DEVELOPMENT OF SYNTHETICALLY USEFUL METHODOLOGIES FOR APPLICATIONS IN THE PREPARATION OF FUNCTIONAL MOLECULES

By

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List of Publications arising from the thesis

Journals

1. "PyC60-naphthacrown system: a new supramolecular recognition element", D. Pal, K. Kundu, S. K. Nayak and S. Bhattacharya, *Spectrochimica Acta Part A: Molecular and Biomolecular Spectroscopy*, **2015**, *138*, 958-963.

2. "Camphor-10-sulfonic acid catalyzed condensation of 2-naphthol with aromatic/aliphatic aldehydes to 14-aryl/alkyl-14*H*-dibenzo[*a*,*j*]xanthenes", K. Kundu and S. K. Nayak, *J. Serb. Chem. Soc.* **2014**, *79*, 1051-1058.

3. "Synthesis and bioevaluation of some phenolic diarylpropanes as anti-cancer agents", K. Kundu, M. Tyagi, B. S. Patro, S. Chattopadhyay and S. K. Nayak, *Org. Comm.* **2014**, *7*, 85-97.

4. "Spectroscopic and structural insights on supramolecular interaction between fullerenes and a naphthacrown based macrocyclic receptor in solution", A. Ray, D. Pal, K. Kundu, S. K. Nayak and S. Bhattacharya, *J. Spectrosc. Dyn*. **2013**, 3: 16.

5. "(±)-Camphor-10-sulfonic acid catalyzed direct one-pot three-component Mannich type reaction of alkyl (hetero)aryl ketones under solvent-free conditions: application to the synthesis of aminochromans", K. Kundu and S. K. Nayak, *RSC Adv*. **2012**, *2*, 480-486.

6. "Steric factor driven external association of xanthenocrown-5 and *bis*-napthalenocrown-6 with *bis*-(benzimidazolium)propane borontetrafluoride", A. Karmakar, K. Kundu, S. Ghosh, T. Chaudhuria, S. K. Nayak, and C. Mukhopadhyay, *Communicated*.

Conferences

1. "Design and synthesis of calix crowns for selective extraction of metal ions", K. Kundu and S. K. Nayak, Poster Presentation at "Interdisciplinary Symposium on Materials Chemistry" **2014**.

2. "Low-valent titanium mediated intra-molecular reductive deoxygenation in keto-amides: application to the synthesis of densely substituted pyrroles", K. Kundu and S. K. Nayak, Poster Presentation at "Interdisciplinary Symposium on Materials Chemistry" **2014**.

3. "Development of new protocols for the synthesis of *O*-heterocycles", K. Kundu and S. K. Nayak, Poster Presentation at "Chemistry Research Scholar Meet" **2011**.

4. "Design and synthesis of $[3.1]_2$ metacyclophanes as novel molecular hosts", K. Kundu and S. K. Nayak, Poster Presentation at "Interdisciplinary Symposium on Materials Chemistry" **2010**

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Dedicated to…..

My Beloved Parents and Brother

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CONTENTS

		Page No.
SYNOPSIS		i
LIST OF FIGURES		xiii
LIST OF TABLES		xvi
CHAPTER 1: Introduction to the Development of New Synthetic Protocols and Functional Molecules		
1.1	An introduction to organic synthesis	001
1.1.1	Target oriented synthesis	002
1.1.2	Method oriented synthesis	003
1.2	Aim of the thesis	004
1.3.	Heterocyclic compounds	004
1.3.1	Oxygen-heterocycles	005
1.3.1a	4-Aminochromans	006
1.3.1b	Xanthenes and benzoxanthenes	007
1.3.2	Nitrogen heterocycles	009
1.3.2a	Pyrrole derivatives	010
1.4	Supramolecular chemistry	011
1.4.1	Calixarenes	012
CHAPTER 2: Mannich-type Reactions under Solvent Free Conditions: Syntheses of *β*-Amino Carbonyl Compounds		
2.1	Preamble	015
2.1.1	The Mannich reaction	015
2.1.1a	Classical Mannich reaction	015
2.1.1b	Shortcomings / limitations of Mannich reactions	016
2.2	Present Work	018

2.2.1	CSA-catalyzed Mannich-type reaction of aliphatic ketones with various aldehydes and amines	020
2.2.2	CSA-catalyzed Mannich-type reaction of aromatic ketones with various aldehydes and amines	022
2.3	Conclusion	029
2.4	Experimental	029

CHAPTER 3: Important Uses of Mannich Adducts in the Syntheses of *O*/*N*-Heterocycles

3.1	Preamble	043
3.1a	*O*-Heterocycles: synthesis of 4-aminochromans	043
3.2a	Present work: synthesis of 4-aminochromans	045
3.1b	*N*-Heterocycles: synthesis pyrrole derivatives	050
3.2b	Present work: synthesis of densely substituted pyrroles	052
3.3	Conclusion	058
3.4	Experimental	058

CHAPTER 4: Camphor-10-sulfonic Acid Catalyzed Condensation of 2-Naphthol with Aldehydes: Synthesis of Dibenzo[a,j]Xanthenes

4.1	Preamble	070
4.1.1	Synthesis of xanthenes and benzoxanthenes	070
4.2	Present work	072
4.2.1	CSA-catalyzed condensation of 2-naphthol with benzaldehyde	072
4.2.2	Synthesis and use of 1,1-bis-(2-hydroxynaphthyl)-phenylmethane (**3**) as precursor in the synthesis of napthalenocrown-6	074
4.2.3	Library synthesis of 14-aryl-14H-dibenzo[a,j]xanthenes	078

4.2.3a	Condensation of 2-naphthol with liquid aromatic aldehydes	079
4.2.3b	Condensation of 2-naphthol with solid aromatic aldehydes	080
4.2.3c	Condensation of 2-naphthol with aliphatic aldehydes	083
4.2.4	CSA-catalyzed condensation of 2-naphthol with benzaldehyde and 1,3-dicarbonyl compounds	086
4.3	Conclusion	087
4.4	Experimental	088

CHAPTER 5: Synthesis of Calixarene/Homocalixarene-based Metacyclophanes for Their Potential Use as Functional Materials

5.1	Preamble	100
5.1.1	Calix[n]arene-crown ethers	100
5.1.2	Homocalixarenes	102
5.2	Present Work	103
5.2.1	Design and synthesis of some novel rigidized calix[4]crowns	103
5.2.2	Synthesis of [3.1.3.1] homocalixarenes	112
5.2.3	Applications of phenolic 1,3-diaryl propane as anti-cancer agent	117
5.3	Conclusion	124
5.4	Experimental	125

OVERALL CONCLUSIONS 139

REFERENCES 141

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SYNOPSIS OF Ph. D. THESIS

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SYNOPSIS

This thesis describes the development of novel and user friendly synthetic methodologies and optimization of the existing ones, for their use in the synthesis of important functional molecules. The content of the thesis has been divided into following five chapters.

Chapter 1 Introduction to the Development of New Synthetic Protocols and Functional Molecules

Organic compounds are the basis of all earthly life and constitute a significant part of human endeavors in chemistry. Synthetic organic chemistry primarily involves constructing complex molecules from simple ones. It is divided into two great landscapes: the total synthesis, where the synthetic chemists study how step by step it is possible to build a structure usually with biologically importance, and the methodologies which introduce new reactions. The knowledge in organic synthesis has enabled us to create functional molecules for new materials such as plastics, new dyes to color fabrics, new and efficient drugs to cure diseases.

Among millions of chemical compounds identified by the end of the second millennium, more than two-thirds are fully or partially aromatic and approximately half are heterocyclic. The presence of heterocycles in all kinds of organic compounds of interest in electronics, biology, optics, pharmacology, material sciences and so on is very well known[1]. Almost all the synthetic drugs are heterocycles. Among different heterocycles, chromans, xanthenes, densely substituted pyrroles are important as chemotherapeutic agents and have found wide clinical applications. Besides, xanthenes and pyrroles are also known to possess interesting photo-physical properties to use them as basic scaffold in designing advanced materials.

Supra-molecular chemistry plays a major role in different bio-chemical reactions in living organisms. To mimic natural processes, past two decades has witnessed enormous

effort by synthetic organic chemists to develop macro-cyclic molecules for selective encapsulation of various metal ions and neutral molecules. In this endeavor various macro-cyclic molecules including crown ethers, cyclodextrins, calixarenes, cucurbiturils have been developed. Among various calixarene oligomers such as calix[4]-, calix[6]- and calix[8]arene, calix[4]arenes have shown great promise in supra-molecular chemistry due to their pre-organized architecture which is a prerequisite feature for the development of efficient macro-cyclic host[2].

Synthesis of different functional molecules mainly involves development of novel carbon-carbon/carbon-heteroatom bond forming reactions. In recent years, considerable attention is devoted towards selective, atom-economic and environmentally benign protocols for achieving such organic transformations. Secondly, synthetic methodologies are designed to use and generate substances that possess little or no toxicity to human health and the environment. To this end several green reagents/catalysts have been developed for selective and non-hazardous chemical processes using solvent-free conditions or by using innocuous solvents/auxiliaries.

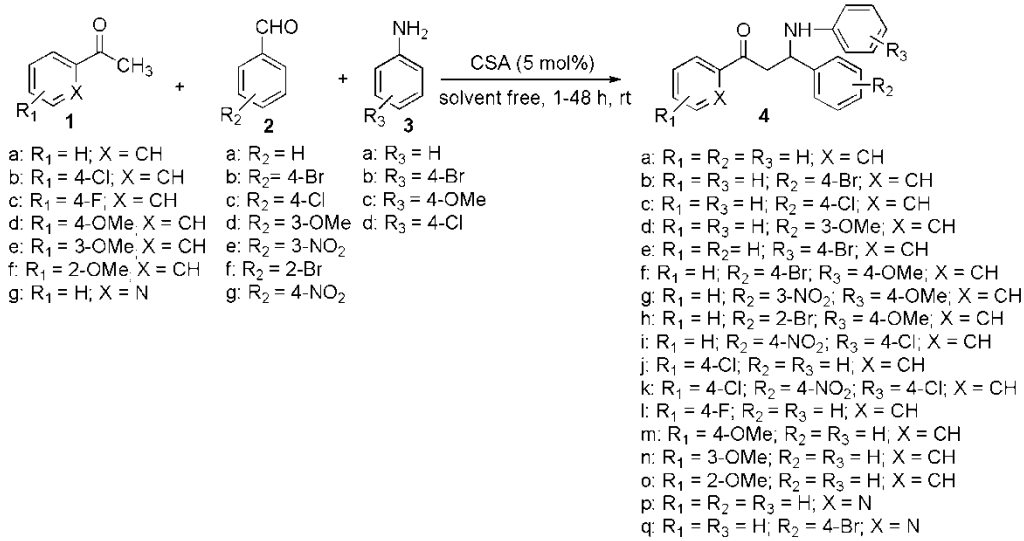
Keeping this in view, our work was focused on the development of novel, user-friendly and environmentally benign synthetic methodologies for convenient organic transformations and library synthesis. Application of some of these compounds in the synthesis of some important functional molecules have also been investigated which are discussed in following four chapters.

Chapter 2 Mannich-type Reaction under Solvent Free Conditions: Syntheses of *β*-Amino Carbonyl Compounds

The Mannich reaction, involving carbon-carbon bond formation between an enolizable ketone (nucleophile) and a schiff base (electrophile) is an atom-economic process and

provides one of the most basic and useful methods for the synthesis of *β*–amino carbonyl compounds[3]. These *β*–amino carbonyl compounds are versatile building blocks as they can be utilized in the synthesis of various nitrogen containing natural products and pharmaceuticals.

Use of metal free small organic molecules as catalysts has been one of the strategies to develop green organic reactions. To this end, we explored the efficacy of camphor sulfonic acid (CSA) as catalyst in Mannich-type reaction. Preliminary investigation of three component Mannich-type reactions of acetophenone (**1a**), benzaldehyde (**2a**) and aniline (**3a**) using CSA (10 mol%) as a catalyst in one-pot, under solvent-free conditions at room temperature yielded the desired *β*–amino carbonyl compound (**4a**) in 89% yield. By varying catalyst concentration in this reaction, we found 5 mol% of catalyst loading is sufficient to afford the desired product both in terms of yield and reaction time.



Scheme 1.1: (±)-CSA catalyzed one-pot three-component Mannich-type reaction

To see the scope and limitations of our protocol, different substituted aromatic aldehydes and aromatic amines were reacted with different aromatic/hetero(aromatic) ketones under optimized reaction conditions (Scheme 1.1). In all the cases smooth reaction

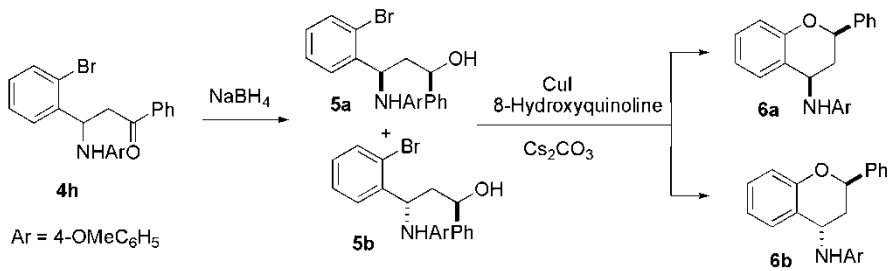
were observed to afford the *β*–amino ketones **4b–q** in moderate to high yields[4]. Moreover, the present CSA catalyzed methodology was found to be superior to the existing methods both in terms of yield and reaction time.

Chapter 3 Important Uses of Mannich Adducts in the Syntheses of *O*/*N*- Heterocycles

This chapter deals with application of Mannich adducts in the synthesis of i) *O*-heterocycles such as 4-aminochromans and ii) *N*-heterocycles such as densely substituted pyrroles.

I. *O*-Heterocycles: synthesis of 4-aminochromans

Among various oxygen-heterocycles, 4-aminochromans have attracted considerable attention as they have been used as modulators of calcium and potassium channels affecting cardiac activity of the blood pressure[5]. In view of their pharmaceutical importance, we felt that the Mannich adduct derived from ortho-bromo substituted *β*–aminoalcohol in principle should undergo intra-molecular etherification to afford 4-aminochroman skeleton. To this end, the Mannich adduct **4h** was reduced with $NaBH_4$ to yield a mixture of *syn*- and *anti*-isomers of bromo substituted *β*–aminoalcohol (**5a** and **5b**). Both the *β*–aminoalcohols were subjected to successful intra-molecular etherification using CuI/8-hydroxyquinoline combination as catalyst to afford 4-aminochromans **6a** and **6b** respectively (Scheme 2.1). The relative stereochemistry of 4-aminochromans **6a** and **6b** were determined by XRD[4] analysis.

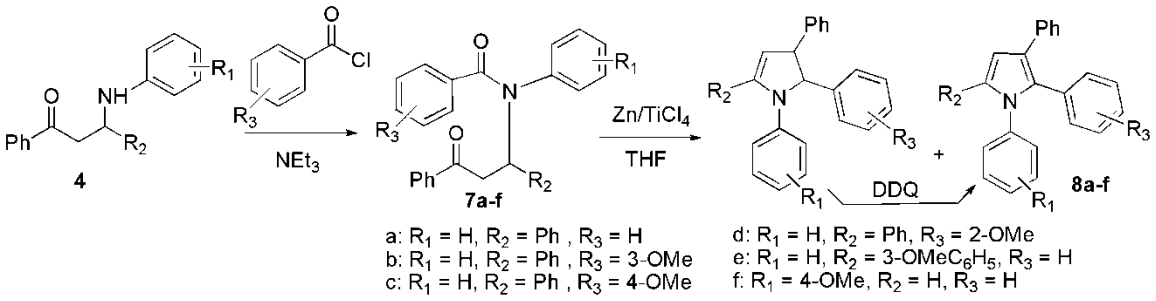


Scheme 2.1: Application of the Mannich adducts in the synthesis of *O*-heterocycles

II. *N*-Heterocycles: synthesis of densely substituted pyrroles

Densely substituted pyrroles are important structural elements in many bioactive natural products, therapeutic compounds, and new organic materials. Consequently, the efficient assembly of this class of molecule is a significant objective in synthetic chemistry[6]. As discussed above (Chapter 2), we have developed a protocol for the library synthesis of *β*–amino ketones (Mannich adducts) by using CSA as a catalyst[4]. Reaction of *β*–amino ketone **4a** with benzoyl chloride afforded the corresponding amide (**7a**) which was subjected to low-valent titanium reagent (prepared from $TiCl_4$/Zn) to afford a mixture of tetraphenyl dihydropyrrole and tetraphenylpyrrole. The mixture were then subjected to DDQ oxidation to obtain the 1,2,3,5-tetra-phenylpyrrole (**8a**) as the only product.

To see the scope of this reaction, a series of *β*–keto amides (**7b-f**) were prepared and subjected to LVT mediated reductive deoxygenation followed by DDQ oxidation to afford a library of 1,2,3,5-tetraryl-pyrrole (**8b-f**) in moderate to good yield. Incidentally, this is the first approach towards the synthesis of densely substituted pyrroles from Mannich adducts using LVT chemistry.



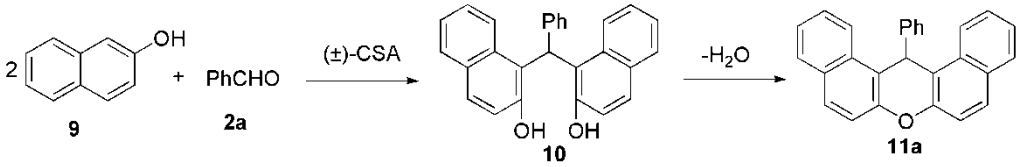
Scheme 2.2: Application of the Mannich adducts in the synthesis of *N*-heterocycles

Chapter 4 Camphor-10-sulfonic Acid Catalyzed Condensation of 2-Naphthol with Aldehydes: Synthesis of Dibenzo[a,j]Xanthenes

Xanthenes are an important class of *O*-heterocycles as they possess several useful biological and photophysical properties[7]. Since CSA has been proved as an highly efficient

catalyst for the activation of imines in the Mannich type reactions of enolizable ketones, it was of considerable interest to explore its catalytic potential for the activation of aldehydes in the condensation of 2-naphthol (**9**) with aldehydes to afford dibenzoxanthenes. For preliminary studies, 2-naphthol (**9**) was reacted with benzaldehyde (**2a**) in presence of CSA (Table 4.1).

Table 4.1: (±)-CSA-catalyzed condensation of 2-naphthol (**9**) with benzaldehyde (**2a**)



9 **2a** **10** **11a**

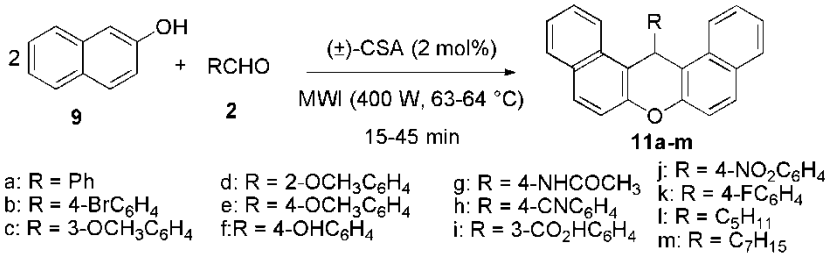
Entry	Reaction conditions[a]	(±)-CSA, mol %	Time (h)	**10** (% Yield)[b]	**11a** (% Yield)[b]
1	25 °C	20	16.0	75	21
2	80 °C	15	2.0	-	89
3	MWI, 63-64 °C	2	0.25	-	88

[a]2-naphthol was reacted with aldehydes (0.55 equiv) under solvent-free conditions. [b]isolated yields.

After screening different reaction conditions, we found that at room temperature with 20 mol% of CSA the reaction got completed, but instead of dibenzoxanthene (**11a**), the compound *bis*-(2-naphthol), **10** was obtained as the major product. Bis-(2-naphthol) was then exploited further to the synthesis of xanthenocrown ethers, which has been successfully used as supra-molecular hosts[8].

When the same reaction was done at an elevated temperature (80 °C) the reaction got completed with 15 mol% catalyst at 2 h to give the dibenzoxanthene as the only product; no *bis*-(2-naphthol) was isolated. Doing the reaction under microwave irradiation (MWI) increased the reaction rate considerably and the reaction got completed in only 15 mins with only 2 mol% of catalyst[9]. Using the microwave assisted protocol aromatic aldehydes (**2**) with different electronic substitutions were reacted with 2-naphthol to generate a series of dibenzoxanthenes (**11a-k**) in good to excellent yields[9] (Scheme 4.1).

In contrast to aromatic aldehydes, condensation of aliphatic aldehydes (1-hexanal and 1-octanal) with 2-naphthol yielded dibenzoxanthenes as the sole product in good yields; no intermediate *bis*-(2-naphthol) was isolated. The reaction rate got increased significantly under microwave irradiation to give the dibenzoxanthenes (**11l-m**) in excellent yields (Scheme 4.1).



Scheme 4.1: Microwave assisted (±)-CSA catalyzed synthesis of 14-aryl-14*H*-dibenzo[*a*,*j*]xanthene (**11a-m**)

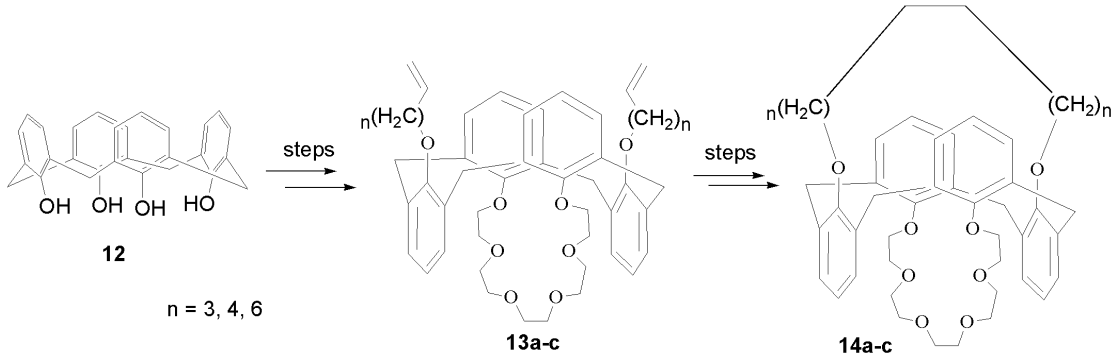
Chapter 5 Synthesis of Calixarene/Homocalixarene-based Metacyclophanes and Their Potential Use as Functional Materials

This chapter deals with (i) design and synthesis of some novel rigidized calix[4]crowns, (ii) synthesis of $[3.1]_2$ homocalixarenes and iii) use of one of the synthetic intermediates *i.e.* phenolic 1,3-diaryl propane as anti-cancer agent.

Design and synthesis of some novel rigidized calix[4]crowns

Calixarenes and related meta-cyclophanes, having pre-organized three-dimensional architecture are attractive matrices in host-guest chemistry[2]. In particular, calix[4]crowns have shown high affinity for the complexation of alkali and alkaline-earth metal cations[10]. Among different calix[4]-crown ethers, *bis*(1-octyloxy)calix[4]crown-6 in its 1,3-alternate conformation is well known for its high affinity and selectivity towards Cs (K_{Cs+}/K_{Na+} > 33000)[11]. The excellent extraction ability of this compound has prompted us to design and synthesize some surrogate of 1,3-dialkyloxycalix[4]arene-crown-6 (**14a-c**) molecules with increased rigidity for establishing structure-activity relationship.

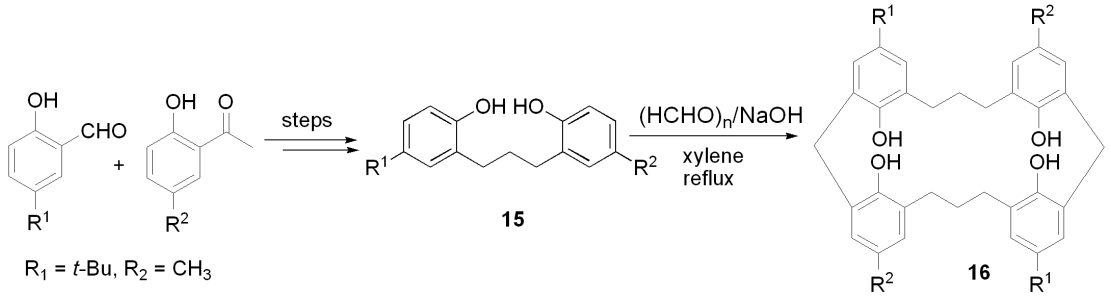
Synthesis of most of calix[4]crowns involves i) 1,3-dilakylation of calix[4]arene (**12**) with alkyl iodide followed by ii) anchoring of crown ether moiety through the remaining two phenolic-OH groups. However, we have optimized the reaction conditions to get the corresponding 1,3-dialkylated calix[4]arene using alkylbromide/K_2CO_3/KI in acetonitrile in good yields and at lesser reaction time. The same strategy were used to prepare various 1,3-dialkenylated calix[4]arene which were further reacted with pentaethyleneglycol ditosylate to afford calix-crown-6 (**13a-c**). Synthesis of the desired rigidized calix crowns (**14a-c**) has been achieved from the calix-crowns (**13a-c**) by using ring closing metathesis as the key step (Scheme 5.1).



Scheme 5.1: Synthesis of rigidized calix[4]crowns

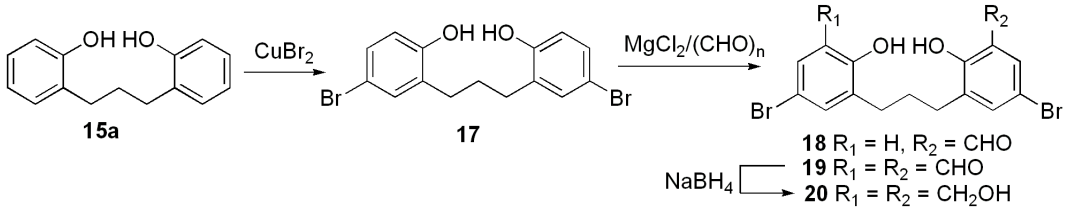
Synthesis of metacyclophane [3.1]$_2$ homocalixarenes and cytotoxic activity studies of intermediate 1,3-diaryl propanes againt human cancer cell line

Homocalixarenes are calixarenes having at least one bridging group larger than the methylene group[12]. The base-catalysed condensation of phenols with formaldehyde, commonly utilized for the preparation of normal calixarenes, has been successfully applied to the synthesis of [3.1.3.1] metacyclophane, **16** in our study. This synthetic route involved the preparation of the key intermediate 1,2-*bis*(5-substituted-2-hydroxyphenyl)propanes **15** in high yields by classical aldol condensation of 5-substituted-2-hydroxybenzaldehyde with 5-substituted-2-hydroxy ketone followed palladium catalyzed hydrogenation (Scheme 5.2).



Scheme 5.2: Synthesis of [3.1.3.1] homocalixarenes

In a recent report, 1,3-diarylpropane derivatives was found to display cytotoxicity activity against human cancer lines[13]. For better understanding on the mechanism of action, syntheses of two non-brominated **15a-b** and four brominated **17-20** phenolic diarylpropanes (Scheme 5.2, 5.3) have been achieved and their cytotoxic activity was studied against human cancer A549 lines[14]. Among all the compounds, **15a** showed pronounced cytotoxicity which can be explained by induced apoptosis and a G1 cell cycle arrest by augmenting cellular ROS status. In contrast, bromo-substituted 1,3-diarylpropanes (**17-20**) displayed cytotoxicity mainly due to necrosis.



Scheme 5.3: Synthesis of phenolic 1,3-diarylpropanes

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LIST OF FIGURES

Figure	Title	Page No.
	Chapter 1	
1a	Benzo-fused oxygen-heterocycles	005
1b	Biologically active chroman-4-amine-containing compounds	005
1c	Xanthene isomers with different orientation of annulations	008
1d	Xanthene derivatives with varied bioactivities	009
1e	Some well-known dyes that are derived from the xanthene nucleus	011
1f	Pyrrole-containing compounds relevant for drugs and materials	022
1g	Host-guest chemistry	022
1h	Representation of calix[4]arene and designation of the faces	033
1i	The four conformations of calix[4]arenes: a) cone conformation b) partial cone, c) 1,3-alternate and d) 1,2-alternate.	033
	Chapter 2	
2a	Application of Mannich bases and their derivatives as medicine	033
2b	Structure of camphor-10-sulfonic acid (CSA)	038
2c	^{1}H-NMR of **2d**	038
2d	Library synthesis	040
2e	^{1}H-NMR of **6a**	063

2f	Library synthesis of β–amino (hetero)aromatic ketones	066
2g	^{1}H-NMR of **6l**	071
2h	^{1}H-NMR of **6p**	071

Chapter 3

3a	1H-NMR of 2a	074
3b	^{1}H-NMR of **2b**	075
3c	^{1}H-NMR of **3a**	075
3d	^{1}H-NMR of **3b**	075
3e	ORTEP diagram of compound **3a**	075
3f	^{1}H-NMR of **5a**	079
3g	^{1}H-NMR of **6a**	079
3h	^{13}C-NMR of **6a**	126
3i	Library synthesis of pyrroles	126

Chapter 4

4a	^{1}H-NMR of **3**	126
4b	^{1}H-NMR of **4a**	126
4c	^{1}H-NMR of **5**	129
4d	UV-vis absorption spectrum of the titration experiment consisting mixture of (a) C_{60} and **5** (b) C_{70} and **5**	129
4e	Steady state fluorescence spectral variation of **5** in presence of (a) C_{60} and (b) C_{70} in toluene	130
4f	Steady state fluorescence spectral variation of 5 in presence of PyC_{60} in toluene	130
4g	^{1}H-NMR of **4g**	131

4h	^{1}H-NMR of **4l**	134
4i	^{1}H-NMR of **4m**	152
4j	Library synthesis	152

Chapter 5

5a	Conformers of calix[4]crown ethers with different ion selectivities	156
5b	Calixcrown ethers with varied ionophoric properties	156
5c	Homocalixarenes with different cavity sizes	158
5d	*Bis*(1-octyloxy)calix[4] crown-6	158
5e	Design of rigidized calix[4]crowns	159
5f-A	^{1}H-NMR of **6a**	159
5f-B	^{13}C-NMR of **6a**	160
5g-A	^{1}H-NMR of **6b**	159
5g-B	^{13}C-NMR of **6b**	160
5h-A	^{1}H-NMR of **6c**	159
5h-B	^{13}C-NMR of **6c**	160
5i	[3.1.3.1] Homocalix[4]arene (**H-1, H-2**)	160
5j	^{1}H-NMR of **10a**	161
5k	^{1}H-NMR of **10b**	161
5l	^{1}H-NMR of **11**	161
5m	Chemical structure of the 1,3-diarypropanes from *C. griffithii* stem	118
5n	^{1}H-NMR of **12**	161
5o	^{1}H-NMR of **13**	161
5p	^{1}H-NMR of **14**	161
5q	^{1}H-NMR of **15**	161

5r	Dose-dependent cytotoxicity of the diarylpropanes **10a/b, 12-15** against human lung carcinoma A549 cells. **(A)** Effect of compounds **10a/b, 12-15**. **(B)** Effect of compound **10a** over a wide dose range	123
5s	Alteration of A549 cells morphology as revealed by phase-contrast microscopy	161

LIST OF TABLES

Table	Title	Page No.
2a	Mannich-type reactions of cyclohexanone, benzaldehyde and aniline using CSA (5 mol%) in different solvents	019
2b	Reactions of cyclic ketones with different imines using CSA	021
2c	Optimization of catalyst loading in the Mannich type reaction of acetophenone (**3a**) with benzaldehyde (**4a**) and aniline (**5a**) using CSA	023
2d	Screening of catalysts for the three-component reaction of **3a**, **4a** and **5a** at ambient temperature under solvent-free conditions	025
2e	(±)-CSA catalyzed one-pot three-component Mannich reaction of methyl (hetero)aryl ketones with aromatic aldehydes and aromatic amines	026
3a	Crystal data and structure refinement for **3a**	049

3b	Synthesis of substituted pyrroles	057
4a	CSA-catalyzed condensation of 2-naphthol (**1**) with benzaldehyde (**2a**) silyl chlorides	073
4b	Optimization of the reaction conditions for the (±)-CSA-catalyzed condensation of 2-naphthol with benzaldehyde for the synthesis of **4a**	079
4c	Microwave assisted CSA catalyzed condensation of 2-naphthol (**1**) with liquid aromatic aldehydes (ArCHO) to 14-aryl-14*H*-dibenzo[*a*,*j*]xanthenes (**4b-f**)	080
4d	Optimization of the reaction conditions for the CSA-catalyzed microwave-assisted condensation of 2-naphthol with **2g**	081
4e	Microwave assisted CSA catalyzed condensation of 2-naphthol (**1**) with solid aromatic aldehydes to 14-aryl-14*H*-dibenzo[*a*,*j*]xanthenes **(4h-k)**	082
4f	CSA catalyzed condensation of 2-naphthol (**1**) with aliphatic aldehydes to 14-aryl-14*H*-dibenzo[*a*,*j*]xanthenes (**4l, m**)	083
4g	CSA-catalyzed condensation of 2-naphthol with benzaldehyde and 1,3-dicarbonyl compounds	087
5a	Optimization of the additives for the alkylation reactions of calix[4]arene	106

CHAPTER 1

Introduction to the Development of New Synthetic Protocols and Functional Molecules

1.1 An introduction to organic synthesis

Organic chemistry is a highly creative branch of science which involves study of carbon-containing compounds. This branch of chemistry started as the chemistry of life and natural carbon compounds for understanding chemical reactions in living organisms and products derived from them but now has been broadened to include carbon, hydrogen containing compounds along with other elements, especially oxygen, nitrogen, sulfur, phosphorus, halogens etc.[1] At the end of the last century, the number of these carbon-containing compounds amounted to 15 million with an annual increase of circ. 600,000 compounds.

Life is based on carbon's ability to form diverse structures and an endless number of different carbon based molecules. We are living in a world which is largely shaped by organic compounds. The food that we eat is essentially a mixture of organic compounds. The changes which the food undergoes in our bodies are organic chemical reactions. The clothes that we wear (wool, cotton, leather, synthetics) are all organic in character. The soaps, cosmetics, perfumes, oils, plastics, explosives, rubber, dyestuffs, paper, insecticides, and many more are all organic compounds. The sources of primary energy we still use every day (petroleum, natural gas, coal) are organic in nature. In the medical field, organic compounds are indispensable. Antibiotics, sulpha drugs, alkaloids, aspirin, iodoform, and many are organic compounds. There is hardly any industry which is not dependent on organic compounds. Therefore, organic chemistry has contributed to the development of society from biological and industrial point of view as well as to understand life processes and to the efforts to improve the quality of life.

It is obvious that the basic objective in organic chemistry is the construction of variety of functional molecules to perform innumerable tasks and synthesis of organic compounds thus has developed into one of the most important branches of organic chemistry. Synthetic organic chemistry involves the art of building-up complex molecular structures of organic compounds putting together smaller and easily accessible (commercially available) compounds. The field of synthetic organic chemistry has now been extremely developed. Even many complicated and attractive compounds of natural origin, such as palytoxin, taxol, just to give a couple of examples, have been synthesized in laboratory. In order to render a synthetic strategy applicable for utilization in commercial purposes special attention has been provided to minimize the cost and time required for the process. Therefore, there is an increasing effort in training to simplify and automate the synthetic processes as much as possible. The efforts of synthetic organic chemists thus has been devoted not only to the total synthesis of complex organic compounds (*target oriented synthesis*), but also to the development of new synthetic methods (*method oriented synthesis*).

1.1.1 Target oriented synthesis[2]

The goal of *target oriented synthesis* is the complete chemical synthesis of complex organic molecules from simple, commercially available or natural precursors. Total synthesis may be accomplished either *via* a linear or convergent approach. Different functional molecules, such as naturally occurring bioactive compounds, rationally designed bioactive entities, compounds of commercial interest like drugs, flavors, pharmaceuticals, and new materials etc., are the most common and interesting targets of target oriented

synthesis. The major look out here is the search of an effective protocol which provide high yield of product with low cost ingredients in considerable time utilization.

1.1.2 Method oriented synthesis[3]

The *method oriented synthesis* is devoted to the development of new reagents, new catalysts, new reactions and work-up procedures that can improve a synthetic process. Methodology research usually involves three main stages: *discovery*, *optimization*s, and studies of *scope and limitations*. The discovery requires extensive knowledge of chemical reactivities of appropriate reagents. Optimization is a process in which one or two starting materials are tested in the reaction by varying different reaction conditions such as temperature, solvent, reaction time, etc., until the optimum conditions for product yield and purity are obtained. Finally, the scope and limitations of the methodology are tested by extending it to a broad range of substrates. Total syntheses of important functional molecules are sometimes done to showcase the new methodology and demonstrate its value in a real-world application. On the other hand, *target oriented synthesis* may prompt the creation of new synthetic methodologies.

The essence of organic synthesis is the formation of both single and multiple bonds between two or more carbon atoms or between many combinations of carbon and various heteroatoms, most notably oxygen, nitrogen, sulfur and phosphorus. In the course of last 150 years many very selective and efficient reactions for the formation of carbon-carbon/carbon-heteroatom bonds have been introduced. In recent years, for achieving such organic transformations considerable attention is devoted towards selective, atom-economic and environmentally benign protocols. For practical applications, additional hurdles include industrial standards of safety and purity. Thus synthetic methodologies are

designed to use and generate substances that possess little or no toxicity to human health and the environment. To this end several reagents/catalysts have been developed for selective and non-hazardous chemical processes using solvent-free conditions or by using innocuous solvents/auxiliaries.

1.2 Aim of the thesis

The aim of this doctoral thesis was to develop new efficient synthetic methods for the formation of carbon-carbon/carbon-heteroatom bonds and apply this methodology to tackle synthetic problems encountered in the synthesis of some important functional molecules such as *O*-heterocycles (aminochromans and xanthenes), *N*-heterocycle (densely substituted pyrroles) and supramolecular-macrocyclic hosts (calixarenes and homocalixarenes). Therefore, a survey of literatures was carried out and presented here as follows.

1.3 Heterocyclic compounds

Heterocyclic compounds,[4] also called heterocycles form by far the largest of classical divisions of organic chemistry and are of immense importance biologically and industrially. Among the approximately 20 million chemical compounds identified by the end of the second millennium, more than two-thirds are fully or partially aromatic and approximately half are heterocycles. Heterocyclic compounds are formed when at least one carbon in a carbocyclic ring is replaced by another element such as nitrogen, oxygen and sulphur *etc*. Although, heterocyclic compounds structurally resemble carbocyclic compounds, but the presence of the heteroatoms in heterocyclic compounds has a strong influence on their physical, chemical and biological properties. Heterocyclic compounds can be divided into two broad areas: aliphatic and aromatic. The reactivities of aliphatic

heterocycles are not too different from the usual non-cyclic derivatives and their properties are particularly influenced by the presence of ring strain. In contrast, the aromatic heterocyclic compounds, behave in a manner similar to benzene in some of their properties but their reactivities are usually more complex since there is a combined influence of aromatic system and the heteroatoms.

The presence of heterocycles is well known in the field of electronics, biology, optics, pharmacology, material sciences and so on.[4d] Beside the vast distribution of heterocycles in natural products, they are also the key components of biological molecules such as DNA and RNA, the most important macromolecules of life. Nucleotides, the building blocks of our genes are derivatives of pyrimidine and purine ring structures. Chlorophyll and heme, the oxygen carriers in plants and animals respectively are derivatives of large porphyrin rings. Many natural drugs such as papaverine, theobromine, quinine, emetine, theophylline, atropine, procaine, codeine, reserpine and morphine are heterocycles.[4e-g] Almost all the compounds we know as synthetic drugs such as diazepam, chlorpromazine, isoniazid, metronidazole, azidothymidine, barbiturates, antipyrine, captopril and methotrexate are heterocyclic in nature.[4h]

1.3.1 Oxygen-heterocycles

Oxygen heterocycles constitute an important class of heterocyclic compounds mainly because of their natural abundance and diverse biological functions.[5] This class of compounds are particularly important because they are prevalent in many essentials of life.[6] The interest in this type of compounds stems from the fact that sugars, which plays important biological roles in our body contain five membered (furanose) and six membered (pyranose) oxygen heterocycles as their building blocks. In addition to this, many natural and semi synthetic oxygen heterocyclic compounds are well known for their

therapeutic values[7] such as Taxol (anticancer), Digoxin (CHF treatment), Cyclosporine A (immunosuppressant), Lovastatin (hypolipidemic) etc. Among different oxygen heterocycles, the benzo-fused, in which the heterocyclic ring is fused to benzene ring, are found as a key structural unit in natural products, pharmaceuticals and biologically active compounds (Fig. 1a).[8] Essential natural products, such as Vitamin E and Vitamin C contain six-membered benzo-fused pyran nuclei and reduced furan ring systems respectively. Therefore, benzo-fused oxygen heterocycles are of great synthetic interest.

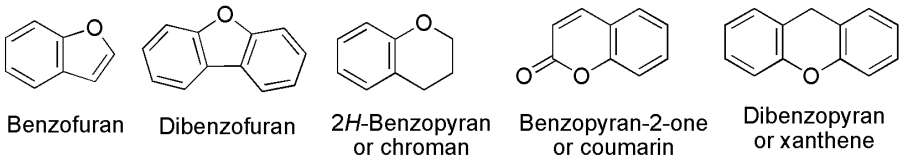

Figure 1a: Benzo-fused oxygen-heterocycles.

1.3.1a 4-Aminochromans

Chromans or 2*H*-benzopyran is an important class of benzo-fused oxygen heterocycles in which the benzene ring is fused to pyran ring. Among different chromans, the 4-aminochroman derivatives are of great importance in recent years since they exhibit a vast range of biological activities such as antihypertensive and antiischemic behavior.[9] They also act as modulators of potassium and calcium channels influencing the activity of the heart and blood pressure.[9, 10] This class of heterocycles has been used as core scaffolds in an increasing number of recent drug discovery programs (Fig. 1b). For example, cromakalim (BRL 34915) is a potassium channel activators or openers, which have been extensively evaluated for antihypertensive effects in animals.[9a,10] Chroman-4-amine sulfonamide has been found to be a potent $K_v1.5$ potassium channel blocker (IC_{50} = 0.11 μM) with good selectivity over the block of hERG.[11] Also, diaminochromancarboxamide

is a 0.8 nM inhibitor of the human bradykinin B1 receptor showing in vivo efficacy against hypotension and inflammatory pain.[12]

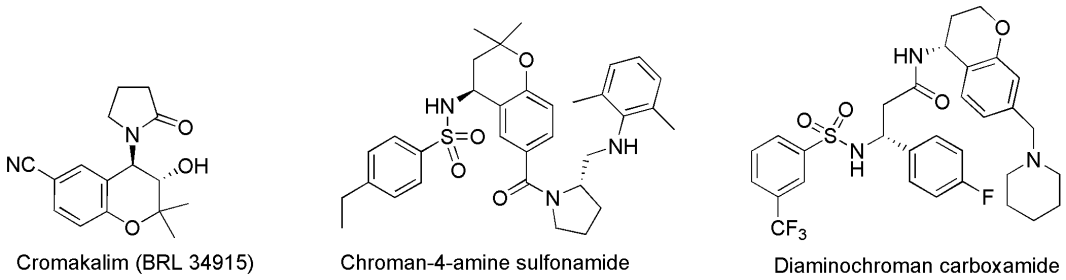

Figure 1b: Biologically active chroman-4-amine-containing compounds.

1.3.1b Xanthenes and benzoxanthenes

Xanthenes and benzoxanthenes are important class of oxygen heterocycles which has been studied over decades because of their widespread biological and photophysical activities. Xanthenes are the poly-aromatic cyclic ether compounds where aromatic rings are fused to tetrahydropyran ring. The xanthene nucleus corresponds to dibenzo[*b,e*]pyran and is also referred to as 9*H*-xanthene. Benzoxanthene and dibenzoxanthene derivatives exist as different possible isomers, which differ in their orientation of annulations. Figure-1c represents the method of nomenclature in xanthene derivatives with some examples.

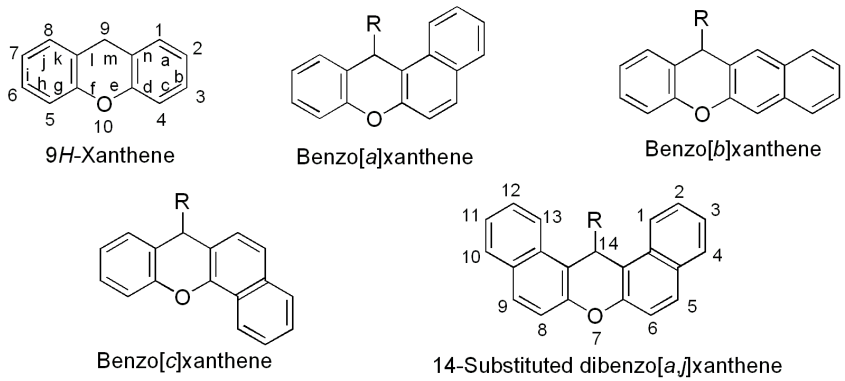

Figure 1c: Xanthene isomers with different orientation of annulations.

Xanthene derivatives are the core scaffolds in large number of naturally occurring as well as synthetic derivatives and occupy a prominent position in medicinal chemistry[13] (Fig.

1d). They are known to exhibit a broad spectrum of pharmaceutical activities such as anti-bacterial,[14] anti-inflammatory,[15] anti-viral,[16] and analgesic[17] activities. There are reports of some 9,9-dimethylxanthene moieties which shows antimalarial activities with the inhibitory action towards trypanothionereductase enzyme.[18] Different 9*H*-xanthene derivatives have been identified as positive allosteric modulators of metabotropic (mGlu) receptors[19] and potentnon-peptidic inhibitors of recombinant human calpain I.[20] Xanthene derivatives also demonstrate efficacy as antagonists for paralyzing the action of zoxazolamine[21] and in photodynamic therapy.[22] In addition, xanthenediones are found as structural building blocks in a number of natural products[23] and have been used as versatile synthons because of the inherent reactivity of the inbuilt pyran ring.[24] They have also been used as rigid carbon skeletons for the construction of new chiral bidentate imine ligands with potential applications in catalytic processes.[25]

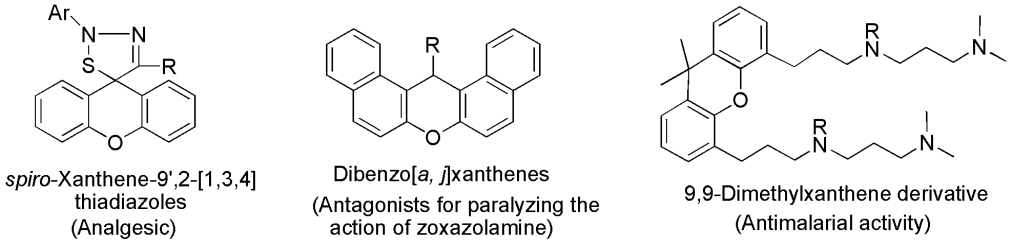

Figure 1d: Xanthene derivatives with varied bioactivities.

Xanthenes and the related condensed ring system are an excellent source of brilliant fluorescent dyes[26] (Fig. 1e) and are widely used in chemical biology as tracers for biological substances, such as proteins, DNAs, sugars with high sensitivity and selectivity.[27] Besides, they are also used in laser technologies[28]. Fluorone, fluorescein, rosamine, rhodamine, rhodamine B and rhodamine 6G are some well-known dyes that are derived from the xanthenes nucleus. Compounds derived from xanthene are being used to develop polymer photo-imaging systems which have numerous applications primarily in

the printing and electronic industry[29]. Spiro[fluorene-9,9′-xanthene] derivatives serve as the building blocks for blue light emitting materials having high thermal stability.[30] Xanthene dyes are also utilized in fabricating dye doped materials having interesting optical applications in holography, optical computing and holographic interferometry.[31]

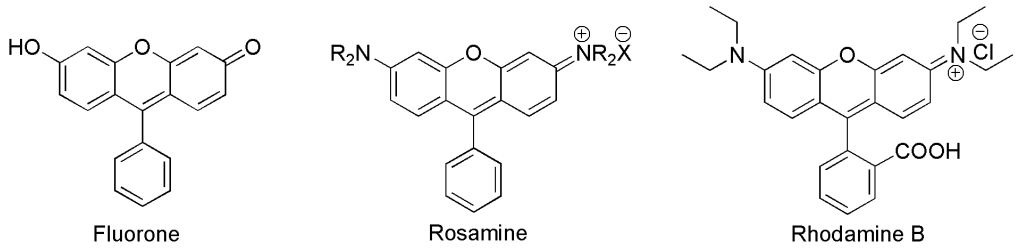

Figure 1e: Some well-known dyes that are derived from the xanthene nucleus.

1.3.2 Nitrogen heterocycles

Nitrogen heterocycles are among one of the most important structural classes of chemical substances, which are particularly well represented among natural products such as vitamins, hormones, antibiotics, and alkaloids, as well as pharmaceuticals, herbicides, dyes, and many more.[32] Owing to their interesting biological properties, natural and synthetic *N*-heterocyclic compounds are very often involved as key components in biological processes. Many synthetic nitrogen heterocycles have wide spread uses as antiviral, antibacterial, antifungal, anti-inflammatory, antioxidants, anticancer, analgesics, anticonvulsants sedatives and hypnotics agents.[33] In nature too, especially in plant kingdom they have made indelible mark as insecticides, pesticides, weed killers rodenticides, etc. Certain *N*-heterocycles are used as anti AIDS agents and has been found to be a potent inhibitor of HIV reverse transcription and licensed in several countries for the treatment of AIDS patient[34] and also as virucides which inhibited HIV in human lymphocytes.[35] The multifaceted properties and captivating structures of them encouraged chemists over the years to keep on synthesizing new and novel nitrogen heterocycles with

versatile pharmacological activities. Among them, pyrroles, pyrrolidines, piperidines, azetidines, phenanthridines, indoles, quinolines, and isoquinolines have gained considerable attention in organic synthesis, medicinal chemistry and materials science.

1.3.2a Pyrrole derivatives

Among different *N*-heterocycles, pyrrole and its derivatives are ubiquitous in nature. It was first isolated in 1857 from the products of bone pyrolysis, and identified as biologically relevant molecule when it was recognized as a key structural fragment of heme and chlorophyll, two essential pigments for life.[36] Densely substituted pyrroles are key structural element in a broad range of natural products and drug molecules, and are also of growing relevance in materials science[37] (Fig. 1f). For example, lamellarin, lukianol, ningalin, polycitone, and storniamide A are some of the naturally occurring *tetra*- and *penta*-substituted pyrroles isolated from marine sponge which shows wide range of biological activity, including reversal of multidrug resistance, cytotoxicity, HIV-1 integrase inhibition, and antibiotic activity.[38]

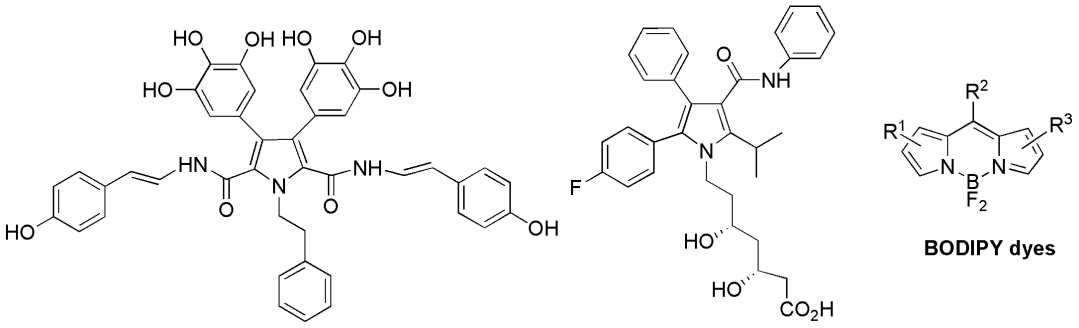

Figure 1f: Pyrrole-containing compounds relevant for drugs and materials.

Beside natural products, pyrrole substructures are present in large number of synthetic drugs such as, non-steroidal anti-inflamatory agent tolmetin,[39] the anticancer drug candidate tallimustine[40] and the cholesterol-lowering agent atorvastatin (Lpitor®),[41] one of

the top-selling drugs worldwide. They are also particularly important in functional materials including semiconducting materials derived from hexa(*N*-pirrolyl)benzene,[42] glucose sensors based on polypyrrole-latex materials[43] and fluorescent dyes 4,4-difluoro-4-boradipyrrin system, BODIPY.[44]

1.4 Supramolecular chemistry

Supramolecular chemistry is often defined as "the chemistry beyond the molecule" or "the chemistry of the noncovalent bond". It deals with chemical systems made up of a discrete number of assembled molecular subunits or components. While traditional chemistry focuses on covalent bond within the molecules, supramolecular chemistry examines the weaker and reversible non-covalent interactions between the molecules.[45] These interactions include Van der Waals interactions, dipole-dipole interactions, hydrogen bonding, hydrophobic effects, interaction between ions and π-π stacking. The non-covalent interactions play major role in different bio-chemical processes in living organisms. To mimic natural processes, past two decades has witnessed enormous effort by synthetic organic chemists to develop host macro-cyclic molecules with cavities for selective encapsulation of various metal ions and neutral molecules as guest (*Host-Guest Chemistry*, Fig. 1g). In this endeavor various macro-cyclic supramolecular hosts including crown ethers, cyclodextrins, calixarenes, cucurbiturils *etc.* have been developed.

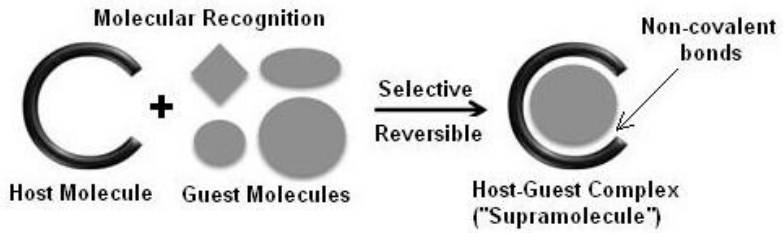

Figure 1g: Host-guest chemistry.

1.4.1 Calixarenes

Among different macrocycles, "calix[n]arenes" and related metacyclophanes having pre-organized three-dimensional structures are attractive matrices which comprises of an important domain in supramolecular chemistry.[46] They represents molecular baskets which exist in a 'cup' like shape with a defined upper-rim, lower-rim and central annulus (Fig. 1h). The name "calixarene" is derived from the Greek *calyx* meaning vase or chalice and *arene* which indicates the presence of the aromatic building blocks.[47] Calixarenes are cyclic oligomers prepared by base-catalyzed condensation of *para*-substituted phenols with formaldehyde. The easy large scale preparation and chemical transformability of this molecule together with its "tunable" structure has made calixarene an attractive candidate for molecular design strategies to perform innumerable tasks. Calixarenes can exist in

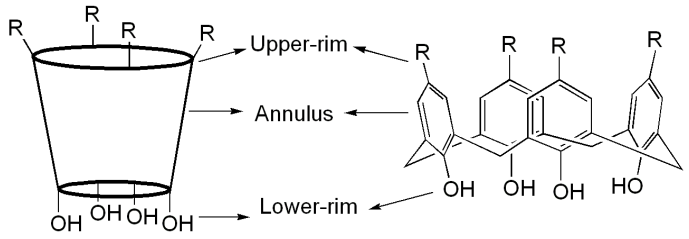

Figure 1h: Representation of calix[4]arene and designation of the faces.

several conformations because of two possible rotational modes of the phenol unit: the oxygen through the annulus rotation and the *para* substituent through the annulus rotation.[48] For example, calix[4]arenes can exist in four different conformations; cone, partial cone, 1,3 alternate and 1,2 alternate (Fig. 1i).[49] Calixarenes are conformationally mobile at room temperature.[50] The intramolecular hydrogen bonding that occurs between the OH groups and non-bonding steric hindrance also play a part in the degree of conformational flexibility.[49] The energy difference between the cone and the partial cone, 1,3-alternate and 1,2-alternate for calix[4]arene is 16.2, 19.8 and 30.2 kcal mol^{-1}

respectively.[51] Introduction of various substituents in these molecules can restrict their mobility and they can attain a particular conformation, for example most calix[4]arenes functionalized at the lower-rims with ester or ether groups are held in a partial cone conformation and are conformationally rigid at room temperature.[49] The different conformations of calix[4]arene has been assigned by NMR and XRD data. As the number of phenolic residues increases in the calixarene, the number of possible conformations increases. For example, as discussed above calix[4]arenes have four conformers, while calix[6]arenes and calix[8]arenes have eight and sixteen conformations

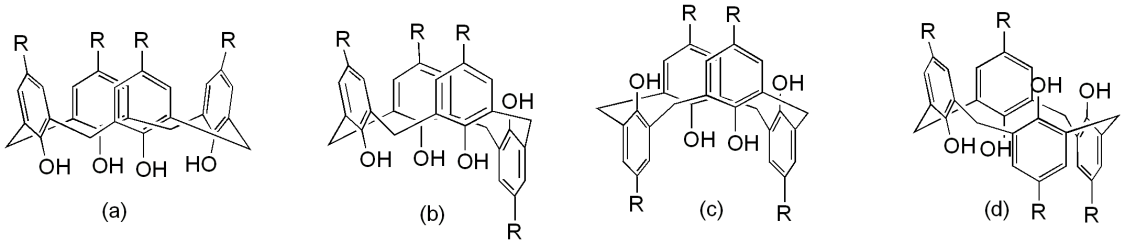

Figure 1i: The four conformations of calix[4]arenes: a) cone conformation b) partial cone, c) 1,3-alternate and d) 1,2-alternate.

respectively.[47] Considerable synthetic efforts have been invested in the last few years for the modification of calixarene skeleton.[46,47] The receptor properties of calixarenes are governed not only by the type of substitution but highly controlled by the nature of its conformation. Their controlled synthetic functionalization and versatile complexation properties[52] has allowed the use of these compounds in supramolecular chemistry as molecular scaffolds for the construction of various receptors such as highly-selective metal-ion complexation agent,[53] ionophores in catalysis,[54] ion sensitive electrodes,[55] optical sensors,[56] chiral recognition devices for solid phase extraction[57] and many more.

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CHAPTER 2

Mannich-type Reactions under Solvent Free Conditions: Syntheses of β-Amino Carbonyl Compounds

2.1 Preamble

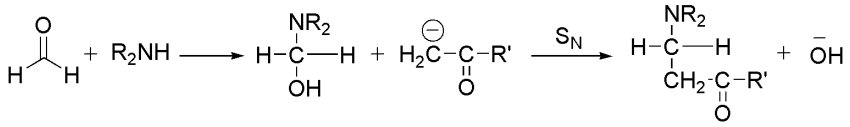
As discussed in Chapter 1, one of the aims of this thesis was to develop efficient synthetic methods for the formation of carbon-carbon bonds so that we could apply this methodology to the synthesis of small functional molecules. Here in Chapter 2, we are going to explore our findings in an environmentally benign synthetic methodology for the carbon-carbon bonds formation reaction, namely, Mannich type reactions.

2.1.1 The Mannich reaction

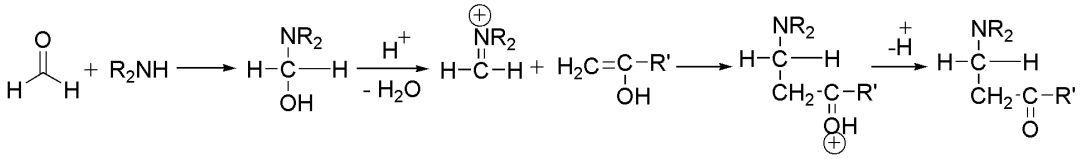
The Mannich reaction, involving carbon-carbon bond formation between an enolizable ketone (nucleophile) and a schiff base (electrophile) is an atom-economic process and provides one of the most basic and useful methods for the syntheses of β–amino carbonyl compounds.[58] These also serve as important intermediates in the synthesis of various valuable pharmaceuticals and bio-active natural products.[59,60]

2.1.1a Classical Mannich reaction

The amino alkylation of CH-acidic compounds was described by several authors as early as in the 19th century. However, it was Carl Mannich[61] who was the first to recognize the enormous significance of this reaction (Scheme 2a,b), and it was he who extended the chemistry into a broad based synthetic methodology through systematic research. The product of this reaction was referred to as Mannich base. Mannich bases and its derivatives such as 1,3-aminoalcohols or Michael acceptors, which are easily formed from Mannich reactions are of particular interest due to their biological activities and use as synthetic building blocks and find great use in, for example, medicinal chemistry (Fig. 2a). Again intramolecular versions of these reactions are used for the biomimetic preparation of natural products, and many other applications.



Scheme 2a: The base catalyzed Mannich reaction.



Scheme 2b: The acid catalyzed Mannich reaction.

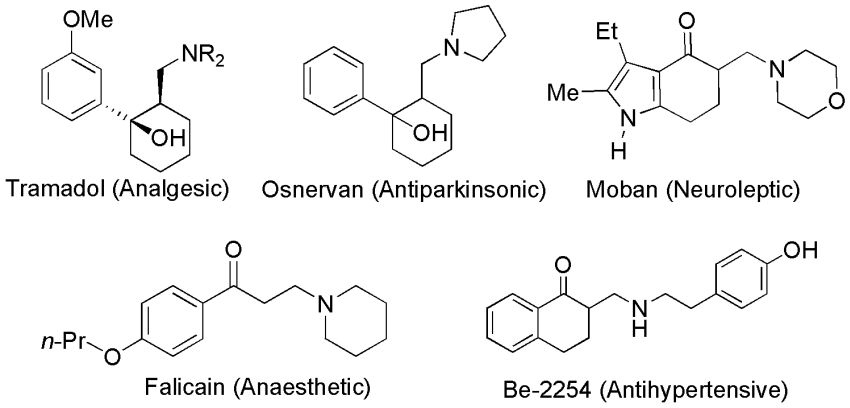
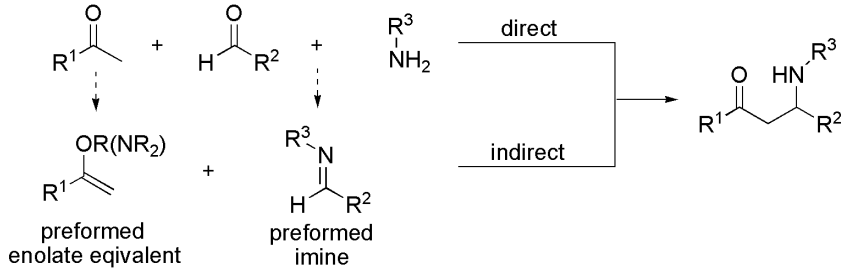


Figure 2a: Application of Mannich bases and their derivatives as medicine.

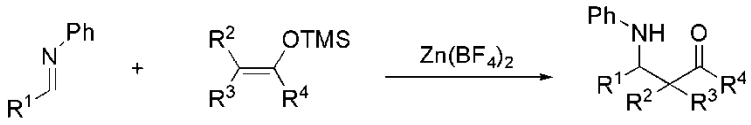
2.1.1b Shortcomings / limitations of Mannich reactions

The classical Mannich reaction is plagued by drastic reaction conditions, substrate limitations, and long reaction time.[62] To overcome the drawbacks of the classical method, indirect (two-component) and direct (three-component) Mannich reactions of acyclic ketones have been realized by various Brønsted and Lewis acids (Scheme 2c).



Scheme 2c: Direct and indirect Mannich-type recations.

However, most of these methods suffer from drawbacks including the use of large amount of catalysts, expensive catalysts, requiring special efforts for catalyst preparation, toxic reagents, elevated reaction temperature, low yields and longer reaction time. Although, most of the reports for direct three component one-pot Mannich reaction deals with acyclic and alicyclic ketones as nucleophiles,[63] only few catalysts, $H_3PW_{12}O_{40}$,[64] $HClO_4$-SiO_2,[65] $NbCl_5$,[66] $BiCl_3$,[67] DBSA,[68] and $SnCl_2$[69] *etc*. have been developed using aromatic ketones as nucleophiles. This may be due to the poor nucleophilicity of aromatic ketones as compared to that of acyclic/alicyclic ketones. To increase the nucleophilicity, silylenolates or silyl ketene acetals of aromatic ketones were also been used.[70] The Lewis acid catalyzed condensation between silylenol ethers and preformed imines has been reported (Scheme 2d).[70c] However, many imines tend to be unstable during purification by chromatography, distillation or prolonged storage. Thus, from the practical point of view, it is desirable to use three component one pot strategy, involving the *in situ* formation of imine intermediate from aldehydes and amines followed by the reaction with the nucleophile to afford the desired product. Nevertheless, many Lewis acids cannot be used in Mannich-type reaction because they decompose or deactivate in the presence of amines and water produced during the formation of imine. Therefore, there is still a demand for the development of effective protocols for the synthesis of aromatic ketone derived *β*–amino carbonyl compounds under mild conditions using inexpensive catalysts.



Scheme 2d: Two-component Mannich-type reaction of imines and silylenol ether.

2.2 Present Work

Currently, there is a growing effort on the development of economical and environmentally benign processes based on the principles of green chemistry. Use of metal free small organic molecules as catalysts has been an important strategy to develop green organic reactions. Camphor-10-sulfonic caid (CSA, Fig. 2b) is an inexpensive, commercially available and metal free molecule. It has been used for the epoxide ring opening[71], Michael-type Friedel Craft reaction[72], nitro-aldol reaction[73] *etc.* Again, literature report shows that Mannich-type reactions can be catalyzed by different sulfonic acids such as TsOH, dodecylbenzenesulfonic acid (DBSA), polystyrene-supported sulfonic acid (Ps-SO_3H) with moderate to good yields[70b]. This prompted us to study the catalytic effect of camphor sulfonic acid (CSA) in the three-component Mannich-type reactions.

In continuation of our efforts towards the development of newer synthetic methodologies, we report herein an efficient CSA catalyzed one-pot three-component Mannich type reaction of –1) aliphatic ketones with aldehydes and amines and 2) aromatic ketones with aldehydes and amines – to yield β-amino ketones in good to excellent yields without any side reactions. The scope and limitation of our protocol has been exemplified by using a variety of aromatic aldehydes and aromatic amines.

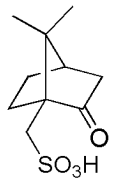
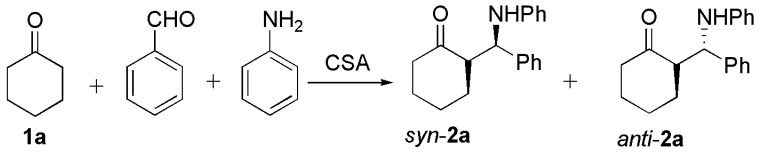


Figure 2b: Structure of camphor-10-sulfonic acid (CSA).

2.2.1 CSA-catalyzed Mannich-type reaction of **aliphatic** ketones with various aldehydes and amines

We started our journey here by using commercially available CSA as a catalyst for the three component one-pot condensation reaction of reactive cyclic ketones such as cyclohexanone with benzaldehyde and aniline in acetonitrile (Scheme 2e). Gratifyingly, the reaction took place with complete consumption of the starting material with moderate yield and diastereoselectivity (Table 2a, entry 1). We then studied the effect of solvents in the above reaction (Table 2a). It was interesting to see that the reaction got completed in 10 min in water with better diastereoselectivity (Table 2a, entry 2). To see the role of solvent in the above reaction, reaction under solvent free conditions (Green Chemistry) was carried out. Interestingly, the reaction of a mixture of cyclohexanone (**1a**), aniline, benzaldehyde and CSA (5 mol%) proceeded smoothly to completion within 10 min at room temperature under solvent free conditions providing the desired product (**2a**) in very high yield (92%) with high diastereoselectivity (80 : 20) favouring *anti*-diastereomer (Table 2a, entry 3).



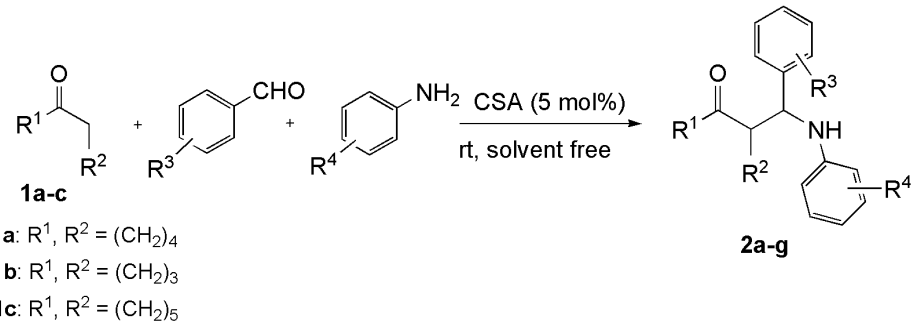
Scheme 2e: One-pot, three-component Mannich-type reactions using CSA.

Table 2a: Mannich-type reactions of cyclohexanone, benzaldehyde and aniline using CSA (5 mol%) in different solvents

Entry	Solvent	Time	Product (% yield)[a]	*Anti* : *syn*[b]
1	Acetonitrile	4 h	**2a** (40)	65 : 35
2	Water	10 min	**2a** (80)	82 : 18
3	No solvent	10 min	**2a** (92)	80 : 20

[a]isolated yield of a mixture of *syn*- and *anti*-isomer; [b] from ^{1}H-NMR spectrum.

In order to generalize the above protocol, the condensation of different cyclic ketones with different amines and aldehydes were performed (Scheme 2f, Table 2b) under the optimized reaction conditions (Table 2a, entry 3) as described for compound **2a**. Beside three-component reactions, we have also studied the two-component Mannich reactions (with preformed imines) using the same optimized conditions. We have seen there were no such dissimilarities, including yield and diastereoselectivity in three and two-component Mannich-type reactions. The reaction time, yield and diastereoselectivity of the reaction depend significantly on the ketones. Cyclohexanone (**1a**) was seen to be the most reactive and underwent a cleaner reaction (Table 2b, entry 1-5) providing very high yield (75-100%) with moderate diastereoselectivities (72 : 28 to 90 : 10). A representative ^{1}H-NMR spectra of *β*–amino aliphatic ketone such as **2d** is presented in Fig. 2c. However, the reaction time with the substituted benzaldehyde and substituted aniline was longer as compared to that of unsubstituted one. The lower membered cyclic ketone,



Scheme 2f: Mannich-type reactions of aliphatic ketones using CSA.

cyclopentanone (**1b**) was unable to show either good yield or selectivity of the product **2f** (Table 2b, entry 6). But the higher membered cyclic ketone, cycloheptanone (**1c**) reacted smoothly to produce the desired product (**2g**) in moderate isolated yield (Table 2b, entry 7). Thus, we have made a library of Mannich adducts (**2a-g**, Fig. 2d) using CSA catalyzed

three component reaction of cyclic ketones, aromatic aldehydes and aromatic amines under solvent free conditions.

Table 2b: Reactions of cyclic ketones with different imines using CSA

Entry	Ketones	R^3	R^4	Product	Time	Yield (%)	*Anti* : *syn*[c]
1	**1a**	H	H	**2a**	10 min	92[a]	80 : 20
2	**1a**	4-Br	H	**2b**	1 h	75[a,b]	72 : 28
3	**1a**	H	4-OCH_3	**2c**	1 h	77[b]	85 : 15
4	**1a**	4-Br	4-OCH_3	**2d**	1 h	100[a,b]	90 : 10
5	**1a**	3-NO_2	4-OCH_3	**2e**	0.5 h	90[a,b]	80 : 20
6	**1b**	H	H	**2f**	10 min	15[b]	45 : 55
7	**1c**	H	H	**2g**	1.5 h	65[a]	55 : 45

[a] three-component reactions; [b] reactions were carried out with preformed imines; [c] determined by ^{1}H-NMR spectrum.

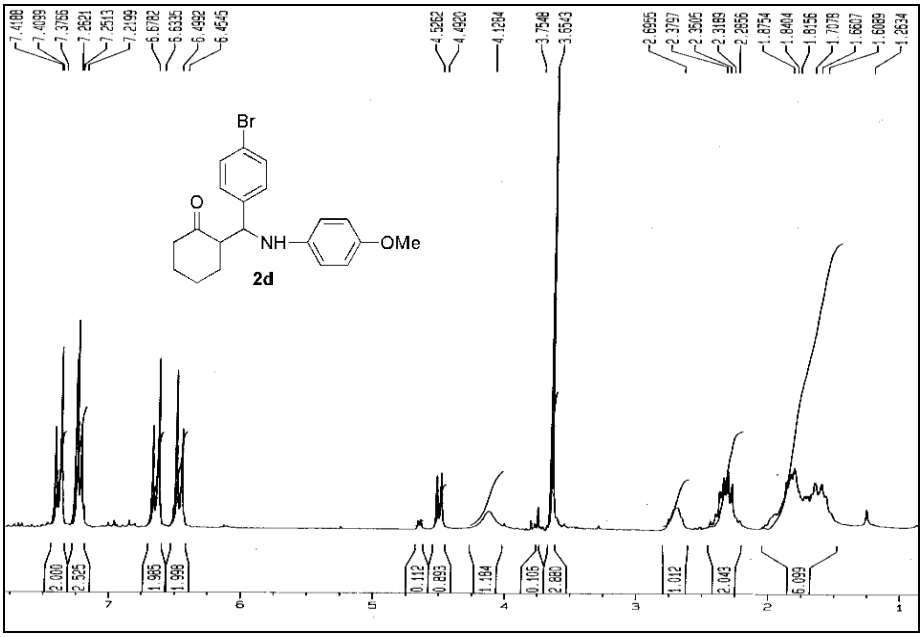


Figure 2c: ^{1}H-NMR of **2d**.

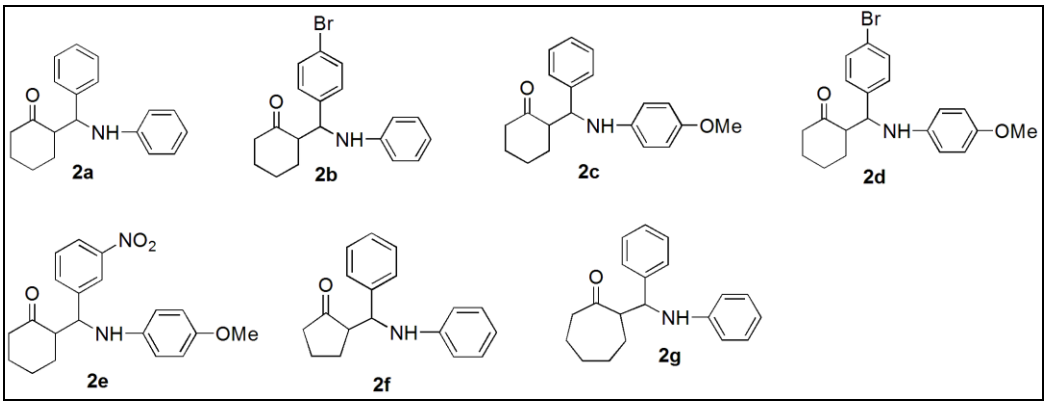
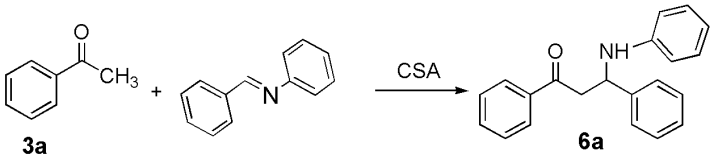


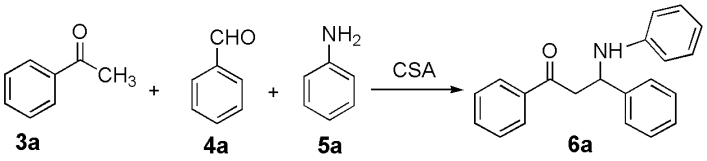
Figure 2d: Library synthesis.

2.2.2 CSA-catalyzed Mannich-type reaction of aromatic ketones with various aldehydes and amines

With the above encouraging result in hand, we wanted to extend the use of CSA in the Mannich reaction with aromatic ketones as nucleophiles. As discussed before, the efficient methods for Mannich reaction with aromatic ketones as the nucleophile are less documented probably due to the poor nucleophilicity of aromatic ketones as compared to that of acyclic/cyclic aliphatic ketones. In our preliminary study, we have at first



Scheme 2g: Two-componentMannich-type reaction of acetophenone using CSA.



Scheme 2h: Three-componentMannich-type reaction of acetophenone using CSA.

tried to see the efficiency of CSA as catalyst in two-component Mannich reaction. Thus, a reaction of acetophenone (**3a**) was carried out with pre-formed *N*-benzylideneaniline under solvent free conditions using CSA (10 mol%) as catalyst (Scheme 2g). Gratifyingly, the

reaction got completed in 4 h at ambient temperature to afford the corresponding *β*–amino ketone in good yield (89%).[75] Encouraged by this result, the three component one-pot Mannich reaction of **3a**, with benzaldehyde (**4a**) and aniline (**5a**) was investigated (Scheme 2h, Table 2c). Expectedly, the reaction proceeded smoothly to afford the adduct **6a** (Fig. 2e) with similar yield (89%) as that obtained in two component reactions. In order to find out the optimal catalyst loading, the three-component reaction was then carried out with varied amount of CSA (0-10 mol%) (Table 2c). In absence of the catalyst **6a** was not formed at all and both **3a** and *N*-benzylideneaniline were recovered (Table 2c, entry 1). However, the same reaction using 2 mol% catalysts proceeded smoothly to produce the desired product, **6a** in moderate isolated yield (78%) (Table 2c, entry 2). The spectral data (IR, NMR and MS) of **6a** was matched with its reported data. It appears that increasing catalyst loading to 5 mol% provide a very clean reaction with excellent yield of 89%

Table 2c: Optimization of catalyst loading in the Mannich type reaction of acetophenone (**3a**) with benzaldehyde (**4a**) and aniline (**5a**) using CSA

Entry	(±) CSA (mol %)	Time (h)	% Yield[a] of **6a**
1	0	6	–[b]
2	2	5	78
3	5	4	89
4	10	4	89

[a]Isolated yield (with respect to aniline); [b] **3a** and *N*-benzylideneaniline were recovered.

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at a reasonable reaction time (Table 2c, entry 3). However, use of catalyst >5% neither improved the yield nor the reaction time (Table 2c, entry 4). Therefore 5 mol% CSA was found to be the optimized catalyst loading to get the best results and the same condition

was used for all subsequent reactions. To demonstrate the preparative utility of this protocol, the reaction of **3a** with **4a** and **5a** under the optimized reaction conditions (Table 2c, entry 3) was carried out on 100 mmol scale. To our satisfaction, the reaction proceeded smoothly under solvent free conditions to afford **6a** in 89% isolated yield. Use of (1S)-(+)-camphor-10-sulfonic acid as catalyst (5 mol%) in the above reaction also afforded **6a** in similar yield (90%). However, no chiral induction in **6a** was observed.

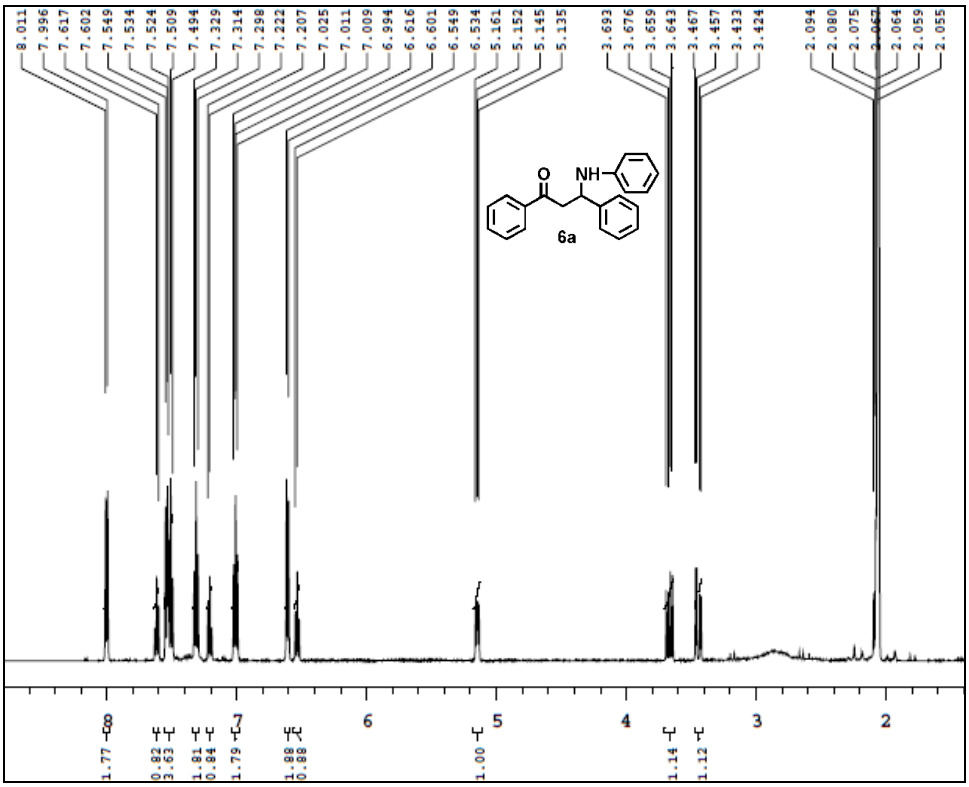


Figure 2e: ^{1}H-NMR of **6a**.

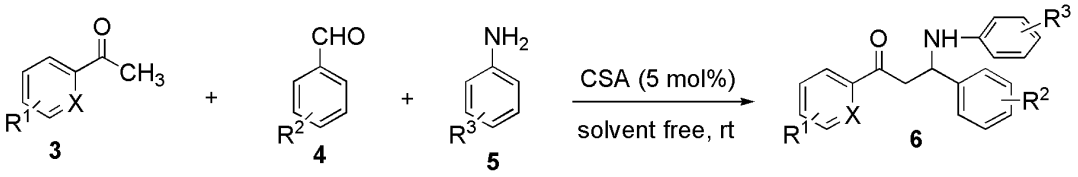
Encouraged by the above results, the efficiency of CSA was compared with some of the reported catalysts in the three-component coupling of **3a**, **4a** and **5a** under identical reaction conditions and the results are summarized in Table 2d. Thus, use of $BiCl_3$, $NbCl_5$, $HClO_4$-SiO_2, and$SnCl_2$ as catalystsyielded the adduct **6a** in 69%, 50%, 68% and 53% yields respectively. On the basis of the above results, it was concluded that CSA is indeed superior to many of the reported catalysts. In an effort to extend and explore the scope and

Table 2d: Screening of catalysts for the three-component reaction of **3a**, **4a** and **5a** at ambient temperature under solvent-free conditions

Entry	Catalyst (mol%)	Time (h)	% Yield[a]
1	$BiCl_3$ (5)	4	69
2	$NbCl_5$ (5)	4	50
3	$HClO_4$-SiO_2 (5)	4	68
4	$SnCl_2$ (5)	4	53
5	**(±)-CSA (5)**	**4**	**89**

[a]Isolated yield (with respect to aniline).

limitations of the present protocol, different aromatic aldehydes and aromatic amines with both electron-donating and electron-withdrawing groups were selected to undergo one-pot three-component Mannich reaction with (hetero)aromatic ketones under optimized conditions (Scheme 2i). The results of this study are summarized below in Table 2e



a: R^1 = H; X = CH
b: R^1 = 4-Cl; X = CH
c: R^1 = 4-F; X = CH
d: R^1 = 4-OMe; X = CH
e: R^1 = 3-OMe; X = CH
f: R^1 = 2-OMe; X = CH
g: R^1 = H; X = N

a: R^2 = H
b: R^2= 4-Br
c: R^2 = 4-Cl
d: R^2 = 3-OMe
e: R^2 = 3-NO_2
f: R^2 = 2-Br
g: R^2 = 4-NO_2

a: R^3 = H
b: R^3 = 4-Br
c: R^3 = 4-OMe
d: R^3 = 4-Cl

Scheme 2i: CSA catalyzed three-component Mannich reaction of aromatic ketones**.**

whereas, the structure of the Mannich adducts are presented in Fig. 2f. In all the cases smooth reactions were observed to afford the *β*–amino ketones, **6b-q** in moderate to high yields (Table 2e, entries 2-17). However, the reaction time for acetophenone with

substituted aromatic aldehydes and substituted aromatic amines were longer as compared to that of benzaldehyde and aniline. The yield of the reaction product **6l** (Fig. 2g) was found lower where fluorinated-acetophenone (**3c**) was used. In contrast to aromatic ketones, reactions with hetero-aromatic ketone such as 2-acetyl pyridine (**3g**) were much faster to yield Mannich adducts, **6p,q** in high yield (Table 2e, entries 16-17). A representative ^{1}H-NMR spectra of *β*–amino hetero-aromatic ketone such as **6p** is presented in Fig. 2h.

Table 2e: (±)-CSA catalyzed one-pot three-component Mannich reaction of methyl (hetero)aryl ketones with aromatic aldehydes and aromatic amines[a]

Entry	Ketone	Aldehyde	Amine	Time (h)	Product	% Yield[b]
1	**3a**	**4a**	**5a**	4	**6a**	89
2	**3a**	**4b**	**5a**	8	**6b**	83
3	**3a**	**4c**	**5a**	8	**6c**	75
4	**3a**	**4d**	**5a**	6	**6d**	88
5	**3a**	**4a**	**5b**	15	**6e**	100
6	**3a**	**4b**	**5c**	24	**6f**	42
7	**3a**	**4e**	**5c**	48	**6g**	60
8	**3a**	**4f**	**5c**	17	**6h**	75
9	**3a**	**4g**	**5d**	24	**6i**	82
10	**3b**	**4a**	**5a**	24	**6j**	51
11	**3b**	**4g**	**5d**	24	**6k**	60
12	**3c**	**4a**	**5a**	20	**6l**	37

Entry	Ketone	Aldehyde	Amine	Time (h)	Product	% Yield[b]
13	**3d**	**4a**	**5a**	20	**6m**	60
14	**3e**	**4a**	**5a**	20	**6n**	53
15	**3f**	**4a**	**5a**	20	**6o**	62
16	**3g**	**4a**	**5a**	1	**6p**	90
17	**3g**	**4b**	**5a**	1	**6q**	84

[a] Reaction conditions: 1.2 equiv. of ketone, 1.1 equiv. of aromatic aldehyde, 1.0 equiv. of aromatic amine and 5 mol% of CSA at ambient temperature; [b] isolated yield (with respect to aromatic amines).

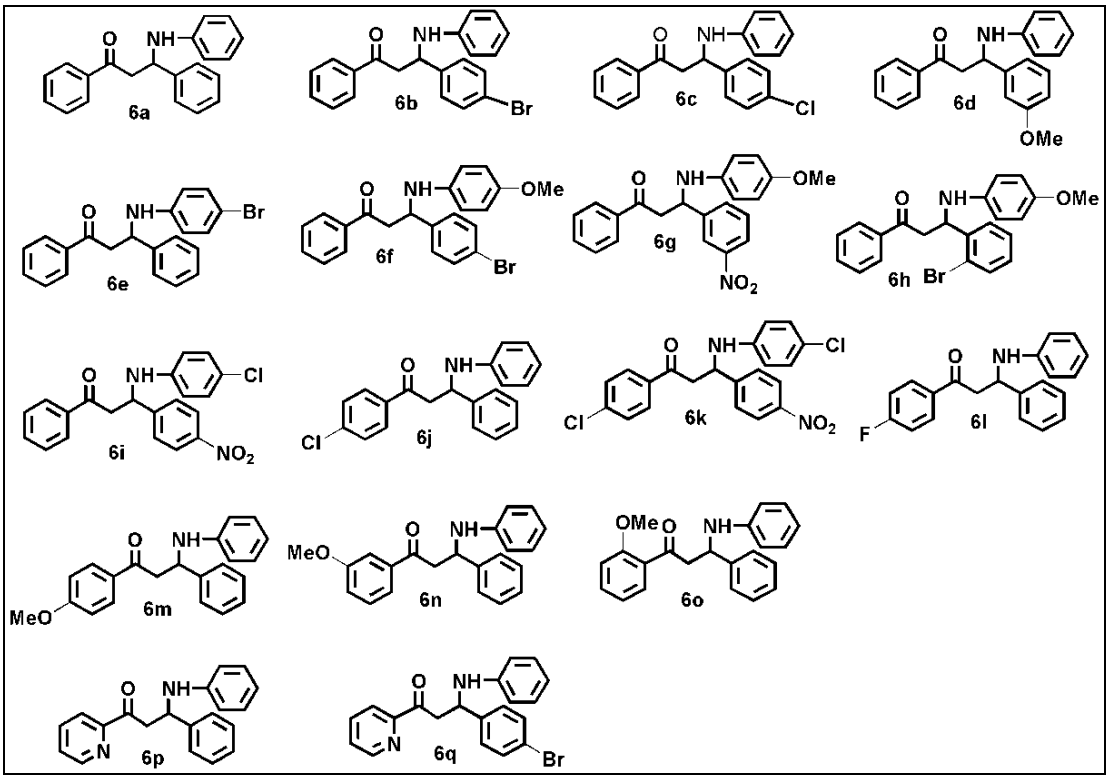


Figure 2f: Library synthesis of *β*–amino (hetero)aromatic ketones.

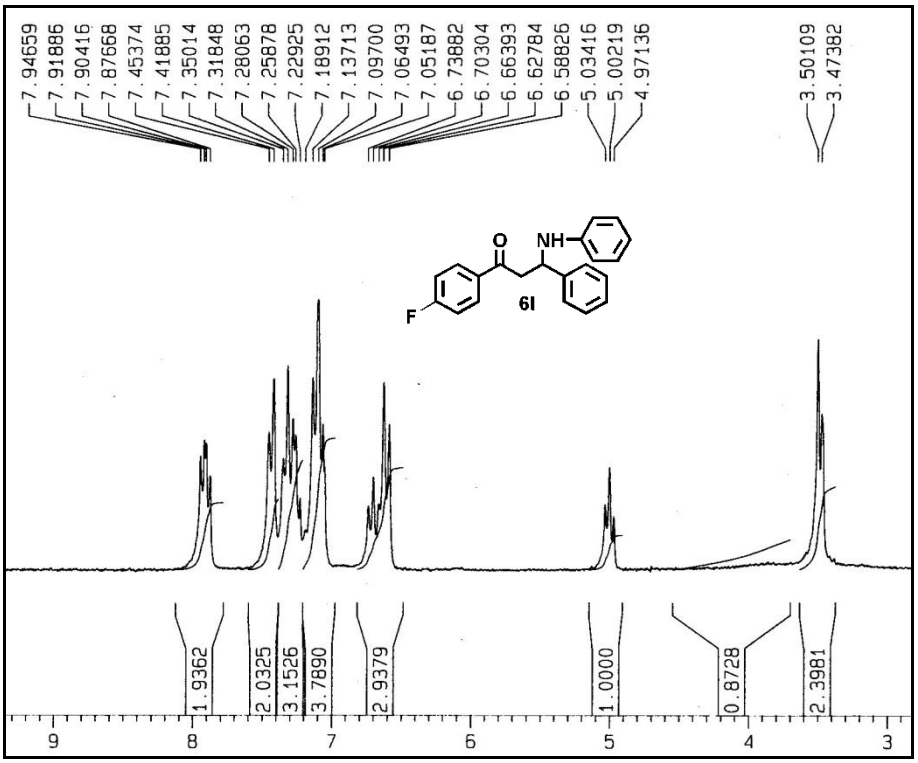


Figure 2g: ^{1}H-NMR of **6l**.

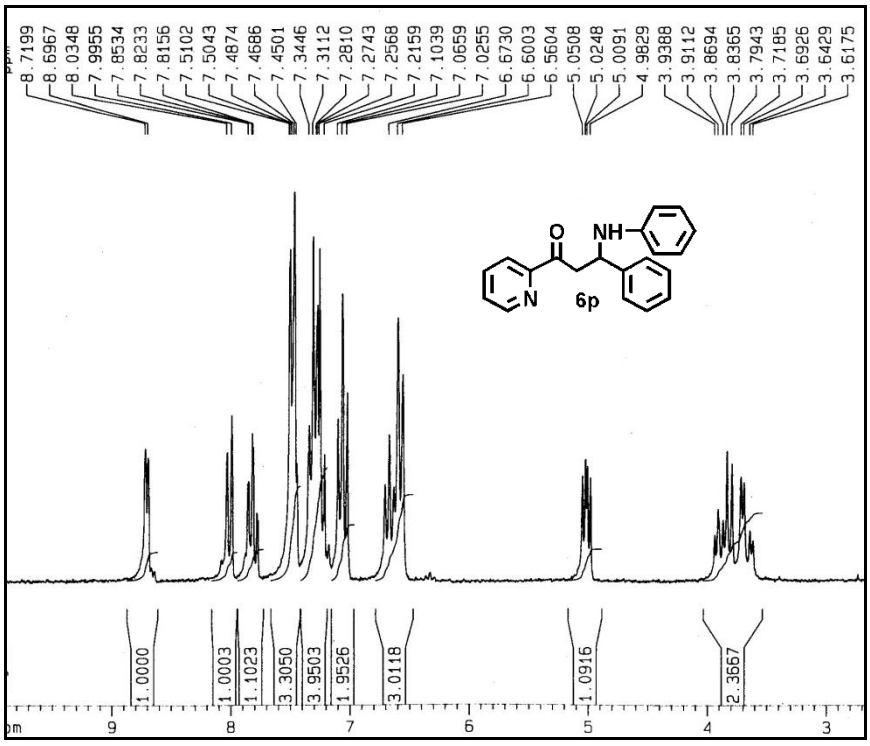


Figure 2h: ^{1}H-NMR of **6p**.

2.3 Conclusion

In conclusion, we have developed a very simple, efficient and practical method for the one-pot three-component Mannich-type reaction of reactive as well as unreactive ketones with aromatic aldehydes and aromatic amines using camphor-10-sulfonic acid as catalyst.[74] Mannich reactions of cyclic ketones with different imines (formed in situ from aromatic aldehydes and anilines) with 5 mol% CSA afforded the desired product in moderate to high yields under solvent free conditions. Less reactive ketones such as aromatic ketones, also afforded the Mannich adduct in high yields with 5 mol% of CSA under solvent free conditions. The significant features of the protocol include solvent-free conditions, inexpensive catalyst, mild reaction conditions, easy work up and high yields of the products which make it a valuable contribution for the synthesis of β-amino carbonyl compounds.

2.4 Experimental

General information

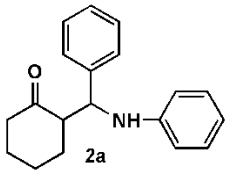
Melting points were determined using Fisher-Johns melting point apparatus and are uncorrected. IR spectra were scanned with a Jasco FT IR 4100 spectrophotometer. The ^{1}H and ^{13}C-NMR spectra were recorded with a Bruker AC 200/300 or Varian VNMR 500 spectrometer. Spectra were referenced to residual chloroform (δ 7.25 ppm, ^{1}H; 77.0 ppm, ^{13}C). Low resolution mass spectra were recorded with a Varian 500 mass spectrometer (ESI). High resolution mass spectra were recorded with a Q-TOF (YA-105) micromass spectrometer (ESI, Ar). All reactions were carried out under an argon atmosphere. (±)-Camphor-10-sulfonic acid (CSA) was purchased from USA and was used as such. Spectral data of known compounds was in accordance with those reported in the literature while the unknown compounds were characterized by IR, NMR and HRMS data.

2.4.1 General procedure for three component Mannich reactions of aliphatic ketones under solvent free conditions

Aniline or substituted anilines (1 equiv.) and benzaldehyde or substituted benzaldehydes (1.2 equiv.) were added to liquid ketones (1.3 equiv.) at room temperature and stirred well until the reaction mixture became homogeneous. Required amount of CSA was then added to the reaction mixture with stirring. After completion, the reaction mixture was quenched with saturated aqueous sodium bicarbonate solution and extracted three times with ethyl acetate. The organic extracts were combined, washed with brine, dried over anhydrous Na_2SO_4 and concentrated under reduced pressure. The residue was purified by column chromatography on silica gel using hexane/ethylacetate as eluent to give the Mannich bases.

2-(Aminophenyl(phenyl)methyl)cyclohexanone (2a)

Following the general procedure as described in 2.4.1, aniline (466 mg, 5 mmol), benzaldehyde (636 mg, 6 mmol), cyclohexanone (638 mg, 6.5 mmol) and CSA (58 mg, 0.25 mmol, 5 mol%) gave the Mannich base **2a** (1.28 g, 92%) with *anti*/*syn* = 80/20. **IR (film):** υ 3398, 2934, 1702, 1601, 1504, 1317, 867, 732 cm^{-1}; **^{1}H-NMR (200 MHz, $CDCl_3$):** (mixture of *syn*- and *anti*-isomer): δ 1.65-1.84 (m, 6H), 2.41 (m, 2H), 2.91 (m, 1H), 4.58 (d, *J* = 7.2 Hz, 0.8H, *anti*), 4.78 (d, *J* = 4.5 Hz, 0.2H, *syn*), 6.59-6.69 (m, 3H), 7.07 (m, 2H), 7.24-7.36 (m, 5H); **^{13}C-NMR (50 MHz, $CDCl_3$):** (*anti* only): δ 23.4, 27.7, 31.0, 41.5, 57.2, 57.7, 113.4, 117.3, 125.9, 127.1, 128.2, 128.8, 141.5, 147.0, 212.9.

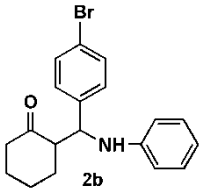


2a

2-(Aminophenyl-(4-bromophenyl)methyl)cyclohexanone (2b)

Following the general procedure as described in 2.4.1, aniline (93 mg, 1 mmol), 4-bromobenzaldehyde (222 mg, 1.2 mmol), cyclohexanone (127 mg, 1.3 mmol) and CSA (11 mg, 0.05 mmol, 5 mol%) gave the Mannich base **2b** (268 mg, 75%) with *anti*/*syn* =

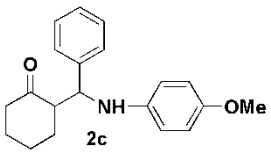
72/28. **IR (film):** υ 3374, 2938, 2864, 1703, 1680, 1601, 1499, 1487, 1315, 1275, 1072, 1009, 909, 732, 693 cm^{-1}; **^{1}H-NMR (200 MHz, $CDCl_3$):** (mixture of *syn*- and *anti*-isomer): δ 1.70-1.92 (m, 6H), 2.31-2.46 (m, 2H), 2.78 (m, 1H), 4.60 (d, *J* = 6.5 Hz, 0.72H, *anti*), 4.74 (d, *J* = 4.2 Hz, 0.28H, *syn*), 6.55 (d, *J* = 7.9 Hz, 2H), 6.67 (m, 1H), 7.09 (m, 2H), 7.24-7.30 (m, 2H), 7.41-7.45 (m, 2H); **^{13}C-NMR (50 MHz, $CDCl_3$):** (mixture of *syn*- and *anti*-isomer): δ 23.4, 24.7, 26.9, 27.7, 28.7, 31.4, 41.9, 42.3, 56.2, 56.8, 56.9, 57.6, 113.7, 113.9, 117.9, 120.6, 120.8, 129.0, 129.3, 131.3, 131.4, 140.5, 146.5, 146.9, 211.0, 212.3.



2b

2-(4-Methoxyaminophenyl(phenyl)methyl)cyclohexanone (2c)

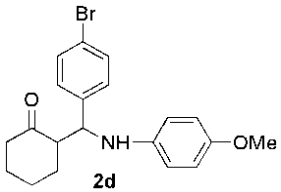
Following the general procedure as described in 2.4.1, Schiff base (106 mg, 0.5 mmol), cyclohexanone (63 mg, 0.65 mmol) and CSA (5 mg, 0.03 mmol, 5 mol%) gave the Mannich base **2c** (119 mg, 77%) with *anti*/*syn* = 85/15. **IR ($CHCl_3$):** υ 3394, 2936, 2863, 1703, 1615, 1558, 1487, 1316, 1248, 1075, 827, 754, 668 cm^{-1}; **^{1}H-NMR (200 MHz, $CDCl_3$):** (mixture of *syn*- and *anti*-isomer): δ 1.64-1.87 (m, 6H), 2.38 (m, 2H), 2.76 (m, 1H), 3.66 (s, 3H), 4.58 (d, *J* = 7.38 Hz, 0.85H, *anti*), 4.67 (d, *J* = 4.1 Hz, 0.15H, *syn*), 6.53 (d, *J* = 8.2 Hz, 2H), 6.67 (d, *J* = 8.0 Hz, 2H), 7.21-7.40 (m, 5H); **^{13}C-NMR (50 MHz, $CDCl_3$):** (*anti* only): δ 23.4, 27.7, 31.0, 41.5, 55.4, 57.2, 58.9, 114.4, 115.13, 127.0, 127.2, 128.3, 141.5, 141.0, 152.0, 212.8.



2c

2-(4-Methoxyaminophenyl(4-bromophenyl)methyl)cyclohexanone (2d)

Following the general procedure as described in 2.4.1, 4-methoxyaniline (61 mg, 0.5 mmol), 4-bromobenzaldehyde (111 mg, 0.6 mmol), cyclohexanone (63 mg, 0.65 mmol) and CSA (7 mg, 0.03 mmol, 5 mol%) gave the Mannich base **2d** (194 mg, 100%) with *anti*/*syn* = 90/10. **IR (film):** υ 3393, 2936, 2862, 2831, 1703, 1618, 1590, 1511, 1486, 1449, 1404,

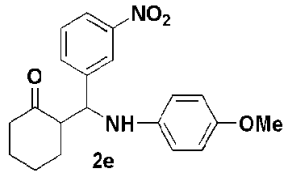


2d

1296, 1238, 1125, 1071, 820, 759, 646 cm^{-1}; **^{1}H-NMR (200 MHz, $CDCl_3$):** (mixture of *syn*- and *anti*-isomer): δ 1.61-1.88 (m, 6H), 2.29-2.34 (m, 2H), 2.70 (m, 1H), 3.65 (s, 3H), 4.51 (d, *J* = 6.8 Hz, 0.9H, *anti*), 4.66 (d, *J* = 4.2 Hz, 0.1H, *syn*), 6.48 (d, *J* = 8.9 Hz, 2H), 6.66 (d, *J* = 8.9 Hz, 2H), 7.24 (d, *J* = 8.4 Hz, 2H), 7.40 (d, *J* = 8.4 Hz, 2H); **^{13}C-NMR (50 MHz, $CDCl_3$):** (*anti* only): δ 23.8, 27.7, 31.2, 41.8, 55.5, 57.0, 58.5, 114.5, 115.2, 120.7, 129.1, 129.2, 131.3, 140.7, 152.2, 212.3.

2-(4-Methoxyaminophenyl(3-nitrophenyl)methyl)cyclohexanone (2e)

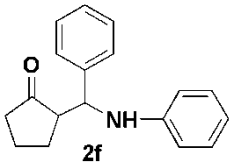
Following the general procedure as described in 2.4.1, 4-methoxyaniline (615 mg, 0.5 mmol), 3-nitrobenzaldehyde (91 mg, 0.6 mmol), cyclohexanone (64 mg, 0.65 mmol) and CSA (7 mg, 0.03 mmol, 5 mol%) gave the Mannich base **2e** (159 mg, 90%) with *anti*/*syn* = 80/20. **IR (film):** υ 3394, 3018, 2938, 2863, 2833, 1704, 1613, 1512, 1464, 1450, 1353, 1291, 1240, 1179, 1036, 821, 759, 667 cm^{-1}; **^{1}H-NMR (200 MHz, $CDCl_3$):** (mixture of *syn*- and *anti*-isomer): δ 1.61-1.90 (m, 6H), 2.37 (m, 2H), 2.85 (m, 1H), 3.65 (s, 3H), 4.64 (d, *J* = 5.7 Hz, 0.8H, *anti*), 4.78 (d, *J* = 4.4 Hz, 0.2H, *syn*), 6.49 (d, *J* = 8.7 Hz, 2H), 6.66 (d, *J* = 8.7 Hz, 2H), 7.44 (t, *J* = 7.8 Hz, 1H), 7.77 (d, *J* = 7.5 Hz, 1H), 8.04 (d, *J* = 8.0 Hz, 1H), 8.22 (s, 1H); **^{13}C-NMR (50 MHz, $CDCl_3$):** (*anti* only): δ 24.3, 27.7, 31.7, 42.2, 55.5, 56.8, 58.8, 114.7, 115.3, 122.1, 122.4, 129.2, 133.7, 140.2, 144.2, 148.3, 152.5, 211.9.



2e

2-(Aminophenyl(phenyl)methyl)cyclopentanone (2f)

Following the general procedure as described in 2.4.1, Schiff base (181 mg, 1 mmol), cyclopentanone (109 mg, 1.3 mmol) and CSA (12 mg, 0.05 mmol, 5 mol%) gave the Mannich base **2f** (40 mg, 15%) with *anti*/*syn* = 45/55. **IR (film):** υ 3377, 2938, 1724, 1608, 1514, 1320, 850, 743 cm^{-1}; **^{1}H-NMR (200 MHz, $CDCl_3$):** (mixture of *syn*- and *anti*-isomer): δ 1.74-2.72 (m, 6H), 2.97 (m, 1H), 4.53 (d, *J* =

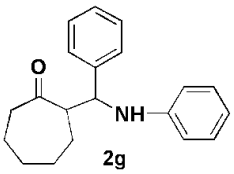


2f

7.5 Hz, 0.45H, *anti*), 4.75 (d, *J* = 4.1 Hz, 0.55H, *syn*), 6.57-7.52 (m, 10H); **^{13}C-NMR (50 MHz, $CDCl_3$):** (mixture of *syn*- and *anti*-isomer): δ 20.7, 20.9, 26.1, 26.9, 39.5, 40.0, 53.6, 54.3, 57.9, 59.3, 113.9, 114.4, 117.7, 118.1, 127.4, 127.6, 127.7, 128.8, 128.9, 129.2, 129.3, 141.1, 141.9, 147.0, 147.8, 219.6, 220.8.

2-(Aminophenyl(phenyl)methyl)cycloheptanone (2g)

Following the general procedure as described in 2.4.1, aniline (93 mg, 1 mmol), benzaldehyde (127 mg, 1.2 mmol), cycloheptanone (146 mg, 1.3 mmol) and CSA (12 mg, 0.05 mmol, 5 mol%) gave the Mannich base **2g** (191 mg, 65%) with *anti*/*syn* = 55/45. **IR (film):** υ 3387, 2929, 1696, 1512, 1464, 1075, 824, 660 cm^{-1}; **^{1}H-NMR (200 MHz, $CDCl_3$):** (mixture of *syn*- and *anti*-isomer): δ 1.27-2.07 (m, 8H), 2.20-2.50 (m, 2H), 2.85-2.98 (m, 1H), 4.50 (d, *J* = 7.7 Hz, 0.55H, *anti*), 4.63 (d, *J* = 4.7 Hz, 0.45H, *syn*), 6.51-7.37 (m, 10H); **^{13}C-NMR (50 MHz, $CDCl_3$):** (mixture of *syn*- and *anti*-isomer): δ 24.7, 25.0, 26.9, 27.7, 28.3, 28.9, 29.1, 29.6, 42.5, 44.0, 58.3, 58.6, 60.0, 60.2, 113.4, 117.2, 117.3, 127.1, 128.3, 128.4, 128.9, 140.3, 141.2, 146.7, 215.6, 216.1.



2g

2.4.2 Typical procedure for two-component Mannich reaction of acetophenone (3a) and *N*-benzylideneaniline under solvent-free conditions

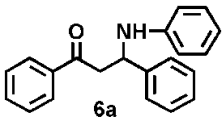
To a mixture of **3a** (1.32 g, 11 mmol) and *N*-benzylideneaniline (1.81 g, 10 mmol), (±)-CSA (0.23 g, 10 mol%) was added and stirred at ambient temperature. After completion of the reaction (monitored by TLC), the thick mass was quenched with 10% aqueous $NaHCO_3$ solution. The pale yellow solid was filtered, washed with water and dried in air. Recrystallization of the crude product from ethyl acetate-hexane mixture yielded pure adduct **6a** as a colorless solid in 89% yield.

2.4.3 General procedure for one-pot three-component Mannich reaction under solvent-free conditions

To a mixture of methyl (hetero)aryl ketone (**3**), benzaldehyde/substituted benzaldehyde (**4**) and aniline/substituted aniline (**5**) CSA (5 mol%) was added and the mixture was stirred at ambient temperature. After completion of the reaction (disappearance of aromatic amine; monitored by TLC), the thick mass was quenched with 10% aqueous $NaHCO_3$ solution, extracted with ethyl acetate, washed with water, brine and dried (Na_2SO_4). Removal of solvent yielded the crude product which was purified by crystallization/column chromatography over silica gel to give the pure adducts **6a-q**. The identity and purity of the products are confirmed by IR, ^{1}H-NMR, ^{13}C-NMR, and HRMS (for unknown compounds) spectroscopic analysis.

1,3-Diphenyl-3-(phenylamino)propan-1-one (6a)

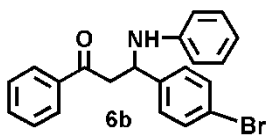
Following the general procedure as described in 2.4.3, **3a** (14.4 g, 120 mmol), **4a** (11.7 g, 110 mmol) and **5a** (9.3 g, 100 mmol) gave the product **6a** (89%) as colorless solid. **MP:** 169-170 °C (lit.[75] 169-170 °C); **IR ($CHCl_3$):** υ 3384, 3019, 2399, 1671, 1600, 1509, 1449,



6a

1417, 1291, 1214, 1077, 1002, 856, 756, 668 cm^{-1}; **^{1}H-NMR (500 MHz, CD_3COCD_3):** δ 3.45 (dd, *J* = 17.0, 5.0 Hz, 1H), 3.67 (dd, *J* = 17.0, 8.5 Hz, 1H), 5.15 (dd, *J* = 8.5, 5.0 Hz, 1H), 6.53 (t, *J* = 7.5 Hz, 1H), 6.61 (d, *J* = 7.5 Hz, 2H), 6.99-7.03 (m, 2H), 7.21 (t, *J* = 7.5 Hz, 1H), 7.31 (t, *J* = 7.5 Hz, 2H), 7.49-7.55 (m, 4H), 7.60-7.63 (m, 1H), 8.00 (d, *J* = 7.5 Hz, 2H); **^{13}C-NMR (50 MHz, $CDCl_3$):** δ 46.0, 55.3, 114.4, 118.4, 126.5, 127.4, 128.2, 128.7, 128.8, 129.1, 133.4, 136.6, 142.4, 146.2, 198.1.

3-(4-Bromophenyl)-1-phenyl-3-(phenylamino)propan-1-one (6b)



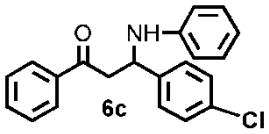
6b

Following the general procedure as described in 2.4.3, **3a** (721 mg, 6 mmol), **4b** (1.02 g, 5.5 mmol) and **5a** (465 mg, 5 mmol) gave the product **6b** (83%) as colorless solid. **MP:** 128-129 °C (lit.[65]130-131 °C); **IR ($CHCl_3$):** υ

3394, 3019, 1681, 1601, 1504, 1448, 1214, 1010, 755, 695, 666 cm^{-1}; **^{1}H-NMR (200 MHz, $CDCl_3$):** δ 3.51 (d, *J* = 6.2 Hz, 2H), 4.96 (t, *J* = 6.2 Hz, 1H), 6.60 (d, *J* = 7.8 Hz, 2H), 6.77 (t, *J* = 7.3 Hz, 1H), 7.12 (t, *J* = 7.6 Hz, 2H), 7.30-7.53 (m, 7H), 7.88 (d, *J* = 7.4 Hz, 2H); **^{13}C-NMR (50 MHz, $CDCl_3$):** δ 45.6, 55.2, 114.9, 119.2, 121.3, 128.1, 128.5, 128.7, 129.2, 131.9, 133.6, 136.5, 141.1, 145.4, 197.6; **MS (ESI)**: *m/z* 381 (M+2, 71), 379 (M, 98), 354 (13), 325 (13), 283 (22), 281 (13), 265 (13), 262 (86), 260 (100), 150 (20), 138 (27), 122 (20), 116 (37), 105 (76).

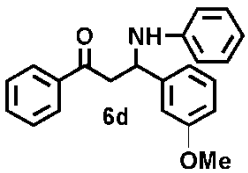
3-(4-Chlorophenyl)-1-phenyl-3-(phenylamino)propan-1-one(6c)

Following the general procedure as described in 2.4.3, **3a** (721 mg, 6 mmol), **4c** (773 mg, 5.5 mmol) and **5a** (465 mg, 5 mmol) gave the product **6c** (75%) as colorless solid. **MP:** 115-116 °C (lit.[75]117-118 °C); **IR ($CHCl_3$):** υ 3399, 3019, 2399, 1682, 1601, 1504, 1448, 1407, 1215, 1013, 825, 756, 690 cm^{-1}; **^{1}H-NMR (200 MHz, $CDCl_3$):** δ 3.56 (d, *J* = 6.4 Hz, 2H), 5.00 (t, *J* = 6.4 Hz, 1H), 6.65 (d, *J* = 7.9 Hz, 2H), 6.77 (t, *J* = 7.3 Hz, 1H), 7.13 (t, *J* = 7.8 Hz, 2H), 7.26-7.62 (m, 7H), 7.87-7.91 (m, 2H); **^{13}C-NMR (50 MHz, $CDCl_3$):** δ 46.0, 54.3, 114.0, 118.1, 127.8, 128.1, 128.7, 128.9, 129.1, 133.0, 133.4, 136.7, 141.5, 146.7, 197.8; **MS (ESI):** *m/z* 337 (M+2, 23), 335 (M, 58), 218 (34), 217 (21), 216 (100), 105 (37).



3-(3-Methoxyphenyl)-1-phenyl-3-(phenylamino)propan-1-one(6d)

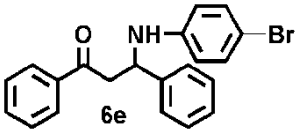
Following the general procedure as described in 2.4.3, **3a** (721 mg, 6 mmol), **4d** (749 mg, 5.5 mmol) and **5a** (465 mg, 5 mmol) gave the product **6d** (88%) as colorless solid. **MP:** 106-107 °C; **IR ($CHCl_3$):** υ 3406, 3017, 2938, 2835, 1683, 1601, 1505, 1465, 1449, 1435, 1216, 1181, 1046, 871, 692 cm^{-1}; **^{1}H-NMR (200 MHz, $CDCl_3$):** δ 3.47-3.54 (m, 2H), 3.78 (s, 3H), 4.99 (t, *J* = 6.9 Hz, 1H), 6.61-6.81 (m, 4H), 7.03-7.29 (m, 5H), 7.41-7.58 (m, 3H), 7.92 (d, *J* = 7.3 Hz, 2H); **^{13}C-NMR (50**



MHz, $CDCl_3$): δ 46.1, 55.0, 55.1, 112.3, 112.6, 114.1, 118.0, 118.7, 128.1, 128.6, 129.0, 129.7, 133.3, 136.8, 144.6, 146.8, 160.0, 198.1; MS (ESI) *m/z* 331 (M, 46), 212 (100), 105 (23); **HRMS:** *m/z* calcd for $C_{22}H_{22}NO_2$ (M+H): 332.1651; found: 332.1645.

3-(4-Bromophenylamino)-1,3-diphenylpropan-1-one (6e)

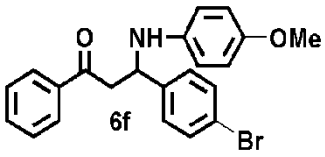
Following the general procedure as described in 2.4.3, **3a** (721 mg, 6 mmol), **4a** (583 mg, 5.5 mmol) and **5b** (860 mg, 5 mmol) gave the product **6e** (100%) as colorless solid. **MP:**



180-181 °C; **IR ($CHCl_3$):** υ 3368,3019, 1665, 1593, 1576, 1504, 1447, 1407, 1312, 1283, 1070, 916, 848 cm^{-1}; **^{1}H-NMR (200 MHz, $CDCl_3$):** δ 3.65 (d, *J* = 6.2 Hz, 2H), 4.97 (t, *J* = 6.2 Hz, 1H), 6.61 (d, *J* = 8.6 Hz, 2H), 7.18-7.61 (m, 10H), 7.88 (d, *J* = 7.5 Hz, 2H); **^{13}C-NMR (50 MHz, CD_3COCD_3):** δ 47.3, 54.7, 116.0, 127.5, 127.8, 128.9, 129.3, 129.4, 132.2, 133.8, 138.1, 144.4, 148.1, 197.7; **MS (ESI):** *m/z* 381 (M+2, 32), 380 (M+1, 23), 379 (M, 35), 311 (16), 262 (85), 261 (19), 260 (100), 105 (65); **HRMS:** *m/z* calcd for $C_{21}H_{19}NOBr$ (M+H): 380.0650; found: 380.0648.

3-(4-Methoxyphenylamino)-3-(4-bromophenyl)-1-phenylpropan-1-one (6f)

Following the general procedure as described in 2.4.3, **3a** (721 mg, 6 mmol), **4b** (1.02 g,

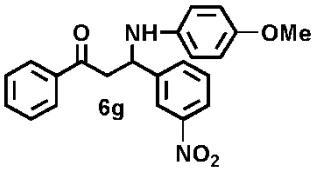


5.5 mmol) and **5c** (616 mg, 5mmol) gave the product **6f** (42%) as colorless solid. **MP:** 114-115 °C; **IR ($CHCl_3$):** υ 3389, 3061, 3013, 2951, 2832, 1904, 1682, 1602, 1510, 1485, 1448, 1330, 1298, 1234, 1178, 1071, 1036, 818, 763, 689 cm^{-1}; **^{1}H-NMR (200 MHz, $CDCl_3$):** δ 3.45-3.49 (m, 2H), 3.69 (s, 3H), 4.89 (t, *J* = 6.5 Hz, 1H), 6.52-6.58 (m, 2H), 6.63-6.73 (m, 2H), 7.30-7.37 (m, 2H), 7.40-7.48 (m, 4H), 7.53-7.61 (m, 1H), 7.87-7.90 (m, 2H); **^{13}C-NMR (50 MHz, $CDCl_3$):** δ 45.9, 54.8, 55.4, 114.6, 115.2, 120.7, 127.9, 128.1, 128.4, 131.5, 133.2, 136.4, 140.7, 142.2,

152.3, 197.6; **MS (ESI):** *m/z* 411 (M+2, 74), 410 (M+1, 77), 409 (M, 100), 292 (23), 290 (27), 105 (14); **HRMS:** *m/z* calcd for $C_{22}H_{21}NO_2Br$ (M+H): 410.0756; found: 410.0752.

3-(4-Methoxyphenylamino)-3-(3-nitrophenyl)-1-phenylpropan-1-one (6g)

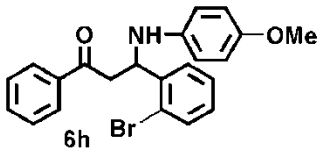
Following the general procedure as described in 2.4.3, **3a** (721 mg, 6 mmol), **4e** (831 mg, 5.5 mmol) and **5c** (616 mg, 5mmol) gave the product **6g** (60%) as colorless solid. **MP:** 76-



77 °C; **IR ($CHCl_3$):** υ 3394, 3014, 2934, 2832, 1681, 1596, 1530, 1448, 1351, 1239, 1099, 1035, 821, 760, 686 cm^{-1}; **^{1}H-NMR (200 MHz, $CDCl_3$):** δ 3.50 (d, *J* = 6.1 Hz, 2H), 3.68 (s, 3H), 4.08 (br, 1H), 5.05 (t, *J* = 6.1 Hz, 1H), 6.52 (d, *J* = 8.9 Hz, 2H), 6.70 (d, *J* = 9.0 Hz, 2H), 7.39-7.60 (m, 4H), 7.79-7.91 (m, 3H), 8.04-8.08 (m, 1H), 8.32 (s, 1H); **^{13}C-NMR (50 MHz, $CDCl_3$):** δ 45.8, 54.8, 55.5, 114.7, 115.4, 121.5, 122.3, 128.0, 128.7, 129.6, 133.0, 133.6, 136.3, 140.3, 145.6, 148.5, 152.6, 197.3; **MS (ESI):** *m/z* 377 (M+1, 65), 376 (M, 100), 273 (13), 257 (61), 210 (14), 164 (12), 105 (24); **HRMS:** *m/z* calcd for $C_{22}H_{21}N_2O_4$ (M+H): 377.1501; found: 377.1505.

3-(4-Methoxyphenylamino)-3-(2-bromophenyl)-1-phenylpropan-1-one (6h)

Following the general procedure as described in 2.4.3, **3a** (721 mg, 6 mmol), **4f** (1.02 g,

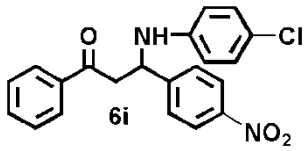


5.5 mmol) and **5c** (616 mg, 5mmol) gave the product **6h** (75%) as colorless solid. **MP:** 60-61 °C; **IR ($CHCl_3$):** υ 3396, 3015, 2933, 2832, 2400, 1966, 1682, 1596, 1512, 1463, 1440, 1291, 1216, 1180, 1098, 819, 761, 689 cm^{-1}; **^{1}H-NMR (200 MHz, $CDCl_3$):** δ 3.42-3.54 (m, 1H), 3.69 (s, 3H), 3.74-3.85 (m, 1H), 5.28-5.34 (m, 1H), 6.58-6.72 (m, 4H), 7.07-7.14 (m, 1H), 7.22-7.30 (m, 1H), 7.40-7.47 (m, 2H), 7.53-7.60 (m, 2H),7.68-7.72 (m, 1H), 7.95 (d, *J* = 7.5 Hz, 2H); **^{13}C-NMR (50 MHz, $CDCl_3$):** δ 43.9, 54.9, 55.5, 114.7, 115.0, 122.6, 127.9, 128.2, 128.4, 128.5, 128.7, 133.0, 133.3, 136.6, 140.6, 141.3, 152.4, 198.3; **MS (ESI):** *m/z* 412 (M+3, 65), 411

(M+2, 37), 410 (M+1, 65), 357 (17), 326 (18), 293 (16), 292 (95), 291 (20), 290 (100), 105 (12); **HRMS:** *m/z* calcd for $C_{22}H_{21}NO_2Br$ (M+H): 410.0756; found: 410.0748.

3-(4-Chlorophenylamino)-3-(4-nitrophenyl)-1-phenylpropan-1-one (6i)

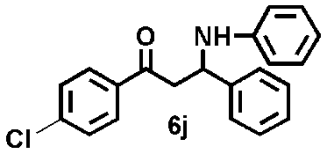
Following the general procedure as described in 2.4.3, **3a** (721 mg, 6 mmol), **4g** (831 mg, 5.5 mmol) and **5d** (638 mg, 5mmol) gave the product **6i** (82%) as yellowish solid. **MP:**



127-128 °C (lit.[69] 129-131 °C); **IR ($CHCl_3$):** υ 3394, 3019, 2927, 1679, 1598, 1495, 1348, 1214, 1180, 1093, 855, 754, 688 cm^{-1}; **^{1}H-NMR (200 MHz, $CDCl_3$):** δ 3.52 (d, *J* = 6.0 Hz, 2H), 5.05 (t, *J* = 6.0 Hz, 1H), 6.46 (d, *J* = 8.6 Hz, 2H), 7.04 (d, *J* = 8.6 Hz, 2H), 7.41-7.48 (m, 2H), 7.58-7.62 (m, 3H), 7.88 (d, *J* = 7.3 Hz, 2H), 8.16 (d, *J* = 8.5 Hz, 2H); **^{13}C-NMR (50 MHz, $CDCl_3$):** δ 45.4, 54.0, 114.8, 122.8, 123.9, 127.3, 128.0, 128.7, 128.9, 133.7, 136.1, 144.9, 147.0, 150.2, 197.0; **MS (ESI):** *m/z* 383 (M+3, 26), 382 (M+2, 29), 381 (M+1, 58), 380 (M, 75), 292 (12), 286 (8), 263 (49), 262 (17), 261 (100), 105 (9).

1-(4-Chlorophenyl)-3-phenyl-3-(phenylamino)propan-1-one (6j)

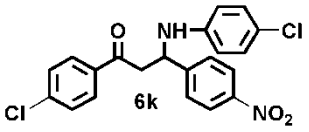
Following the general procedure as described in 2.4.3, **3b** (928 mg, 6 mmol), **4a** (583 mg, 5.5 mmol) and **5a** (465 mg, 5 mmol) gave the product **6j** (51%) as colorless solid. **MP:**



120-121 °C (lit.[75] 119-120 °C); **IR ($CHCl_3$):** υ 3377, 3019, 2922, 2399, 1918, 1683, 1601, 1589, 1504, 1431, 1358, 1215, 1177, 1094, 832, 755, 699 cm^{-1}; **^{1}H-NMR (200 MHz, $CDCl_3$):** δ 3.55-3.58 (m, 2H), 5.02 (t, *J* = 6.5 Hz, 1H), 6.67-6.81 (m, 3H), 7.10-7.17 (m, 2H), 7.24-7.47 (m, 7H), 7.80 (d, *J* = 8.4 Hz, 2H); **^{13}C-NMR (50 MHz, $CDCl_3$):** δ 46.0, 55.2, 114.2, 118.3, 126.4, 127.5, 128.8, 129.0, 129.1, 129.5, 135.2, 139.9, 142.5, 146.5, 197.0; **MS (ESI):** *m/z* 337 (M+2, 11), 335 (M, 39), 320 (25), 319 (14), 318 (72), 212 (26), 183 (13), 182 (100), 141 (10), 139 (20).

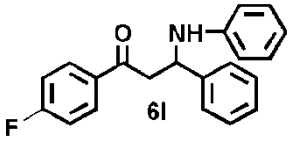
3-(4-Chlorophenylamino)-1-(4-chlorophenyl)-3-(4-nitrophenyl)propan-1-one (6k)

Following the general procedure as described in 2.4.3, **3b** (928 mg, 6 mmol), **4g** (831 mg, 5.5 mmol) and **5d** (638 mg, 5mmol) gave the product **6k** (60%) as yellowish solid. **MP:** 125-126 °C; **IR ($CHCl_3$):** υ 3396, 3019, 2908, 2850, 1671, 1590, 1402, 1348, 1215, 1178, 856, 700 cm^{-1}; **^{1}H-NMR (200 MHz, $CDCl_3$):** δ 3.51 (m, 2H), 5.05 (t, *J* = 6.2 Hz, 1H), 6.48 (d, *J* = 8.7 Hz, 2H), 7.06 (d, *J* = 8.7 Hz, 2H,), 7.41-7.45 (m, 2H), 7.61 (d, *J* = 8.7 Hz, 2H), 7.80-7.84 (m, 2H), 8.18 (d, *J* = 8.7 Hz, 2H); **^{13}C-NMR (50 MHz, $CDCl_3$):** δ 45.3, 54.5, 115.3, 123.7, 124.1, 127.5, 129.2, 129.5, 134.6, 140.4, 144.5, 147.4, 149.7, 195.8; **HRMS:** *m/z* calcd for $C_{21}H_{17}N_2O_3Cl_2$ (M+H): 415.0616; found: 415.0618.



1-(4-Flurophenyl)-3-phenyl-3-(phenylamino)propan-1-one (6l)

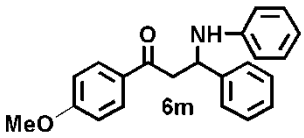
Following the general procedure as described in 2.4.3, **3c** (829 mg, 6 mmol), **4a** (583 mg, 5.5 mmol) and **5a** (465 mg, 5 mmol) gave the product **6l** (37%) as colorless solid. **MP:** 119-120 °C; **IR ($CHCl_3$):** υ 3399, 3015, 2956, 2925, 2855, 1684, 1600, 1505, 1409, 1358, 1215, 1156, 839, 758 cm^{-1}; **^{1}H-NMR (200 MHz, $CDCl_3$):** δ 3.49 (d, *J* = 6.4 Hz, 2H), 5.00 (t, *J* = 6.4 Hz, 1H), 6.59-6.74 (m, 3H), 7.05-7.19 (m, 4H), 7.23-7.35 (m, 3H), 7.44 (d, *J* = 7.0 Hz, 2H), 7.88-7.95 (m, 2H); **^{13}C-NMR (50 MHz, $CDCl_3$):** δ 46.0, 54.9, 113.9, 115.5, 115.9, 117.9, 126.3, 127.4, 128.7, 129.1, 130.7, 130.9, 133.2, 142.7, 146.8, 163.3, 168.3, 196.5; **MS (ESI):** *m/z* 320 (M+1, 86), 302 (26), 285 (12), 183 (16), 182 (100), 123 (48); **HRMS:** *m/z* calcd for $C_{21}H_{19}NOF$ (M+H): 320.1451; found: 320.1449.



1-(4-Methoxyphenyl)-3-phenyl-3-(phenylamino)propan-1-one (6m)

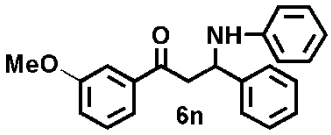
Following the general procedure as described in 2.4.3, **3d** (901 mg, 6 mmol), **4a** (583 mg, 5.5 mmol) and **5a** (465 mg, 5 mmol) gave the product **6m** (60%) as colorless solid. **MP:** 124-125 °C; **IR ($CHCl_3$):** υ 3380, 3021, 2921, 1658, 1600, 1511, 1454, 1407, 1215, 1028,

833, 746, 688 cm^{-1}; **^{1}H-NMR (200 MHz, $CDCl_3$):** δ 3.40-3.62 (m, 2H), 3.87 (s, 3H), 4.98 (t, *J* = 6.8 Hz, 1H), 6.64-6.77 (m, 3H), 6.91(d, *J* = 8.9 Hz, 2H), 7.07-7.16 (m, 2H), 7.23-7.36 (m, 3H), 7.44-7.48 (m, 2H), 7.87-7.91 (d, *J* = 8.9 Hz, 2H); **^{13}C-NMR (50 MHz, $CDCl_3$):** δ 45.9, 55.3, 55.4, 113.9, 114.1, 117.9, 126.4, 127.2, 128.7, 129.0, 130.0, 130.5, 143.0, 146.9, 163.8, 196.7; **HRMS:** *m/z* calcd for $C_{22}H_{22}NO_2$ (M+H): 332.1651; found: 332.1637.



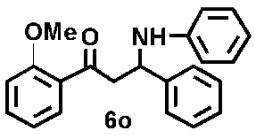
1-(3-Methoxyphenyl)-3-phenyl-3-(phenylamino)propan-1-one (6n)

Following the general procedure as described in 2.4.3, **3e** (901 mg, 6 mmol), **4a** (583 mg, 5.5 mmol) and **5a** (465 mg, 5 mmol) gave the product **6n** (53%) as colorless solid. **MP:** 104-105 °C; **IR ($CHCl_3$):** υ 3398, 3020, 2835, 1681, 1600, 1504, 1452, 1428, 1267, 1216, 1042, 751, 692 cm^{-1}; **^{1}H-NMR (200 MHz, $CDCl_3$):** δ 3.45-3.66 (m, 2H), 3.83 (s, 3H), 5.02 (t, *J* = 6.7 Hz, 1H), 6.64-6.78 (m, 3H), 7.08-7.16 (m, 3H), 7.24-7.38 (m, 4H), 7.44-7.49 (m, 4H); **^{13}C-NMR (50 MHz, $CDCl_3$):** δ 46.2, 55.2, 55.4, 112.5, 114.1, 118.1, 119.9, 120.8, 126.4, 127.4, 128.8, 129.1, 129.6, 138.2, 142.8, 146.7, 160.0, 198.0; **HRMS:** *m/z* calcd for $C_{22}H_{22}NO_2$ (M+H): 332.1651; found: 332.1638.



1-(2-Methoxyphenyl)-3-phenyl-3-(phenylamino)propan-1-one (6o)

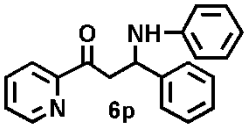
Following the general procedure as described in 2.4.3, **3f** (901 mg, 6 mmol), **4a** (583 mg, 5.5 mmol) and **5a** (465 mg, 5 mmol) gave the product **6o** (62%) as colorless solid. **MP:** 105-106 °C; **IR ($CHCl_3$):** υ 3419, 3018, 2840, 1670, 1599, 1505, 1455, 1436, 1295, 1215, 1024, 755, 668 cm^{-1}; **^{1}H-NMR (200 MHz, $CDCl_3$):** δ 3.57-3.66 (m, 2H), 3.91 (s, 3H), 4.93-5.00 (m, 1H), 6.61-6.75 (m, 3H), 6.94-7.01 (m, 2H), 7.06-7.13 (m, 2H), 7.19-7.35 (m, 3H), 7.43-7.52 (m, 3H), 7.63 (dd, *J* = 7.9, 2.0 Hz, 1H); **^{13}C-NMR (50 MHz, $CDCl_3$):** δ 51.3, 55.2, 55.5, 111.6, 113.8, 117.6, 120.9, 126.4,



127.0, 128.3, 128.6, 129.0, 130.5, 133.7, 143.3, 147.1, 158.4, 200.5; **HRMS:** *m/z* calcd for $C_{22}H_{22}NO_2$ (M+H): 332.1651; found: 332.1638.

3-Phenyl-3-(phenylamino)-1-(pyridin-2-yl)propan-1-one (6p)

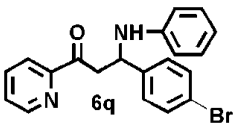
Following the general procedure as described in 2.4.3, **3g** (727 mg, 6 mmol), **4a** (583 mg, 5.5 mmol) and **5a** (465 mg, 5 mmol) gave the product **6p** (90%) as colorless solid. **MP:**



120-121 °C; **IR ($CHCl_3$):** υ 3394, 3374, 3019, 2923, 1688, 1602, 1511, 1495, 1318, 1215, 1078, 994, 863 cm^{-1}; **^{1}H-NMR (200 MHz, $CDCl_3$):** δ 3.62-3.94 (m, 2H), 5.02 (dd, *J* = 8.4, 5.2 Hz, 1H), 6.56-6.71 (m, 3H), 7.07 (t, *J* = 7.6 Hz, 2H), 7.18-7.34 (m, 3H), 7.45-7.51 (m, 3H), 7.78-7.88 (m, 1H), 8.02 (d, *J* = 7.9 Hz, 1H), 8.71 (d, *J* = 4.6 Hz, 1H); **^{13}C-NMR (50 MHz, $CDCl_3$):** δ 45.7, 55.4, 113.6, 117.4, 122.1, 126.4, 127.1, 127.2, 128.6, 128.9, 136.9, 143.1, 146.9, 148.8, 153.3, 199.7; **HRMS:** *m/z* calcd for $C_{20}H_{19}N_2O$(M+H): 303.1497; found: 303.1484.

3-(4-Bromophenyl)-3-(phenylamino)-1-(pyridin-2-yl)propan-1-one (6q)

Following the general procedure as described in 2.4.3, **3g** (727 mg, 6 mmol), **4b** (1.02 g, 5.5 mmol) and **5a** (465 mg, 5 mmol) gave the product **6q** (84%) as colorless solid. **MP:**



116-117 °C; **IR ($CHCl_3$):** υ 3395, 3019, 2399, 2332, 1696, 1602, 1506, 1486, 1315, 1215, 1071, 995, 876 cm^{-1}; **^{1}H-NMR (200 MHz, $CDCl_3$):** δ 3.58-3.91 (m, 2H), 4.96 (dd, *J* = 8.2, 5.2 Hz, 1H), 6.55 (d, *J* = 7.9 Hz, 2H), 6.69 (t, *J* = 7.6 Hz, 1H), 7.04-7.17 (m, 2H), 7.34-7.52 (m, 5H), 7.79-7.87 (m, 1H), 8.01 (d, *J* = 7.7 Hz, 1H), 8.70 (d, *J* = 4.3 Hz, 1H); **^{13}C-NMR (50 MHz, $CDCl_3$):** δ 45.5, 54.9, 113.6, 117.7, 120.8, 122.2, 127.3, 128.2, 129.0, 131.7, 137.0, 142.2, 146.6, 148.8, 153.1, 199.3; **MS (ESI):** *m/z* 382 (M+2, 43), 381 (M+1, 97), 380 (M, 72), 365 (19), 363 (15), 290 (66), 288 (55), 272 (65), 263 (23), 262 (84), 260 (100), 235 (13), 225 (16), 197 (28), 124 (23), 122 (81); **HRMS:** *m/z* calcd for $C_{20}H_{18}N_2OBr$ (M+H): 381.0602; found: 381.0600.

CHAPTER 3

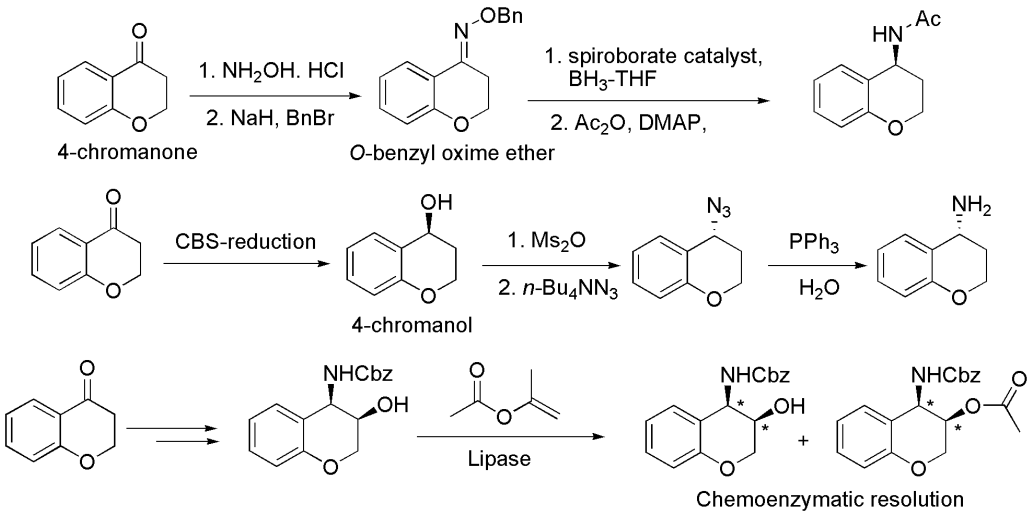
Important Uses of Mannich Adducts in the Syntheses of *O*/*N*-Heterocycles

3.1 Preamble

In Chapter 2, a new and efficient methodology for the synthesis of a variety of *β*–amino ketones (Mannich adducts) using CSA as the catalyst has been discussed. This chapter would be dedicated to the applications of some of those Mannich adducts in the synthesis of heterocycles through proper synthetic manipulations of carbonyl and amine functions. To this end, use of *β*–amino ketones as synthons in the synthesis of oxygen- and nitrogen-heterocycles such as 4-aminochromans and substituted pyrroles will be discussed.

3.1a *O*-Heterocycles: synthesis of 4-aminochromans

In view of the pharmaceutical importance of 4-aminochroman derivatives, as discussed in Chapter 1, the synthesis of their skeleton has become an interesting and challenging task for synthetic organic chemists.[76-87] To achieve its synthesis 4-chromanone has been used as the key scaffolds by many research groups (Scheme 3a).[77,78] Huang *et. al*.

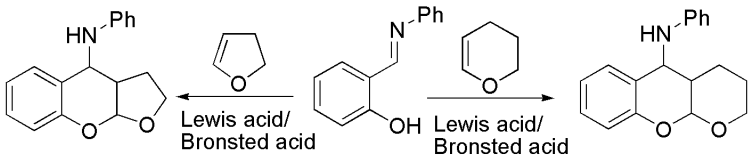


Scheme 3a: Synthesis of 4-aminochromans from 4-chromanones.

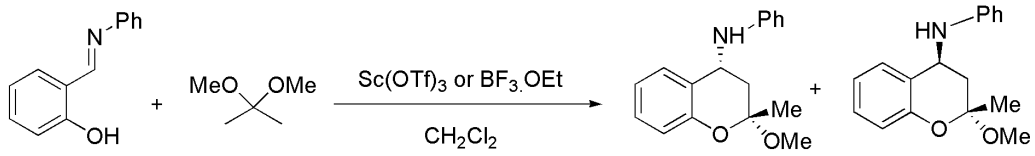
have used asymmetric borane reduction of *O*-benzyl oxime ethers derived from 4-chromanone with a spiroborate catalyst.[77a] Voight *et. al*. have successfully reduced 4-chromanone enantioselectively to 4-chromanol by Corey-Bakshi-Shibata (CBS)-reduction

followed by azide inversion and reduction to obtain 4-aminochroman skeleton.[78a] Other approaches include chemoenzymatic resolution by employing kinetic acylation of the alcohol moiety in 4-(benzyloxycarbonylamino)chroman-3-ol derived from 4-chromanone.[77b]

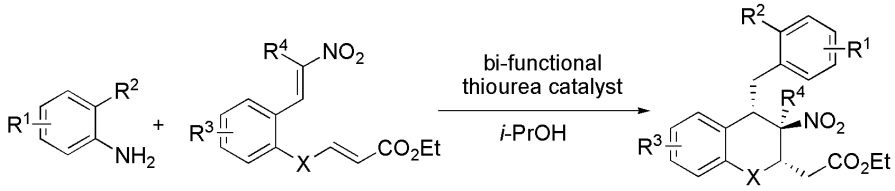
Synthesis of various fused furano and pyrano 4-amino benzopyrans derivatives has been reported by using aza-Diels-Alder type reaction of *o*-hydroxybenzaldimines and electron rich alkenes like 3,4-dihydro-2H-pyran (DHP) and 2,3-dihydrofuran (DHF) (Scheme 3b).[79-84] Different proton acids or lewis acids such as lithium tetrafluoroborate ($LiBF_4$),[79] indium trichloride ($InCl_3$),[80] PPh_3-$HClO_4$ (TPP),[81] chiral BINOL-derived phosphoric acid,[82] *N*-triflylphosphoramide[83] and molecular iodine[84] have been used as catalyst in this type of reactions. Another important approach for synthesis of this 4-aminochroman skeleton is the $Sc(OTf)_3$ or BF_3-etherate catalyzed reactions of *o*-hydroxy-benzaldimines and 2,2-dimethoxypropane (Scheme 3c).[85] Notably, Wang *et. al*. have reported asymmetric cascade aza-Michael-Michael addition reaction of anilines with nitroolefinenoates to provide 4-aminochromans in high enantioselectivities (Scheme 3d).[86] To the best of our knowledge, the only intramolecular route for synthesis of this class of compounds is indium-mediated cyclization of chiral hydrazones by Samanta *et. al*.[87] (Scheme 3e). In spite of these available methods new efficient, selective, and facile protocols are still in strong demand for synthesis of the discussed class of molecules.



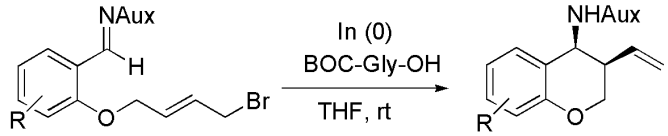
Scheme 3b: Aza-Diels-Alder type reaction of *o*-hydroxybenzaldimines.



Scheme 3c: Synthesis of 4-aminochroman derivatives using $Sc(OTf)_3$ as catalyst.



Scheme 3d: Asymmetric cascade aza-Michael-Michael addition reaction.

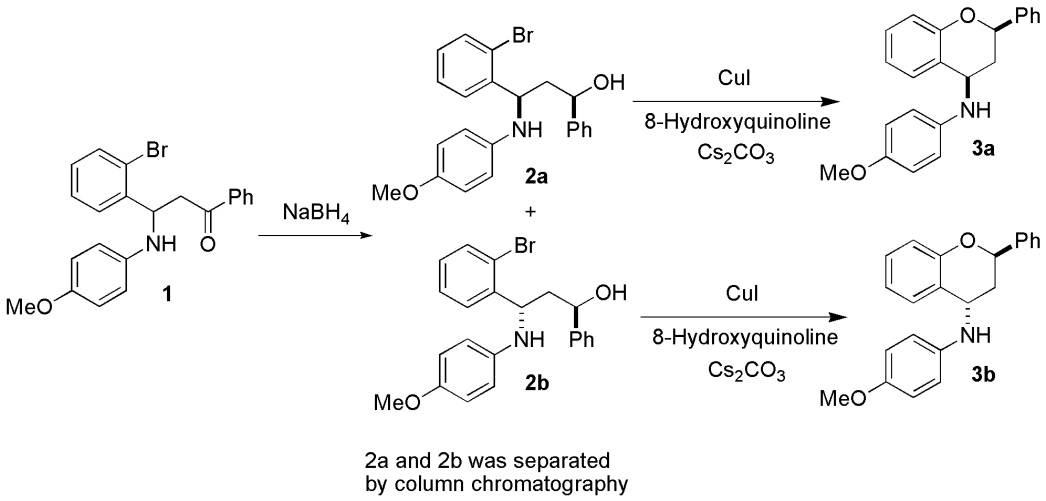


Scheme 3e: Intramolecular route to the synthesis of 4-aminochromans.

3.2a Present work: synthesis of 4-aminochromans

Earlier, Buchwald and co-workers demonstrated an elegant protocol for carbon-oxygen bond forming reaction between aryl bromides/iodides and aliphatic alcohols to produce aromatic ethers using CuI/tetramethyl-1,10-phenanthroline combination as catalyst.[88] However, the reactivity of aryl bromides in this system were poor than their iodide counterparts. Subsequently, Hu *et al.*[89] reported an alternate protocol using CuI/8-hydroxyquinoline as catalyst for carbon-oxygen bond forming reaction between alcohols and aryl bromides. Keeping this in view, we felt that the Mannich adduct derived bromo substituted *β*–aminoalcohol in principle should undergo intramolecular etherification to afford 4-aminochroman skeleton. To this end, the Mannich adduct **1** was first reduced with $NaBH_4$ to yield a mixture of *syn*- and *anti*-isomers of bromo substituted *β*–aminoalcohol (**2a** and **2b)** which were separated by column chromatography (silica). The isolated yield of **2a** and **2b** was found to be 64% and 27% respectively (Scheme 3f). To our delight, both

2a (Fig. 3a) and **2b** (Fig. 3b) underwent intramolecular etherification using CuI/8-hydroxyquinoline combination as catalyst affording 4-aminochromans **3a** and **3b** respectively albeit in moderate yields of 38% and 35% respectively (Scheme 3f).



Scheme 3f: Synthesis of 4-aminochromans from Mannich adduct.

As the relative stereochemistry of **3a** (Fig. 3c) and **3b** (Fig. 3d) could not be ascertained from their ^{1}H-NMR spectral data, we opted for XRD spectra to determine the relative stereochemistry between C(2) and C(4). Although suitable single crystal of **3a** was obtained, inspite of many trials quality crystals of **3b** for XRD was not obtained. Single-crystal XRD data of **3a** revealed its *cis*-geometry [(2*R**,4*R**)-3,4-dihydro-*N*-(4-methoxyphenyl)-4-amino-2-phenyl-2H-chromene] (Fig. 3e, Table 3a). On the basis of the XRD data of **3a**, compound **3b** was designated as *trans*-isomer, [(2*R**,4*S**)-3,4-dihydro-*N*-(4-methoxyphenyl)-4-amino-2-phenyl-2H-chromene]. Accordingly, compounds **2a** and **2b** were designated as *anti*-[(1*R**,3*R**)-3-(4-methoxyphenylamino)-3-(2-bromophenyl)-1-phenyl-propan-1-ol] and *syn*-isomer [(1*R**,3*S**)-3-(4-methoxyphenylamnio)-3-(2-bromophenyl)-1-phenyl-propan-1-ol] respectively. Thus a single Mannich adduct could be successfully converted to two geometrical isomers of 4-aminochromans. It is important to mention that although various catalysts have been developed and successfully used for

Mannich type reaction so far, this is the first report on the utilization of the aromatic ketone derived Mannich adduct in the synthesis of *O*-heterocycles.

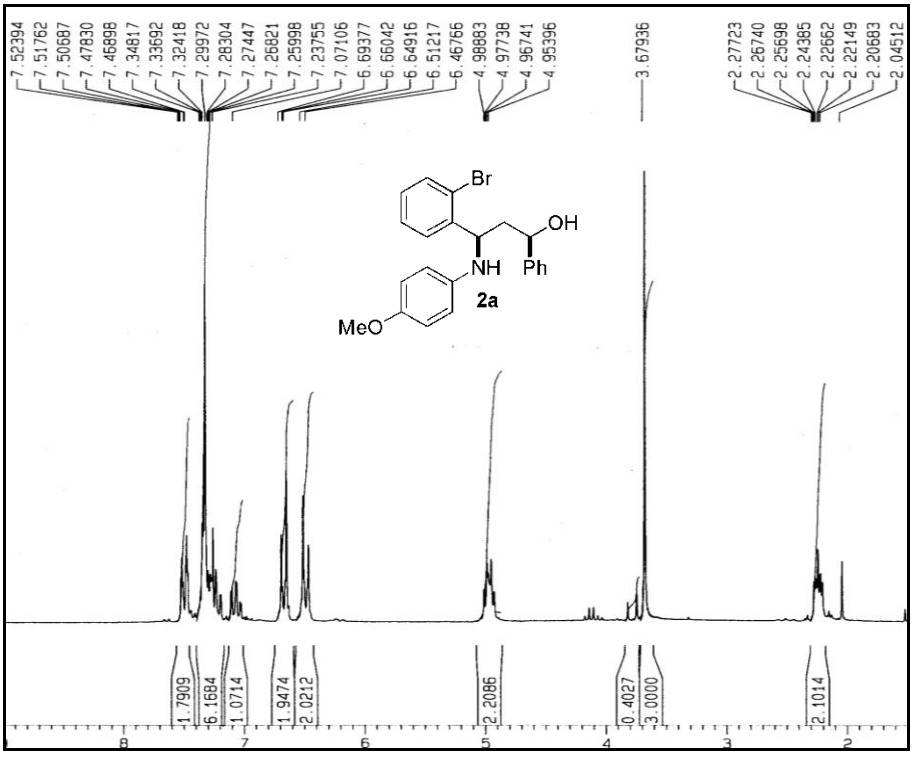


Figure 3a: ^{1}H-NMR of **2a**.

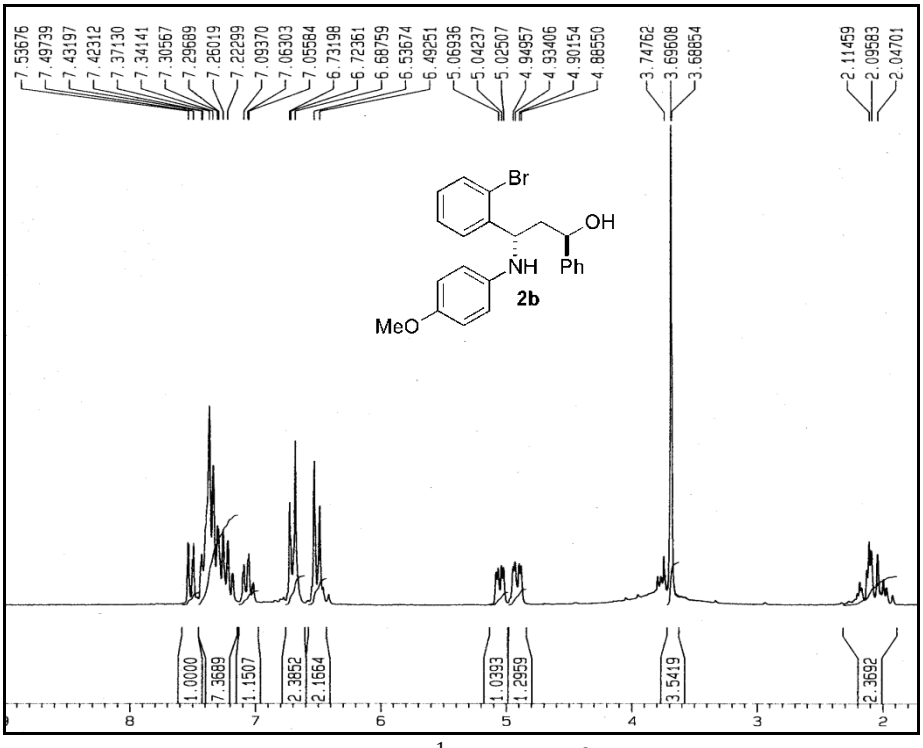


Figure 3b: ^{1}H-NMR of **2b**.

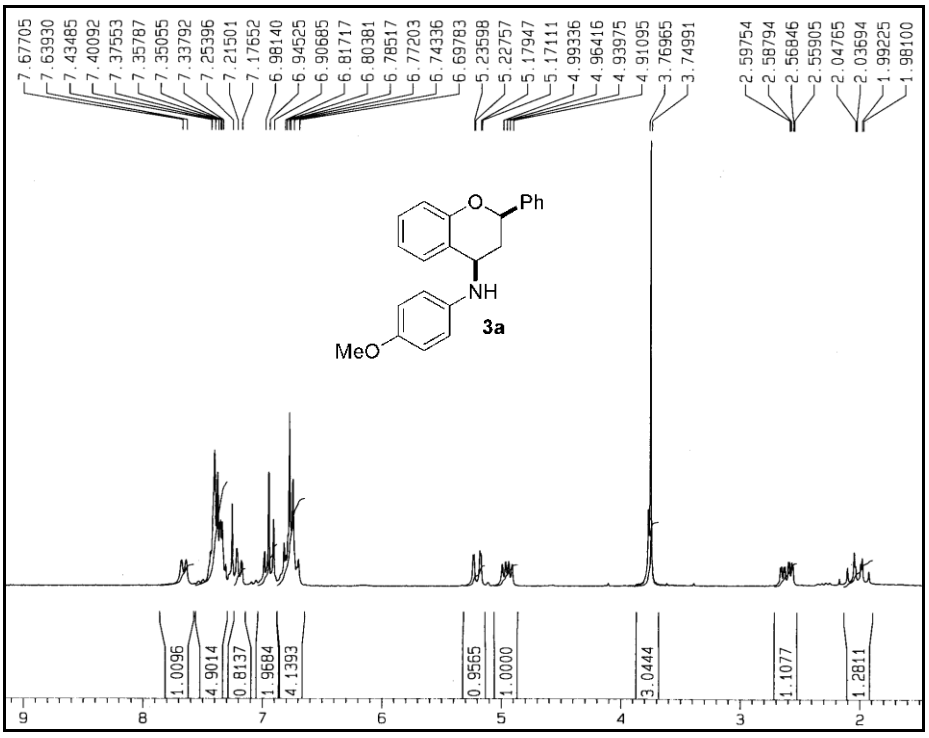


Figure 3c: ^{1}H-NMR of **3a**.

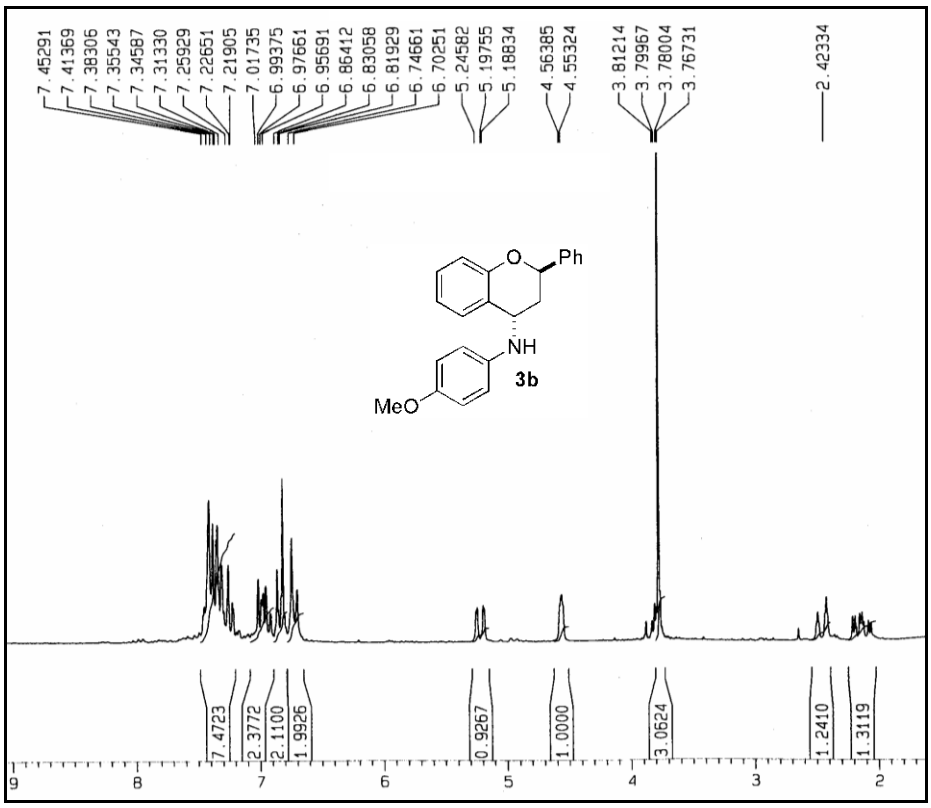


Figure 3d: ^{1}H-NMR of **3b**.

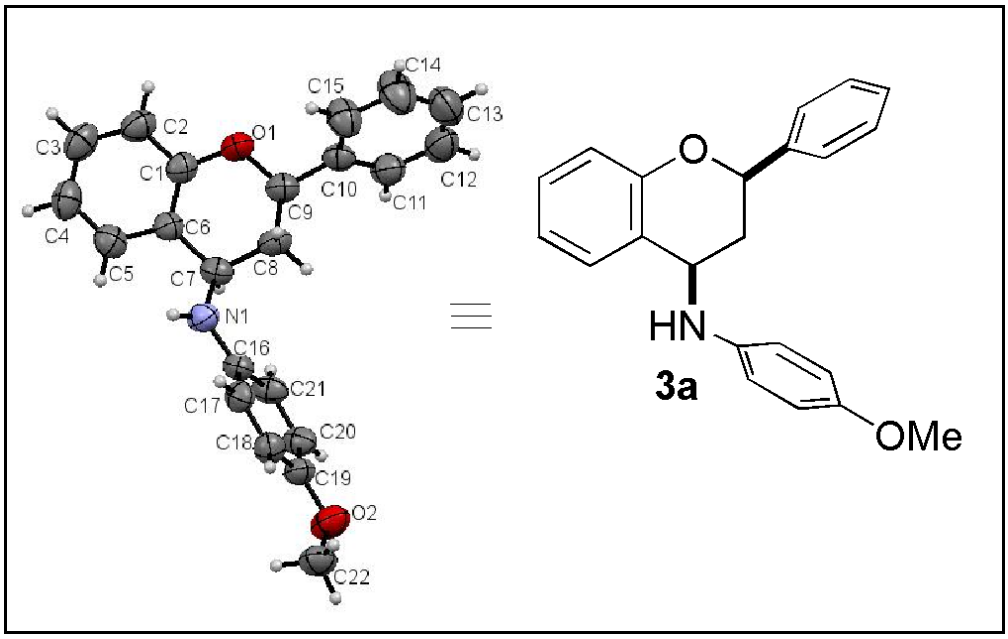


Figure 3e: ORTEP diagram of compound **3a**.

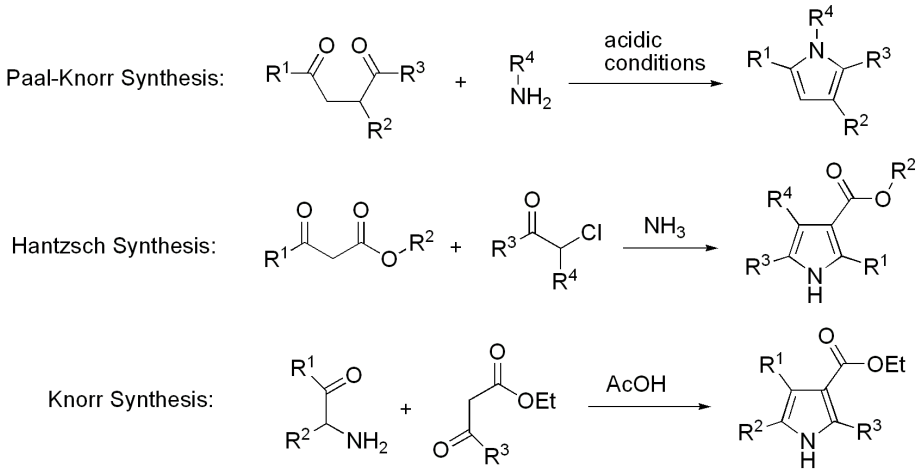
Table 3a: Crystal data and structure refinement for **3a**

Identification code	barc025
Empirical formula	C22 H21 N O2
Formula weight	331.40
Temperature	293(2) K
Wavelength	0.71073 A
Crystal system, space group	Orthorhombic, P c a b
Unit cell dimensions	a = 8.5808(7) A alpha = 90 deg.
	b = 46.211(4) A beta = 90 deg.
	c = 8.7745(8) A gamma = 90 deg.
Volume	3479.3(5) A^3
Z, Calculated density	8, 1.265 Mg/m^3
Absorption coefficient	0.081 mm^-1
F(000)	1408
Crystal size	0.32 x 0.28 x 0.23 mm
Theta range for data collection	3.35 to 25.00 deg.

Limiting indices	-10<=h<=10, -54<=k<=54, -8<=l<=10
Reflections collected / unique	24296 / 3063 [R(int) = 0.0859]
Completeness to theta = 25.00	99.8 %
Absorption correction	Semi-empirical from equivalents
Max. and min. transmission	0.9817 and 0.9747
Refinement method	Full-matrix least-squares on F^2
Data / restraints / parameters	3063 / 0 / 227
Goodness-of-fit on F^2	0.862
Final R indices [I>2sigma(I)]	R1 = 0.0497, wR2 = 0.0941
R indices (all data)	R1 = 0.1316, wR2 = 0.1117
Largest diff. peak and hole	0.251 and -0.235 e.A^-3

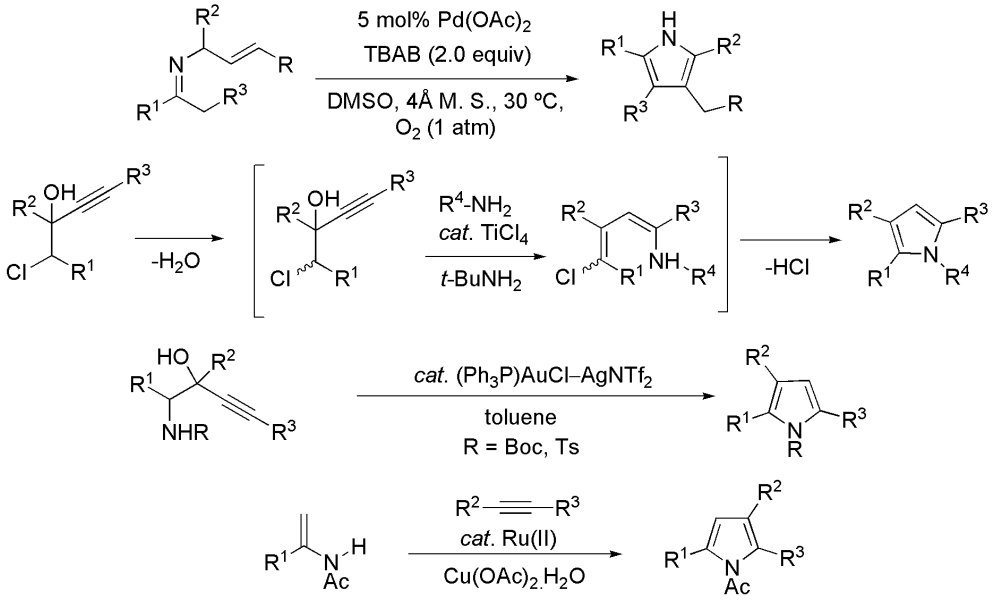
3.1b *N*-Heterocycles: synthesis pyrrole derivatives

As discussed in Chapter 1, pyrroles and their derivatives are one of the most important class of *N*-heterocycles abundant in a broad range of bioactive natural products, drug molecules and new organic materials. In view of its importance, their synthetic methods have gained much attention and a lot of amazing progress has been achieved in the past decades.[90] The construction of the pyrrole ring system typically involves a multistep approach from preformed intermediates. Classical methods (Scheme 3g) for synthesis of substituted pyrroles are i) Paal-Knorr cyclization reaction of 1,4-diketones and amines,[91] ii) Hantzsch pyrrole synthesis, based on the reaction between β-ketoesters, ammonia (or amines) and α-haloketones[92] and iii) Knorr reaction of α-aminoketones and β-ketoesters.[93] Besides classical pyrrole synthesis, efficient and benign approaches, using new building blocks as well as transition metal catalyzed synthetic methodologies have been developed to access multi-functionalized pyrroles.[94] Some contemporary



Scheme 3g: Classical route to the synthesis of pyrroles.

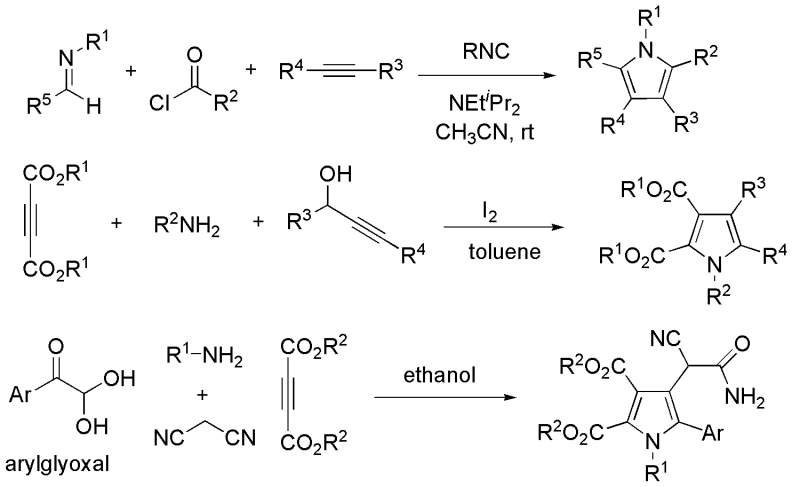
transition-metal-based strategies (Scheme 3h) include aerobic palladium(II)-catalyzed C-H dehydrogenative intramolecular cyclization of imines,[95] titanium-catalyzed intermolecular hydroaminations of (*E*/*Z*)-chloroenynes,[96] cationic gold(I)-mediated intramolecular cyclization of 1-amino-3-alkyn-2-ols,[97] ruthenium-catalyzed oxidative annulation of enamides with alkynes.[98]



Scheme 3h: Transition metal catalyzed strategies for synthesis of substituted pyrroles.

However, an alternate and more direct strategy to afford the pyrrole core is the combination of multiple reactants in a single flask (multicomponent reactions, MCR)

(Scheme 3i).[99] The direct synthesis of pyrroles from imines, acid chlorides, and alkynes mediated by isocyanides have been reported[100] by Arndtsen *et.al*. Recently, one-pot iodine catalyzed synthesis of penta substituted pyrroles has been reported from propargylic alcohols, amines, and di-alkylacetylenedicarboxylates.[101] Another four-component domino



Scheme 3i: Synthesis of pyrrole derivatives by employing MCR strategy.

reaction of arylglyoxal monohydrate, aniline, dialkyl but-2-ynedioate and malononitrile has been developed by Feng *et. al*.[102] However, some of these new methods have significant limitations, such as tedious workup procedures, harsh reaction conditions, low yields, long reaction times *etc*. Therefore, a simple, efficient method for pyrrole synthesis employing simple building blocks which can be prepared by minimum number of steps still remains an attractive goal.

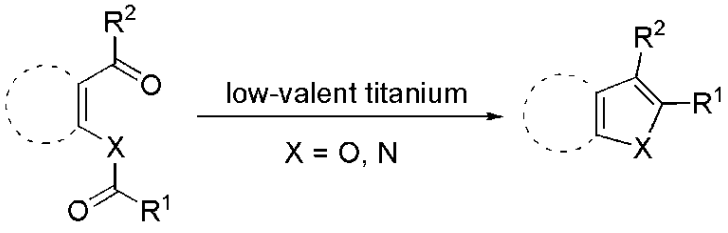
3.2b Present work: synthesis of densely substituted pyrroles

As mentioned earlier, we have developed a CSA catalyzed protocol for the library synthesis of *β*–amino ketones (Mannich adducts). In continuation to our efforts towards the development of newer synthetic methodologies, and the increasing importance on the synthesis of substituted pyrroles, herein we have developed an efficient low-valent

titanium reagent mediated synthesis of densely substituted pyrroles from *β*-amino-carbonyl compounds *via* intra-molecular reductive deoxygenation of keto-amides.

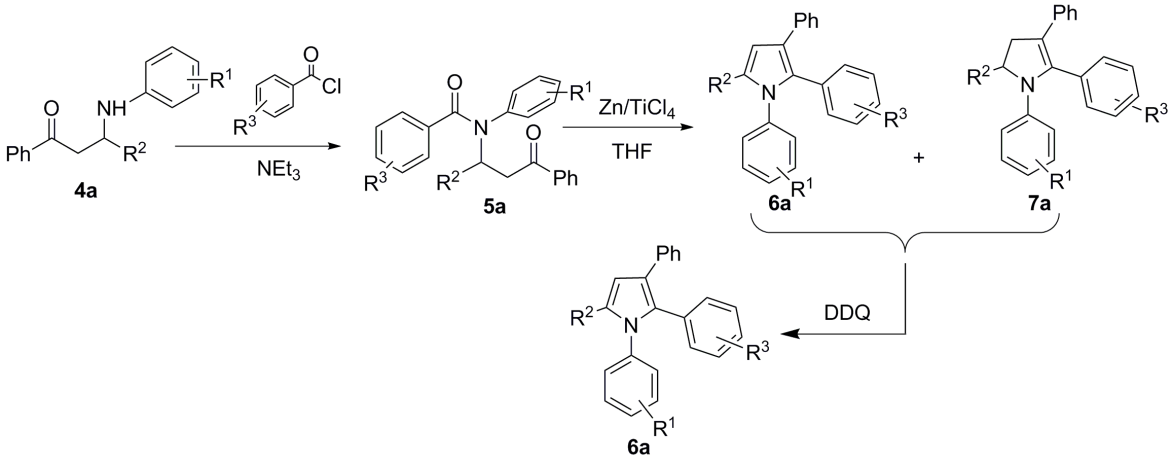
Low-valent titanium mediated intra-molecular reductive deoxygenation in keto-amides

Low-valent titanium mediated reductive coupling of carbonyl compounds commonly known as McMurry reactions after one of the discoverers, has acquired great importance in preparative organic chemistry as it has served as key steps in a variety of applications such as synthesis of strained olefins, heterocyclic compounds, and macrocyclic ring systems to complex natural products including paclitaxel.[103] The uniqueness of this low valent titanium (LVT) reagent lies in its high oxophilicity and reducing ability. Over the years, considerable effort has been made to extend the scope of this low–valent titanium chemistry beyond the classical reductive dimerization of aldehydes and ketones to alkenes (McMurry reaction).[104] Titanium has been efficiently used to promote intramolecular coupling of carbonyl groups with distinctly different redox potentials such as oxo-ester or oxo-amide for synthesis of different heterocycles[105] (Scheme 3j). Keeping this in view, we envisaged that the Mannich adduct derived benzamides can be used in the synthesis of pyrrole skeleton by means of intra-molecular keto-amide coupling. For our initial studies, *β*-amino ketone (**4a**) derived from acetophenone, benzaldehyde and aniline was reacted with benzoyl chloride in presence of



Scheme 3j: Low-valent titanium induced oxo-ester or oxo-amide coupling.

triethylamine to afford corresponding benzamide (**5a**, Fig. 3f) in 80% yield (Scheme 3k). Earlier, LVT mediated intra-molecular reductive deoxygenation of keto-ester and keto-amides to corresponding benzo[*b*]furan and indoles have been developed in our laboratory.[105h,i] In view of this, we attempted intra-molecular keto-amide coupling of **5a** in the presence of the LVT reagent ($TiCl_4$/Zn/THF). To our delight, successful intra-molecular reductive deoxygenation occurred to afford a mixture of desired 2,3-dihydro-1,2,4,5-tetraphenylpyrrole (**7a**) and 1,2,3,5-tetraphenylpyrrole (**6a**) (Scheme 3k).



Scheme 3k: Synthesis of densely substituted pyrroles from Mannich adduct.

Since compound **6a** and **7a** have close R_f in TLC and are very difficult to be separated by column chromatography the mixture of these pyrrole products were subjected to oxidation with 2,3-dichloro-5,6-dicyano-1,4-benzoquinone (DDQ) (Scheme 3k). In this reaction the mixture of **6a** and **7a** got converted into a single product 1,2,3,5-tetraphenyl-1-*H*-pyrrole (**6a**). The pyrrole product (**6a**) was characterized by ^{1}H-NMR (Fig. 3g, the aromatic proton of the pyrrole ring was assigned at δ = 6.72 ppm), ^{13}C-NMR (Fig. 3h, the unsubstituted aromatic carbon of the pyrrole ring was assigned at δ = 110.0 ppm) and mass spectrum.

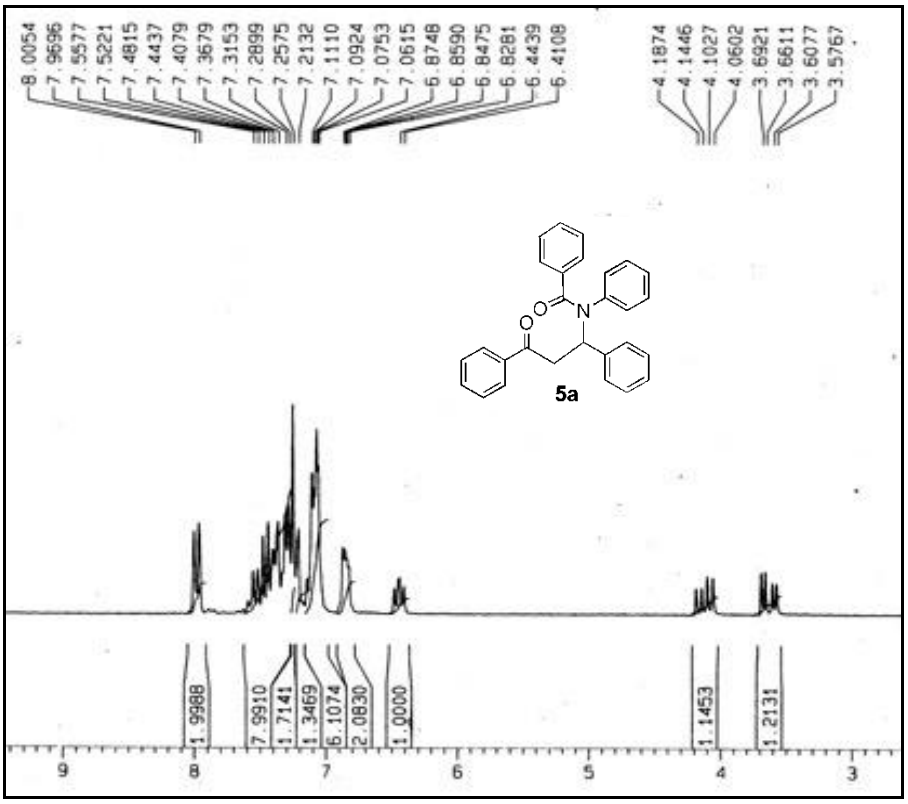


Figure 3f: ^{1}H-NMR of **5a**.

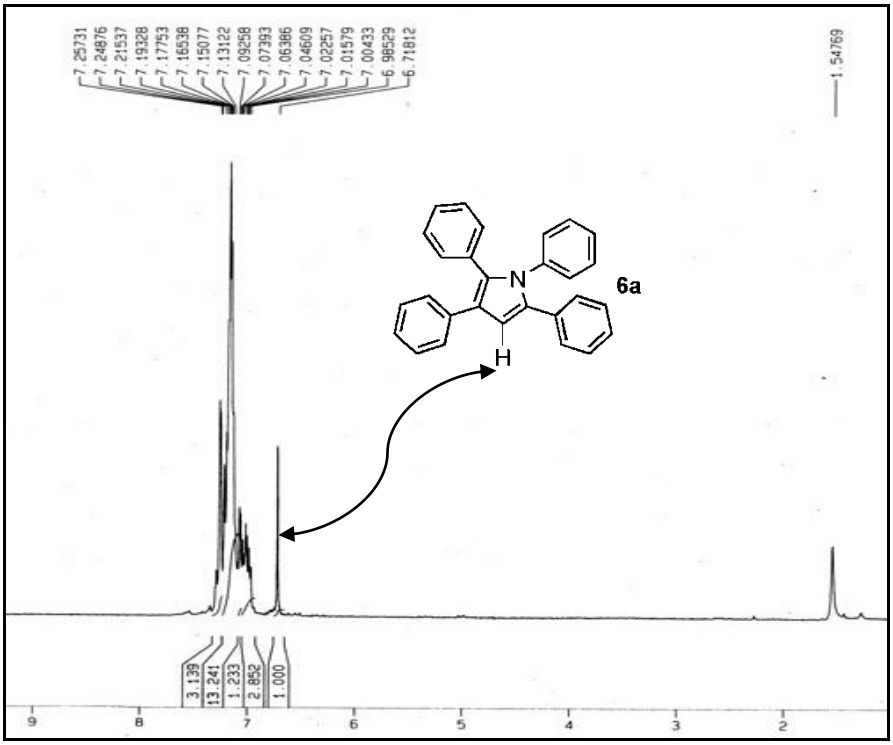


Figure 3g: ^{1}H-NMR of **6a**.

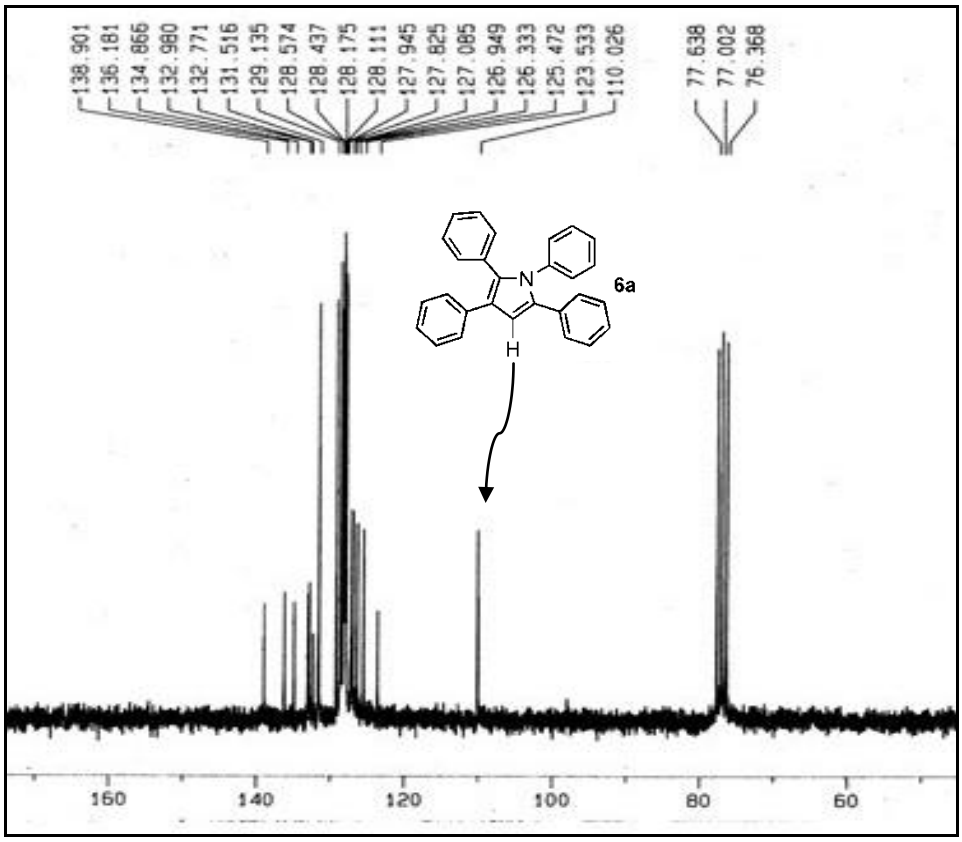
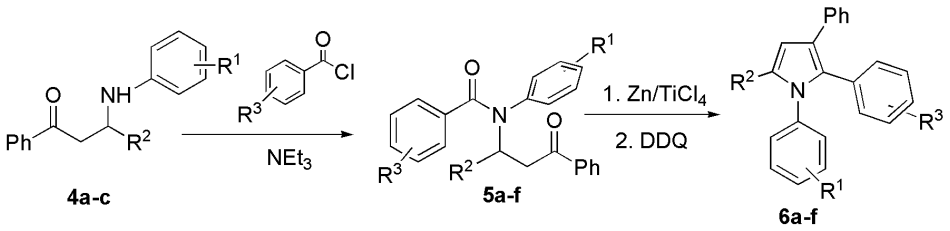


Figure 3h: ^{13}C-NMR of **6a**.

To see the scope and limitations of our protocol a series of benzamides (**5a-f**) were synthesized by reacting different Mannich adducts (**4a-c**) with different benzoyl chlorides with varied substitutions in good to excellent yields (80-98%, Table 3b). After successful synthesis of these Mannich-adduct derived β-amido-carbonyl compounds, each of them was subjected to low-valent titanium mediated reductive intra-molecular keto-amide coupling. In all the cases, we got a mixture of dihydropyrrole and pyrrole as the product. DDQ oxidation of the mixture of these pyrrole products gave the tetra/triphenyl substituted pyrrole in moderate to good yield (40-70%, Table 3b). Incidentally, this is the first approach towards the synthesis of densely substituted pyrroles (Fig. 3i) from Mannich adducts using LVT chemistry.

Table 3b: Synthesis of substituted pyrroles



Entry	**4**	R^3	% Yield[a] of **5**	% Yield[b] of **6**
1	**4a** (R^1 = H, R^2 = Ph)	H	80 (**5a**)	65 (**6a**)
2	**4a** (R^1 = H, R^2 = Ph)	3-OMe	97 (**5b**)	67 (**6b**)
3	**4a** (R^1 = H, R^2 = Ph)	4-OMe	83 (**5c**)	63 (**6c**)
4	**4a** (R^1 = H, R^2 = Ph)	2-OMe	98 (**5d**)	40 (**6d**)
5	**4b** (R^1 = H, R^2 = 3-OMeC_6H_5)	H	82 (**5e**)	42 (**6e**)
6	**4c** (R^1 = 4-OMe, R^2 = H)	H	99 (**5f**)	70 (**6f**)

[a]Isolated yield of **5**; [b] Two steps yield of **6.**

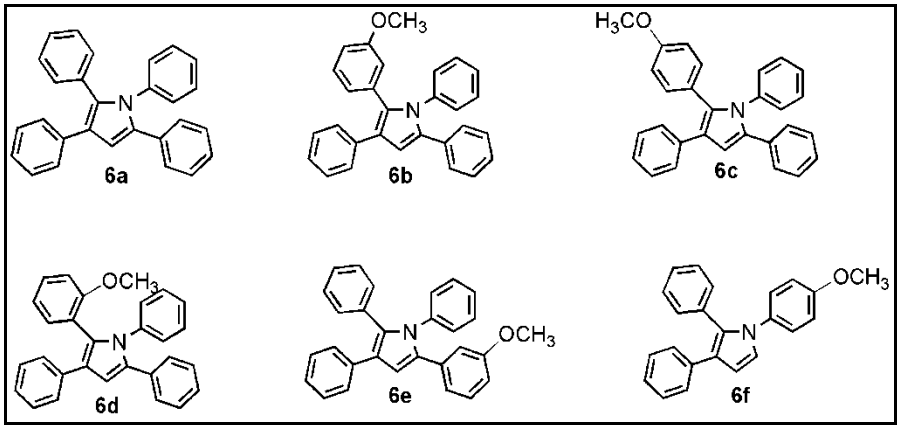


Figure 3i: Library synthesis of pyrroles.

3.3 Conclusion

In conclusion, a simple, efficient and practical method for the synthesis of oxygen-heterocycles, namely, 4-aminochromans from Mannich adducts, synthesized by our protocol has been developed *via* an unprecedented route involving intramolecular etherification with CuI/8-hydroxyquinoline.[75] As another application of the versatile Mannich bases we have optimized a reaction methodology to convert *β*–amino carbonyl compounds to pyrroles. Towards this, Mannich adduct derived from acetophenone, benzaldehyde and aniline was reacted with benzoyl chloride in presence of triethylamine to get the corresponding benzamide. And finally, intramolecular keto-amide coupling in the presence of the LVT reagent followed by DDQ oxidation produced our desired product, pyrrole. Further, a series of benzamides, synthesized from various Mannich adducts with different benzoyl chlorides were used to make a library of highly substituted pyrroles.

3.4 Experimental

3.4.1 Synthesis of the Mannich adduct 1

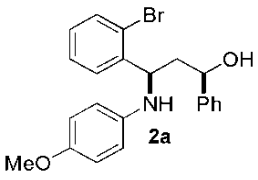
Reaction procedures and characterization data of compound **1** are described in Chapter 2 (experimental section, 2.4.3).

3.4.2 Typical procedure for the syntheses of *β*-aminoalcohols 2a and 2b

To a stirred solution of **1** (4.87 g, 11.9 mmol) in dry methanol (25 ml) at 0-5 °C was added $NaBH_4$ (0.45 g, 11.9 mmol) portion wise. After stirring for 2.5 h at 0 °C, the reaction mixture was quenched with saturated aqueous NH_4Cl solution. Methanol was removed under vacuo, extracted with ethylacetate, washed with water, brine and dried (Na_2SO_4). Removal of solvent yielded the crude product, which was purified by silica gel column chromatography to afford pure *β*–aminoalcohols, **2a** (64%) and **2b** (27%).

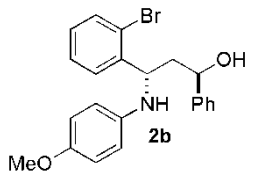
3-(4-Methoxyphenylamino)-3-(2-bromophenyl)-1-phenylpropan-1-ol (2a)

IR (neat): υ 3427, 3061, 3028, 2830, 1882, 1809, 1619, 1514, 1454, 1232, 1024, 913 cm^{-1}; **^{1}H-NMR (200 MHz, $CDCl_3$):** δ 2.21-2.28 (m, 2H), 3.68 (s, 3H), 4.93-5.01 (m, 2H), 6.49 (d, *J* = 8.9 Hz, 2H), 6.67 (d, *J* = 8.9 Hz, 2H), 7.03-7.10 (m, 1H), 7.19-7.35 (m, 6H), 7.47-7.52 (m, 2H); **^{13}C-NMR (50 MHz, $CDCl_3$):** δ 43.8, 55.5, 71.9, 114.7, 114.8, 122.7, 125.6, 127.3, 127.5, 127.8, 128.3, 132.9, 140.6, 141.8, 144.0, 152.0; **HRMS:** *m/z* calcd for $C_{22}H_{23}NO_2Br$ (M+H): 412.0912; found: 412.0906.



3-(4-Methoxyphenylamino)-3-(2-bromophenyl)-1-phenylpropan-1-ol (2b)

IR (neat): υ 3378, 3062, 2929, 1618, 1604, 1566, 1513, 1463, 1237, 1036, 914, 754 cm^{-1}; **^{1}H-NMR (200 MHz, $CDCl_3$):** δ 2.00-2.19 (m, 2H), 3.70 (s, 3H), 4.92 (dd, *J* = 9.7, 3.1 Hz, 1H), 5.06 (dd, *J* = 8.8, 3.4 Hz, 1H), 6.51 (d, *J* = 8.8 Hz, 2H), 6.71 (d, *J* = 8.8 Hz, 2H), 7.01-7.09 (m, 1H), 7.18-7.43 (m, 7H), 7.52 (d, *J* = 7.9 Hz, 1H); **^{13}C-NMR (50 MHz, $CDCl_3$):** δ 45.7, 55.5, 58.2, 74.3, 114.7, 115.4, 122.7, 125.5, 127.4, 127.6, 128.3, 132.8, 140.7, 142.3, 144.2, 152.4; **HRMS:** *m/z* calcd for $C_{22}H_{23}NO_2Br$ (M+H): 412.0912; found: 412.0910.



3.4.3 Typical procedure for the synthesis of 4-aminochroman (3a) from *β*-aminoalcohol (2a)

To a mixture of CuI (0.02 g, 0.1 mmol), 8-hydroxyquinoline (0.03 g, 0.2 mmol) and Cs_2CO_3 (1.30 g, 4 mmol) at ambient temperature under argon, was added a solution of compound **2a** (0.82 g, 2 mmol) in dry toluene (5 ml). The reaction mixture was further refluxed for 24 h when TLC showed the total consumption of **3a**. The reaction mixture was brought to room temperature and diluted with dichloromethane (20 ml). The brown slurry was passed through Celite pad to remove the inorganic salts. Dichloromethane was

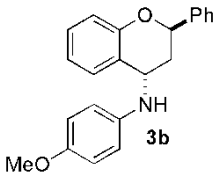
removed under vacuo and the crude residue was purified by silica gel column chromatography to afford colorless solid 4-aminochroman **3a (**38%).

4-(4-Methoxyphenylamino)-2-phenylchroman (3a)

MP: 118-119 °C; **IR ($CHCl_3$):** υ 3399, 3064, 2922, 1609, 1579, 1511, 1484, 1232, 1035, 916, 759, 698 cm^{-1}; **^{1}H-NMR (200 MHz, $CDCl_3$):** δ 1.93-2.17 (m, 1H), 2.61 (ddd, *J* = 13.4, 5.8, 1.9 Hz, 1H), 3.75 (s, 3H), 4.95 (dd, *J* = 10.7, 5.8 Hz, 1H), 5.20 (dd, *J* = 11.3, 1.9 Hz, 1H), 6.70-6.82 (m, 4H), 6.91-6.98 (m, 2H), 7.18-7.22 (m, 1H), 7.31-7.43 (m, 5H), 7.66 (d, *J* = 7.6 Hz, 1H); **^{13}C-NMR (50 MHz, $CDCl_3$):** δ 37.3, 50.4, 55.8, 77.5, 115.1, 115.3, 116.9, 120.9, 124.7, 126.0, 127.5, 128.0, 128.6, 128.8, 140.8, 141.0, 152.7, 155.1; **HRMS:** *m/z* calcd for $C_{22}H_{22}NO_2$ (M+H): 332.1651; found: 332.1635. **X-Ray crystallographic data:** Single crystal X-ray structural studies of **6a** were performed on a CCD Oxford Diffraction XCALIBUR-S diffractometer. Data were collected at 293(2) K using graphite-monochromated Mo K_α radiation (λ_α = 0.71073 Å). The structure was solved by direct methods using SHELXS-97 and refined by full matrix least-squares with SHELXL-97, refining on F^2. The positions of all the atoms were obtained by direct methods. All non-hydrogen atoms were refined anisotropically. Formula: $C_{22}H_{21}NO_2$, *M* = 331.40, colorless crystals, crystal size: 0.32 × 0.28 × 0.23 mm^3, orthorhombic, space group: Pcab, cell parameters: a = 8.5808(7) Å, b = 46.211(4) Å, c = 8.7745 Å, α = 90°, β = 90°, γ = 90°, V = 3479.3(5) $Å^3$, ρ_{calcd}= 1.265 mg/m^3, μ = 0.081 mm^{-1}, Z = 8, of 24296 reflections, 3063 were unique. CCDC-828034 contains the supplementary crystallographic data (excluding structure factors) for the structure in this paper. Copies of these data can be obtained, free of charge from The Cambridge Crystallographic Data Centre *via www.ccdc.cam.ac.uk/data_request/cif*.

4-(4-Methoxyphenylamino)-2-phenylchroman (3b)

Following the procedure as described in 3.4.3, the product **3b** was isolated as viscous oil (35%). **IR ($CHCl_3$):** υ 3402, 3013, 2916, 1608, 1509, 1460, 1218, 1034, 769 cm^{-1}; **^{1}H-NMR (200 MHz, $CDCl_3$):** δ 2.06-2.21 (m, 1H), 2.41-2.49 (m, 1H), 3.78 (s, 3H), 4.55-4.58 (m, 1H), 5.22 (dd, *J* = 11.5, 1.8 Hz, 1H), 6.72 (d, *J* = 8.8 Hz, 2H), 6.84 (d, *J* = 8.8 Hz, 2H), 6.96-7.02 (m, 2H), 7.22-7.45 (m, 7H); **^{13}C-NMR (50 MHz, $CDCl_3$):** δ 35.4, 49.0, 55.8, 73.6, 115.2, 117.4, 120.8, 122.2, 126.2, 127.9, 128.5, 129.4, 130.5, 141.0, 153.0, 155.2; **HRMS:** *m/z* calcd for $C_{22}H_{22}NO_2$ (M+H): 332.1651; found: 332.1645.



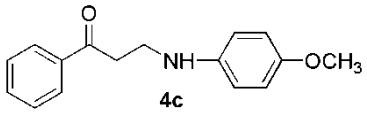
3b

3.4.4 Synthesis of the Mannich adduct 4

Reaction procedures and characterization data of compound **4a**, **4b** are described in Chapter 2 (experimental section, 2.4.3).

1-Phenyl-3-(phenylamino)propan-1-one (4c)

To a mixture of 4-methoxyanisole (1.86 g, 15 mmol), paraformaldehyde (0.50 g, 16.5 mmol) and acetophenone (2.16 g, 18.0 mmol), (±)-CSA (0.17 g, 0.75 mmol) was added and the mixture was stirred at ambient temperature. After 20 h, the reaction mixture was quenched with 10% aqueous $NaHCO_3$ solution, extracted with ethyl acetate, washed with water, brine and dried (Na_2SO_4). Removal of solvent yielded the crude product which was purified by column chromatography over silica gel to give the pure Mannich adduct (**4c**) as colorless solid in 52% yield. **IR (thin flim):** υ 3360, 3001, 2902, 2833, 1672, 1504, 1409, 1379, 1282, 1205, 1182, 1112, 1033, 817, 688 cm^{-1}; **^{1}H-NMR (200 MHz, $CDCl_3$):** δ 3.31 (t, *J* = 6.1 Hz, 2H), 3.58 (t, *J* = 6.1 Hz, 2H), 3.75 (s, 3H), 6.69-6.78 (m, 4H), 7.42-7.57 (m, 3H), 7.91-7.96 (m, 2H); **^{13}C-**



4c

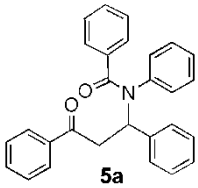
NMR (50 MHz, $CDCl_3$): δ 37.6, 40.0, 55.7, 114.7, 114.9, 128.0, 128.6, 133.3, 136.7, 141.7, 152.4, 199.3.

3.4.5 General procedure for the benzoylation of Mannich adduct

Benzoyl chloride/ substituted benzoyl chloride (1.5 equiv.) was added to a mixture of Mannich adducts (1 equiv.) and triethylamine (1.5 equiv.) in dry dichloromethane at 0 °C under argon atmosphere with constant stirring. Then the reaction mixture was allowed to come to room temperature (25 °C). After completion of the reaction, dichloromethane was evaporated out and the reaction mixture was quenched with water and extracted three times with ethylacetate. The organic extracts were combined, washed with brine, dried over anhydrous Na_2SO_4 and concentrated under reduced pressure. The residue was purified by column chromatography on silica gel using hexane/ethylacetate as eluent to give the benzoylated Mannich adducts, **5**.

***N*-(3-oxo-1,3-diphenylpropyl)-*N*-phenylbenzamide (5a)**

Following the general procedure as described in 3.4.5, Mannich adduct **4a** (4.0 g, 13.3 mmol), benzoylchloride (2.81 g, 20.0 mmol) and triethylamine (2.02 g, 20.0 mmol) gave



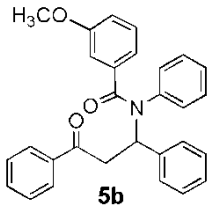
5a

the benzoylated-Mannich adduct **5a** (4.30 g, 80%). **IR (thin flim):** υ 3007, 1681, 1639, 1593, 1577, 1490, 1446, 1319, 1213, 1076, 1028, 987, 746, 690 cm^{-1}; **^{1}H-NMR (200 MHz, $CDCl_3$):** δ 3.63 (dd, *J* = 16.9, 6.2 Hz, 1H), 4.12 (dd, *J* = 16.9, 8.5 Hz, 1H), 6.44 (t, *J* = 8.0 Hz, 1H), 6.83-6.87 (m, 2H), 7.06-7.15 (m, 6H), 7.21-7.59 (m, 10H), 7.99 (d, *J* = 7.2 Hz, 2H); **^{13}C-NMR (50 MHz, $CDCl_3$):** δ 40.6, 58.4, 127.1, 127.4, 127.6, 128.0, 128.1, 128.3, 128.5, 129.1, 129.7, 129.9, 133.0, 136.7, 136.8, 139.5, 141.5, 171.0, 197.5.

3-Methoxy-*N*-(3-oxo-1,3-diphenylpropyl)-*N*-phenylbenzamide (5b)

Following the general procedure as described in 3.4.5, Mannich adduct **4a** (1.50 g, 5.0

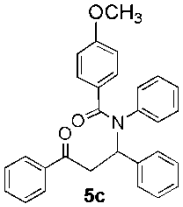
mmol), 3-methoxybenzoylchloride (1.28 g, 7.5 mmol) and triethylamine (0.76 g, 7.5 mmol) gave the benzoylated-Mannich adduct **5b** (2.10 g, 97%). **IR (thin flim):** υ 3061, 1672, 1636, 1595, 1585, 1496, 1366, 1211, 1135, 1036, 943, 804, 771, 690 cm^{-1}; **^{1}H-NMR (200 MHz, $CDCl_3$):** δ 3.62 (s, 3H), 3.64 (dd, *J* = 11.2, 4.4 Hz, 1H), 4.12 (dd, *J* = 11.2, 5.7 Hz, 1H), 6.43-6.47 (m, 1H), 6.67-6.71 (m, 1H), 6.78-6.88 (m, 4H), 6.98 (t, *J* = 5.1 Hz, 1H), 7.08-7.10 (m, 3H), 7.28-7.58 (m, 8H), 7.98 (d, *J* = 5.0 Hz, 2H); **^{13}C-NMR (50 MHz, $CDCl_3$):** δ 40.4, 55.0, 58.2, 113.3, 115.6, 120.9, 127.1, 127.6, 128.0, 128.3, 128.5, 128.6, 129.5, 133.1, 136.7, 137.8, 139.4, 141.4, 158.6, 170.6, 197.5.



5b

4-Methoxy-*N*-(3-oxo-1,3-diphenylpropyl)-*N*-phenylbenzamide (5c)

Following the general procedure as described in 3.4.5, Mannich adduct **4a** (1.50 g, 5.0 mmol), 4-methoxybenzoylchloride (1.28 g, 7.5 mmol) and triethylamine (0.76 g, 7.5 mmol) gave the benzoylated-Mannich adduct **5c** (1.8 g, 83%). **IR (thin flim):** υ 3048, 1672, 1647, 1595, 1527, 1450, 1343, 1251, 1171, 1020, 876, 833, 700, 690 cm^{-1}; **^{1}H-NMR (200 MHz, $CDCl_3$):** δ 3.65 (dd, *J* = 18.0, 6.4 Hz, 1H), 3.68 (s, 3H), 4.12 (dd, *J* = 18.0, 8.2 Hz, 1H), 6.36-6.40 (m, 1H), 6.58 (d, *J* = 8.8 Hz, 2H), 6.84-6.89 (m, 2H), 6.93-6.98 (m, 1H), 7.08-7.12 (m, 3H), 7.18-7.23 (m, 2H), 7.26-7.64 (m, 7H), 7.95-7.99 (m, 2H); **^{13}C-NMR (50 MHz, $CDCl_3$):** δ 40.6, 55.0, 58.6, 112.8,113.7, 120.3, 126.9, 128.0, 128.3, 128.5, 128.7, 128.8, 129.5, 130.5, 133.1, 136.7, 139.5, 142.1, 160.2, 170.6, 197.7.

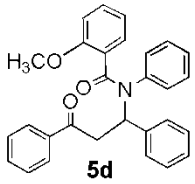


5c

2-Methoxy-*N*-(3-oxo-1,3-diphenylpropyl)-*N*-phenylbenzamide (5d)

Following the general procedure as described in 3.4.5, Mannich adduct **4a** (1.50 g, 5.0 mmol), 2-methoxybenzoylchloride (1.28 g, 7.5 mmol) and triethylamine (0.76 g, 7.5 mmol) gave the benzoylated-Mannich adduct **5d** (2.13 g, 98%). **IR (thin flim):** υ 3059,

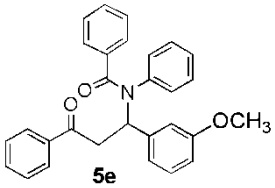
2833, 1690, 1644, 1598, 1491, 1449, 1389, 1372, 1334, 1248, 983, 744, 698 cm^{-1}; **^{1}H-NMR (200 MHz, $CDCl_3$):** δ 3.65 (dd, *J* = 18.0, 6.4 Hz, 1H), 3.68 (s, 3H), 4.12 (dd, *J* = 18.0, 8.2 Hz, 1H), 6.48-6.54 (m, 2H), 6.70 (t, *J* = 7.4 Hz, 1H), 6.78-6.82 (m, 2H), 6.92-7.09 (m, 5H), 7.26-7.35 (m, 3H), 7.40-7.59 (m, 5H), 8.00 (d, *J* = 7.0 Hz, 2H); **^{13}C-NMR (50 MHz, $CDCl_3$):** δ 40.9, 54.9, 57.1, 110.2, 119.9, 127.2, 127.3, 127.5, 127.8, 128.1, 128.2, 128.5, 129.6, 129.7, 133.0, 136.9, 139.5, 140.2, 154.6, 169.4, 197.4.



5d

***N*-(1-(3-methoxyphenyl)-3-oxo-3-phenylpropyl)-*N*-phenylbenzamide (5e)**

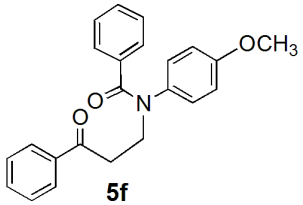
Following the general procedure as described in 3.4.5, Mannich adduct **4b** (1.0 g, 3.02 mmol), benzoylchloride (0.68 g, 4.53 mmol) and triethylamine (0.46 g, 4.53 mmol) gave the benzoylated-Mannich adduct **5e** (1.08g, 82%). **IR (thin flim):** υ 3055, 2937, 1658, 1596, 1578, 1491, 1447, 1434, 1251, 1017, 981, 770, 688 cm^{-1}; **^{1}H-NMR (200 MHz, $CDCl_3$):** δ 3.65 (dd, *J* = 17.0, 6.2 Hz, 1H), 3.80 (s, 3H), 4.11 (dd, *J* = 17.0, 8.5 Hz, 1H), 6.45-6.52 (m, 1H), 6.84-7.30 (m, 13H), 7.45-7.63 (m, 4H), 8.00-8.08 (m, 2H); **^{13}C-NMR (50 MHz, $CDCl_3$):** δ 40.6, 55.2, 58.0, 113.2, 113.8, 120.3, 127.1, 127.6, 128.0, 128.3, 128.5, 128.6, 129.5, 133.1, 136.7, 137.8, 139.4, 141.4, 158.6, 170.6, 197.5.



5e

***N*-(4-methoxyphenyl)-*N*-(3-oxo-3-phenylpropyl)benzamide (5f)**

Following the general procedure as described in 3.4.5, Mannich adduct **4c** (0.60 g, 2.34 mmol), benzoylchloride (0.49 g, 3.51mmol) and triethylamine (0.36 g, 3.51 mmol) gave the benzoylated-Mannich adduct **5f** (0.83 g, 99%). **IR (thin flim):** υ 3059, 2836, 1679, 1636, 1578, 1508, 1446, 1245, 1148, 1028, 975, 836, 722, 690 cm^{-1}; **^{1}H-NMR (200 MHz, $CDCl_3$):** δ 3.40 (t, *J* = 7.5 Hz, 2H), 3.72 (s, 3H), 4.28 (t, *J* = 7.5 Hz, 2H), 6.72 (d, *J* = 8.8 Hz, 2H), 6.96 (d, *J* =



5f

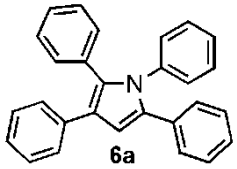
8.8 Hz, 2H), 7.10-7.23 (m, 3H), 7.27-7.31 (m, 2H), 7.40-7.59 (m, 3H), 7.94-7.99 (m, 2H); **^{13}C-NMR (50 MHz, $CDCl_3$):** δ 36.2, 47.0, 55.2, 114.3, 127.6, 128.0, 128.5, 128.6, 128.7, 129.5, 133.1, 135.8, 136.0, 136.5, 158.0, 170.6, 198.5.

3.4.6 General procedure for the synthesis of densely substituted pyrrole from benzoylated Mannich-adduct

To an ice cooled suspension of zinc dust (8 equiv.) in dry THF under argon, $TiCl_4$ (4 equiv.) was added dropwise. The mixture was warmed to room temperature and heated at reflux (3 h). The black suspension thus obtained was cooled in an ice bath and a solution of benzoylated Mannich adduct (**5a-f**, 1 equiv.) in THF was added to it. The mixture was further refluxed (2 h), cooled to room temperature, diluted with ether and quenched with 10% aqueous K_2CO_3 solution (10 mL). The heterogeneous mixture was filtered through celite and washed with ethyl-acetate. The filtrate was dried (Na_2SO_4), solvent removed and subsequently purified by column chromatography on silica gel using hexane/ethylacetate as eluent to give a mixture of pyrrole products (**6** and **7**). To a stirred solution of the mixture of pyrrole products in dry dichloromethane was added 2,3-dichloro-5,6-dicyano-1,4-benzoquinone (DDQ) (1.2 equiv.) in portions under argon atmosphere at ambient temperature. After 4 h, dichloromethane was evaporated to obtain a solid mass which was purified by column chromatography on silica gel using hexane/ethylacetate as eluent to give pure pyrrole product **6a-f**.

1,2,3,5-Tetraphenyl-1*H*-pyrrole (6a)

Following the general procedure as described in 3.4.6, compound **5a** (2.1 g, 5.2 mmol) gave the pure product **6a** (1.25 g, 65%). **IR (thin flim):** υ 3059, 3028, 1597, 1492, 1483, 1452, 1369, 1334, 1211, 1157, 1076, 1028, 914, 796, 771, 756, 692 cm^{-1}; **^{1}H-NMR (200 MHz, $CDCl_3$):** δ 6.72 (s, 1H),

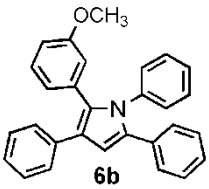


6a

7.00-7.09 (m, 4H), 7.13-7.22 (m, 13H), 7.25-7.29 (m, 3H); **^{13}C-NMR (50 MHz, $CDCl_3$):** δ 110.0, 123.5, 125.5, 126.3, 126.9, 127.1, 127.8, 127.9, 128.1, 128.2, 128.4, 128.6, 129.1, 131.5, 132.3, 132.8, 133.0, 134.9, 136.2, 138.9; **HRMS:** *m/z* calcd for $C_{28}H_{22}N$ (M+H): 372.1752; found: 372.1748.

2-(3-Methoxyphenyl)-1,3,5-triphenyl-1H-pyrrole (6b)

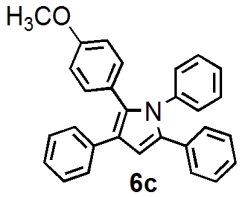
Following the general procedure as described in 3.4.6, compound **5b** (1.7 g, 3.9 mmol) gave the pure product **6b** (1.05 g, 67%). **IR ($CHCl_3$):** υ 3018, 1599, 1497, 1483, 1454, 1375, 1215, 1162, 1041, 862, 699 cm^{-1}; **^{1}H-NMR (200 MHz, $CDCl_3$):** δ 3.53 (s, 3H), 6.56 (s, 1H), 6.67-6.73 (m, 2H), 7.04-7.29 (m, 17H); **^{13}C-NMR (50 MHz, $CDCl_3$):** δ 55.1, 110.1, 113.5, 116.3, 124.1, 125.6, 126.4, 127.2, 128.0, 128.2, 128.3, 128.5, 128.6, 128.9, 129.1, 131.9, 132.9, 133.8, 134.8, 136.1, 138.8, 158.9; **Anal.** (calcd for $C_{29}H_{23}NO$: C, 86.75; H, 5.77. found: C, 86.72; H, 5.72).



6b

2-(4-Methoxyphenyl)-1,3,5-triphenyl-1H-pyrrole (6c)

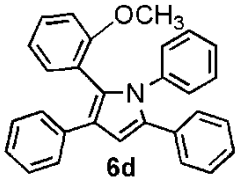
Following the general procedure as described in 3.4.6, compound **5c** (1.38 g, 3.2 mmol) gave the pure product **6c** (0.81 g, 63%). **IR ($CHCl_3$):** υ 3061, 2934, 2834, 1598, 1508, 1496, 1486, 1375, 1287, 1246, 1175, 1030, 909, 835, 732, 698 cm^{-1}; **^{1}H-NMR (200 MHz, $CDCl_3$):** δ 3.76 (s, 3H), 6.69 (s, 1H), 6.73-6.75 (m, 2H), 6.99-7.04 (m, 4H), 7.17-7.33 (m, 13H); **^{13}C-NMR (50 MHz, $CDCl_3$):** δ 55.0, 109.7, 113.3, 123.1, 124.9, 125.3, 126.2, 127.0, 127.9, 128.0, 128.1, 128.5, 129.1, 132.0, 132.6, 132.9, 134.5, 136.2, 138.8, 158.5; **Anal.** (calcd for $C_{29}H_{23}NO$: C, 86.75; H, 5.77. found: C, 86.71; H, 5.75).



6c

2-(2-Methoxyphenyl)-1,3,5-triphenyl-1H-pyrrole (6d)

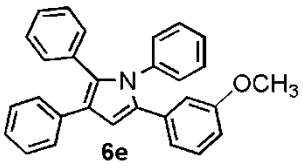
Following the general procedure as described in 3.4.6, compound **5d** (1.6 g, 3.7 mmol) gave the pure product **6d** (0.59 g, 40%). **IR ($CHCl_3$):** υ 3063, 3007, 2933, 2834, 1664, 1598, 1497, 1484, 1467, 1376, 1245, 1215, 1121, 1027, 944, 696, 667 cm^{-1}; **^{1}H-NMR (200 MHz, $CDCl_3$):** δ 3.42 (s, 3H), 6.75 (d, *J* = 8.4 Hz, 1H), 6.82 (s, 1H), 6.85-6.89 (m, 1H), 7.01-7.05 (m, 2H), 7.13-7.35 (m, 15H); **^{13}C-NMR (50 MHz, $CDCl_3$):** δ 54.8, 109.5, 110.6, 120.3, 122.0, 123.5, 125.2, 126.1, 126.6, 127.3, 127.9, 128.0, 128.3, 129.0, 129.5, 133.0, 133.4, 134.4, 136.2, 139.1, 158.0; **Anal.** (calcd for $C_{29}H_{23}NO$: C, 86.75; H, 5.77. found: C, 86.72; H, 5.73).



6d

5-(3-Methoxyphenyl)-1,2,3-triphenyl-1*H*-pyrrole (6e)

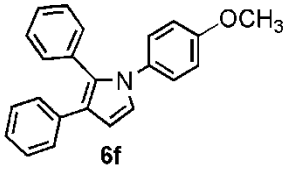
Following the general procedure as described in 3.4.6, compound **5e** (0.82, 1.9 mmol) gave the pure product **6e** (0.32 g, 42%). **IR ($CHCl_3$):** υ 3017, 2927, 2854, 1599, 1497, 1464, 1451, 1372, 1215, 1163, 1044, 914, 851, 699, 668 cm^{-1}; **^{1}H-NMR (200 MHz, $CDCl_3$):** δ 3.58 (s, 3H), 6.61-6.63 (m, 1H), 6.69-6.79 (m, 3H), 6.99-7.10 (m, 4H), 7.12-7.22 (m, 9H), 7.26-7.30 (m, 3H); **^{13}C-NMR (50 MHz, $CDCl_3$):** δ 54.9, 110.0, 112.7, 113.4, 121.0, 123.4, 125.5, 126.9, 127.1, 127.8, 128.0, 128.1, 128.5, 128.9, 129.1, 131.4, 132.2, 132.6, 134.1, 134.6, 136.0, 138.8, 159.0; **Anal.** (calcd for $C_{29}H_{23}NO$: C, 86.75; H, 5.77. found: C, 86.71; H, 5.76).



6e

1-(4-Methoxyphenyl)-2,3-diphenyl-1*H*-pyrrole (6f)

Following the general procedure as described in 3.4.6, compound **5f** gave the pure product **6f** (70%). **IR ($CHCl_3$):** υ 3019, 2927, 2854, 1600, 1513, 1439, 1295, 1244, 1215, 1029, 669 cm^{-1}; **^{1}H-NMR (200 MHz, $CDCl_3$):** δ 3.77 (s, 3H), 6.52 (d, *J* = 2.8 Hz, 1H), 6.75-6.811 (m, 2H), 6.92 (d, *J* = 2.8 Hz, 1H), 6.98-7.04 (m, 3H), 7.05-7.10 (m, 2H), 7.11-7.18 (m, 4H), 7.20-7.22



6f

(m, 4H); **^{13}C-NMR (50 MHz, $CDCl_3$):** δ 55.4, 109.4, 113.9, 123.1, 123.8, 125.3, 126.8, 127.2, 128.0, 128.1, 128.3, 130.1, 131.1, 132.4, 133.4, 136.5, 158.0; **Anal.** (calcd for $C_{29}H_{23}NO$: C, 84.89; H, 5.89. found: C, 84.82; H, 5.90).

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CHAPTER 4

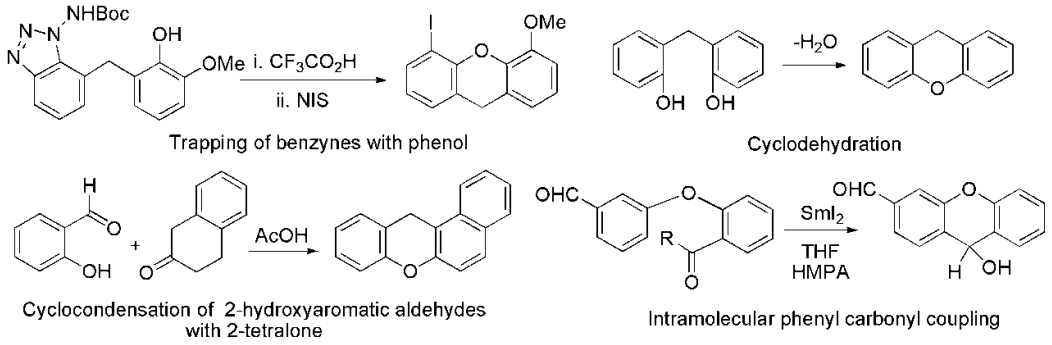
Camphor-10-sulfonic Acid Catalyzed Condensation of 2-Naphthol with Aldehydes: Synthesis of Dibenzo[*a,j*]Xanthenes

4.1 Preamble

This chapter deals with the innovation of new methodology for the synthesis of xanthenes and benzoxanthenes. As discussed in chapter 2 and 3, CSA is a novel catalyst for catalyzing Mannich-type reaction in an environmentally benign approach. Herein we would discuss about our findings on CSA catalyzed one-pot condensation of 2-naphthol with aldehydes to dibenzoxanthenes.

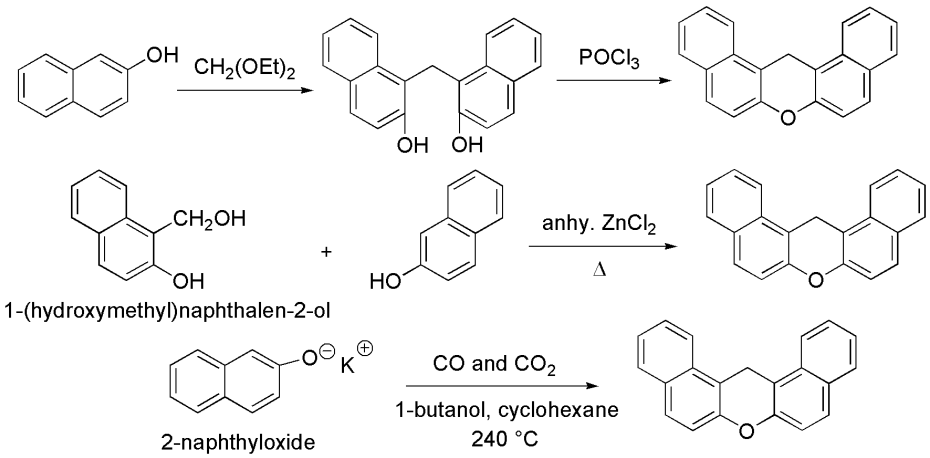
4.1.1 Synthesis of xanthenes and benzoxanthenes

As discussed in Chapter 1, xanthenes and benzoxanthenes are important class of oxygen heterocycles which displays diverse biological and spectroscopic properties. The versatility of this class of compounds has attracted many synthetic and medicinal chemists towards their preparation and scaffold manipulation by using different improved procedures. Several methods (Scheme 4a) have been reported for the synthesis of xanthenes and benzoxanthenes which include trapping of benzynes with phenols,[106] cyclodehydration,[107] cyclocondensation of 2-hydroxyaromatic aldehydes with 2-tetralone[108] and intramolecular phenyl carbonyl coupling reactions of benzaldehydes with acetophenones.[109]



Scheme 4a: Different routes for synthesis of xanthene derivatives.

Also, dibenzo[*a*,*j*]xanthenes and related compounds have been synthesized from the reaction of 2-naphthol with diethoxymethane,[110] 1-(hydroxymethyl)naphthalen-2-ol[111] and carbonmonoxide[112] (Scheme 4b). In addition, various catalysts, including $TaCl_5$,[113]



Scheme 4b: Different routes for synthesis of dibenzoxanthenes.

$Sr(OTf)_2$,[114] $Yb(OTf)_3$,[115] sulfamic acid,[116] iodine,[117] amberlyst-15,[118] cyanuric chloride,[119] CAN[120], BF_3:SiO_2,[121] P_2O_5 or $InCl_3$,[122] $Sc[N(SO_2C_8F_{17})_2]_3$,[123] $RuCl_3.nH_2O$,[124] PEG-SO_3H,[125] ionic liquid,[126] DPA or DSA,[127] nano-SPA,[128] nano-$SnCl_4.SiO_2$,[129] DBSA,[130] tungstophosphoric acid[131] and functionalized mesoporous materials[132] were found to catalyze condensation reactions of 2-naphthol with different aldehydes to afford 14-substituted-14*H*-dibenzo[*a*,*j*]xanthenes. However, many of the reported methodologies suffer from one or more disadvantages such as long reaction time, use of toxic and expensive catalysts, harsh reaction conditions *etc*. Keeping this in view, as well as the increasing importance of benzoxanthenes in pharmaceutical industry, still there is a necessity for the development of an efficient, environmentally benign and inexpensive catalyst for their synthesis. Herein, we report a convenient microwave-assisted synthesis of 14-aryl/alkyl-14*H*-dibenzo[*a*,*j*]xanthenes from 2-naphthol and aromatic/aliphatic aldehydes using (±)-camphor-10-sulfonic acid as a catalyst.

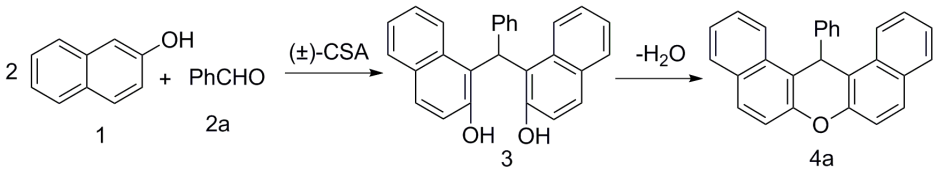
4.2 Present work

In continuation of our efforts towards the development of newer synthetic methodologies using CSA as an inexpensive catalyst, we have studied the condensation reactions of *β*–naphthol and aldehydes. This chapter would be dedicated to our efforts for the library synthesis of 14-substituted-14*H*-dibenzo[*a*,*j*]xanthenes by using a simple and efficient methodology that intuitively showed the efficacy of microwave in chemical reactions as already established by synthetic chemists in various synthetically useful reactions. As discussed in Chapter 2, camphor-10-sulfonic acid (CSA) is a commercially available, inexpensive and easy to handle reagent which has been used by us as a catalyst for the activation of imines (electrophile) in the Mannich type reaction of the enolizable ketones (nucleophile).[75] Therefore, it was our considerable interest to study whether CSA could also activate aldehydes in the condensation of aldehydes and 2-naphthol under varied reaction conditions.

4.2.1 CSA-catalyzed condensation of 2-naphthol with benzaldehyde

In a preliminary study, the reaction of 2-naphthol (**1**) with benzaldehyde (**2a**, 0.55 equiv.) was carried out at ambient temperature (25 °C) with (±)-CSA (5 mol%) under solvent-free conditions (Scheme 4c). The reaction was found to be very sluggish as both the intermediate 1,1-*bis*-(2-hydroxynaphthyl)phenylmethane (**3**) as well as dehydrated product 14-phenyl-14*H*-dibenzo[*a*,*j*]xanthene (**4a**) were isolated in 55% and 10% yields respectively along with unreacted **1** (~18%) and **2a** (~10%) after stirring for 24 h (Table 4a, entry 1). Compounds **3** (Fig. 4a) and **4a** (Fig. 4b) were fully characterized by physical and spectroscopic (IR, ^{1}H-NMR, ^{13}C-NMR and MS) analysis. Increase in catalyst loading (10 mol%) (25 °C, 24 h) led to the marginal improvement in the yields of both **3** and **4a**

although small amount of starting materials were still recovered (Table 4a, entry 2). However, with 20 mol% of the catalyst, both the starting materials were consumed while **3** and **4a** were isolated in 75% and 21% yields respectively (Table 4a, entry 3).[133]



Scheme 4c: CSA-catalyzed condensation of 2-naphthol with benzaldehyde.

Table 4a: CSA-catalyzed condensation of 2-naphthol (**1**) with benzaldehyde (**2a**)

Entry	Reaction conditions[a]	(±)-CSA, mol%	Time (h)	**3** (% Yield)[b]	**4a** (% Yield)[b]
1	25 °C	5	24.0	55	10
2	25 °C	10	24.0	63	14
3	**25 °C**	**20**	**16.0**	**75**	**21**

[a]2-naphthol was reacted with aldehydes (0.55 equiv.) under solvent-free conditions; [b] isolated yields.

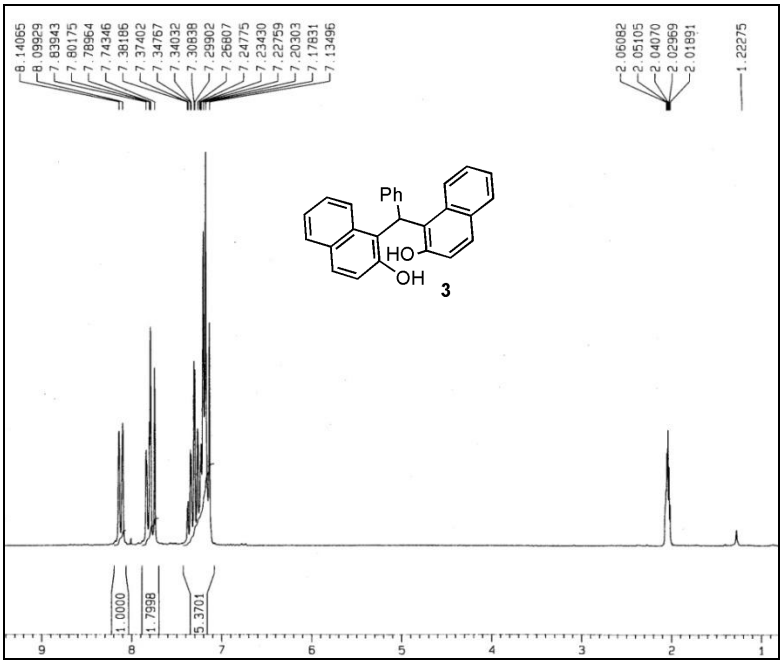


Figure 4a: ^{1}H-NMR of **3**.

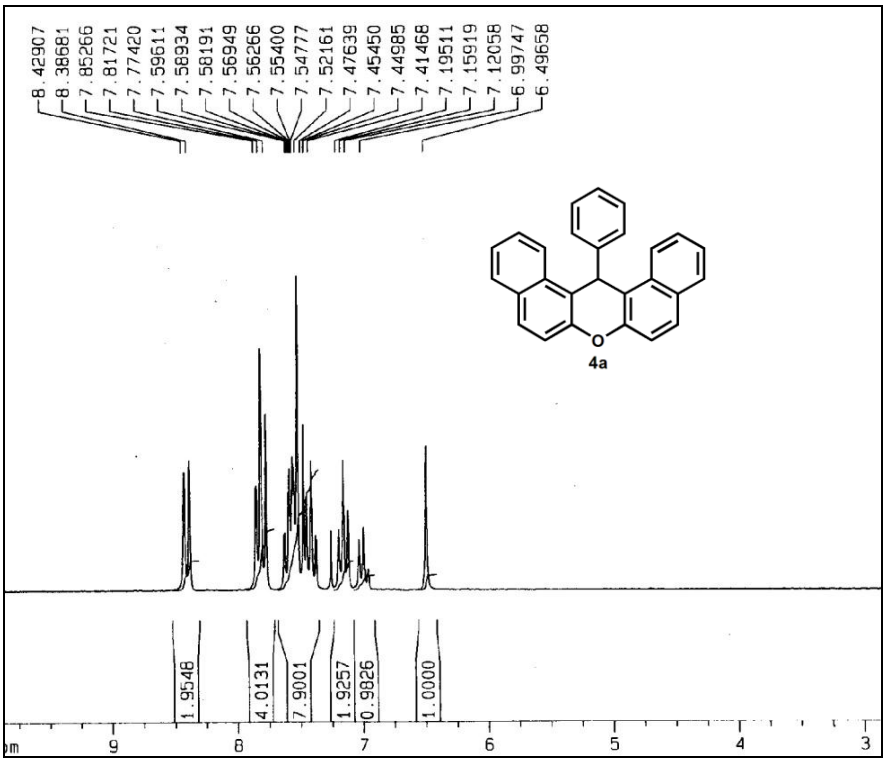
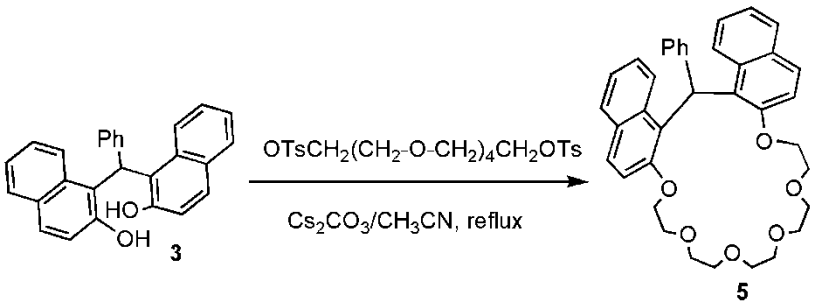


Figure 4b: ^{1}H-NMR of **4a**.

4.2.2 Synthesis and use of 1,1-*bis*-(2-hydroxynaphthyl)phenylmethane (3) as precursor in the synthesis of napthalenocrown-6

It is important to note that isolation of **3** from the one-pot reaction of **1** and **2** is very difficult as it undergoes facile cyclodehydration to **4**. To the best of our knowledge, there is a single report[115] so far on isolation of *bis*-(2-naphthol) (**3**) via $Yb(OTf)_3$ catalyzed condensation of **1** and **2a** in ionic liquid. Therefore, we were interested in optimization the CSA catalyzed methodology so that the reaction can be freezed at the intermediate 1,1-*bis*-(2-hydroxynaphthyl)phenylmethane (**3**) stage (Table 4a, entry 3). Compound **3** is an important class of tethered *bis*-(2-naphthol), which in principle can be exploited further to the synthesis of variety of macrocycles including crown ethers. To this end, reaction of **3** with pentaethyleneglycol ditosylate and K_2CO_3 in acetonitrile was found to produce the corresponding crown ether **5** (Fig. 4c) in good yield (Scheme 4d).



Scheme 4d: Synthesis of *bis*-napthalenocrown-6.

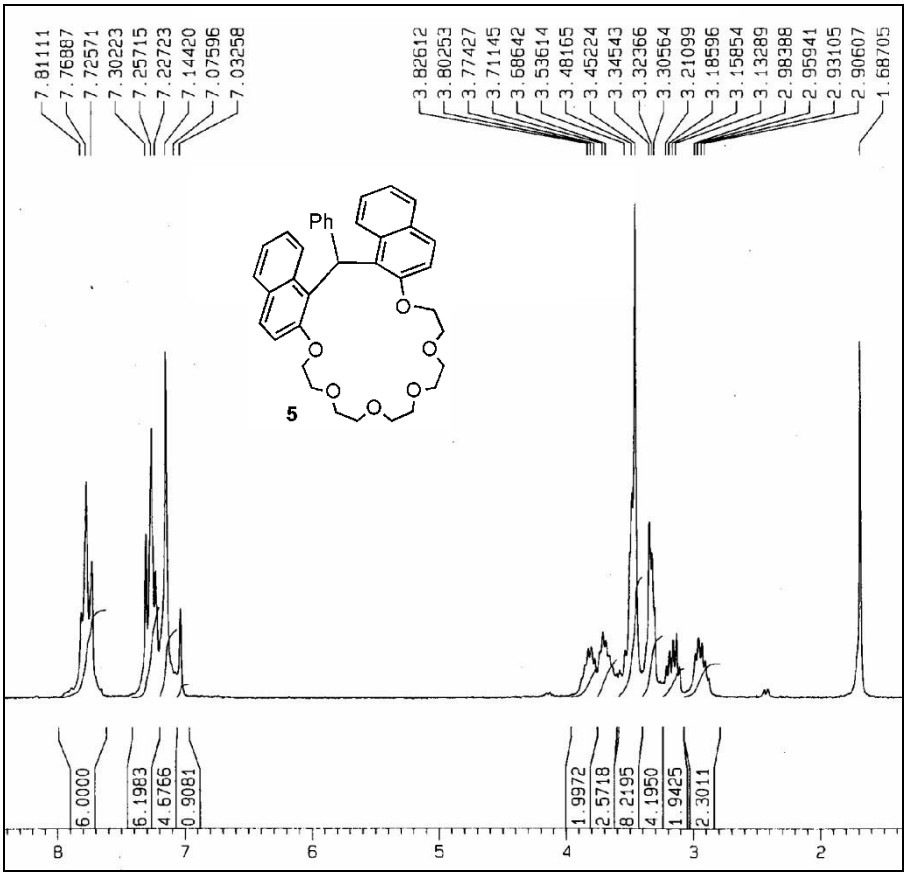


Figure 4c: ^{1}H-NMR of **5**.

Crown ethers are vastly used as electron donors in the host-guest interaction studies with different metal ions and organic electron acceptors. Keeping this in view, study on supramolecular interaction of naphthacrown **5** with fullerenes (C_{60} and C_{70}) as electron acceptors was initiated. Studies on both UV-vis absorption and steady state fluorescence was carried out to understand the mode of interaction of fullerenes with **5** in toluene.[134]

The UV-vis titration experiments for both the fullerene C_{60} and C_{70} solutions showed a systematic increase in the absorbance value for the broad 400–700 nm absorption band (resulting from a forbidden singlet-singlet transition in case of fullerenes) as a result of complexationbetween fullerenes and **5** (Fig 4d). The spectral data clearly indicates the formation of 1:1 complex in both the cases.

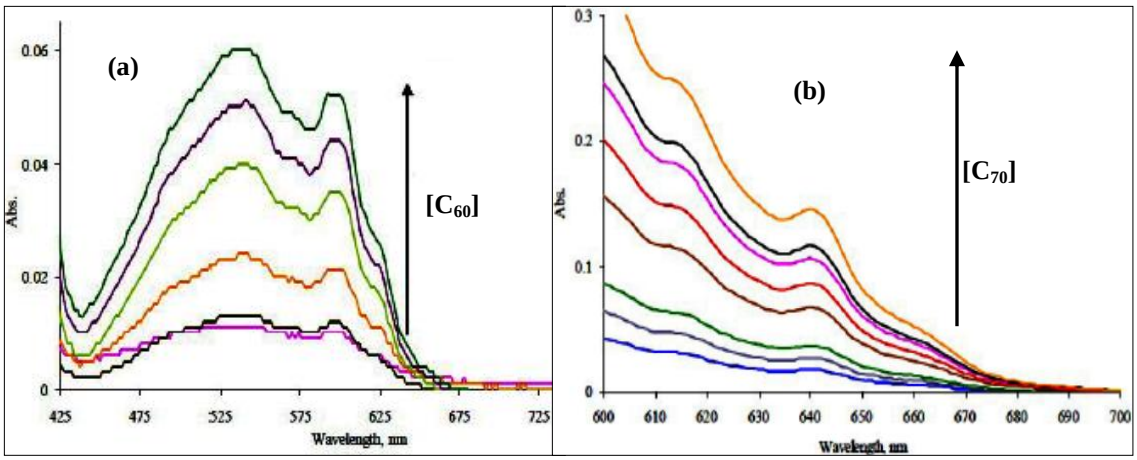


Figure 4d: UV-vis absorption spectrum of the titration experiment consisting mixture of (a) C_{60} and **5** (b) C_{70} and **5**.

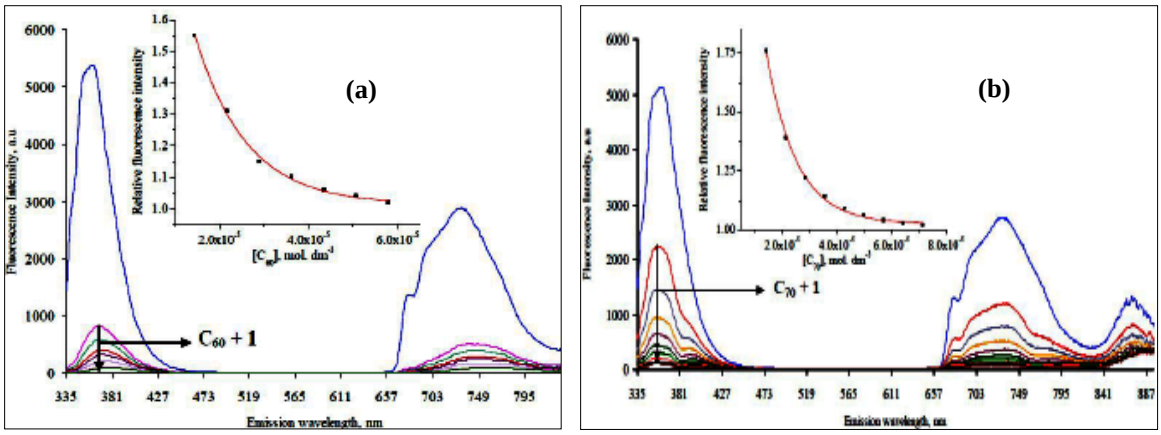


Figure 4e: Steady state fluorescence spectral variation of **5** in presence of (a) C_{60} and (b) C_{70} in toluene.

The steady state fluorescence experiments showed efficient quenching of the fluorescence intensity of **5** in presence of both C_{60} and C_{70} (Fig 4e), favoring the evidence of energy-transfer deactivation of the excited singlet state of **5** in presence of C_{60} and C_{70}. The most fascinating feature of the fluorescence investigations was the observation of emissive state CT for the C_{70}-**5** system located at 381 nm. This peak exhibited a significant red shift with the increasing concentration of C_{70} (Fig 4e). From the experimental data we found that **5** binds both C_{60} and C_{70} very effectively with binding constants in the range of (6.1 to 7.3) × 10^4 $dm^3.mol^{-1}$. Both ^{13}C-NMR and hybrid density functional calculations established end-on binding motif of C_{70} towards **5** during complexation.

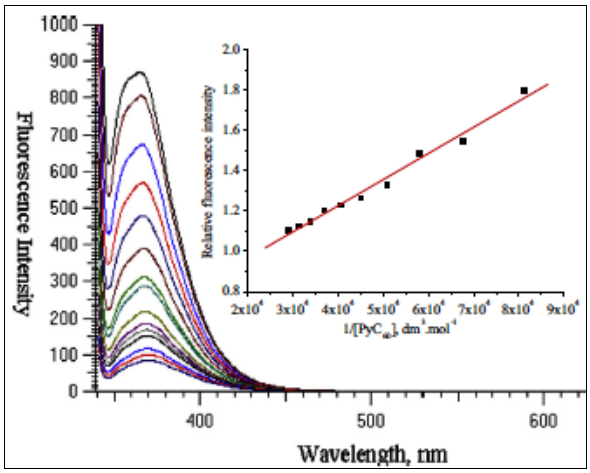


Figure 4f: Steady state fluorescence spectral variation of **5** in presence of PyC_{60} in toluene.

Encouraged by the above results, we were also interested to understand the complexation mechanism of **5** with another macromolecule fulleropyrrolidine (PyC_{60}).[135] In order to know the nature of binding here also steady state UV–vis titration experiments and steady state fluorescence measurements (Fig 4f) were carried out for PyC_{60}–**5** solution in toluene. It was observed that both PyC_{60} and **5** attract each other spontaneously in toluene. The binding constant (K) value of this new supramolecular recognition element was determined to be ~5.83 × 10^4 $dm^3.mol^{-1}$. Apart from steady state fluorescence

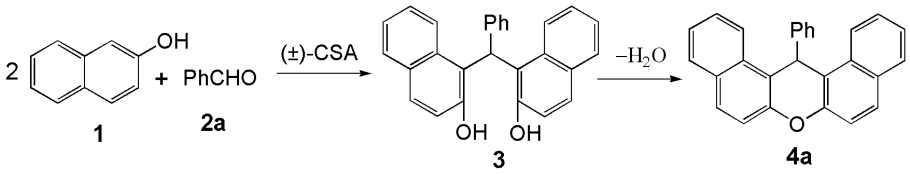
measurements, we have performed detailed nanosecond time-resolved fluorescence experiment for PyC_{60}-**5** supramolecule. Lifetime measurement revealed a static quenching mechanism behind the deactivation of photoexcited state of **5** in presence of PyC_{60}. The results obtained from these complexation studies would definitely reinforce bridged cyclic crown ether as one of the most suitable fragments for the molecular recognition of various macrocyclic receptor(s) in near future.

4.2.3 Library synthesis of 14-aryl-14*H*-dibenzo[*a,j*]xanthenes

In the previous section, we have discussed that in the CSA catalyzed condensation of 2-naphthol and benzaldehyde, the intermediate **3** can be selectively prepared by carrying out the reaction at ambient temperature. However, when the same condensation was carried out at an elevated temperature (80 °C) with 10 mol% CSA (Scheme 4c) both the starting materials **1** and **2a** were consumed and **4a** was isolated as a sole product in 81% yield with no trace intermediate **3** after 8 h (Table 4b, entry 1). Further increase in catalyst loading (15 mol%) led to completion of the reaction within 2 h at 80 °C to yield **4a** as the sole product in 89% yield (Table 4b, entry 2). Microwave irradiation (MWI) is known to be an important tool in organic synthesis to improve the selectivity, rate enhancement and reduction of thermal degradative byproducts.[136] To reduce the catalyst loading as well as the reaction time required for the condensation at high temperature, reaction of **1** with **2a** (0.55 equiv.) was carried out without-solvent using varied amount (±)-CSA (2-10 mol%) under MWI (400 W, 63-64 °C) when **4a** was obtained as the sole product in 88-89% yields (Table 4b, entries 3-5). The reaction without using CSA as catalyst did not yield any product (**4a**); both the starting compounds were recovered (Table 4b, entry 6). As evidenced from Table 4b, optimal catalyst loading for microwave-assisted condensation

was found to be 2 mol% to afford **4a** in 88% yield and therefore the same conditions were used for subsequent reactions that use liquid aromatic aldehyde.

Table 4b: Optimization of the reaction conditions for the (±)-CSA-catalyzed condensation of 2-naphthol with benzaldehyde for the synthesis of **4a**



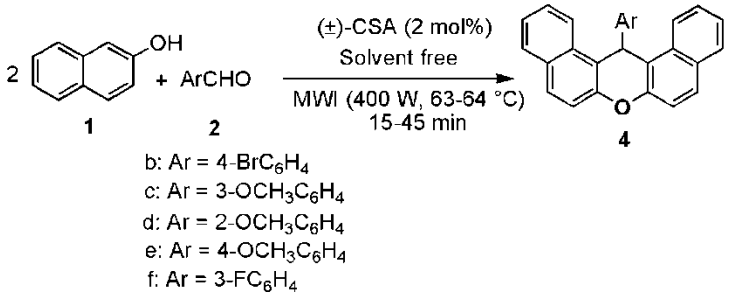
Entry	Reaction conditions[a]	(±)-CSA, mol%	Time (h)	**3** (% Yield)[b]	**4a** (% Yield)[b]
1	80 °C	10	8.0	-	81
2	80 °C	15	2.0	-	89
3	MWI, 63-64 °C	10	0.25	-	89
4	MWI, 63-64 °C	5	0.25	-	88
5	**MWI, 63-64 °C**	**2**	**0.25**	**-**	**88**
6	MWI, 63-64 °C	0	0.50	-	0

[a]2-naphthol was reacted with aldehydes (0.55 equiv.) under solvent-free conditions; [b] isolated yields.

4.2.3a Condensation of 2-naphthol with liquid aromatic aldehydes

To see the scope and generality of our methodology, CSA catalyzed condensation of 2-naphthol with a variety of liquid aromatic aldehydes (**2b-f**) were investigated under MWI and solvent free conditions (Scheme 4e) as optimized for benzaldehyde (Table 4b, entry 5). In all the cases, the desired dibenzoxanthenes were obtained in good to high yields and the results are summarized in Table 4c. The electronic effect of the substituents in the aromatic aldehydes was found to have minimal effect as evidenced by the high yield of the corresponding dibenzoxanthenes almost in all the cases (**4b-f**) (Table 4c, entries 1-5). However, moderate yield of **4d** derived from 2-methoxybenzaldehyde (**2d**) can be

explained by the large steric strain (by the bulky methoxy group) involved during the cyclodehydration step to dibenzoxanthene (Table 4c, entry 3).



Scheme 4e: Condensation of 2-naphthol with liquid aromatic-aldehydes.

Table 4c: Microwave assisted CSA catalyzed condensation of 2-naphthol (**1**) with liquid aromatic aldehydes (ArCHO) to 14-aryl-14*H*-dibenzo[*a*,*j*]xanthene[a](**4b-f**)

Entry	Aldehydes	Product	Time (min)	% Yield[b]	Melting point (°C)	
					Found	Reported
1	**2b**	**4b**	30	82	293-294	295-296
2	**2c**	**4c**	15	98	177-178	179-180
3	**2d**	**4d**	45	54	258-259	258-260
4	**2e**	**4e**	15	88	207-208	205-206
5	**2f**	**4f**	30	95	256-257	259

[a]reaction conditions: 2-naphthol, aldehydes (0.55 equiv.), (±)-CSA (0.02 equiv.) was irradiated in a microwave reactor at 400 W; 63-64 °C for 15-45 min; [b]isolated yields.

4.2.3b Condensation of 2-naphthol with solid aromatic aldehydes

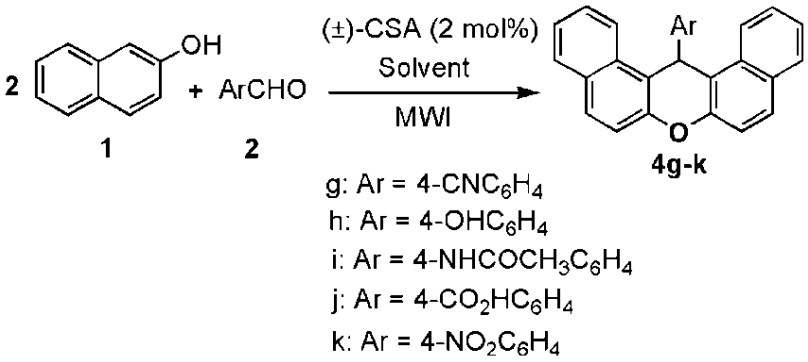
To generalize the above discussed microwave-assisted reactions for solid aromatic aldehydes, we have started screening different solvents (Scheme 4f). Towards optimization,

the microwave-active solvents *viz.* H_2O and DMF without changing catalyst loading was seen to be unreactive and lower yielding respectively, when 4-cyanobenzaldehyde (**2g**) was reacted with 2-naphthol to produce cyanodibenzoxanthene (**4g**) (Table 4d, entry 1, 2). Interestingly, in the case of solid aromatic aldehyde 4-cyanobenzaldehyde, when acetonitrile (0.25 ml/mmol) was used as solvent to make a uniform slurry cyanodibenzoxanthene, **4g** (Fig. 4g) was isolated in 86% yield (Table 4d, entry 3).

Table 4d: Optimization of the reaction conditions for the CSA-catalyzed microwave-assisted condensation of 2-naphthol with **2g**

Entry	Solvent	MWI time (min)	% Yield of **4g**
1	DMF	60	-
2	H_2O	60	32
3	**Acetonitrile**	**30**	**86**

Using the optimized reaction conditions (Table 4d, entry 3), other solid aldehydes (**2h-k)** were found to produce very good to excellent yield of the desired product (**4h-k**) (Table 4e, entry 1-4).



Scheme 4f: Condensation of 2-naphthol with solid aromatic-aldehydes.

Table 4e: Microwave assisted CSA catalyzed condensation of 2-naphthol (**1**) with solid aromatic aldehydes to 14-aryl-14*H*-dibenzo[*a*,*j*]xanthene[a] **(4h-k)**

Entry	Aldehydes	Product	Time (min)	% Yield[b]	Melting point (°C)	
					Found	Reported
1	**2h**	**4h**	45	61	138-139	138-140
2	**2i**	**4i**	45	86	153-154	-
3	**2j**	**4j**	30	85	>300	-
4	**2k**	**4k**	30	84	>300	310-311

[a]reaction conditions: 2-naphthol, aldehydes (0.55 equiv.), (±)-CSA (0.02 equiv.) in acetonitrile (0.25ml/mmol) was irradiated in a microwave reactor at 400 W; 63-64 °C for 15-45 min; [b]isolated yields.

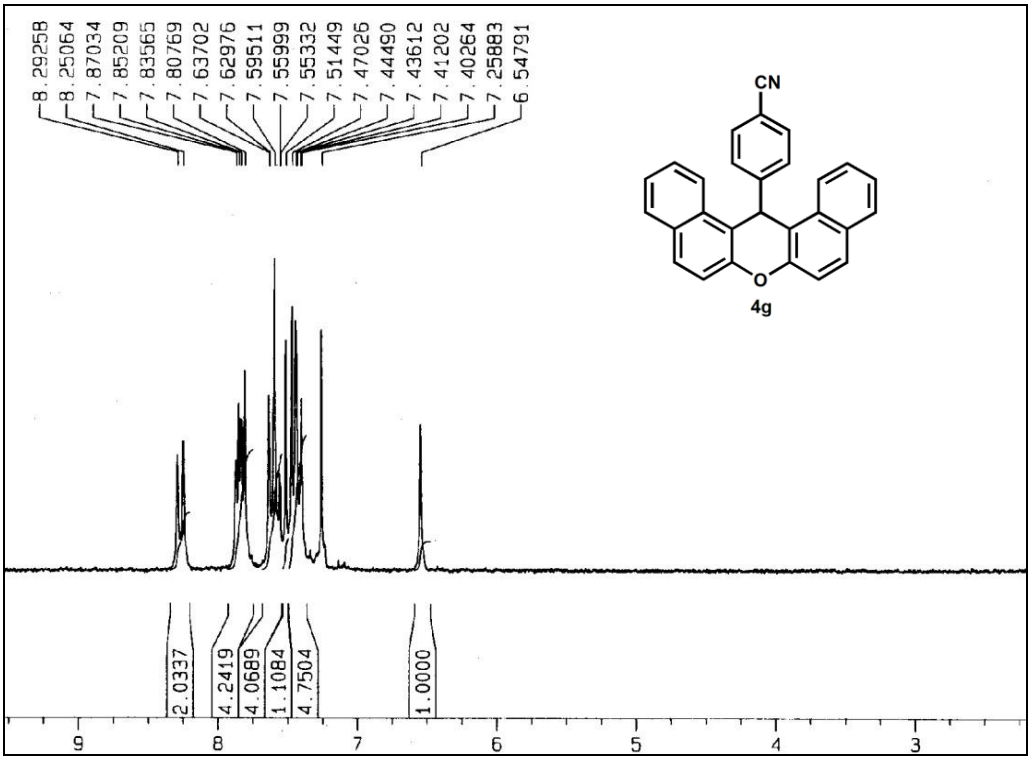
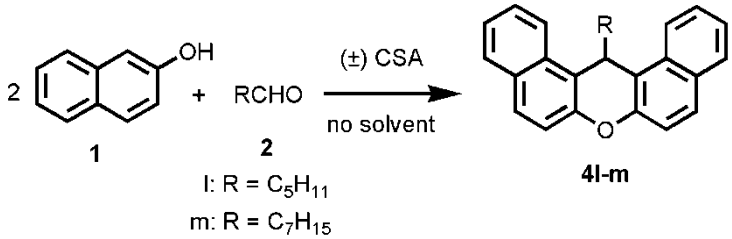


Figure 4g: [1]H-NMR of **4g**.

4.2.3c Condensation of 2-naphthol with aliphatic aldehydes

To explore the generality of the catalyst and the methodology further, CSA catalyzed condensation of 2-naphthol (**1**) with aliphatic aldehydes were also investigated. In contrast to benzaldehyde, CSA catalyzed (10 mol%) condensation of **1** with 1-hexanal (**2l**) at 25 °C without-solvent (24 h) led to complete consumption of starting materials and 14-(*n*-pentyl)-dibenzoxanthene (**4l**) was obtained as the sole product in 73% yield (no trace of the corresponding 1,1-*bis*-(2-hydroxynaphthyl)hexane was detected) (Scheme 4g, Table 4f, entry 1). Similarly, reaction with 1-octanal (**2m**) led to the formation of 14-(*n*-heptyl)-dibenzoxanthene (**4m**) as the only product (Table 4f, entry 4). Thus it can be inferred that



Scheme 4g: Condensation of 2-naphthol with aliphatic aldehydes.

Table 4f: CSA catalyzed condensation of 2-naphthol (**1**) with aliphatic aldehydes to 14-aryl-14*H*-dibenzo[*a*,*j*]xanthene(**4l, m**)

Entry	Product	(±)-CSA (mol%)	Reaction conditions	Time	% Yield of **4**[a]
1		10	25 °C	24 h	73
2	**4l**	5	80 °C	20 min	93
3		2	MWI	15 min	92
4		10	25 °C	24 h	70
5	**4m**	5	80 °C	20 min	86
6		2	MWI	15 min	95

[a]isolated yields

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aliphatic aldehyde derived intermediate bis-naphthol undergo facile cyclodehydration as compared to its aromatic counterpart. However, at higher temperature (80 °C), both the reactions (with 1-hexanal and 1-octanal) were completed in 20 minutes with lower catalyst loading (5 mol%) to afford the corresponding dibenzoxanthenes in 93% and 86% yields respectively (Table 4f, entry 2, 5). Moreover, the above reactions under MWI got completed in 15 min with less catalyst loading (2 mol%) as compared to high temperature reactions to afford the corresponding dibenzoxanthenes, **4l** (Fig. 4h) and **4m** (Fig. 4i) in 92% and 95% respectively (Table 4f, entry 3, 6). Most of the catalysts[122-124,127] reported so far for the condensation of **1** with aliphatic aldehydes furnished corresponding dibenzoxanthenes in longer reaction time and moderate yields. In conclusion, CSA has displayed its catalytic efficiency in the faster condensation of **1** with both aliphatic and aromatic aldehydes to afford corresponding alkyl/aryl substituted dibenzoxanthenes in high yields (Fig. 4j). Incidentally, the catalytic potential of CSA in terms of reaction time and yield was found to be superior / similar to most of the catalysts reported so far.

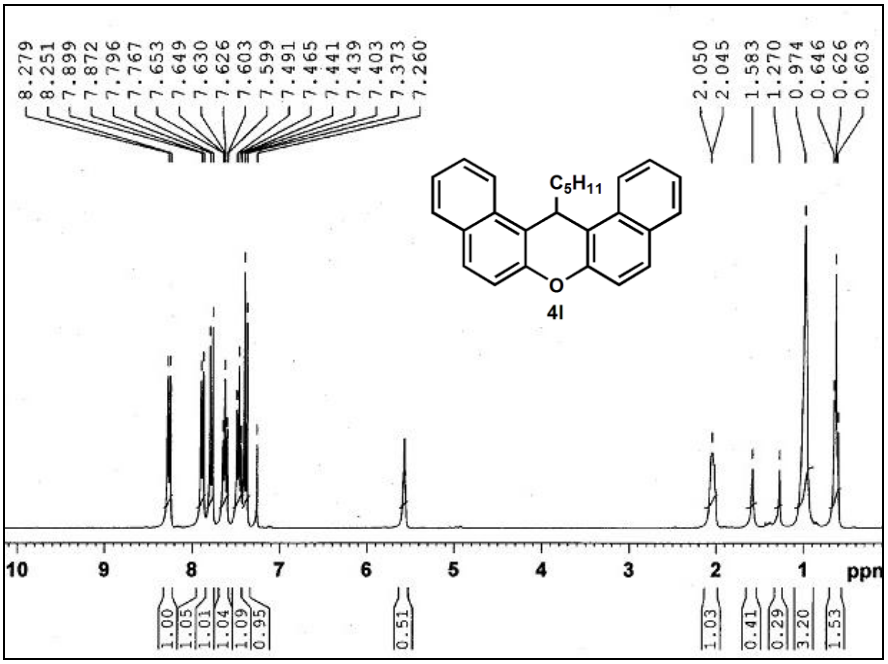


Figure 4h: ^{1}H-NMR of **4l**.

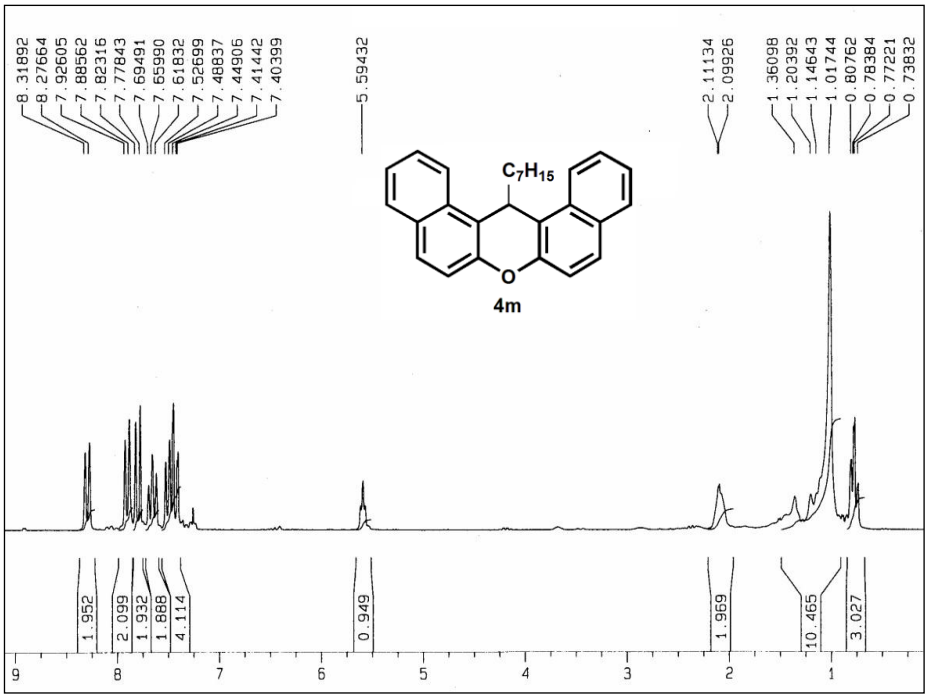


Figure 4i: ^{1}H-NMR of **4m**.

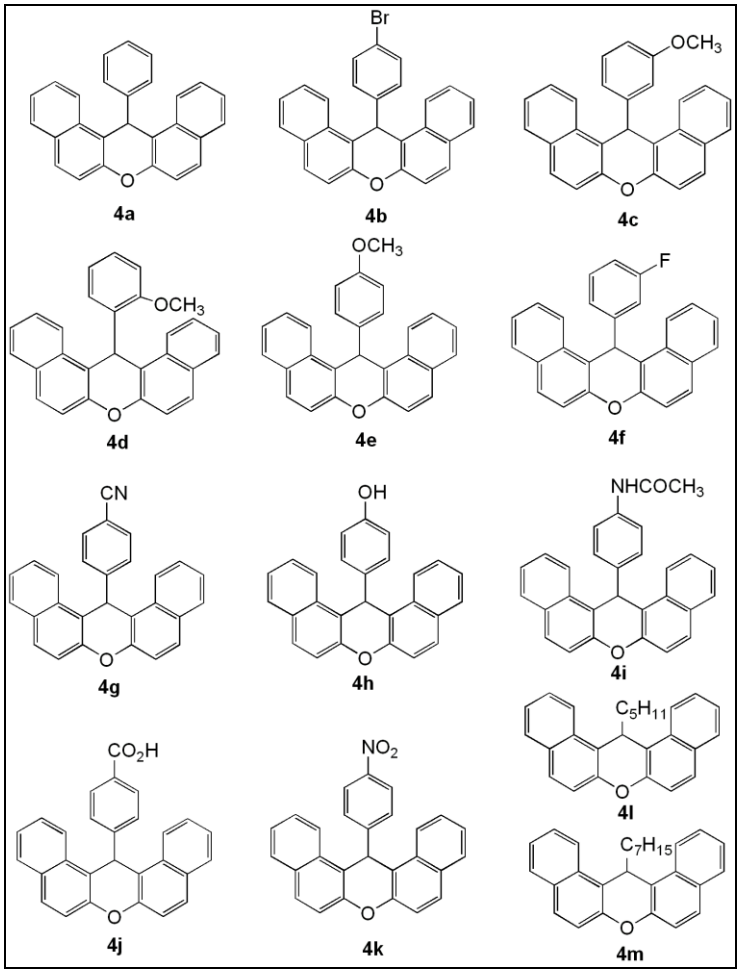
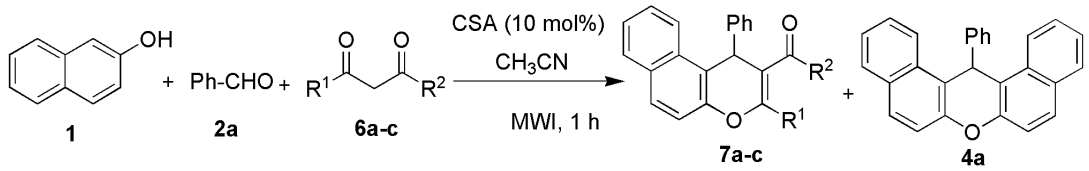


Figure 4j: Library synthesis.

4.2.4 CSA-catalyzed condensation of 2-naphthol with benzaldehyde and 1,3-dicarbonyl compounds

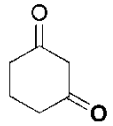
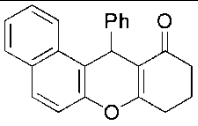
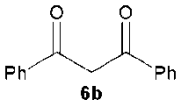
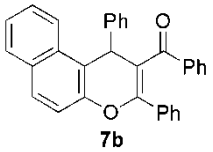
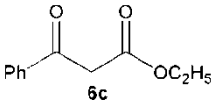
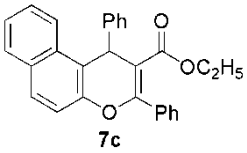
Mechanistically, in all the condensations discussed above, two molecules of 2-naphthol are acting as nucleophiles to make the dibenzoxanthene skeleton (aldehyde: 2-naphthol = 1:2). It was of interest to explore catalytic efficiency of CSA in the condensation with two different nucleophiles. As methylene group in 1,3-dicarbonyl compounds are known to act as good nucleophiles, CSA-catalyzed three component one-pot reaction of **1**, **2a** and 1,3-dicarbonyl compounds (**6**) in 1:1:1 ratio was investigated (Scheme 4h). Thus microwave-assisted reaction of 2-naphthol, benzaldehyde and cyclohexan-1,3-dione (**6a**) with CSA (10 mol%) in acetonitrile yielded the cross condensation product **7a** as the major product along with dibenzoxanthene **4a** (Table 4g, entry 1). Similar result was observed when dibenzoyl methane (**6b**) was used in place of cyclohexan-1,3-dione (Table 4g, entry 2). However, the reaction with ethylbenzoylacetate (**6c**) under the same reaction conditions afforded the cross condensation product **7c** in poor yield and homo-condensation product **4a** was isolated as the major product. This may be due to the acidic hydrolysis of **6c** to benzoyl acetic acid under the reaction conditions



Scheme 4h: 2-Naphthol with benzaldehyde and 1,3-dicarbonyl compounds.

which in turn undergo facile decarboxylation to acetophenone and therefore the required amount of nucleophile **6a** is not available for the condensation with 2-naphthol (Table 4g, entry 3). This has been substantiated by the isolation in substantial amount (~60%) of acetophenone from the crude reaction product.

Table 4g: CSA-catalyzed condensation of 2-naphthol with benzaldehyde and 1,3-dicarbonyl compounds

Entry	**6**	**7**	% Yield of **7**[a]	% Yield of **4a**[a]
1	 **6a**	 **7a**	**7a** (65)	28
2	 **6b**	 **7b**	**7b** (67)	21
3	 **6c**	 **7c**	**7c** (22)	63

[a]Isolated yields.

4.3 Conclusion

In conclusion, a simple, efficient and green protocol for the synthesis of 14-substituted-14*H*-dibenzo[*a*,*j*]xanthenes from aromatic/aliphatic aldehydes and 2-naphthol under microwave irradiation using CSA as catalyst has been developed. Synthesis of the intermediate *bis*-(2-naphthol), a precursor for crown ether, in the condensation with aromatic aldehydes has also been accomplished by carrying out the reaction at ambient temperature. The intermediate *bis*-(2-naphthol) has been successfully utilized in the synthesis of a naphthacrown based macrocyclic receptor, which has been effectively used for molecular recognition of fullerenes (C_{60} and C_{70}) and fulleropyrrolidine (PyC_{60}) in toluene. The simplicity of its synthetic route will favor its use as a photoactive component in the construction of different supramolecular assembly in near future. Cross condensation of 2-naphthol with 1,3-dicarbonyl compounds and aldehydes were also successfully carried

out using CSA as catalyst. The short reaction time, simple work up procedure, and easy isolation of the products in good yields are some of the salient features of this new protocol.

4.4 Experimental

General information

All microwave-assisted reactions were carried out in an Anton Paar microwave reactor (model SYNTHOS 3000). Melting points were determined using Fisher-Johns melting point apparatus and are uncorrected. IR spectra were scanned with a Jasco FT IR 4100 spectrophotometer. The ^{1}H and ^{13}C-NMR spectra were recorded with a Bruker AC 200/300 spectrometer. Spectra were referenced to residual chloroform (δ 7.25 ppm, ^{1}H; 77.0 ppm, ^{13}C). Low resolution mass spectra were recorded with a Varian 500 mass spectrometer (ESI). Microanalysis was performed with vario Micro elemental analyzer. (±)-Camphor-10-sulfonic acid was purchased from Aldrich and was used as such. Spectral data of known compounds was in accordance with those reported in the literature while the unknown compounds were characterized by spectral (IR, ^{1}H-NMR, ^{13}C-NMR, MS) and microanalytical data.

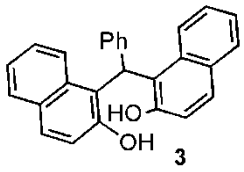
4.4.1 Typical procedure for the CSA catalyzed condensation of 2-naphthol (1) and benzaldehyde (2a) at ambient temperature

A mixture of benzaldehyde (0.265 g, 2.5 mmol), 2-naphthol (0.720 g, 5.0 mmol) and (±)-camphor-10-sulphonic acid (116 mg, 0.50 mmol, 20 mol% with respect to **2a**) was stirred at ambient temperature (25 °C). After 16 h the reaction mixture was quenched with saturated aqueous sodium bicarbonate solution and extracted with ethyl acetate. The organic layer was washed with water, brine and dried (Na_2SO_4). Removal of solvent

afforded a thick mass which was purified by silica gel column chromatography (0-20% EtOAc-hexane as eluant) to afford pink solid **3** (75%) and colorless solid **4a** (21%).

1,1-Bis-(2-hydroxynaphthyl)phenylmethane[115] **(3)**

MP: 195-196 °C; **IR ($CHCl_3$):** υ 3471, 3423, 3019, 1618, 1597, 1513, 1491, 1468, 1390, 1253, 1046, 877 cm^{-1}; **^{1}H-NMR (200 MHz, $CDCl_3$):** δ 7.13-7.38 (m, 12H, ArCHAr, ArH),

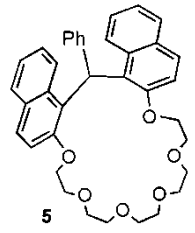


3

7.74-7.84 (m, 4H, ArH), 8.12 (d, *J* = 8.3 Hz, 2H, ArH); **^{13}C-NMR (50 MHz, $CDCl_3$):** δ 43.0, 120.1, 120.4, 123.6, 123.7, 126.8, 127.5, 128.8, 129.1, 129.7, 130.0, 130.5, 135.2, 143.3, 154.0; **MS (ESI):** *m/z* 376 (M, 25), 375 (M−H, 95), 353 (8), 349 (11), 339 (16), 337 (10), 325 (10), 321 (100), 311 (11), 309 (16), 293 (22), 283 (9), 265 (16), 231 (58), 143 (39); **HRMS:** *m/z* calcd for $C_{27}H_{20}O_2Na$ (M+Na): 399.1361; found: 399.1365.

Synthesis of bis-napthalenocrown-6 (5)

A mixture of *bis*-(2-naphthol) **3** (0.790 g, 2.1 mmol), pentaethyleneglycolditosylate (1.26 g, 2.3 mmol, 1.1 equiv.) and Cs_2CO_3 (1.73 g, 5.3 mmol, 2.5 equiv.) in dry acetonitrile (30 ml) was refluxed for 8 h when TLC showed absence of both **3** and the ditosylate. The solvent was removed under vacuo, cooled, quenched with 1N HCl and extracted with ethyl acetate. The organic layer was washed with water, brine and dried (Na_2SO_4). Removal of solvent afforded a thick mass which was purified by silica gel column chromatography (using $CHCl_3$ as eluant) to afford light yellow solid **5** (0.948 g, 78%). **MP:** 155-156 °C; **IR**



5

($CHCl_3$): υ 3058, 3016, 2874, 1622, 1598, 1511, 1492, 1451, 1451, 1295, 1259, 1243, 1215, 1176, 928, 806, 697 cm^{-1}; **^{1}H-NMR (200 MHz, $CDCl_3$):** δ 2.88-2.98 (m, 2H, O*C*$H_2$$CH_2$O), 3.10-3.21 (m, 2H, O*C*$H_2$$CH_2$O), 3.31-3.35 (m, 4H, 2 × O*C*$H_2$$CH_2$O), 3.45-3.48 (m, 8H, 4 × O*C*$H_2$$CH_2$O), 3.69-3.71 (m, 2H, O*C*$H_2$$CH_2$O), 3.77-3.83 (m, 2H, O*C*$H_2$$CH_2$O), 7.03-7.14 (m, 6H,

ArCHAr, ArH), 7.23-7.30 (m, 6H, ArH), 7.73-7.81 (m, 6H, ArH); **^{13}C-NMR (50 MHz, $CDCl_3$):** δ 43.9, 68.4, 68.9, 70.3, 116.1, 122.7, 124.0, 124.8, 125.2, 125.8, 127.5, 128.1, 128.2, 128.7, 129.4, 133.4, 144.9, 155.2; **MS (APCI):** *m/z* 579 (M+H, 70), 578 (M, 100), 577 (M−H, 43), 259 (35), 171 (31), 169 (25); **HRMS:** *m/z* calcd for $C_{37}H_{39}O_6$ (M+H): 579.2747; found: 579.2731.

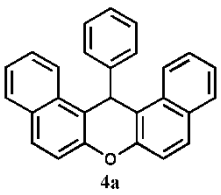
4.4.2 Typical procedure for the solvent-free condensation of 2-naphthol (1) with benzaldehyde (2a) to dibenzoxanthene (4a) at elevated temperature conditions

A mixture of 2-naphthol (1.44 g, 10 mmol), benzaldehyde (0.584 g, 5.5 mmol) and (±)-CSA (0.192 g, 15 mol%) was heated at 80 °C without any solvent. After completion of the reaction (monitored by TLC), the pinkish solid formed was quenched with water, filtered, washed with water and dried in air. The crude solid was recrystallized with hexane-ethyl acetate to afford pure **4a** (1.60 g, 89%).

4.4.3 Typical procedure for the solvent-free condensation of 2-naphthol (1) with benzaldehyde (2a) to dibenzoxanthene (4a) under microwave irradiation

A mixture of 2-naphthol (1.44 g, 10 mmol), benzaldehyde (0.584 g, 5.5 mmol) and (±)-CSA (0.026 g, 2 mol%) was taken in the microwave vessel and irradiated (400 W, 63-64 °C). After 15 min, TLC showed complete consumption of both the starting materials and formation of **4a** as the only product. The solid thus formed was quenched with water, filtered, washed with water and dried in air. The crude solid was recrystallized with hexane-ethyl acetate to afford pure **4a** (1.59 g, 88%).

14-Phenyl-14*H*-dibenzo[*a*,*j*]xanthene[113] (4a)

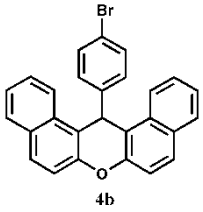

4a

MP: 187-188 °C (lit. 186-187 °C); **IR ($CHCl_3$):** υ 3061, 3017, 2924, 1592, 1456, 1401, 1251, 1215, 962, 808 cm^{-1}; **^{1}H-NMR (200 MHz, $CDCl_3$):** δ 6.50 (s, 1H, ArCHAr), 6.96-7.03 (m, 1H, ArH), 7.12-7.20 (m, 2H, ArH), 7.38-7.63 (m, 8H, ArH), 7.77-7.85 (m, 4H, ArH), 8.41 (d, *J* = 8.5 Hz, 2H,

ArH); **^{13}C-NMR (50 MHz, $CDCl_3$):** δ 38.0, 117.3, 117.9, 122.6, 124.1, 126.3, 126.6, 128.2, 128.4, 128.6, 128.7, 131.0, 131.4, 145.0, 148.7; **MS (EI):** *m/z* 358 (M, 20), 281 (100), 252 (13), 250 (8).

14-(4-Bromophenyl)-14*H*-dibenzo[*a,j*]xanthenes[122] (4b)

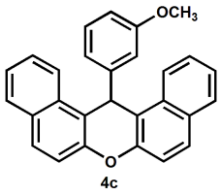
Following the procedure as described in 4.4.3, the product **4b** was isolated as colorless solid (82%). **MP:** 293-294 °C (lit. 295-296 °C); **IR ($CHCl_3$):** υ 3019, 2906, 1633, 1482, 1214 cm^{-1}; **^{1}H-NMR (200 MHz, $CDCl_3$):** δ 6.45 (s, 1H, ArCHAr), 7.23-7.27 (m, 2H, ArH), 7.37-7.50 (m, 6H, ArH), 7.54-7.62 (m, 2H, ArH), 7.78-7.86 (m, 4H, ArH), 8.31 (d, *J* = 8.4 Hz, 2H, ArH); **^{13}C-NMR (50 MHz, $CDCl_3$):** δ 37.4, 116.7, 118.0, 120.2, 122.4, 124.3, 126.9, 128.9, 129.1, 129.8, 131.1, 131.2, 131.5, 143.9, 148.7; **HRMS:** *m/z* calcd for $C_{27}H_{18}BrO$ (M+H): 437.0536; found: 437.0533.



4b

14-(3-Methoxyphenyl)-14*H*-dibenzo[*a,j*]xanthenes[113] (4c)

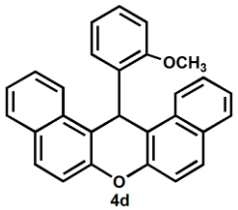
Following the procedure as described in 4.4.3, the product **4c** was isolated as colorless solid (98%). **MP:** 177-178 °C (lit. 179-180 °C); **IR ($CHCl_3$):** υ 3018, 2938, 1593, 1486, 1457, 1432, 1400, 1215 cm^{-1}; **^{1}H-NMR (200 MHz, $CDCl_3$):** δ 3.63 (s, 3H, OCH_3), 6.46 (s, 1H, ArCHAr), 6.50-6.56 (m, 1H, ArH), 7.03-7.19 (m, 3H, ArH), 7.37-7.50 (m, 4H, ArH), 7.59 (td, *J* = 7.7, 1.3 Hz, 2H, ArH), 7.81 (t, *J* = 8.3 Hz, 4H, ArH), 8.40 (d, *J* = 8.4 Hz, 2H, ArH); **^{13}C-NMR (50 MHz, $CDCl_3$):** δ 37.9, 54.9, 110.9, 114.9, 117.1, 117.9, 120.7, 122.7, 124.1, 126.7, 128.7, 128.8, 129.2, 131.0, 131.4, 146.5, 148.7, 159.6; **MS (ESI):** *m/z* 389 (M+H, 13), 388 (M, 14), 387 (M−H, 10), 363 (8), 297 (9), 282 (40), 281 (100).



4c

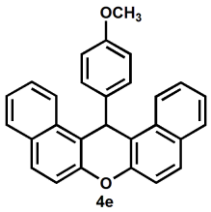
14-(2-Methoxyphenyl)-14H-dibenzo[a,j]xanthene[122] **(4d)**

Following the procedure as described in 4.4.3, the product **4d** was isolated as colorless solid (54%). **MP:** 258-259 °C (lit. 258-260 °C); **IR ($CHCl_3$):** υ 3019, 1641, 1459, 1404, 1243, 1215 cm^{-1}; **^{1}H-NMR (200 MHz, $CDCl_3$):** δ 4.27 (s, 3H, OCH_3), 6.60-6.67 (m, 1H, ArCHAr), 6.84-7.00 (m, 3H, ArH), 7.19 (dd, *J* = 7.6, 1.6 Hz, 1H, ArH), 7.35-7.57 (m, 6H, ArH), 7.78 (t, *J* = 8.0 Hz, 4H, ArH), 8.58 (d, *J* = 8.4 Hz, 2H, ArH); **^{13}C-NMR (50 MHz, $CDCl_3$):** δ 30.3, 55.6, 110.6, 117.9, 118.5, 121.7, 123.3, 124.1, 126.6, 127.5, 128.4, 130.7, 130.8, 132.1, 134.6, 148.8, 153.8; **MS (APCI):** *m/z* 389 (M+H, 100), 388 (M, 9), 282 (32), 281 (79), 246 (12).



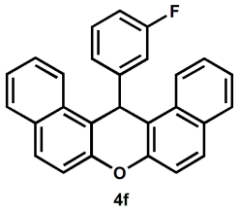
14-(4-Methoxyphenyl)-14H-dibenzo[a,j]xanthene[113] **(4e)**

Following the procedure as described in 4.4.3, the product **4e** was isolated as colorless solid (88%). **MP:** 207-208 °C (lit. 205-206 °C); **IR ($CHCl_3$):** υ 3017, 2955, 2399, 1607, 1509, 1432, 1215 cm^{-1}; **^{1}H-NMR (200 MHz, $CDCl_3$):** δ 3.61 (s, 3H, OCH_3), 6.45 (s, 1H, ArCHAr), 6.67 (d, *J* = 8.7 Hz, 2H, ArH), 7.37-7.62 (m, 8H, ArH), 7.80 (t, *J* = 8.8 Hz, 4H, ArH), 8.38 (d, *J* = 8.5 Hz, 2H, ArH); **^{13}C-NMR (50 MHz, $CDCl_3$):** δ 37.1, 55.0, 113.8, 117.5, 117.9, 122.7, 124.1, 126.7, 128.6, 128.7, 129.1, 131.1, 131.4, 137.3, 148.7, 157.9; **MS (EI):** *m/z* 388 (M, 22), 281 (100), 252 (20), 250 (11), 92 (13), 77 (14), 64 (6).



14-(3-Flurophenyl)-14H-dibenzo[a,j]xanthene[116] **(4f)**

Following the procedure as described in 4.4.3, the product **4f** was isolated as colorless solid (95%). **MP:** 256-257 °C (lit. 259 °C); **IR ($CHCl_3$):** υ 3019, 2926, 2854, 2399, 2347, 1592, 1458, 1401, 1249, 1215 cm^{-1}; **^{1}H-NMR (200 MHz, $CDCl_3$):** δ 6.48 (s, 1H, ArCHAr), 6.65-6.73 (m, 1H,ArH), 7.05-7.18 (m, 2H, ArH), 7.33-7.51 (m, 5H, ArH), 7.59 (t, *J* = 7.3 Hz, 2H, ArH), 7.82 (t, *J* =



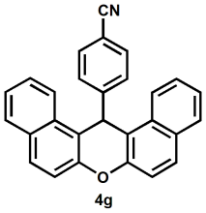
7.7 Hz, 4H, ArH), 8.34 (d, *J* = 8.5 Hz, 2H, ArH); **^{13}C-NMR (50 MHz, $CDCl_3$):** δ 37.6, 113.2, 113.6, 115.0, 115.5, 116.7, 118.0, 122.4, 123.7, 123.8, 124.3, 126.9, 128.8, 129.1, 129.6, 129.8, 131.0, 131.3, 147.3, 147.4, 148.8, 160.5, 165.4; **MS (EI):** *m/z* 376 (M, 8), 281 (100), 252 (14), 250 (8), 141 (6).

4.4.4 General procedure for the condensation of 2-naphthol (1) with solid aromatic aldehyde (2g-k) to dibenzoxanthene (4g-k) under microwave irradiation

A mixture of 2-naphthol, aldehydes (**2g-k**) (0.55 equiv.), (±)-CSA (0.02 equiv.) in acetonitrile (0.25 ml/mmol) was was taken in the microwave vessel and irradiated (400 W, 63-64 °C). After 15-45 min, the reaction mixture was cooled to ambient temperature, quenched with saturated aqueous sodium bicarbonate solution and extracted with ethyl acetate. The organic layer was washed with water, brine and dried (Na_2SO_4). Removal of solvent afforded a thick mass which was purified by silica gel column chromatography to afford pure dibenzoxanthene (**4g-k**).

14-(4-Cyanophenyl)-14H-dibenzo[a,j]xanthene[115] (4g)

Following the procedure as described in 4.4.4, the product **4g** was isolated as colorless solid (86%). **MP:** 294-295 °C (lit. 291-292 °C); **IR ($CHCl_3$):** υ 3019, 2930, 2400, 2225, 1633, 1414, 1237, 1215 cm^{-1}; **^{1}H-NMR (200 MHz, $CDCl_3$):** δ 6.55 (s, 1H, ArCHAr), 7.40-7.51 (m, 6H, ArH), 7.55-7.64 (m, 4H, ArH), 7.81-7.87 (m, 4H, ArH), 8.27 (d, *J* = 8.4 Hz, 2H, ArH); **^{13}C-NMR (75 MHz, $CDCl_3$):** δ 38.0, 115.9, 118.0, 118.6, 122.1, 124.6, 127.1, 128.9, 129.0, 129.5, 131.0, 131.1, 132.1, 132.4, 148.8, 150.0; **MS (EI):** *m/z* 383 (M, 18), 281 (100), 252 (17), 250 (10), 192 (9), 141 (10), 126 (6), 102 (13), 75 (8).

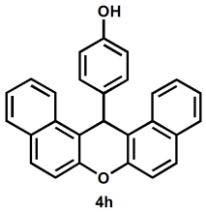


4g

14-(4-Hydroxyphenyl)-14H-dibenzo[a,j]xanthene[123](4h)

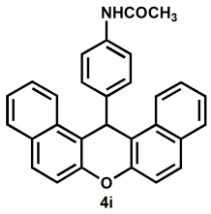
Following the procedure as described in 4.4.4, the product **4h** was isolated as pink solid (61%). **MP:** 138-139 °C (lit. 138-140 °C); **IR ($CHCl_3$):** υ 3535, 3402, 3070, 3019, 2926,

1609, 1592, 1509, 1458, 1431, 1401, 1241, 1214, 1173 cm^{-1}; **^{1}H-NMR (200 MHz, $CDCl_3$):** δ 6.43 (s, 1H, ArCHAr), 6.58 (d, *J*= 8.5 Hz, 2H, ArH), 7.34-7.49 (m, 6H, ArH), 7.58 (td, *J* = 7.6, 1.2 Hz, 2H, ArH), 7.80 (t, *J* = 8.6 Hz, 4H, ArH), 8.36 (d, *J* = 8.4 Hz, 2H, ArH); **^{13}C-NMR (50 MHz, $CDCl_3$):** δ 37.1, 115.3, 117.5, 117.9, 122.7, 124.1, 126.7, 128.6, 128.7, 129.3, 131.1, 131.4, 148.7, 153.9; **MS (EI):** *m/z* 374 (M, 20), 281 (100), 252 (15), 250 (6), 178 (6).



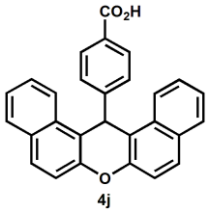
14-(4-Acetamidophenyl)-14H-dibenzo[a,j]xanthene (4i)

Following the procedure as described in 4.4.4, the product **4i** was isolated as colorless solid (86%). **MP:** 153-154 °C; **IR ($CHCl_3$,):** υ 3436, 3019, 1634, 1513, 14107, 1320, 1240, 1215 cm^{-1}; **^{1}H-NMR (200 MHz, $CDCl_3$):** δ 1.99 (s, 3H,NHCO*CH_3*), 6.45 (s, 1H, ArCHAr), 7.02 (br, 1H, NH), 7.21-7.26 (m, 3H, ArH), 7.36-7.49 (m, 5H, ArH), 7.56 (t, *J* = 7.6 Hz, 2H, ArH), 7.80 (t, *J* = 7.9 Hz, 4H, ArH), 8.34 (d, *J* = 8.5 Hz, 2H, ArH); **^{13}C-NMR (50 MHz, $CDCl_3$):** δ 24.0, 37.3, 117.0, 117.8, 119.9, 122.5, 124.2, 126.7, 128.6, 128.7, 128.8, 130.9, 131.3, 136.0, 141.0, 148.5, 168.4; **MS (ESI):** *m/z* 438 (M+Na, 100), 416 (M+H, 60), 281 (10), 175 (19), 164 (8), 151 (16), 139 (26), 131 (18), 122 (26); **Anal.** (calcd for $C_{29}H_{21}NO_2$: C, 83.83; H, 5.09; N, 3.37. found: C, 83.58; H, 5.44; N 3.08); **HRMS:** *m/z* calcd for $C_{29}H_{22}NO_2$ (M+H): 416.1651; found: 416.1653.



14-(4-Carboxyphenyl)-14H-dibenzo[a,j]xanthene (4j)

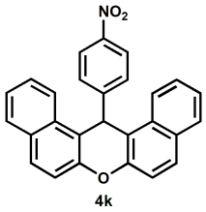
Following the procedure as described in 4.4.4, the product **4j** was isolated as colorless solid (85%). **MP:** >300 °C; **IR ($CHCl_3$,):** υ 3428, 3019, 1679, 1604, 1421, 1214, 1080, 1018 cm^{-1}; **^{1}H-NMR (200 MHz, $CDCl_3$):** δ 6.55 (s, 1H, ArCHAr), 7.37-7.53 (m, 4H, ArH), 7.58-7.62 (m, 4H, ArH), 7.78-7.86 (m, 6H, ArH), 8.32 (d, 2H, *J* = 8.4 Hz, ArH); **^{13}C-NMR (75 MHz, $CDCl_3$):** δ 38.1,



116.3, 118.0, 122.3, 124.4, 127.0, 128.4, 128.9, 129.3, 130.5, 130.7, 131.0, 131.3, 148.7, 150.8, 170.9; **MS (ESI):** *m/z* 403 (M+H, 9), 402 (M, 25), 401 (M−H, 100), 397 (25), 369 (13), 358 (7), 340 (8), 326 (5), 281 (5), 277 (19), 259 (8), 215 (9); **Anal.** (calcd for $C_{28}H_{18}O_3$: C, 83.57; H, 4.51. found: C, 83.36; H, 4.73); **HRMS:** *m/z* calcd for $C_{28}H_{19}O_3$ (M+H): 403.1334; found: 403.1352.

14-(4-Nitrophenyl)-14H-dibenzo[a,j]xanthene[122] **(4k)**

Following the procedure as described in 4.4.4, the product **4k** was isolated as yellow solid (84%). **MP:** >300 °C (lit. 310-311 °C); **IR ($CHCl_3$,):** υ 3019, 1634, 1516, 1340, 1250, 1239, 1106, 1014 cm^{-1}; **^{1}H-NMR (200 MHz, $CDCl_3$):** δ 6.60 (s, 1H, ArCHAr), 7.40-7.69 (m, 8H, ArH), 7.81-7.86 (m, 4H, ArH), 7.97-8.01 (m, 2H, ArH), 8.28 (d, *J* = 8.5 Hz, 2H, Ar); **^{13}C-NMR (50 MHz, $CDCl_3$):** δ 37.8, 115.8, 118.0, 122.0, 123.8, 124.6, 127.2, 128.9, 129.0, 129.6, 131.1, 146.3, 148.8, 151.9; **HRMS:** *m/z* calcd for $C_{27}H_{17}NNaO_3$ (M+Na): 426.1101; found: 426.1100.



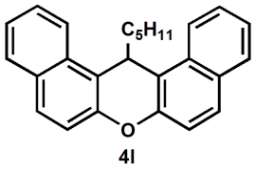
4k

4.4.5 General procedure for the condensation of 2-naphthol (1) with aliphatic aldehyde (2l, m) to dibenzoxanthene (4l, m) under microwave irradiation

A mixture of 2-naphthol, aldehydes (**2l, m**) (0.55 equiv.), (±)-CSA (0.02 equiv.) was irradiated in a microwave reactor at 400 W; 63-64 °C for 15 min.The reaction mixture was then cooled to ambient temperature, quenched with saturated aqueous sodium bicarbonate solution and extracted with ethyl acetate. The organic layer was washed with water, brine and dried (Na_2SO_4). Removal of solvent afforded a thick mass which was purified by silicagel column chromatography (0-10% EtOAc-hexane as eluant) to afford pure dibenzoxanthene (**4l**,**m**).

14-Pentyl-14H-dibenzo[a,j]xanthene (4l)

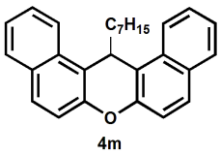
Following the procedure as described in 4.4.5, the product **4l** was isolated as colorless solid (92%). **MP:** 94-95 °C; **IR ($CHCl_3$,):** υ 3070, 2956, 2932, 2857, 1622, 1591, 1516, 1457, 1435, 1400, 1254, 1240, 956, 907, 815 cm^{-1}; **^{1}H-NMR (300 MHz, $CDCl_3$):** δ 0.63 (t, *J* = 6.5 Hz, 3H, $C_4H_8CH_3$), 0.97 (m, 6H,$CH_2C_3H_6CH_3$), 2.05 (m, 2H, ArCHCH_2), 5.57 (t, *J* = 4.3 Hz, 1H, ArCHAr), 7.39 (d, *J* = 9.0 Hz, 2H, ArH), 7.47 (t, *J* = 7.7 Hz, 2H, ArH), 7.63 (dd, *J* = 7.5, 1.2 Hz, 2H, ArH), 7.78 (d, *J* = 8.7 Hz, 2H, ArH), 7.89 (d, *J* = 8.1 Hz, 2H, ArH), 8.27 (d, *J* = 8.4 Hz, 2H, ArH); **^{13}C-NMR (75 MHz, $CDCl_3$):** δ 13.9, 22.4, 24.4, 30.9, 31.9, 35.8, 116.5, 117.5, 122.4, 124.0, 126.5, 128.1, 128.8, 130.9, 131.4, 149.9; **MS (EI):** *m/z* 352 (M, 2), 281 (100), 140 (14), 126 (4); **Anal.** (calcd. for $C_{26}H_{24}O$: C, 88.60; H, 6.86. found: C, 88.28; H, 6.63); **HRMS:** *m/z* calcd for $C_{26}H_{25}O$ (M+H): 353.1905; found : 353.1912.



4l

14-Heptyl-14H-dibenzo[a,j]xanthene (4m)

Following the procedure as described in 4.4.5, the product **4m** was isolated as viscous liquid (95%). **IR ($CHCl_3$,):** υ 3067, 2928, 2854, 1622, 1591, 1515, 1457, 1434, 1400, 1240, 1157, 1140, 960, 861, 813 cm^{-1}; **^{1}H-NMR (200 MHz, $CDCl_3$):** δ 0.77 (t, *J* = 7.1 Hz, 3H, $C_6H_{12}CH_3$), 1.02-1.36 (m, 10H, $C_5H_{10}CH_3$), 2.10-2.11 (m, 2H, ArCHCH_2), 5.59 (t, *J* = 4.3 Hz, 1H, ArCHAr), 7.36-7.53 (m, 4H, ArH), 7.66 (t, *J* = 7.7 Hz, 2H, ArH), 7.80 (d, *J* = 8.9 Hz, 2H, ArH), 7.91 (d, *J* = 8.1 Hz, 2H, ArH), 8.30 (d, *J* = 8.5 Hz, 2H, ArH); **^{13}C-NMR (50 MHz, $CDCl_3$):** δ 13.9, 22.4, 24.8, 28.9, 29.6, 30.9, 31.6, 35.9, 116.6, 117.4, 122.3, 123.9, 126.4, 128.0, 128.7, 131.0, 131.4, 149.9; **Anal.** (calcd for $C_{28}H_{28}O$: C, 88.38; H, 7.42. found: C, 87.95; H, 7.87); **HRMS:** *m/z* calcd for $C_{28}H_{29}O$ (M+H): 381.2218; found: 381.2212.



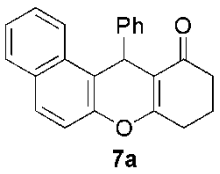
4m

4.4.6 General procedure for the CSA-catalyzed reaction of 2-naphthol, benzaldehyde and 1,3-dicarbonyl compounds (6a-c) under microwave irradiation

A mixture of benzaldehyde (0.530 g, 5.0 mmol), 2-naphthol (0.720 g, 5.0 mmol), 1,3 di-carbonyl compound (5.0 mmol) and (±)-camphor-10-sulphonic acid (10 mol%) in dry acetonitrile (5 ml) was taken in a closed vessel and irradiated in a microwave reactor at 400 W (65 °C). After 1 h, the reaction mixture was cooled to ambient temperature, quenched with saturated aqueous sodium bicarbonate solution and extracted with ethyl acetate. The organic layer was washed with water, brine and dried (Na_2SO_4). Removal of solvent afforded a thick mass which was purified by silica gel column chromatography (0-10% EtOAc-hexane as eluant) to afford pure **7a-c**.

9,10-Dihydro-12-phenyl-8*H*-benzo[*a*]xanthene-11(12*H*)-one[114] (7a)

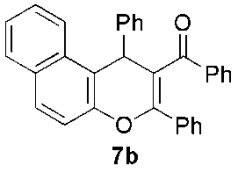
Following the general procedure as described in 4.4.6, the product **7a** was isolated as colorless solid (65%). **MP:** 200-201 °C (lit. 202-203 °C); **IR ($CHCl_3$):** υ 3062, 2954, 1648, 1595, 1398, 1375, 1228, 1187 cm^{-1}; **^{1}H-NMR (200 MHz, $CDCl_3$):** δ 2.04-2.09 (m, 2H, $CH_2CH_2CH_2$), 2.36-2.57 (m, 2H, $CH_2CH_2CH_2$), 2.70-2.85 (m, 2H, $CH_2CH_2CH_2$), 5.79 (s, 1H, ArCHAr), 7.11-7.30 (m, 3H, ArH), 7.37-7.50 (m, 5H, ArH), 7.79-7.83 (m, 2H, ArH), 8.01 (d, J = 8.4 Hz, 1H, ArH); **^{13}C-NMR (50 MHz, $CDCl_3$):** δ 20.1, 27.6, 34.6, 36.9, 115.5, 116.8, 117.6, 123.6, 124.8, 126.1, 126.9, 128.2, 128.3, 128.4, 128.7, 131.3, 131.4, 145.0, 147.7, 165.5, 196.9; **MS (EI):** *m/z* 326 (M, 19), 249 (100), 193 (6), 165 (13).



7a

2-Benzoyl-1,3-diphenyl-1*H*-benzo[*f*]chromene (7b)

Following the general procedure as described in 4.4.6, the product **7b** was isolated as colorless solid (67%). **MP:** 179-180 °C; **IR ($CHCl_3$):** υ 3061, 3019, 1649, 1597, 1517, 1466, 1447, 1402, 1336, 1215, 1023, 1012 cm^{-1}; **^{1}H-NMR (200 MHz, $CDCl_3$):** δ 5.92 (s, 1H, ArCHAr), 6.97-7.26 (m, 9H, ArH), 7.37-7.48

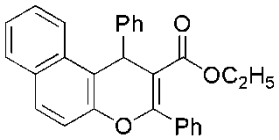


7b

(m, 9H, ArH), 7.83 (d, *J* = 8.9 Hz, 2H, ArH), 7.97 (d, *J* = 8.5 Hz, 1H, ArH); **^{13}C-NMR (50 MHz, $CDCl_3$):** δ 41.3, 115.4, 116.3, 117.3, 123.5, 124.6, 126.6, 126.9, 127.6, 127.9, 128.1, 128.5, 128.6, 129.0, 129.2, 129.6, 131.2, 131.4, 131.7, 133.8, 138.6, 144.5, 148.7, 154.2, 198.0; **Anal. (**calcd for $C_{32}H_{22}O_2$: C, 87.65; H, 5.06. found: C, 87.57; H, 5.08).

2-Carboethoxy-1,3-diphenyl-1*H*-benzo[*f*]chromene (7c)

Following the general procedure as described in 4.4.6, the product **7c** was isolated as



7c

viscous liquid (22%). **IR ($CHCl_3$):** υ 3060, 3024, 2982, 2929, 1695, 1644, 1622, 1595, 1516, 1492, 1446, 1333, 1223, 1072 cm^{-1}; **^{1}H-NMR (200 MHz, $CDCl_3$):** δ 0.98 (t,*J* = 7.1 Hz, 3H, $CO_2CH_2\mathit{C}H_3$), 4.03 (q, *J* = 7.1 Hz, 2H, $CO_2\mathit{C}H_2CH_3$), 5.85 (s, 1H, ArCHAr), 7.17-7.21 (m, 1H, ArH), 7.26-7.33 (m, 2H, ArH), 7.38-7.60 (m, 10H, ArH), 7.78-7.85 (m, 2H, ArH), 8.09 (d, *J* = 8.2 Hz, 1H, ArH); **^{13}C-NMR (50 MHz, $CDCl_3$):** δ 13.3, 39.1, 60.0, 108.4, 116.8, 116.9, 123.0, 124.5, 126.4, 126.7, 127.5, 128.1, 128.2, 128.7, 129.2, 130.8, 131.3, 135.0, 145.0, 148.1, 157.8, 166.9; **MS (ESI):** *m/z* 429 (M+Na, 100), 407 (8), 399 (11), 368 (18), 349 (7), 317 (11), 301 (7), 246 (9), 215 (9); **Anal.** (calcd for $C_{28}H_{22}O_3$: C, 82.74; H, 5.46. found: C, 82.84; H, 5.54).

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CHAPTER 5

Synthesis of Calixarene/Homocalixarene-based Metacyclophanes for Their Potential Use as Functional Materials

5.1 Preamble

The present chapter deals with our findings on one of the important and most studied class of functional molecules called calixarenes. Particular emphasis was put on the synthesis of different types of calixarene/homocalixarene based functional molecules, especially calixcrowns and homocalixarenes derivatives.

5.1.1 Calix[n]arene-crown ethers

Among different functionalized calixarenes, calix[n]arene-crown ethers, also called calixcrowns, are one of the most widely investigated class of cation (alkali, alkaline-earth metal, ammonium and transition metal ions) binding ligands.[137,138] As the name suggests they possess two kinds of receptor elements *viz*. calixarene and crown ether, joined *via* the phenolic oxygen of calix component. These ligands were synthesized by bridging two lower rim hydroxyl groups *via* an intramolecular polyether chain. Introducing a crown ether loop at the lower-rim not only increases the cation binding ability of the parent calix[n]arene, but also allows control of the selectivity through the modulation of the crown ether ring size.[138] This is due to the co-operative effect arising from both calixarene and crown ether moieties and thus exhibit superior reorganization ability as compared to its crown ether counterparts.[139]

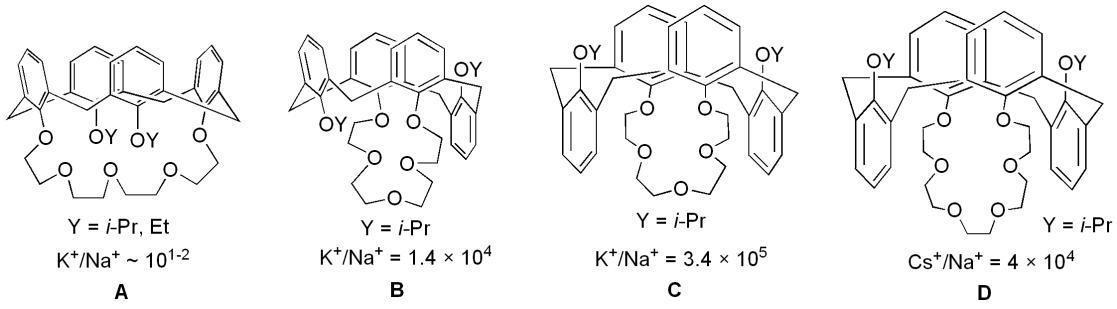


Figure 5a: Conformers of calix[4]crown ethers with different ion selectivities.

Ungaro and co-workers[140] were the first to develop a successful synthetic protocols for calix[4]-crowns such as l,3-dihydroxycalix[4]arene-crown-5 and l,3-dihydroxycalix[4]-crown-6. In his pioneering work, Reinhoudt[141] has explored different ways of making a number of calixcrown dialkyl ether derivatives. According to them, the ionophoric properties of calixcrown ethers vary significantly with their conformations as well as number of oxygen in the crown ether part. The cone conformers of calix[4]crown-5 (**A**, Fig. 5a) are selective for K^+ ions in presence of Na^+ ions, but the discrimination between the ions is found to be modest (~10^{1-2}). In contrast, the partial cone conformer of calix[4]crown-5 (**B**, Fig. 5a) shows an impressive K^+/Na^+ selectivity of 1.4×10^4, whereas its 1,3 alternate conformer (**C**, Fig. 5a) has been shown to be especially strong K^+ binder (K_{assoc}, $M^{-1} = 6.76 \times 10^9$) with very high K^+/Na^+ selectivity (3.4×10^5).[141c] In comparison to **C**, the di-iosopropylcalix[4]crown-6 (**D**), with a increased oxygen atom at the crown part shows especially high selectivity for Cs^+ in presence of Na^+ ($K_{Cs^+/Na^+} = 4000$) in its 1,3-alternate conformation.[141d] *p-tert*-Butylcalix[6]crown (**E**, Fig. 5b), bridged across the

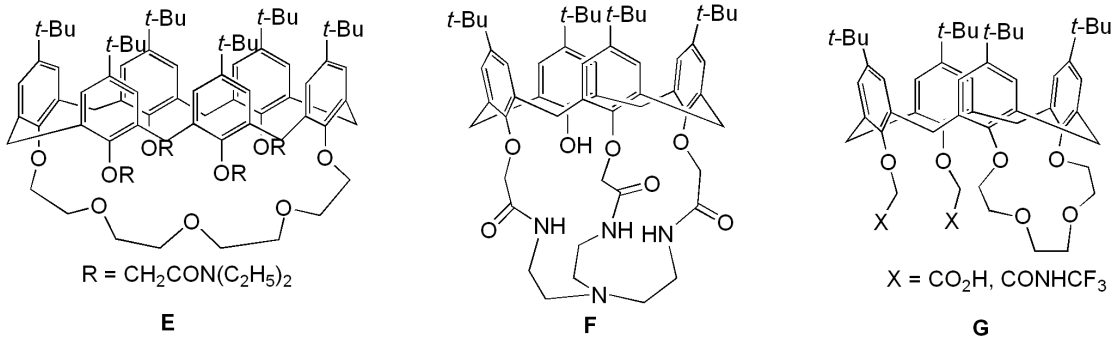


Figure 5b: Calixcrown ethers with varied ionophoric properties.

1,4 positions with a crown moiety are reported[142a] to be receptors for quaternary ammonium cations. Calix[4]azacrown (**F**, Fig. 5b) has been shown to be effective in the complexation of lanthanides (Eu^{3+}, Tb^{3+}, Nd^{3+}, Er^{3+}, La^{3+})[142b] whereas, *p-tert*-

Butylcalix[4]arene crown-4 compounds (**G**, Fig. 5b) with a pair of di-ionizable groups (e.g. CO_2H, $NHSO_2CF_3$) at the lower rim show a high selectivity for Ba^{2+}.[142c]

5.1.2 Homocalixarenes

The name "homocalixarenes" is used in a broader sense to refer metacyclophanes where at least one, but not necessarily all, of the bridges is larger than methylene (Fig. 5c).[143] Their conformational and ionophoric properties often differ significantly from those of their calixarene analogues and are, therefore, not only enlarged calixarenes but also known as a separate important family of host compounds. Typical methods for synthesis of

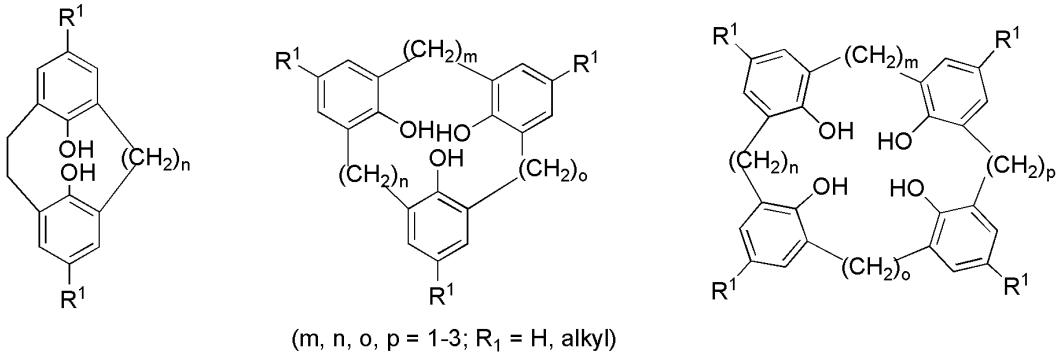


Figure 5c: Homocalixarenes with different cavity sizes.

homocalixarenes fall into two categories, "one-pot" and "convergent", analogous to those well-known for calixarenes. The one-pot procedures include approaches such as Müller-Röscheisen cyclization,[144] cyclization with *p*-(toluenesulfonyl)methyl isocyanide[145] and malonate cyclization.[146] Convergent routes involve methodologies such as sulfur extrusion,[147] Nafion-*H* catalyzed cyclobenzylation,[148] cross-coupling reactions using organometallic reagents[149] and condensation with aldehydes.[150] Excellent ionophores derived from homocalixarenes have been obtained by introduction of functional groups similar to those used in calixarene based ionophores.[151-153]

5.2 Present work

The present chapter deals with the design and synthesis of various exotic calix[4]crown and homocalixarene derivatives as functional materials and is divided into three parts, namely (i) design and synthesis of some novel rigidized calix[4]crowns, (ii) synthesis of $[3.1]_2$ homocalixarenes, and iii) use of one of the synthetic intermediates *i.e.* phenolic 1,3-diaryl propane as anti-cancer agent.

5.2.1 Design and synthesis of some novel rigidized calix[4]crowns

^{137}Cs is one of the major radio-isotope present in high level waste (HLW), emanating from the PUREX (Plutonium Uranium Reduction Extraction) process, which contains host of fission products, activation products and minor actinides. Presently, management of high level radioactive waste involves its vitrification in glass matrices followed by burial in deep geological repositories. Due to its high energy γ radiation (661.9 keV), heat output (0.42W/g) and relatively long half-life ($t_{½}$ = 30.1 years), ^{137}Cs poses major concern to the vitrified glass matrices. Therefore, separation of radio cesium from the nuclear waste is essential to resolve the MANREM problem (personnel radiation exposure during radioactive waste handling) and also can reduce the risk of waste matrix deformation. Moreover, the isolated ^{137}Cs can be utilized as an alternative radiation source in the place of the commonly employed ^{60}Co for a variety of purposes including sterilization of medical accessories, preservation of food, sewage sludge treatment, etc. Accordingly, several techniques have been adopted for the recovery of radio-cesium from various waste streams which include precipitation, solvent extraction and ion exchange.[153] The solvent extraction method appears to be fast and reagents such as calix[4]crowns have been shown to be highly selective for Cs(I) in presence of large concentration of sodium ion. Therefore, significant efforts have been directed towards the use of 1,3-

dialkyloxycalix[4]arene-crown-6 in the sensing, monitoring and remediation of Cs.[154] High affinity and selectivity towards Cs was only reported for some calix[4]arenes-crown-6 bearing alkyl chains (i.e. *i*-propyl, *n*-propyl, and *n*-octyl) in the 1,3-alternate conformation.[141,155] Among different calix[4]-crown ethers, *bis*(1-octyloxy)calix[4]crown-6 (Fig. 5d) in its 1,3-alternate conformation is well known for its high affinity and selectivity towards Cs ($K_{Cs+}/K_{Na+} > 33000$) in presence of Na.[156] The high separation factor has been accounted by the complexation of cesium with the crown ether (ion-dipole interaction) and cation-π interaction of cesium with the two aromatic rings bearing the alkoxy chains. However, still there are some operational issues regarding third phase formation during its use in pilot scale solvent extraction of Cs ion possibly due to hydrophobic-hydrophilic interactions. The excellent extraction ability of

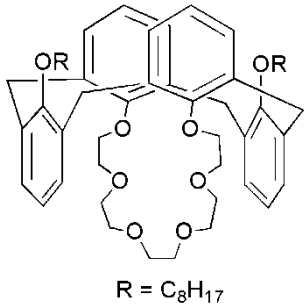


Figure 5d: Bis(1-octyloxy)calix[4] crown-6.

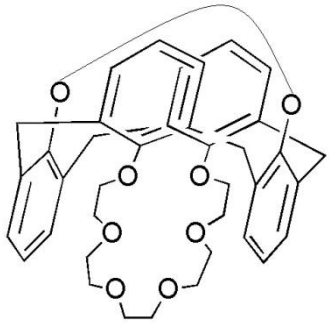
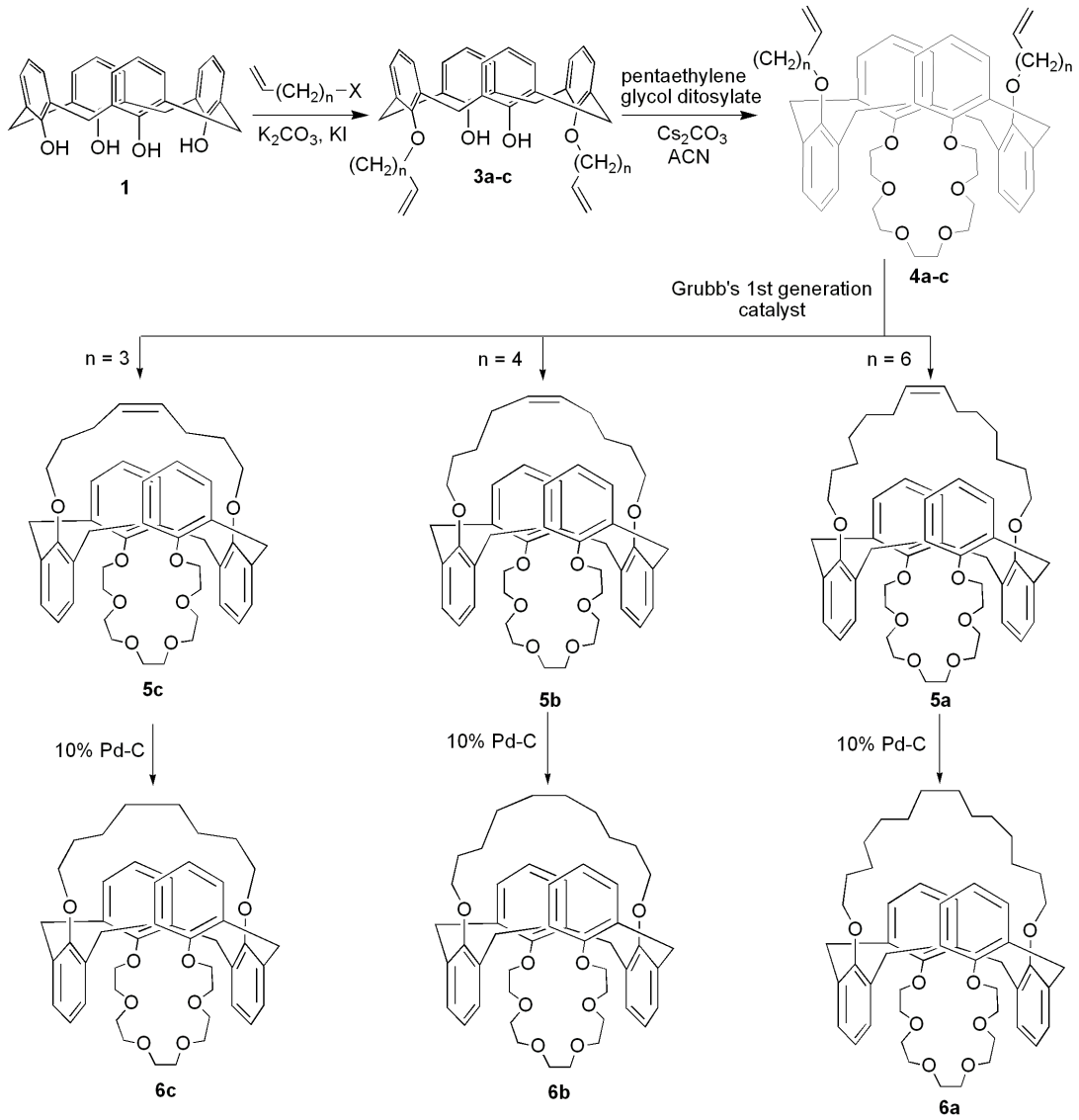


Figure 5e: Design of rigidized calix[4]crowns.

1,3-*bis*(1-octyloxy)calix[4]crown-6 for selective extraction of cesium has prompted us to design and optimize its structure to augment their extraction behavior further. To this end, synthesis of some 1,3-cyclodialkyloxycalix[4]arene-crown-6, with similar functionality but having a more rigid structure was initiated. Our strategy (Fig. 5e) was based on joining the two alkyl chains of 1,3-dialkyloxycalix[4]arene-crown-6 to a rigidized cyclic ether, which in principle can improve the binding ability or selectivity in metal ion extraction due to the modification of ring strain.

Towards making a comparative study with our designed molecules (**6a-c**), having varied alkyl chain length between the two 1,3-oxo groups, we have started our synthesis from calix[4]arene (**1**) as delineated in Scheme 5a. We planned to achieve the synthesis of **6a-c**



Scheme 5a: Synthesis of rigidized calix[4]crown, **6a-c**.

by catalytic hydrogenation of **5a-c**, which in turn could be assembled by intramolecular ring-closing metathesis of two terminal alkenes in 1,3-dialkenyloxy calix[4]arene crown-6 (**4a-c**). The compounds **4a-c** can be synthesized by intramolecular etherfication of two phenolic groups of dialkyl ethers (**3a-c)** of calix[4]arene (**1**) with corresponding pentaethyleneglycol ditosylate. Although looks simple, one of the key steps in the total

synthesis (Scheme 5a) was the preparation of 1,3-dialkenyl calix[4]arene (**3a-c**) in cone conformation in good yield. Conventional procedures for the synthesis of 1,3-dialkyl calix[4]arene in cone conformation with shorter iodo-alkanes are often high yielding.[153] However, dialkylation of calix[4]arene with long chain alkyl halides (C5 to C8) are very slow and takes several days for completion.[141d] Out of various long chain alkyl halides, iodoalkanes are found to be superior in terms of both time and yield. As iodo-alkanes are usually expensive material effort was put on using bromoalkanes as electrophiles along with some cheap and readily available additives. For optimization of reaction conditions, at first a control reaction was carried out with calix[4]arene, 1-bromooctane (2.5 equiv.), and K_2CO_3 (2.5 equiv.) in acetonitrile under refluxing conditions (5 days) when 1,3-dioctyl calix[4]arene (**2**) was obtained in modest yield (46%) along with small amount of unreacted calix[4]arene (Table 5a, entry 1). Gratifyingly, addition of

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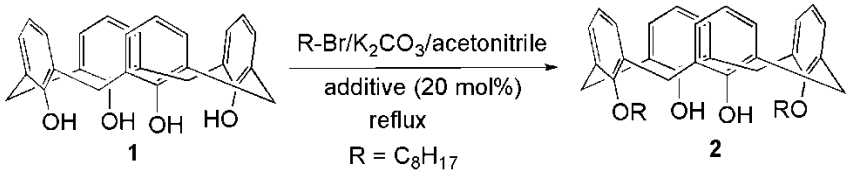
Table 5a: Optimization of the additives for the alkylation reactions of calix[4]arene



1 Calix[4]arene — **2** 1,3-Dialkylated product

Entry	Additive (20 mol%)	Reaction time	%Yield of **2**[a]
1	no additive	5 days	46
2	KI	48 h	75
3	TMAI	48 h	63
4	TBAI	48 h	69
5	THAI	48 h	65

[a] Isolated yield.

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potassium iodide (KI, 20 mol%) as additive increased the rate of the reaction drastically and **2** (Fig. 5f) was obtained in 75% yield in 48 h (Table 5a, entry 2). Use of other additives having iodide ion source such as tetramethylammonium iodide (TMAI), tetrabutylammonium iodide (TBAI) and tetrahexylammonium iodide (THAI) also led to the formation of **2** in 63%, 69% and 65% yields respectively (Table 5a, entry 3-5). Thus in the 1,3-dialkylation of calix[4]arene with alkyl bromide, KI was found to be an excellent additive in terms of both cost and reaction yield (Table 5a).

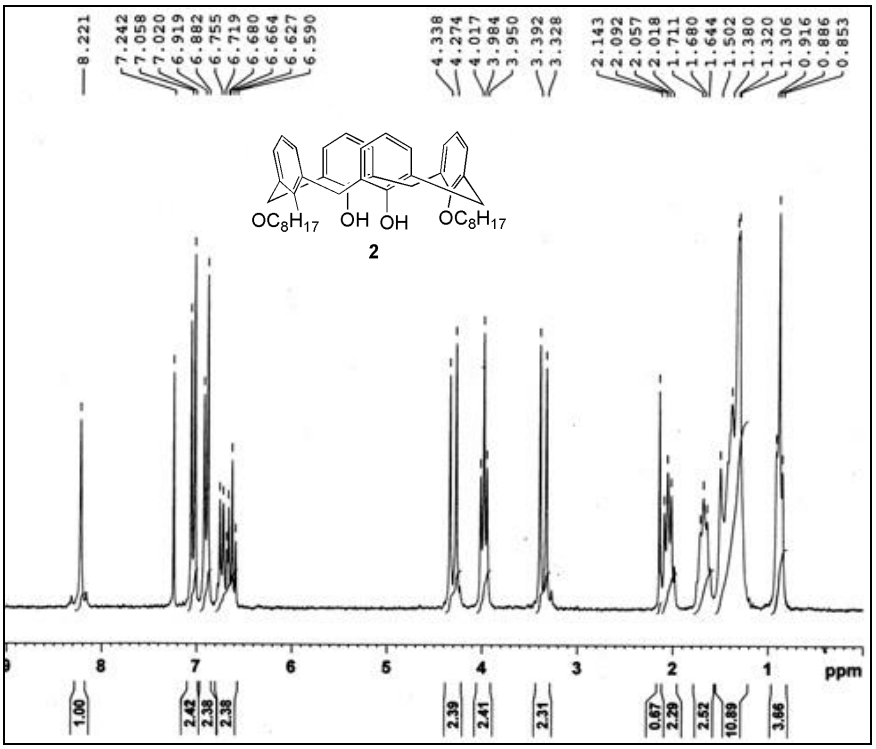


Figure 5f: ^{1}H-NMR of **2**.

With optimized reaction conditions in hand, 1,3-dialkylation of calix[4]arene was carried out with 8-bromo-1-octene to afford 1,3-dioctenyl calix[4]arene (**3a**, Scheme 5a) in 67% isolated yield. The product **3a** was characterized from ^{1}H-NMR resonances *viz*. multiplets at δ 5.01-5.12 and δ 5.84-5.98 (two terminal –CH=CH_2) and a pair of doublets at δ 3.44 and δ 4.38 (2 × 4H, $ArCH_2Ar$; cone conformation). The concentration

independent hydroxyl stretching bands at 3290 cm^{-1} in the IR spectrum and a D_2O exchangeable singlet at δ 8.31 ppm in the ^{1}H-NMR spectrum indicated presence of intramolecularly hydrogen bonded –OH groups in the compound. The conformation of **3a** was further substantiated by the presence of CH_2 peak at δ 31.4 in the 13C-NMR spectrum which is typical for cone conformation of calix[4]arene. As Cs_2CO_3 is known to direct crown ethers to assume 1,3-alternate conformation the remaining two phenolic –OH groups of compound **3a** was alkylated with pentaethyleneglycol ditosylate by using Cs_2CO_3 in acetonitrile to obtain *bis*(1-octenyloxy)calix[4]crown-6, 1,3-alternate (**4a**, Scheme 5a) in 66% yield. The IR and ^{1}H-NMR spectra of **4a** were devoid of characteristic absorption of –OH groups which proved complete alkylation of the four hydroxyl groups in calix[4]arene has occurred. A sharp singlet at δ 3.79 ppm for eight protons in the ^{1}H-NMR spectrum and signal at δ 37.8 ppm in the ^{13}C-NMR spectrum indicates that the compound is in 1,3-alternate conformation. Subsequently, **4a** was subjected to Grubb's 1st generation catalyst in dicholoromethane for metathesis. Gratifyingly, successful intramolecular ring closure metathesis of two terminal double bonds was observed and the alkene bridged calix[4]crown-6, **5a** was obtained in 60% isolated yield. No inter-molecularly coupled product was isolated. Spectroscpic data HRMS (M+K, *m/z* = 857.4389) of the isolated product matches with the desired compound **5a**. The ^{1}H-NMR spectrum (δ 3.84 ppm, s, 8H) and ^{13}C-NMR spectrum (δ 38.3 ppm) conforms its 1,3-alternate conformation. The desired rigidized calixcrown (**6a**) with 14 carbon alkyl chain was then successfully achieved by catalytic hydrogenation of **5a** with Pd-C in 81% yield. The structure of **6a** has been elucidated based on its spectral data (IR, NMR (Fig. 5g-A,B), HRMS). The 1,3-alternate conformation of **6a** was also assigned on the basis of its ^{1}HNMR and ^{13}C NMR data.

In order to establish the relationship between number of intervening bridge carbon atoms and their ionophoric behavior two other calix[4]arene crown-6 (**6b,c**) with relatively shorter alkyl chain length (n = 8, 10) were also synthesized. This necessarily involved 1,3-dialkylation of calix[4]arene (**1**) with 6-bromo-1-hexene and 5-bromo-1-pentene respectively followed by the same sequence of reactions as described in case of **6a**. Structure and conformation of both **6b** and **6c** was unequivocally established by spectral data. Based on the NMR spectral data the dialkylated calix[4]arene (**3b-c**) was found to be in cone conformation while all the calix[4]crown-6 compounds (**4b-c**, **5b-c**, **6b-c**) were found to be in 1,3-alternate conformation. The ^{1}H-NMR and ^{13}C-NMR spectra of the final calix[4]arene crown-6 (**6b-c**) were presented in Fig. 5h-A,B and Fig. 5i-A,B respectively. The ionophoric studies of the synthesized calix-crown compounds are currently underway.

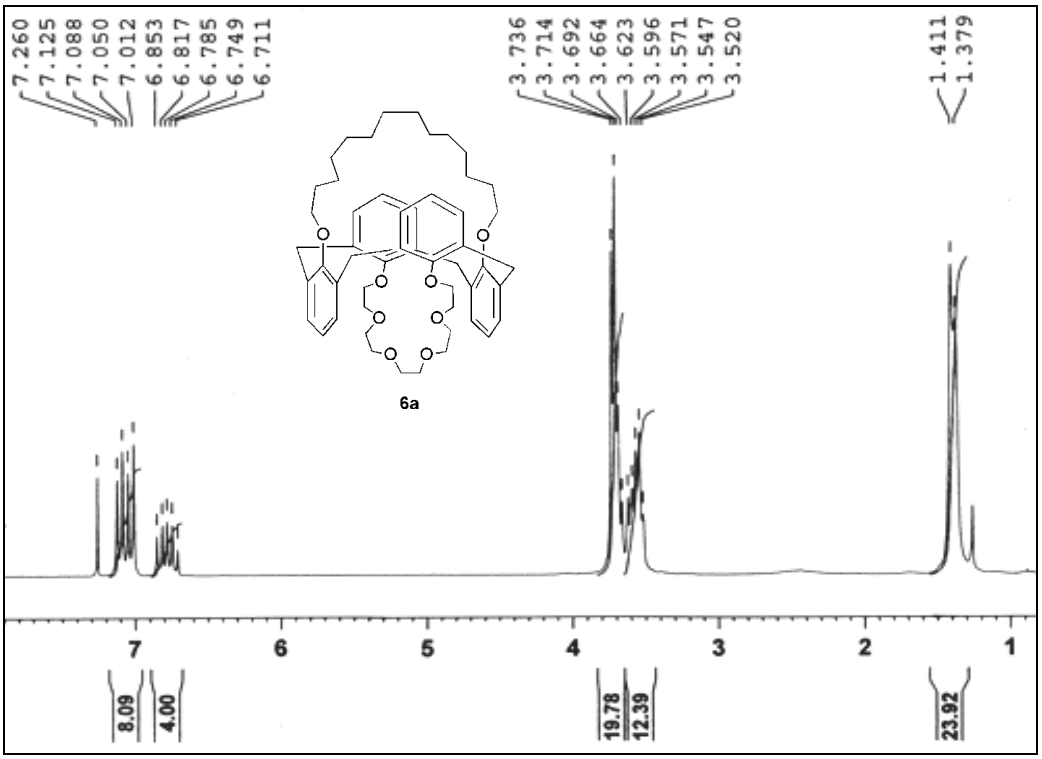


Figure 5g-A: ^{1}H-NMR of **6a**.

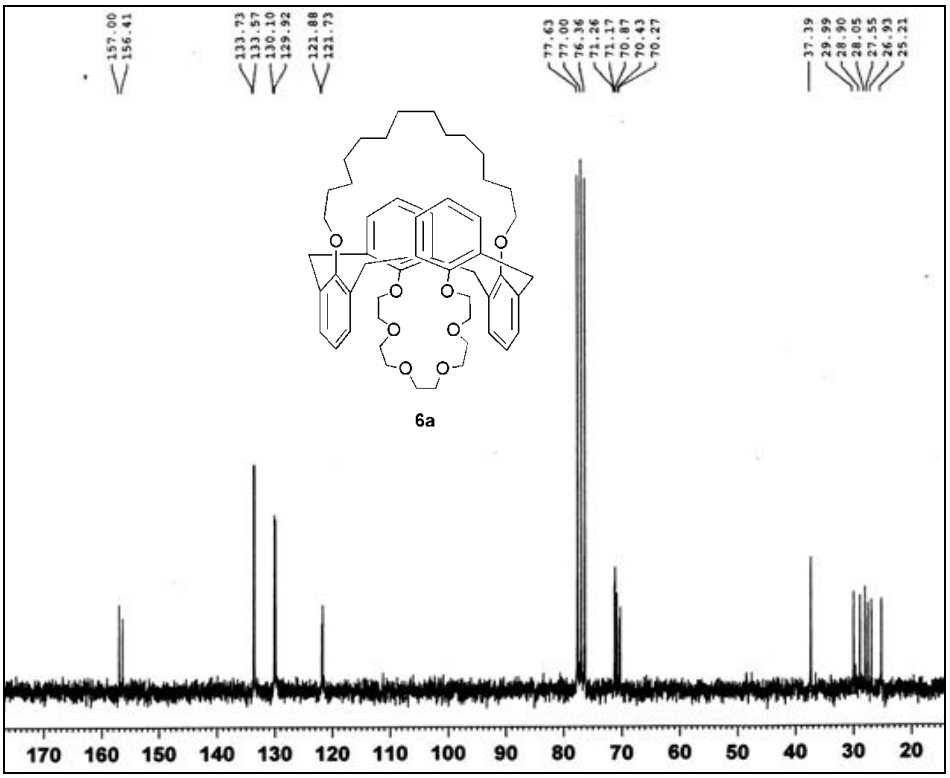


Figure 5g-B: ^{13}C-NMR of **6a**.

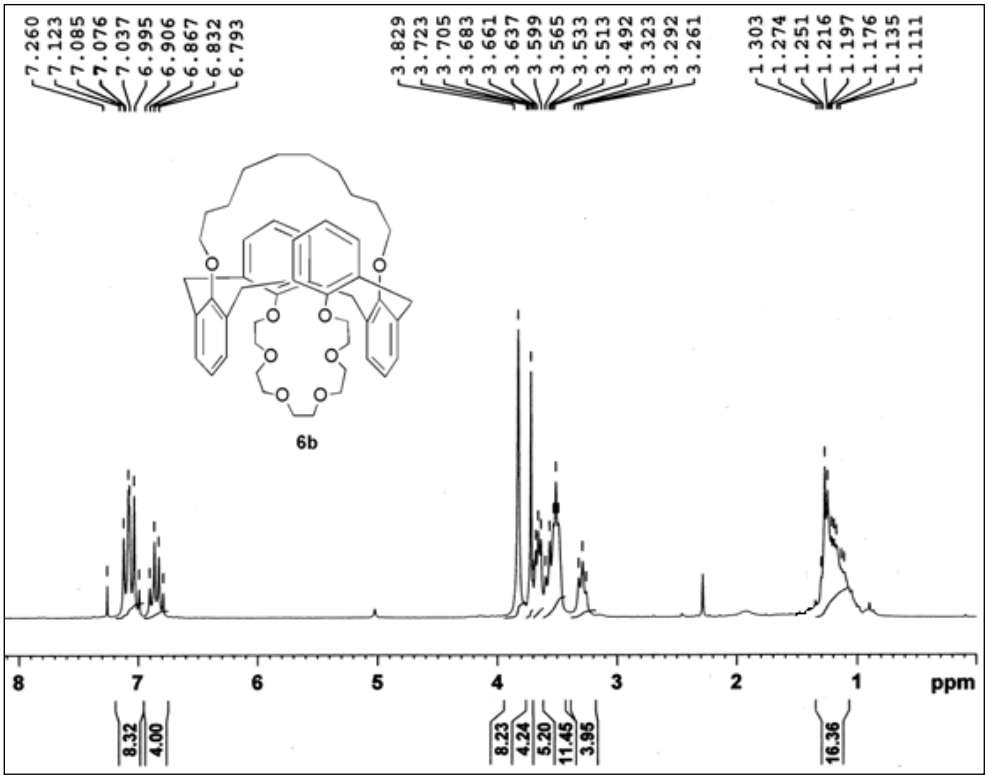


Figure 5h-A: ^{1}H-NMR of **6b**.

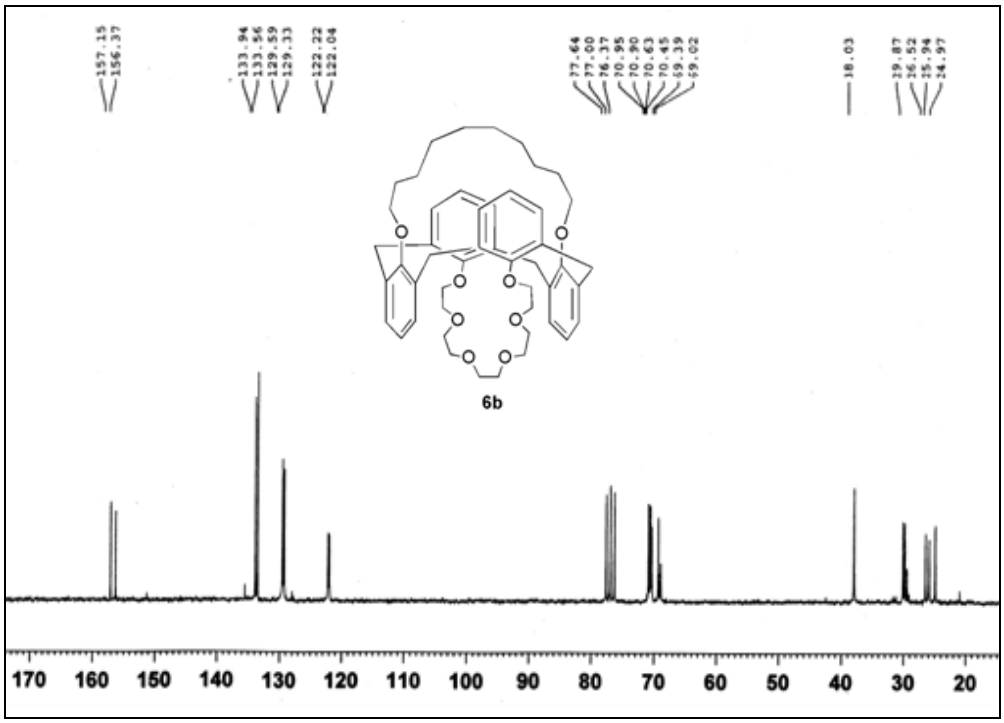


Figure 5h-B: ^{13}C-NMR of **6b**.

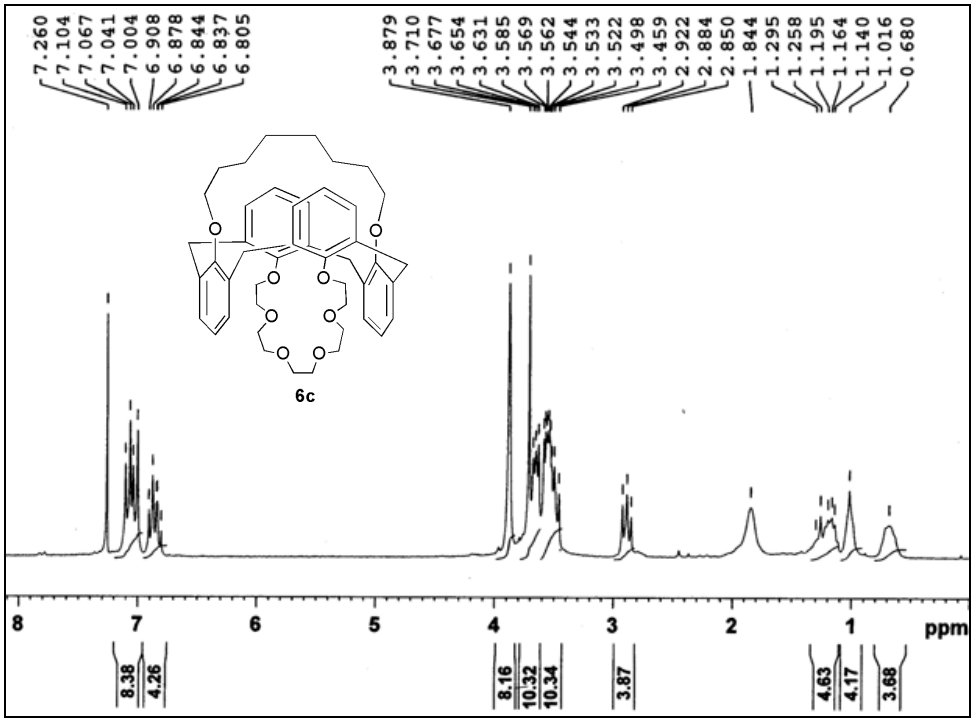


Figure 5i-A: ^{1}H-NMR of **6c**.

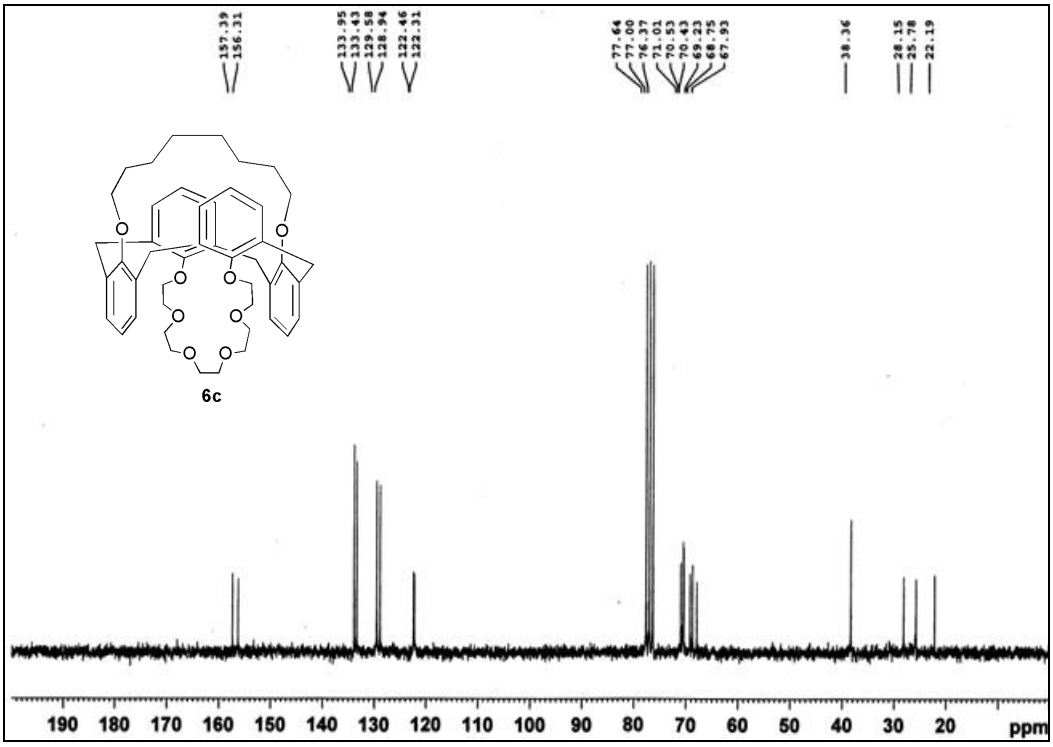


Figure 5i-B: ^{13}C-NMR of **6c**.

5.2.2 Synthesis of [3.1.3.1] homocalixarenes

One of the important members of homocalixarene class of molecules is [3.1.3.1] homocalix[4]arene (Fig 5j). As discussed before, it is a structural analogue close to calix[4]arene, having four phenolic groups but instead of all four methylene bridges present in calix[4]arene it has alternate propane and methylene bridges. Therefore it has larger cavity size as compared to calix[4]arene as evidenced by its ability to hold bigger metal ions. For instance, both *cone*- and *partial cone*-conformation of [3.1.3.1] homocalixarene, **H-1** (Fig 5i) (R = (2-pyridyl)methyl) exhibited high selectivity and extractability for Ag^+ which was found to be superior to those of dibenzopyridino-18-crown-6.[152c] Whereas, **H-2** (Fig 5i, R = $CH_2COOC_2H_5$, CH_2COO*t*-Bu) preferred to exist in *1,2-alternate* conformation and showed strong Rb^+ affinities comparable with that for 18-crown-6.[153] In contrast to calixarenes, very few reports are available for the synthesis of

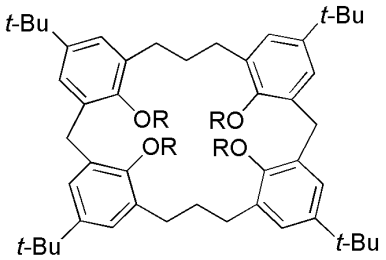
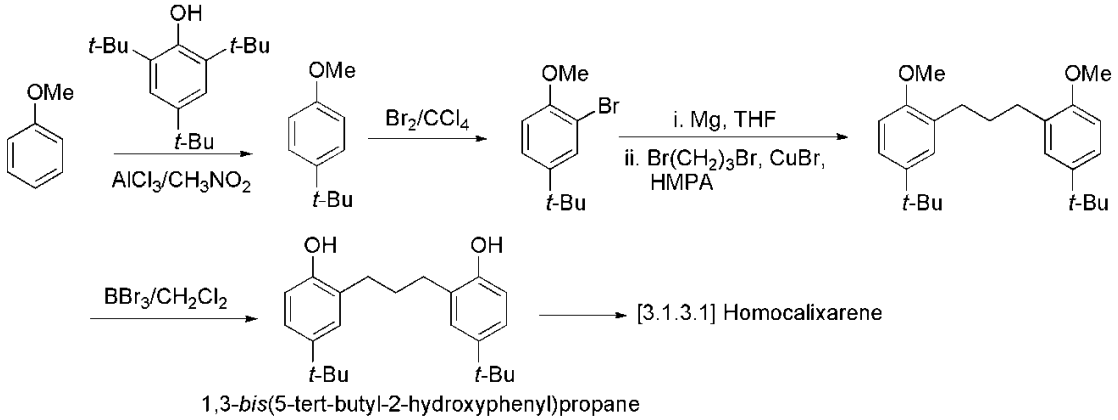


Figure 5j: [3.1.3.1] Homocalix[4]arene (**H-1, H-2**).

homocalixarenes with bigger cavity size.[150a,b, 157] The literature reports on the synthesis of homocalixarenes often involves multiple steps and are low yielding. So far there is a single report on the synthesis of propane-bridged metacyclophanes, tetrahydroxy [3.1.3.1] homocalix[4]arene by Yamoto *et. al*.[150a] Their synthetic strategy (Scheme 5b) involved the synthesis of the key intermediate, 1,3-*bis*(5-*tert*-butyl-2-hydroxyphenyl)propane, which was prepared in four steps involving Grignard reaction as the crucial step. Therefore, large scale synthesis of such metacyclophanes using organometallic reagents looks practically difficult.



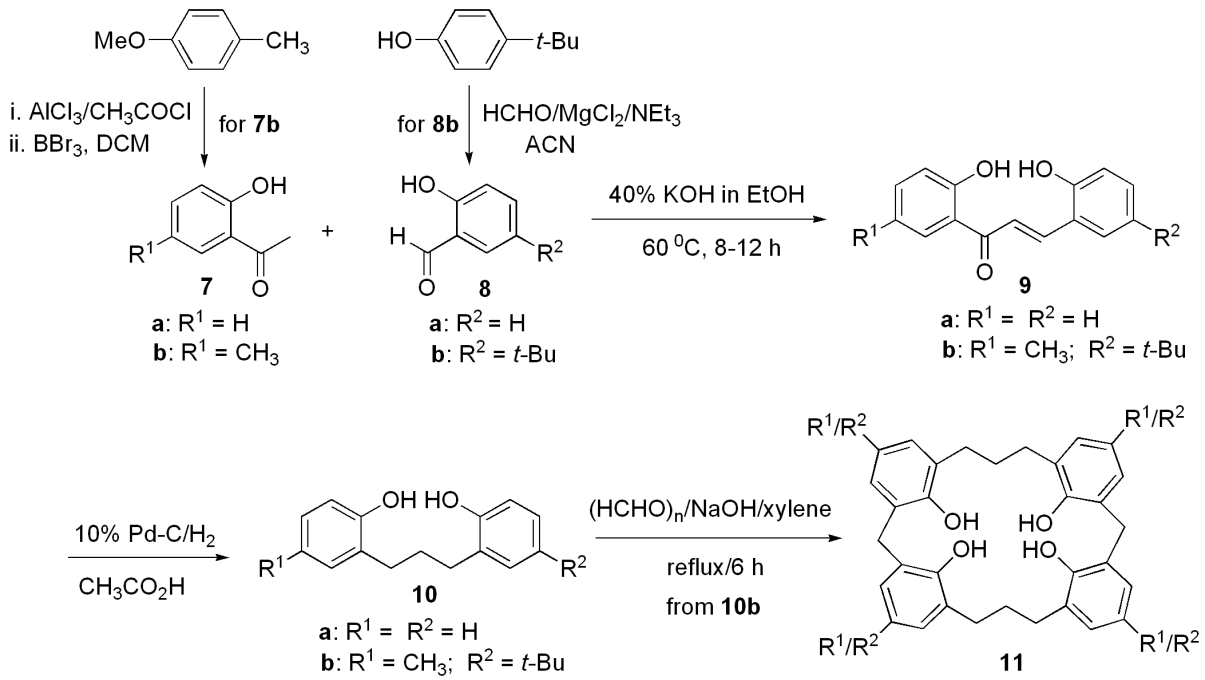
Scheme 5b: Synthesis of [3.1.3.1]homocalixarene by Yamato *et.al.*

In continuation of our work on supramolecular chemistry of calixarenes, we wanted to develop a simple and convenient protocol for the synthesis of propane-bridged metacyclophanes (Scheme 5c), so that they can be prepared in large scale without the use of sophisticated reagents. As 1,3-*bis*(5-*tert*-butyl-2-hydroxyphenyl)propane is an important

synthon in the synthesis of [3.1.3.1] type of metacyclophanes, we initiated a programme for its large scale synthesis involving classical reactions and cheap materials. Aldol condensation of bezaldehydes and acetophenones is one of most easy and popular classical methods to achieve chalcone moieties. Keeping this in view, we envisaged that 1,3-*bis*(5-substituted-2-hydroxyphenyl)propanes (**10**), which are the key intermediates in the synthesis of $[3.1]_n$ metacyclophanes (**11**) can be achieved by catalytic hydrogenation of both olefin and ketone function of *bis*-(5'-substituted-2'-hydroxy)chalcones (**9**). Therefore, Aldol condensation of commercially available 2-hydroxy-acetophenone (**7a)** with 2-hydroxy-benzaldehyde (**8a)** was carried out with ethanolic KOH to produce the chalcone, **9a** in 73% isolated yield. In order to make substituted chalcone such as **9b**, the corresponding 2'-hydroxy-acetophenone (**7b)** and 2-hydroxy-benzaldehyde (**8b)** was synthesized. Thus, 2'-hydroxy-5'-methyl acetophenone (**7b**) was obtained by Friedel-Craft acetylation of 4-methylanisole followed by demethylation using BBr_3 (Scheme 5c). Strikingly, this synthesis has been achieved in a single pot without isolation of the intermediate acetylated product before demethylation in 73% yield. Substituted 2-hydroxy-benzaldehyde, 5-*tert*-butyl-2-hydroxybenzaldehyde (**8b**) was obtained in 96% yield by formylation reaction of 4-*tert*-butyl-phenol with $MgCl_2/(HCHO)_n$ in dry CH_3CN (Scheme 5c). Aldol condensation of **7b** with **8b** using ethanolic KOH furnished the chalcones, **9b** in 75% yield. ^{1}H-NMR spectra of **9b** showed a pair of doublet at δ 7.85 and δ 8.10 ppm assigned as the double bonded CH protons whereas the characteristic absorption of -C**H**O and -COC**H**$_3$ groups were absent. Catalytic hydrogenation of **9a,b** with 10% Pd-C in acetic acid led to concomitant reduction of both olefin and ketone functions to afford **10a** (84 %, Fig. 5j) and the key intermediate, 1,2-*bis*(5-substituted-2-hydroxyphenyl)propanes **10b** (72%, Fig. 5k). The product **10b**, was characterized by the appearance of two sets of

multiplets at δ 1.91–2.05 ppm (-CH_2-, aliphatic) and δ 2.60–2.70 ppm (benzylic) protons after successful hydrogenation.

Finally, condensation of **10b** with paraformaldehyde and aqueous NaOH in xylene yielded 9,16,25,32-tetrahydroxy[3.1.3.l]metacyclophane (**11**) in 43% isolated yield (Scheme 5c) following the procedure developed by by Gutsche *et al*.[158] The structure of **11** has been elucidated on the basis of its spectral data. For instance, the mass spectral data for **11** (M^+ *m/z* = 620) strongly support cyclic structure of the compound. The ^{1}H-NMR spectrum (Fig. 5m) of macrocycle **11** showed broad peaks for *tert*-butyl, methyl, methylene, aromatic and phenolic OH protons at room temperature due to rapid conformational flipping as expected. It showed concentration independent hydroxyl stretching bands in the 3254 cm^{-1} region of the IR spectrum and a signal at δ 9.65 ppm in the ^{1}H-NMR spectrum, indicative of intramolecular hydrogen bonding and the cyclic nature of compound.



Scheme 5c: Synthesis of [3.1.3.1] homocalix[4]arene.

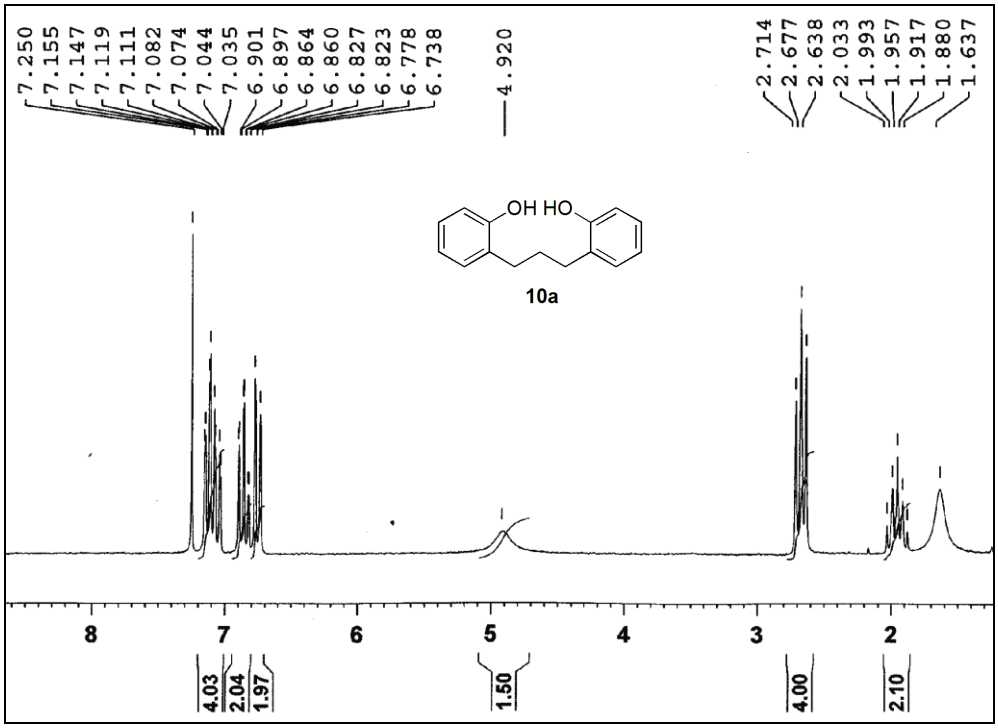


Figure 5k: ^{1}H-NMR of **10a**.

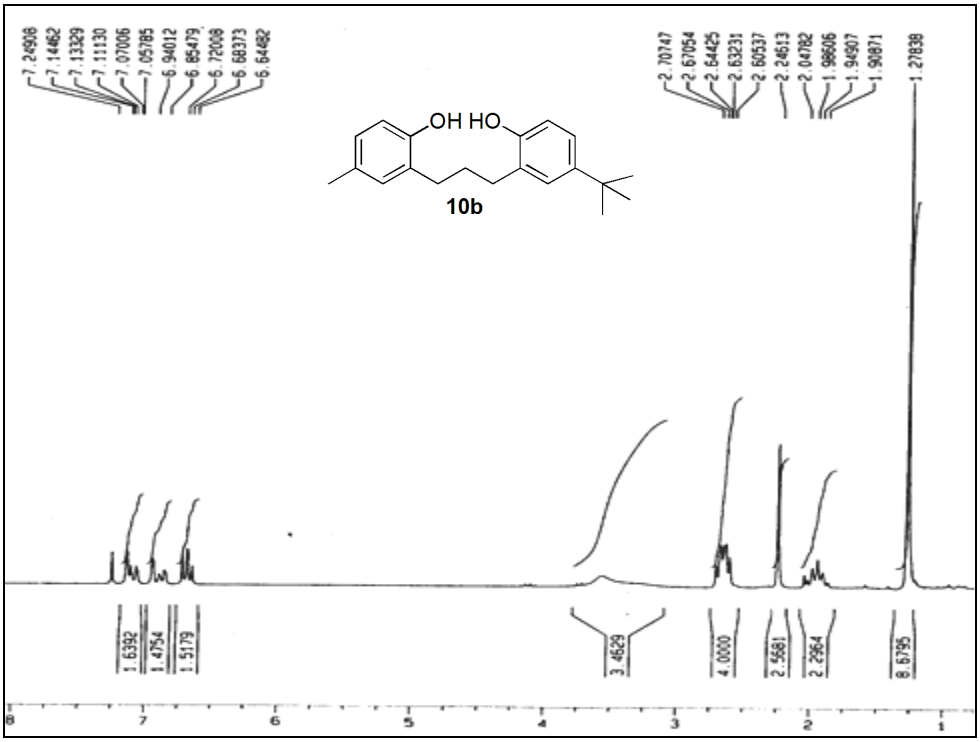


Figure 5l: ^{1}H-NMR of **10b**.

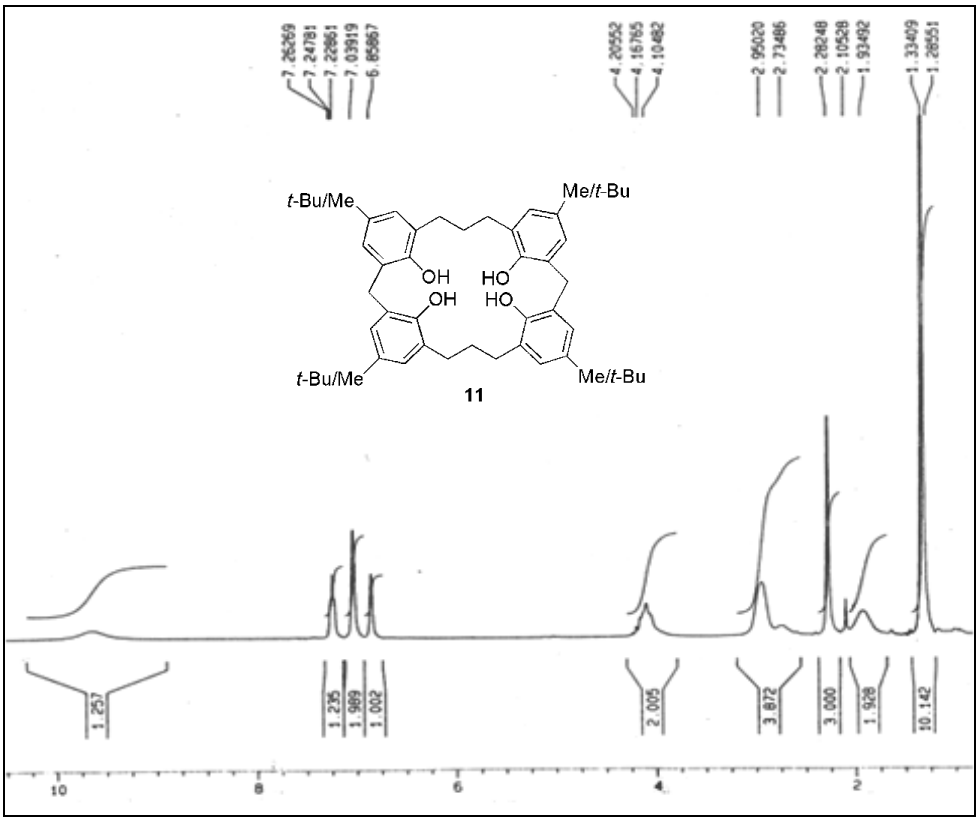
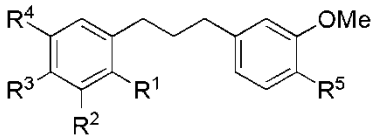


Figure 5m: ^{1}H-NMR of **11**.

5.2.3 Applications of phenolic 1,3-diaryl propane as anti-cancer agent

Arylpropanoids are the major family of 'polyphenols' and constitute a large part of our daily diet. Using human cell cultures in vitro, and in vivo animal models, the phenylpropanoids have been shown to modulate molecular and cellular processes.[159] Hence there has been increasing interest in this class of compounds as anticancer, anti-virus, anti-inflammatory, and antibacterial agents as well as UV screens for cosmetic products. Some of these compounds are reported to reduce the doses of antibiotics and eliminate drug resistance.[160] Of particular interest is the cancer chemopreventive and anti-tumor-promoting effects of some phenylpropanoids.[161,162] Recently, isolation of three new, **I-K** and one known, **L** 1,3-diarylpropanes (Fig. 5n) from the MeOH extract of stems of the vine *Combretum griffithii* (Combretaceae) has been reported.[163] The aqueous decoction of

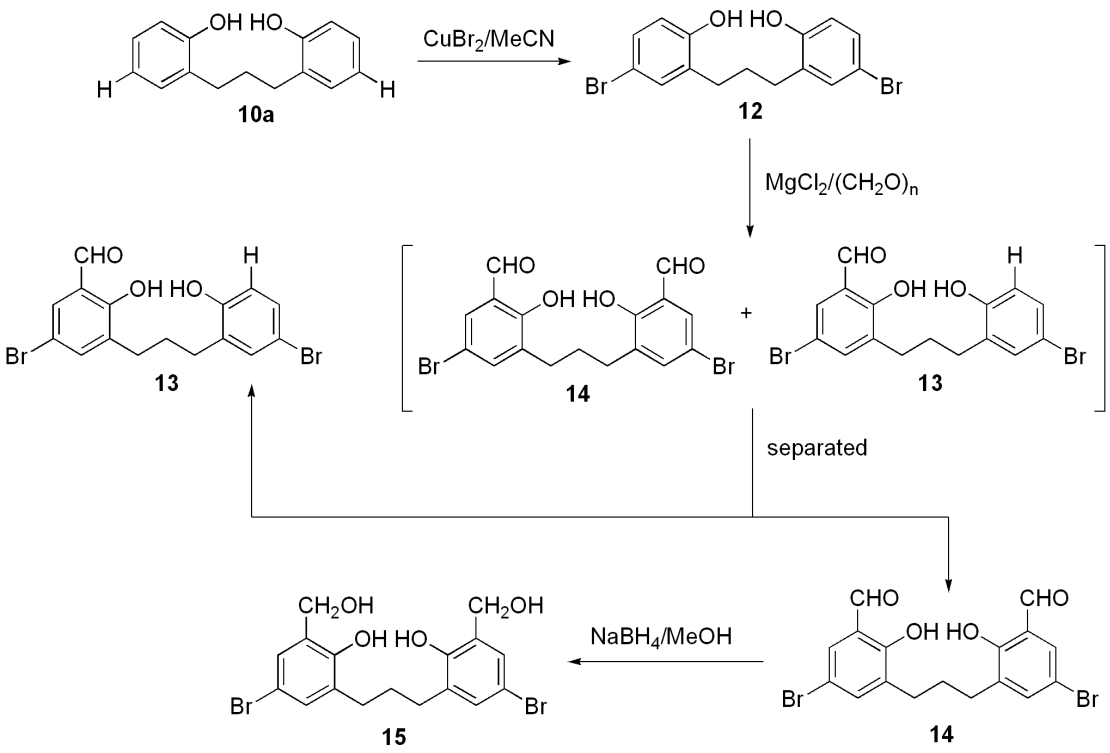
the plant (known as "Khaminkhruea"[164]) in Thai stems is traditionally used by local people for hepatitis treatment.[165] The 1,3-diarylpropanes **I-L** from *C. griffithii* stem extract were toxic to the KB oral human epidermal carcinoma cell line, with the relative potency as **K** >> **I ~ L** > extract >> **J**. Compound **K** was also cytotoxic against human NCI-H187 (IC_{50} = 1.08 μg/mL) and MCF7 (IC_{50} = 6.75 μg/mL) cancer cell lines. Compound **L** inhibited *Mycobacterium tuberculosis* (MIC 3.13 μg/mL), but none of these showed any activity against *Plasmodium falciparum*.



I $R^1 = R^4 = OMe$, $R^2 = H$, $R^3 = R^5 = OH$
J $R^1 = R^3 = OMe$, $R^2 = R^5 = OH$, $R^4 = H$
K $R^1 = R^5 = OMe$, $R^2 = H$, $R^3 = R^4 = OH$
L $R^1 = R^5 = OH$, $R^2 = R^4 = H$, $R^3 = OMe$

Figure 5n: Chemical structure of the 1,3-diarypropanes from *C. griffithii* stem.

As discussed in Section 5.2.2, we have successfully formulated a simple synthetic route to produce 1,3-diarylpropanes towards the synthesis of homocalixarenes. In view of the reported pharmaceutical importance of 1,3-diarylpropanes, we were interested in verifying the efficacy of synthesized1,3-diarypropanes in cytotoxic activity. Our primary aim was to examine the effect of bromo-substituted aromatic ring on the proliferation of the A549 cells. To this end, the anti-cancer activity of two non-brominated **10a,b** and four brominated **12-15** diarylpropanes were compared. Given the importance of the phenolic moiety in anti-cancer property, we selected the compounds with phenolic groups at both the aromatic rings. Likewise, the compounds **12-15** possessed brominated aromatic rings. Further, the effect of some additional substitutions on the biological activity of the bromodiarylpropanes was also investigated.



Scheme 5d: Synthesis of phenolic 1,3-diaryl propanes.

General procedure for the synthesis of non-brominated diarylpropanes, **10a,b** is depicted in Scheme 5c. Recently, we have demonstrated that the combination of $CuBr_2/CH_3CN$ can brominate various phenolic compounds exclusively at the para-position.[166] Application of this protocol with **10a** produced the required dibromo compound **12** (Fig. 5o) in almost quantitative yield (Scheme 5d). $MgCl_2$-catalyzed formylation of **12** led to the formation of a mixture of monoformyl **13** (Fig. 5p) and diformyl **14** (Fig. 5q) derivatives in ~2:3 ratio.[167] Separation of the individuals followed by reduction of **14** with $NaBH_4$ in MeOH proceeded uneventfully to furnish the dicarbinol **15** (Fig. 5r) in 71% yield (Scheme 5d).

After successful synthesis of the targeted six diarylpropanes (**10, 12-15**), their anti-proliferative potential was examined against the highly invasive and metastatic human lung cancer A549 cells. To mention here, lung cancer is the second leading cause of cancer-related deaths all over the world, with low survival rates in advanced stages.[168,169]

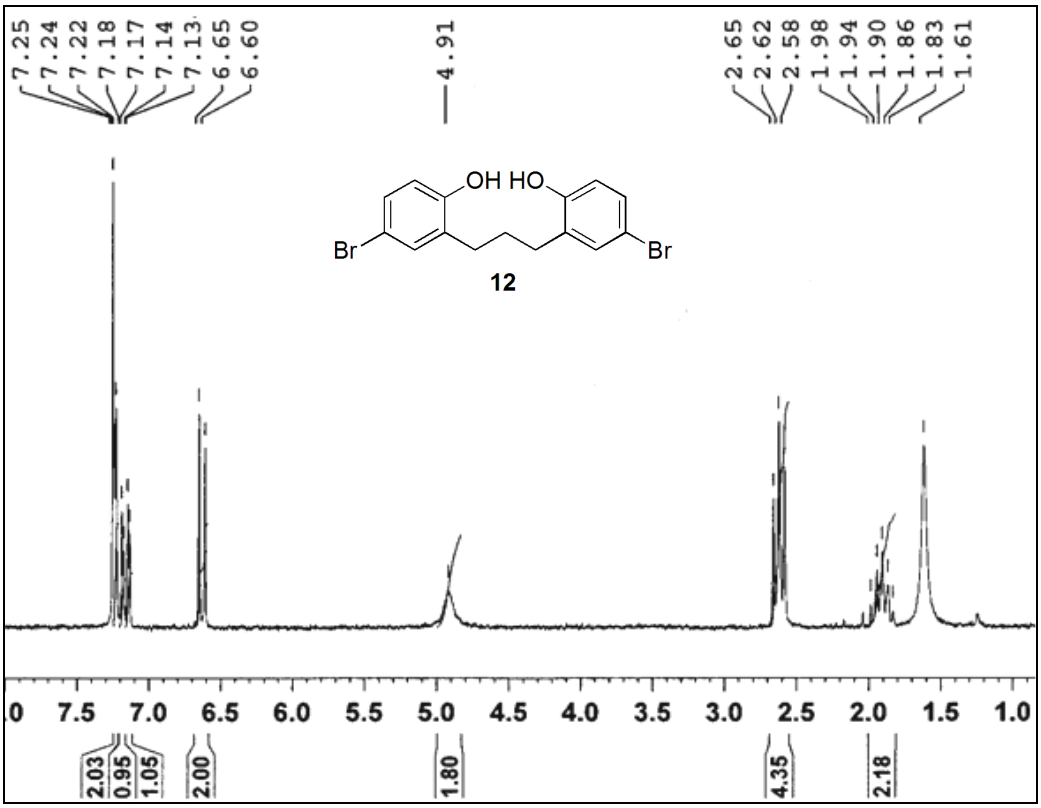


Figure 5o: ^{1}H-NMR of **12**.

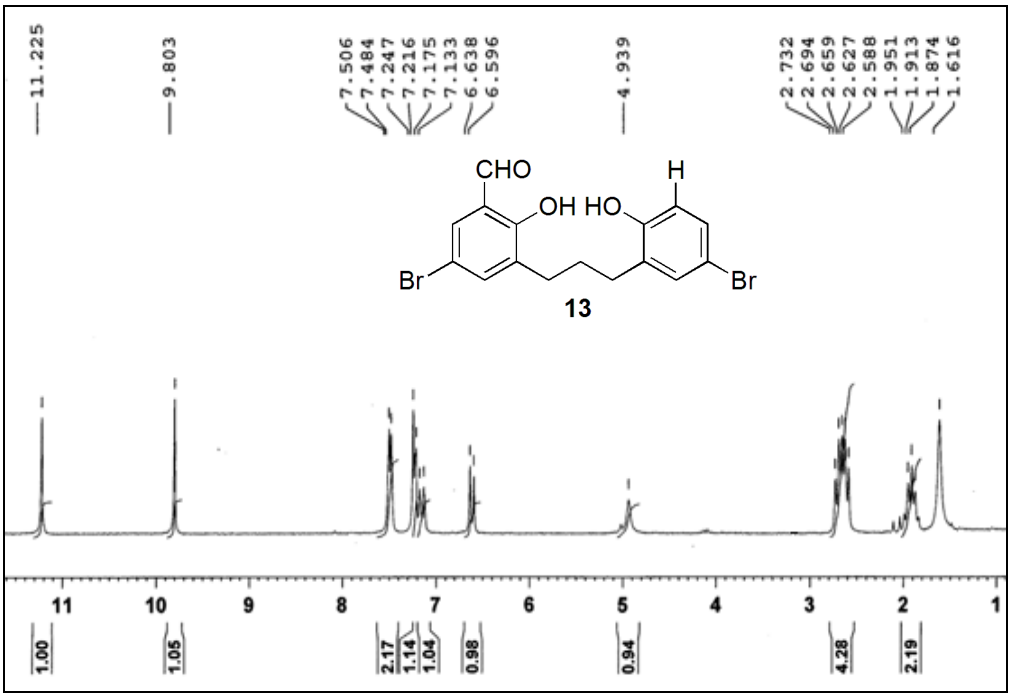


Figure 5p: ^{1}H-NMR of **13**.

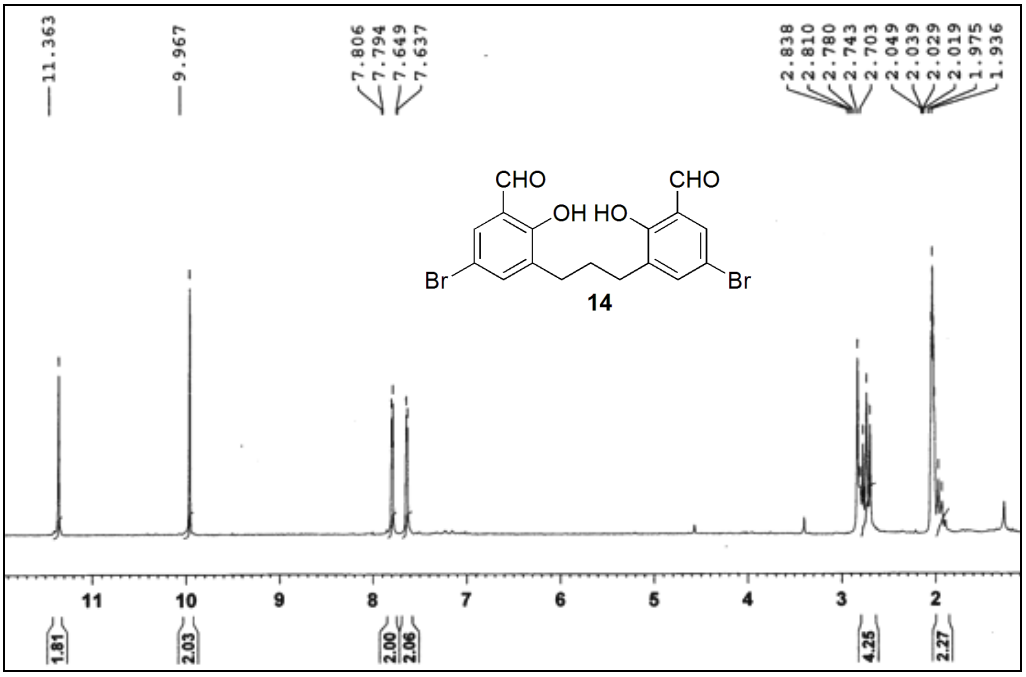


Figure 5q: ^{1}H-NMR of **14**.

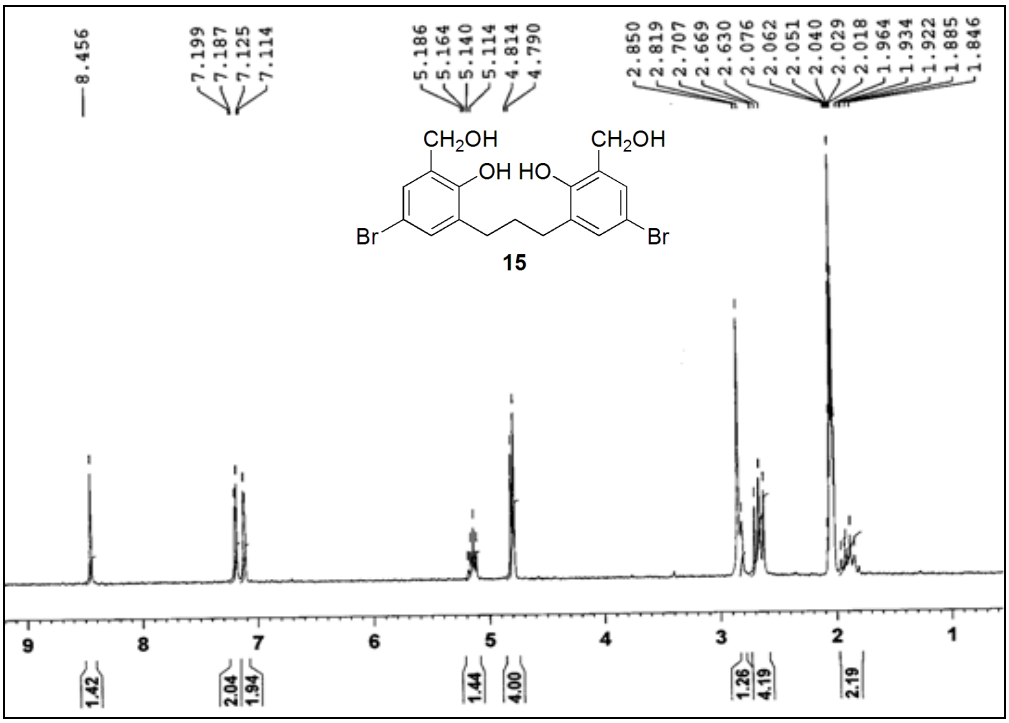


Figure 5r: ^{1}H-NMR of **15**.

Bio-activity studies were performed in collaboration with our colleagues from biology colleagues and the results would be discussed in brief with minimum experimental elaborations as follows. Our MTT results at 48 h revealed that with respect to vehicle treated controls, all the compounds dose-dependently reduced viabilities of the A549 cells (Fig. 5s-A). Based on a detailed dose-dependent MTT assay (Fig. 5s-B) the growth inhibitory IC_{50} value of **10a** was found to be 66.1 ± 3.3 µM. Under identical conditions, the IC_{50} value of the positive control, curcumin was 29.1 ± 2.4 µM. The phase-contrast microscopy (Fig. 5t) showed that amongst the test compounds only **10a** (75 µM) and to some extent **10b** (10 µM) induced significant morphological changes in the A549 cells, as the number of shrinking cells or those with blebbed membranes was notably increased after 48 h. The other compounds induced necrosis, an undesirable mode of cell death. This was further confirmed by fluorescence microscopy after staining with Hoechst and propidium iodide (PI).[170] Our results showed significant necrosis at 3 h in the cells treated with the compounds **10b, 12-15** even at a low concentration (10 µM). The phase-contrast

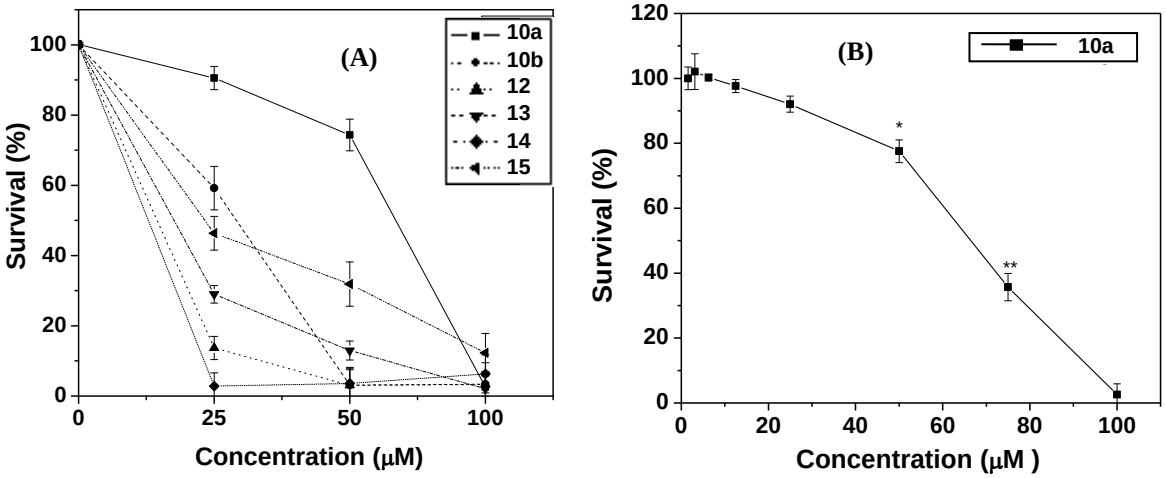


Figure 5s: Dose-dependent cytotoxicity of the diarylpropanes **10a/b, 12-15** against human lung carcinoma A549 cells. **(A)** Effect of compounds **10a/b, 12-15**. **(B)** Effect of compound **10a** over a wide dose range.

and fluorescence microscopy results, obtained with higher concentrations of **10b, 12-15** showed complete cell disruption (data not shown). Hence we did not determine the growth inhibitory IC_{50} values of **10b, 12-15** despite the impressive MTT results (Fig. 5s-A) that showed the relative potency of the test compounds as **14**>**12**>**13**>**15**>**10b**>**10a**. Since only **10a** did not induce any necrosis in the A549 cells, it was chosen for all subsequent studies. Amongst the test samples, the 5/5' positions of **10b** are substituted with two different alkyl groups, while compounds **12-15** contain bromine substitutions in the aromatic ring/s. These will make them more lipophilic compared to compound **10a** that is devoid of any 5/5' substitution. As a result, compounds **10b** and **12-15** may predominantly accumulate at the cell membrane rather than at the mitochondria and/ or nucleus that is required for inducing apoptosis. Instead, these compounds may rupture the cell membrane, leading to necrosis.

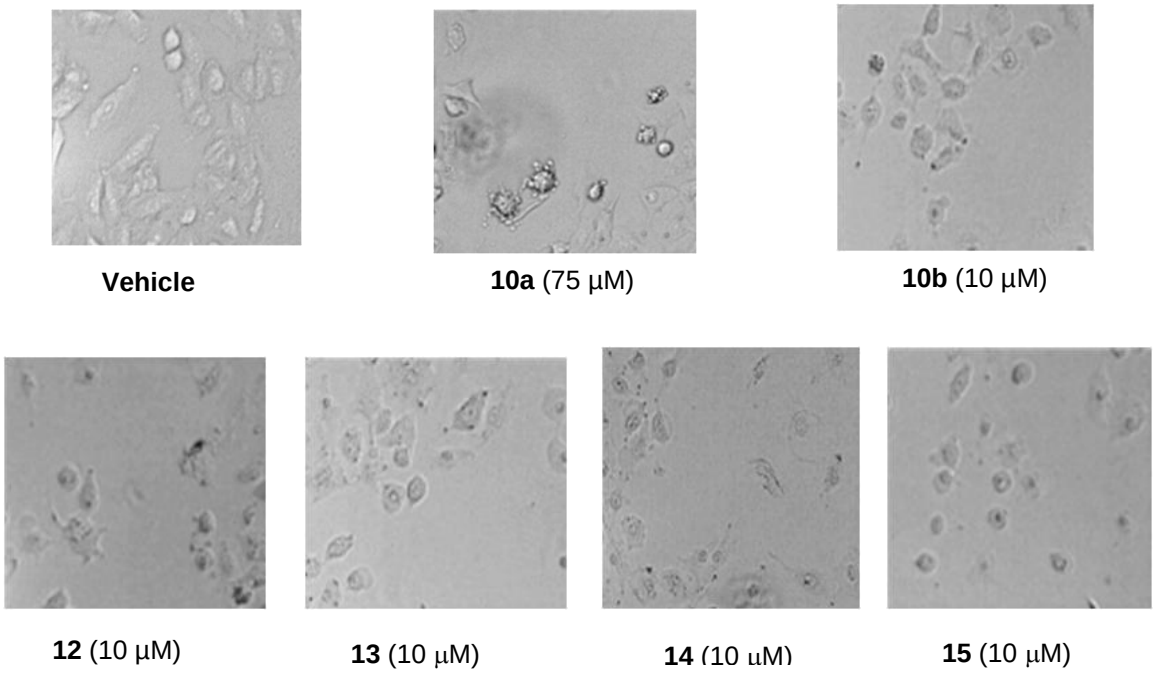


Figure 5t: Alteration of A549 cells morphology as revealed by phase-contrast microscopy.

Treatment of the cells with **10a** (75 μM) increased the ROS generation time-dependently. This suggested that ROS is a potential factor in the cytotoxicity of **10a** to the

A549 cells. The possible inhibitory effect of **10a** (25, 50, 75 and 100 μM) on cell cycle progression at 24 h were analyzed. This showed increase in the G1 population associated with the decrease in the percentage of cells in the S- and G2-phases. Therefore, **10a** induces apoptosis by cell arrest in the G1 phase.

5.3 Conclusion

In conclusion, we have successfully synthesized three rigidized alkyl bridged calix[4]crown-6 derivatives (**6a-c**) in 1,3-alternate conformation for selective extraction of metal ions. The initial 1,3-di-etherification step of this synthesis has been achieved with economically cheap alkyl bromide with suitable iodide salts as the additive. In addition to this, an easy and convenient route to the synthesis of [3.1.3.1] homocalixarene (**11**) with bigger cavity has been developed. Aldol condensation followed by Pd catalyzed hydrogenation has been successfully utilized to achieve the synthesis of the key intermediate, 1,3-*bis*(5-*tert*-butyl-2-hydroxyphenyl)propane in this synthesis. This synthetic strategy has been further explored in the synthesis of two non-brominated (**10a,b**) and four brominated (**12-15**) 1,3-diarylpropane derivatives. The 1,3-diarylpropanes thus synthesized showed pronounced cytotoxicity against the human lung cancer A549 cells. However, the activity of the brominated diarylpropanes (**12-15**) was found to be primarily via necrosis. Interestingly, our results established that **10a** can induce apoptosis to the A549 cells that was mechanistically rationalized in terms of G1 cell cycle arrest and ROS generation.

5.4 Experimental

General information

The chemicals, used for synthesis were procured from Fluka (Seelze, Germany) and Lancaster (UK). Other reagents were of AR grade. All anhydrous reactions were carried out under an Ar atmosphere, using freshly dried solvents. The IR spectra as thin films were scanned with a Jasco model A-202 FT-IR spectrometer. The ^{1}H NMR (200 MHz) and ^{13}C NMR (50 MHz) spectra were recorded with a Bruker AC-200 spectrometer. The chemicals/biochemicals used for the biological experiments were 3-(4,5-dimethylthiazol-2-yl)-2,5-diphenyltetrazolium bromide (MTT), propidium iodide (PI), N-acetylcysteine (NAC), annexin-V kit (all from Sigma Chemicals, St. Luois, MO), Dulbecco's modified Eagle's medium (DMEM, HiMedia, Mumbai), DCFH-DA (Life Technologies, Carlsbad, CA) and fetal bovine serum (FBS, Gibco Life Technologies, Carlsbad, CA).

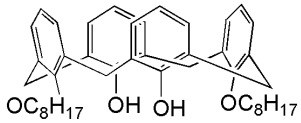
4.4.1 General procedure for synthesis of 25,27-dialkoxy-26,28-dihydroxycalix[4]arene

A suspension of calix[4]arene, **1** (1 equiv.), K_2CO_3 (2.5 equiv.), alkyl bromide (2.5 equiv.) and KI (20 mol%) in acetonitrile was refluxed for 48 h, when TLC showed complete consumption of **1**. The reaction mixture was then quenched with water, acidified with 1N aqueous HCl and extracted with ethyl acetate. The organic layer was washed with water, brine and dried (Na_2SO4). Removal of solvent afforded a thick mass which was purified by silica gel chromatography (gradient elution with hexane-THF mixture) to afford pure **2**/**3**.

25,27-Bis(1-octyloxy)-26,28-dihydroxycalix[4]arene (2)

Following the general procedure as described in 4.4.1, calix[4]arene (424 mg, 1 mmol), K_2CO_3 (345 mg, 2.5 mmol), octyl bromide (482 mg, 2.5 mmol) and KI (83 mg, 0.5 mmol) gave **2** (473 mg, 75%). **IR (solid):** υ 3387, 3062, 1591, 1066, 637 cm^{-1}; **^{1}H-NMR (200**

MHz, $CDCl_3$): δ 0.89 (t, *J* = 6.6 Hz, 6H), 1.30-1.38 (m, 16H), 1.55-1.69 (m, 4H), 2.02-

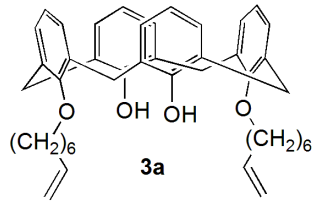


2

2.07 (m, 4H), 3.36 (d, *J* = 12.8 Hz, 4H), 3.98 (t, *J* = 6.8 Hz, 4H), 4.30 (d, *J* = 12.8 Hz, 4H), 6.59-6.76 (m, 4H), 6.90 (d, *J* = 7.4 Hz, 4H), 7.04 (d, *J* = 7.4 Hz, 4H), 8.22 (s, 2H); **^{13}C-NMR (50 MHz, $CDCl_3$):** δ 14.1, 22.7, 25.9, 29.3, 29.5, 30.0, 31.4, 31.9, 76.7, 118.9, 125.2, 128.1, 128.4, 128.8, 133.4, 151.9, 153.3.

25,27-Bis(1-octenyloxy)calix[4]arene (3a)

Following the general procedure as described in 4.4.1, calix[4]arene (4.46 g, 10.5 mmol),

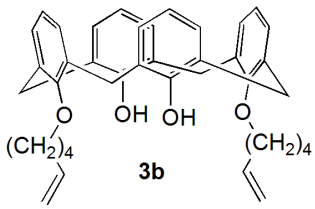


3a

K_2CO_3 (3.61 g, 26.1 mmol), 8-bromo-1-octene (5 g, 26.1 mmol) and KI (867 mg, 5.2 mmol) gave **3a** (4.53 g, 67%). **IR (solid):** υ 3290, 2925, 2855, 1726, 1688, 1455, 1341, 1248, 1197, 993, 908, 754 cm^{-1}; **^{1}H-NMR (200 MHz, $CDCl_3$):** δ 1.40-1.56 (m, 8H), 1.75-1.91 (m, 4H), 2.09-2.18 (m, 8H), 3.44 (d, *J* = 8.6 Hz, 4H), 4.06 (t, *J* = 4.4 Hz, 4H), 4.38 (d, *J* = 8.6 Hz, 4H), 5.01-5.12 (m, 4H), 5.84-5.98 (m, 2H), 6.69-6.79 (m, 4H), 6.96 (d, *J* = 5.0 Hz, 4H), 7.12 (d, *J* = 5 Hz, 4H), 8.31 (s, 2H); **^{13}C-NMR (50 MHz, $CDCl_3$):** δ 25.8, 28.8, 28.9, 29.9, 31.4, 33.8, 76.6, 114.3, 118.9, 125.2, 128.1, 128.4, 128.8, 133.3, 138.9, 152.0, 153.3; **Anal.** (calcd. for $C_{44}H_{52}O_4$: C, 81.95; H, 8.13. found: C, 81.99; H, 8.10.

25,27-Bis(1-hexenyloxy)calix[4]arene (3b)

Following the general procedure as described in 4.4.1, calix[4]arene (5.2 g, 12.3 mmol), K_2CO_3 (4.2 g, 30.7 mmol), 6-bromo-1-hexene (5 g, 30.7 mmol) and KI (1 g, 6.1 mmol)



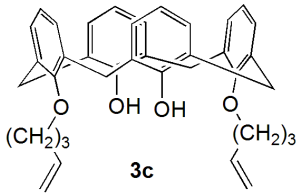
3b

gave the **3b** (6.9 g, 95%). **IR (solid):** υ 3279, 2927, 2861, 1682, 1591, 1639, 1437, 1455, 1247, 1196, 1088, 905, 760 cm^{-1}; **^{1}H-NMR (200 MHz, $CDCl_3$):** δ 1.8-1.87 (m, 4H), 2.04-2.11 (m, 4H), 2.22-2.28 (m, 4H), 3.38 (d, *J* = 6.4 Hz, 4H), 4.01 (t, *J* = 3.2 Hz, 4H), 4.31 (d, *J* = 6.4

Hz, 4H), 5.01-5.12 (m, 4H), 5.85-5.95 (m, 4H), 6.65 (t, *J* = 3.8 Hz, 2H), 6.74 (t, *J* = 3.8 Hz, 2H), 6.91 (d, *J* = 3.8 Hz, 4H), 7.06 (d, *J* = 3.8 Hz, 4H), 8.2 (s, 2H); **^{13}C-NMR (50 MHz, $CDCl_3$):** δ 25.2, 29.3, 31.4, 33.5, 76.4, 114.9, 118.9, 125.2, 128.1, 128.4, 128.9, 133.3, 138.5, 152.0, 153.3; **Anal.** (calcd. for $C_{38}H_{40}O_4$: C, 81.60; H, 7.53. found: C, 81.43; H, 7.47.

25,27-Bis(1-pentenyloxy)calix[4]arene (3c)

Following the general procedure as described in 4.4.1, calix[4]arene (4 g, 9.4 mmol),



3c

K_2CO_3 (3.25 g, 23.6 mmol), 5-bromo-1-pentene (3.5 g, 23.6 mmol) and KI (781 mg, 4.7 mmol) gave **3c** (4 g, 76%). **IR (solid):** υ 3303, 2927, 2864, 1735, 1688, 1456, 1336, 1248, 1216, 1201, 1090, 997, 943, 915, 745 cm^{-1}; **^{1}H-NMR (200 MHz, $CDCl_3$):** δ 2.12-2.25 (m, 4H), 2.52-2.63 (m, 4H), 3.41 (d, *J* = 13.0 Hz, 4H), 4.05 (t, *J* = 6.2 Hz, 4H), 4.35 (d, *J* = 13.0 Hz, 4H), 5.07-5.26 (m, 4H), 5.88-6.09 (m, 2H), 6.64-6.78 (m, 4H), 6.93 (d, *J* = 7.4 Hz, 4H), 7.09 (d, *J* = 7.4 Hz, 4H), 8.23 (s, 2H); **^{13}C-NMR (50 MHz, $CDCl_3$):** δ 29.2, 30.1, 31.4, 75.8, 115.5, 119.0, 125.3, 128.1, 128.4, 128.9, 133.4, 137.9, 151.9, 153.3; **Anal.** (calcd. for $C_{38}H_{40}O_4$: C, 81.40; H, 7.19. found: C, 81.42; H, 7.13.

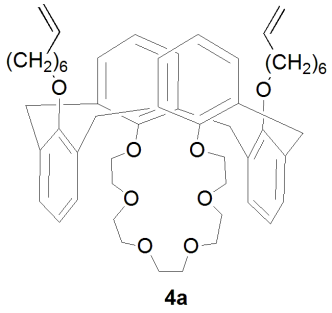
4.4.2 General procedure for the synthesis of 25,27-dialkoxycalix[4]arene-crown-6 1,3 alternate (**4a-c**)

A mixture of 25,27-dialkoxycalix[4]arene (**3a-c**) (1 equiv.), Cs_2CO_3 (3 equiv.) and pentaethyleneglycol di(*p*-toluenesulfonate) (1.1 equiv.) in acetonitrile was refluxed for 16 h when TLC showed complete consumption of **3**. Then acetonitrile was removed and the thick mass was quenched with water, acidified with 1N aqueous HCl and diluted with chloroform. The organic layer was washed with water, brine and dried (Na_2SO_4). The solvent was removed under vacuo to leave an off-white residue which was purified by

silica gel chromatography (gradient elution with hexane-THF mixture) to afford pure calix[4]crown-6 (**4a-c**).

25,27-Bis(1-octenyloxy)calix[4]arene-crown-6, 1,3-alternate (4a)

Following the general procedure as described in 4.4.2, di-(1-octenyloxy)calix[4]arene (**3a**) (1.93 g, 3 mmol), Cs_2CO_3 (2.93 g, 9 mmol) and pentaethyleneglycol di(*p*-toluenesulfonate)

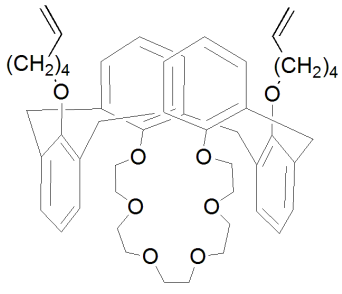


4a

(1.80 g, 3.3 mmol) gave **4a** (1.68 g, 66%). **IR (neat):** υ 3013, 2854, 2921, 1734, 1641, 1457, 1246, 1209, 1120, 906, 704, 761 cm^{-1}; **^{1}H-NMR (200 MHz, $CDCl_3$):** δ 1.17-1.34 (m, 12H), 1.39-1.45 (m, 4H), 2.06-2.13 (m, 4H), 3.40-3.52 (m, 12H), 3.60-3.64 (m, 4H), 3.66-3.69 (m, 4H), 3.73 (s, 4H), 3.79 (s, 8H), 4.97-5.01 (m, 4H), 5.80-5.93 (m, 2H), 6.78-6.88 (m, 4H), 7.03 (d, *J* = 4.9 Hz, 4H), 7.10 (d, *J* = 4.9 Hz, 4H); **^{13}C-NMR (50 MHz, $CDCl_3$):** δ 25.6, 28.9, 29.1, 33.7, 37.8, 69.8, 70.4, 70.9, 71.0, 71.1, 114.2, 122.1, 129.6, 129.7, 133.6, 134.0, 139.0, 156.4, 156.8; **Anal.** (calcd. for $C_{54}H_{70}O_8$: C, 76.56; H, 8.33. found: C, 76.53; H, 8.39.

25,27-Bis(1-hexenyloxy)calix[4]arene-crown-6, 1,3-alternate (4b)

Following the general procedure as described in 4.4.2, di-(1-hexenyloxy)calix[4]arene (**3b**) (5.75 g, 9.78 mmol), Cs_2CO_3 (10.6 g, 29.3 mmol) and pentaethyleneglycol di(*p*-



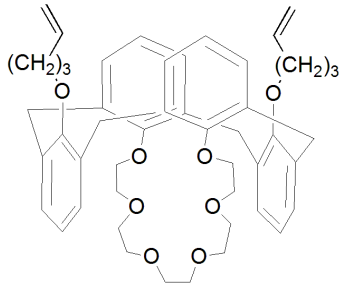
4b

toluenesulfonate) (5.88 g, 10.76 mmol) gave the **4b** (3.89 g, 50%). **IR (neat):** υ 2997, 2862, 1734, 1689, 1585, 1453, 1177, 1245, 1189, 1128, 909, 760 cm^{-1}; **^{1}H-NMR (200 MHz, $CDCl_3$):** δ 1.26-1.30 (m, 8H), 2.01-2.15 (m, 4H), 3.36-3.46 (m, 7H), 3.49-3.68 (m, 14H), 3.71-3.79 (m, 11H), 4.97-5.11 (m, 4H), 5.73-5.93 (m, 2H),

6.78-6.91 (m, 4H), 6.97-7.11 (m, 8H); **^{13}C-NMR (50 MHz, $CDCl_3$):** δ 25.1, 28.8, 33.7, 37.9, 69.8, 70.3, 70.6, 70.9, 71.1, 71.1, 114.4, 122.1, 127.9, 129.7, 129.8, 133.7, 134.0, 138.8, 156.4, 156.9.

25,27-Bis(1-pentenyloxy)calix[4]arene-crown-6, 1,3-alternate (4c)

Following the general procedure as described in 4.4.2, di-(1-pentenyloxy)calix[4]arene (**3c**) (3.75 g, 6.7 mmol), Cs_2CO_3 (9.7 g, 26.8 mmol) and pentaethyleneglycol di(*p*-toluenesulfonate) (4.04 g, 7.4 mmol) gave **4c** (3.46 g, 68%). **IR (neat):** υ 3071, 2903, 1734, 1639, 1454, 1358, 1246, 1205, 1129, 1091, 992, 839, 762 cm^{-1}; **^{1}H-NMR (200 MHz, $CDCl_3$):** δ 1.26-1.43 (m, 4H), 1.84-1.95 (m, 4H), 3.37-3.40 (m, 3H), 3.44-3.51 (m, 6H), 3.56-3.66 (m, 11H), 3.71-3.79 (m, 12H), 4.93-5.01 (m, 4H), 5.68-5.88 (m, 2H), 6.81-6.88 (m, 4H), 6.97-7.11 (m, 8H); **^{13}C-NMR (50 MHz, $CDCl_3$):** δ 28.4, 29.9, 37.9, 69.6, 69.7, 69.8, 70.8, 71.0, 71.1, 114.2, 122.1, 122.2, 129.5, 129.7, 133.7, 133.9, 138.5, 156.4, 156.8; **Anal.** (calcd. for $C_{48}H_{58}O_8$: C, 75.56; H, 7.66. found: C, 75.22; H, 7.65.



4c

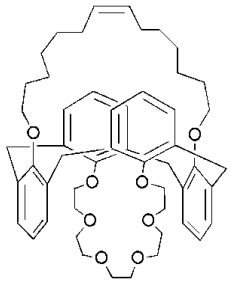
4.4.3 General procedure for the synthesis of (**5a-c**)

To a stirred solution of di-olefin **4a-c** (1 equiv.) in CH_2CI_2 was added Grubb's 1st generation catalyst (5 mol%) in CH_2Cl_2, under exclusion from air and moisture. After 5 h of stirring at room temperature, the solvent was removed under reduced pressure, and the crude reaction mixture purified by silica-gel column chromatography (gradient elution with hexane-THF mixture) to yield the pure calix[4]crowns (**5a-c**) in 1,3 alternate conformation.

Compound 5a

Following the general procedure as described in 4.4.3, di-olefin, **4a** (1.13 g, 1.33 mmol) and Grubb's catalyst (55 mg, 0.07 mmol) gave **5a** (0.65 g, 60%). **IR (neat):** υ 2922, 2852,

1734, 1457, 1247, 1216, 1122, 1007, 918, 760 cm^{-1}; **^{1}H-NMR (200 MHz, $CDCl_3$):** δ 1.04-

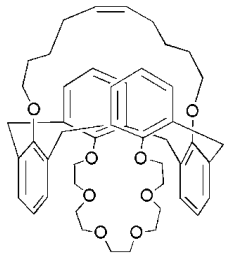


5a

1.42 (m, 16H), 2.07-2.09 (m, 4H), 3.3-3.32 (m, 4H), 3.40-3.42 (m, 8H), 3.51-3.55 (m, 4H), 3.62-3.65 (m, 4H), 3.69-3.70 (m, 4H), 3.84 (s, 8H), 5.33-5.34 (m, 1H), 5.43-5.45 (m, 1H), 6.83-6.89 (m, 4H), 7.00-7.09 (m, 8H); **^{13}C-NMR (50 MHz, $CDCl_3$):** δ 25.6, 27.3, 28.9, 29.4, 29.6, 30.2, 30.4, 32.5, 38.3, 69.6, 69.7, 70.8, 71.2, 122.4, 125.6, 129.2, 129.3, 129.4, 130.1, 131.2, 133.8, 134.3, 156.6, 156.8; **HRMS:** *m/z* calcd for $C_{52}H_{66}O_8K$ (M+K): 857.4389; found: 857.4396.

Compound 5b

Following the general procedure as described in 4.4.3, di-olefin, **4b** (260 mg, 0.33 mmol) and Grubb's catalyst (16 mg, 0.02 mmol) gave **5b** (165 mg, 66%). **IR (neat):** υ 2962,

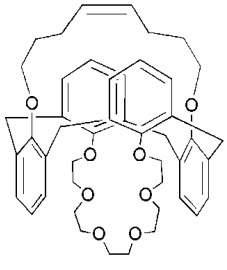


5b

2867, 1735, 1458, 1246, 761 cm^{-1}; **^{1}H-NMR (200 MHz, $CDCl_3$):** δ 1.06-1.29 (m, 8H), 1.82-2.01 (m, 4H), 3.17-3.25 (m, 4H), 3.38-3.55 (m, 10H), 3.58-3.62 (m, 4H), 3.69 (s, 6H), 3.84 (s, 8H), 5.10-5.28 (m, 1H), 5.33-5.38 (m, 1H), 6.77-6.89 (m, 4H), 6.99-7.08 (m, 8H); **^{13}C-NMR (50 MHz, $CDCl_3$):** δ 24.1, 25.5, 27.2, 28.5, 29.2, 30.1, 32.8, 34.0, 38.1, 69.0, 69.2, 69.3, 69.4, 70.5, 70.9, 122.0, 122.1, 122.2, 122.5, 125.3, 128.8, 128.9, 129.1, 129.7, 130.6, 133.4, 133.4, 134.0, 134.1, 156.2, 156.3, 156.5, 156.6.

Compound 5c

Following the general procedure as described in 4.4.3, diolefin, **4c** (3 g, 3.9 mmol) and



5c

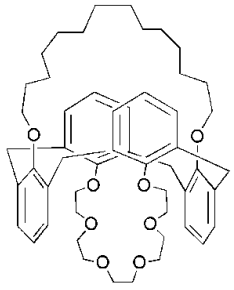
Grubb's catalyst (165 mg, 0.2 mmol) gave **5c** (2 g, 70%). **IR (neat):** υ 2998, 2893, 2857, 1734, 1456, 1248, 1205, 1131, 1117, 1094, 847, 720, 761 cm^{-1}; **^{1}H-NMR (200 MHz, $CDCl_3$):** δ 1.18-1.37 (m, 4H), 1.72-1.95 (m, 4H), 2.81-2.89 (m, 3H), 3.46-3.59 (m, 11H), 3.63-3.68 (m, 6H),

3.71-3.90 (m, 12H), 5.22-5.30 (m, 2H), 6.74-6.92 (m, 4H), 7.02 (d, *J* = 7.4 Hz, 4H), 7.09 (d, *J* = 7.4 Hz, 4H); **^{13}C-NMR (50 MHz, $CDCl_3$):** δ 24.2, 30.6, 38.3, 68.0, 68.6, 69.0, 70.3, 70.5, 71.0, 122.5, 122.7, 128.9, 129.4, 129.6, 133.3, 133.9, 156.3, 157.3; **Anal.** (calcd. for $C_{46}H_{54}O_8$: C, 75.18; H, 7.41. found: C, 75.02; H, 7.42.

4.4.4 General procedure for the synthesis of (6a-c)

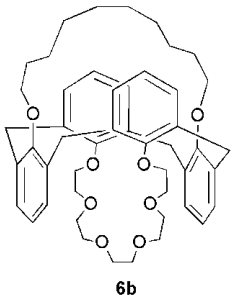
A suspension of the **5a-c** (1 equiv.) and 10% Pd-C in CH_2Cl_2-EtOH (1:5) was stirred under a slight positive pressure of H_2 at ambient temperature. After 24 h the reaction, the mixture was passed through a pad of celite, and the eluate was concentrated in vacuo. The residue was purified by silica-gel column chromatography (gradient elution with hexane-THF mixture) to yield the pure product (**6a-c**) in 1,3 alternate conformation.

Compound 6a


6a

Following the general procedure as described in 4.4.4, **5a** (1 g, 1.2 mmol) and 10% Pd-C (20 mg) gave **6a** (810 mg, 81%). **IR (neat):** υ 2854, 2927, 1735, 1448, 1378, 1248, 1194, 1131, 1055, 946, 922, 755 cm^{-1}; **^{1}H-NMR (200 MHz, $CDCl_3$):** δ 1.30-1.56 (m, 24H), 3.56-3.60 (m, 12H), 3.71-3.73 (m, 20H), 6.74-6.83 (m, 4H), 7.01-7.13 (m, 8H); **^{13}C-NMR (50 MHz, $CDCl_3$):** δ 25.2, 26.9, 27.6, 28.1, 28.9, 30.0, 37.4, 70.3, 70.4, 70.9, 71.2, 71.3, 121.7, 121.9, 129.9, 130.1, 133.6, 133.7, 156.4, 157.0; **HRMS:** *m/z* calcd for $C_{52}H_{69}O_8$ (M+H): 821.4992; found: 821.4995.

Compound 6b

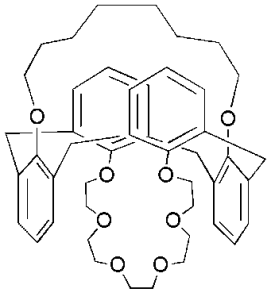

6b

Following the general procedure as described in 4.4.4, **5b** (165 mg, 0.22 mmol) and 10% Pd-C (5 mg) gave **6b** (150 mg, 89%). **IR (neat):** υ 2935, 1735, 1445, 1250, 1035, 752 cm^{-1}; **^{1}H-NMR (200 MHz, $CDCl_3$):** δ 1.11-1.30 (m, 16H), 3.26-3.32 (m, 4H), 3.49-3.60 (m,

11H), 3.64-3.68 (m, 5H), 3.72 (s, 4H), 3.83 (s, 8H), 6.79-6.91 (m, 4H), 7.00-7.12 (m, 8H); **^{13}C-NMR (50 MHz, $CDCl_3$):** δ 25.0, 25.9, 26.5, 29.9, 38.0, 69.0, 69.4, 70.5, 70.6, 70.9, 71.0, 122.0, 122.2, 129.3, 129.6, 133.6, 133.9, 156.4, 157.2.

Compound 6c

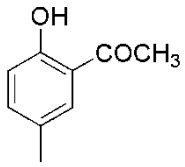
Following the general procedure as described in 4.4.4, **5c** (1.5 g, 2.03 mmol) and 10% Pd-C (40 mg) gave **6c** (1.21 g, 81%). **IR (neat):** υ 2895, 2855, 1735, 1455, 1216, 1248, 1201, 1131, 1094, 1043, 949 760 cm^{-1}; **^{1}H-NMR (200 MHz, $CDCl_3$):** δ 0.60-0.82 (m, 4H), 0.98-1.10 (m, 4H), 1.12-1.29 (m, 4H), 2.85-2.92 (m, 4H), 3.46-3.59 (m, 10H), 3.63-3.71 (m, 10H), 3.88 (s, 8H), 6.81-6.91 (m, 4H), 7.01-7.11 (m, 8H); **^{13}C-NMR (50 MHz, $CDCl_3$):** δ 22.2, 25.8, 28.2, 38.4, 67.9, 68.8, 69.2, 70.4, 70.5, 71.0, 122.3, 122.5, 128.9, 129.6, 133.4, 134.0, 156.3, 157.4; **Anal.** (calcd. for $C_{46}H_{56}O_8$: C, 74.97; H, 7.66. found: C, 74.98; H, 7.61.



6c

4.4.5 Synthesis of 2'-hydroxy-5'-methyl-acetophenone (7b)

To a cooled (0 °C) and stirred solution of 4-methylanisole (1.22 g, 10 mmol) in CH_2Cl_2 was added solid $AlCl_3$ (2 g, 15 mmol) in portions. The reaction was brought to room temperature and stirred till disappearance of the starting material (*cf*. TLC, 2 h). The reaction mixture was then cooled to –40 °C by acetone-dry-ice mixture and of BBr_3 (1.4 ml, 15 mmol) was added dropwise. After 2 h, the reaction mixture was poured in ice-cooled 5% aqueous HCl, and extracted with ethylacetate. The organic layer was washed with water, brine, dried (anhydrous Na_2SO_4), and concentrated under reduced pressure to give the crude product. Purification of the crude compound by column chromatography (silica gel, 5% EtOAc/hexane) gave pure

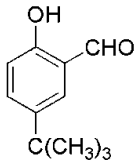


7b

product, **7b** (1.09 g, 73%). **^{1}H NMR (200 MHz, $CDCl_3$):** δ 2.30 (s, 3H), 2.60 (s, 3H), 6.86 (d, *J* = 8.5 Hz, 1H), 7.27 (dd, *J* = 8.6, 1.5 Hz, 1H), 7.49 (s, 1H), 12.01 (s, 1H, OH).

4.4.6 Synthesis of 5-*tert*-Butyl-2-hydroxybenzaldehyde (8b)

To a mixture of 4-*tert*-butyl phenol (9 g, 60 mmol) in dry CH_3CN, triethylamine (23 mL, 168 mmol) and anhydrous $MgCl_2$ (17.7 g, 186 mmol) was added, followed by addition of dry paraformaldehyde (6.48 g, 216 mmol) in portions. The mixture was then refluxed for 20 h when the TLC showed complete consumption of starting material. The reaction mixture thus obtained was cooled, quenched with 5% aqueous HCl and extracted with ethylacteate. The organic layer was washed with water, brine, dried (anhydrous Na_2SO_4), and concentrated under reduced pressure to give the crude compound. Purification of the crude compound by column chromatography (2-5% EtOAc in hexane) afforded the formylated phenol (**8b**) as colorless oil in 96% yield. **IR (neat):** υ 3418, 2964, 1660, 1486, 1265 cm^{-1}; **^{1}H NMR (200 MHz, $CDCl_3$):** δ 1.32 (s, 9H), 6.93 (d, *J* = 10 Hz, 1H), 7.55 (m, 2H), 9.88 (s, 1H, OH), 10.86 (s, 1H, CHO); **^{13}C NMR (50 MHz, $CDCl_3$):** δ 31.1, 34.0, 117.1, 119.9, 129.6, 134.6, 142.6, 159.4, 196.7.



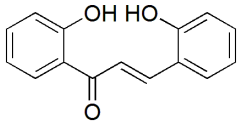
8b

4.4.7 General procedure for the synthesis of chalcones (9a-b)

To a solution of **7a/7b** (50 mmol) and **8a/8b** (50 mmol) in EtOH (10 mL) was added KOH in EtOH (40%, 100 mL). The resultant yellow solution was heated at 60 °C till completion of the reaction (*cf*. TLC, 8-12 h), the mixture poured into ice-water, carefully acidified with aqueous 6N HCl, and extracted with EtOAc (3 × 50 mL). The combined organic extracts were washed with H_2O (2 × 30 mL), brine (2 × 5 mL), dried (Na_2SO_4), and concentrated in vacuo. The residue was purified by column chromatography (silica gel, 7% EtOAc/hexane) to afford pure **9a/9b**.

(*E*)-1,3-*Bis*(2-hydroxyphenyl)prop-2-en-1-one (9a)

Following the general procedure as described in 4.4.7, **9a** was isolated as orange solid

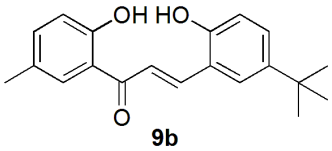


9a

(73% yield); **Mp:** 157-158 °C; **IR ($CHCl_3$):** ν 3329, 3019, 1685, 1630, 1604, 1578, 1488, 1458, 1341, 1304, 1214, 1092, 1066, 1024, 989, 863 cm^{-1}; **^{1}H NMR (200 MHz, $CDCl_3$):** δ 5.95 (broad s, 1H, Ar-O*H*), 6.83-7.04 (m, 4H), 7.30-7.33 (m, 1H), 7.45-7.53 (m, 1H), 7.60 (dd, *J* = 7.8, 1.4 Hz, 1H), 7.84 (d, *J* = 15.7 Hz, 1H), 7.93 (dd, *J* = 8.1, 1.5 Hz, 1H), 8.20 (d, *J* = 15.7 Hz, 1H), 12.92 (s, 1H, chelated Ar-O*H*); **^{13}C NMR (50 MHz, CD_3COCD_3):** δ 116.7, 118.5, 119.3, 120.3, 120.5, 122.2, 129.8, 130.6, 132.8, 136.7, 141.4, 157.8, 164.0, 194.8; **Anal.** Calcd. for $C_{15}H_{12}O_3$: C, 74.99; H, 5.03%. Found: C, 75.16; H, 4.73 %.

(*E*)-3-(5-*tert*-Butyl-2-hydroxyphenyl)-1-(2-hydroxy-5-methylphenyl)prop-2-en-1-one (9b)

Following the general procedure as described in 4.4.7, **9b** was isolated as orange solid (75% yield); **Mp:** 173-174 °C; **IR ($CHCl_3$):** ν 3584, 3210, 3019, 2955, 1634, 1586, 1547,



9b

1489, 1414, 1341, 1308, 1287, 1261, 1214, 1176, 1135, 1111, 1030, 985, 943 cm^{-1}; **^{1}H NMR (200 MHz, $CDCl_3$):** δ 1.33 (s, 9H), 2.34 (s, 3H), 6.79 (d, *J* = 8.4 Hz, 1H), 6.92 (d, *J* = 8.4 Hz, 1H), 7.29-7.33 (m, 2H), 7.54-7.69 (m, 2H), 7.85 (d, *J* = 15.6 Hz, 1H), 8.1 (d, *J* = 15.6 Hz, 1H), 12.83 (broad s, 1H, chelated Ar-O*H*); **^{13}C NMR (50 MHz, CD_3COCD_3):** δ 20.4, 31.7, 34.6, 116.8, 118.7, 120.6, 121.9, 127.1, 128.6, 130.4, 130.6, 138.0, 142.5, 143.4, 156.1, 162.4, 195.2; **Anal.** Calcd. for $C_{20}H_{22}O_3$: C, 77.39; H, 7.14%. Found: C, 77.54; H, 7.44%.

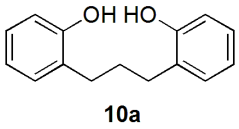
4.4.8 General procedure for the synthesis of 1,3-diarylpropanes (10a-b)

A suspension of the chalcone **9a/9b** (20 mmol) and 10% Pd-C (0.8 g) in glacial acetic acid (100 mL) was stirred under a slight positive pressure of H_2 at ambient temperature. After

completion of the reaction, the mixture was passed through a pad of celite, and the eluate was concentrated in vacuo. The residue was purified by column chromatography (silica gel, 15% EtOAc/hexane) to afford pure **10a/10b**.

1,3-*Bis*(2-hydroxyphenyl)propane (10a)[171]

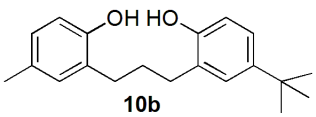
Following the general procedure as described in 4.4.8, **10a** was isolated as light brown solid (84% yield); **Mp:** 95-96 °C; **IR ($CHCl_3$):** ν 3600, 3398, 3019, 2929, 2859, 1590, 1502, 1489, 1455, 1326, 1215, 1168, 1105, 1043, 930, 876 cm^{-1}; **^{1}H NMR (200 MHz, $CDCl_3$):** δ 1.96 (quint, *J* = 7.6 Hz, 2H), 2.68 (t, *J* = 7.6 Hz, 4H), 4.92 (broad s, 2H, Ar-O*H*), 6.76 (d, *J* = 8.0 Hz, 2H), 6.82-6.90 (m, 2H), 7.04-7.16 (m, 4H); **^{13}C NMR (50 MHz, $CDCl_3$):** δ 29.7, 30.0, 115.4, 120.7, 127.0, 128.4, 130.1, 153.4; **Anal. Calcd.** for $C_{15}H_{16}O_2$: C, 78.92; H, 7.06%. Found: C, 79.10; H, 7.11%.



10a

1-(2-Hydroxy-5-methylphenyl)-3-(2-hydroxy-5-*tert*-butylphenyl)propane (10b)

Following the general procedure as described in 4.4.8, **10b** was isolated as colorless solid (72%); **Mp:** 74-75 °C; **IR ($CHCl_3$):** ν 3401, 3016, 2962, 2863, 1705, 1610, 1509, 1421, 1268, 1218, 1126, 1111, 818 cm^{-1}; **^{1}H NMR (200 MHz, $CDCl_3$):** δ 1.27 (s, 9H), 1.91-2.05 (m, 2H), 2.25 (s, 3H), 2.60-2.70 (m, 4H), 3.52 (broad s, 2H, Ar-O*H*), 6.68 (t, *J* = 7.6 Hz, 2H), 6.85-6.94 (m, 2H), 7.06-7.14 (m, 2H); **^{13}C NMR (50 MHz, $CDCl_3$):** δ 20.3, 29.9, 30.3, 30.4, 31.4, 33.8, 115.2, 115.5, 123.7, 127.1, 127.4, 127.8, 128.3, 129.8, 130.8, 143.4, 150.8, 150.9; **Anal. Calcd.** for $C_{20}H_{26}O_2$: C, 80.50; H, 8.78%. Found: C, 80.16; H, 8.61%.

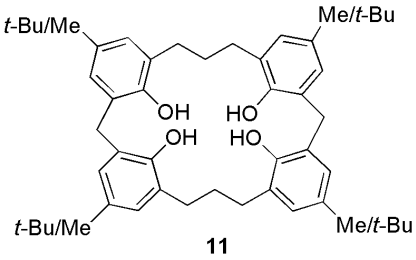


10b

4.4.9 Synthesis of [3.1.3.1] homocalixarene (11)

To a mixture of **10b** (1.19 g, 4 mmol) and paraformaldehyde (240 mg, 8 mmol) in *p*-xylene (40 mL) was added under argon and with vigorous stirring aqueous 5M aqueous NaOH (1 mL). The reaction mixture was refluxed for 6 h (*cf*. TLC), cooled, acidified with dilute 1M

HCl (15 mL), extracted with ethylacetate, and dried (Na_2SO_4). The solvent was evaporated

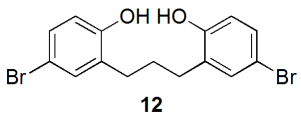


11

to yield a crude product which was purified by column chromatography (15-20% EtOAc in hexane) over silica gel to yield pure [3.1.3.1] homocalixarene (**11**) in 43% yield. **IR (KBr):** υ 3254, 3008, 2955, 2865, 1601, 1483, 1393, 1286, 1214, 1036, 878, 787 cm^{-1}; **^{1}H-NMR (200 MHz, $CDCl_3$):** δ 1.33 (s, 18H), 1.93 (broad s, 4H), 2.28 (s, 6H), 2.95 (broad s, 8H), 4.10-4.21 (m, 4H), 6.86 (s, 2H), 7.04 (s, 4H), 7.22-7.26 (m, 2H), 9.65 (broad s, 4H); **^{13}C-NMR (50 MHz, $CDCl_3$):** δ 20.5, 31.5, 31.9, 32.1, 32.4, 32.8, 33.5, 34.0, 125.3, 125.3, 125.7, 126.0, 128.5, 128.7, 128.9, 129.0, 129.5, 129.9, 128.8, 130.4, 131.1, 144.5, 147.4, 147.5; **MS (ESI):** *m/z* 621 (M+H, 8), 620 (M, 100), 148 (30).

4.4.10 Synthesis of 1,3-*bis*(5-bromo-2-hydroxyphenyl)propane (12)

A solution of **10a** (0.46 g, 2.0 mmol) and $CuBr_2$ (1.88 g, 8.4 mmol) in dry MeCN (10 mL) was stirred at ambient temperature till the completion of the reaction (*cf.* TLC, 8 h). The



12

reaction mixture was concentrated in vacuo, H_2O (20 mL) was added to the mixture, extracted with EtOAc (2 x 10 mL), and the extract was passed through a pad of celite. The celite bed was washed with EtOAc (2 × 5 mL) and the organic extract washed with H_2O (2 × 10 mL) brine (5 mL), and dried (Na_2SO_4). Removal of the solvent in vacuo followed by purification by column chromatography (silica gel, 15% EtOAc/ hexane) of the residue afforded colorless solid **12** (98%). **Mp:** 132-133 °C; **IR ($CHCl_3$):** ν 3602, 3233, 3019, 2927, 2859, 1492, 1455, 1428, 1321, 1214, 1171, 1123 cm^{-1}; **^{1}H NMR (200 MHz, $CDCl_3$):** δ 1.90 (quint, *J* = 7.5 Hz, 2H), 2.62 (t, *J* = 7.5 Hz, 4H), 4.92 (broad s, 2H, Ar-O*H*), 6.63 (d, *J* = 8.4 Hz, 2H), 7.16 (dd, *J* = 8.4, 2.5 Hz, 2H), 7.23-7.24 (m, 2H); **^{13}C NMR (50 MHz, $CDCl_3$):** δ 29.2, 29.5, 112.8,

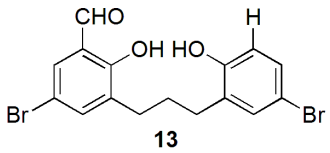
117.0, 129.9, 130.5, 132.8, 152.6; **Anal.** Calcd. for $C_{15}H_{14}Br_2O_2$: C, 46.66; H, 3.65; Found: C, 47.04; H, 3.65%.

4.4.11 Formylation of 12

To a stirred solution of **12** (3.89 g, 10 mmol), Et_3N (7.80 mL, 56 mmol), and anhydrous $MgCl_2$ (5.90 g, 62 mmol) in dry MeCN (100 mL) was added paraformaldehyde (2.16 g, 72 mmol) in portions. The mixture was refluxed for 8 h, cooled to room temperature, acidified with aqueous 3N HCl, and extracted with Et_2O (3 × 15 mL). The ether layer was washed with H_2O (2 × 10 mL), brine (5 mL), and dried (Na_2SO_4). Removal of the solvent in vacuo followed by purification by column chromatography (silica gel, 10% EtOAc/ hexane) of the residue afforded pure colorless solid **13** (33%) and **14** (47%).

1-(5-Bromo-3-formyl-2-hydroxyphenyl)-3-(5-bromo-2-hydroxyphenyl)propane (13)

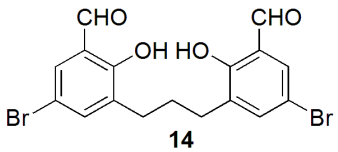
Mp: 135-136 °C; **IR ($CHCl_3$):** ν 3584, 3325, 3019, 2922, 2859, 1714, 1658, 1608, 1493, 1446, 1269, 1214, 1042 cm^{-1}; **^{1}H NMR (200 MHz, $CDCl_3$):** δ 1.87-1.95 (m, 2H), 2.59-2.73 (m, 4H), 4.94 (broad s, 1H, Ar-O*H*), 6.62 (d, *J* = 8.4 Hz, 1H), 7.13-7.18 (m, 1H), 7.22 (m, 1H), 7.48-7.51 (m, 2H), 9.80 (s, 1H), 11.23 (s, 1H, chelated Ar-O*H*); ^{13}C NMR (50 MHz, $CDCl_3$): δ 28.7, 29.2, 29.8, 111.1, 111.3, 117.2, 122.0, 129.9, 131.5, 132.8, 134.0, 134.1, 139.5, 154.8, 158.9, 197.4; **Anal.** Calcd. for $C_{16}H_{14}Br_2O_3$: C, 46.41; H, 3.41; Found: C, 46.63; H, 3.65%.



13

1,3-*Bis*(5-bromo-3-formyl-2-hydroxyphenyl)propane (14)

Mp: 156-157 °C; **IR ($CHCl_3$):** ν 3390, 3019, 2932, 2842, 1731, 1658, 1606, 1437, 1263, 1214, 1047, 998 cm^{-1}; **^{1}H-NMR (200 MHz, CD_3COCD_3):** δ 1.97 (quint, *J* = 7.7 Hz, 2H), 2.74 (t, *J* = 7.7 Hz, 4H), 7.64 (d, *J* = 2.4 Hz, 2H), 7.80 (d, *J* = 2.4 Hz, 2H), 9.97 (s, 2H), 11.36 (s, 2H, chelated Ar-O*H*); **^{13}C-**

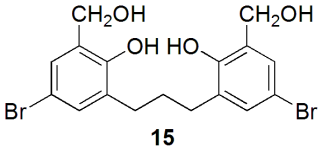


14

NMR (50 MHz, CD_3COCD_3): δ 30.4, 31.3, 111.3, 122.4, 134.0, 134.5, 139.8, 159.2, 197.8; **Anal. Calcd.** for $C_{17}H_{14}Br_2O_4$: C, 46.18; H, 3.19; Found: C, 46.32; H, 3.22%.

4.4.12 Synthesis of 1,3-*Bis*(5-bromo-2-hydroxy-3-hydroxymethylphenyl)propane (15)

To an ice-cooled solution of **14** (0.88 g, 2 mmol) in dry MeOH (10 mL) was added $NaBH_4$



15

(0.08 g, 2 mmol) and the mixture and stirred at 0 °C till complete consumption of **14** (*cf.* TLC, 3 h). The reaction was quenched with aqueous saturated NH_4Cl solution (5 mL) and concentrated in vacuo. The residue was extracted with EtOAc (3 × 10 mL), the organic extract washed with H_2O (2 × 10 mL) and brine (5 mL), and dried (Na_2SO_4). Removal of the solvent in vacuo followed by purification by column chromatography (silica gel, 30% EtOAc/hexane) of the residue afforded colorless solid **15 (**71%). **Mp:** 174-175 °C; **IR ($CHCl_3$):** ν 3395, 3297, 3019, 2927, 2854, 1468, 1451, 1427, 1353, 1214, 1020 cm^{-1}; **^{1}H NMR (200 MHz, CD_3COCD_3):** δ 1.89 (quint, *J* = 7.7 Hz, 2H), 2.67 (t, *J* = 7.7 Hz, 4H), 4.80 (d, *J* = 4.8 Hz, 4H), 5.14 (t, *J* = 4.8 Hz, 2H, CH_2-O*H*), 7.12 (d, *J* = 2.5 Hz, 2H), 7.20 (d, *J* = 2.5 Hz, 2H), 8.45 (s, 2H, Ar-O*H*); **^{13}C NMR (50 MHz, CD_3COCD_3):** δ 29.5, 30.0, 62.4, 110.9, 127.7, 128.5, 131.2, 131.9, 153.4; **Anal.** Calcd. for $C_{17}H_{18}Br_2O_4$: C, 45.77; H, 4.07; Found: C, 45.90; H, 3.96%.

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OVERALL CONCLUSIONS

In this thesis, new efficient synthetic methods for the formation of carbon-carbon/carbon-heteroatom bonds have been developed for synthesis of different important functional molecules. Mainly I focused on synthesis of *O*-heterocycles (aminochromans and xanthenes), *N*-heterocycle (highly substituted pyrroles) and supramolecular-macrocyclic hosts (calixarenes and homocalixarenes).

In this context initially our work was dedicated to the development of a simple, efficient and practical method for one-pot three-component Mannich-type reactions involving enolizable ketones, aldehydes and amines for synthesis of *β*–amino carbonyl compounds, which are useful synthons for the total synthesis of various bio-active compounds. Here we have identified inexpensive and easily available camphor-10-sulfonic acid (CSA) as an efficient catalyst thus making the reaction metal free. Furthermore, the solvent-free conditions, easy work up procedures and high yields of the products has made this methodology a valuable contribution for the synthesis of *β*-amino carbonyl compounds. Some of the properly designed *β*-aminocabonyl compounds synthesized by our protocol were then successfully converted into a novel class of bio-active *O*-heterocycles namely, 4-amino chromans *via* an unprecedented route involving intramolecular etherification with CuI/8-hydroxyquinoline. As another application, synthetic elaboration of *β*-aminocabonyl compounds to *N*-heterocycle namely, highly functionalized pyrroles has also been accomplished. Here McMurry type intramolecular reductive keto-amide coupling in *β*-amidocarbonyl compounds, derived from Mannich adducts has been successfully achieved as the key step followed by DDQ oxidation to afford a library of highly substituted pyrroles.

The versatility of CSA as a catalyst was further explored in condensation reaction of 2-naphthol and aldehydes for synthesis of another important class of *O*-heterocycle, dibenzoxanthenes. The short reaction time, simple work up procedure, and easy isolation of the

products in good yields are some of the salient features of this new protocol. Notably, tunability of this condensation reaction either towards the final pyran derivative, 14-substituted-14H-dibenzo[a,j]xanthenes or isolation of the its precursor bis-(2-hydroxynaphthyl)methane derivatives have been successfully accomplished. *Bis*-(2-hydroxynaphthyl) methane derivatives thus synthesized has been elaborated further to the synthesis of a new class of crown ethers which has displayed strong affinity for fullerene-60/70.

Also, the thesis deals with design and synthesis of some novel rigidized alkyl bridged calix[4]crown-6 derivatives in 1,3-alternate conformation as ionophores for selective extraction of radio-cesium from acidic nuclear waste. The initial 1,3-di-etherification step of this synthesis has been achieved with economically cheap alkyl bromide with suitable iodide salts as the additive. In addition to this, an easy and convenient route to the synthesis of [3.1.3.1] homocalixarene with bigger cavity has been developed, which are otherwise very difficult to accomplish. Aldol condensation followed by Pd catalyzed hydrogenation has been successfully utilized to achieve the synthesis of the key intermediate, 1,3-*bis*(hydroxyaryl)propanes in this synthesis. 1,3-*bis*(hydroxyaryl)propane derivatives thus synthesized was tested for their anti-cancer activities which revealed interesting results.

Thus it can be concluded that the thesis has well-documented some efficient novel strategies for the synthesis of different important class of molecules which effectively justifies the title of the thesis. The overall findings of this thesis will definitely be helpful in encountering different synthetic problems of synthetic organic chemistry as well as supramolecular chemistry.

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