HYPERVALENT IODONIUM-CATALYSED DEBENZYLATION OF ARYL BENZYL ETHERS

by

MOKOENA TANKISO LEBOHANG

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PROMOTER: Dr S J MKHIZE

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DECLARATION

I, the undersigned, hereby declare that the research in this thesis is my original work, which has not been partly or fully submitted to any other university/faculty in order to obtain a degree.

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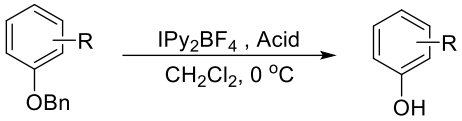
T L Mokoena

DEDICATION

This work is dedicated to my family and laboratory friends for their unparalleled support in this project. The special dedication to my mother who passed away before she can see the results of her unwavering support and love through my studies. The special thanks to my son Letlotlo and partner Lebohang. I could not have achieved the knowledge and skill to be able to sharpen my science, all thanks to my supervisor Dr Mkhize for being at guidance with his extraordinary passion and love for chemistry. I will also like to acknowledge the financial support from grow your own timber UNISA project.

ABSTRACT

This work entails an alternative, convenient and efficient debenzylation method for phenolic benzyl ethers containing electron-rich substituents on the phenolic ring using a catalytic amount of Barluenga's reagent (IPy_2BF_4) in the presence of triflic acid as shown in Scheme 1.



Scheme 1: Proposed general method for the debenzylation of benzyl ethers using IPy_2BF_4 in acidic conditions

A number of mono-substituted aryl benzyl ethers containing electron donating (EDG) or electron withdrawing group (EWG) substituent at the *ortho, meta and para* position were employed to probe the electron effect of the debenzylation method. The electron donating groups (EDG) showed better rates as compared to electron withdrawing groups (EWG), while halogenated (mon-substituted) derivatives showed lower yields. We found that this method works better than previously published methods for debenzylation of a number of estrone derivatives.

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ABBREVIATIONS

δ	Chemical shift in ppm
aq.	Aqueous
Ar	Aromatic
BBr_3	Tribromide
BnBr	Benzyl bromide
Boc	*t*-Butyloxycarbonyl
br	Broad
brs	Broad singlet
cat.	Catalytic
Cys	Cystein
CH_2Cl_2	Dichloromethane / Methylene chloride
CH_3CN	Acetonitrile
d	Doublet
dd	Doublet of doublets
dt	Doublet of triplets
DMSO	Dimethylsulfoxide
EDG	Electron donating group
EDT	1,2-ethanedithiol
Et_3N	Triethylamine
Et_2O	Diethyl ether
EtOAc	Ethyl acetate
EtOH	Ethanol
EWG	Electron withdrawing group
g	Grams
HCl	Hydrochloric acid
hr	Hour
IPy_2BF_4	*Barluenga's* reagent
HRMS	High-resolution mass spectrometry
Hz	Hertz
IR	Infrared spectrometry
J	Coupling constant

m	Meta
m	Multiplet
M^+	Molecular ion
MeOH	Methanol
MEM	2-methoxyethoxymethyl ether
mg	Milligram(s)
MHz	Megahertz
mL	Millilitre(s)
MOM	methoxymethyl ether
mmol	Millimole(s)
Mp	Melting point
MsCl	Methanesulfonyl chloride
MTM	Methylthiomethyl
m/z	Mass to charge ratio
NMR	Nuclear magnetic resonance
NNRTI	Non-nucleoside reverse transcriptase inhibitor
Pd/C	Palladium-on-carbon
Pka	
rt	Room temperature
s	Singlet
S_N1	Unimolecular nucleophilic substitution
S_N2	Bimolecular nucleophilic substitution
t	Triplet
td	Triplet of doublets
TFA	Trifluoroacetic acid
TfOH	Triflic acid
THF	Tetrahydrofuran
TLC	Thin-layer chromatography
q	Quartet
UV/Vis	Ultra-violet/visible spectrum

Chapter 1

1 Introduction

1.1 General background

Before organic chemists saw a need to develop and synthesize natural compounds, the necessity to classify functional groups was not realized[1,2,3]. That remained until Emile Fisher, one of the pioneers who took the lead in synthesis and alteration of existing sugars, experienced many problems arising from incompatibility of functional structures within the molecules, which ultimately led to realization of protecting groups[1,3,4]. These problems resulted in the intensive research in order to circumvent them, which was discovered to be laborious and costly in terms of time, finance, and the yield[3,4]. Hence, the best way was to deactivate the interfering groups and 'the protecting group chemistry' was then born[2].

Protecting groups are essential additions in synthesis as they have a plethora of applications in the systematic synthesis in organic molecules[5,6]. The unavoidable and essentiality has resulted in numerous usage of protecting groups for different alterations[3]. Protecting groups are mostly applied as the means to mask a functional group that is deemed susceptible to the subsequent reaction conditions[3,7].

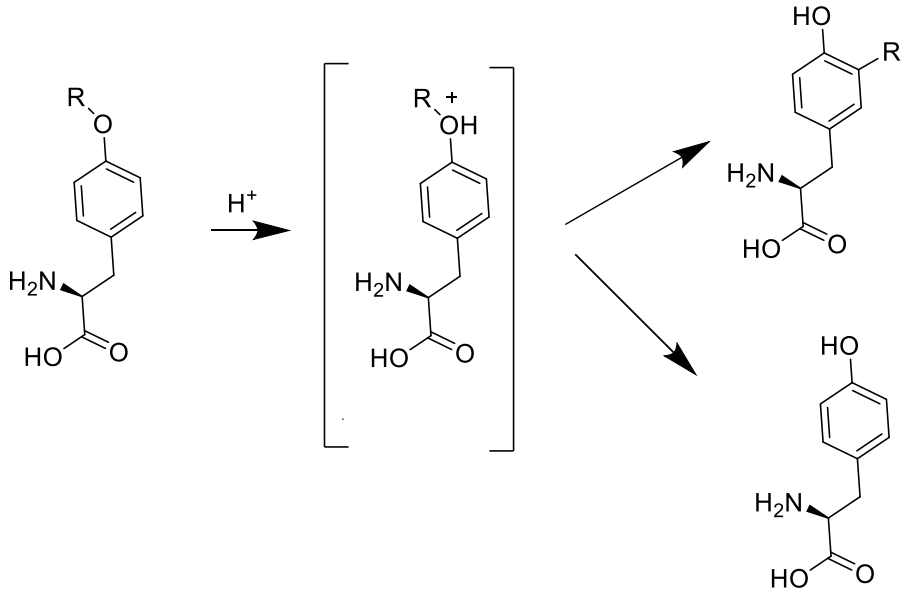
In most cases, protection is coupled with deprotection, which is also usually as challenging as the initial protection[3]. This dictates the conditions that must be optimized to give a better yield with limited or no side reactions. The deprotection methods are developed regularly in order to suit the uniqueness of the molecule to be deprotected. The deprotection, like protection, is also a thoughtful process that take many things in cognizance that being: the rate of cleavage, formation of side reactions, purification process, and all of which are governed by cost of reagents and availability[2].

Protecting using benzyl group has been applied intensively for its easy insertion in functional groups of interest; the hydroxyl protection, forming an ether, in aryl compounds is one of the most conducive technique, hence it was employed in this work[8]. The interest is stimulated by the tendency of aryl group to undergo migration of the benzyl cation to either *ortho* or *para* in absence of substituents in those regions. This setback was first observed while trying to protect

the amino acid tyrosine during peptide synthesis. The hydroxyl group of amino acid tyrosine has been mostly protected by benzyl group due to its structural stability. Though benzylated phenols are known to undergo acidic-mediated debenzylation, the major drawback of this methodology is the subsequent reaction of the substrate benzyl ether (particularly in the case of phenols bearing electron-donating substituents) with the benzyl electrophile that is produced during the cleavage of benzyl ether, which results in the migration of the benzyl of an *ortho/para*-benzyl substituted phenol. Expansion of these conditions of suppressing the benzyl carbocation side reactions by Kiso *et al*[9]. included the use of additives such as (catalytic) acid (triflic acid, (TfOH) or a large excess of nucleophilic benzyl scavenger (e.g. thioanisole, termed `push and pull` mechanism). This suppresses the production of side products and helps with purification, but these conditions also have their drawbacks such as the formation of other side products as well as difficulties in purifying the product also from them during separation[9].

Acidolytic removal of side chain protecting groups and cleavage of the peptide resin linkage with strong acids produces carbocation[6]. It was during the synthesis of proteins from amino acids, which needed to be protected and this what was noticed to form side reactions due to oxygen to carbon migration species readily alkylate sensitive side chains, such as those of cysteine (cys), tyrosine (tyr), and transient receptor potential (trp)[10,11]. Addition of nucleophiles, so-called scavengers, can quench the carbocation by trapping the formed benzylic carbocation, which is formed during the cleavage of benzyl ethers alkylation of cysteine (cys) can be prevented by thiol-containing scavengers, such as 1,2-ethanedithiol (EDT) which possess sulphur that is more reactive and a better nucleophile than cysteine; this enables the preclusion of side reactions[12].

The abovementioned study that involved the protection and deprotection in peptide synthesis elucidated the following challenge and shortcoming; tyrosine (tyr) was benzylated through intra- or intermolecular mechanisms, especially when the side chain is protected as a benzyl ether. To circumvent these challenges intramolecular alkylation can be suppressed using more acid stable protecting groups, aromatic scavengers, such as phenol, cresols or anisole are recommended to decrease intermolecular side reactions. Scheme 2 shows the acid mediated cleavage of protected tyrosine, the carbocation released may attack either the tyrosine *ortho* or *para*. The *para* part in tyrosine is already occupied; the *ortho* one becomes the target as it becomes one unneeded side reaction[9,10].



Scheme 2: Inter and intramolecular alkylation of tyrosine (try)

1.2 Ethers as protecting groups

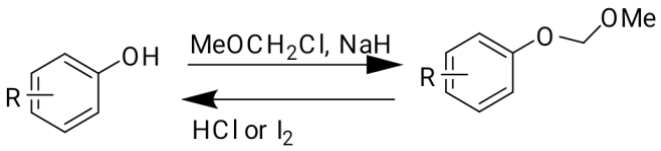
Before proceeding to benzyl ethers, examination of the most commonly used ethers for protection during synthesis and the conditions of their cleavage is of significance. The insight on methyl ethers, methoxymethyl ethers, methylthiomethyl ethers and allyl ethers in terms of how different methods of formation and cleavage have influenced their evolution. In this case, there is a contrast between alkyl ethers and the alkoxyalkyl that are commonly used in protection and how they can be used efficiently and correctly for different reaction objectives. There is always a continuous need to develop new and unique methods of protecting and deprotecting of alcohols/phenols. This is motivated by their ubiquitous nature in many natural and synthetic presences. This contrast is essential as it serve as a guide in the pursue to alter existing natural compounds or in synthesis of new targeted products[13].

Methylation of phenolic hydroxyl group has been the most preferred technique to mask the susceptible hydroxyl oxygen due to its stability against an array of reagents and various experimental conditions[14]. Unfortunately, the same stability act as a pitfall in the times of removal of methyl protecting group. This has resulted in employing harsh conditions including strong acids or bases, alkali metals, oxidising or reducing agents, which in most cases results in production of undesired side reactions and subsequently low yields accompanied with difficulties of purification. This is usually applied as long term protection in orthogonal

systematic protection. The orthogonal application of both labile groups and methyl ethers protection has been of great use for the synthesis of complex constituents. The methyl ethers are synthesized *via* adaptation of Williamson ether synthesis where a base is used as depicted in Scheme 3. Sodium hydroxide (NaOH) is used as base to deprotonate the substrate and dimethyl sulphate methylate as methylating agent. The cleavage is achieved by boron tribromide (BBr_3), one of the strong lewis acids with effective demethylating capabilities[15].

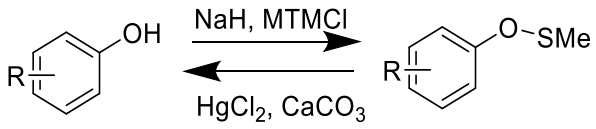
Scheme 3: Protection and deprotection of methyl ethers

Methoxymethyl ethers (MOM) serves as suitable alternative to methyl ethers due to their robustness in comparison to methyl ethers. They fall under the alkoxyalkyl ethers; and offers another worthy dimension in the alcohols and phenol protection. Similar to the methyl ethers, the methoxy ethers do not influence the symmetry of compounds or leads to complex spectroscopic analysis, which makes it advantageous to employ compared to tetrahydropyranylation. It is also stable in most experimental conditions that are basic; inert from oxidising, reducing agents, nucleophiles and electrophiles. The disadvantage involves its intolerance towards acidic medium. Nonetheless, the mild acidic conditions serve as an additional advantage during removal of methoxymethyl ethers (MOM). The protection and deprotection reagents for formation of methoxymethyl ether and cleavage are outlined in Scheme 4. The formation methoxymethyl ethers (MOM) is achieved by sodium hydride as a base and methoxymethyl chloride alkalyting agent, meanwhile cleavage using strong acid (hydrochloric acid) or molecular iodine[16-17].



Scheme 4: Protection and deprotection of Methoxymethyl ethers (MOM)

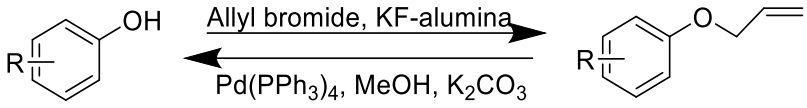
Methylthiomethyl ethers (MTM) have similar stability to methyl ethers towards strong bases or mild acids. Methylthiomethyl withstand aqueous acetic acid that dioxane and tetrahydropyranal ethers (THP) cannot survive due to their prone to hydrolyse in acid medium. The advantage it offers is that it can be removed in the presence of acetyl protecting groups such as methoxymethyl ether (MOM) and 2-methoxyethoxymethyl ether (MEM). The disadvantages includes its susceptibility to oxidation when compared to methyl ethers and methoxymethyl ethers (MOM), cannot survive strong oxidants (e.g. peracids, and chromium [Cr(VI)] and poisons the palladium-based catalysts). The formation of methylthiomethyl ethers (MTM) is by reacting a phenol with sodium hydride in the presence of methythiomethyl chloride as depicted in the Scheme 5. The cleavage is achieved by employing heavy metals that have high affinity for sulphur. Heavy metal mercury in the form of mercury chloride and calcium carbonate as a buffer for acid sensitive substrate can be utilized as shown in Scheme 3[18].



Scheme 5: Protection and deprotection of Methylthiomethyl ethers (MTM)

Allyl ethers are the important addition in the development of orthogonal variety in protecting groups. They were originally developed as protecting groups for carbohydrates hydroxyl groups. This was due to their robustness and compatibility to most reactions especially the glycosidation required for synthesis of oligosaccharides. They have salient limitation when it comes to strong electrophiles, for example bromine are forbidden as they promote catalytic hydrogenation. They are better compared to aforementioned protection varieties, as they are extremely stable to strong acid (e.g. pH = 1) and can survive moderately strong base. The challenge of allyl ethers lies in their resilience to easily cleave off. This mitigated by the ability of the double bond to rearrange into conjugation with oxygen atom to form a labile enol ether which can undergo hydrolysis or oxidation. The challenge of using allyl ethers is mostly based on the challenge of finding a suitable and gentle initiator of double bond rearrangement. , Giggs developed a novel method using potassium tert-butoxide (t-BuOK) in dimethyl sulfoxide

(DMSO) as initiator of double bond rearrangement, ,the problem with this method it requires harsh conditions and elevated temperatures. It is still applied if the substrate is robust and less sensitive. The prevalence of using allyl ethers in orthogonal setting increased as milder methods of initiating double bond rearrangement were found. The transition metals that are usually employed are palladium-carbon in methanol. The allyl ethers are usually formed from allyl bromide in basic conditions, which can be a limit if they tamper with existing functional groups. Scheme 6 shows the formation of allyl ether from allyl bromide and potassium fluoride-alumina. On the other hand, the deprotection is achieved by catalytic tetrakis(triphenylphosphine)palladium (0) [$Pd(PPh_3)_4$] in methanol with potassium carbonate as the base. This is the less harsh method compared to other previously developed methods[19].



Scheme 6: Protection and deprotection of ally ethers

1.3 Benzyl ethers formation and cleavage

Benzyl ethers are the most used and well developed ways of protecting hydroxyl groups and phenols. This is due to the ease in insertion and cleavage into many substrates without altering them. They possess same robustness as compared to methyl ethers. They offer uniqueness in terms of their resistance to aqueous acidic and basic mediums, also offer resistance from attack by metal hydrides (sodium hydride), reducing agents (formic acid) or mild oxidising agents (pyridinium chlorochromate). They have been found to be prone to exposure to elevated temperatures in the presence of metal hydrides such as lithium aluminium hydrides. The formation of benzyl ethers and the variety of ways of cleavage need to be explored to provide viable alternatives in case where conditions have negative effect on the existing functional groups[20].

1.3.1 Benzyl ethers formation

In the centre of this useful protection method, the importance lies in the variety of conditions of formation. The formation of ethers by a base is given credit to the curiosity of Alexander Williamson, which was elucidated by forming ethers from alcohols. The Williamson ether synthesis is a substitution nucleophilic bi-molecular (SN_2) reaction in which an alkoxide ion is turned into a nucleophile by a base. The Williamson's limitation of only using a base is compensated by other two methods in acidic and neutral environments. The acid medium is usually formed from the trichloroacetimidates. In cases, the existing intricate structure is labile/prone to both acid and basic media. This requires a neutral medium for insertion of benzyl; the preactivated pyridium salt has shown to provide this alternative. Figure 1 shows the basic, acidic and neutral ingredients for inserting benzyl group[21].

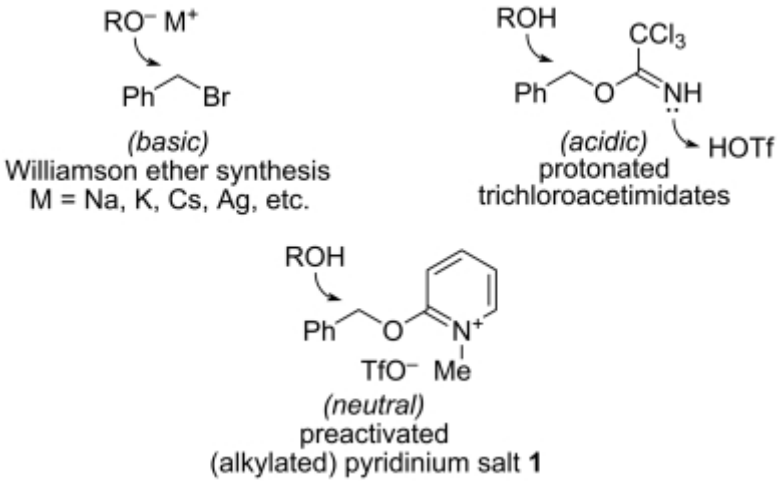


Figure 1: Protection methods for inserting benzyl

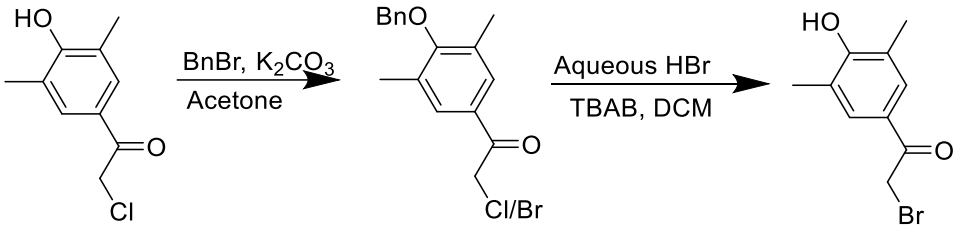
1.3.2 Benzyl ethers cleavage

As much as being important to protect a desired group, so as the removal/cleavage of the protecting group. The criteria expected to be met for successful and efficient cleavage of protecting group mirrors the one's for protection. Few conditions that have to be attained such as chemoselectivity (that means the reagents employed for removal of the designated group should only target that group), duration of reaction and reasonable yield. Chemoselectivity

limit the number of side reactions. Yet another important aspect is the yield, which has to be very good (i.e., above 80%). The duration of the reaction is also of paramount importance; with preferably shorter reaction times are essential from economic viewpoint. Nowadays there is greater emphasis and recommendation of green chemistry, hence the use of environmentally friendly reagents are desirable. All these factors are encompassed by one essential factor, i.e. the overall cost from the beginning to final product as determined by the yield[22].

The focus falls on the debenzylation of benzyl groups. Most of the available debenzylation methods were found by chance or existing one being enhanced. These methods discovered for debenzylation were found in pursue of other reactions, which led to the cleavage with concurrent achievement of the goal in hand, or only cleavage.

Bhalerao et al.[13] reported that when methylene chloro-substituent was subjected to benzylation with benzyl bromide, the product compound **2** resulted in the mixture of bromo and chloro derivatives (see Scheme 7). In pursue of having only methylene bromo, compound **2** was refluxed with hydrobromic acid in the presence of tetrabutyl ammonia to give compound **3,** this did not only convert compound **2** to fully brominated compound **3** but the benzyl group was cleaved. This method had advantages of being able to be remove the benzyl ether in the presence of methoxy protecting groups, while disadvantages include that it only works with substrates that have substituents *ortho* and *para* position[23].



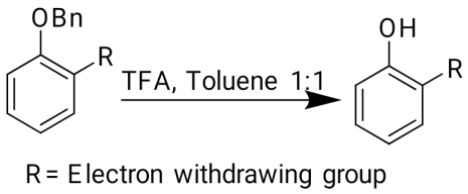
1 **2** **3**

Scheme 7: Benzyl cleavage of protection methods for inserting benzyl

In pursue to find a mild and efficient *O*-debenzylation, Fletcher and Gunning explored the trifluoroacetic acid effect on different substrates[24] . The focus of their communication was more about the electron withdrawing substituents. The *ortho* substituents were easily and swiftly debenzylated in comparison to the *meta* and *para* substituent, this let them to propose that the

chelation has the effect on the rates of debenzylation. The authors focus on only the electron withdrawing substituent was informed by the tendency of the electron donating substituents to enrich the aryl to act as benzyl cation scavenger. This usually leads to many side reactions, which complicates purification[24].

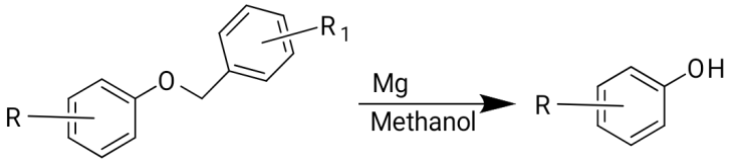
The effect of cation captors was also investigated for their abilities to improve yields and purities. PCresol, anisole and triethylsilane were explored, however, there was no significant influence on the product formation. Unfortunately, there was reduction on the quantity of the product. The more nucleophilic scavenger thioanisole as an additive to the solvent toluene gave better purities and high yields. The rates of debenzylation were found to be attributed mostly to the structure of the phenol substrate. The advantage of TFA mediated debenzylation is that is mild and does not need cation scavengers to accelerate reaction rates. The reaction times are reasonably shorter and provided alternative for electron withdrawing substituted compounds. The downside of this chelation effect could not be applicable to electron donating substituents, which are usually having problem of forming side reaction from O-C migration. Scheme 8 shows the general conditions of ratios (1:1) of TFA to toluene used cleavage[24].



Scheme 8: TFA mediated debenzylation

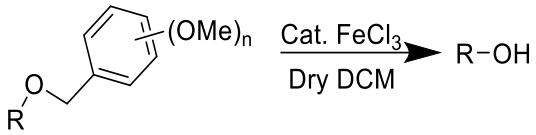
Some benzyl groups used in the protection are substituted with either donating or withdrawing group. These groups have a tremendous effect on the rates and effectiveness of the deprotecting reagents. For example, Huang *et al*[25] reported that a mixture of Mg (magnesium) and methanol resulted in reductive debenzylation. In this case, the substrate of interest were *O*-(carboxylate-benzyl) and *O*-(nitro-benzyl)-phenols[25]. During optimization, it was found that increasing the equivalence of magnesium is more relevant to good yield than increasing reaction time. It is worth to note that the findings involved when this reagent was applied to protecting groups *p*-CO_2Me-benzyl, *m*-CO_2Me(Et)-benzyl and *p*-NO_2-benzyl (which are substituted with good electron withdrawing groups) resulted in excellent yields of the desired phenols. This was different from the clean benzyl groups which shown stability against the reductive agents

magnesium (Mg), but the electron deficient benzyl groups were very labile to reductive reagents and were smoothly debenzylated within reasonable times. The benzyl groups with either halogen or alkyl groups needed large quantities of Mg to promote debenzylation cleavage. The advantage was found to be good yield. This technique may solve the challenges that come with formation of side reactions. The problem comes when there are functional groups within substrate that can undergo reduction. Scheme 9 shows the conditions for reductive cleavage of benzyl ether[25].



Scheme 9: Reductive cleavage using magnesium in methanol

The use of Lewis acid for debenzylation is also very prevalent. The iron chloride is able to debenzylate but in this regard it is used as a catalyst as reported by Sawama, *et al.*[26]. The catalytical amount of the iron chloride cleanly and swiftly debenzylate the electron donating substituted benzyl and produce the short chain polymer as the side product. The non-substituted benzyl group is not affected by the catalytic amount of iron chloride; it remains stable under these conditions. Iron chloride ($FeCl_3$) effectively catalyzes the deprotection of methoxyphenylmethyl-type ethers in a self-cleaving manner to produce oligomeric derivatives and alcohols. Remarkably, the highly pure product of alcohols can be obtained without silica gel column chromatography by using the 2, 4-dimethoxyphenylmethyl group as a protective group. The benzyl group is usually removed as toluene, when attached to oxygen atom in ethers, acetals, alcohols, to nitrogen in amino or to sulphur in thioester. The catalytic hydrogenolysis offers less harsh conditions for debenzylation, good quantitative yields, minimization of the side reactions and simplicity in terms of technicalities. The advantages of it come with limitations of experimental conditions, as every reaction requires unique approach. Scheme 10 shows the iron chloride ($FeCl_3$) in dichloromethane (DCM)[26].



Scheme10: Debenzylation by Lewis acid ($FeCl_3$)

1.4 The benzyl ether application in carbohydrates and proteins

The derivatives that involve natural products like carbohydrates and amino acids have offered many challenges in synthesis. The many functional groups in both proteins and carbohydrates makes it difficult to perform the desired reaction in their presence, which is the main reason why so many protecting and deprotecting methods have been developed in this field[27].

1.4.1 Protection and deprotection of carbohydrates

The application of benzyl ethers has been extensively applied in the journey for the synthesis of an array of carbohydrates derivatives[27]. In the pursue from both the chemists and biologist to explore the medical and biological possibilities, the challenge has been the highly functionalized carbohydrates. They possess large number of hydroxyl groups, which may be sensitive to some reaction conditions. These hydroxyl groups are usually in different position in the carbohydrates this offers disadvantages and advantages. The advantage is that different environments offers unique reactivity, this offers an array of new compounds. The disadvantage is with hydroxyl group reacting to similar environment which offers limited selectivity. In order to achieve desired carbohydrates derivatives, the orthogonal methods that include benzyl ethers and other protecting groups have been commonly employed. The benzyl ethers and its derivatives have been reliable for their resistance to many harsh conditions. Their removal by hydrogenolysis has also offered an additional advantage compared to other groups, which requires harsh conditions[28-29].

1.4.2 Protection and deprotection of proteins

Another significant role of benzyl ethers has been their utilization in peptide synthesis. The synthesis of amino acids peptide chains requires protection since amino acids possess a lot of functionalities including amino, carboxylic acids, thiols and hydroxyls groups. The amino acids serine (ser), threonine (thr) and hydroxyproline (hyp) which are prone to dehydration or o-acylation, usually linked, with oxygen to nitrogen migration after deprotection of amino acids. In peptide synthesis, the hydroxyl group of aforementioned amino acids is protected by ethers, especially benzyl ether owing to its stability in comparison to carbamates and esters. The benzyl ether and scavengers are usually used concurrently to minimize benzyl carbocation attack on the substrate[9]. For example, the peptide synthesis of tyrosine (tyr) without protection lead to acylation of the phenol group because of the formation of the phenolate ion under basic conditions, which has nucleophillicity[30,31] . The electron rich aromatic ring is also susceptible to alkylation on the *ortho* position. Most protection methods for ser, thr and hyp are ineffective because of the acidity of the phenol group in tyrosine (tyr), hence the benzyl ether are preferred due their stability[30].

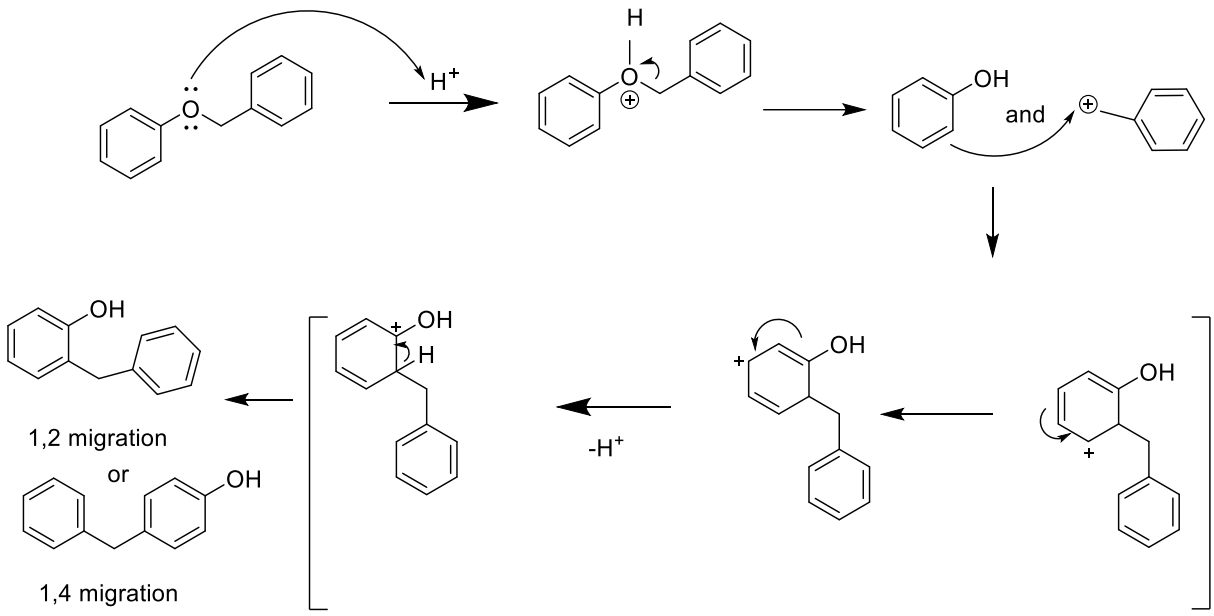
The reaction involving acid mediated cleavage of benzyl ethers usually results in the formation of benzylic carbocation along with targeted phenol. The benzylic carbocation formed is very electrophilic, hence it will attack a nucleophile at its vicinity. This has been the main concern of acid mediated benzyl ether cleavage as intermolecular benzylation of the deprotected phenol is attacked at *ortho* or *para* positions. Most of the early research works and findings of O-C migration has been with amino acids and ways to thwart this side reaction was also done mostly on amino acids. The findings obtained in peptide synthesis involving tyrosine the scavengers where used to derive better and efficient methods to minimize the side reactions and benzylic carbocation attack on the electron rich aryls[9,10,30,31].

1.5 Limitations of benzyl ethers and their solutions

There are many solutions for each potential factor hence over the years alternative protecting groups have been developed or, commonly, new methods have been developed to limit the formation of side reactions. The requirement to add the scavengers that are highly nucleophilic which may further add to side reaction and diminishing of yield has created a necessity to

explore more viable and efficient alternatives. For this purpose, we will limit our discussion to alternative deprotection methods for benzyl ethers.

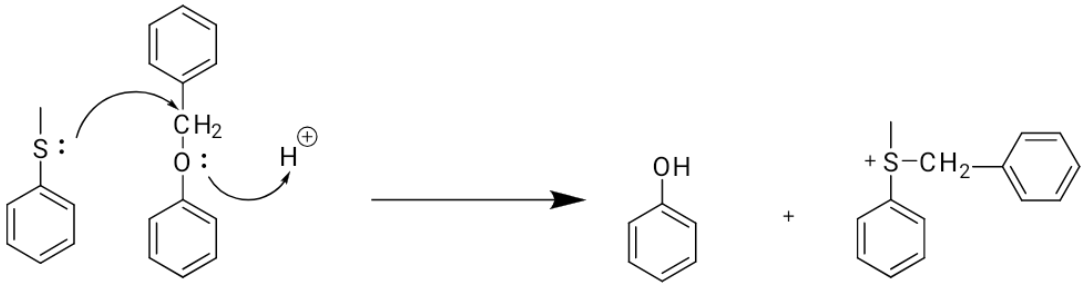
The side reactions are the most disturbing use of protecting groups as they augment a number of impurities in the reaction. This results in the tediousness that involves the purification of the desired product. This can worsen if the side reactions happen on the substrate of the expected compound, as this is the case with reactions involving the debenzylation of the aryl group that has electron donating substituents. This does not only affect the purity, but it also diminishes the yield of the targeted compound. The O-C migration is well known impurity that is prevalent in debenzylation of phenyl benzyl ethers. This method involves the migration of benzyl cation from the ether's oxygen to the *ortho* and/or *para* position of the resulting phenol, as shown in Scheme 11[10].



Scheme 11: Fries rearrangement

Kiso and company resolved to the use thiol scavengers, which are used to inhibit the forming electrophilic intermediate from reacting with the activated resulting phenol. In their case, the highly reactive scavengers are prone to the reactive intermediates, which mostly are the benzylic cation as seen in Scheme 12, thus eliminating the electrophilic intermediate to a less reactive thiol adduct. However, this also created another challenge as in some cases resulted into other unexpected side reactions, thus increasing the scope of impurities. Hence, then other

methods mimicking these aforementioned inhibitors were been developed, such as methanesulfonic acid (CH_3OSO_3H) or trifluoromethanesulfonic acid (CF_3OSO_3H)[10] .



Scheme 12: Thioanisole scavengers

1.6 Aims and Objectives

The aim of this study is to develop a phenol debenzylation method employing *Barluenga's* reagent as a catalyst in an acid medium, apply the benzylation method for deprotection of estrone derivatives and propose the mechanism of debezylyation via *Barluenga's* reagent and triflic acid.

The project was thus had the following objectives:

- Investigate conditions for hypervalent iodine debenzylation in acid an medium and in an appropriate solvent
- Synthesize phenol containing benzyl ethers containing in *ortho*, *meta* and *para* substituents to the hydroxyl group
- To investigate the effect of the position of the substituent
- To investigate the electronic effect EDG and EWG of the substituents
- To synthesize a number of 3-benzylestrone derivatives
- To investigate benzylation of estrone derivatives using *Barluenga`s* reagent
- To propose a plausible mechanism for the debenzylation employing *Barluenga`s* reagent

Chapter 2

2 Results and Discussion

2.1 Chapter overview

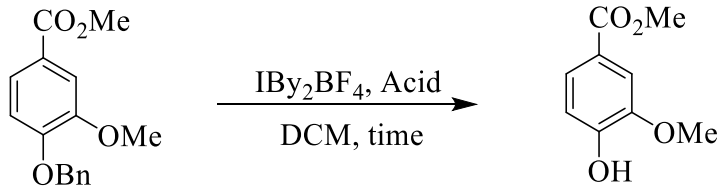
This chapter will present results and discussion of the development of IPy_2BF_4 as the potential and effective candidate for debenzylation of a variety of aryl substituted compounds. This will commence with the important step in any method development that being optimization of reaction conditions. The optimized conditions will be applied to variety of substrates with substituents that are either EWG , EDG, halogenated and mixture of either EWG and/or EDG and/or halogenated. This is also applied in debenzylation estrone derivatives that are candidates as potential anticancer drugs. The proposed method of how this reagent debenzylate will also be presented.

2.2 Investigation of IPy_2BF_4 catalyzed-reaction in the presence of common laboratory acids.

In developing of our new debenzylation method, we commenced our investigation by screening various common laboratory acids as promoters. Starting with (Entry 1, Table 2.1) which indicated that acid was required for the reaction to proceed. With this information, acids of higher pKa's were preferred as a start, due to ease in handling. The acetic acid (AcOH) and triflouroacetic acid (TFA) were employed as part of weak acids. Applied as substitute for triflic acid at a ratio of 1:1 to the substrate, without changing the conditions. After 24 hours at room temperature, TLC showed no formation of new product and this was further confirmed by NMR, only showing the ^{1}H NMR peaks corresponding to the starting material. On the other hand, sulfonate derivatives, namely, sulfuric acid (H_2SO_4), methane sulfonic acid (MsOH) and triflic acid (TfOH) all gave the debenzylated product **5**. When employing sulphuric acid, the formation of a new spot was observed on the TLC within an hour, and all starting material was consumed within 6 hours. After the completion, the reaction was then diluted with ice-cold water, followed by the classical extraction using dichloromethane (DCM (2 x10 mL)), and then the organic was washed with water (10 mL) and dried in magnesium sulfate ($MgSO_4$). After the removal of the solvent, the crude was subjected to column chromatography using hex:

EtOAc (2:8), to yield the compound **5.** The compound was confirmed by ^{1}H NMR, which showed the absence of the benzyl methylene peak at δ 5.50 ppm and of the aromatic peaks from δ 7.00-8.00 ppm. The yield further increased when using methane sulfonic acid (MsOH) to 70%, which was satisfactory as compare to 97% yield obtained when using triflic acid. This confirmed our hypothesis that stronger sulphonate-derived acids with lower pKa than sulphuric acid are better acid promoters. Additionally, this was also confirmed by the observation that other acids with similar acid strength as sulfuric acid such as *p*-Toluene sulfonic acid were not able to give the desired product, remaining labile in the reaction. In the absence of an acid (Entry 1, Table 2.1), no reaction was observed, indicating that an acid is essential for the reaction, as the absence of it showed no reaction

Table 2.1 **Investigation of IPy_2BF_4 catalyzed-reaction in the presence of common laboratory acids.**



4 **5**

Entry	Acid	time (h)[b]	Yield[c] (%)	Pka
1	-	24	N.R	-
2	AcOH	24	N.R	4.76
3	H_3PO_4	24	N.R	2.15
4	TCA	24	N.R	0.66
5	TFA	24	N.R	0.23
6	HNO_3	24	N.R	-1.3
7	MsOH	24	20	-1.9
8	$pTsOH.H_2O$	6	N.R	-2.8
9	H_2SO_4	0.5	70	-3
10	TfOH	0.2	97	-14.70

2.3 Investigation of IPy_2BF_4 catalysed-reaction in the presence of common laboratory solvents

With the above results obtained employing 1 equivalent of triflic acid in dichloromethane (DCM), we decided to use the same conditions to study the effect of solvents. Commencing with chloroform we were able to obtain a reasonable 50% yield after purification, with column chromatography. We then turned our attention to aromatic solvents, namely benzene and toluene, being chosen based on solubility and structural similarity to the substrate. Surprisingly the aromatic solvents resulted in an inseparable mixture within an hour based on time taken for total consumption of starting material. The use of acetonitrile (CH_3CN) also gave similar results as the aromatic solvents. We then concluded that aromatic solvents and acetonitrile were not suitable for the reaction, probably they promoted benzyl migration and/or other side reactions. We then turned our attention to alky ethers due to their ubiquitous presence in laboratories. Accordingly, following the same conditions as described earlier, with tetrahydrofuran (THF) and diethyl ether we were able to isolate 30% and 5% yields respectively. Although these results are far better to aromatic solvents and acetonitrile they fell short to the yield of dichloromethane. It will be worth to mention that the lower yields as noticed in ether solvents were corresponded by high impurities, which resulted in laborious separation of the product. We therefore concluded that dichloromethane (DCM) is a solvent of choice for the debenzylation in the presence of *Barluenga's reagent* and triflic acid. The results tabulate in Table 2.2 below.

Table 2.2 Investigation of IPy_2BF_4 catalyzed-reaction in the presence of common laboratory solvents.

Entry	Solvent	Time (h)	Yield (%)
1	Benzene	1	complex mixture
2	Toluene	1	complex mixture
3	Acetonitrile	1	complex mixture
4	Diethyl ether	0.2	5
5	Tetrahydrofuran	0.2	30
6	Chloroform	0.2	55

2.4 Effectiveness of IPy2BF4.

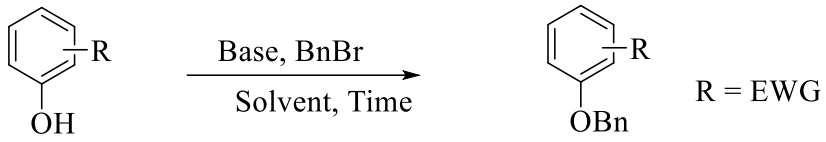
We then turned our attention to the effect of the *Barluenga's reagent* (IPy_2BF_4). The omission of *Barluenga's reagent* (IPy_2BF_4) (Entry 1, Table 2.3) resulted in the formation of an unresolvable mixture, which was hardly surprising as the strong triflic acid without scavengers is known to cause benzyl migration in aryls with electron-donating substituents. The implication of various equivalence were tried out starting from the high equivalence of 1.5 (Entry 2, Table 2.3) which within an hour gave the yield of 70 %. We then investigated 1.3 equivalence (Entry 3, table 2.3), in which we obtained a satisfactory yield of 72 %, a slight improvement from previous results. We envisaged that perhaps lower amount of the reagent needed, as supported by the fact that the reddish colour due to the presence of iodine that did not disappear, indicating that total consumption did not occur. With the aforementioned results, we further lowered the equivalent to 0.8 (Entry 4, Table 2.3), which proved to have even better improvement in comparison to 1.5 and 1.3 equivalences by obtaining a yield of 78 % in an hour. With this trend, we were prompted to even go further on lowering *Barluenga's reagent* (IPy_2BF_4) equivalence to 0.5 (Entry 5, Table 2.3) equivalence, surprisingly the yield dropped to 73 %, notably within 12 minutes. Surprisingly, 0.2 equivalence gave a 97 % yield, which was far better with regard to yield of the aforementioned equivalences. The attempt to lower the equivalence to 0.1 (Entry 7, Table 2.3) still resulted in the substrate be consumed within the 12 minutes, but unfortunately the yield receded to 83 %.This suggests that only the catalytic amount of *Barluenga's reagent* (IPy_2BF_4) is needed.

Table 2.3 Barluenga's reagent (IPy2BF4) varied equivalence effect on reaction time and yield.

Entry	IPy_2BF_4	Time (h)	Yield (%)
1	-	1	complex mixture
2	1.5	1	70
3	1.3	1	72
4	0.8	1	78
5	0.5	0.2	73
6	0.2	0.2	97
7	0.1	0.2	83

2.5 Synthesis of Benzyl ether

With an effective protocol for hypervalent iodine catalyzed aryl debenzylation, a number of *O*-benzyl-protected phenols were prepared using standard procedure in the reaction using our optimized conditions of IBy_2BF_4 (0.2 eq) and TfOH (1.0 eq) in DCM at 0^oC temperature , (Entry 6, Table 2.3). We envisaged commencing with two groups, the mono-substituted and the multisubtituted group. The monosubstituted group was further devided into three groups, whether they contain a EWG, EDG or halogen. We commenced our investigation by synthesizing benzyl ethers containing the EWG either at the *ortho, meta* or *para* position.



6 **7**

Scheme 13: Generalized scheme for synthesis of EWG benzyl ethers

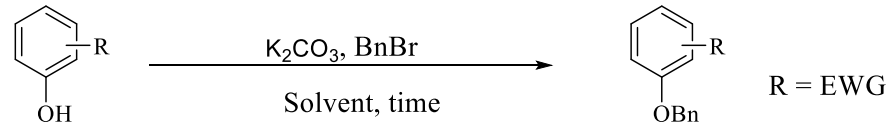
2.5.1 Benzylation of electron withdrawing groups (EWG) substrates

The phenol **8** was dissolved in an aprotic solvent such as dimethyl formamide (DMF) or acetone; this followed by addition of a base such as potassium carbonate or cesium carbonate and addition of benzyl bromide to obtain the desired benzyl ether **9**. The synthesis of methyl 2-(benzyloxy) benzoate **9a** was accomplished as described by Dalton *et al*[32], methyl salicylate **9a** and anhydrous potassium carbonate were dissolved in dimethyl formamide (DMF), benzyl bromide was added over the period of 5 minutes while stirring.After 12 hours, the reaction quenched with water and the compound **9a** extracted by EtOAc-hex mixture (3:1). The purified product **9a** was obtained by column chromatography in 82 % yield. Product **9a** was confirmed using NMR spectroscopy and the incorporated benzyl group confirmed by the presence of singlet at δ 5.19 ppm integrating for two protons, corresponding to the methylene protons and the additional aromatic protons in the ^1H NMR spectrum. ^{13}C NMR spectrum showed the presence of methylene carbon at 70.4 ppm and aromatic carbons at δ 126.7 (2×C), 127.7, 128.5 (2×C), 136.7 ppm. Compound **9a** , **9e**[33],**9f**[34] **9g**[35], **9i**[36]**, 9j**[37]**, 9k**[38]**, 9m**[39]**, 9n**[39] **and 9l**[40], were

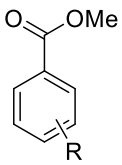
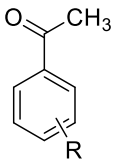
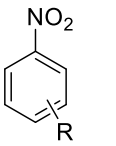
prepared similarly. The aforementioned compounds and their yield can be found in a Table 2.4 below. The ^{1}H NMR corresponded to published data as referenced above.

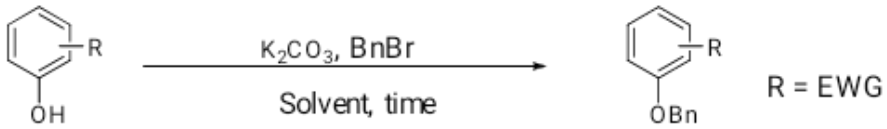
Employing the method by Dias *et al*[41], methyl 3-(benzloxy) benzoate **9b** was synthesized by adding the potassium carbonate (K_2CO_3) and benzyl bromide to the solution of methyl 3-hydroxybenzoate **9b** in acetone. The starting material disappeared on the TLC after 4 hours, in which water was added and the aqueous layer extracted with chloroform. The organic layer recrystallized in hexane to afford **9b** in 90 % yield. The product methyl 3-(benzloxy) benzoate **9b** was confirmed by NMR spectroscopy which showed singlet at 5.18 ppm integrating for 2 protons corresponding to methylene protons and additional aromatic protons in the ^{1}H NMR spectrum. Compound **9b, 9c**[42]**, 9d**[43]and **9h**[14], were prepared similarly. The compounds and their yields are tabulated in the Table 2.4 below. ^{1}H NMR corresponded to published data

Table 2.4 Benzylation of electron withdrawing groups (EWG) substrates

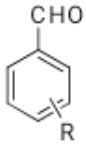
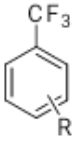


8 **9**

Substrate		Solvent	Time(hrs)	Yield
	**a**:R = 2-OH	DMF	12	82
	b:R = 3-OH	Acetone	2	90
	c:R = 4-OH	Acetone	5	93
	**d**:R = 2-OH	Acetone	12	93
	e:R = 3-OH	DMF	12	92
	f:R = 4-OH	DMF	12	95
	**g**:R = 2-OH	DMF	6	89
	h:R = 3-OH	Acetone	6	90
	i:R = 4-OH	DMF	6	90



8 9

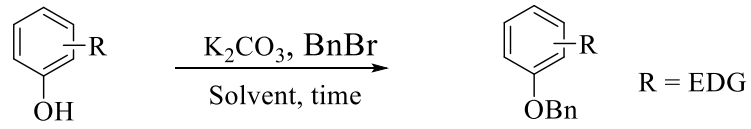
Substrate		Solvent	Time(hrs)	Yield
	j:R = 2-OH	DMF	12	90
	k:R = 3-OH	DMF	12	92
	l:R = 4-OH	DMF	12	95
	m:R = 3-OH	DMF	10	90
	n:R = 4-OH	DMF	10	86

2.5.2 Benzylation of electron donating groups (EDG) substrates

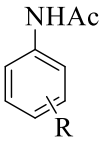
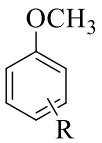
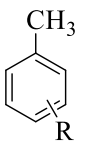
The synthesis of *N*-(2-(benzyloxy)phenyl)acetamide **11a** was accomplished as described by Kakefunda *et al*[44], *N*-(2-hydroxyphenyl)acetamide **10a** and anhydrous potassium carbonate (K_2CO_3) were dissolved in acetonitrile (CH_3CN), this was allowed to stir in room temperature for 5 minutes, benzyl bromide was added during this period. Then After 12 hours, acetonitrile (CH_3CN) evaporated, the reaction quenched with water and extracted by ethyl acetate. The purified product **11a** was obtained by column chromatography in 84 % yield. Product **11a** was confirmed using ^{1}H NMR spectroscopy and the incorporated benzyl group confirmed by the presence of singlet at δ 5.14 ppm integrating for two protons, corresponding to the methylene protons and the additional aromatic protons integrating for 5 protons. Employing the method by Zhou *et al*[45],methyl *N*-(3-(benzyloxy)phenyl)acetamide **11b** was synthesized by adding the potassium carbonate (K_2CO_3) and benzyl bromide to the solution of *N*-(3-hydroxyphenyl)acetamide **10b** in dimethyl formamide(DMF). The starting material disappeared on the thin layer chromatography (TLC) after 8 hours, in which water was added and the crude was extracted with ethyl acetate. The organic layer was purified via column chromatography EtOAc-hex mixture (3:7) to afford **11b** in 91 % yield. The product *N*-(3-(benzyloxy)phenyl)acetamide **11b** was confirmed by NMR spectroscopy which showed singlet at 5.15 ppm integrating for 2 protons corresponding to methylene and aromatic protons in the

^{1}H NMR spectrum. Compound **11b**, **11g**[46], **11h**[47] and **11i**[48] were prepared similarly and the compounds and yields are tabulated in the Table 2.5 below. The synthesis of *N*-(4-(benzyloxy)phenyl)acetamide **11c** was accomplished as described by Schmidt *et al*[49], *N*-(2-hydroxyphenyl)acetamide **10c** and anhydrous potassium carbonate (K_2CO_3) were dissolved in acetone ,this was allowed to stir at room temperature for 10 minutes while adding benzyl bromide. After 6 hours refluxing, the reaction quenched with water, and extracted by EtOAc-hex mixture, washed with brine and dried in magnesium sulfate ($MgSO_4$). The purified product **11c** was obtained by column chromatography in 93 % yield. Product **11c** was confirmed using ^{1}H NMR spectroscopy and the incorporated benzyl group confirmed by the presence of singlet at δ 5.19 ppm integrating for two protons, corresponding to the methylene and the additional aromatic protons in the ^{1}H NMR spectrum. Compound **11c, 11d**[50]**, 11e**[48],and **11f**[48] were prepared similarly

Table 2.5 Benzylation of electron donating groups (EDG) substrates



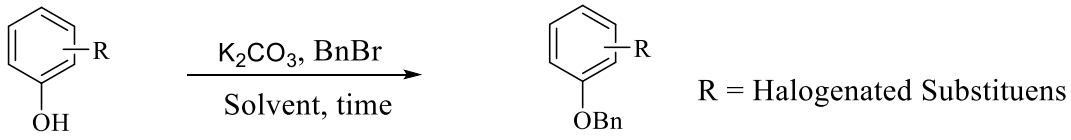
10 **11**

Substrate		Solvent	Time(hrs)	Yield
	**a**:R = 2-OH	Acetonitrile	16	84
	b:R = 3-OH	DMF	8	91
	c:R = 4-OH	Acetone	5	86
	**d**:R = 2-OH	Acetone	4	83
	e:R = 3-OH	Acetone	4	80
	f:R = 4-OH	Acetone	4	87
	**g**:R = 2-OH	DMF	6	76
	h:R = 3-OH	DMF	6	87
	i:R = 4-OH	DMF	6	72

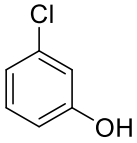
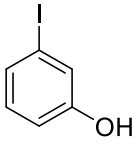
2.5.3 Benzylation of halogenated substrates

Compound 1-(benzyloxy)-3-chlorobenzene **13a** was synthesized by method adopted from Yu *et al*[51], acetonitrile(CH_3CN) was utilized to dissolve 3-chlorophenol **12a** and potassium carbonate (K_2CO_3) with addition of benzyl bromide. The reaction was refluxed overnight, cooled to room temperature. Purified product **13a** was obtained using column chromatography EtOAc-hex (3:7) mixture in 93 % yield. The Product was confirmed using ^1H NMR spectroscopy the added benzyl group confirmed by the presence of singlet at δ 5.08 ppm integrating for two protons, corresponding to methylene and additional peaks in aromatic region for benzyl protons ^1H NMR spectrum. This was in agreement with published data.Employing the method by Kutz *et al*[52], 1-(benzyloxy)-3-iodobenzene **13b** was synthesized by adding the potassium carbonate (K_2CO_3) and benzyl bromide to the solution of methyl 3-hydroxybenzoate **12b** in acetone. The starting material disappeared on the TLC after 8 hours, in which water was added and the crude extracted with chloroform. The organic layer was recrystallized in hexane to afford **13b** in 92 % yield. The product 1-(benzyloxy)-3-iodobenzene **13b** was confirmed by NMR spectroscopy that showed singlet at 5.03 ppm integrating for 2 protons corresponding to methylene protons and additional aromatic protons in the ^1H NMR spectrum. The results are tabulated in Table 2.6 below.

Table 2.6 Benzylation of halogenated substrates



12 **13**

Substrate		Solvent	Time(hrs)	Yield
	**a**	Acetonitrile	5	93
	**b**	Acetone	4	92

2.5.4 Preparation of substrates with mixed substituents

We then turned our attention to preparation of phenol ethers bearing mixed type of substituents. The strategies used were similar to the ones employed earlier for benzylation, and in the preceding compounds and they are summarized in Table 2.7. Briefly, compound **15a**, 4-(benzyloxy)-3-methoxybenzaldehyd was synthesized as described by Chanat *et al*[53], employing potassium carbonate (K_2CO_3) and benzyl bromide in dimethyl formamide (DMF) to afford product **15a** in 83 % yield. The ^{1}H NMR was in agreement with published data, and compound **15a, 15c, 15e and 15h** were synthesized similarly.

Employing the method by Han *et al*[54], 4-(benzyloxy)-2-bromo-5-methoxybenzaldehyde **15b** was synthesized similarly to the above, but the solvent was changed to ethanol. Following the ealier reported procedure; compound **15b** was obtained in yield 83 %**.** 2-(Benzyloxy)naphthalene **15d** was accomplished by dissolving naphthalen-2-ol **14d** and potassium carbonate in acetonitrile (CH_3CN) with addition of benzyl bromide using the method by Velasco *et al*[55], compound **15d** was afforded in 91 % yield.

The synthesis of 1-(4-(benzyloxy)-3-methoxyphenyl)ethan-1-one **15f** was accomplished as described by Helong *et al*[56]**,** 1-(4-hydroxy-3-methoxyphenyl)ethan-1-one **14f** and anhydrous potassium carbonate (K_2CO_3) were dissolved in acetone, this was allowed to stir in room temperature for 5 minutes, benzyl bromide was added during this period. After refluxing for 7 hours, the reaction was quenched with water and extracted by EtOAc-hex mixture (5:1). The purified product **15f** obtained by column chromatography in 94 % yield. Product **15f** was confirmed using NMR spectroscopy and the incorporated benzyl group confirmed by the presence of singlet at δ 5.14 ppm integrating for two protons, corresponding to the methylene and the was also additional aromatic protons in the ^{1}H NMR spectrum.

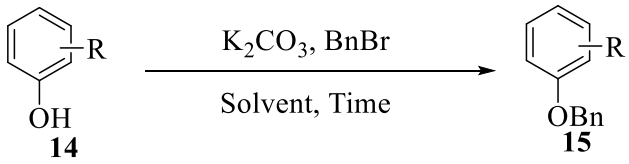
Compound **14g** was synthesized in two sequential procedures, following a procedure by Cabiddu[57], D-mannose was added to acetic anhydride (Ac_2O), followed by a catalytic amount of molecular iodine (I_2). The reaction was heated to 50 °C for overnight while being stirred, then diluted with saturated sodium thiosulfate ($Na_2S_2O_3$) and further stirred for 10 minutes. The crude was extracted with ethyl acetate (EtOAc), washed with saturated sodium bicarbonate ($NaHCO_3$) dried over magnesium sulfate ($MgSO_4$) and evaporated to dryness to afford colourless oil in 93 % yield. The addition of the five acetyl groups was confirmed by ^{1}H NMR

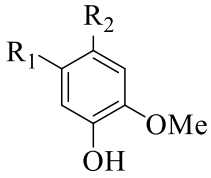
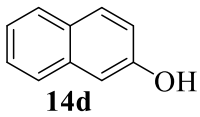
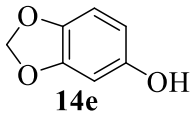
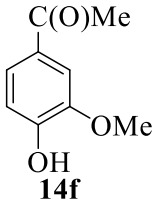
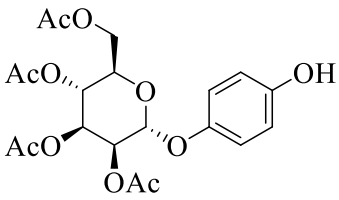
which showed appearance of singlets at δ 2.01, 2.03, 2.07, 2.17 and 2.17 ppm, each integrating for three protons. Without any further purification, the above crude was dissolved in dichloromethane (DCM), 4-(benzyloxy)phenol and two drops of boron trifluoride diethyl etherate (BF_3OEt_2) were added to the solution, the mixture was then stirred for 24 hours at room temperature. The reaction was quenched by addition of ice-cold water, the organic layer was separated using dichloromethane (DCM) and dried over magnesium sulfate ($MgSO_4$). The crude product was purified by chromatography (EtOAc:hex = 10:3) to give **15g** in 33% yield. Product **15g** was confirmed using ^{1}H NMR spectroscopy and the incorporated benzyl group was confirmed by the presence of singlet at δ 5.01 ppm integrating for two protons, corresponding to the methylene protons and the additional aromatic protons in the ^{1}H NMR spectrum integrating for 2, 4 and 3 protons observed at δ (7.10-7.07), (7.37-7.29) and (7.55-7.52) ppm respectively.

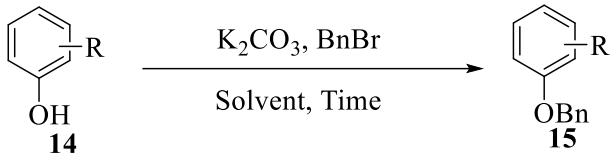
Employing the method by Aaron *et al*[58] (13*S*)-3-(Benzyloxy)-2-bromo-13-methyl-6,7,8,9,11,12,13,14,15,16-decahydro-17*H*-cyclopenta[*a*]phenanthren-17-one **15i** was synthesized in acetonitrile (CH_3CN). After extraction with chloroform, the crude was recrystallized in hexane to afford **15i** in 82 % yield. The product **15i** was confirmed by ^{1}H NMR spectroscopy that showed singlet at δ 5.06 ppm integrating for 2 protons corresponding to methylene and aromatic protons in the ^{1}H NMR spectrum

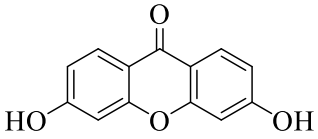
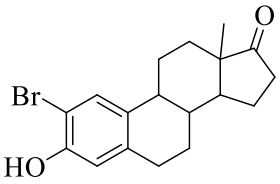
Compound **17** (13*S*)-3-(Benzyloxy)-2-(4-fluorophenyl)-13-methyl-6,7,8,9,11,12,13,14,15,16-decahydro-17*H*-cyclopenta[a]phenanthren-17-one was synthesized from compound **15i** using Negishi coupling**.** The prepared compound was characterized with the aid of NMR (^{1}H and ^{13}C), ^{19}F NMR, IR and mass spectrometric techniques. ^{1}H NMR spectroscopy revealed a singlet resonating at 5.06 ppm integrating for 2 protons which corresponds to the methylene, the aromatic region of the ^{1}H NMR spectra of this compound, revealed the presence of additional signals due to the incorporated fluorinated aryl substituent. The ^{19}F NMR, On the other hand, showed signals at δ -116-176 ppm and ddd, J = 3.1, 5.1, 9.0 corresponding to the *para* fluorine coupling with the carbons. compound **17** structure and NMR can be seen on the appendix.

Table 2.7 Benzylation of mixed substrates



Substrate		Solvent	Time(hours)	Yield
	**14a** R1=H,R2=CHO	DMF	16	83
	14b R1=Br,R2=CHO	Ethanol	18	83
	14c R1=Br,R2=CO2H	DMF	16	85
 **14d**		Acetonitrile	24	91
 **14e**		DMF	8	93
 **14f**		Acetone	7	94
 **14g**		DCM	24	33

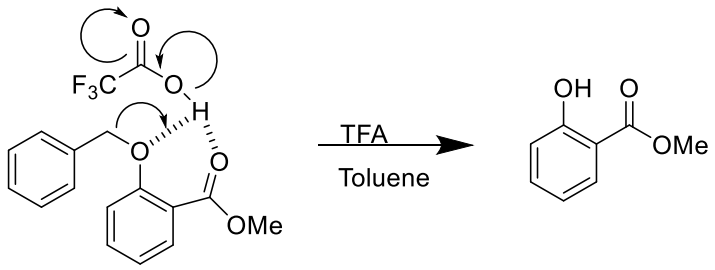


Substrate	Solvent	Time(hours)	Yield
 **14h**	DMF	14	85
 **14i**	Acetonitrile	12	86

2.6 The debenzylation of the substrates

2.6.1 Debenzylation of electron withdrawing group (EWG) substrates

With an effective protocol for hypervalent iodine catalyzed aryl debenzylation, we then attempted to debenzylate a number of *O*-benzyl-protected phenols in the reaction using our optimized conditions of *Barluenga's reagent* (IBy_2BF_4) (0.2 eq) and TfOH (1.0 eq) in dichloromethane (DCM) at 0^oC temperature and the results are shown in Table 2.8 below . Starting with substrates containing electron withdrawing groups, formation of compound **8a** was completed in 20 minutes while compounds **9b** and **9c** were debenzylated 45 minutes, the *ortho* substituted compound **9a** gave the fastest time compared to *meta* **9b** and *para* **9c** substituted compounds. We have expected the ortho-debenzylation to form the fastest, due to ortho-chalating effect. As shown in scheme 14 ,the debenzylation via trifluoroacetic acid (TFA) is initiated first by the protonation of the phenol ether oxygen, the lone pairs availability of ether oxygen results in faster reaction times. The slower reactions of the para and meta electron withdrawing groups in relation to ortho functionalized aryl benzyl ethers process stems from the ortho chelating ability as shown in the proposed mechanism in Scheme 14 below. The formation of four-member intermediate facilitates the fast and easy protonation of benzyl ether.

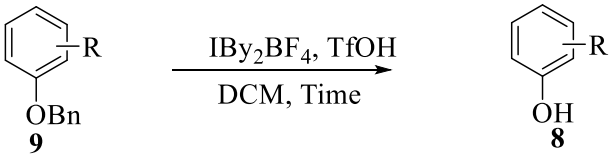


Scheme 14: Proposed chelation mechanism to account for accelerated TFA-mediated debenzylation with *ortho*-substituted phenols

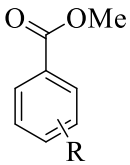
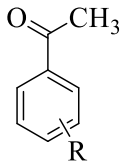
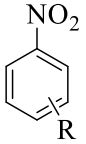
Compounds **9d**, **9e** and **9f** took equal time of 30 minutes to debenzylate, indicating there is no effect from the position of phenol; this also sidelined the effect of chelating in reaction rates for this specific debenzylation. Where the nitro group was chosen as the electron withdrawing substituent, compound **9g** took an hour to debenzylate to contrast of compounds **9h** and **9i** with both coming to debenzylation in 30 minutes. Seemingly, the strong withdrawing nature of the nitro group seemed to reverse the chelating effect, probably due to the absence of electrons for coordination as they delocalized to the positively changed nitrogen in the center. Compound **9j** was the swiftest to debenzylate among the electron withdrawing chosen substrates, being debenzylated in just 15 minutes, in agreement to the chelating effect shown by other carbonyl-containing group. The other aldehyde substituted compounds **9k** and **9l** came to complete debenzylation in 30 minutes and 1 hour respectively this could be attributed to lack of chelating. The trifluorinated substituted compounds **9m** and **9n** debenzylated in 30 and 40 minutes respectively. The revelation of the results stated above showed limited correlation that could be attributed to the chelating that happens between the carbonyl oxygen lone pairs, the benzyl ether oxygen and the proton from triflic acid as this increases the rate in which the triflic acid is deprotonated and subsequently debenzylation rate of the *ortho* substituted benzyl to the electron withdrawing group as observed by Fletcher and Gunning[24]. The chelating effect in regard to *Barluenga's reagent* (IPy_2BF_4) proved to play partial role in terms of the rate of the reaction as there is minor differences in the rate of debenzylation as this was highlighted by compounds **9d**-**9f** coming to completion around equal time of 30 minutes as carbonyl containing compounds. This served as affirmation to the proposed mechanism that for the debenzylation to occur the *Barluenga's reagent* (IPy_2BF_4) plays a vital role as initiator rather

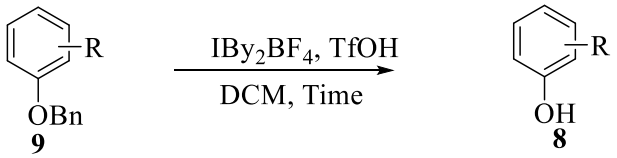
than a proton donor as the final stage of the reaction, which usually plays a role in chelation for the increased rate of debenzylation in cases where the acid is an initiator. Generally, in most cases the corresponding phenol products were obtained in high yields in less than 1h for phenols containing electron-withdrawing groups (EWG) as tabulated in Table 2.8. The regio-chemistry of the electron-donating substituents on the phenyl ring did not significantly affect these reaction outcomes of the *O*-benzyl-protected phenols with electron-withdrawing groups All the compounds electron withdrawing compounds (EWG) their phenolic ring were swiftly and sufficiently debenzylated in less than 1 hour, with less than <5% of the undesired c-benzylated by-products.

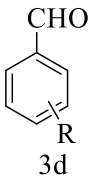
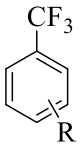
Table 2.8 Substrate scope of IPy_2BF_4-catalysed debenzylation of EWG in the presence of triflic acid·



9 **8**

Substract		Timeb	Yield (%)c
	**a**:R= 2-OBn	20 min	83
	b:R=3-OBn	45 min	86
	c:R=4-OBn	45 min	90
	**d**:R= 2-OBn	30 min	72
	e:R=3-OBn	30 min	77
	f:R=4-OBn	30 min	93
	**g**:R= 2-OBn	1 hr	95
	h:R=3-OBn	30 min	90
	i:R=4-OBn	30 min	95



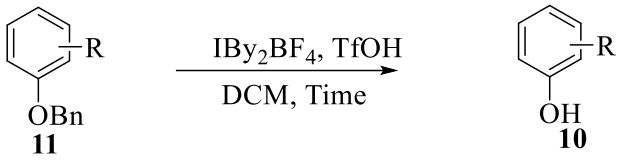
Substract		Timeb	Yield (%)c
 3d	**j**:R= 2-OBn	15 min	92
	k:R=3-OBn	30 min	85
	l:R=4-OBn	1 hr	90
	**m**:R=3-OBn	30 min	96
	n:R=4-OBn	40 min	92

2.6.2 IPy_2BF_4-catalysed debenzylation of EDG in the presence of triflic acid

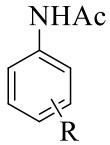
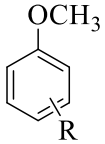
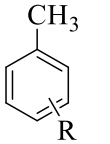
The focus was turned into electron donating groups (EDG) applying the same procedure as the one for electron withdrawing groups. Unfortunately, the presence of an electron-donating substituent on the phenolic ring resulted in a much slower reaction times, with a substantial amount of starting material remaining after 24 hours in most cases. This necessitated a slight modification of the procedure, by allowing the reaction to warm to room temperature after 30 minutes. It is important to note that in the case of the electron donating groups (EDG), the addition of more than one equivalent *Barluenga's reagent* (IPy_2BF_4) of shortened the reaction's completion time but led to a significant increase in by-product formation, in some cases as an unresolvable mixture. Compounds **11a**, **11b** and **11c** were all debenzylated in 30 minutes, these compounds contained the strongest electron donating substituents in relation to the selected electron donating groups (EDG) substituted substrates (Table 2.9). The electron donating groups in aryl benzyl usually does result in O→C benzyl migration (Friedel–Crafts reaction) with the use of other acids e.g. Trifluoroacetic acid. The use of *Barluenga's reagent* (IPy_2BF_4) and triflic acid manage to give the pure products. The methoxy-substituted compounds **11d**, **11e** and **11f** took 30 minutes for *ortho* and 1.5 hours for both the compounds that are *para* and *meta* substituted to debenzylate. Methyl substituted compound **11g** took 18 hours before complete debenzylation, compound **11k** the *meta* substituted completed the starting material in 12 hours and the thin layer chromatography(TLC) shown the disappearance of compound **11i** in 24 hours. As the strength of the electron donating group (EDG) weakens

the rate in which debenzylation occurs decreases, this is observed by the time increase of methyl substituted compound **11g** in 18hours,compound **11h** in12 hours and compound **11i** in 24 hours compared to compounds **11a**, **11b** and **11c** who were all debenzylated in 30 minutes. .It should be alluded that the regiochemistry of the substituents seems to play no significant role in debenzylation rates.

Table 2.9 Substrate scope of IPy_2BF_4-catalysed debenzylation of EDG in the presence of triflic acid.



11 **10**

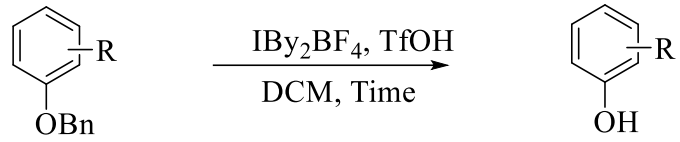
Substrate		Time	Yield (%)
	**a**:R = 2-OBn	30 min	56
	b:R = 3-OBn	30 min	82
	c:R = 4-OBn	30 min	78
	**d**:R = 2-OBn	30 min	83
	e:R = 3-OBn	1.5 hr	80
	f:R = 4-OBn	1.5 hr	87
	**g**:R = 2-OBn	18 hr	76
	h:R = 3-OBn	12 hr	87
	i:R = 4-OBn	24 hr	72

2.6.3 IPy_2BF_4-catalysed debenzylation of halogenated aryls in the presence of triflic acid

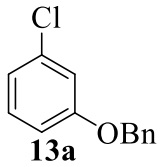
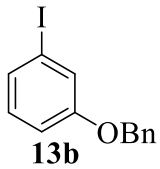
The strong electronegativity of halogens makes the inductive nature while the lone pairs are responsible for resonance. The halogen in aryl compounds have dual purpose to σ-withdraw and also, π-donate electrons. The seems to be the interference of halogens to our debenzylating reagents as they were having many unresolved byproducts, this can be due to their donating and withdrawing abilities. The other noteworthy observation is the halogenated substrates compounds **13a** and **13b** required much longer times for a reaction to show formation of new

products, this could been another factor for unresolved products formation. This is shown in Table 2.10 below.

Table 2.10 Substrate scope of IPy_2BF_4-catalysed debenzylation of halogenated aryls in the presence of triflic acid



13 **12**

Substract	Timeb	Yield (%)
 **13a**	4 h	unresolved
 **13b**	4 h	unresolved

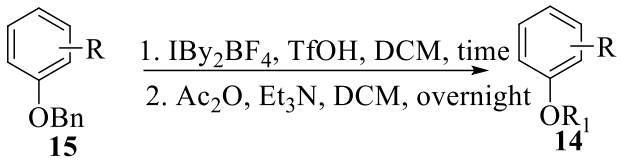
2.6.4 IPy_2BF_4-catalysed debenzylation of mixed groups in the presence of triflic acid

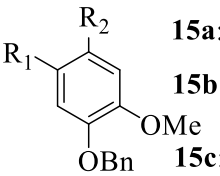
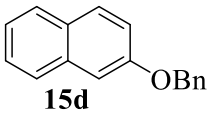
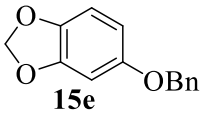
Continuing with the above debenzylation protocol, we also examined phenols with mixed substituents, in the cases where it was difficult to separate the product, we resolved to employing acetylation. The acetylation post-reaction was useful in assisting with purification by resolving the mixture into distinct separate compounds, Table 2.11. Substrates containing at least one electron withdrawing group (EWG) as a substituent, smoothly gave the desired products (**14a-c**, **14g**), while the absence gave low yields compound **14e** or often resulting in mixture of unresolvable products compound **14d**.

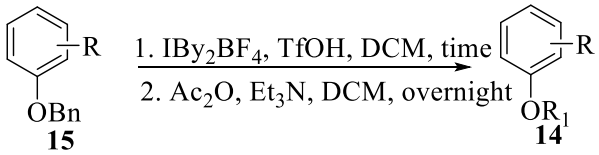
In most cases, the product was adequately pure after work-up but with low resolution, hence we envisaged substitution of protecting group could be done without the need for further purification, thus avoiding the time-consuming purification process. The acetylated products were easy to separate with chromatography, accordingly, after work-up employing standard procedure of quenching with saturated sodium thiosulfate (Na_2SO_3) and the crude product was

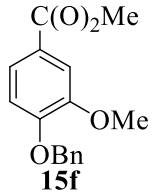
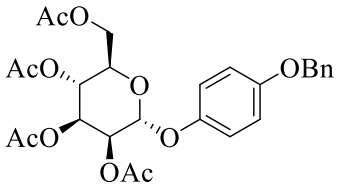
re-dissolved in dichloromethane in the presence of acetyl anhydride (Ac_2O) and triethylamine (Et_3N) base, the results are depicted in Table 2.11. Notably, comparing both occasions there was little effect in the yield, highlighting the suitability and the ease of this protocol for protecting group-replacement.

Table 2.11 Substrate scope of IPy_2BF_4-catalysed debenzylation of mixed groups in the presence of triflic acid.



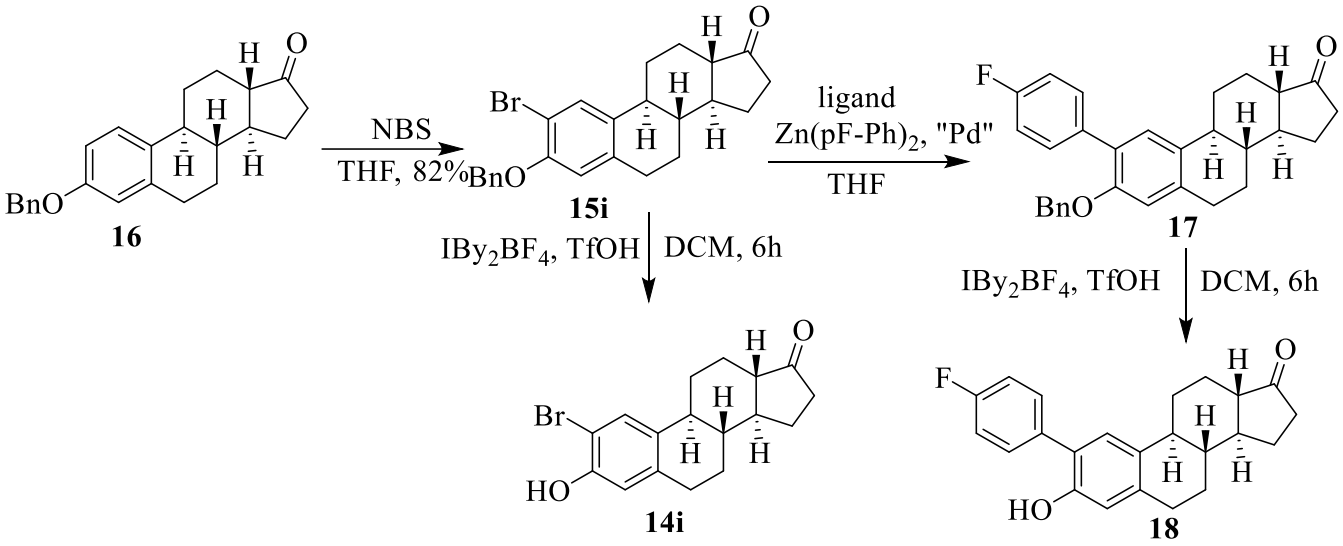
Substract	Debenzylation Time	Debenzylation Yieldc (%)	Acetylation Yieldc (%)
 **15a**: R_1 = H, R_2 = CHO	45 min	92	93
15b: R_1 = Br_2, R_2 = CHO	2h	88	90
15c: R_1 = Br_2, R_2 = CO_2H	20 min	95	Reaction not carried
 **15d**	8 h	-d	Reaction not carried
 **15e**	2 h	48	Reaction not carried



Debenzylation			Acetylation
Substract	Time	Yieldc (%)	Yieldc (%)
 **15f**	20 min	90	88
 **15g**	10 min	74	Reaction not carried

2.7 Synthesize and debenzylation of estrone derivatives

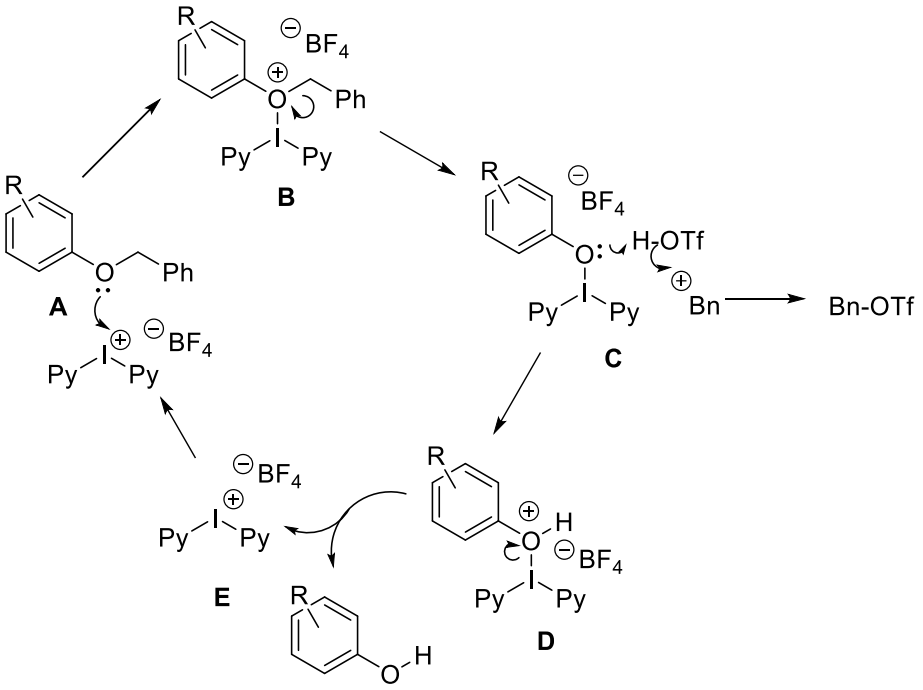
As part of our studies on the synthesis of estrone-based anti-cancer drugs such as candidate compound **18** shown in Scheme 15, we decided to explore application of our method to debenzylation of an A-ring case[59]. Hence, estrone benzyl ether compound **16** was brominated with N-Bromosuccinimide (NBS) to give aryl bromide compound **15i**. The insertion of para fluoro phenyl ring on the aryl bromide was done by Negishi reaction as shown in Scheme 15 was successfully achieved in the presence of palladium ligand complex to give (13S)-3-(benzyloxy)-2-(4-fluorophenyl)-13-methyl-6,7,8,9,11,12,13,14,15,16-decahydro-17H-cyclopenta[a]phenanthren-17-one, compound **17**[60]. Using the above debenzylation procedure, we were able to obtain compound **14i** and **18** in 64 and 73 % yields respectively, Scheme 15 which was better than palladium carbon catalysed debenzylation in terms of yield and rates. The debenzylation of compounds **15i** and **17** was performed employing the above mentioned procedure to yield the desired compounds in good yields. It should be mentioned that in both cases, C-alkylation was not observed and debenzylated compounds did not need any further purifications after work-up. Compounds **15i**, **14i**, **17** and **18** will be applied further in biological assays.



Scheme 15: Debenzylation of estrone derivatives

2.8 Our proposed mechanism of *Barluenga's* reagent debenzylation

The *Barluenga's* reagent (IPy_2BF_4) has been useful as the oxidising agent for many alcohols and ethers[61]. This iodonium salt offers a plenty of advantages in comparison to transition metals, which are often toxic or expensive[62]. The iodonium salt is preferred for their environmental friendliness and requirement of mild conditions. .It possess the potential to act as an oxidising agent and an electrophile[61]. The *Barluenga's* reagent (IPy_2BF_4) which produces iodonium oxidant and tetrafluoroborate anion $(BF_4)^-$,the latter being a preferred weakly coordinating ligand to this reactive iodonium oxidant[61,63]. Tetrafluoroborate anion $(BF_4)^-$ allows the iodonium oxidant to be released easily since is the poor nucleophile and chemically inactive to most reactive species. Iodine has the greatest size and most polarizable of the known halogens. This size allows it to take many hypervalent states[61,64]. With the above properties of the *Barluenga's* reagent (IPy_2BF_4) in mind we proposed reaction mechanism as depicted in Scheme 16 below.



Scheme 16**:** Proposed mechanism of IPy_2BF_4-catalysed debenzylation of phenols in the presence of triflic acid

The first step could involves reaction of the model substrate (**A**), protected by benzyl group its oxygen lone pairs attacking bis-pyridine iodonium. The iodium act as oxidising agent to form oxonium ion (**B**). The oxonium ions, which are formed by oxygen bonded to three bonds, are transient owing to their unstable electron deficient oxygen. The instability of the oxonium leads to subsequent substitution nucleophilic unimolecular (S_N1-type) heterolysis of **B** to afford phenoxyiodonium species (**C)** and a benzyl carbocation denoted Bn^+, the latter being intercepted by one of the poorly nucleophilic species in the medium, probably triflate to form benzyltriflate. Tetrafluoroborate anion $(BF_4)^-$ is assumed to be poor nucleophile in comparison with triflate. This is attributable to symmetrical shape that distribute the negative charge across tetrafluoroborate anion (BF_4)[65,61,64].This is deemed to occur concurrently as the phenoxyiodonium species (**C)** get protonated by triflic acid. The benzyl carbocation is captured by triflate anion, with **D** expulsion and regeneration of *Barluenga's* reagent as catalyst, in order to afford the product as a deprotected substituted phenol (**E**). Faster rate with electron-withdrawing substituents would imply that cleavage of **B** to **C** according to this mechanism is rate determining, in view of destabilization of the oxonium ion by electron-withdrawal accelerating the cleavage step.

Chapter 3

3 Materials and Methods

3.1 Chemicals

Chemicals were prepared in the laboratory or were purchased from Aldrich Chemical Companies and used without further purification. Products were characterized by comparison of their physical data with those of authentic samples. Reactions were monitored by Analytical thin layer chromatography, which was performed on pre-coated Merck silica gel $60F_{254}$ plates, and visualized by UV or by staining with ceric ammonium molybdate or dilute suphuric acid (H_2SO_4) in ethanol (EtOH). All solvents were dried under standard methods.

3.2 Characterization techniques

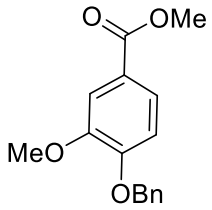
Column chromatography was carried out on silica gel. ^{1}H NMR (proton nuclear magnetic spectroscopy) spectra were recorded on 300 or 500 MHz in $CDCl_3$ or DMSO-d_6 and ^{13}C NMR (carbon nuclear magnetic spectroscopy) spectra were recorded on 125 MHz in DMSO-d_6 or d-acetone. Chemical shifts (ppm) were recorded with tetramethylsilane (TMS) as the internal reference standard. Multiplicities are given as: s (singlet), d (doublet), t (triplet), dd (doublet of doublets), q (quartet) or m (multiplet).

IR spectra were recorded on a Fourier-transform infrared spectroscopy (FT-IR) spectrometer and only major peaks are reported in cm^{-1}. High Resolution Mass Spectrometry (HR-MS) was obtained using a Q-TOF instrument equipped with ESI source.

Products were characterized by comparison of their physical data with those of authentic samples. Reactions were monitored by Analytical thin layer chromatography which was performed on pre-coated Merck silica gel $60F_{254}$ plates, and visualized by UV or by staining with ceric ammonium molybdate or dilute H_2SO_4 in EtOH. All solvents were dried under standard method.

3.3 Selected Representative Procedures for synthesis of benzyl ethers

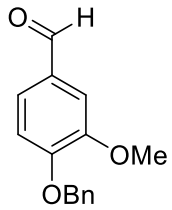
Methyl 4-(benzyloxy)-3-methoxybenzoate



15f

Methyl 4-hydroxy-3-methoxybenzoate (1.00 g, 5.49 mmol), potassium carbonate (1.50 g, 10.92 mmol) were added to 20 ml DMF, thereafter benzyl bromide (0.80 ml , 6.58 mmol) was added and mixture was stirred at 100 °C for 3 hrs. The reaction was quenched with 20 mL water and extracted with EtOAc (20 mL×3). The combined organic solutions were washed with H_2O (20 mL×3) and brine (20 mL), dried, and evaporated. Column chromatography of the residue (EtOAc:*n*-hex = 8:2) resulted into a white solid which was re-crystallized in EtOH and collected (1.30 g 86% yield). The NMR data was comparable to the published data.[66] ^{1}H NMR (300 MHz, CDCl3): δ = 3.88 (s, 3H), 3.93 (s, 3H) 5.21(s, 2H), 6.89 (d, 1H, *J* = 8.1 Hz), 7.45-7.31 (m, 5H), 7.56 (d, 1H, 1.8 Hz), 7.61 (dd, 1H, *J* = 1.8 Hz and 8.1 Hz).

4-(Benzyloxy)-3-methoxybenzaldehyde

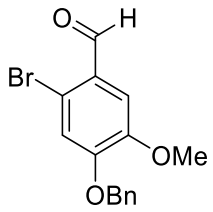


15a

Vanillin (1.00 g, 6.50 mmol) and K_2CO_3 (1.80 g, 13.14 mmol) in DMF (20 mL) was stirred at room temperature for an hour. BnBr (3 mL, 13.14 mmol) was added into the reaction mixture. The reaction was heated for 3 hrs at 100 °C. The reaction was than quenched with water (30 mL) and extracted with a 50% ethyl acetate in hexane mixture (3 x 20 mL). The combined organic layer was washed with water (2x 20 mL), dried, filtered and concentrated under

reduced pressure. The crude product was purified by chromatography (EtOAc:*n*-hex = 10:3) to yield (1,30 g, 81% yield) of compound **15a**. The NMR data was comparable to the published data.[67] ^{1}HNMR (300 MHz, $CDCl_3$): δ = 3.92 (s, 3H), 5.23 (s, 2H), 6.98 (1H, d, J = 8.1Hz), 7.36-7.42 (m, 7H), 9.82 (s, 1H).

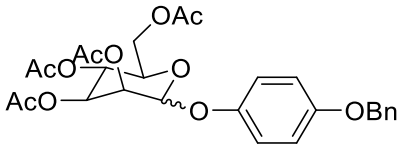
4-(Benzyloxy)-2-bromo-5-methoxybenzaldehyde



15b

In 20 mL MeOH, **15a** (0.40 g, 1.65 mmol) was added, then $AgNO_3$ (0.55 g, 3.30 mmol) followed by Br_2 (0.12 mL, 2.48 mmol).The mixture was stirred for 24 hours room temperature, then $Na_2S_2O_3$ saturated solution was added and further stirred for 10 min. The solids were filtered and the residue evaporated under reduced pressure. The crude was purified via column chromatography (EtOAc:*n*-hex = 10:3) to give **15b** (1.5 g, 87 %). The NMR data was comparable to the published data.[68] NMR (300 MHz, $CDCl_3$): δ = 3.91 (s, 3H), 5.20 (s, 2H), 7.10 (s, 1H), 7.43 (s, 1H), 7.45-7.35 (m, 5H), 10.17 (s, 1H).

(2R, 3R, 4S, 5S)-2-(Acetoxymethyl)-6-(4-(benzyloxy)phenoxy)tetrahydro-2H-pyran-3,4,5-triyl triacetate

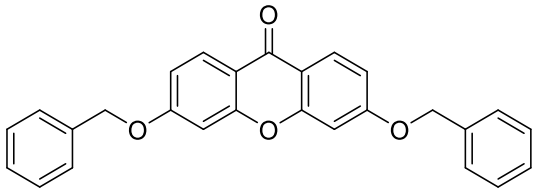


15g

D-mannose (1.00 g, 5.55 mmol) was added to 20 mL Ac_2O, followed a catalytic amount of I_2. The reaction was heated to 50 °C for overnight while being stirred. Then diluted with saturated $Na_2S_2O_3$ (10 mL) and further stirred for 10 min. Extracted with EtOAc (3 x 10 mL), washed with sat.$NaHCO_3$ (2×20 mL) dried over $MgSO_4$ and evaporated to dryness to afford colourless oil (2 g, 93 %),^{1}H NMR (300 MHz, $CDCl_3$) : δ = 2.01 (s, 3H), 2.03 (s, 3H), 2.07(s, 3H), 2.17

(s,3H), 2.17(s, 3H), 4.14-4.04 (m, 2H), 4.25 (m, H), 5.29 (m, 1H), 5.4 (m, 2H), 6.08 (d, *J* = 1,8 Hz,1H). To the above crude was added DCM (15 mL), 4-(benzyloxy)phenol (1.10 g 5.49 mmol) and two drops of BF_3OEt_2, the mixture stirred for 24 hrs. The reaction was quenched by addition of ice-cold water. The organic layer was separated using DCM (2 x 10 mL) and dried over $MgSO_4$ The crude product was purified by chromatography (EtOAc:hex = 10:3) to give **15g**, (0.9 g, 33%) from the acylated sugar. ^{1}H NMR (300 MHz, $CDCl_3$) : δ = 2.02 (s, 3H), 2.04 (s, 3H), 2.10 (s, 3H), 2.18(s, 3H), 4.15-4.05 (m, 2H), 4.23-4.28 (m, 1H), 5.01 (s, 2H), 5.44-5.35 (m, 3H), 5.55 (d, *J* = 3.3, 1H), 6.87 (d, *J* = 8.8, 2H), 6.87 (d, *J* = 8.8, 2H), 7.42-7.25 (m, 5H).[69]

3,6-Bis(benzyloxy)-9*H*-xanthen-9-one

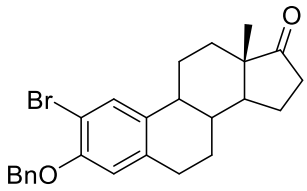


3,6-bis(benzyloxy)-9*H*-xanthen-9-one

15h

3,6-dihydroxy-9*H*-xanthen-9-one [70] (1.00g, 4.39 mmol), potassium carbonate (1.50 g ,10.92 mmol) were added to 20 ml Acetone, thereafter benzyl bromide (0.8 ml, 6.58 mmol) was added and the stirring mixture was refluxed for 16 hrs. The reaction was quenched with 30 mL water and extracted with EtOAc (20 mL×3). The combined organic solutions were washed with H_2O (20 mL×3) and brine (20 mL), dried, and evaporated. Column chromatography of the residue (EtOAc:*n*-hex = 2:8) resulted into a white solid which was re-crystallized in EtOH and collected 1**5h** as a white solid. IR (ATR): 1714, 1457, 1276, 1174, 848 cm^{-1}. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 5.18 (s, 4H), 6.93 (d, 2H, *J* = 2.1 Hz), 7.02 (dd, 2H, *J* = 2.1 and 8.7 Hz), 7.49-7.37 (m, 10H), 8.24 (d, 2H); ^{13}C NMR (75 MHz, $CDCl_3$): δ = 70.5, 101.2, 113.4, 116.0, 127.5, 128.2, 128.4, 128.8, 135.7, 157.9, 163.7. HRMS ESI (m/z): for $C_{27}H_{20}NaO_4$; calcd. for $[M + Na]^+$, 431.1259; found, 431.1261

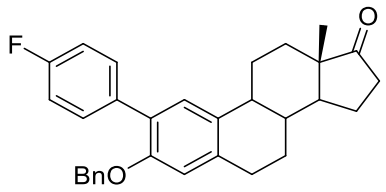
(13*S*)-3-(Benzyloxy)-2-bromo-13-methyl-6, 7, 8, 9, 11, 12,13, 14, 15, 16-decahydro-17*H*-cyclopenta[a]phenanthren-17-one



14i

3-(benzyloxy) estrone[71] (180.00 mg, 0.50 mmol) was dissolved in THF (15 mL) and NBS (114.00 mg, 0.75 mmol) was added. The mixture was stirred at rt for 3 hrs, the solvent was then evaporated off, and the crude product was purified by column chromatography with (EtOAc:*n*-hex = 1:9) as eluent. Compound **14i** was obtained as a white solid (189 mg, 86%).[72] ^{1}H NMR (300MHz, CDCl3): δ =0.93 (s, 3H), 1.27-1.20 (m, 3H), 1.64-1.50 (m, 4H), 2.18-1.99 (m, 3H), 2.49-2.47 (m, 2H), 2.70-2.65 (m, 1H), 2.91-2.87 (m, 2H), 5.06 (s, 2H), 6.66 (s, 1H), 7.13 (s, 1H), 7.48-7.33(m, 5H).

(13*S*)-3-(benzyloxy)-2-(4-fluorophenyl)-13-methyl-6,7,8,9,11,12,13,14,15,16-decahydro-17*H*-cyclopenta[a]phenanthren-17-one



17

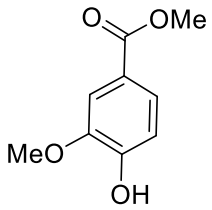
Compound **14i** (0.09 g,0.26 mmol) was added to a dry two necked round bottom flask followed by $Pd_2(dba)_3$ (5 mol %), Zn(*p*F-ph)$_2$ (1.2 eq), P(cy)$_3$ (5 mol %) dissolved into 10 mL anhydrous THF refluxed for 16 hours at 80 °C the solvent was then evaporated off, and the crude product was purified by column chromatography with (EtOAc:*n*-hex = 1:9) as eluent. Compound **17** was obtained as a white solid (0.09 g, 74%) ^{1}H NMR (300 MHz, $CDCl_3$) : δ = 0.95 (s, 3H) , 1.67-1.47 (m, 4H), 2.19-1.95 (m, 4H), 2.33-2.32 (m, 1H), 2.47-2.44 (m, 2H), 2.56-2.51 (m, 2H), 2.98-2.95 (m, 2H), 5.06 (s, 2H), 6.81(s, 1H), 7.10-7.07 (m, 3H), 7.37-7.29 (m, 4H), 7.55-7.52 (m, 3H); ^{13}C NMR (75 MHz,$CDCl_3$): δ = 13.9, 21.6, 26.0, 26.6, 29.6, 31.6, 35.9, 38.4, 44.0, 48.0, 50.42, 70.6, 113.6, 114.7 ($^{2}J_{C\text{-}F}$ = 20.8 Hz, C_{Ar}) 126.8, 127.6,128.0, 128.4, 131.1

($^{3}J_{C\text{-}F}$ = 7.6 Hz, C_{Ar}) 132.6, 134.6 ($^{4}J_{C\text{-}F}$ = 2.8 Hz, C_{Ar}) 137.1, 137.2, 153.6, 161.9 ($^{1}J_{C\text{-}F}$ = 238.3 Hz, CF_{Ar}), 220.8; ^{19}F NMR ($CDCl_3$, 282) -116-176 (1F, ddd, *J* = 3.1, 5.1,9.0). HRMS ESI (m/z): for $C_{31}H_{31}FNaO_2$; calcd. for $[M + Na]^+$, 477.2206; found, 447.2207

3.4 General procedure for debenzylation of phenol ethers

The ether (1 eq), and *Barluenga's* reagen (IPy_2BF_4) (0.2 eq) in dichloromethane (DCM) were cooled to 0 ^{o}C in ice bath. After which TfOH (1.0 eq) was added. The reaction was monitored until TLC showed complete disappearance of the starting material. The reaction was quenched with ice-water (5 mL), the organic separated, then further extracted with CH_2Cl_2 (5 m x 2). The combined organic extracts were washed with Na_2SO_3 (5 mL), brine (5 mL), and dried over $MgSO_4$. The solvent was then evaporated off, and the crude product was subjected to flash chromatography.

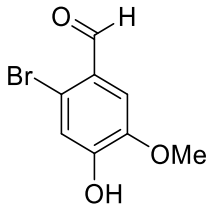
Methyl 4-hydroxy-3-methoxybenzoate



14f

From ether **15f**, compound **14f** was obtained as a white powder after being isolated by chromatography employing (EtOAc : *n*-Hex = 2:5). (0.70 g, 80 %). ^{1}H NMR (300 MHz, $CDCl_3$) : δ = 3.89 (s, 3H) 3.95 (s, 3H) 6.03 (d, OH, 9.9 Hz) 6.94 (d, 1H, 8.1 Hz) 7.55 (d, 1H, 1.8 Hz) 7.63 (dd, 1H, *J* = 1.8 and 8.1 Hz) Product was confirmed by NMR comparison to reported data.[66]

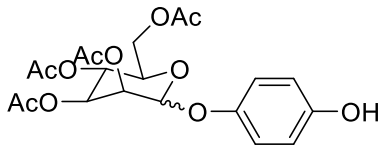
2-Bromo-4-hydroxy-5-methoxybenzaldehyde



14b

From ether **15b**, compound **14b** was obtained as a white powder was isolated by chromatography employing (EtOAc:*n*-Hex = 2:5). (0.80 g, 74 %). ^{1}H NMR (300 MHz, $CDCl_3$): δ = 3.95 (s, 3H), 6.22 (s, OH), 7.18 (s, 1H), 7.43 (s, 1H), 10.17 (s, 1H).

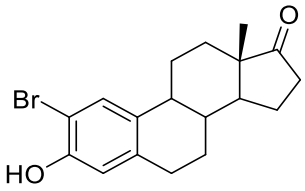
(2R, 3R, 4S, 5S)-2-(Acetoxymethyl)-6-(4-hydroxyphenoxy)tetrahydro-2H-pyran-3,4,5-triyl triacetate



14g

From ether **15g**, compound **14g**[73] was obtained as a brown oil after being isolated by chromatography employing (EtOAc-*n*-Hex = 2:5) to (1.2 g, 76 %). NMR (300 MHz, $CDCl_3$) : δ = 2.04 (s, 3H), 2.05 (s, 3H), 2.06 (s, 3H), 2.19 (s, 3H), 2.35 (s, OH), 4.16-4.07 (m, 2H), 4.28 (m, 1H), 5.43-5.32 (m, 3H), 5.54 (d, *J* = 3.3, 1H), 6.75 (d, 2H, *J* = 9.0 Hz), 6.93 (d, 2H, *J* = 9.0)

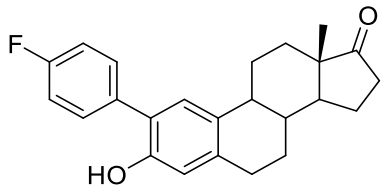
2-Bromo-13α-estra-1, 3, 5 (10)-trien-17-one



15i

From ether **14i**, compound **15i**[72] was obtained as a white powder after being isolated by chromatography employing (EtOAc - *n*-Hex = 1:5) to (96.0 mg, 64%). ^{1}H NMR (300 MHz, $CDCl_3$) δ = 0.94 (s, 3H), 1.70-1.41 (m, 6H), 2.28-1.95 (m, 4H), 2.37-2.34 (m 1H), 2.57-2.52 (m, 2H), 2.84-2.87 (m, 2H), 5.36 (s, 1H, OH), 6.78 (s, 1H), 7.37 (s, 1H).

2-(*p*-Fluorophenyl)-3-hydroxyestra-1,3,5(10)-trien-17-one



18

From ether **17**, compound **18** was obtained as a white powder after being isolated by chromatography employing (EtOAc - *n*-Hex = 1:5) to (50.0 mg, 73 %). ^{1}H NMR ($CDCl_3$): δ = 0.94 (s, 3H), 1.75-1.42 (m, 4H) 2.26-1.90 (m, 4H), 2.35-2.25 (m, 1H), 2.46-2.34 (m, 2H), 2.62-2.45 (m, 2H), 3.02-2.89 (m, 2H), 5.36 (br-s, OH, 1H), 6.74 (s, 1H), 7.18 (m, 3H), 7.46 (m, 2H); ^{13}C NMR (DMSO-d_6): δ = 14.3, 21.6, 26.0, 26.6, 29.5, 31.2, 35.8, 38.4, 43.8, 47.8, 50.0, 115.3 ($^{2}J_{C\text{-}F}$ = 20.8 Hz, C_{Ar}), 116.2, 124.6, 127.5, 129.1, 131.3($^{3}J_{C\text{-}F}$ = 7.5 Hz, C_{Ar}), 132.0 ($^{4}J_{C\text{-}F}$ = 2.5 Hz, C_{Ar}), 137.0, 152.3, 160.4 ($^{1}J_{C\text{-}F}$ = 241.3 Hz, CF_{Ar}), 220.2. HRMS ESI (m/z): for $C_{24}H_{25}FNaO_2$; calcd. for $[M + Na]^+$, 387.1736; found, 387.1732

Chapter 4

4 Conclusion

For this project the preliminary studies were carried out to determine optimum conditions. The results showed that an acid is a requirement for reaction to proceed. This led to determine the most efficient and easily available acid. The sulfonic acids showed to be better promoters than other common acids, with the ones with lower pKa values giving better yields. The attention was turned to solvents, among tested solvents only chloroform,in comparison to dichloromethane was promising, while others gave complex mixtures and/or poor yields i.e., less than 50%. Therefore, dichloromethane (DCM) was taken as the solvent of choice. The effect of *Barluenga's* reagent (IPy2BF4) equivalence was also explored. It showed to be optimum at 0.2 equivalence, this shows only a catalytic amount is sufficient for debenzylation. These parameters gave optimized condition, which helped to explore their effect to different substrates. The substrates were benzylated via William reaction with potassium carbonate as the base and benzyl bromide as benzylating agent. The variety of solvents including DMF, acetone and acetonitrile were used depending on the solubility of substrates. The electron withdrawing groups (EWGs) gave better average debenzylation reaction rates when compared to electron donating groups (EDGs) and mixed substituted substrates. The *ortho*, *meta* and *para* substituted EDGs and EWGs showed no correlation to debenzylation rates. The estrone derivatives gave better yields without any side reactions. In conclusion, it was demonstrated that a stoichiometric amount of *Barluenga's* reagent (IPy_2BF_4) in a strongly acidic medium cleanly debenzylates a range of substituted phenolic benzyl ethers. This method can be used as alternative for deprotection of O-benzyl protective group in organic synthesis. Moreover, the simplicity of this method makes it an attractive new entry into the removal of benzyl ether to organic chemist. The important observation/comparison is that the *Barluenga's* reagent (IPy2BF4) gave better yield than palladium carbon catalyzed debenzylation.

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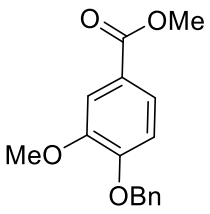
Appendix



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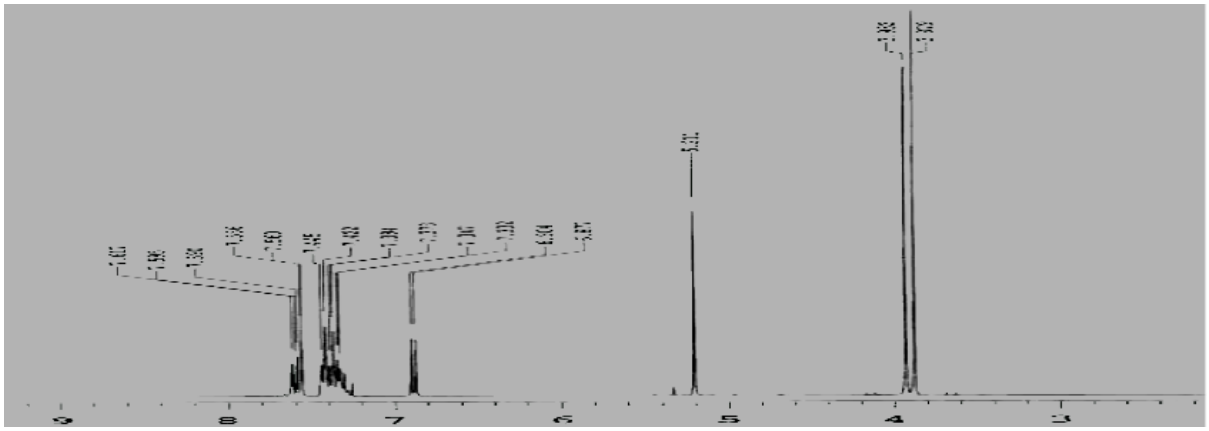
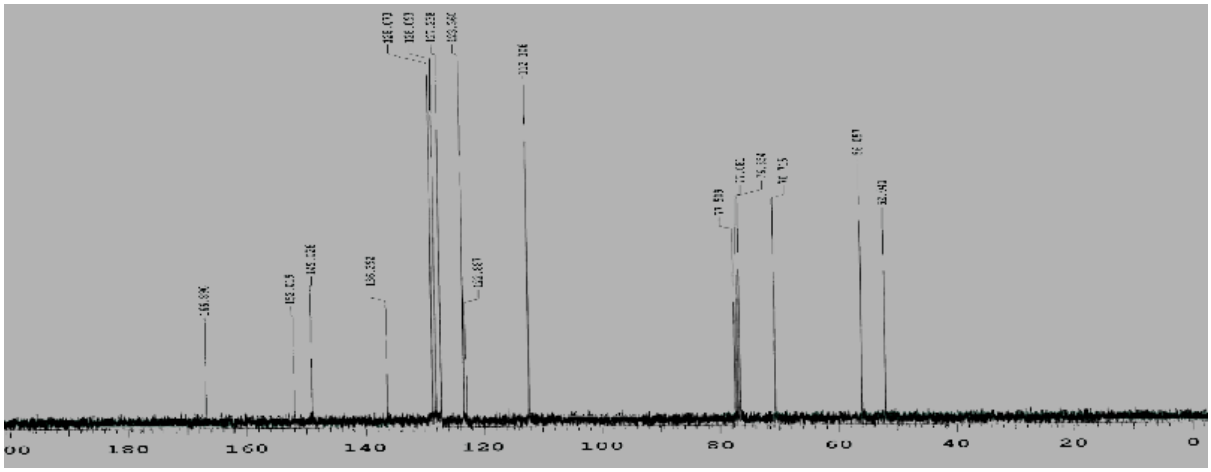
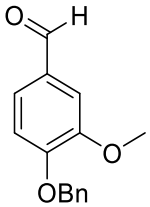




^{1}H and ^{13}C NMR spectra of 4-(benzyloxy)-3-methoxybenzoate **14f**.



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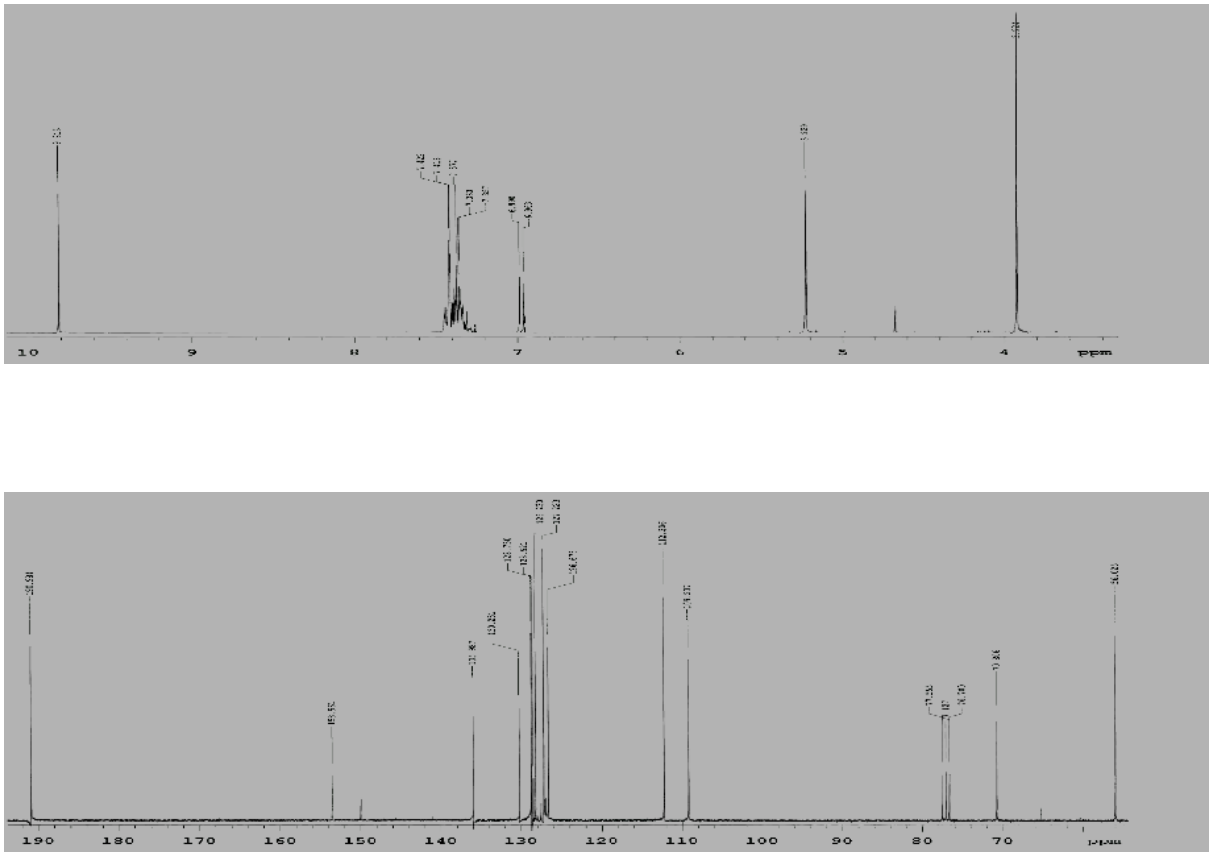

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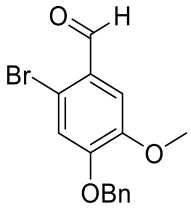

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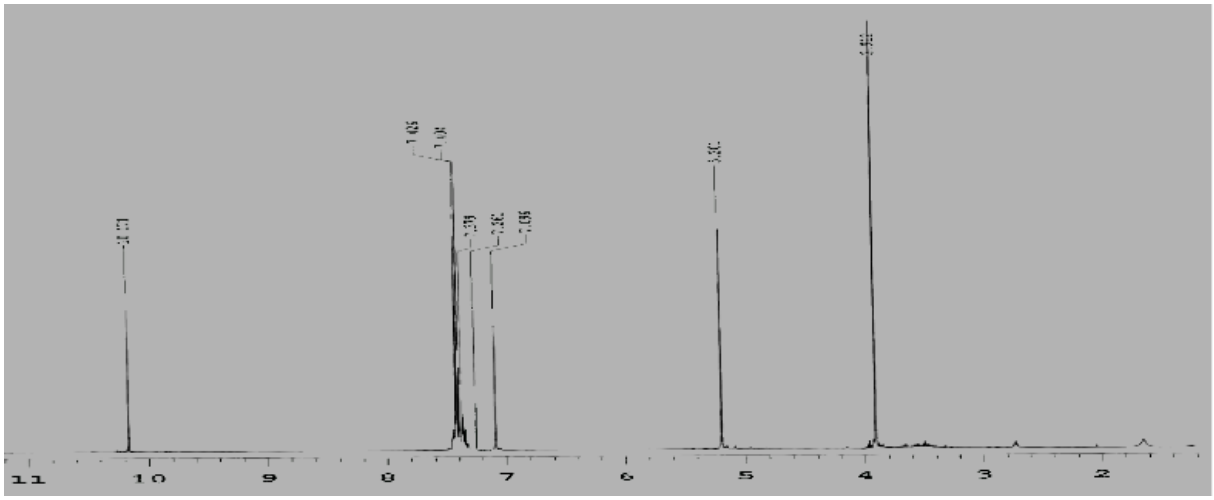
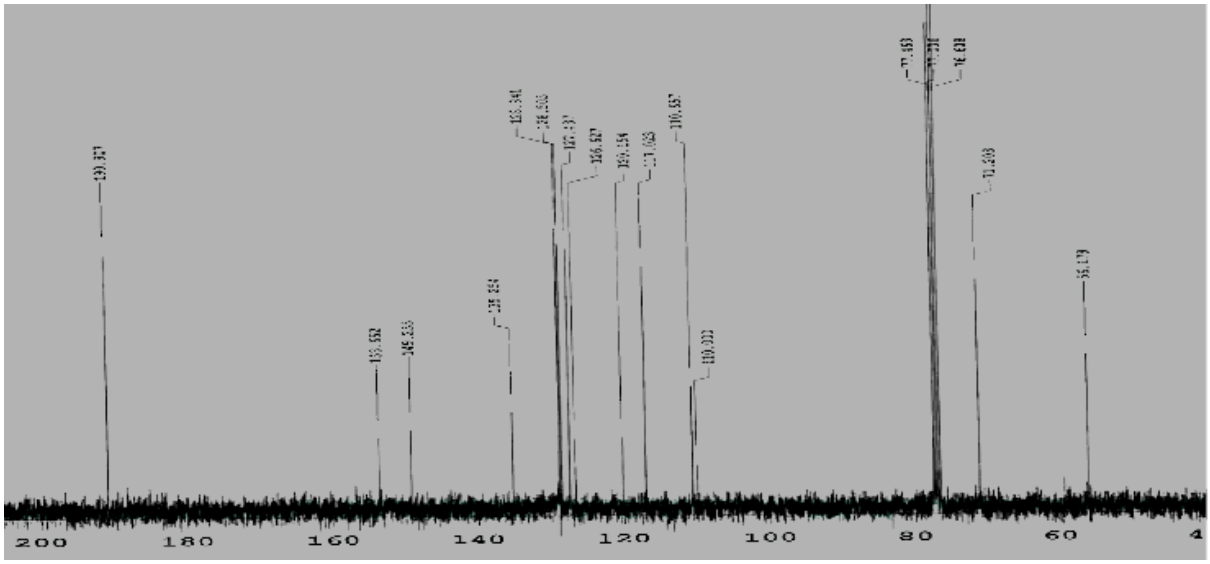
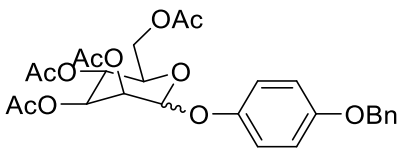




^{1}H and ^{13}C NMR spectra 4-(benzyloxy)-2-bromo-5-methoxybenzaldehyde **15b**



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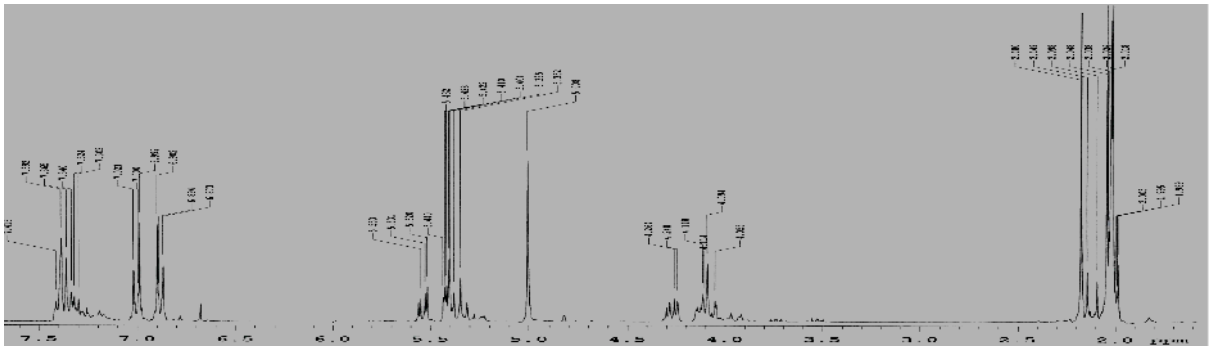
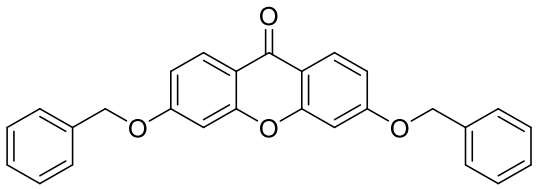


^{1}H NMR of (2R,3R,4S,5S)-2-(acetoxymethyl)-6-(4-(benzyloxy)phenoxy)tetrahydro-2H-pyran-3,4,5-triyl triacetate **15g**



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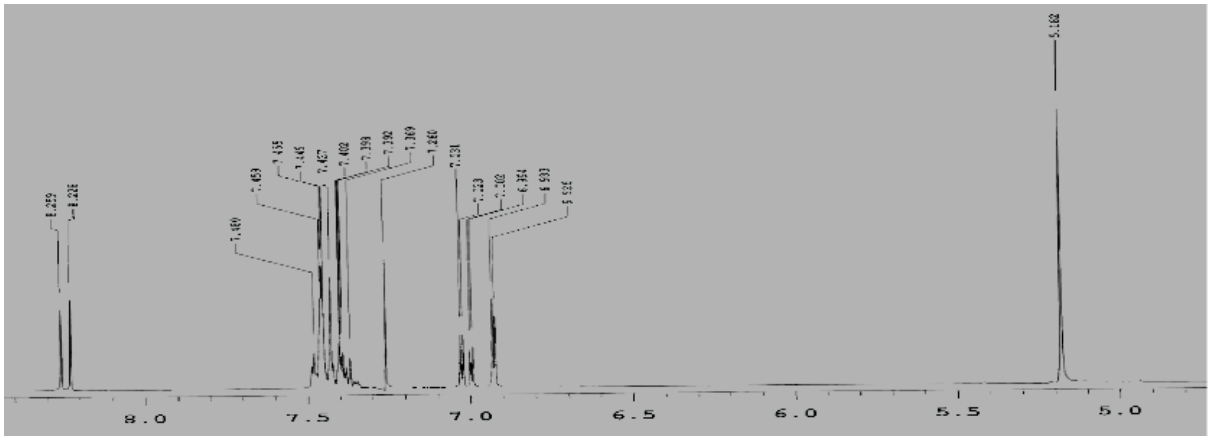
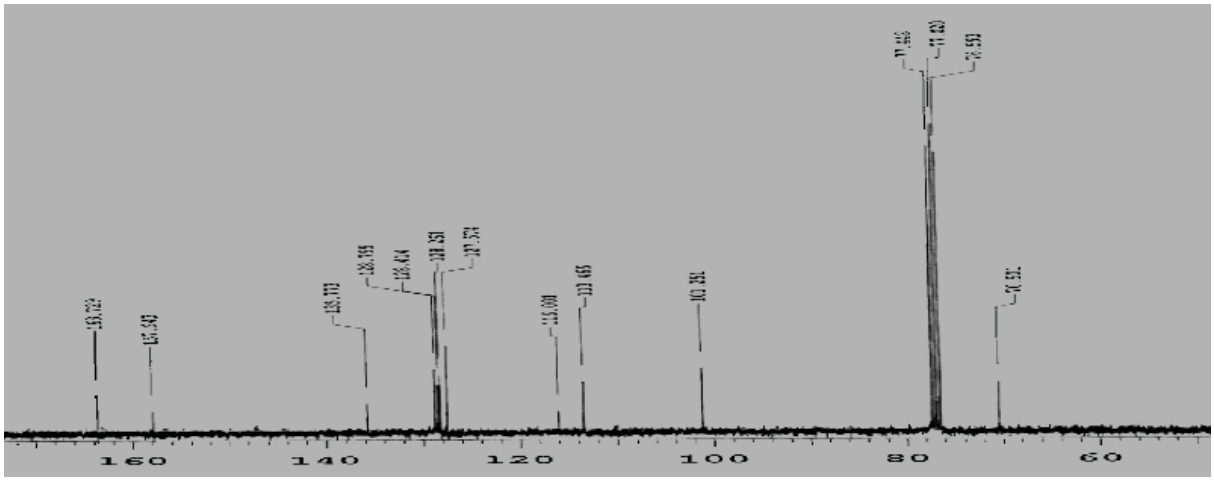
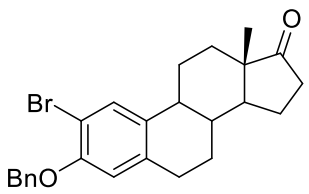




^{1}H and ^{13}C NMR spectra 3,6-bis(benzyloxy)-9H-xanthen-9-one 1**5h**



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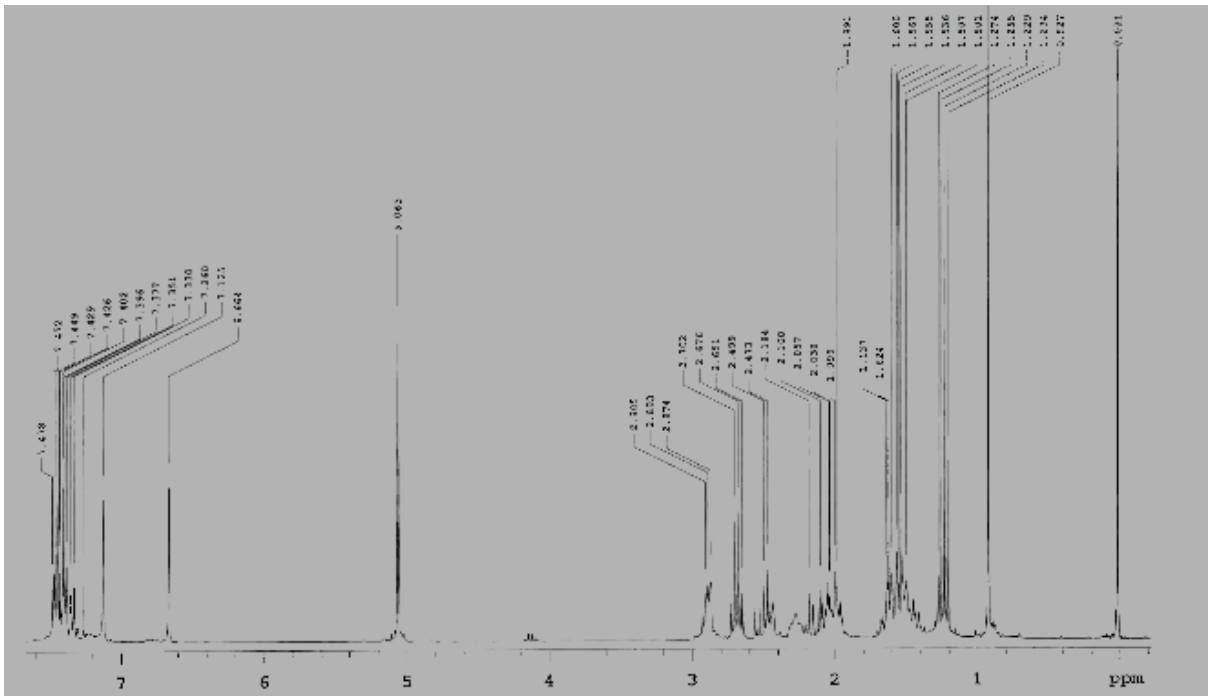
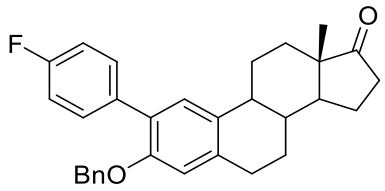


^{1}H NMR of (13*S*)-3-(benzyloxy)-2-bromo-13-methyl-6, 7, 8, 9, 11, 12, 13, 14, 15, 16-decahydro-17H-cyclopenta[a]phenanthren-17-one **15i**



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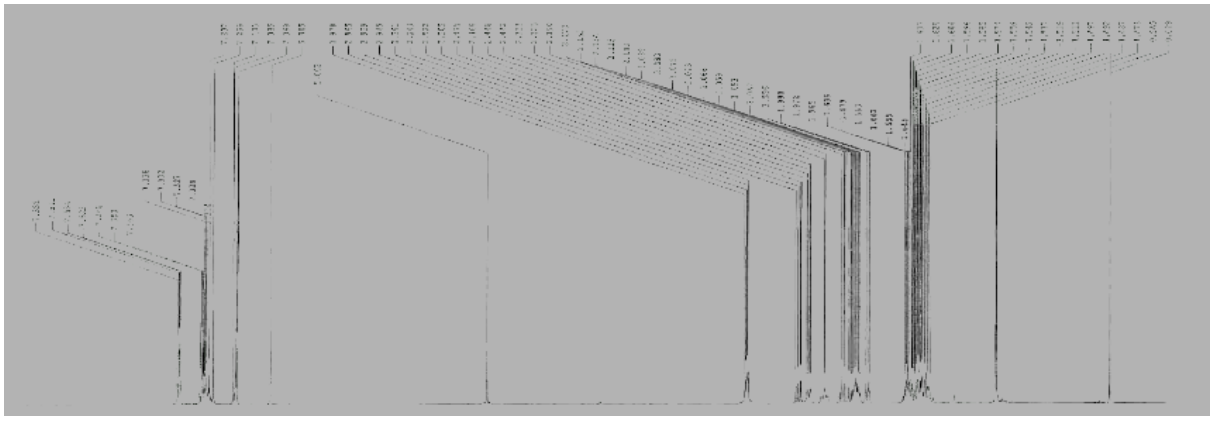
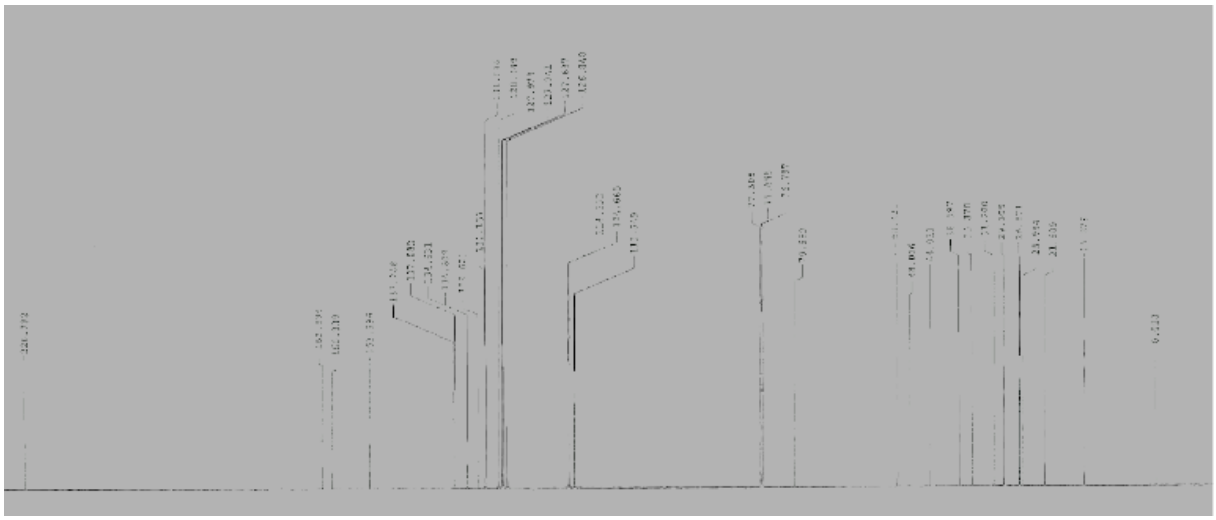
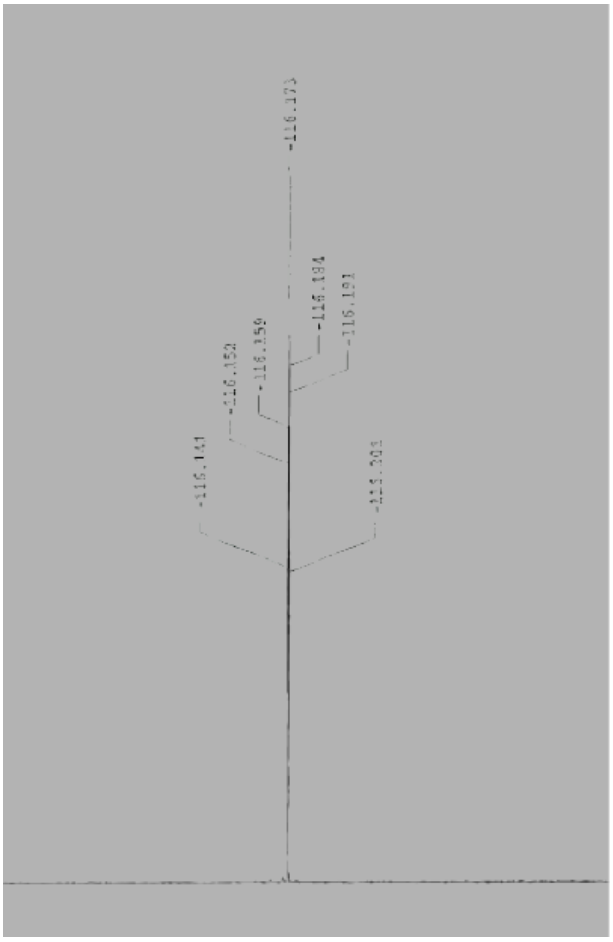
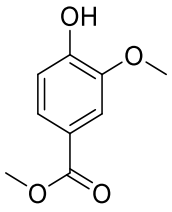




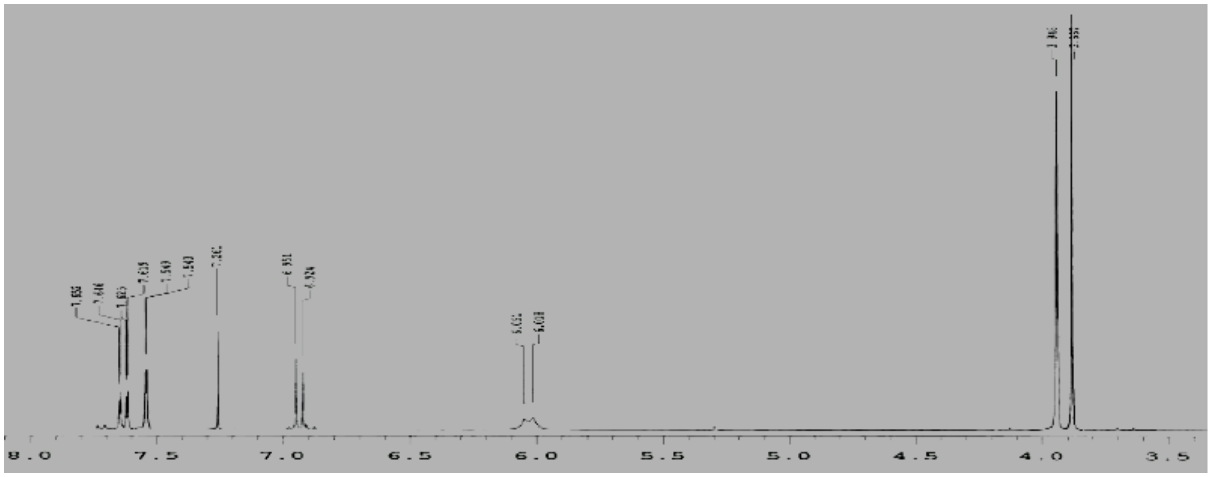


^{1}H, ^{13}C and ^{19}F NMR of (13*S*)-3-(benzyloxy)-2-bromo-13-methyl-6,7,8,9,11,12,13,14,15,16-decahydro-17H-cyclopenta[a]phenanthren-17-one **17**

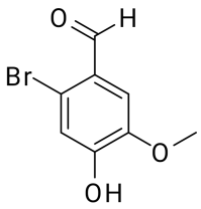
Debenzylation



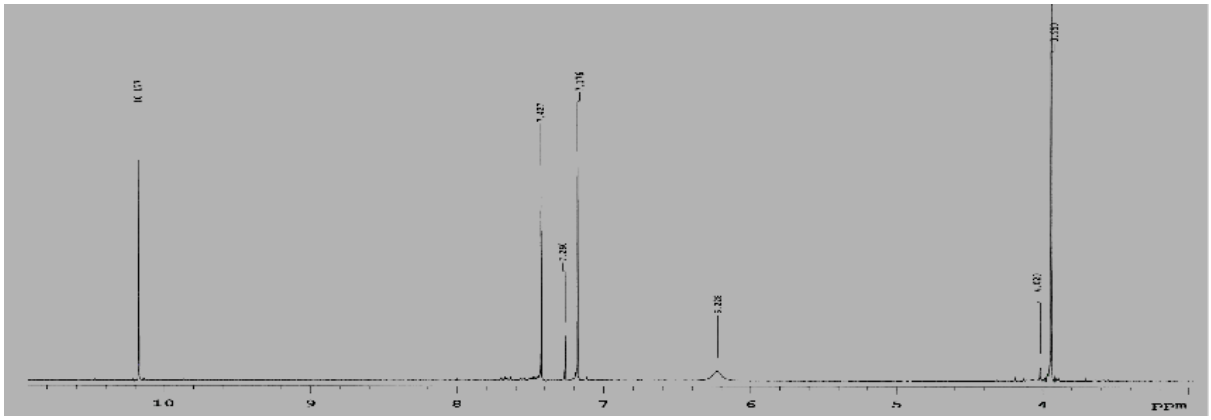
14f

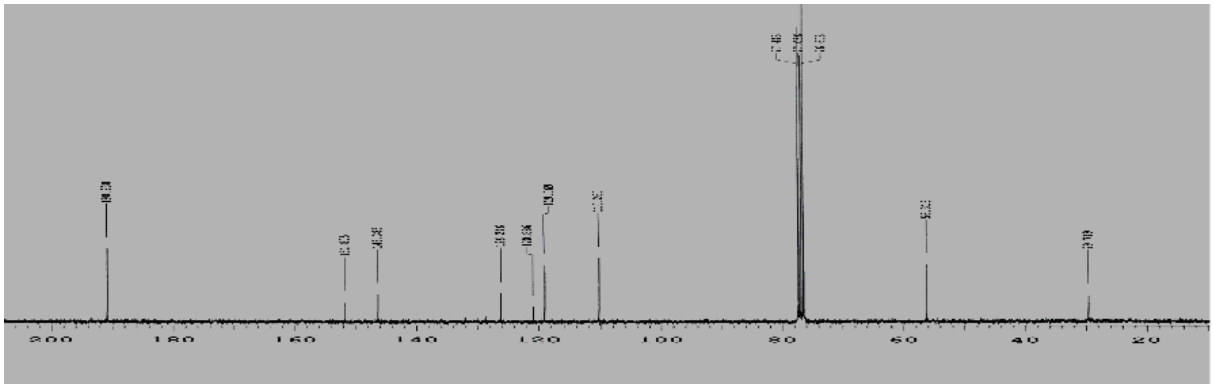


^{1}H NMR of Methyl 4-hydroxy-3-methoxybenzoate **14f**

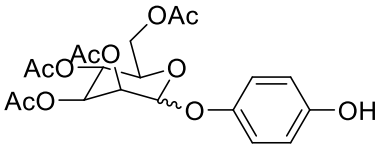


14b

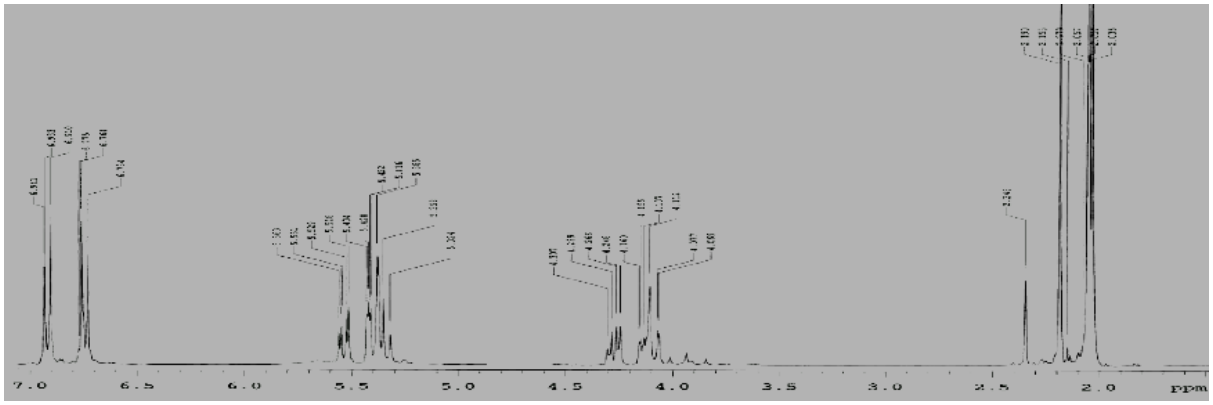




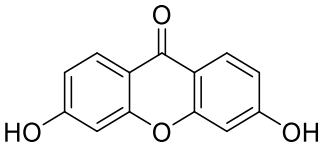
^{1}H and ^{13}C NMR Synthesis of 2-bromo-4-hydroxy-5-methoxybenzaldehyde **14b**



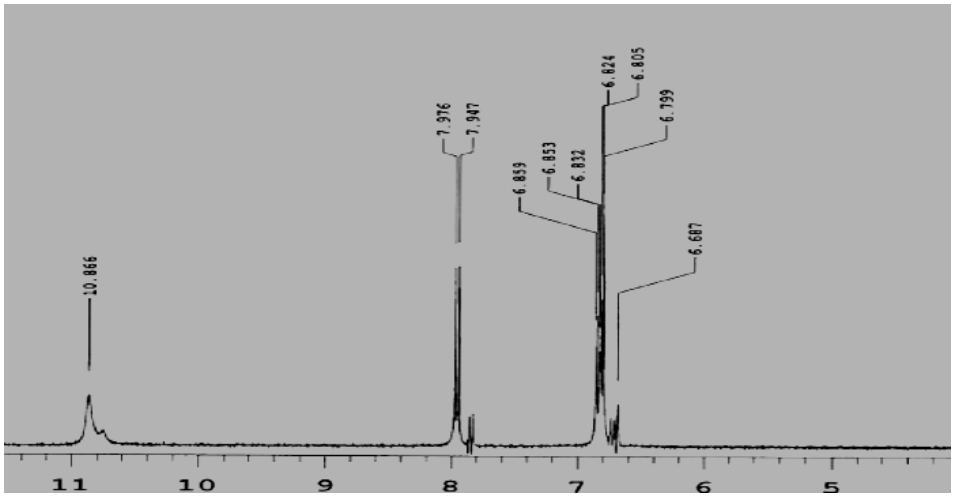
14g



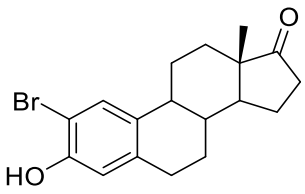
^{1}H NMR of (2R,3R,4S,5S)-2-(acetoxymethyl)-6-(4-hydroxyphenoxy)tetrahydro-2H-pyran-3,4,5-triyl triacetate **14g**



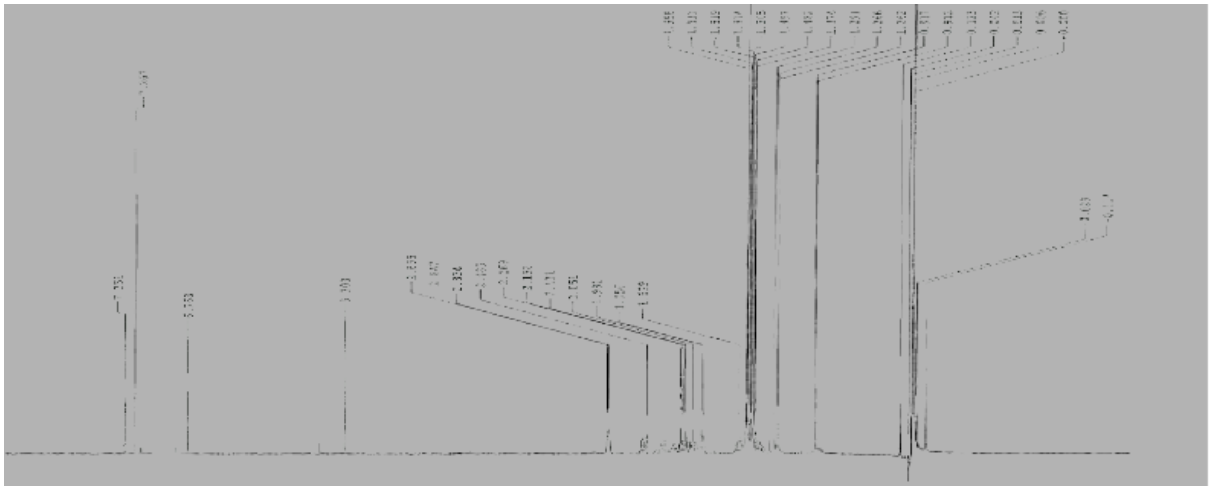
14h



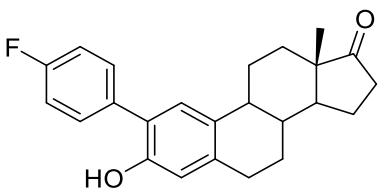
^{1}H NMR of 3,6-dihydroxy-9H-xanthen-9-one **14h**



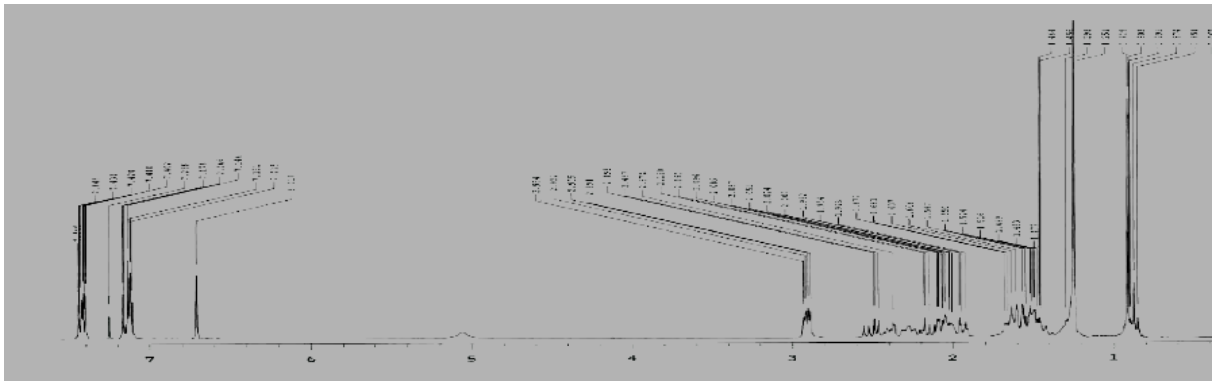
14i

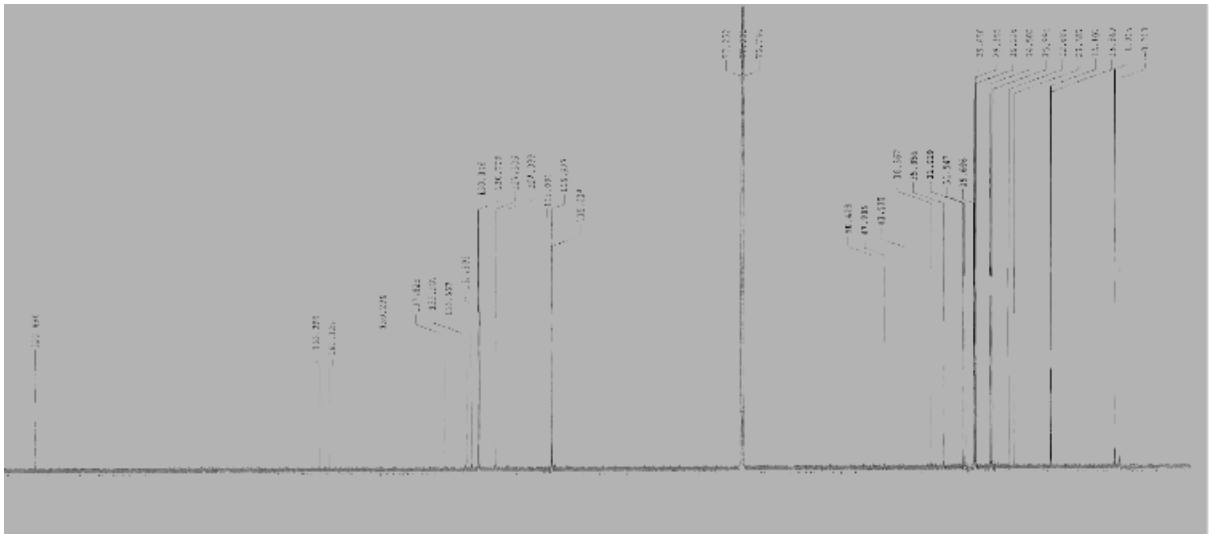


^{1}H NMR of 2-Bromo-13α-estra-1,3,5(10)-trien-17-one **14i**



18





^{1}H and ^{13}C NMR Synthesis of 2-(*p*-fluorophenyl)-3-hydroxyestra-1,3,5(10)-trien-17-one **18**