ABSTRACT

Over the past two centuries, the contributions of organic synthesis in the welfare of human beings have been quite remarkable. In fact, advances in organic synthesis can be clearly sensed when one realizes the requirement of medicines for relief of human sufferings, from the easing of pain to cures for various infectious diseases. Thus, organic synthesis has a huge impact on public health where treatments for majority of life threatening diseases have been developed. With small molecule drugs, globally countless lives are saved/extended, resulting in a steady increase in life expectancy. Small molecules have been utilized as powerful tools because of their ability to interact with biological macromolecules to exert specific effects, frequently in a selective and dose-dependent manner. In the fields of medicinal chemistry and chemical genetics, the use of small organic molecules to modulate biological functions deliberately and selectively has rapidly attracted immense scientific growth.

Among wide varieties of small organic molecules, oxygen atom-containing heterocycles are an important class of the heterocyclic compounds. Almost all families of oxa-heterocyclic natural products, found in all kingdoms of life, display some level of biological activity. A subgroup of oxygen atom-containing heterocycles is benzoxacycles in which an oxa-heterocyclic ring is fused to a benzene ring. Benzoxacycles are of special interest due to their fascinating structural diversity and the interesting biological activities of molecules containing these heterocyclic units. 2,3-Dihydrobenzofuran, chroman (also known as chromane, 3,4-dihydro-2*H*-1-benzopyran and 3,4-dihydro-2*H*-chromene), and 1,4-benzodioxane skeletons constitute a large proportion of benzoxacyclic compounds. 1-Benzoxapane (also known as 2,3,4,5-tetrahydrobenzoxepine) is also a significant structural motif that is featured in several bioactive natural products and synthetic molecules.

The research work described in this thesis mainly involves the synthesis of chroman derivatives together with a very few related heterocycles such as 2,3-dihydrobenzofuran, 1,4-benzodioxane and 1-benzoxepane scaffolds.

The thesis entitled "**Stereoselective Synthesis of Functionalized Chromans and Related Heterocycles via Intramolecular Cyclization Reactions of Epoxides, Aziridines, and Vicinal Diols**" is organized under seven chapters.

Chapter 1: Recent Advances in the Stereoselective Synthesis of Chroman Derivatives via Ar–O, ArO–C, and Ar−C Bond-Forming Intramolecular Cyclizations of Epoxides, Aziridines, and Vicinal Diols

The **Chapter 1** begins with the discussion of importance of organic synthesis for the welfare of human beings. It is followed by a brief discussion about the role of small molecules derived from natural products, combinatorial chemistry, and diversity oriented synthesis (DOS). Next, importance of heterocycles as a special class of small organic molecules is discussed. As this thesis mainly involves the synthesis of chroman derivatives, special emphasis is given on the biological and medicinal importances of chroman derivatives. This chapter also summarises the most common synthetic routes to chroman derivatives. One subsection is dedicated to the properties, synthesis and importance of epoxides, aziridines, and vicinal diols. Finally, an overview of the recent synthetic developments of chroman derivatives using epoxide, aziridine, and vicinal diol building blocks is given.

Chapter 2: Diastereoselective Synthesis of *trans*-4-Arylchroman-3-ols via Ar–C Bond-Forming Intramolecular Friedel–Crafts Epoxide-Arene Cyclization Reaction and Its Application in the Synthesis of *cis*-4-Arylchroman-3-ols and Chroman-Fused 2,3-Dihydrobenzofuran

Chroman-3-ol is a ubiquitous structural unit in a large number of biologically important natural products and synthetic compounds. **Chapter 2** describes our efforts on the diastereoselective synthesis of diverse *trans*-4-arylchroman-3-ols via $TsOH{\cdot}H_2O$ catalyzed diastereoselective Friedel–Crafts epoxide-arene cyclization of *trans*-2-aryl-3-(aryloxymethyl)oxiranes. The protocol involved conducting reactions in AR-grade toluene/MeCN under open air, did not require strict anhydrous conditions, and eluded the use of expensive Lewis/ Brønsted acids. This method also allowed scale-up from milligram- to gram-scale. The exact nature of this fundamentally unique reaction (stepwise vs concerted) could vary depending on the substrate; however, the synthetic effectiveness was clearly evident, with 26 *trans*-4-arylchroman-3-ols could be prepared in moderate to high yields with complete regio- and diastereoselectivity. Furthermore, this methodology was suitable for the introduction of phenolic-OH groups on both the aromatic rings, thereby creating opportunities for the synthesis of complex molecules. Moreover, we could develop a methodology to convert *trans*-4-arylchroman-3-ols to

their corresponding *cis*-isomers, and demonstrated the potential for further transformations by synthesizing a chroman-fused 2,3-dihydrobenzofuran derivative.

Chapter 3: *syn*-Diastereoselective Synthesis of Chroman-Fused Tetralins via Ar–C Bond-Forming Intramolecular Friedel–Crafts Epoxide-Arene Cyclization Reaction

The fusion of two or more privileged scaffolds leads to geometrically well-defined rigid polycyclic structures with enhanced receptor-binding selectivity. Thus, a number of approaches to the design and synthesis of structurally diverse, privileged structure-based polycyclic molecules with multiple chiral centers have been developed by many synthetic chemists. **Chapter 3** elaborates our efforts on the development of a convenient Brønsted acid- catalyzed, metal-free, stereoselective synthesis of 6a,7,8,12b-tetrahydro-6*H*-naphtho[2,1-c]chromen-6a-ols. Our worries concerning the formation *syn*-*anti* mixture of 6a,7,8,12b-tetrahydro-6*H*-naphtho[2,1-*c*]chromen-6a-ols and their probable conversion to naphthopyran derivatives via dehydration of tertiary-OH group were laid to rest. The easy accessibility of the starting materials, the mild reaction conditions, and the importance of products as B-ring-modified analogues of the natural product brazilin should make this synthetic work a useful addition in the diversity-oriented synthesis of natural-product like molecules. Additionally, the angular –OH group of one of the synthesized products was reductively removed by a diastereoselective method which should be useful in future for preparing libraries of chroman-fused tetralins with anti-stereochemistry at the ring junction.

Chapter 4: Studies on the Synthesis of (+)-Nebivolol Intermediates via Ar–O and ArO–C Bond-Forming Reactions of Vicinal Diols

In the past 20 years, the exploitation of Sharpless asymmetric dihydroxylation as the source of chirality in the synthesis of acyclic molecules and saturated heterocycles has been remarkable ─ however, synthetic utility of this tool toward chiral benzo-annulated heterocycles are relatively limited. Thus, in the search for wider applications of Sharpless asymmetric dihydroxylation-derived diols for the synthesis of benzo-annulated heterocycles, in the **Chapter 4** of this thesis, we report our studies in the asymmetric synthesis of (*R*)-1-((*R*)-6-fluorochroman-2-yl)ethane-1,2-diol, (*R*)-1-((*S*)-6-fluorochroman-2-yl)ethane-1,2-diol and (*S*)-6-fluoro-2-((*R*)-oxiran-2-yl)chroman, which have been used as late stage intermediates for the asymmetric synthesis of the antihypertensive drug (*S*,*R*,*R*,*R*)-nebivolol. The construction of 2-substituted chroman

derivatives using phenolic-OH mediated intramolecular ring-opening of *syn*-2,3-diol ester-derived cyclic orthoester or intramolecular S_NAr reaction of a triol containing a tethered 2,5-difluorophenyl substituent were unsuccessful. However, exposure of β-hydroxy-α-tosyloxy esters to a one-pot, three-step process (debenzylation-epoxidation-intramolecular epoxide ring opening) enabled us to achieve the target molecules. To the best of our knowledge, this is the first use of Sharpless asymmetric dihydroxylation as the sole source of chirality for the synthesis of nebivolol intermediates.

Chapter 5: Studies on the Diastereoselective Synthesis of 2-Amino-2-(chroman-2-yl)ethanols via Ar–C Bond-Forming Dienone-Phenol Rearrangement of Spirocyclohexadienone Scaffolds

β-Amino alcohol, also known as vicinal amino alcohol or 1,2-amino alcohol, is a privileged motif that serve as an indispensable structural unit in a very large number of bioactive compounds, clinical drugs, agrochemicals, and natural products. Although diverse β-amino alcohols have been synthesized over past several decades, to the best of our knowledge, 2-amino-2-(chroman-2-yl)ethanols have never been reported in the literature. In the **Chapter 5**, we have described our efforts toward the synthesis of 2-amino-2-(chroman-2-yl)ethanols for which we chose a particularly attractive but challenging synthetic route involving an one-pot dienone-phenol rearrangement and Boc-deprotection as key step. Unfortunately, in the end, the synthesis was embittered as we were unable to effect this crucial rearrangement reaction. While disappointed with failure of the planned synthesis of 2-amino-2-(chroman-2-yl)ethanols, we were delighted to find that the study provided synthetic access to spiro-fused cyclohexadienone ─ tetrahydrofuran-embedded glycine derivatives as a new class of nonproteinogenic α-amino acid derivatives via an intramolecular oxidative dearomatization reaction ─ spirocyclization. Spirocyclohexadienones are present as substructures in many bioactive natural products, pharmaceuticals, and compounds for diverse other applications. During the past decades, diverse functionalized spirocylcohexadienones have been reported ─ but those bearing an α-amino acid derivative moiety (like the compounds synthesized by us) have never been synthesized. Such hybrid compounds bearing two different well-known pharmacophores might be useful in the drug discovery process.

Chapter 6: Diastereoselective Synthesis of 2-(*N*-Tosylamido)-2-(chroman-2-yl)ethanols and Related Compounds via ArO–C Bond-Forming Intramolecular Aziridine Ring-Opening

N-Activated aziridines serve as versatile building blocks to generate (protected)aminoethyl fragment-bearing compounds via inter- and intramolecular nucleophilic ring-opening reactions. Today, the portfolio of nucleophiles used in the manipulations of aziridine ring-opening chemistry includes diverse carbon- and hetero-nucleophiles. However, to the best of our knowledge, intramolecular aziridine ring-opening has never been reported. In the **Chapter 6**, we report the first exploitation of phenolate ions as nucleophiles for the diastereo- and regioselective intramolecular ring-opening of *N*-tosylaziridines. This simple method could be used to synthesize functionalized 2,3-dihydrobenzofuran, chroman, 1,4-benzodioxane, and 1-benzoxepine derivatives. The *exo-tet* nucleophilic cyclizations were shown to proceed very rapidly in a completely regio- and diastereoselective fashion. Such a study has not only broadened the impact of aziridines as synthetic building blocks, but also unveiled a new entry to the synthesis benzo-fused oxa-heterocycles under transition-metal-free conditions.

Chapter 7: Diastereoselective Synthesis of 6,7-Dihydrobenzo[*f*]benzo[4,5]imidazo [1,2-*d*][1,4]oxazepines via Sequential ArO–C Bond-Forming Intramolecular Epoxide Ring-Opening and Ar–O Bond-Forming Intramolecular S_NAr Reactions

Benzimidazoles represent an important class of nitrogen containing fused heterocycles. Among different classes of benzimidazoles, 2-arylbenzimidazoles are a unique group of heterocyclic architectures that are commonly present in a large number of pharmacologically active compounds which shows a wide spectrum of biological activities. In the final chapter of the thesis, **Chapter 7**, we have demonstrated the efficiency of sequential epoxide ring-opening and intramolecular S_NAr reactions as the keys step in the synthesis of hitherto unreported 6,7-dihydrobenzo[*f*]benzo[4,5] imidazo[1,2-*d*][1,4]oxazepines. The reactions proceeded with complete regioselectivity and high overall yields. The protocol was experimentally convenient, user- and environmentally friendly requiring simple, inexpensive, and readily available starting materials. Moreover, we also demonstrated that the protocol could be successfully extended to construct chroman-linked and benzoxazepine-fused benzimidazoles. The synthetic routes appeared to be fairly general ones.