Novel Cascade Approaches for the Synthesis of Carbo- and Heterocycles

A thesis submitted for the partial fulfillment of

the degree of Doctor of Philosophy

by

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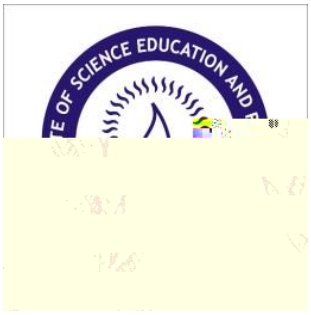

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DECLARATION

The work presented in the thesis entitled "***Novel cascade approaches for the synthesis of carbocycles and heterocycles***" has been carried out by me under the supervision of **Dr. Sripada S. V. Rama Sastry** in the Department of Chemical Sciences, Indian Institute of Science Education and Research (IISER) Mohali.

This work has not been submitted in part or full for a degree, diploma or a fellowship to any other university or institute.

Whenever contributions of others are involved, every effort is made to indicate this clearly with due acknowledgments of whomsover assisted during work and discussions. This thesis is a bona fide record of original work done by me and all sources listed within have been detailed in the bibliography.

Siddheshwar K. Bankar

Date:

Place:

In my capacity as the supervisor of the candidate, I certify that the above statements made by the candidate are true to the best of my knowledge.

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SUMMARY

The polycyclic acetals are recognized as essential part of substructures widely present in natural products and pharmaceutically relevant compounds. Due to their biological activity, these oxabicycles are frequent targets in total synthesis. Among them, oxygen, sulfur and nitrogen containing heterocycles in their frameworks are proven to shows defined physical, chemical and biological properties. On the other hand, arenes and heteroarenes fused carbocycles are abundant in a diverse range of bioactive natural product and Pharmaceuticals relevant compound. Among them, indenes and pentannulated heteroarenes consisting of indole, thiophene, and benzothiophene have occupied a distinct place in pharmaceuticals and material science. The importance of polycyclic acetals and cyclopenta[*b*]annulated arenes and heteroarenes inspired the development of several synthetic strategies to access polycyclic acetals and pentannulated arens and heteroarenes by using metals. However, the development of general, efficient methods starting from readily accessible starting materials remain an emerging research area.

The thesis entitled "*Novel cascade Approaches for the Synthesis of Carbo- and Heterocycles*" describes the efforts towards novel approaches to the synthesis of developed polycyclic acetals and pentannulated arenes and heteroarenes. The content of the thesis has been divided into two parts. Part A content four sections and Part B content two sections. In all sections, a brief introduction is provided. The compounds are sequentially numbered (bold), and references are marked sequentially as superscript and listed at the end of the thesis.

The first section highlights acid, base and palladium-mediated strategies such as [5+2], [4+2] and radical reactions leading to wide variety of heteroannular acetals.

Our ongoing research on chemistry of heteroaryl carbinols, for the development of potentially green and diversity oriented approach towards the synthesis of heteroannular acetals. We designed a substrates acetoxy pyranone and 1,3-dicarbonyl compounds. The second section of thesis demonstrates the bi-, tri-, tetra and spirocyclic furopyranones *via* Michael addition followed by transacetalization in situ formed oxonium ion. On the other hand when we used alkoxy or aryloxy pyranone and treated 1,3-dicarbonyl compounds surprisingly generates bi-, tri-, and tetracyclic bisacetals in good to excellent yield, *via* Michael addition followed by

cycloetherification. The generality and synthetic utility of this strategy was further demonstrated to synthesis of natural product cores.

In third section describes the one-pot approach for the synthesis of 1,4-dioxinones, 1,4-dithiienones and 1,4-oxathiienones in moderate to good yield *via* Michael addition followed by transacetalization in situ formed oxonium ion by utilizing Lewis acid. After successful development of synthesis of oxygen and sulfur containing heterocycles, further we elaborated this methodology to synthesis core structure of alliuocide G natural product.

In fourth section describes the one-pot approach to the synthesis of 2-benzofuranyl-3-hydroxyacetones, furocoumarins, and pyran-fused benzofurans in good to excellent yield by utilizing Lewis acid. The synthetic sequence involves first acid-catalyzed transacetalization followed by unusual Fries-type oxygen to carbon rearrangement subsequently aromatization and oxa-Michael addition to generates pyrane fused benzofurans. Which leads to the acid-catalyzed ring opening and aromatization to furnish benzofuran derivatives. The synthetic utility of this methodology was further demonstrated to the synthesis of 5,5-spiroketal compounds, by using *N*-bromosuccinimide.

In part B second section describes a new approach to the synthesis of highly substituted cyclopentadienes, indenes and cyclopentane-fused heteroarenes in good to excellent yields by utilizing palladium-catalyzed intramolecular Trost-Oppolzer-type Alder-ene reaction of 2,4-pentadienyl acetates and strylbenzyl acetates. The synthetic sequence involves first p-complex formation which is electrophilic nature of Tsuji-Trost reaction, then ene-type of reaction which is nucleophilic nature which leads to the formation of cyclopentenyl cation. Followed by loss of proton to generate tetrasubstituted cyclopentadiene subsequently reductive elimination and 1,3-hydride shift to obtain tetrasubstituted cyclopentadiene. We showed the synthetic utility of this strategy to the formal total synthesis of paucifloral F natural product.

LIST OF ABBREVIATIONS

Ac	Acetyl
Aq	Aqueous
ABq	AB quartet
Atm	Atmospheric
BBEDA	*N*, *N*′-bis-(benzylidene)ethylenediamine
BINAP	2, 2′-bis(diphenylphosphino)-1, 1′-binaphthyl
Bn	Benzyl
Boc	*tert*-butyloxycarbonyl
bpy	2, 2′-bipyridine
Brs	broad singlet
calcd	calculated
cbz	carboxybenzyl
CFL	compact fluorescent lamp
COD	cyclooctadiene
d	doublet
DABCO	1,4-diazabicyclo[2.2.2]octane
DBU	1,8-diazabicylo[5.4.0]undec-7-ene
dba	dibenzylideneacetone
DCE	dichloroethane
DCM	dichloromethane
dd	doublet of doublet
Ddd	doublet of a doublet of doublet
DMA	dimethylacetamide
DMAP	4-dimethylaminopyridine
DME	dimethoxyethane
DMF	*N*, *N*′-dimethyl formamide
DMSO	dimethyl sulfoxide
dq	doublet of quartet

dpbp	2,6-bis(diphenylphosphino)benzophenone
dppb	1,4-bis(diphenylphosphino)butane
dppe	1,2-bis(diphenylphosphino)ethane
dppp	1,3-bis(diphenylphosphino)propane
dr	diasteriomeric ratio
dt	doublet of triplet
DTBMP	2,6-di-*tert*-butyl-4-methylpyridine
ee	enantiomeric excess
eq.	equivalents
ESI	electron spray ionization
FT-IR	Fourier transform infrared spectroscopy
h	hour(s)
HMDS	hexamethyldisilazane
HRMS	high resolution mass spectrum
Hz	Hertz
ppm	parts per million
IBX	2-iodoxybenzoic acid
J	coupling constant
LDA	lithium di-isopropyl amide
m	multiplet
mg	milli gram(s)
MHz	mega hertz
min	minute(s)
mL	milliliter(s)
mmol	milli mole(s)
m.p.	melting point
MS	molecular sieves
m/z	mass/charge
NBS	*N*-bromosuccinimide
NIS	*N*-iodosuccinimide

PMB	4-methoxy benzyl
PTSA	*p*-toluenesulfonic acid
q	quartet
qd	quartet of doublet
RT	room temperature
s	singlet
t	triplet
t-Bu	*tert*-butyl
td	triplet of doublet
TMEDA	tetramethylethylenediamine
Tf	trifluoromethanesulfonate
TFAA	trifluoroacetic anhydride
TFE	trifluoroethanol
TMS	trimethylsilyl
TPPTS	3，3′，3″-phosphanetriyltris trisodium salt
tert	tertiary
THF	tetrahydrofuran
THA	tetrahexylammonium
TMS	tetramethylsilane
TLC	thin layer chromatography

Part A

Section 1

General introduction about polycyclic acetals

Heteroannular acetals containing fused [5.5] and [6.5] ring system occur in a wide variety of natural products and biologically relevant compounds (Fig. 1). Due to their biological and pharmacological activity, these oxabicycles are frequent targets in total synthesis.[1]

Among them, heterocycles possessing oxygen, sulfur, and nitrogen in their frameworks are proven to shows defined physical, chemical and biological properties.[2] Polycyclic fused [6.6] heteroannular acetals show antidiabetic, anti-Alzheimer, antitumor, anticoagulant, insecticidal, hypotic and antifungal activities. For example, furopyran core containing natural product Erysenegalensein J was isolated from Cameroonian medicinal plant *Erythrina sensegalensis*, exhibits antiviral activity (Fig. 1.). Alliuocide G was isolated from *Allium cepa*, and this molecule shows in vitro α-amylase inhibitory activity and radical scavenging potency. Pittosporatobiraside A was isolated from the flowers of *Pittosporum tobira.* Pittosporum tobira is widely distributed in Japan. The leaves and roots of this plant have been used as a remedy of skin disease. Various aromadendrene-type sesquiterpene glycosides such as Pittosporatobiraside A and B were isolated from leaves of *Pittosporum tobira.*[3]

Bicyclic bisacetals core containing natural product durumhemiketalolides A was isolated from *Lobophytum durum* which shows anti-inflammatory activity and antibacterial activity against *Salmonella enteritidis.* The dihydropyranobenzofuran core containing natural products chafuroside A and B were isolated from the Oolong tea leaves of *Camellia sinesis*. It shows anti-oxidant activity and anti-inflammatory activity.[4] The tea is made from green leaves of *Camellia sinesis* and is the most widely consumed beverage after water in daily life worldwide. Erinacines

B contains 1,4-dioxin moiety which was isolated from *Hericium erinaceum* which shows potent stimulating activity of nerve growth factor synthesis.[5] Stimulators of NGF-synthesis have been expected to become drugs for degenerative neu peripheral nerve regeneration.

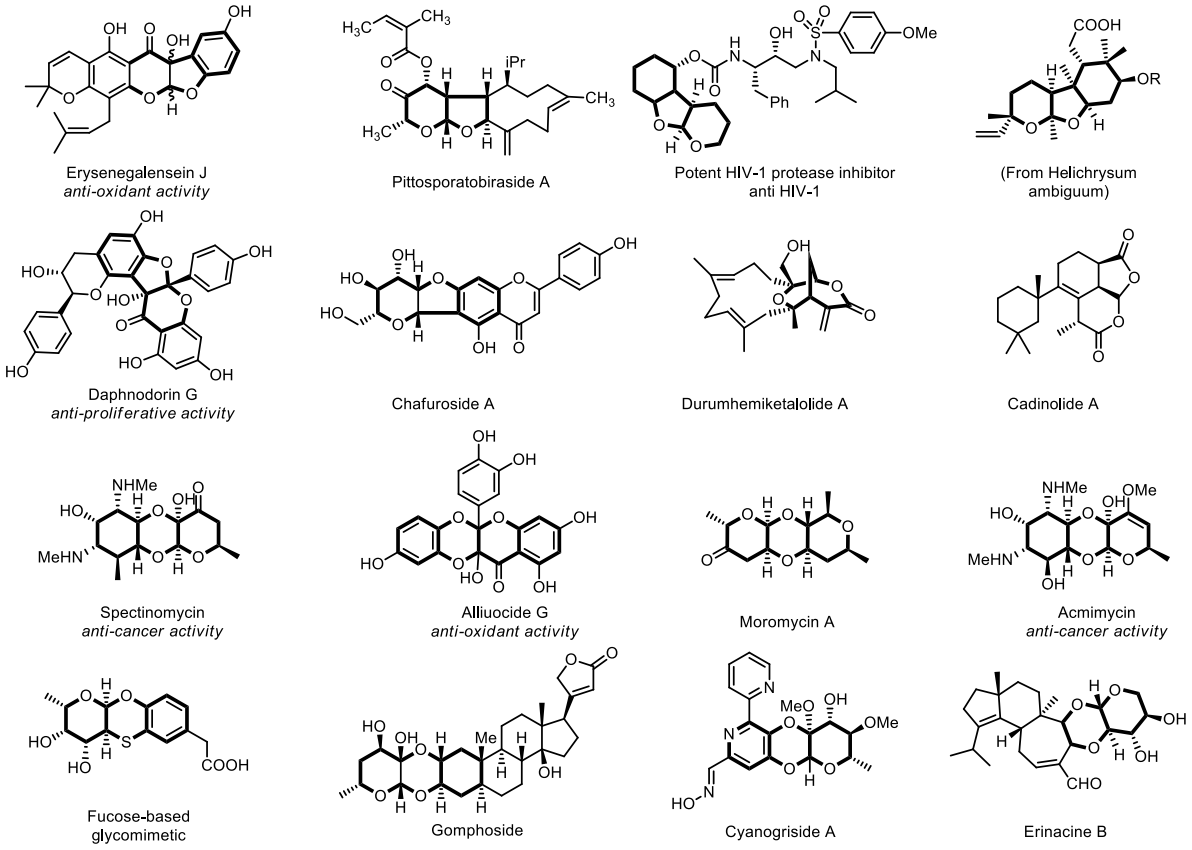
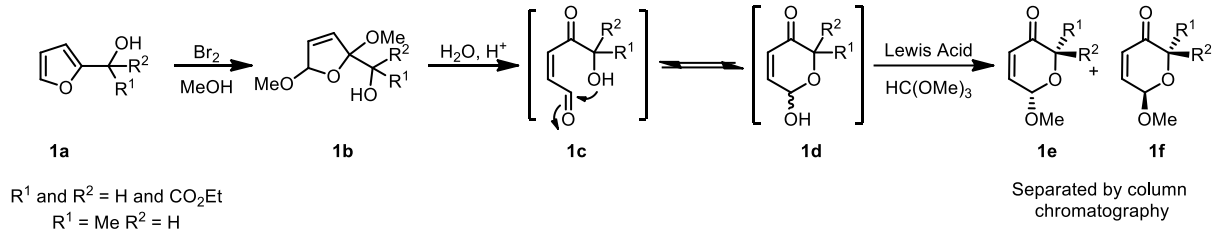


Figure 1: Representative examples of bioactive compounds

These aforementioned importances of polycyclic acetals in synthetic organic chemistry to develop efficient synthetic protocols. Towards this, various methods such as acid-catalyzed transacetalization, palladium-catalyzed glycosylation, base-mediated Michael addition, [3+2], [5+2], and 4+2] cycloaddition reactions, have been reported. In the next few subsections, a few important methods leading to a wide variety of polycyclic acetals are described.

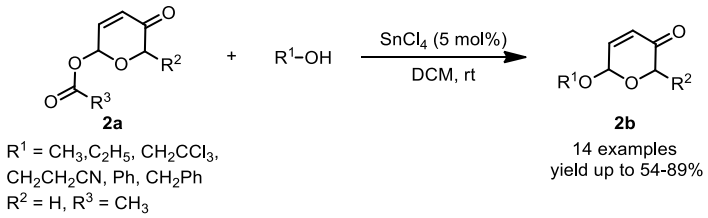
1.1: Acid-catalyzed transacetalizations

In 1971, Achmatowicz *et al.*[6] reported the synthesis of pyranone acetals **1e** and **1f** (Scheme 1). The reaction of furfuryl alcohols **1a** in presence of methanol with Br_2 delivered 2,5-dimethoxy-2,5-dihydrofurans **1b**, which was treated under mild acidic condition generate diketo compounds **1c** through the cleavage of acetal center and rearrangement to furnish pyranone alcohols **1d**. The protection of pyranone alcohols using methyl orthoformate in the presence of Lewis acid furnished pyranone ethers **1e** and **1f** as *cis*- and *trans*- isomer.



Scheme 1: Achmatowiczôs synthesis of pyrano

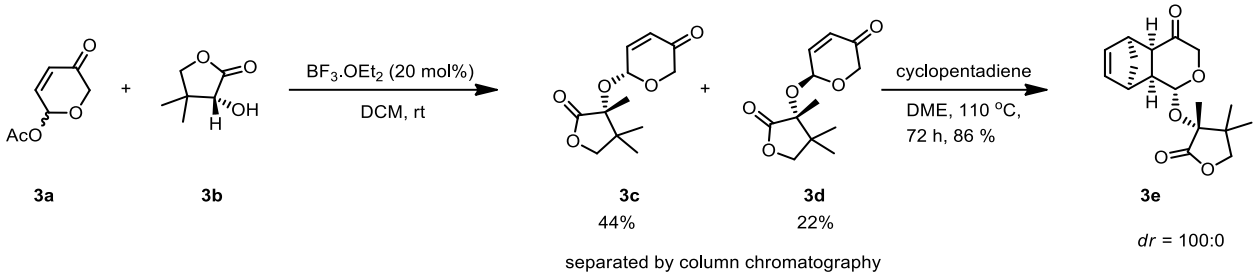
In 1979, Grynkiewicz *et al.*[7] reported the synthesis of 6-alkoxy-2,3-dihydro-6*H*-pyran-2-ones **2b** from the 6-aceloxy derivatives **2a** (Scheme 2). The reaction of acetoxy pyranones **2a** with alcohols in the presence of tin(IV) chloride generated pyranone ethers **2b**. A variety of pyranone ether analogs were synthesized in moderate to good yield. This alkoxy pyranone was further used for the synthesis of glucose derivatives.



Scheme 2: Grynkiewicz-catalyzed transacetalization

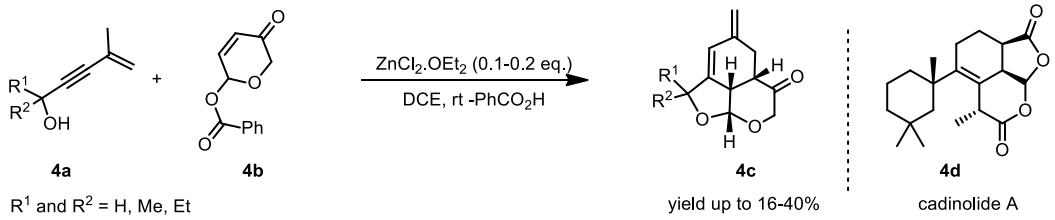
In 1991, Feringa *et al.*[8] established an asymmetric Diels-Alder reaction and Michael type addition reaction with (*R*)-pantolactone-substituted-*2H*-pyran-3(6*H*)-one (Scheme 3). The pyranone acetate **3a** and (*R*)-pantolactone **3b** were subjected under the $BF_3.OEt_2$ condition for the formation of a mixture of diastereomers **3c** and **3d**, which were separated by column chromatography. Thereafter, the major isomer of the **3c** was used for different chemical reactions.

For example, the reaction of chiral alkoxy pyranone **3c** and cyclopentadiene underwent [4+2] cycloaddition reaction to furnish corresponding product **3e** in good yield and diastereoselectivity.



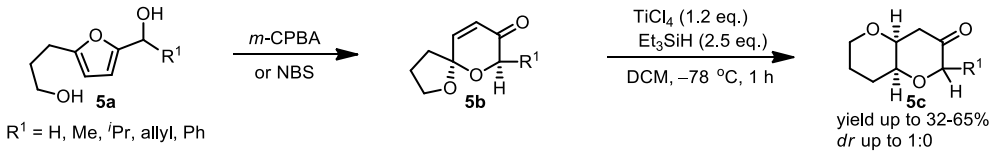
Scheme 3: F e r i n g a - A ld e r reaction on chiral acetoxy pyranone

In 1993, Hoffmann *et al.*[9] described the synthesis of the tricyclic core of marine natural product **4d** (Scheme 4). The fused tricyclic conjugated dienes **4c** were synthesized from pyranone benzoates **4b** and 4-methylpent-4-en-2-yn-1-ols **4a** in the presence of $ZnCl_2$.monoetherate. The overall reaction sequence involves transacetalization followed by [4+2] cycloaddition reaction.



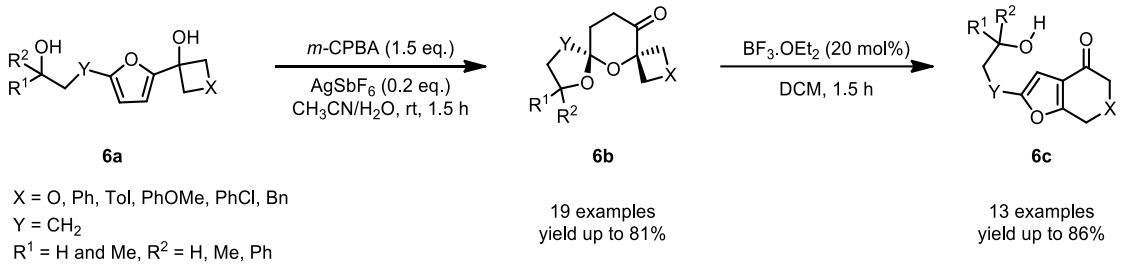
Scheme 4: Hoffmann's catalyzed Diels Alder reaction on acetoxy pyranone

In 2012, Tong *et al.*[10] developed a novel double cascade synthetic strategy for the synthesis of diastereoselective *cis*-fused bicyclic ethers **5c** *via* Achmatowicz rearrangement reaction of substituted furfuryl alcohols **5a** to generate spiroketals **5b** (Scheme 5). Followed by chemo- and diastereoselective reduction and subsequent oxa-Michael addition furnished bicyclic ethers **5c** in moderate to good yield. A wide variety of fused bicyclic ethers were synthesized by utilizing this methodology.



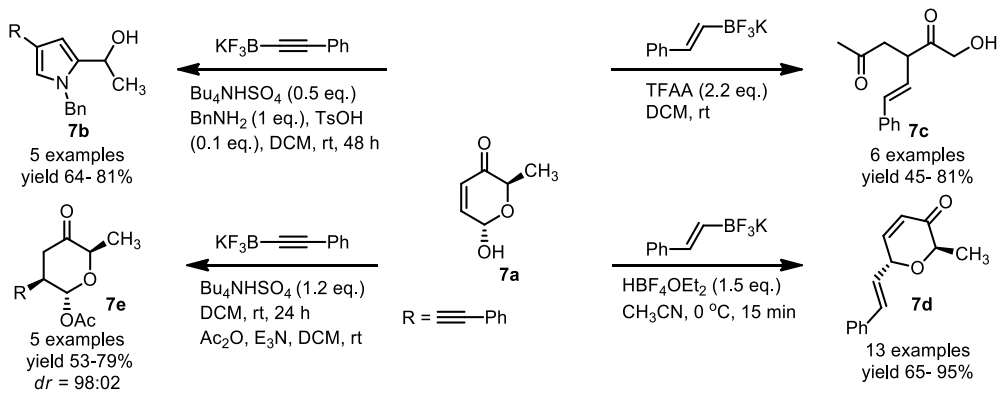
Scheme 5: T o n g ' s s y n t h e s i s o f b i c y c l i c e t

In 2018, Yin *et al.*[11] described one-pot approach for the synthesis of dihydrobenzofuranones **6c** by employing intramolecular Achmatowicz rearrangement of hydroxyalkyl furanyl cyclobutanols **6a** to generate dispiroacetals **6b** (Scheme 6). The bis-spiro acetals **6b** were subjected under Lewis acid-mediated condition *via* ring expansion to furnish dihydrobenzofuranones **6c** in good to excellent yields.



Scheme 6: Yin's synthesis dihydrobenzofuranones dispiroacetals an

In 2018, Csaky *et al.*[12] reported the selective functionalization of pyranone alcohols **7a** by utilizing potassium organotetrafluroborates under the metal-free conditions with styrenes, phenylacetylenes, and benzyl amines to provide dihdropyranones **7d**, tetrahedropyranones **7e**, 1,4-dicarbonyl compounds **7c** and functionalized pyrroles **7b** in good to excellent yield and high diastereoselectivity (Scheme 7).

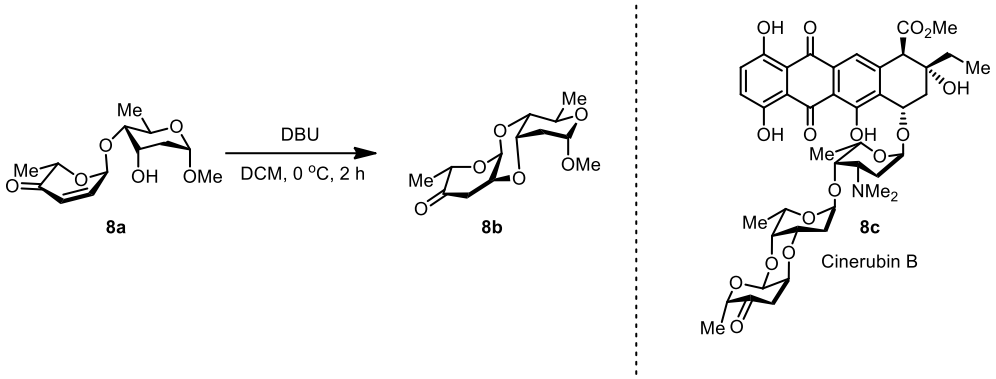


Scheme 7: Csaky's selective functionalization

1.2: Base-mediated Michael addition reactions

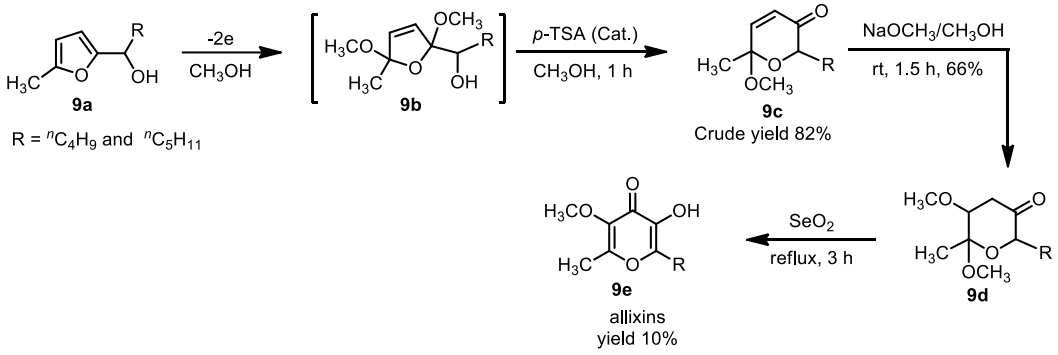
In 1990, Thiem *et al.*[13] reported the synthesis of disaccharide subunits of anthracycline antibiotic cinerubin B **8c** (Scheme 8). Towards this, the reaction of enone ether of glucose

derivative **8a** under base-mediated condition delivered the bridge disaccharide **8b** through oxa-Michael addition reaction.



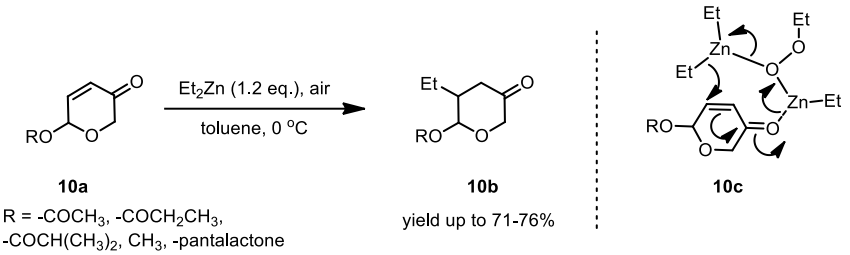
Scheme 8: Thiemô s -mediated oxa-Michael reaction

In 1998, Matsumura *et al.*[14] reported a facile synthesis of allixin **9e** and its related compounds (Scheme 9). The reaction of furfuryl alcohol **9a** under electrochemical oxidation generated the intermediate **9b**, which was treated in the presence of acid furnished pyranone ether **9c**. Subsequently, a base-mediated oxa-Michael reaction and SeO_2-mediated oxidation sequence afforded the allixins **9e**.



Scheme 9: Ma t s u mfacile synthesis of allixin analogs

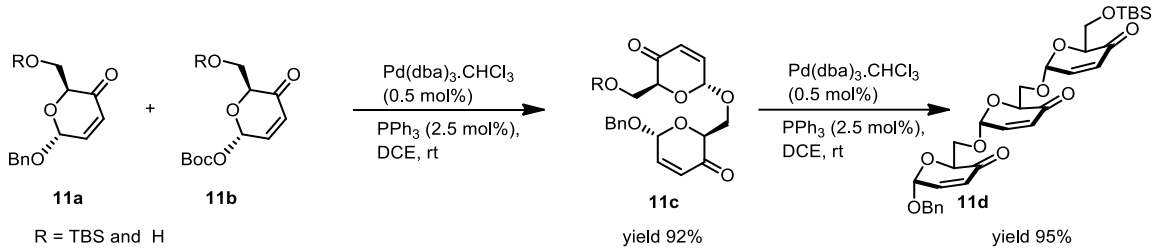
In 2000, Feringa *et al.*[15] developed 1,4-addition of diethylzinc on pyranone acetate **10a** (Scheme 10). The reaction of acyloxy or alkoxy pyranones **10a** with diethylzinc, in the presence of oxygen atmosphere generated Michael adducts **10b** in good yield. The reaction underwent *via* diethyl zinc peroxide complex **10c**.



Scheme 10: Feringaô s 1,4-addition of diethylzinc on pyranone acetate

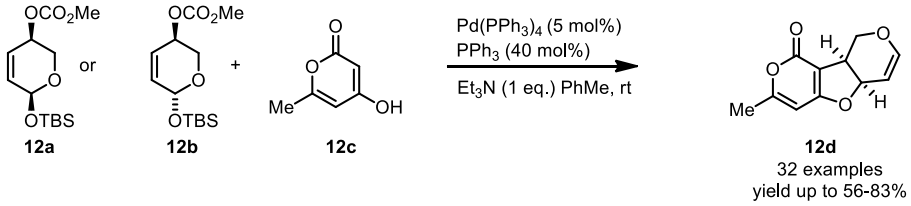
1.3: Palladium-catalyzed glycosylations

In 2004, *et al.*[16] Dave described the de novo synthesis of oligosaccharides **11d** *via* palladium-catalyzed glycosylation reaction of **11a** with **11b** (Scheme 11). A variety of natural and unnatural sugar derivatives could be accessed by employing this method. The key feature of this reaction was highly diastereoselective reduction and dihydroxylation for the synthesis of monosaccharide and oligosaccharide.



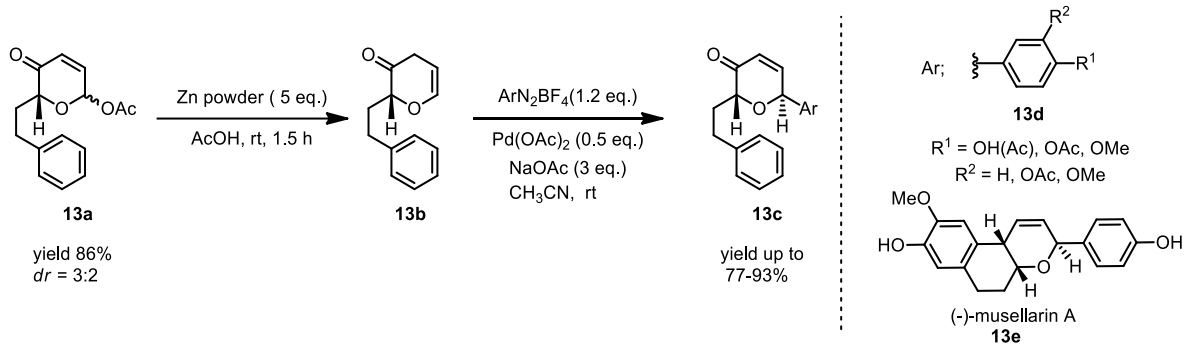
Scheme 11: O ô D o h e de novo synthesis of oligosaccharides *via* palladium-catalyzed glycosylation reaction

In 2013, Harvey *et al.*[17] established regioselective palladium-catalyzed allylic alkylation for the synthesis of furopyrans **12d** (Scheme 12). Cyclic *b*-dicarbonyl **12c** react with dihydropyran **12a** or **12b** to generate furopyran **12d** in moderate to good yields. Interestingly, both *cis*- and *trans* dihydropyrans **12a** or **12b** deliver the only fused *cis*-ring product. Both the allylic carbonate and siloxy group on the dihydropyran substrate control the regioselectivity of product.



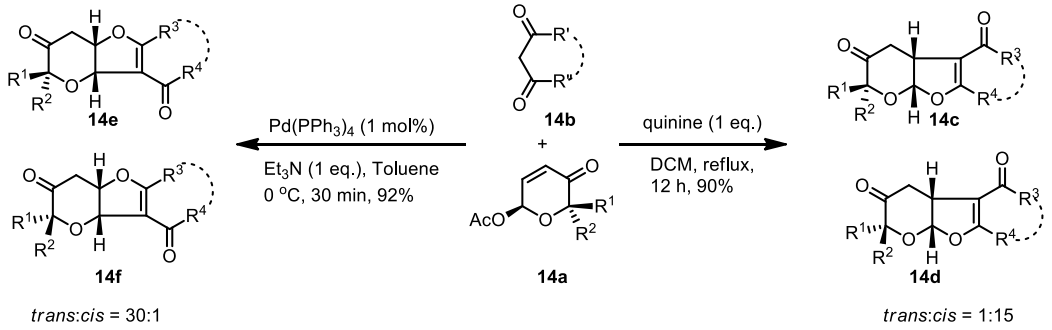
Scheme 12: H a r v e y regioselective palladium-catalyzed allylic alkylation for the synthesis of furopyrans

In 2015, Tong *et al.*[18] reported regio- and diastereoselective arylation of pyranone acetate **13a** (Scheme 13). The reaction underwent Zn-mediated reductive *g*-deoxygenation to form adduct **13b** followed by Heck-Matsuda reaction leading to the stereoselective synthesis of *trans*-dihdropyranone **13c**. The synthetic utility of this methodology was further demonstrated in the asymmetric synthesis of (-) musellarin A **13e**.



Scheme 13: Tong's regio- and diastereoselective *trans*-selective arylation

In 2016, Tong *et al.*[19] reported regio- and diastereoselective oxa-[3+2] cycloaddition reactions by utilizing Achmatowicz rearrangement product **14a** (Scheme 14). Acetoxy pyranones **14a** and 1,3-dicarbonyl compounds **14b** underwent Tsuji-Trost type reaction to deliver the bicyclic furopyrans **14e** and **14f**. On the other hand, same reactants in the presence of base furnished furopyrans **14c** and **14d** in good yield and excellent diastereoselectivity.

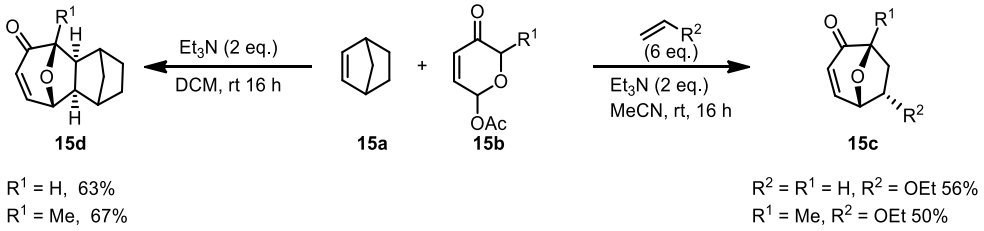


Scheme 14: Tong's Diastereoselective [3+2] cycloaddition reactions by employing Achmatowicz rearrangement product

1.4: [5+2] Cycloaddition approaches

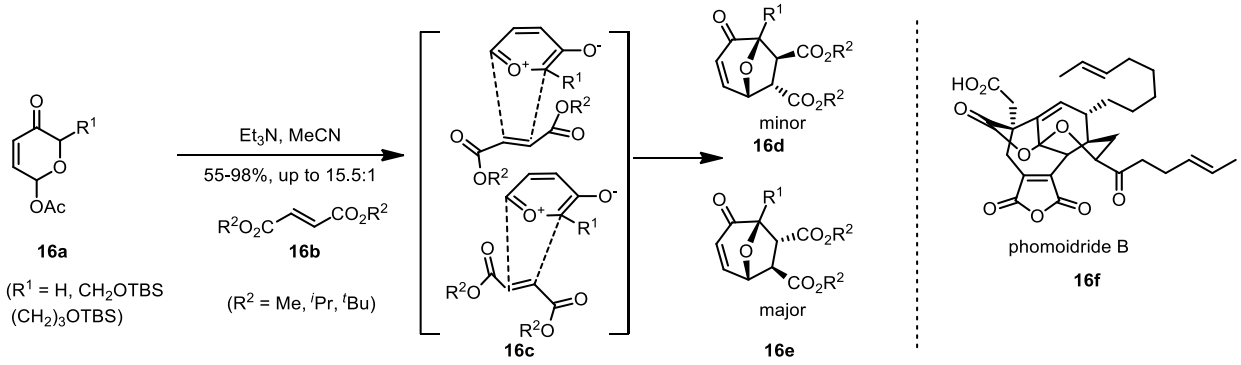
In 1983, Sammes *et al.*[20] reported intermolecular [5+2] cycloaddition reaction using the electron rich and strained olefins, such as ethyl vinyl ether and norbornadiene **15a** (Scheme 15).

The reaction of acetoxy pyranones **15b** with norbornadiene **15a** under the base-mediated condition delivered fused carbocycles **15d** in moderate yield and excellent diastereoselectivity. On the other hand, ethyl vinyl ether or styrene under base-mediated condition furnished seven membered carbocycles **15c**. An excess amount of the olefin was required to trap the dipolar intermediate and to prevent the side products.



Scheme 15: S a m m e s ô s [5 + 2] c y c l o a d d i t i o n r e

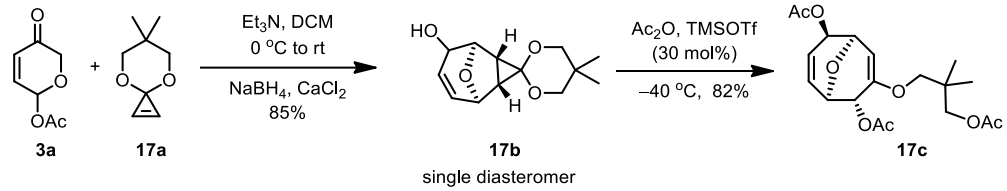
In 2001, Ohkata *et al.*[21] developed the synthesis of seven membered carbocycles **16e** with minor isomer **16d** through [5+2] cycloaddition reaction under base-mediated condition (Scheme 16). The reaction of dialkyl fumarates **16b** with acetoxy pyranones **16a** generated seven membered carbocycles **16e** *via* oxidopyrylium intermediates **16c**. They have observed when employing larger groups (R^1 = CH_2OTBS, R^2 = ^{t}Bu) on the parent substrate lead to higher degree of stereocontrol up to 15.5:1 because of minimizing unfavorable steric interaction in the preferred transition state geometry **16c**. Further, this intermediate **16c** was used for the synthesis of natural product phomoidride B **16f**.



Scheme 16: O h k a t a ô s s y n t h e s i s o f s e v e n m e m b e r e d c a reaction

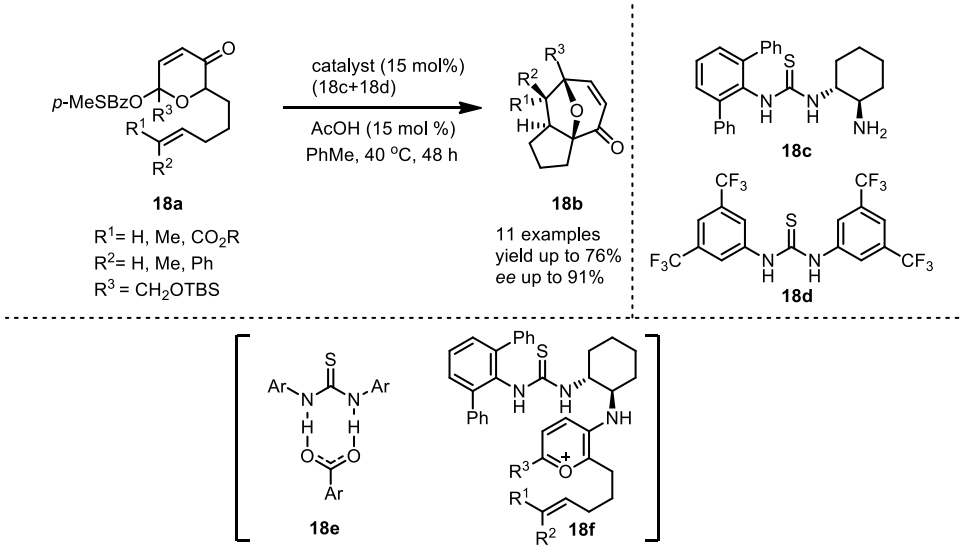
In 2002, Mascarenas *et al.*[22] have presented the synthesis of 1,5-oxa-bridged cyclooctenes by utilizing stereoselective [5+2] cycloaddition reaction **17c** (Scheme 17). The reaction of acetoxy

pyranone **3a** and cyclopropenone acetal **17a** furnished seven-member carbocycle **17b** and subsequent ring opening of cyclopropane unit generated highly functionalized 1,5-oxa-bridged cyclooctene **17c** bearing four stereocentres.



Scheme 17: Mascarenasôs [5+2] cycloaddition

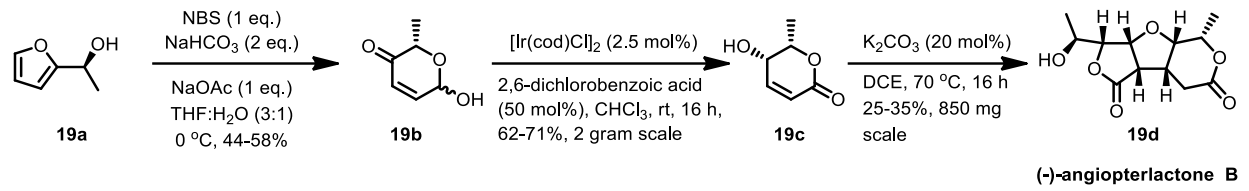
In 2011, Jacobsen *et al.*[23] came up with an asymmetric intramolecular [5+2] cycloaddition reaction by employing thiourea catalyst **18e** (Scheme 18). The reaction of acetoxy pyranones **18a** under the dual catalytic system, one was the chiral primary thiourea **18c** and second being achiral thiourea **18d** to deliver seven membered carbocycles **18b** in excellent yields and enantioselectivity. This reaction proceeded through oxidopyrylium intermediate **18f**. The experimental evidence showed that new type of co-operative catalyst was playing a crucial role to generate reactive pyrylium ion pair **18f** which underwent subsequent cycloaddition reaction**.** This approach marks an important milestone in this field.



Scheme 18: Jacobsen's enantioselective intramolecular [5+2] cycloaddition reaction

In 2017, Lawrence *et al.*[24] reported the asymmetric total synthesis of (-)-angiopterlactone B **19d** (Scheme 19). By employing Achmatowicz rearrangement as the key step, oxidative

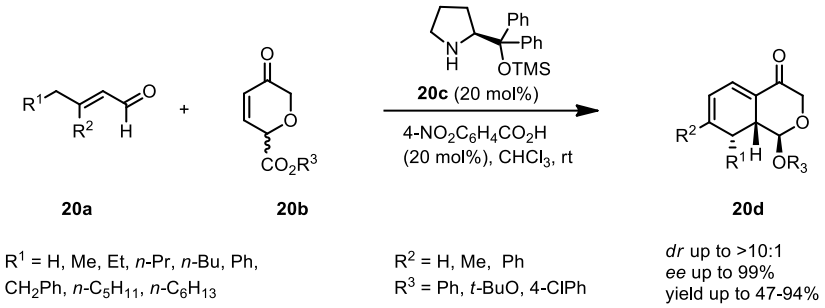
rearrangement of furfuryl alcohol **19a** to pyranone alcohol **19b** and subsequent transformations provided efficient access to (-)-angiopterlactone B **19d**.



Scheme 19: Lawrence's synthesis of (-)-angiopterlactone B

1.5: [4+2] Cycloaddition approaches

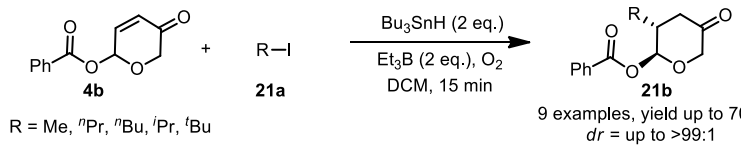
In 2012, Vicario *et al.*[25] reported a facile asymmetric synthesis of substituted tetrahydro isochromanes **20d** bearing three contiguous chiral centers (Scheme 20). By utilizing chiral proline-base catalyst **20c** through [4+2] cycloaddition reaction, a wide variety of *a,b*-unsaturated aldehydes **20a** and acyloxy pyranones **20b** under mild conditions afforded the desired product **20d** in excellent enantioselectivities and yields.



Scheme 20: Vicario's synthesis of substituted tetrahydro isochromanes

1.6: Radical approaches

In 2007, Sibi *et al.*[26] developed the radical-mediated Michael addition reaction of pyranones benzoates **4b** to access functionalized *b*-pyrones **21b** in good yield and high diastereoselectivity (Scheme 21). A wide variety of *b*-pyrones were synthesized by using this strategy.



Scheme 21: Sibi's Michael reaction on pyranone benzoate

Section 2

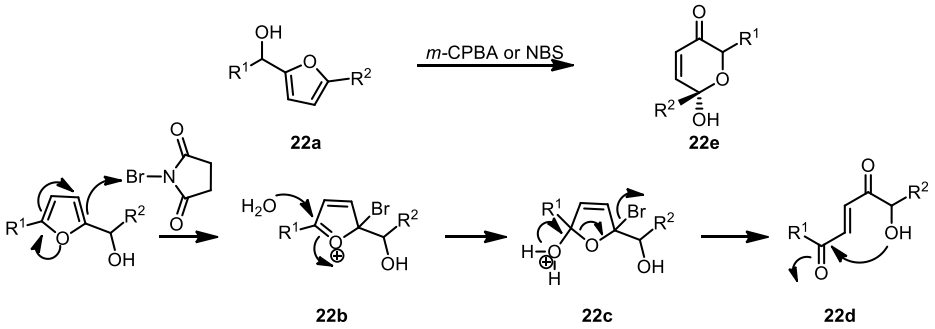
Metal-free access to functionalized polycyclic acetals under mild aqueous conditions

In the last few decades, there has been an immense focus on the practice of green chemistry. The study of "green chemistry" is the study of the efficiency of the reaction and the ideas behind decreasing waste in the synthetic sequence.[27] One way of improving the productivity of a synthetic sequence is to utilize green solvent like water. Such solvents are useful for carrying out reaction especially in industrial chemistry.

Several methods have been developed to construct heterocyclic template. To date, general approaches for the synthesis of tetrahydropyrans involves oxa-Michael reaction,[28] and Prins cyclisation reaction.[29] Despite the availability of a wide range of methods for the synthesis of substituted tetrahydropyran derivatives, these methods have limitations with respect to limited substrate scope, availability of starting materials and harsh reaction conditions. However, furan and its derivatives are commercially available and it can also be synthesized from mono-and polysaccharides. Pyranone acetals received significant attention due to its electrophilic and nucleophilic nature and formation of oxidopyrylium intermediate for the synthesis of a wide range of natural product as well as complex molecules in an efficient manner.

Polycyclic heteroannular acetals are a part of diverse range of natural products and pharmaceutically relevant compounds which show anti-fungal, anti-cancer, anti-bacterial, and anti-HIV activity.[30] Among them, fused bicyclic acetals, tetrahydrofuropyrans or furopyrans are associated in many biologically significant compounds for example, erinacine J, pittosporatobiraside A, and daphnodorins.[31] During the past few decades, there has been much consideration towards the synthesis of furopyran and bicyclic acetals derivatives because of their biological activity. The presence of intricate structural features coupled with biological activities have made these oxabicycles interesting and challenging synthetic targets.

Achmatowicz rearrangement involves the conversion of furan to dihydropyran. This reaction is very useful for the synthesis of natural products and pharmaceutical compounds. This rearrangement was first reported by Achmatowicz in 1971. Here, furfuryl alcohol **22a** was treated with NBS to deliver *a,b*-unsaturated pyranone alcohol **22e** (Scheme 22). The plausible mechanism of this rearrangement involves first bromination of furfuryl alcohol **22a** to generate intermediate **22b** followed by the ring opening to form the 1,4-diketo compound **22d**. Then the free hydroxyl group attacks the adjacent carbonyl centre in 1,2 fashion to furnish pyranone alcohol **22e**.



Scheme 22: General representation of the Achmatowicz reaction

Achmatowicz rearrangement is a versatile tool for the preparation of tetrahydropyrans, [32]dihydropyanones,[33] *ŭ*-lactones,[34] spiroacetals,[35] polysaccharide, and sugar derivatives. Heteroannular acetals are part of a diverse range of natural products and pharmaceuticals. There have been many reports of Achmatowicz rearrangement. To date, mostly *N*-bromosuccinimide and water, [36] and *meta*-chloroperbenzoic acid [37] are used to carry out this rearrangement. Though the existing methods have contributed significantly to the development of this area, these methods