PROJECT COMPLETION REPORT

DST Start-Up Research Grant (Young Scientists)

(Sanction no: **SB/FT/CS-073/2013 dated 20.05.2014**)

1.	**Title of the project:**	Asymmetric Syntheses of New Classes of Unnatural α-Amino Acid Derivatives
2a.	**Principal Investigator(s)**	Dr. Sajal Kumar Das (PI) Assistant Professor Department of Chemical Sciences, Tezpur University, Napaam, Tezpur, Dist.- Sonitpur, Assam- 784028
2b.	**Co-Investigator(s):**	None
3a.	**Implementing Institution(s):**	Tezpur University, Napaam, Tezpur, Dist.- Sonitpur, Assam- 784028
3b.	**Collaborating Institution(s):**	None
4.	**Date of commencement:**	25. 07. 2014
5.	**Planned date of completion:**	24.07.17
6.	**Actual date of completion:**	24.07.17

7. Objectives as stated in the project proposal:

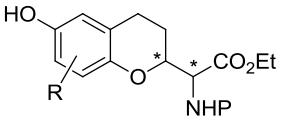
The original aim of this study was to synthesize chroman and related benzo-annulated oxa-heterocycles-based nonproteinogenic α-amino acid derivatives and their applications in the synthesis linked heterocycles.

8. Deviation made from original objectives if any, while implementing the project and reasons thereof:

Basically, major part of the original objectives has been fulfilled. However, under certain cases number of racemic substrates was more than the corresponding enantiopure ones. The rather unpredictable nature of designed strategy in some cases dictated a number of model studies with easily accessible racemic substrates prior to its finalization with enantiopure ones which are normally more difficult to prepare owing to the cost factor. Additionally, to make the application of benzo-fused oxo-heterocycles ring construction much wider, the original aim of the study has also been extended to other classes of small organic molecules containing such heterocycles.

9. Experimental work giving full details of experimental set up, methods adopted, data collected supported by necessary table, charts, diagrams & photographs:

First, the asymmetric synthesis of chroman-based unnatural amino acids **1 (**2-(chroman-2-yl)glycine esters) was undertaken (Figure 1). A number of different routes were studied which are described below.

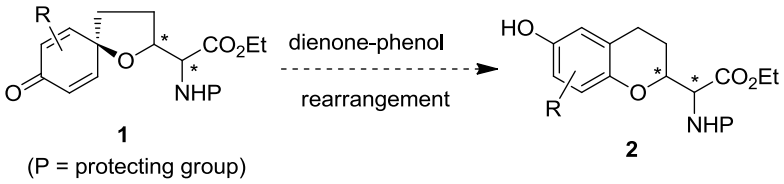


1 (P = protecting group)

Figure 1: 2-(Chroman-2-yl)glycine esters as the first targets.

FIRST STRATEGY:
ATTEMPTED SYNTHESIS OF 2-(CHROMAN-2-YL)GLYCINE ESTERS VIA DIENONE-PHENOL REARRANGEMENT

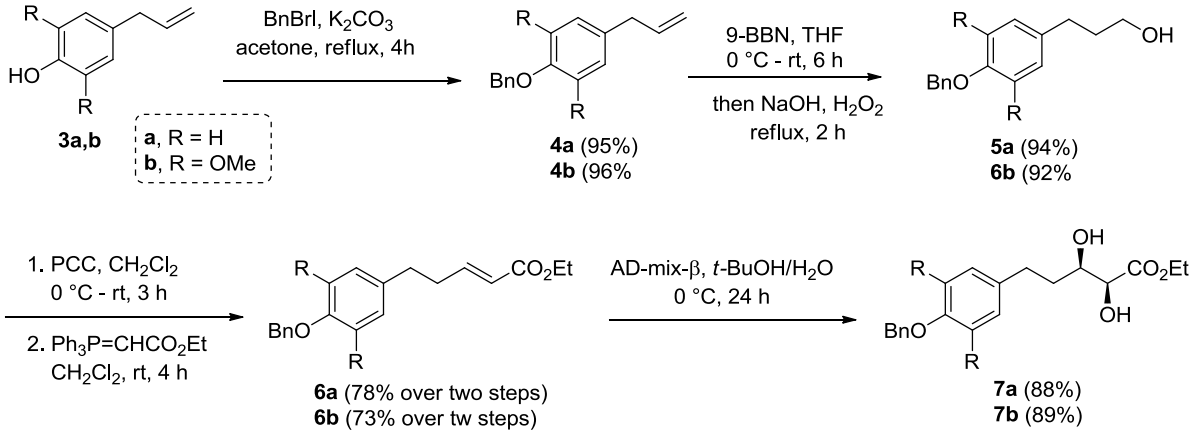
First, we sought to establish a synthetic route for the preparation of 2-(chroman-2-yl)glycine esters **2** via acid-catalyzed/mediated dienone-phenol rearrangement of spirocyclohexadienone-embedded glycine esters **1** (Scheme 1).



1 (P = protecting group) **2**

Scheme 1. First envisioned synthetic approach for 2-(chroman-2-yl)glycine esters.

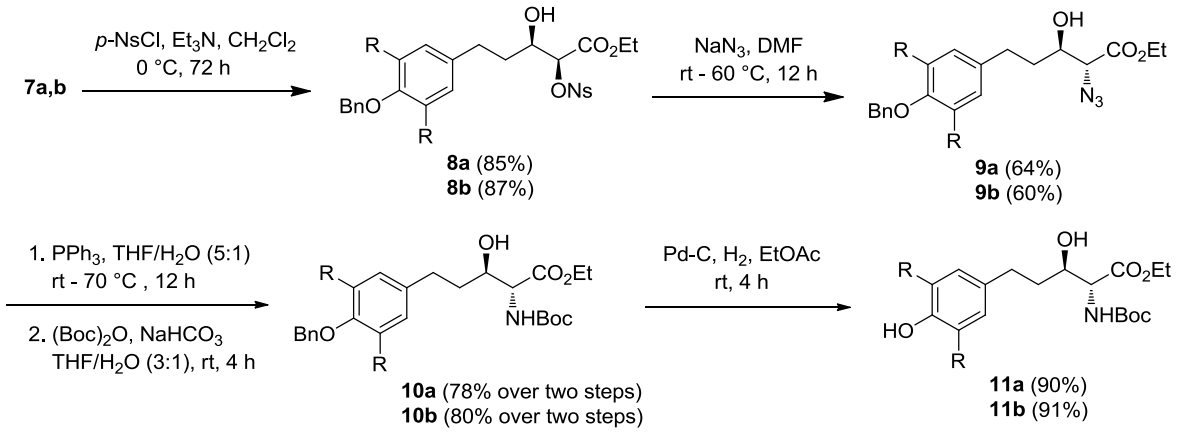
As shown in Scheme 2, we first set out to synthesize enantiomerically pure α,β-dihydroxy esters **7a** and **7b** that would be used as starting materials for the synthesis of spirocyclohexadienone-embedded glycine esters bearing a symmetrically substituted phenol moiety. Compounds **7a** and **7b** were conveniently prepared in from commercially available phenols **3a** and **3b**, respectively.



Scheme 2. Synthesis of precursor diols.

Thus, benzylation of **3a** and **3b** with BnBr in the presence of K_2CO_3 followed by hydroboration (9-BBN)─oxidation (H_2O_2, NaOH) of the resulting compounds **4a,b** gave primary alcohols **5a** and **5b**, respectively. PCC oxidation of **5a,b** followed by Wittig olefination of the resulting crude aldehydes with $Ph_3P{=}CHCO_2Et$ furnished **6a** and **6b**, respectively. Dihydroxylation of **6a,b** under employing AD-mix-β under Sharpless asymmetric dihydroxylation provided α,β-dihydroxy esters **7a** and **7b**, respectively.

Next, regioselective mononosylation of **7a,b** followed by azidation of the resulting β-hydroxy-α-nosyloxy esters **8a,b** with NaN_3 afforded β-hydroxy-α-azido esters **9a** and **9b**, respectively (Scheme 3). Staudinger reduction (PPh_3, THF, H_2O) of **9a,b** followed by Boc protection of the resulting crude amines yielded N-Boc-protected β-hydroxy- α-amino esters **10a** and **10b**, respectively. For wider applicability in synthesis it seemed appropriate to use Boc protecting group as it would be readily removable during a deprotection step. Finally, compounds **10a,b** were subjected to debenzylation reaction with Pd-C and H_2 to afford phenols **11a** and **11b**, respectively.



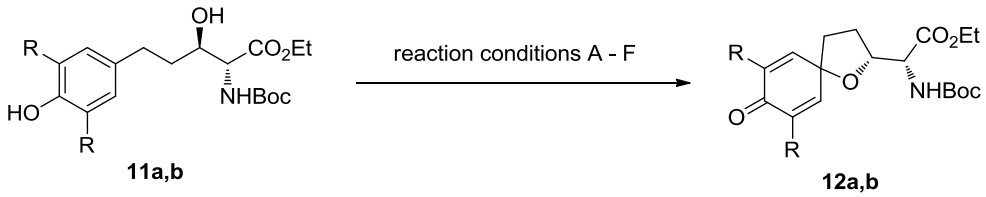
Scheme 3. Synthesis of N-Boc-protected β-hydroxy-α-amino esters.

With the key compounds **11a**,**b** in hand, our attention was turned for their conversion to spirocyclohexadienone-embedded glycine esters **12a**,**b**. Toward that objective, we decided to employ hypervalent iodine(III)-based reagents to effect the oxidative dearomatization of **11a**,**b** under six different reaction conditions A─D (Table 1).

Treatment of compounds **11a**,**b** with phenyliodine(III) diacetate (PIDA) (Table 1, conditions A) in MeCN led to complete consumption of starting materials within 15 min and formation of desired products **12a**,**b**, albeit in very low yields (Table 1, entry 1). The other well-known hypervalent iodine(III) reagent, i.e., phenyliodine(III) bis(trifluoroacetate) (PIFA) in MeCN (conditions B) also furnished similar yields (entry 2). To obtain the desired products **12a**,**b** in a more desirable yields, trifluoroethanol (TFE) and hexafluoroisopropanol (HFIP) were screened under conditions C─D (entries 3–6). The screening showed that the reaction using PIDA as the oxidizing agent and HFIP as a solvent (conditions E) gave best results ─ 47% and 52% yields for **12a** and **12b**, respectively (entry 5).

With the establishment of successful spirocyclization reaction conditions, the stage was set for the much anticipated dienone-phenol rearrangement of **12a** and 12**b**. Unfortunately, we were unable to convert **12a,b** to 2-(chroman-2-yl)glycine esters **13a,b** under a variety of literature known conditions; starting materials were either decomposed or a complex product mixture was generated (Table 2).

Table 1. Optimizations of reaction conditions for spirocyclization of **11a-b**.



11a,b **12a,b**

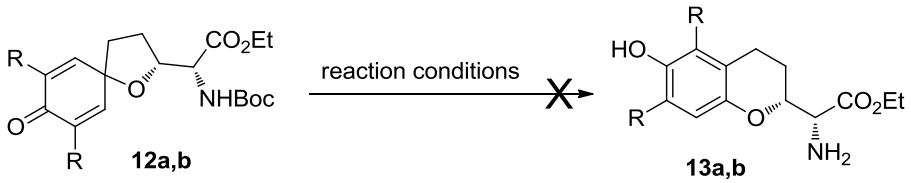
conditions A **11a** or **11b** (1 mmol), PIDA (1.2 mmol) MeCN (5 mL), 0 °C - rt, 15 min	conditions B **11a** or **11b** (1 mmol), PIFA (1.2 mmol) pyridine (0.3 mL), MeCN (5 mL) 0 °C - rt, 15 min	conditions C **11a** or **11b** (1 mmol), PIDA (1.2 mmol) TFE (5 mL), 0 °C - rt, 15 min
conditions D **11a** or **11b** (1 mmol), PIFA (1.2 mmol) pyridine (0.3 mL), TFE (5 mL) 0 °C - rt, 15 min	conditions E **11a** or **11b** (1 mmol), PIDA (1.2 mmol) HFIP (5 mL), 0 °C - rt, 15 min	conditions F **11a** or **11b** (1 mmol), PIFA (1.2 mmol) pyridine (0.3 mL), HFIP (5 mL) 0 °C - rt, 15 min

entry	conditions	yield[a]
1	A	27% (**7a**) 36% (**7b**)
2	B	29% (**7a**) 35% (**7b**)
3	C	36% (**7a**) 44% (**7b**)
4	D	35% (**7a**) 41% (**7b**)
5	**E**	47% (**7a**) 52% (**7b**)
6	F	39% (**7a**) 44% (**7b**)

[a]Isolated yields after chromatographic purification.

While disappointed with failure of the planned synthesis of 2-(chroman-2-yl)glycine esters, we were delighted to find that the study provided synthetic access to spirocyclohexadienone containing glycine esters through an intramolecular oxidative dearomatization reaction. Spirocyclohexadienones, containing a quaternary carbon center, 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 **12a**,**b** have never been synthesized. Such hybrid compounds bearing two different well-known pharmacophores might be useful in the drug discovery process. Simplicity of the experimental procedures in the overall reaction sequence should make this method a general route to a wide variety of spirocylcohexadienone-bearing α-amino acid derivatives.

Table 2. Attempted one-pot dienone-phenol rearrangement and Boc-deprotection of **12a,b**[a]

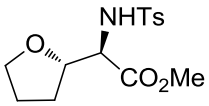


entry	conditions[a]	result
1	$BF_3 \cdot OEt_2$, 0 °C – rt,	decomposition
2	TsOH, CH_2Cl_2, rt, 1 h	complex product mixture
3	TsOH, MeCN, 80 °C, 1 h	complex product mixture
4	TsOH, EtOH, 80 °C, 1 h	decomposition
5	TsOH, 1:1 H_2O/MeOH, 60 °C, 1 h	decomposition
6	TFA, CH_2Cl_2, rt, 2 h	complex product mixture
6	HCl, $CHCl_3$, 60 °C, 1 h	complex product mixture

[a]Four equiv of each reagent, 0.1 M substrate concentration.

It is important to mention that these synthesized spirocylcohexadienone-bearing α-amino acid derivatives are new derivatives of 2-(tetrahydrofuran-2-yl)glycine derivative (Figure 2), synthesis and applications of which has been described in the literature on numerous occasions.

representative chiral heterocycle-containing literature reported α-amino acids:



2-(tetrahydrofuran-2-yl)glycine derivative

chiral chroman-containing α-amino acids synthesized by us:

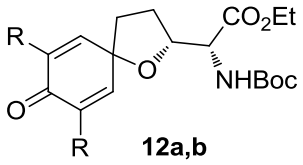


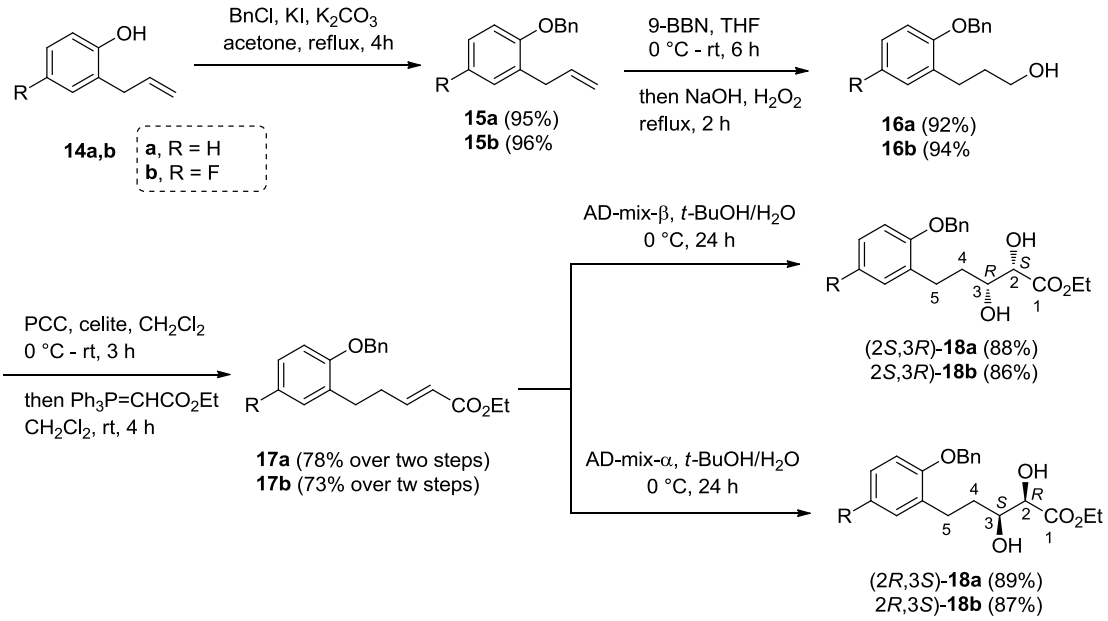
Figure 2.

SECOND STRATEGY

ASYMMETRIC SYNTHESIS OF 2-AMINO-2-(CHROMAN-2-YL)ETHANOLS VIA CHROMAN-BASED α-HYDROXY ESTERS

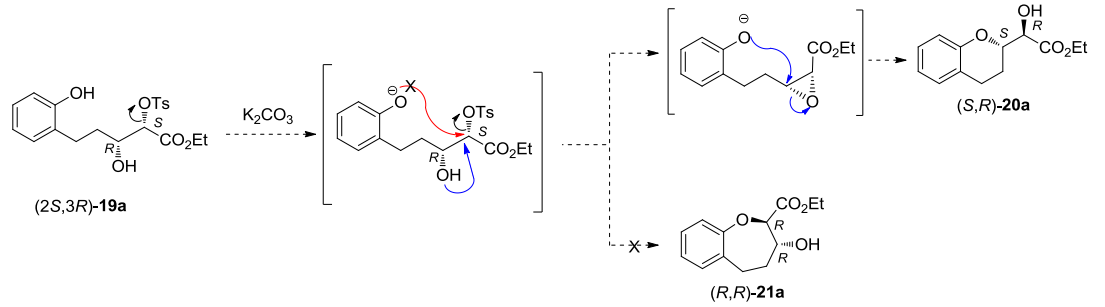
With the disappointing observations in the attempted conversion of **12a,b** to **13a,b**, we turned our attention for an alternative strategy to access 2-(chroman-2-yl)glycine esters. Since α-hydroxy esters can serve as precursors for the synthesis of α-amino esters, our next aim was to utlize with chroman-based α-hydroxy esters to synthesize 2-(chroman-2-yl)glycine esters.

Toward that objective, 2-allylphenols **14a,b** were converted *syn*-2,3-dihydroxy esters (2*S*,3*R*)-**18a,b** and (2*R*,3*S*)-**18a,b** (Scheme 4) following similar reaction pathways as that describes in the Scheme 2.



Scheme 4. Synthesis of diols.

Previously a three step reaction sequence involving epoxidation/debenzylation/epoxide ring-opening has been used to convert a β-hydroxy-α-tosyloxy ester into the corresponding 2-substituted chroman derivative.[1] However, it has been reviewed that not only benzylic epoxides but also non-benzylic epoxides are sensitive to the standard hydrogenation/debenzylation conditions. Whereas benzylic epoxides are highly sensitive to hydrogenation conditions, non-benzylic epoxides, depending on the reaction conditions, may produce traces to significant amount of side-products via hydrogenolysis. Thus, we decided to modify the above-mentioned synthetic route to significantly increase the overall yield. We hypothesized that this problem might be circumvented by performing the debenzylation reaction prior to the epoxide ring formation. We also speculated that compound (2*S*,3*R*)-**19a**, in the presence of a base, might undergo a sequential epoxidation-intramolecular epoxide ring opening to produce (*S*,*R*)-**20a** (Scheme 5), and the formation of benzoxepane (*S*,*R*)-**21a** via intramolecular displacement of –OTs group by ArO^- would not take place.

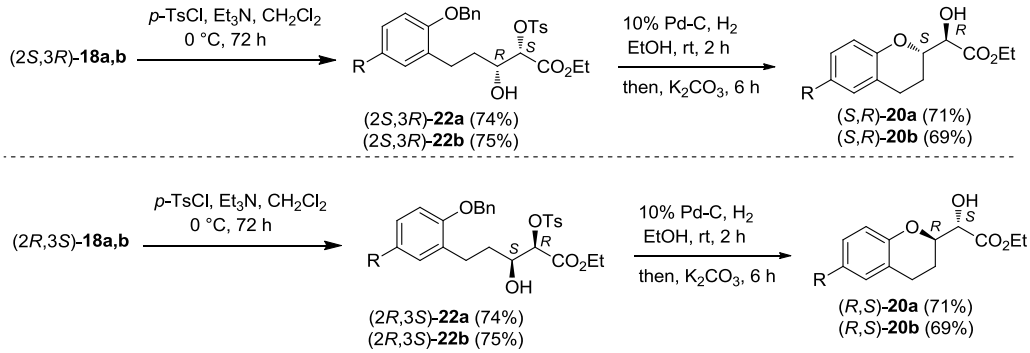


Scheme 5. Speculation of one-pot epoxidation/epoxide ring-opening.

To test this hypothesis, first compound (2*S*,3*R*)-**19a** was subjected to the debenzylation reaction with 10% Pd-C in EtOH under H_2 atmosphere (Scheme 6) at rt. After completion of the debenzylation process (2 h), K_2CO_3 was added to the reaction mixture in the same reaction vessel. We were happy to find that the reaction mixture, after being run for an additional 6 h, provided compound (*S*,*R*)-**20a** in 70% yield which

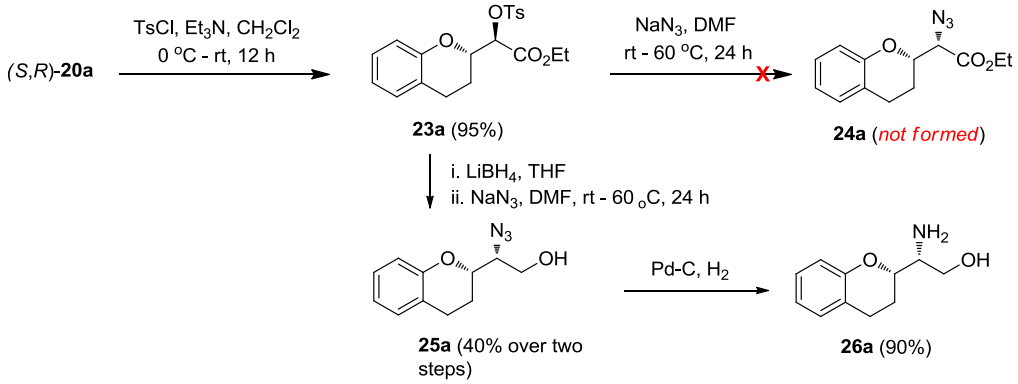
was significantly higher than the literature yield (53%) for the similar transformation. Similar strategy was applied for the synthesis of (*S*,*R*)-**20b** and (*R*,*S*)-**20b**.

With compounds (*S*,*R*)-**20a,b** and (*R*,*S*)-**20a,b** in hand, we first turned our focus to quickly investigate the conversion of (*S*,*R*)-**20a** into 2-(chroman-2-yl)glycine ester **4** (Scheme 7). Thus, first tosylation of compound (*S*,*R*)-**20a** was performed with 4-TsCl (1.05 equiv) and Et_3N in CH_2Cl_2 and the resulting tosylate **23a** was then subjected to azidation reaction with NaN_3 in DMF.



Scheme 6. Synthesis of chroman-based α-hydroxy esters.

Unfortunately, all attempts to introduce the azide functionality by the S_N2 displacement of the -OTs group failed, resulting in either recovery or decomposition of the starting material. Changing the leaving group from -OTs to -OTf, or direct azidation of (*S*,*R*)-**20a** under Mitsunobu conditions ($(PhO)_2P(O)N_3$, DEAD, Ph_3P) also did not produce any positive result (not shown here). Delightfully, when we reduced the ester functionality to the alcohol group (conversion of **23a** into **25a**), azidation worked, albeit in moderate yield.

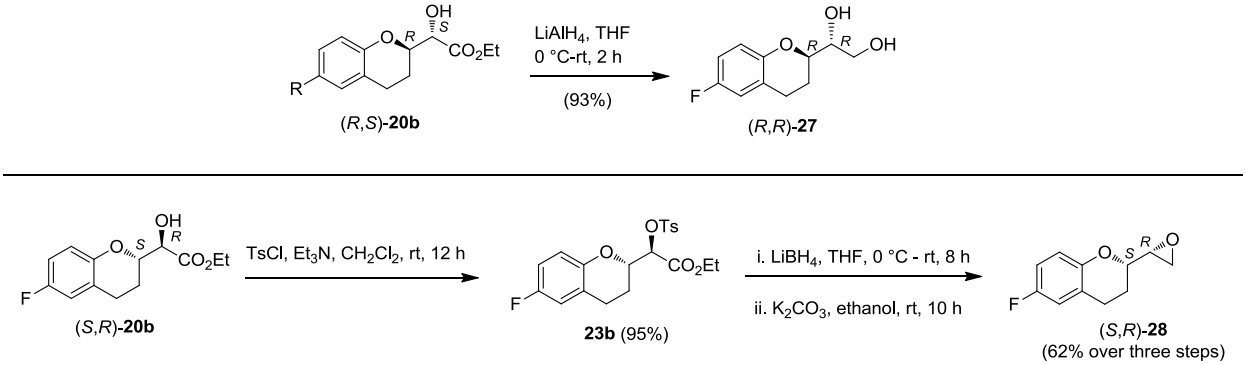


Scheme 7. Synthesis of chroman-based β-amino alcohol.

Subsequent reduction of the azide group by H_2, Pd-C yielded chroman-based amino alcohol **26** which should be useful as a precursor of chroman-based unnatural amino acid.

ADDITIONAL WORK FROM THE SECOND STRATEGY

As shown in the scheme 8, (*R*,*S*)-**20b** and (*S*,*R*)-**20b** were further utilized in the synthesis of (*R*)-1-((*R*)-6-fluorochroman-2-yl)ethane-1,2-diol (*R*,*R*)-**27** and (*S*)-6-fluoro-2-((*R*)-oxiran-2-yl)chroman (*S*,*R*)-**28**, which have previously utilized as late-stage intermediates for the synthesis of clinical drug (*S*,*R*,*R*,*R*)-nebivolol ─ a third-generation β-adrenergic receptor antagonist (β-blocker).[2]

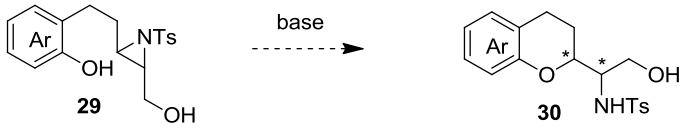


Scheme 8. Synthesis of late-stage (*S*,*R*,*R*,*R*)-nebivolol intermediates.

THIRD STRATEGY

SYNTHESIS OF CHROMAN- AND 1-BENZOXEPANE-BASED B-AMINO ALCOHOLS USING PHENOXIDE ION-MEDIATED INTRAMOLECULAR RING-OPENING REACTIONS

We recognized that a base-mediated intramolecular ring-opening reaction of **29** bearing an *N*-activated aziridine ring with a tethered phenol might provide chroman-based amino alcohol derivative **30** (Scheme 9).

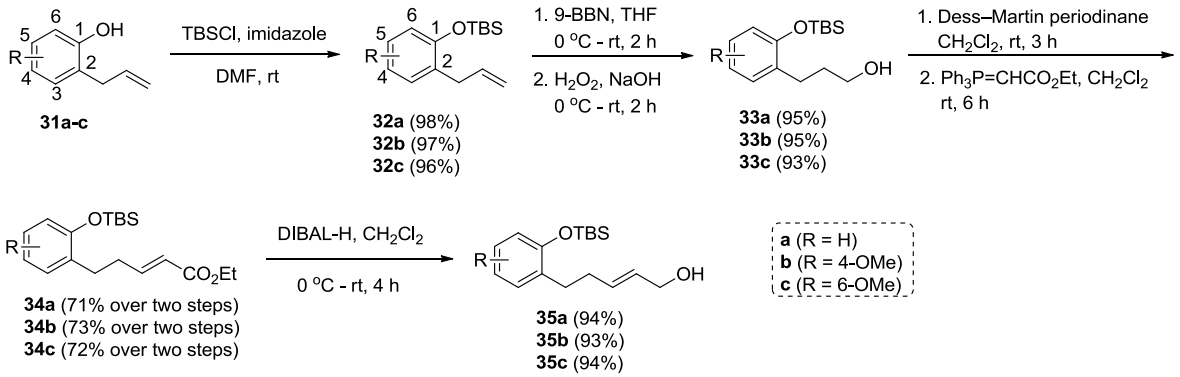


Scheme 9

Additionally, this would not only unveil a new entry to the synthesis benzo-fused oxa-heterocycles but also broaden the impact of aziridines as synthetic building blocks. Surprisingly, however, to the best of our knowledge, such a process has heretofore not been reported. In this section, we describe our results that allowed us to efficiently access chroman- and 1-benzoxepane-based amino alcohol derivatives via phenoxide ion-mediated intramolecular aziridine-ring opening in completely regio-, and diastereoselective manner under transition-metal-free conditions.

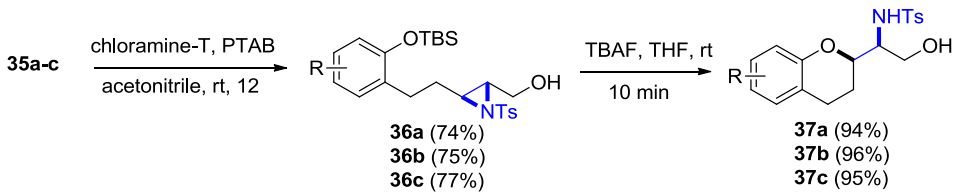
We started our investigation by synthesizing phenol-tethered aziridines as model substrates from known 2-allylphenols. As shown in Scheme 10, starting from 2-allylphenols **31a-c**, we prepared *tert*-butyldimethylsilyl (TBS)-protected *E*-allylic alcohols **35a-c** in a high overall yielding reaction sequence. With compounds **35a-c** in our hand, we focused on the synthesis of the corresponding *N*-tosyl aziridines.

Aziridination of **35a-c** under Sharpless conditions[3] (Chloramine-T and trimethylphenylammonium tribromide (PTAB)) provided aziridines **36a-c** in good yields (Scheme 11).



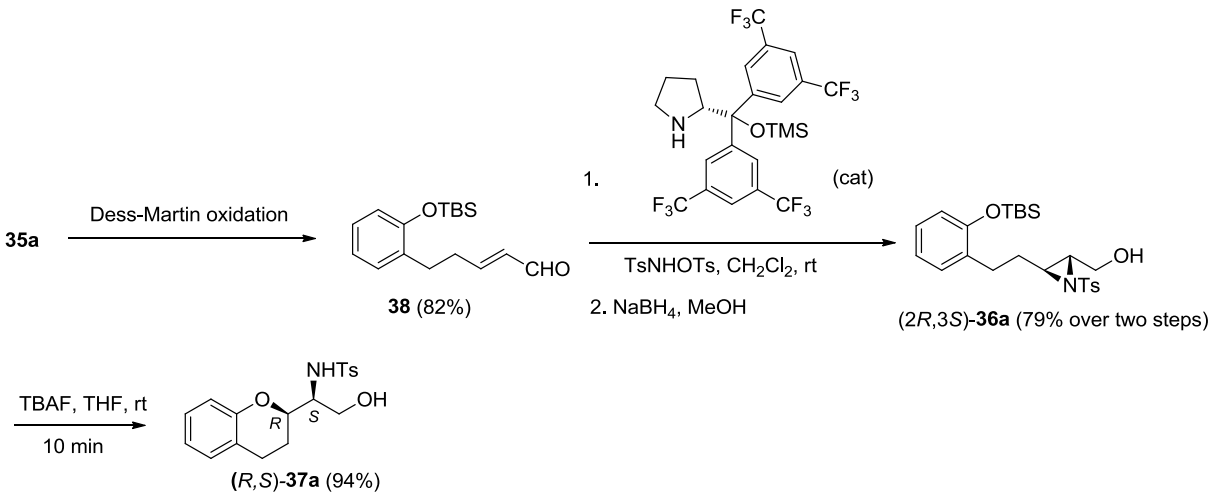
Scheme 10. Synthesis of TBS-protected *E*-allylic alcohols.

We were now ready to study their intramolecular aziridine ring-opening reactions. Our protocol involved a typical TBS deprotection reaction conditions which involved treatment of **36a-c** with tetrabutylammonium fluoride (TBAF) in THF. In this way, we were delighted to see very clean reactions of aziridines **36a-c**, providing the corresponding chroman-based amino alcohol derivatives **37a-c** in excellent yields.



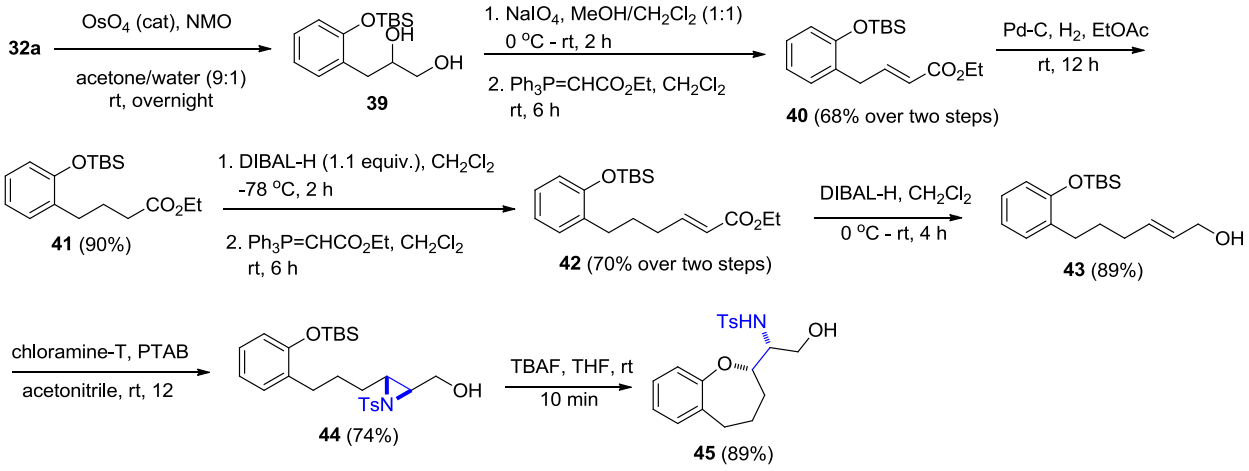
Scheme 11. Synthesis of chroman-based amino alcohol derivatives by intramolecular aziridine ring-opening.

An asymmetric version of this methodology was then developed using chiral aziridine (2*R*,3*S*)-**36a** which was synthesized from unsaturated aldehyde **38a** under Jørgensen's organocatalytic aziridination conditions (Scheme 12).[4]



Scheme 12. Asymmetric synthesis of chroman-based amino alcohol derivatives by intramolecular aziridine ring-opening.

Finally, this intramolecular aziridine ring-opening chemistry was further elaborated towards synthesis of 1-benzoxepane based amino alcohol derivative **45** (Scheme 13).

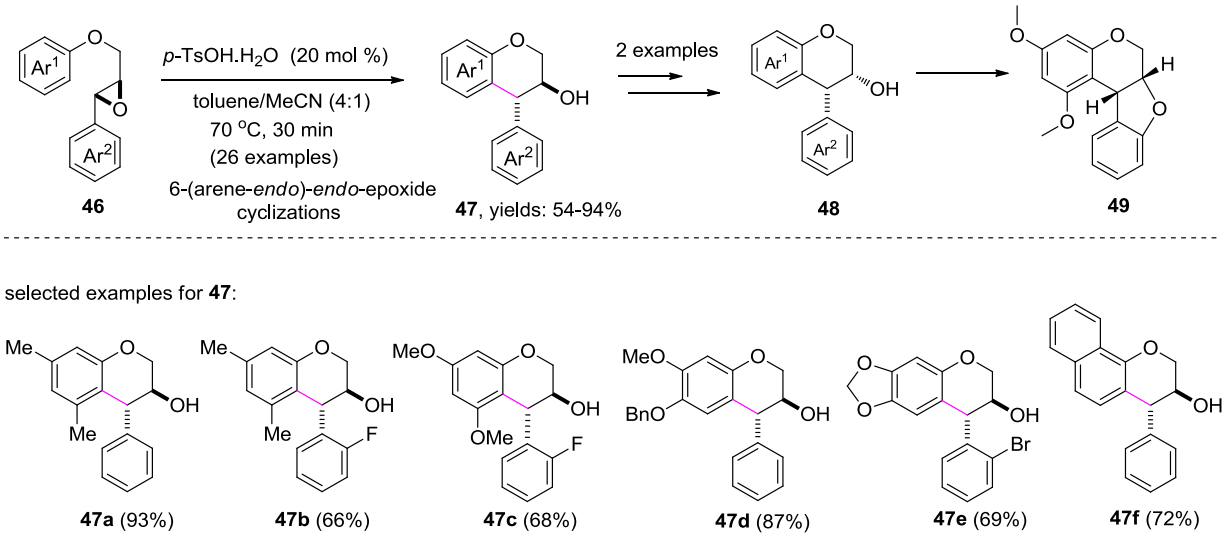


Scheme 13. Synthesis of 1-benzoxepane-based amino alcohol derivatives by intramolecular aziridine ring-opening.

ADDITIONAL WORK ON THE STEREOSELCTIVE SYNTHESIS OF CHROMAN DERIVATIVES

1. Diastereoselective synthesis of diverse *trans*-4-arylchroman-3-ols:

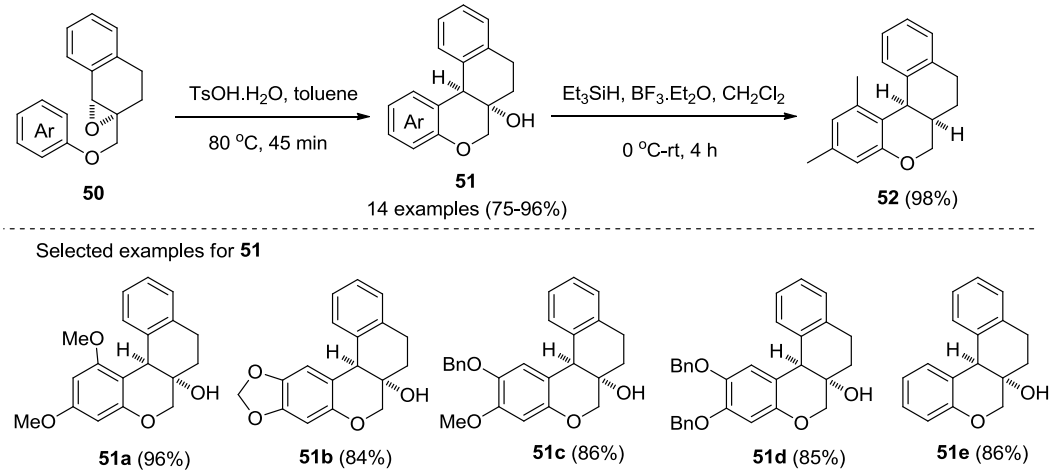
In another synthetic studies related to chroman-based compounds, an operationally simple and metal-free method for the synthesis of a series of *trans*-4-arylchroman-3-ols via Brønsted acid ($TsOH{\cdot}H_2O$) catalyzed stereoselective intramolecular Friedel–Crafts alkylation of electron-rich arenes by tethered epoxides was developed (Scheme 14).



Scheme 14. Diastereoselective synthesis of diverse *trans*-4-arylchroman-3-ols:

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

We have developed a convenient Brønsted acid- catalyzed, metal-free, stereoselective synthesis of 6a,7,8,12b-tetrahydro-6*H*-naphtho[2,1-c]chromen-6a-ols (Scheme 15). To the best of our knowledge, this is the first example of the generation of such type of chroman-fused tetralins.

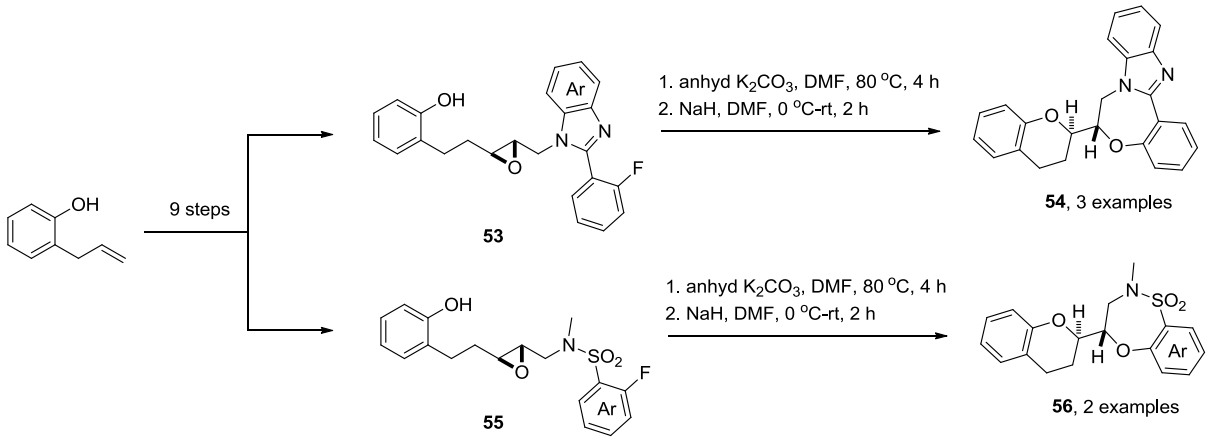


Scheme 15: TsOH·H_2O (20 mol%)-catalyzed synthesis of chroman-fused tetralins.

The easy accessibility of the starting materials, the mild reaction conditions, and the importance of products as B-ring-modified analogues of 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 has been 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.

3. Diastereoselective synthesis of chroman-linked benzoxazepines and benzosultams via sequential ArO–C bond-forming intramolecular epoxide ring-opening and Ar–O bond-forming intramolecular S_NAr reactions:

Finally, we have demonstrated the synthesis of hitherto unreported chroman-linked benzoxazepines and benzosultams via sequential ArO–C bond-forming intramolecular epoxide ring-opening and Ar–O bond-forming intramolecular S_NAr reactions (Scheme 16). This method proceeds with complete regioselectivity with high overall yields. The protocol is experimentally convenient, user- and environmentally friendly requiring simple, inexpensive, and readily available starting materials.



Scheme 16: Diastereoselective synthesis of chroman-linked benzoxazepines and benzosultams.

10. Detailed analysis of results indicating contributions made towards increasing the state of knowledge in the subject:

1. For the efforts towards the asymmetric synthesis 2-(chroman-2-yl)glycine esters via dienenone-phenol rearrangement of spirocyclic cyclohexadienone derivatives (Schemes 2 and 3; Tables 1 and 2):

Past few decades have witnessed tremendous exploitation of nonproteinogenic α-amino acids in the construction of designer peptides and proteins.[5] The utilization is largely attributed to the fact that incorporation of such amino acids into peptides/proteins can alter the chemical, biophysical, and pharmacokinetic properties of the latter compounds. The worth of nonproteinogenic α -amino acids in organic/medicinal chemistry are further enriched by their utility as building blocks in the synthesis of diverse biologically active (non-peptide) compounds, organocatalysts, chiral ligands and auxiliaries. Tremendous advances have already been made in the stereoselective synthesis of large number of nonproteinogenic α -amino acids. For the full potential of this class of compounds to be realized in the above-mentioned applications, however, it is necessary to expand the pool of existing α -amino acids. Thus, to broaden the diversity, it is highly desirable to synthesize new varieties of α -amino acids, particularly those bearing a heterocycle moiety.

There are a large number of chroman ring-containing natural and synthetic compounds which display wide spectrum of biological activities, establishing this structural unit as “privileged scaffold” in

medicinal chemistry.[6] However, little effort has been directed toward the synthesis of chroman-containing α-amino acids.

On the other hand, acid-catalyzed/mediated dienone-phenol rearrangement of appropriate spirocyclic cyclohexadienone systems (1-oxaspiro[4.5]deca-6,9-dien-8-ones) is a powerful tool for the synthesis of chroman derivatives with free phenolic-OH group on the benzene ring.[7] Employing dienone-phenol rearrangement as a key step, the synthesis of 2-unsubstitued chromans is well established. However, there exist only limited reports on the synthesis of 2-functionalized ones using this strategy, although synthesis of these later compounds would greatly increase the structural diversity of chroman derivatives. *Based on these facts and knowing the biological relevance of chroman ring system, and drawing inspiration from the literature reports describing the synthesis of 2-(tetrahydrofuran-2-yl)glycine, we targeted 2-(chroman-2-yl)glycine esters via acid-catalyzed/mediated dienone-phenol rearrangement of spirocyclohexadienone-embedded glycine esters*.

We have given our efforts toward the synthesis of 2-(chroman-2-yl)glycine esters for which we first 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-(chroman-2-yl)glycine esters, we were delighted to find that the study provided synthetic access to spirocyclohexadienone containing glycine esters through an intramolecular oxidative dearomatization reaction. Spirocyclohexadienones, containing a quaternary carbon center, 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 a α-amino acid derivative moiety have never been synthesized. Such hybrid compounds bearing two different well-known pharmacophores might be useful in the drug discovery process. Simplicity of the experimental procedures in the overall reaction sequence should make this method a general route to a wide variety of spirocylcohexadienone-bearing α-amino acid derivatives.

2. For the asymmetric synthesis of chroman-based amino alcohols using α-hydroxy ester building blocks (Schemes 4 - 7):

Sharpless asymmetric dihydroxylation (SAD) has been a workhorse as a synthetic tool for accessing enantiopure vicinal-diols. The extensive work in this field has resulted in the discovery of a number of cinchona alkaloid-derived ligands which allow dihydroxylation of alkenes of almost all substitution patterns with high enantioselectivity. Noteworthy is that SAD is not limited to only *E*-allylic alcohols in its choice of substrates as is the Sharpless asymmetric epoxidation (SAE) process. Moreover, SAD is much more superior in terms of operational simplicity as unlike SAE, it can be run at 0 °C in water as a co-solvent and under an open atmosphere of air.

Application of SAD-derived vicinal diols in the synthesis of acyclic molecules and saturated heterocycles has been astonishing. However, their utilities in the synthesis of chiral benzo-annulated heterocycles are relatively limited.

In the search for an alternative synthetic route for 2-(chroman-2-yl)glycine esters, next we have studied the synthesis and applications of chroman-based α-hydroxy esters.

Exposure of β-hydroxy-α-tosyloxy esters to a one-pot, three-step process (debenzylation-epoxidation-intramolecular epoxide ring opening) enabled us to achieve chroman-based α-hydroxy esters in high

yields. To our dismay, again, introduction of the azido functionality on the tosylate derivatives of these compounds was a complete failure which might be due the presence of an electron withdrawing ester group (which could promote elimination rather than substitution). Delightfully, when we reduced the ester functionality to the alcohol group, the azidation worked, albeit in low yield. Subsequent reduction of the azide group by H_2, Pd-C yielded chroman-based amino alcohol which should be useful as a precursor of chroman-based unnatural amino acid.

3. For the asymmetric synthesis of nebivolol intermediates using chroman-based α-hydroxy ester building blocks (Scheme 8):

Nebivolol is a chroman-based antihypertensive drug that was first reported in the racemic form. A number of syntheses of nebivolol and their intermediates have been described in the literature. However, to the best of our knowledge, nebivolol or its intermediates have never been synthesized using Sharpless asymmetric dihydroxylation as the sole source of chirality.

In the context of further exploiting Sharpless asymmetric dihydroxylation-derived chroman-based α-hydroxy ester building blocks, we could efficiently synthesize (*R*)-1-((*R*)-6-fluorochroman-2-yl)ethane-1,2-diol and (*S*)-6-fluoro-2-((*R*)-oxiran-2-yl)chroman─which have previously utilized as late-stage intermediates for the synthesios of (S,R,R,R)-nebivolol.

4. For the stereoselective synthesis of chroman- and 1-benzoxepane-based amino alcohols via phenoxide-mediated intramolecular aziridine ring opening (Schemes 10-13):

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.[8] Along this line, intermolecular ring-opening of aziridines by phenols/phenoxide ions have been reported in the literature. However, these reactions often suffer from disadvantages such as long reaction times, low yields, expensive reagents and tedious operation. These shortcomings have been critical obstructions for further advances in the aziridine ring-opening chemistry, and attributed mainly to the poor nucleophilicity of phenols/phenoxide ions. Moreover, regioselectivity can also be a problematic issue for such reactions, making the scenario further complicated. Excellent regioselectivities are usually obtained with terminal and aryl/vinyl-substituted aziridines, while regiocontrol is generally difficult to grasp for the ring-opening of unsymmetrically-disubstituted ones. Thus, use of phenols as hetero-nucleophiles in the stereo- and regioselective ring-opening of unsymmetrical di- and tri-substituted aziridines has received considerably less attention. In fact, only a few reports have carefully studied this aspect. Fine tuning of the steric and electronic effects on the two aziridine-carbon atoms have been the key for the success. We reasoned that the intramolecular versions of these reactions, driven by the entropy factor and guided by the Baldwin's rules, should be more synthetically apposite. Furthermore, chemo-, regio-, and stereoselective intramolecular aziridine ring-opening reactions by tethered phenols should be synthetically eye-catching because they could afford functionalized benzo-fused oxa-heterocycles, such as 2,3-dihydrobenzofuran, chroman, 1,4-benzodioxane, and 1-benzoxepine derivatives. While it is remarkable to consider the huge abundance of these heterocycles in bioactive natural products and synthetic molecules, equally striking

is the development of new approaches for their synthesis involving various advantageous features, such as complete atom-economy, shorter reaction time, ambient temperature, operational simplicity, and high yields.

A plethora of methods is available for the stereo- and regioselective synthesis of these privileged heterocyclic systems, but the most commonly reported methods are intramolecular S_NAr reaction, transition-metal-catalyzed C-O bond formation reaction, and Mitsunobu reaction, with each approach has its own advantages and disadvantages. We recognized a base-mediated intramolecular ring-opening reaction of an N-activated aziridine ring with a tethered phenol might provide such a platform which would not only unveil a new entry to the synthesis benzo-fused oxa-heterocycles but also broaden the impact of aziridines as synthetic building blocks. Surprisingly, however, to the best of our knowledge, such a process has heretofore not been reported.

In this work, we could efficient access chroman, and 1-benzoxepine-based amino alcohol via phenoxide ion-mediated intramolecular aziridine-ring opening in completely regio-, and diastereoselective manner under transition-metal-free conditions. The approach enabled the preparation of functionalized building blocks susceptible to further derivatization with potential implications in medicinal chemistry

5. For the work on the synthesis 4-arylchroman-3-ols (Scheme 14):

The chroman core constitutes a privileged structural motif of a wide range of bioactive natural products and synthetic compounds of pharmaceutical interest. Among several classes of chroman-based natural products, catechins (flavan-3-ols/2-arylchroman-3-ols) are a group of naturally-occurring flavonoids that share the 2-arylchroman-3-ol basic backbone bearing highly electron rich aryl rings. These compounds possess a broad spectrum biological activities—some of them potentially very much important. Not surprisingly, there have been significant activities toward the synthesis of these molecules and their derivatives to explore and improve the biological profiles. A common feature of catechins is that they undergo oxidative oligomerization in vivo through the benzylic position of the C-ring and hence potential bioaccessibility of parent catechins is reduced. Along this line, we hypothesize that with the congeneric 4-arylchroman-3-ols, the relevant biological activities might not be compromised and oxidative oligomerization might be suppressed. However, in sharp contrast to the well-explored chemistry and biology of flavan-3-ols, the synthetic and bioevaluation studies of 4-arylchroman-3-ols has not yet been explored systematically.

On the other hand, epoxides have found widespread use in organic synthesis because of their easy availability in racemic as well as enantiomerically pure forms, and proficiency to undergo regio- and stereoselective ring-opening reactions. For example, there have been reports of the synthesis of substituted carbo- and heterocyclic compounds via intramolecular Friedel-Crafts epoxy-arene (IFCEA) cyclization— one of the several possible synthetic transformations of epoxides. In this aspect, racemic and enantiomerically pure *trans*-4-aryl-3-hydroxychromans have been synthesized via IFCEA cyclization. Mainly, transition metal-based Lewis acid catalysts have been used efficiently for this purpose. However, one of the drawbacks of transition metal-based catalysts is the requirement of strict anhydrous conditions. This requires the inclusion of some special attention to handle very small amount of the catalyst used in the synthetic procedures and hence carrying these reaction on large-scale applications may be troublesome. In this regard, identification of transition-metal-free conditions is important because such procedures generally have obvious advantages in terms of cost, nontoxicity and

environmental compatibility For the synthesis of *trans*-4-arylchroman-3-ols, these limitations have recently been overcome successfully with the use of 1,1,3,3,3-hexafluoroisopropanol (HFIP) as a reaction medium which could also act as promoter for the IFCEA cyclization (Scheme 1). However, the use of specialized Brønsted acid like this particular fluorinated alcohol, and its expensive commercial availability can be considered as preventive factors for the general use of this method. Added to this, B-aryl rings of the reported *trans*-4-arylchroman-3-ols typically have been limited to phenyl and 4-bromophenyl rings, which significantly limit the application of this method in organic synthesis. Also, until now there has been no report of the synthesis of this class of molecules with free phenolic-OH group on both the A and B phenyl rings—a structural requirement for their possible biological activity and further structural elaboration toward more complex molecules. Therefore, these disadvantages and the cost effectiveness of the methodology and insufficient literature on synthesis of diverse 4-arylchroman-3-ols brought us an attention to initiate a systematic synthetic study through the development of an affordable alternative catalyst system for this conversion. We postulated that this issue could be alleviated by the use of easily accessible and affordable Brønsted acids (transition-metal-free condition).

We have performed a systematic study on the synthesis of diverse 4-arylchroman-3-ols via easily accessible and affordable Brønsted acid $TsOH.H_2O$ catalyzed diastereoselective IFCEA cyclization. The exact nature of this fundamentally unique reaction (stepwise vs concerted) can vary depending on the substrate; however, the synthetic effectiveness is clearly evident, with trans-4-arylchroman-3-ols being prepared in moderate to high yields with complete regio- and diastereoselectivity. The protocol involved conducting reactions in AR-grade toluene and MeCN under open air, did not require strict anhydrous conditions, and eluded the use of expensive Lewis/ Brønsted acids. Also, this method was scalable, and suitable for the introduction of phenolic-OH groups on both the aromatic rings, which should provide good opportunities for the synthesis of complex molecules. Thus, the reaction protocol was blessed with the advantage of synthetic and operational simplicity. Additionally, we have developed 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. Such a combination of two privileged structural motifs is highly relevant for drug discovery and development.

6. For the work on the synthesis chroman-fused tetralins (Scheme 15):

Fusion of two or more privileged scaffolds leads to geometrically well-defined rigid polycyclic structures with enhanced receptor-binding selectivity. Thus, the design and synthesis of structurally diverse, privileged structure-based polycyclic molecules with multiple chiral centers has been intensely studied during the past 15 years. Moreover, on many occasions natural-product like molecules exhibit more potent biological activities than the parent natural products .

We have developed a convenient Brønsted acid- catalyzed, metal-free, stereoselective synthesis of 6a,7,8,12b-tetrahydro-6*H*-naphtho[2,1-c]chromen-6a-ols as B-ring-modified analogues of brazilin using starting materials derived from inexpensive 1-tetralone and phenol derivatives. Our worries concerning the formation cis-trans mixture of 6a,7,8,12b-tetrahydro-6*H*-naphtho[2,1-c]chromen-6a-ols and their probable conversion to of naphthopyran derivatives via dehydration of tertiary-OH group were laid to rest. To the best of our knowledge, this is the first example of the generation of such type of chroman-fused tetralins. The easy accessibility of the starting materials, the mild reaction conditions, and the importance of products as B-ring-modified analogues of brazilin should make this synthetic work a useful addition in the diversity-oriented synthesis of natural-product like molecules. Morever, since

enantiomerically pure/enriched epoxides are compatiable under IFCEA cyclization this methodology should also be applicable with the enantioenriched substartes. Additionally, the angular –OH group of one of the synthesized products has been reductively removed by a diastereoselective method which should be useful in future for preparing libraries of chroman-fused tetralins with trans-stereochemistry at the ring junction.

7. For the work on the diastereoselective synthesis of chroman-linked benzoxazepines and benzosultams (Scheme 16):

Benzimidazoles represent an important class of nitrogen containing fused heterocycles. There is a wide structural diversity for benzimidazole derivatives. This heterocycle-fused ring system has been recognized as a privileged pharmacophore in drug design, and extensive research has been reported in this field profiting from the versatile modification of its scaffold. Among different classes of benzimidazoles, 2-arylbenzimidazoles are a unique group of heterocyclic architectures that is commonly present in a large number of pharmacologically active compounds which shows a wide spectrum of biological and pharmacological properties. It is therefore not surprising that many synthetic methods have been developed to reach 2-arylbenzimidazoles.

On the other hand, the synthesis of privileged structure-based, nitrogen-containing polycyclic molecules has inspired numerous research groups because they exhibit a wide range of remarkable bio-activities. A variety of methods are available for the formation of such compounds, but the synthesis under complete regio-and stereocontrol with a high level of diversity points remains a challenging problem. Hence, straightforward and diversity-oriented synthetic approaches to structurally diverse benzimidazole-fused derivatives are highly anticipated to assist rapid development of heteropolycyclic aromatic compound-based drug leads.

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 chroman-linked, benzimidazole-fused benzoxazepines and benzosultams. This method proceeds with complete regioselectivity with high overall yields.The protocol is experimentally convenient, user- and environmentally friendly requiring simple, inexpensive, and readily available starting materials. The synthetic routes appear to be fairly general ones. Furthermore, the method is highly modular and adaptable for the preparation of libraries of privileged heterocycle-based small organic molecules in a short sequence of reactions.

References:

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3. Jeong, J. U.; Tao, B.; Sagasser, I.; Henniges, H.; Sharpless, K. B. *J. Am. Chem. Soc.* **1998**, *120*, 6844– 6845.
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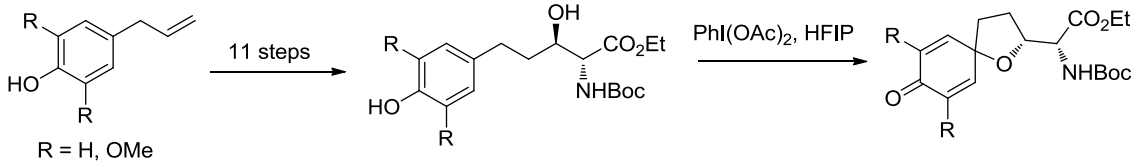
7. For a review on dienone-–phenol rearrangement, see: Miller, B. *Acc. Chem. Res*. **1975**, *8*, 245-256. For recent examples of dienone–phenol rearrangement of spirocyclohexadienones or spiro-type intermediates, see: (b) Wada, Y.; Otani, K.; Endo, N.; Kita, Y.; Fujioka, H. *Chem. Commun.* **2010**, *46*, 797–799; (c) Glushkov, V. A.; Rotermel, E. V.; Odegova, T. F.; Shklyaev, Y. V. *Russ. J. Org. Chem*. **2011**, *47*, 1318–1322; (d) Moisan, L.; Wagner, M.; Comesse, S.; Doris, E. Tetrahedron Lett. **2006**, *47*, 9093–9094; (e) Yoshida, M.; Nozaki, T.; Nemoto, T.; Hamada, Y. *Tetrahedron* **2013**, *69*, 9609– 9615.
8. For recent reviews, see: (*a*) X.-E. Hu, *Tetrahedron*, **2004**, *60*, 2701-2743; (*b*) P.-F. Lu, *Tetrahedron*, **2010**, *66*, 2549-2560; (*c*) P.-A. Wang, *Beilstein J. Org. Chem*., **2013**, *9*, 1677–1695; (*d*) C.-Y. D. Huang and A. G. Doyle, *Chem. Rev*., **2014**, *114*, 8153–8198; (*e*) G. Callebaut, T. Meiresonne, N. De Kimpe, and S. Mangelinckx, *Chem. Rev*., **2014**, *114*, 7954–8015; (f) H. Ohno, *Chem. Rev*., **2014**, *114*, 7784–7814.

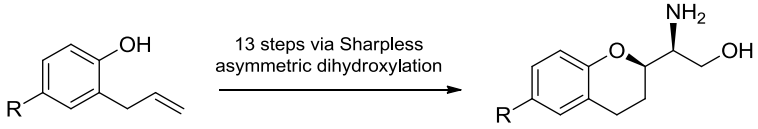
12. Conclusions summarizing the achievements and indication of scope for future work:

SUMMARY OF THE ACHIEVEMENTS

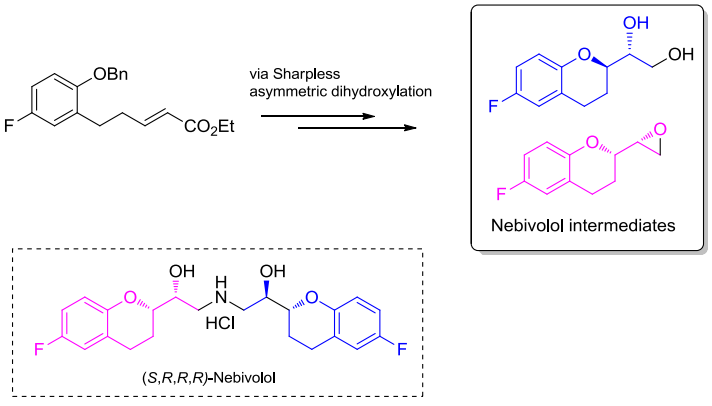
1. First asymmetric synthesis of spirocylcohexadienone-bearing α-amino acid derivatives ─ a new class of nonproteinogenic α-amino acids ─ has been achieved.



2. Asymmetric synthesis of 2-amino-2-(chroman-2-yl)ethanols via chroman-based α-hydroxy esters has been achieved.

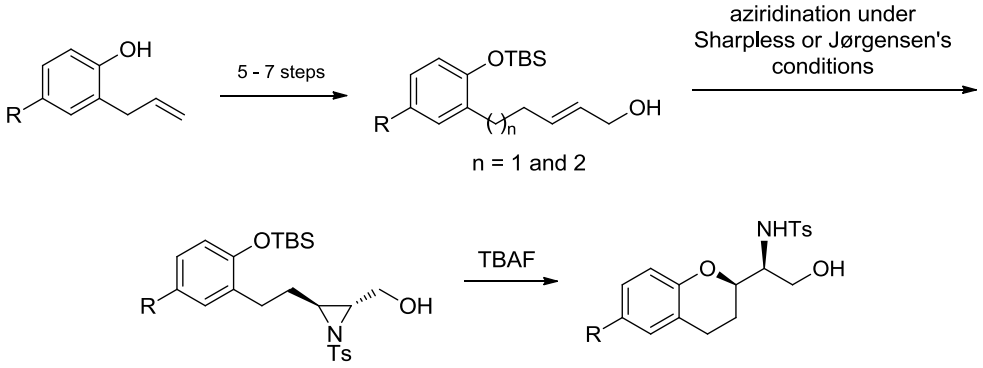


3. Asymmetric synthesis of late-stage nebivolol intermediates using chroman-based a-hydroxy ester building blocks has been achieved.

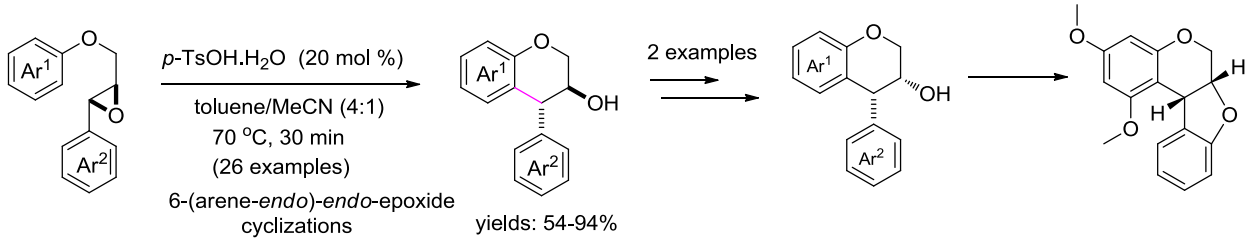


4. First racemic/asymmetric synthesis of chroman- and 1-benzoxepane-based β-amino alcohols has been

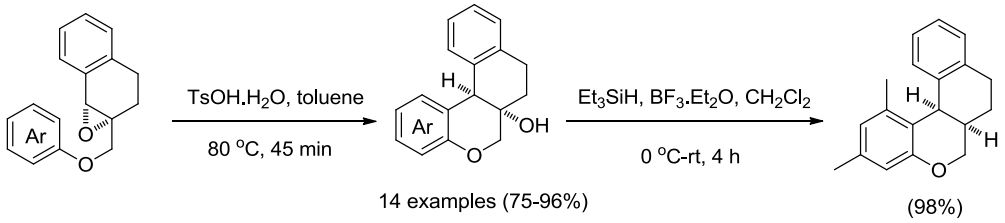
achieved using phenoxide ion-mediated intramolecular ring-opening reactions.



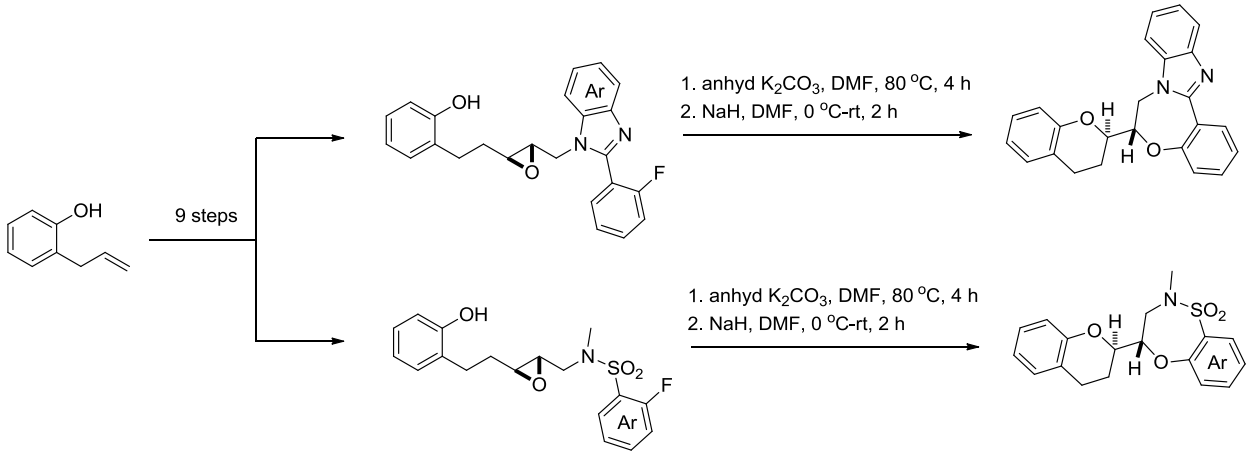
5. An operationally simple and metal-free method for the synthesis of a series of *trans*-4-arylchroman-3-ols via Brønsted acid ($TsOH{\cdot}H_2O$) catalyzed stereoselective intramolecular Friedel–Crafts alkylation of electron-rich arenes by tethered epoxides was developed.



6. We have also developed a convenient Brønsted acid- catalyzed, metal-free, stereoselective synthesis of 6a,7,8,12b-tetrahydro-6*H*-naphtho[2,1-c]chromen-6a-ols as natural product-like molecules.



7. Finally, we have also demonstrated the synthesis of hitherto unreported chroman-linked benzoxazepines and benzosultams via sequential ArO–C bond-forming intramolecular epoxide ring-opening and Ar–O bond-forming intramolecular S_NAr reactions.



SCOPE FOR FUTURE WORK

The methodologies (1-4) have the potential for the application in the synthesis of 2,3-dihydrobenzofuran- and related benzo-annulated oxa-heterocycles-based enantiomerically pure nonproteinogenic α-amino acids. Such a strategy would allow us to create these classes of nonproteinogenic α-amino acids containing contiguous stereocenters potentially of any desired configuration. These amino acids should be useful as synthetic intermediates for different bioactive compounds or as peptidomimetic constituents. The methodologies (5-7) have the potential for the application in the synthesis of libraries of privileged structure-based small organic molecules.

13. S&T benefits accrued:

i. List of Research publications

1. Brønsted acid-catalysed intramolecular ring opening of 2-(aryloxymethyl)-3-aryloxiranes leading to *trans*-4-arylchroman-3-ols: scope and limitations Runjun Devi, Tapasi Kalita and **Sajal Kumar Das***
   RSC Adv., **2015**, *5*, 39692.

2. Synthesis of diverse catechin congeners via diastereoselective intramolecular epoxy-arene cyclization
   Runjun Devi, Dimpee Gogoi, Prerona Bora and Sajal Kumar Das*
   Tetrahedron, **2016**, *72*, 4878.

3. *cis*-Diastereoselective synthesis of chroman-fused tetralins as B-ring-modified analogues of brazilin.
   Dimpee Gogoi, Runjun Devi, Pallab Pahari, Bipul Sarma and Sajal Kumar Das*
   Beilstein J. Org. Chem. **2016**, *12*, 2816–2822.

4. Studies directed toward the exploitation of vicinal diols in the synthesis of (+)-nebivolol intermediates.
   Runjun Devi, and Sajal Kumar Das*
   Beilstein J. Org. Chem. **2017**, *13*, 571.

5. Recent Advances in the Intramolecular Reactions of Epoxides with Arenes and Heteroarenes
   Sajal Kumar Das*
   Asian J. Org. Chem. **2017**, *3*, 243-256.

6. Synthesis of Tetrahydroquinoline-Embedded Bridged Benzothiaoxazepine-1,1-dioxides
   Hemi Borgohain, Runjun Devi, Divya Dheer, Biraj Jyoti Borah, Ravi Shankar, Sajal Kumar Das*
   Euro. J. Org. Chem. **2017**, 6671–6679.

7. Efforts towards the synthesis of 2-(chroman-2-yl)glycine esters: an efficient route to spirocyclohexadienone-embedded glycine esters
   Runjun Devi and Sajal Kumar Das*
   Manuscript submitted

8. Stereoselective synthesis of benzo-fused oxygen heterocycles via phenoxide-ion mediated intramolecular aziridine ring-opening.
   Runjun Devi and **Sajal Kumar Das**
   Manuscript submitted.

ii. Manpower trained on the project:

a) Research Scientists or Research Associates : 0

b) No. of Ph.D. produced: 1 (thesis going to be submitted in March-April)

c) Other Technical Personnel trained: 4 MSc students have done their project work

iii. Patents taken, if any: None

13. Financial Position:

No	Financial Position/ Budget Head	Funds Sanctioned	Expenditure	% of Total Expenditure
I	Equipment	6,70,000.00	6,64,689.00	27.89
II	Salaries/ Manpower costs	17,50,000.00	17,18,609.00	72.11
III	Supplies & Materials			
IV	Contingencies			
V	Travel			
VI	Overhead Expenses			
VII	Others, if any (Bank Interest)	5486.00	N/A	N/A
	Total	24,25,486.00	23,83,298.00	100%

14. Procurement/ Usage of Equipment

S No	Major Equipment (Model and Make)				
1.	Sanctioned List	Procured Model & Make	Cost (₹ in Lakhs)	Working	Utilisation Rate (%)
2.	Rotary Evaporator with vacuum pump and related accessories	Ika Rotary evaporator: RV-10 Digital V, Vacuum pump: MPC 095Z	4.71450	Yes	100%
3.	Hot Air Oven	Ikon IK-109	0.36436	Yes	100%
4.	UV Cabinet	JSGW	0.07560	Yes	100%
5.	Magnetic Stirrer	Ika RH Basic 1	0.67998	Yes	100%
6.	High vacuum pump	HHV PUMPS FD20	0.67898	Yes	100%
7.	Printer	HP Printer Laserjet M 1005 MFP	0.14014	Yes	100%
8.	Refrigerator-310 ltrs, 4 star, GIDC (*from overhead money*)	LG GLM322RLTL(PV,PZ,SU)	0.34290	Yes	100%

b) Plans for utilizing the equipment facilities in future:

All the purchased equipment are currently in working conditions and being utilized in our laboratory.

Name and Signature with Date

a._____ _____

Dr Sajal Kumar Das

(Principal Investigator)

b._____

(Co-Investigator)

Annexure-II

STATEMENT OF EXPENDITURE

For the period 1st April, 2017 – 24th July, 2017

1. SERB Sanction Order No and date : **SB/FT/CS-073/2013 dated 20.05.2014**
2. Name of the PI : **Dr. SAJAL KUMAR DAS**
3. Total Project Cost : **24,80,000.00 (Sanctioned amount)**
4. Revised Project Cost (if applicable) : **NA**
5. Date of Commencement : **July 25, 2014**
6. Statement of Expenditure (month wise expenditure incurred during current financial year)

Month & year	**Expenditure incurred/committed**
April, 2017	nil
May, 2017	16,000
June, 2017	16,000
July, 2017	16,000
August, 2017	16,000

7. Grant received in each year
   a. 1st Year : 12,70,000
   b. 2nd Year : 5,50,000
   c. 3rd Year : 6,00,000
   d. Interest, if any : 5,486
   e. Total (a+b+c+d) : 24,25,486

Annexure-II

Statement of Expenditure
For the period 1st April, 2017 – 24th July, 2017

Sr No (I)	Sanctioned Heads (II)		Total fund available for expenditure including the bank interest (In ₹) (25th July, 2014 – 24th July, 2017 (III))				Expenditure Incurred				Total Expenditure till 24th ~~31st March~~ July, 2017 (VIII = IV + V+ VI+VII) In ₹	Balance as on ~~31st~~ 24th ~~March~~ July 2017 (IX = (III – VIII) In ₹	Require-ment of Funds upto ~~31st~~ 24th ~~March~~ July 2017 In ₹
			1st Year (25th July, 2014 – 31st March, 2015) (IIIA)	2nd Year (1st April, 2015 – 31st March, 2016) (IIIB)	3rd Year (1st April, 2016 – 24th July, 2017) (IIIC)	Total (IIIA + IIIB + IIIC)	1st Year (25th July, 2014 – 31st March, 2015) (IV) In ₹	2nd Year (1st April, 2015 – 31st March, 2016) (V)	3rd Year 2016-17 (1st April, 2016 – 31st March, 2017) (VI)	3rd Year 2016-17 (1st April, 2017 – 24th July, 2017) (VII)			
1.	Recurring	Manpower costs	6,00,000	5,50,000	6,00,000	17,50,000	1,10,645	1,68,000	1,84,000	64,000	14,18,824	(24,25,486-23,83,298) = 42,188	N/A
2.		Consumables					3,00,362	2,42,873	2,35,600	nil			
3.		Travel					9,959	26,159	15,490	nil			
4.		Contingencies					36,915	24,821	nil	nil			
5.		Overhead					99,860	99,926	99,999	nil	2,99,785		
6.	Non-Recurring	Equipment	6,70,000	nil	nil	6,70,000	6,64,689	nil	nil	nil	6,64,689		
7.	Bank interest		---	2,393	3,093	5486	N/A	N/A	N/A	N/A	N/A		
8.	Total		12,70,000	5,52,393	6,03,093	**24,25,486**	12,22,430	5,61,779	5,35,089	64,000	**23,83,298**		

Name of Principal Investigator: Dr. SAJAL KUMAR DAS

Signature of PI: SKdas Date: 6.2.18	Signature of the Finance Officer Date: 9/2/18 Finance Officer Tezpur University	Signature of the Registrar: Date: Registrar Tezpur University

UTILIZATION CERTIFICATE

(FOR THE 1st April, 2017 – 24TH JULY 2017)

1. Title of the Project: **Asymmetric Syntheses of New Classes of Unnatural □-Amino Acid Derivatives**
2. Name of the Institution: **Tezpur University**
3. Name of the Principal Investigator: **Dr. Sajal Kumar Das**
4. Science and Engineering Research Board (SERB) Sanction order No & date sanctioning the project: (First financial sanction order) **SB/FT/CS-073/2013 dated 20.05.2014**
5. Head of account as given in the original sanction order: **Non-Recurring and Recurring**
6. Amount brought forward from the previous Financial year quoting SERB letter no and date in which the authority to carry forward the said amount was given
   i. Amount: ₹ **1,06,188.00**
   ii. Letter No. N/A
   iii. Date:
7. Amount received during the financial year (SERB Sanction order no and date)
   i. Amount: NIL
   ii. Letter No. N/A
   iii. Date:
8. Total amount that was available for expenditure (excluding commitments) during the financial year (Sr. No. 6 + 7)
   ₹ 1,06,188.00
9. Actual Expenditure (excluding commitment): **₹ 64,000.00**
10. Balance amount available at the end of the project (July 24, 2017) **₹ (1,06,188.00- 64,000.00) = ₹ 42,188.00**
11. Unspent balance refunded (details of demand draft): : ₹ 42,188.00
    SBI Demand Draft
    NO: 050525
    Dated: 23/02/2018
12. Amount to be carried forward to the next financial year : **N/A**

Finance Officer

UTILIZATION CERTIFICATE

Certified that out of the unspent balance of ₹ **1,06,188.00** of the previous financial year (1st April, 2016 – 31st March 2017), a sum of ₹ **64,000.00** has been utilized by **Dr. SAJAL KUMAR DAS** for the purpose of **implementation of research project** vide SERB order No. **SB/FT/CS-073/2013** dated **17/10/2016**, and that the unspent balance of ₹ **42,188** has been refunded vide Demand Draft no. 050525 dated 23/02/2018.

Signature of PI: Date: 6.2.18	Signature of the Finance Officer Date: 9/2/18 Finance Officer Tezpur University	Signature of the Registrar: Date: Registrar Tezpur University