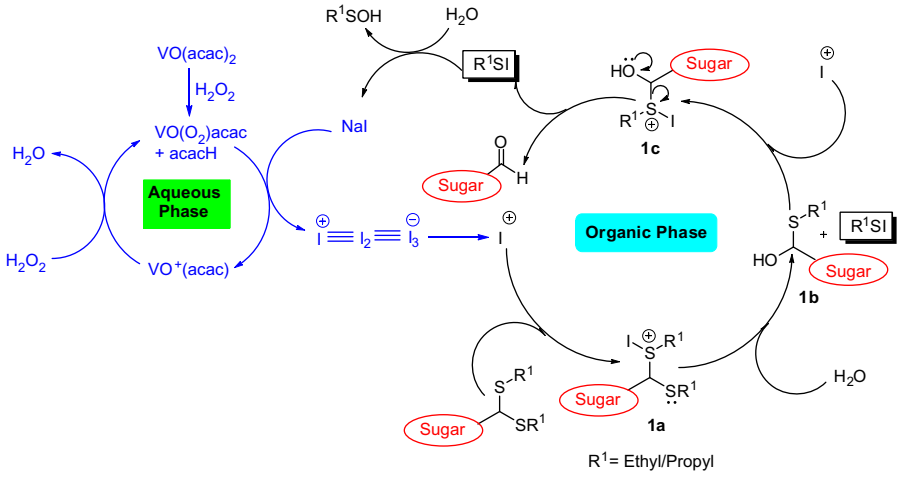
Entry	$VO(acac)_2$ (mol %)	Solvent	30% H_2O_2 mL (mmol)	NaI (mmol)	Time (h)	Yield[b] (%)
1	No catalyst	DCM	1.2 (10)	1	5	NR[c]
2	10	DCM	1.2 (10)	1	5	32
3	15	DCM	1.2 (10)	1	5	50
4	20	DCM	1.2 (10)	1	3	68
5	25	DCM	1.2 (10)	1	3	65
6	20	DCM	1.2 (10)	0.5	3	39
7	20	DCM	0.6 (5)	1	3	50
8	20	DCM	2.2 (20)	1	3	64
9	20	Acetonitrile	1.2 (10)	1	3	6
10	20	Ethyl acetate	1.2 (10)	1	3	10
11	20	Ethanol	1.2 (10)	1	3	NR[c]

[a] Reaction was carried out using 1 mmol of 2,3,4,5-tetra-*O*-acetyl-D-ribose diethyl dithioacetal.
[b] Isolated yield.
[c] No reaction.

Table 2
Deprotection of dithioacetals of sugar[a]

Entry	Substrate	Product	Time (h)	Yield[b] (%)
1	 4	 15	3	68
2	 5	 16	3	76
3	 6	 17	3	64
4	 7	 18	2.5	92
5	 8	 19	3	70
6	 9	 20	3.5	75
7	 10	 16	4.5	73
8	 11	 18	4.5	86
9	 12	 19	5	68
10	 13	 21	4	88
11	 14	 22	2.5	66

[a] The reaction was performed using 0.2 mmol of $VO(acac)_2$, 10 mmol of H_2O_2, and 1 mmol of NaI.
[b] Isolated yields.



Scheme 2. Plausible mechanism for deprotection of dithioacetals of sugars.

0–5 °C. After 20 min, the solution turned into yellow from a bluish green. Then, NaI (0.149 g, 1 mmol) was added into the above reaction mixture followed by making it in 1 mL of water. The color changed instantly from yellow to a dark-brown color. Subsequently, the substrate (1 mmol) in CH_2Cl_2 (2 mL) was added instantly into it. The reaction was monitored by TLC until the consumption of the

starting material was complete. The reaction mixture was extracted with EtOAc (3 × 25 mL) and the organic layer was washed with 10% sodium thiosulfate solution to remove excess iodine. Finally, the organic layer was washed with water and dried over anhyd Na_2SO_4. The solvent was evaporated on rotary evaporator and the crude product was purified by column chromatography using 20:80 EtOAc–hexane.

1.2.1. 2,3,4,5-Tetra-*O*-acetyl-*aldehydo*-D-ribose (15)

White solid; mp 96–97 °C (lit[6] 93–94 °C); $[\alpha]_D^{25}$ −12.4 (*c* 1.0, MeOH); IR (KBr): 1748 (CO) cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 2.0 (s, 3H), 2.05 (s, 3H), 2.08 (s, 3H), 2.18 (s, 3H), 4.15 (dd, J = 4.4 Hz, J = 12.8 Hz, 1H), 4.34 (dd, J = 2.0 Hz, J = 8.4 Hz, 1H), 5.26–5.31 (m, 1H), 5.44 (d, J = 2.0 Hz, 1H), 5.60 (dd, J = 2.4 Hz, J = 9.2 Hz, 1H), 9.53 (s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 20.4, 20.7 (3C), 61.4, 68.3, 68.4, 76.7, 169.1, 169.5, 169.8, 170.6, 193.2. Anal. Calcd for $C_{13}H_{18}O_9$ (318.28): C, 49.06; H, 5.70. Found: C, 48.93; H, 5.61.

1.2.2. 2,3,4,5-Tetra-*O*-acetyl-*aldehydo*-L-arabinose (16)

White solid; mp 115–116 °C; $[\alpha]_D^{25}$ −60.0 (*c* 2.0, $CHCl_3$); IR (KBr): 1749 (CO) cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 2.07 (s, 3H), 2.07 (s, 3H), 2.07 (s, 3H), 2.08 (s, 3H), 4.16–4.20 (m, 1H), 4.31 (dd, J = 2.4 Hz, J = 12.4 Hz, 1H), 5.24–5.28 (m, 1H), 5.38 (d, J = 2.0 Hz, 1H), 5.68 (dd, J = 2.4 Hz, J = 9.2 Hz, 1H), 9.73 (s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 20.5, 20.7, 20.9 (2C), 61.7, 67.4, 68.2, 76.1, 169.8, 169.9, 170.9 (2C), 194.1. Anal. Calcd for $C_{13}H_{18}O_9$ (318.28): C, 49.06; H, 5.70. Found: C, 48.94; H, 5.61.

1.2.3. 2,3,4,5,6-Penta-*O*-acetyl-*aldehydo*-D-glucose (17)

White solid; mp 118–119 °C (lit[6] 116–117 °C), $[\alpha]_D^{25}$ +4.2 (*c* 2.0, $CHCl_3$); IR (KBr): 1749 (CO) cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 2.04 (s, 9H), 2.10 (s, 3H), 2.18 (s, 3H), 4.07 (dd, J = 5.2 Hz, J = 12.4 Hz, 1H), 4.25 (dd, J = 2.8 Hz, J = 12.8 Hz, 1H), 5.08–5.13 (m, 1H), 5.25 (d, J = 5.2 Hz, 1H), 5.48 (dd, J = 3.6 Hz, J = 7.6 Hz, 1H), 5.57 (dd, J = 3.6 Hz, J = 4.8 Hz, 1H), 9.50 (s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 20.4, 20.5, 20.6, 20.77, 20.83, 61.8, 68.3, 68.4, 68.6, 75.2, 169.4, 169.6, 169.8, 169.9, 170.7, 194.0. Anal. Calcd for $C_{16}H_{22}O_{11}$ (390.34): C, 49.23; H, 5.68. Found: C, 49.11; H, 5.60.

1.2.4. 2,3,4,5,6-Penta-*O*-acetyl-*aldehydo*-D-galactose (18)

White solid; mp 105–110 °C (lit[6] 106–110 °C), $[\alpha]_D^{25}$ −6.0 (*c* 2.0, $CHCl_3$); IR (KBr): 1750 (CO) cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 2.04 (s, 3H), 2.05 (s, 3H), 2.11 (s, 3H), 2.12 (s, 3H), 2.22 (s, 3H), 3.90 (dd, J = 3.6 Hz, J = 11.2 Hz, 1H), 4.28 (dd, J = 5.2 Hz, J = 11.6 Hz, 1H), 5.29 (d, J = 15.6 Hz, 1H), 5.37 (t, J = 5.6 Hz, 1H), 5.47 (d, J = 10.0 Hz, 1H), 5.65 (d, J = 9.6 Hz, 1H), 9.46 (s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 20.6, 20.8 (4C), 62.1, 66.4, 67.7 (2C), 75.9, 170.3, 170.5, 170.8 (3C), 193.9. Anal. Calcd for $C_{16}H_{22}O_{11}$ (390.34): C, 49.23; H, 5.68. Found: C, 49.09; H, 5.58.

1.2.5. 2,3,4,5,6-Penta-*O*-acetyl-*aldehydo*-D-mannose (19)

Syrup; $[\alpha]_D^{25}$ +23.6 (*c* 1.0, CH_2Cl_2); IR (KBr): 1749 (CO) cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 2.05 (s, 3H), 2.06 (s, 3H), 2.09 (s, 3H), 2.11 (s, 3H), 2.17 (s, 3H), 4.09–4.14 (m, 1H), 4.21 (dd, J = 2.8 Hz, J = 10.0 Hz, 1H), 5.03 (dd, J = 0.8 Hz, J = 7.6 Hz, 1H), 5.12–5.17 (m, 1H), 5.45–5.50 (m, 2H), 9.41 (s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 20.4, 20.5, 20.6, 20.7, 20.8, 61.8, 67.4, 67.6, 67.8, 74.3, 169.66, 169.7, 169.8, 170.0, 170.6, 195.4. Anal. Calcd for $C_{16}H_{22}O_{11}$ (390.34): C, 49.23; H, 5.68. Found: C, 49.33; H, 5.74.

1.2.6. 2,3,4,5-Tetra-*O*-acetyl-*aldehydo*-L-rhamnose (20)

Syrup; $[\alpha]_D^{25}$ −33 (*c* 0.06, CH_2Cl_2); IR (KBr): 1748 (CO) cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 1.04 (d, J = 6.4 Hz, 3H), 1.87 (s, 3H), 1.91 (s, 3H), 1.93 (s, 3H), 1.97 (s, 3H), 4.78–4.88 (m, 2H), 5.07–5.13 (m, 1H), 5.36 (d, J = 8.0 Hz, 1H), 9.35 (s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 16.6, 20.5, 20.7, 20.8, 21.0, 66.8, 67.4, 71.4, 74.3, 170.0, 170.1 (2C), 170.3, 195.5. Anal. Calcd for $C_{14}H_{20}O_9$ (332.30): C, 50.60; H, 6.07. Found: C, 50.46; H, 6.00.

1.2.7. 5-*O*-Acetyl-2,3,4,6-tetra-*O*-benzyl-*aldehydo*-D-glucose (21)

Syrup; IR (KBr): 1735 (CO) cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 1.90 (s, 3H), 3.62 (dd, J = 4.8 Hz, J = 11.2 Hz, 1H), 3.74 (dd, J = 3.2 Hz, J = 11.2 Hz, 1H), 3.81–3.85 (m, 2H), 3.95–3.97 (m, 1H), 4.30–4.44 (m, 7H), 4.71 (d, J = 11.6 Hz, 1H), 5.11 (d, J = 3.2 Hz, 1H), 7.07–7.23 (m, 20H), 9.59 (s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 21.2, 68.1, 72.5, 73.1, 73.2, 73.7, 74.0, 76.7, 79.7, 80.3, 127.7 (2C), 127.9 (2C), 128.1 (2C), 128.2 (2C), 128.3 (2C), 128.4 (3C), 128.43 (3C), 128.5 (4C), 137.1, 137.2, 137.6, 137.8, 170.0, 200.1. Anal. Calcd for $C_{36}H_{38}O_7$ (582.68): C, 74.21; H, 6.57. Found: C, 74.09; H, 6.48.

1.2.8. 2,3:4,5-Di-*O*-isopropylidene-*aldehydo*-L-arabinose (22)

Syrup; $[\alpha]_D^{25}$ +10 (*c* 0.25, CH_2Cl_2); IR (KBr): 1739 (CO) cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 1.33 (s, 3H), 1.36 (s, 3H), 1.40 (s, 3H), 1.45 (s, 3H), 3.94–4.15 (m, 4H), 4.39 (dd, J = 0.8 Hz, J = 6.0 Hz, 1H), 9.73 (s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 25.3, 26.4, 26.9, 27.2, 67.2, 76.65, 77.9, 83.5, 110.2, 112.1, 200.1. Anal. Calcd for $C_{11}H_{18}O_5$ (230.26): C, 57.38; H, 7.88. Found: C, 57.51; H, 7.97.

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References

1. Khan, A. T.; Sharma, P.; Schmidt, R. R. *J. Carbohydr. Chem.* **1995**, *14*, 1353–1367.
2. Khan, A. T.; Ahmed, W.; Schmidt, R. R. *Carbohydr. Res.* **1996**, *280*, 277–286.
3. Chang, Y. K.; Lee, B. Y.; Kim, D. J.; Lee, G. S.; Jeon, H. B.; Kim, K. S. *J. Org. Chem.* **2005**, *70*, 3299–3302.
4. Pattenden, G.; González, M. A.; Little, P. B.; Millan, D. S.; Plowright, A. T.; Tornos, J. A.; Ye, T. *Org. Biomol. Chem.* **2003**, *1*, 4173–4208.
5. Sun, J.; Han, X.; Yu, B. *Org. Lett.* **2005**, *7*, 1935–1938.
6. Roberts, J. C.; Nagasawa, H. T.; Zera, R. T.; Fricke, R. F.; Goon, D. J. W. *J. Med. Chem.* **1987**, *30*, 1891–1896.
7. Wolfrom, M. L. *J. Am. Chem. Soc.* **1929**, *51*, 2188–2193.
8. Wolfrom, M. L.; Newlin, M. R.; Stahly, E. E. *J. Am. Chem. Soc.* **1931**, *53*, 4379–4383.
9. Tang, C. J.; Wu, Y. *Tetrahedron* **2007**, *63*, 4887–4906.
10. Sambaiah, T.; Fanwick, P. E.; Cushman, M. *J. Org. Chem.* **2001**, *66*, 4405–4408.
11. Eitelman, S. J.; Horton, D. *Carbohydr. Res.* **2006**, *341*, 2658–2668.
12. Ohlsson, J.; Magnusson, G. *Carbohydr. Res.* **2001**, *331*, 91–94.
13. Lichtenthaler, F. W.; Lorenz, K.; Ma, W. Y. *Tetrahedron Lett.* **1987**, *28*, 47–50.
14. Khan, A. T.; Mondal, E.; Sahu, P. R. *Synlett* **2003**, 377–381.
15. Mondal, E.; Bose, G.; Khan, A. T. *Synlett* **2001**, 785–786.
16. Mandal, P. K.; Mishra, A. K. *Synlett* **2007**, 1207–1210.
17. Mondal, E.; Bose, G.; Sahu, P. R.; Khan, A. T. *Chem. Lett.* **2001**, *11*, 1158–1159.
18. Khan, A. T.; Boruwa, J.; Mondal, E.; Bose, G. *Indian J. Chem., Sect. B* **2001**, *40*, 1039–1042.
19. Khan, A. T.; Goswami, P.; Choudhury, L. H. *Tetrahedron Lett.* **2006**, *47*, 2751–2754.
20. Khan, A. T.; Goswami, P. *Tetrahedron Lett.* **2005**, *46*, 4937–4940.
21. Barua, P. M. B.; Sahu, P. R.; Mondal, E.; Bose, G.; Khan, A. T. *Synlett* **2002**, 81–84.
22. Shotwell, J. B.; Krygowski, E. S.; Hines, J.; Koh, B.; Huntsman, E. W. D.; Choi, H. W., ; Schneekloth, J. S., Jr.; Wood, J. L.; Crews, C. M. *Org. Lett.* **2002**, *4*, 3087–3089.
23. Blanc, A.; Toste, F. D. *Angew. Chem., Int. Ed.* **2006**, *45*, 2096–2099.
24. Kantam, M. L.; Neelam, B.; Reddy, C. V.; Chaudhuri, M. K.; Dehury, S. K. *Catal. Lett.* **2006**, *95*, 19–22.
25. Khan, A. T.; Khan, M. M. *Carbohydr. Res.* **2010**, *345*, 2139–2145.

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New three-component condensation reaction: synthesis of 1-[(alkylthio)(phenyl)methyl]-naphthalene-2-ol catalyzed by bromodimethylsulfonium bromide (BDMS)

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ABSTRACT

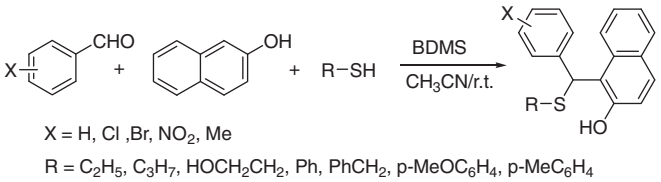
Bromodimethylsulfonium bromide acts as an efficient catalyst for one pot three component condensation reactions of aldehydes, 2-naphthol, and thiols in acetonitrile at room temperature. Various aliphatic and aromatic thiols undergo conjugate addition with in situ generated enone in acetonitrile and provide good yields. The main features of this procedure are mild reaction conditions, good yields, and operational simplicity.

Carbon–sulfur bond formation has versatile application in organic synthesis[1] in view of many recent sulfur-containing natural and pharmaceutical products, which have potent antibiotic, antimicrobial, analgesic, anti-inflammatory, antipsychotic, anti-HIV, and anti-tumor activities.[2] 1,4 Conjugate addition of a thiol nucleophile to an acceptor (alkene or alkyne) activated by an electron-withdrawing group namely the thia-Michael addition constitutes an important C–S bond forming strategy in organic synthesis.[3] The reported methods for thia-Michael addition are mainly focused on the use of acidic and basic catalysts for the direct addition of thiols to Michael acceptors in organic solvents.

Both from an atom-economic point of view as well as simplicity of the procedure, the thia-Michael addition is the preferred method for the preparation of organosulfur compounds. An acid or a base can be used as a promoter for this transformation. Over the years, numerous methods have been reported using a variety of catalysts, such as Cinchona alkaloid-squareamide,[4a] [**L**$Ni_2(CH_3CN)(THF)](ClO_4)_3$,[4b] $InCl_3$,[4c] silica nanoparticles,[4d] (IMesPr)AuCl,[4e] [Ru(acetone)(R,R-BIPHOP-F)Cp][SbF_6],[4f] cinchona alkaloid-derived urea,[4g] NEt_3,[4h] SDS/$NaHCO_3$,[4i] Co/SBA-15,[4j] $VO(OTf)_2$,[4k] silica–alumina supported NEt_3.[4l] It is highly desirable to develop a convenient, environment friendly method for the thia-Michael addition reaction. In this paper, we report the use of BDMS as a highly useful catalyst for the addition of thiols to the in situ generated enones from the reaction of aromatic aldehydes and 2-naphthol. To the best of our knowledge, these compounds are not reported till now.

Bromodimethylsulfonium bromide (BDMS) is a readily available, cheap, and highly efficient reagent[5] as well as a catalyst for various organic transformations.[5] In continuation of the present work on the development of new synthetic method, it has been observed that bromodimethylsulfonium bromide efficiently catalyzes the conjugate addition of various thiols to the in situ generated enones at room temperature (as shown in Scheme 1).

In the beginning of our study, benzaldehyde, 2-naphthol, and ethanethiol were chosen as model substrates. The reaction conditions were optimized for the synthesis of the 1-[(ethylthio)(phenyl)methyl]naphthalene-2-ol in terms of the yield and reaction time. Several reactions were scrutinized using different catalysts and various solvents, such as CH_3CN, DCM, and EtOH. The optimal amount of the reactants, such as benzaldehyde, 2-naphthol, thiol, and BDMS was found to be 1.0, 1.0, 1.1, and 0.1 equiv, respectively (Table 1, entry 3). We have noted that no



X = H, Cl ,Br, NO_2, Me

R = C_2H_5, C_3H_7, $HOCH_2CH_2$, Ph, $PhCH_2$, p-$MeOC_6H_4$, p-MeC_6H_4

Scheme 1. Synthesis of 1-[(alkylthio)(phenyl)methyl]naphthalene-2-ol.

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Table 1
Optimization for reaction conditions[a]

Entry	Catalyst	Solvent	Amount of catalyst (mol %)	Reaction Time (h)	Yield[b] (%)
1	No catalyst	Acetonitrile	0	6.0	0
2	BDMS	Acetonitrile	5	6.0	35
3	BDMS	Acetonitrile	10	6.0	74
4	BDMS	Acetonitrile	15	6.0	75
5	$Fe_2(SO_4)_3H_2O$	Acetonitrile	10	12.0	0
6	CH_3COOH	Acetonitrile	10	12.0	0
7	SiO_2–$HClO_4$	Acetonitrile	10	6.0	60
8	HBr–CH_3COOH	Acetonitrile	10	6.0	64
9	BDMS	DCM	10	6.0	71
10	BDMS	Ethanol	10	6.0	20

[a] All the reactions were carried out with 1 mmol scale.
[b] Isolated yield.

Table 2
Synthesis of 1-[(alkylthio)(phenyl)methyl]naphthalene-2-ol[7]

Entry	Aldehydes	Thiols	Time (h)	Yield[a] (%)
1	Bezaldehyde	Ethanethiol	6	74
2	Benzaldehyde	*n*-Propanethiol	6	73
3	Benzaldehyde	Thiophenol	8	21
4	*p*-Nitrobenzaldehyde	Ethanethiol	5	77
5	*p*-Nitrobenzaldehyde	*n*-Propanethiol	5	78
6	*p*-Nitrobenzaldehyde	Thiophenol	7	62
7	*p*-Chlorobenzaldehyde	*n*-Propanethiol	6	81
8	*p*-Chlorobenzaldehyde	Benzylthiol	6	71
9	*p*-Chlorobenzaldehyde	Thiophenol	8	30
10	*p*-Bromobenzaldehyde	*n*-Propanethiol	6	80
11	*p*-Bromobenzaldehyde	*p*-Methoxythiophenol	5	72
12	*p*-Methylbenzaldehyde	Ethanethiol	6	59
13	*m*-Nitrobenzaldehyde	Ethanethiol	5	77
14	*m*-Nitrobenzaldehyde	Mercaptoethanol	5	65
15	*m*-Bromobenzaldehyde	*p*-Thiocresol	5	70
16	*o*-Nitrobenzaldehyde	Ethanethiol	6	20
17	2-Naphthaldehyde	*p*-Thiocresol	6	73
18	*o*-Chlorobenzaldehyde	Ethanethiol	7	—

[a] Isolated yield.

product is formed in the absence of the catalyst. From this observation, it is obvious that BDMS plays an important role in the formation of the product.

The reaction was studied with other catalysts namely acetic acid, ferric sulfate, silica supported perchloric acid, and HBr–CH_3COOH. The best-suited catalyst for the reaction is BDMS. When 10 mol % of BDMS was used, the reaction proceeded smoothly and the yield was 74% (Table 1, entry 3). Moreover, the yield was found to be affected by the amount of BDMS added. When 0.0, 5, and 15 mol % of BDMS were used, the yield was 0.0%, 35%, and 75%, respectively (Table 1, entries 1, 2, and 4). It was noted that 10 mol % of BDMS was sufficient enough to carry out the reaction. Similarly, the role of solvent in this reaction was studied. Accordingly, the reaction was carried out in various solvents, such as acetonitrile, dichloromethane, and ethanol. It was found that acetonitrile is the most suitable solvent for this reaction.

Having established the optimized reaction condition, it was decided to explore the scope of this domino thia-Michael condensation reaction. Thus, several thiols were treated with a variety of aromatic aldehydes bearing different substituents NO_2, Br, Cl, Me at different positions and 2-naphthol in the presence of BDMS at room temperature in acetonitrile and the results were summarized in Table 2. Almost all reactions worked well with a variety of aromatic aldehydes including those bearing electron-withdrawing and electron-donating groups, such as NO_2, Br, Cl, and Me with ethanethiol, *n*-propanethiol, 2-mercaptoethanol, *p*-thiocresol, *p*-methoxythiophenol, benzylthiol, and thiophenol. The desired compounds were obtained in good to high yield within short reaction time (Table 2, entries 1, 2, 4–8, 10–15, and 17). It was shown that the aromatic aldehydes with electron withdrawing groups reacted faster than the aromatic aldehydes bearing electron donating groups as would be expected. With thiophenol, *p*-chlorobenzaldehyde gives a low yield of 30% (Table 2, entry 9) due to low electrophilicity of C-atom of the aldehyde group in comparison to arylaldehyde bearing nitro group at *para* position (62% yield, Table 2, entry 6). Similarly, the reaction of thiophenol, benzaldehyde, and 2-naphthol provides only 21% yield due to less nucleophilicity of the thiophenol. From these observations, it is quite clear that both electrophilicity of the aldehydic carbon and nucleophilicity of thiols play a crucial role for the formation of product. Furthermore, when *o*-nitrobenzaldehyde along with ethanethiol was taken, then the desired product was obtained in low yield (20%) due to steric hindrance of nitro group at *ortho*-position (Table 2, entry 16). In addition, when o-chlorobenzaldehyde along with ethanethiol was used, then no desired product was obtained (Table 2, entry 18). All these products were characterized by recording melting point, IR, ^1H NMR, ^{13}C NMR spectra, and elemental analysis.[7]

The formation of the 1-[(alkylthio)(phenyl)methyl]naphthalene-2-ol products can be explained as follows: It has been anticipated that bromodimethylsulfonium bromide may react with 2-naphthol to generate dry HBr in the reaction medium. The in situ generated dry HBr catalyzes Knoevenagel condensation between aromatic aldehydes and 2-naphthol to generate intermediate *ortho*-quinone methides (*o*-QMs, **A**)[6] as shown in Scheme 2. Then the intermediate A reacts with thiol to give the desired thia-Michael product.

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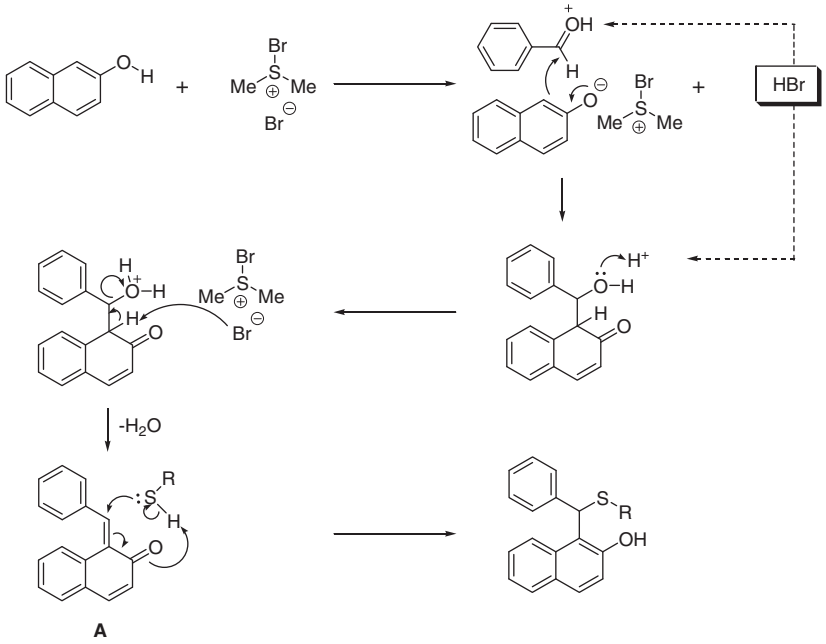

Scheme 2. Proposed mechanism for the formation of product.

In summary, a simple and efficient method for the one pot multicomponent reaction for the synthesis of 1-[(alkylthio) (phenyl) methyl] naphthalene-2-ol using aromatic aldehydes, 2-naphthol, and thiols catalyzed by bromodimethylsulfonium bromide (BDMS) has been devised. The catalyst used is inexpensive and efficient.

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Reference and notes

1. (a) Kondo, T.; Mitsudo, T.-A. *Chem. Rev.* **2000**, *100*, 3205; (b) Gilchrist, T. L. *Heterocyclic Chemistry*, 3rd ed.; Addison Wesley Longman: Essex, 1997; (c) Okazaki, R. In *Organosulfur Chemistry*; Academic: London, 1995; Vol. 1, p 225.
2. (a) Czarnik, A. W. *Acc. Chem. Res.* **1996**, *29*, 112; (b) Nguyen-Ba, N.; Brown, W. L.; Chan, L.; Lee, N.; Brasili, L.; Lafleur, D.; Zacharie, B. *Chem. Commun.* **1999**, 1245; (c) Ashizawa, T.; Kawashima, K.; Kanda, Y.; Gomi, K.; Okabe, M.; Ueda, K.; Tamaoki, T. *Anticancer Drugs* **1999**, *10*, 829; (d) Dewick, P. M. *Medicinal Natural Products*, 2nd ed.; John Wiley & Sons: West Sussex, England, 2002; (e) Vardanyan, R. S.; Hruby, V. J. *Synthesis of Essential Drugs*; Elsevier: Amsterdam, 2006.
3. Perlmutter, P. *Conjugate Addition Reactions in Organic Synthesis*; Pergamon: Oxford, 1992.
4. (a) Dai, L.; Wang, S.-X.; Chen, F.-E. *Adv. Synth. Catal.* **2010**, *352*, 2137; (b) Lee, W.-Z.; Tseng, H.-S.; Wang, T.-L.; Tsai, H.-L.; Kuo, T.-S. *Organometallics* **2010**, *29*, 2874; (c) Dia, R.-M.; Belaqziz, R.; Romane, A.; Antoniotti, S.; Dunach, E. *Tetrahedron Lett.* **2010**, *51*, 2164; (d) Banerjee, S.; Das, J.; Alvarez, R. P.; Santra, S. *New J. Chem.* **2010**, *34*, 302; (e) Corma, A.; Gonzalez-Arellano, C.; Iglesias, M.; Sanchez, F. *App. Catal. A General* **2010**, *375*, 49; (f) Badoiu, A.; Bernardinelli, G.; Besnard, C.; Kundig, E. P. *Org. Biomol. Chem.* **2010**, *8*, 193; (g) Rana, N. K.; Selvakumar, S.; Singh, V. K. *J. Org. Chem.* **2010**, *75*, 2089; (h) O'Byrne, A.; Murray, C.; Keegan, D.; Palacio, C.; Evans, P.; Morgan, B. S. *Org. Biomol. Chem.* **2010**, *8*, 539; (i) Firouzabadi, H.; Iranpoor, N.; Abbasi, M. *Adv. Synth. Catal.* **2009**, *351*, 755; (j) Rajabi, F.; Razavi, S.; Luque, R. *Green Chem.* **2010**, *12*, 786; (k) Chen, C.-T.; Lin, Y.-D.; Liu, C.-Y. *Tetrahedron* **2009**, *65*, 10470; (l) Motokura, K.; Tanaka, S.; Tada, M.; Iwasawa, Y. *Chem. Eur. J.* **2009**, *15*, 10871. and references cited therein.
5. Choudhury, L. H.; Parvin, T.; Khan, A. T. *Tetrahedron* **2009**, *65*, 9513. and references cited therein.
6. (a) Singh, R.; Panda, G. *Org. Biomol. Chem.* **2010**, *8*, 1097; (b) Snyder, S. A.; Breazzano, S. P.; Ross, A. G.; Lin, Y.; Zografos, A. L. *J. Am. Chem. Soc.* **2009**, *131*, 1753; (c) Van De Water, R. W.; Pettus, T. T. R. *Tetrahedron* **2002**, *58*, 5367.
7. *General procedure*: To a mixture of aldehyde (1 mmol) and 2-naphthol (1 mmol) in 3 mL of acetonitrile was added BDMS (0.1 mmol) and kept for stirring at room temperature. Then the corresponding thiol (1.1 mmol) was added into it. The reaction mixture was stirred at room temperature and the progress of the reaction was monitored by TLC. After completion of the reaction, ethyl acetate (25 mL) was added into it and the organic layer was washed with 10 mL of water. The water layer was further extracted using ethyl acetate (2 × 25 mL). The combined organic layer dried over anhydrous sodium sulfate and it was concentrated under rotary evaporator. The crude mixture was purified through silica gel column chromatography and the desired product was obtained by eluting with ethyl acetate and hexane (1:99) mixture.
Spectral data:
1-((Ethylthio)(phenyl)methyl)naphthalen-2-ol (Table 2, entry 1): pale yellow semi-solid; ^{1}H NMR (400 MHz, $CDCl_3$): δ 1.22 (t, J = 7.6 Hz, 3H), 2.45–2.59 (m, 2H), 6.33 (s, 1H), 7.22 (d, J = 9.2 Hz, 2H), 7.27 (t, J = 8.0 Hz, 2H), 7.32 (d, J = 7.6 Hz, 1H), 7.38–7.44 (m, 3H), 7.78 (d, J = 7.6 Hz, 2H), 7.86 (d, J = 7.2 Hz, 1H), 9.08 (s, 1H, OH); ^{13}C NMR (100 MHz, $CDCl_3$): δ 14.4, 26.8, 46.3, 113.5, 120.3, 121.8, 123.3, 127.2, 127.8, 128.4 (2C), 129.0 (2C), 129.2, 129.5, 130.5, 133.4, 138.6, 155.4; IR (KBr, cm^{-1}): 3429 (OH); Anal. Calcd $C_{19}H_{18}OS$ (294.41): requires C, 77.51; H, 6.16. Found C, 77.41; H, 6.22.
1-(Phenyl(propylthio)methyl)naphthalen-2-ol (Table 2, entry 2): pale yellow semi-solid; ^{1}H NMR (400 MHz, $CDCl_3$): δ 0.93 (t, J = 8.0 Hz, 3H), 1.55–1.64 (m, 2H), 2.39–2.46 (m, 1H), 2.52–2.58 (m, 1H), 6.28 (s, 1H), 7.22 (d, J = 8.0 Hz, 2H), 7.26–7.33 (m, 3H), 7.39–7.43 (m, 3H), 7.79 (d, J = 8.4 Hz, 2H), 7.85 (d, J = 8.4 Hz, 1H), 9.14 (s, 1H, OH); ^{13}C NMR (100 MHz, $CDCl_3$): δ 13.5, 22.4, 34.6, 46.7, 113.6, 120.3, 121.8, 123.3, 127.2, 127.8, 128.3 (2C), 128.9 (2C), 129.2, 129.5, 130.4, 133.4, 138.8, 155.3; IR (KBr, cm^{-1}): 3439 (OH); Anal. Calcd $C_{20}H_{20}OS$ (308.44): requires C, 77.88; H, 6.54. Found C, 77.78; H, 6.49.
1-(Phenyl(phenylthio)methyl)naphthalen-2-ol (Table 2, entry 3): pale yellow semisolid. ^{1}H NMR (400 MHz, $CDCl_3$): δ 6.62 (s, 1H), 7.10–7.16 (m, 4H), 7.23–7.36 (m, 7H), 7.51 (dd, J_1 = 1.2 Hz, J_2 = 6.4 Hz, 2H), 7.69–7.73 (m, 2H), 7.80 (d, J = 8.8 Hz, 1H), 8.25 (s, 1H, OH) ppm; ^{13}C NMR (100 Hz, $CDCl_3$): δ 50.6, 115.4, 119.8, 122.3, 123.3, 127.0, 127.7, 127.9, 128.5 (2C), 129.0 (3C), 129.1 (2C), 129.5, 130.4, 131.0 (2C), 132.9, 134.1, 138.5, 154.1 ppm; IR (KBr, cm^{-1}: 3445 (–OH); Anal. Calcd $C_{23}H_{18}OS$ (342.45): requires C, 80.67; H, 5.30. Found C, 80.49; H, 5.21.
1-((Ethylthio)(4-nitrophenyl)methyl)naphthalen-2-ol (Table 2, entry 4): pale yellow solid, mp 127–129 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ 1.25 (t, J = 7.6 Hz, 3H), 2.49–2.65 (m, 2H), 6.36 (s, 1H), 7.22 (d, J = 8.8 Hz, 1H), 7.33 (t, J = 7.6 Hz, 1H), 7.43 (t, J = 8.0 Hz, 1H), 7.57 (d, J = 8.4 Hz, 2H), 7.77–7.83 (m, 3H), 8.11 (d, J = 8.8 Hz, 2H), 8.61 (s, 1H, OH); ^{13}C NMR (100 MHz, $CDCl_3$): δ 14.4, 27.1, 45.4, 113.2, 120.1, 121.7, 123.7, 124.0 (2C), 127.5, 129.4 (3C), 129.6, 131.0, 133.0, 146.6, 147.3, 154.9; IR (KBr, cm^{-1}: 3432 (OH), 1514 (NO_2), 1346 (NO_2); Anal. Calcd $C_{19}H_{17}NO_3S$ (339.41): requires C, 67.24; H, 5.05; N, 4.13. Found C, 67.12; H, 4.97; N, 4.05.
1-((4-Nitrophenyl)(propylthio)methyl)naphthalen-2-ol (Table 2, entry 5): pale yellow semi-solid; ^{1}H NMR (400 MHz, $CDCl_3$): δ 0.95 (t, J = 7.6 Hz, 3H), 1.58–1.65 (m, 2H), 2.44–2.51 (m, 1H), 2.57–2.63 (m, 1H), 6.32 (s, 1H), 7.23

(d, J = 8.4 Hz, 1H), 7.35 (t, J = 7.2 Hz, 1H), 7.44 (t, J = 9.2 Hz, 1H), 7.58 (d, J = 8.4 Hz, 2H), 7.77 (d, J = 8.4 Hz, 1H), 7.82 (d, J = 8.0 Hz, 1H), 7.83 (d, J = 9.2 Hz, 1H), 8.13 (d, J = 8.8 Hz, 2H), 8.71 (s, 1H, OH); ^{13}C NMR (100 MHz, $CDCl_3$): δ 13.6, 22.5, 35.0, 45.9, 113.4, 120.2, 121.7, 123.8, 124.1 (2C), 127.6, 129.5 (3C), 129.7, 131.1, 133.1, 146.8, 147.4, 155.1; IR (KBr, cm^{-1}: 3437 (OH), 1518 (NO_2), 1346 (NO_2); Anal. Calcd $C_{20}H_{19}NO_3S$ (353.43): requires C, 67.97; H, 5.42; N, 3.96. Found C, 67.84; H, 5.31; N, 3.87.

1-((4-Nitrophenyl)(phenylthio)methyl)naphthalen-2-ol (Table 2, entry 6): pale yellow semi-solid; ^{1}H NMR (400 MHz, $CDCl_3$): δ 6.68 (s, 1H), 7.05 (t, J = 7.2 Hz, 1H), 7.10–7.18 (m, 5H), 7.29 (d, J = 7.6 Hz, 2H), 7.56 (d, J = 8.8 Hz, 2H), 7.60–7.64 (m, 3H), 7.95 (d, J = 8.8 Hz, 2H), 9.52 (s, 1H, OH); ^{13}C NMR (100 MHz, $CDCl_3$): δ 49.0, 116.8, 118.6, 123.1, 123.5, 123.6 (2C), 126.9, 127.5, 129.0 (2C), 129.1 (3C), 129.6, 130.5, 130.7 (2C), 132.2, 134.7, 146.6, 147.8, 152.3; IR (KBr, cm^{-1}: 3437 (OH), 1515 (NO_2), 1345 (NO_2); Anal. Calcd $C_{23}H_{17}NO_3S$ (387.45): requires C, 71.30; H,4.42; N, 3.62. Found C, 71.19; H, 4.33; N, 3.51.

1-((4-Chlorophenyl)(propylthio)methyl)naphthalen-2-ol (Table 2, entry 7): Pale yellow solid, mp 88–91 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ 0.85 (t, J = 7.2 Hz, 3H), 1.46–1.56 (m, 2H), 2.31–2.38 (m, 1H), 2.43–2.50 (m, 1H), 6.15 (s, 1H), 7.15 (t, J = 8.4 Hz, 3H), 7.23–7.27 (m, 3H), 7.35 (t, J = 7.6 Hz, 1H), 7.68–7.73 (m, 3H), 8.94 (s, 1H, OH); ^{13}C NMR (100 MHz, $CDCl_3$): δ 13.5, 22.4, 34.7, 45.9, 113.3, 120.3, 121.6, 123.5, 127.3, 129.1 (2C), 129.3, 129.5, 129.8 (2C), 130.7, 133.2, 133.6, 137.3, 155.3; IR (KBr, cm^{-1}: 3436 (OH); Anal. Calcd $C_{20}H_{19}ClOS$ (342.88): requires C, 70.06; H, 5.59. Found C, 69.93; H, 5.49.

1-((Benzylthio)(4-chlorophenyl)methyl)naphthalen-2-ol (Table 2, entry 8): pale yellow semi-solid; ^{1}H NMR (400 MHz, $CDCl_3$): δ 3.51 (d, J = 13.2 Hz, 1H), 3.61 (d, J = 13.6 Hz, 1H), 5.85 (s, 1H), 6.90 (d, J = 6.8 Hz, 2H), 7.07–7.23 (m, 9H), 7.37 (d, J = 8.4 Hz, 2H), 7.71 (t, J = 8.8 Hz, 2H), 8.81 (s, 1H, OH); ^{13}C NMR (100 MHz, $CDCl_3$): δ 37.0, 45.2, 112.8, 120.2, 121.9, 123.5, 127.1, 127.6, 128.8 (2C), 129.0 (2C), 129.1, 129.2 (2C), 129.5, 129.9 (2C), 130.8, 133.1, 133.6, 136.5, 136.8, 155.3; IR (KBr, cm^{-1}: 3430 (OH); Anal. Calcd $C_{24}H_{19}ClOS$ (390.93): requires C, 73.74; H, 4.90. Found C, 73.61; H, 4.99.

1-((4-Chlorophenyl)(phenylthio)methyl)naphthalen-2-ol (Table 2, entry 9): pale yellow semi-solid; ^{1}H NMR (400 MHz, $CDCl_3$): δ 6.56 (s, 1H), 7.12–7.15 (m, 3H), 7.24–7.29 (m, 3H), 7.32–7.38 (m, 4H), 7.42 (d, J = 8.4 Hz, 2H), 7.71 (d, J = 8.8 Hz, 1H), 7.72 (d, J = 8.0 Hz, 1H), 7.74 (d, J = 8.0 Hz, 1H), 8.04 (s, 1H, OH); ^{13}C NMR (100 MHz, $CDCl_3$): δ 50.0, 115.2, 119.9, 122.2, 123.5, 127.2, 128.0, 129.2 (3C), 129.3 (2C), 129.6, 129.9 (3C), 130.6, 131.2 (2C), 132.8, 133.7, 137.2, 154.0; IR (KBr, cm^{-1}: 3450 (OH); Anal. Calcd $C_{23}H_{17}ClOS$ (376.90): requires C, 73.29; H, 4.55. Found C, 73.09; H, 4.46.

1-((4-Bromophenyl)(propylthio)methyl)naphthalen-2-ol (Table 2, entry 10): pale yellow solid, mp 96–99 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ 0.93 (t, J = 7.2 Hz, 3H), 1.54–1.64 (m, 2H), 2.39–2.45 (m, 1H), 2.51–2.58 (m, 1H), 6.21 (s, 1H), 7.21 (d, J = 8.8 Hz, 1H), 7.27 (d, J = 9.2 Hz, 2H), 7.33 (t, J = 7.6 Hz, 1H), 7.39 (d, J = 8.8 Hz, 2H), 7.43 (d, J = 6.8 Hz, 1H), 7.80 (d, J = 8.8 Hz, 3H), 9.01 (s, 1H, OH); ^{13}C NMR (100 MHz, $CDCl_3$): δ 13.6, 22.4, 34.8, 46.0, 113.2, 120.4, 121.6, 121.8, 123.5, 127.3, 129.3, 129.5, 130.1 (2C), 130.7, 132.1 (2C), 133.3, 137.9, 155.3; IR (KBr, cm^{-1}: 3423 (OH); Anal. Calcd $C_{20}H_{19}BrOS$ (387.33): requires C, 62.02; H, 4.94. Found C, 61.93; H, 4.99.

1-((4-Bromophenyl)((4-methoxyphenyl)thio)methyl)naphthalen-2-ol (Table 2, entry 11): pale yellow semi-solid; ^{1}H NMR (400 MHz, $CDCl_3$): δ 3.61 (s, 3H), 6.39 (s, 1H), 6.62 (d, J = 8.8 Hz, 2H), 7.16 (d, J = 8.8 Hz, 1H), 7.23 (t, J = 8.0 Hz, 1H), 7.29–7.35 (m, 5H), 7.37–7.40 (m, 2H), 7.66–7.71 (m, 3H), 8.38 (s, 1H, OH); ^{13}C NMR (100 MHz, $CDCl_3$): δ 51.8, 55.3, 114.8 (2C), 115.0, 119.8, 121.7, 122.1, 123.36, 123.45, 127.0, 129.0, 129.5, 130.2 (2C), 130.5, 132.0 (2C), 132.9, 134.7 (2C), 137.7, 154.0, 160.0; IR (KBr, cm^{-1}: 3437 (OH); Anal. Calcd $C_{24}H_{19}BrO_2S$ (451.38): requires C, 63.86; H, 4.24. Found C, 63.93; H, 4.30.

1-((Ethylthio)(p-tolyl)methyl)naphthalen-2-ol (Table 2, entry 12): pale yellow semi-solid; ^{1}H NMR (400 MHz, $CDCl_3$): δ 1.18 (t, J = 7.6 Hz, 3H), 2.24 (s, 3H), 2.40–2.55 (m, 2H), 6.28 (s, 1H), 7.05 (d, J = 8.0 Hz, 2H), 7.20 (d, J = 8.8 Hz, 1H), 7.27 (t, J = 8.8 Hz, 1H), 7.28 (d, J = 7.6 Hz, 2H), 7.38 (t, J = 8.4 Hz, 1H), 7.75 (d, J = 8.8 Hz, 2H), 7.84 (d, J = 8.8 Hz, 1H), 9.09 (s, 1H, OH); ^{13}C NMR (100 MHz, $CDCl_3$): δ 14.3, 21.2, 26.7, 46.0, 113.7, 120.2, 121.8, 123.2, 127.1, 128.2 (2C), 129.1, 129.4, 129.6 (2C), 130.3, 133.3, 135.6, 137.5, 155.3; IR (KBr, cm^{-1}: 3417 (OH); Anal. Calcd $C_{20}H_{20}OS$ (308.44): requires C, 77.88; H, 6.54. Found C, 77.79; H, 6.46.

1-((Ethylthio)(3-nitrophenyl)methyl)naphthalen-2-ol (Table 2, entry 13): pale yellow semi-solid; ^{1}H NMR (400 MHz, $CDCl_3$): δ 1.25 (t, J = 7.2 Hz, 3H), 2.50–2.65 (m, 2H), 6.37 (s, 1H), 7.24 (d, J = 8.8 Hz, 1H), 7.35 (d, J = 7.2 Hz, 1H), 7.40–7.47 (m, 2H), 7.67 (d, J = 8.0 Hz, 1H), 7.78–7.84 (m, 3H), 8.09 (d, J = 8.4 Hz, 1H), 8.35 (s, 1H), 9.30 (s, 1H, OH); ^{13}C NMR (100 MHz, $CDCl_3$): δ 14.4, 27.1, 45.3, 115.0, 120.3, 121.5, 122.8, 123.6, 123.7, 127.5, 129.4, 129.7, 129.9, 130.1, 133.0, 134.5, 141.2, 148.7, 155.2; IR (KBr, cm^{-1}: 3445 (OH), 1527 (NO_2), 1349 (NO_2); Anal. Calcd $C_{19}H_{17}NO_3S$ (339.41): requires C, 67.24; H, 5.05, N, 4.13. Found C, 67.12; H, 5.14, N, 4.21.

1-(((2-Hydroxyethyl)thio)(3-nitrophenyl)methyl)naphthalen-2-ol (Table 2, entry 14): pale yellow solid, mp 142–145 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ 2.31 (brs, 1H), 2.75 (q, J = 5.6 Hz, 2H), 3.81 (s, 2H), 6.50 (s, 1H), 7.20 (d, J = 8.8 Hz, 1H), 7.32 (t, J = 8.0 Hz, 1H), 7.39 (t, J = 9.2 Hz, 1H), 7.41 (t, J = 8.0 Hz, 1H), 7.68 (d, J = 8.0 Hz, 1H), 7.74 (d, J = 8.4 Hz, 1H), 7.79 (d, J = 8.4 Hz, 2H), 8.08 (d, J = 8.0 Hz, 1H), 8.39 (s, 1H), 9.80 (s, 1H, OH); ^{13}C NMR (100 MHz, CD_3OD): δ 36.3, 45.0, 62.4, 118.6, 119.3, 122.3, 123.7, 123.8, 125.8, 126.8, 129.9, 130.2, 131.0, 133.1, 135.3, 145.6, 149.4, 154.1; IR (KBr, cm^{-1}: 3531 (OH), 1531 (NO_2), 1351 (NO_2); Anal. Calcd $C_{19}H_{17}NO_4S$ (355.41): requires C, 64.21; H, 4.82, N, 3.94. Found C, 64.12; H, 4.71, N, 3.81.

1-((3-Bromophenyl)(*p*-tolylthio)methyl)naphthalen-2-ol (Table 2, entry 15): pale yellow semi-solid; ^{1}H NMR (400 MHz, $CDCl_3$): δ 2.20 (s, 3H), 6.57 (s, 1H), 6.97 (d, J = 8.0 Hz, 2H), 7.16 (t, J = 8.0 Hz, 1H), 7.21 (d, J = 8.8 Hz, 1H), 7.31 (t, J = 7.2 Hz, 1H), 7.35 (d, J = 8.0 Hz, 2H), 7.38–7.43 (m, 2H), 7.46 (d, J = 7.6 Hz, 1H), 7.73–7.77 (m, 3H), 7.80 (d, J = 8.8 Hz, 1H), 8.32 (s, 1H, OH); ^{13}C NMR (100 MHz, $CDCl_3$): δ 21.1, 50.7, 115.0, 119.7, 122.2, 122.9, 123.4, 127.1 (2C), 129.0, 129.5, 130.0 (2C), 130.4, 130.5, 130.9, 131.5 (2C), 131.8 (2C), 132.8, 138.3, 141.2, 153.9; IR (KBr, cm^{-1}: 3436 (OH); Anal. Calcd $C_{24}H_{19}BrOS$ (435.38): requires C, 66.21; H, 4.40. Found C, 66.12; H, 4.34.

1-((Ethylthio)(2-nitrophenyl)methyl)naphthalen-2-ol (Table 2, entry 16): pale yellow semi-solid; ^{1}H NMR (400 MHz, $CDCl_3$): δ 1.25 (s, J = 7.6 Hz, 3H), 2.56–2.64 (m, 2H), 7.23 (s, 1H), 7.25 (d, J = 9.2 Hz, 1H), 7.28 (dd, J_1 = 3.6 Hz, J_2 = 5.6 Hz, 1H), 7.34 (t, J = 6.8 Hz, 1H), 7.38 (dd, J_1 = 3.6 Hz, J_2 = 6.4 Hz, 2H), 7.46 (t, J = 7.6 Hz, 1H), 7.80 (d, J = 8.0 Hz, 1H), 7.84 (d, J = 9.2 Hz, 1H), 7.91 (d, J = 8.4 Hz, 1H), 7.95 (dd, J_1 = 3.6 Hz, J_2 = 5.6 Hz, 1H), 9.55 (s, 1H, OH); ^{13}C NMR (100 MHz, $CDCl_3$): δ 13.9, 27.7, 41.4, 111.4, 120.5, 121.9, 123.7, 125.7, 127.8, 129.0, 129.2, 129.6, 130.6, 131.2, 133.0, 133.5, 133.6, 149.1, 156.5; IR (KBr, cm^{-1}: 3433 (OH), 1528 (NO_2), 1353 (NO_2); Anal. Calcd $C_{19}H_{17}NO_3S$ (339.41): requires C, 67.24; H, 5.05, N, 4.13. Found C, 67.12; H, 5.14, N, 4.19.

1-(Naphthalen-2-yl(p-tolylthio)methyl)naphthalen-2-ol (Table 2, entry 17): White solid, mp 117–120 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ 2.20 (s, 3H), 6.68 (s, 1H), 6.95 (d, J = 7.6 Hz, 2H), 7.21 (d, J = 9.2 Hz, 1H), 7.26 (t, J = 7.6 Hz, 1H), 7.32 (d, J = 8.0 Hz, 2H), 7.33 (t, J = 7.6 Hz, 1H), 7.41–7.46 (m, 2H), 7.67 (dd, J_1 = 2.0 Hz, J_2 = 8.8 Hz, 1H), 7.72–7.76 (m, 3H), 7.77–7.82 (m, 3H), 7.87 (s, 1H), 8.51 (s, 1H, OH); ^{13}C NMR (100 MHz, $CDCl_3$): δ 21.2, 51.9, 115.0, 120.2, 122.2, 123.3, 126.4 (2C), 126.7, 127.1, 127.4, 127.7, 128.3, 128.9, 129.0, 129.5, 130.0 (2C), 130.5, 131.7 (3C), 133.0, 133.1, 133.6, 135.9, 138.2, 154.6; IR (KBr, cm^{-1}: 3434 (OH); Anal. Calcd $C_{28}H_{22}OS$ (406.54): requires C, 82.72; H, 5.45. Found C, 82.82; H, 5.54.