SYNOPSIS
The research work in this thesis entitled “Formal Synthesis of Furanodictines, (-)-Varitriol and Development of Novel Synthetic Processes, Methodologies for Biologically Active Compounds” has been undertaken with an objective to synthesize biologically active carbohydrate based natural products. Further, the other aim was to develop new synthetic processes and methodologies for molecules of biological significance.

The thesis is divided into four chapters; Chapter-1 describes the formal synthesis of furanodictines A and B from the cheap starting material D-glucose. The chapter-2 deals with total synthesis of (-) varitriol and aromatic metabolite RKB 3564S. The Chapter-3 describes the development of new synthetic processes for molecules of biological significance such as the sucralose (artificial sweetener), allolactose (lac operon inducer) and myristicinaldehyde. This chapter is divided into three sections. The final chapter deals with the development of synthetic methodologies for biologically active benzoanthenines and amidonaphths by recyclable solid acid catalyst, tungstated zirconia and potassium dodecatungstocobaltate trihydrate. This chapter is divided into two sections.

Chapter I: Formal synthesis of aminosugars, furanodictine A and B from D-glucose

Many interesting and structurally diverse carbohydrates are components of biologically active natural products. Recently, the amino sugars furanodictines B (1a) and A (1b) were isolated from slime molds Dictyostelium discoideum with absolute configurations of (2R,3R,4S,5R) and (2S,3R,4S,5R), respectively. They exhibit potent neuronal differentiation activity and are the lead structures in the development of novel nerve-rejuvenation drugs. Further, the core bicyclic bis-tetrahydrofurafuran structures also constitute an integral part of several other natural products. We have developed a new synthetic
approach for asymmetric synthesis of 1a and 1b using commercially available D-glucose.

\[
\begin{align*}
\text{1a} \quad & \quad \text{1b}
\end{align*}
\]

**Figure 1**

**Retrosynthetic analysis:**

The retrosynthetic analysis of Furanidictine B (1a) has indicated that the absolute configurations at C(4), C(5) and C(6) are the same as those present in D-glucose at C(3), C(4) and C(5), respectively. The stereocentre at C(3) of 1b can be derived by nucleophilic inversion (S\textsubscript{N}2) of configuration at C(2) of D-glucose by azide. The bicyclic 3,6-anhydro sugar 3 can be constructed through the intramolecular cyclization of the C(3) hydroxyl group with C(6) by a simple protocol developed earlier by us. Similarly furanodictine-A, compound 1b can be obtained from D-glucose by overall retention of configuration at C(3) carbon. Execution of the retrosynthetic plan is summarized in (Scheme 1).

\[
\begin{align*}
\text{1a} & \quad \text{1b} \\
\text{X=NHAc} & \quad \text{Y=NHAc} \\
\text{3} & \quad \text{2} \\
\text{OTf} & \quad \text{OMe} \\
\text{4} & \quad \text{5}
\end{align*}
\]

**Scheme 1**

**Furanodictine B:**

The key intermediate 2 in the synthesis of furanodictine A and B was prepared from D-glucose. The synthetic strategy started with acetonation of D-
glucose to 1,2:5,6-di-O-isopropylidene-α-D-glucofuranoside, followed by controlled hydrolysis in which 5,6-O-isopropylidene group is selectively deprotected to give the triol, 2-O-isopropylidene-α-D-glucofuranoside 4 (mono acetone glucose). The 3,6-anhydro sugar derivative 6 was synthesized by treating glucofuranose 4 with diethylcarbonate and sodium hydride followed by benzylation with benzyl bromide. The bicyclic benzylic ether 6 on methanolysis catalyzed by ion exchange resin IR-120 H⁺ gave the 2-hydroxy derivative 7 as a diastereomeric mixture (anomeric ratio α/β = 2:3). The 2-hydroxy derivative of anhydro sugar 7, was transformed to the key intermediate 2 on reaction with triflic anhydride and pyridine (Scheme 2).

Scheme 2: Reagents and conditions: i) Acetone, H₂SO₄, rt; ii) 0.8% H₂SO₄, aq. MeOH, rt; iii) Diethyl carbonate, sodium hydride; iv) BnBr, NaH, DMF; v) IR 120-H⁺, MeOH, reflux, 2 h; vi) Tf₂O, pyridine, 0 °C to rt, 1 h; vii) NaN₃, DMF, 60 °C, 6 h; viii) Ph₃P, THF–CH₂Cl₂, rt, 3 h; x) Ac₂O, pyridine, CH₂Cl₂, rt, 2 h; xi) Pd(OH)₂/C/H₂, MeOH, 1atm, 2 h.
The key intermediate 2 on nucleophilic displacement (S₂N) with sodium azide afforded the azido derivative 8 which was characterized by IR peak at 2130 cm⁻¹. The reduction of the azido derivative 8 was achieved with triphenyl phosphine followed by acetylated with acetic anhydride in pyridine to give N-acylated compound 9. The acetamide 9 was subjected to hydrogenolysis using palladium hydroxide at atmospheric pressure to provide the required methyl 3,6-anhydro-N-acetylamino β-D-mannofuranoside 10 as a crystalline solid (mp 174–175 °C). The crystalline solid 10 was characterized by ¹H NMR spectrum from the appearance of H-1 at δ 4.97 as a doublet (J = 2.3 Hz), methoxy group at δ 3.36 and acetyl group at δ 2.01. The advanced intermediate 10 was obtained in 13.2% overall yield from D-glucose. The conversion of compound 10 to the natural product FD-B has been reported earlier there by completing the formal synthesis of furanodictine B 1a.

**Synthesis of Furanodictine A:**

In the synthesis of furanodictine A, the key intermediate 2 prepared from D-glucose was utilized. A stereospecific inversion at C 2 position of intermediate 2 was successfully carried out with triflic anhydride and cesium trifluoroacetate to give an alcohol 11. The alcohol was converted to corresponding 2-O-triflate derivative 12 on reaction with triflic anhydride in presence of pyridine in quantitative yield. The nucleophilic displacement (S₂N) reaction of 12 with sodium azide smoothly afforded the azido derivative 13 with inversion of configuration. The azide functionality was reduced with triphenyl phosphine to afford amine 14, which was acetylated with acetic anhydride in pyridine to afford N-acetylated amine 15. Finally, the benzyl group was deprotected by hydrogenolysis using palladium hydroxide to provide the required methyl 3,6-anhydro-N-acetylamino β-D-glucofuranoside 16. The advanced intermediate 16 can be converted to the furanodictine A 1b in two steps, thereby completing the total synthesis of the target compound.
Scheme 3: Reagents and conditions: i) CsOCOCF$_3$; ii) Tf$_2$O, pyridine, 0 °C to rt, 1 h; iii) NaN$_3$, DMF, 60 °C, 6 h; iv) Ph$_3$P, THF-CH$_2$Cl$_2$, rt, 3 h; v) Ac$_2$O, pyridine, CH$_2$Cl$_2$, rt, 2 h; vi) Pd(OH)$_2$/C/H$_2$, MeOH, 1 atm, 2 h.

In this chapter, a simple and efficient route for the formal total synthesis of furanodictine B and furanodictine A has been developed starting from cheap and readily available raw material D-glucose.

Chapter II: Synthesis of (-)-varitriol and development of new synthetic routes to RKB 3564S.

Marine-derived biologically active natural products continue to be a source of potential therapeutic compounds as well as motivation to develop new synthetic strategies for their construction. (+)-Varitriol 17 was isolated from a marine-derived strain of the fungus *Emericella variecolor* and its exhibits significant cytotoxic activity against renal, CNS and breast cancer cell lines. RKB 3564S 18 is an aromatic metabolite of a fungal strain of the *Acremonium sp.* (MST-MF558a) and known for its antitumor and antiangiogenesis activity. Further, it was patented for the treatment of diabetes, obesity, and neuroses, as well as Alzheimer’s and Parkinson’s diseases.
In the present work, the total convergent synthesis of (-)-varitriol by synthesizing the aromatic fragment in a new route and the synthetic approach to the carbohydrate fragment from D-ribose is described.

**Retrosynthetic analysis:**

The retrosynthetic analysis of varitriol is delineated in Scheme 4. The aromatic fragment can be obtained from substituted phenol 19. The bottom carbohydrate portion of varitriol can be derived from D-ribose due to the similarities between the bottom portion of varitriol and the natural carbohydrate D-ribose.

The furanoside 22 serves this purpose quite well with two orthogonal aldehyde surrogates present as a protected primary alcohol and a nitrile functional group. Thus, the β-C-furanoside subunit 20 could readily be derived from the aminal 21,
which in turn would originate from the “pseudo” C2 symmetric compound 22. We envisaged the final key convergence of the styrene derivative 18 with the furanoside 20 via an olefin cross-metathesis reaction.

**Synthesis of aromatic fragment (styrene):**

In the synthesis of aromatic fragment 18, the substituted benzaldehyde 25 was the key intermediate and synthesized from commercially available 2, 3 dimethyl phenol 19 as depicted in Scheme 5. The substituted phenol 19 was protected as methyl ether 23 by methyl iodide, followed by free radical bromination with N-bromosuccinimide to provide tribrominated compound 24. The acetolysis of the tri brominated compound 24 with sodium acetate provided substituted benzaldehyde 25.

The key intermediate 25 on single carbon Wittig olefination with methyl triphenyl phosphonium iodide gave the aromatic intermediate 26. The reduction of ester moiety in 26 under basic medium provided corresponding benzylic alcohol compound 27, which on protection as silyl ether by treating with tert-butylidemethylsilyl chloride afforded the aromatic fragment 18. The substituted styrene 18 was characterized by $^1$H NMR spectrum with the appearance of OTBS peak at $\delta$ 0.11 (s, 6H), 0.95 (s, 9H), and values were in complete agreement with that reported in literature.

![Scheme 5: Reagents and conditions:](image)

i) CH$_3$I, Aq. KOH, TBAH, CH$_2$Cl$_2$ ii) NBS, CCl$_4$, reflux, hv. iii) NaOAc, CH$_3$COOH iv) CH$_2$=PPh$_3$I, THF, rt. v) NaOMe/MeOH, rt. vi) TBSCl/imidazole, DMF, rt.
**Synthesis of carbohydrate fragment:**

The synthesis of carbohydrate fragment, β-C-furanoside subunit 20 started with D-ribose 28 which was converted to a valuable intermediate 1-O-acetyl-2,3,5-tri-O-benzoyl-β-D-ribose 29 (Scheme 6). The protected ribose 29 was converted to cyanosugar 30 by anchimeric assisted nucleophilic addition of a cyanide anion via trimethylsilyl cyanide to the in situ generated oxocarbenium cation derived from 29. The selective deprotection of benzoate with saturated methanolic ammonia gave syn-diol, which was reprotected as acetonide with 2,2-dimethylpropane to afford the intermediate 22.

The key intermediate 22 on reduction of the nitrile functionality with Raney nickel coupled with N,N’-diphenylethylenediamine furnished the corresponding aminal 31. The benzoate ester in aminal 31 was removed by sodium methoxide in methanol, followed by tosylation of the free primary hydroxyl moiety with tosyl chloride in dry pyridine to provide the corresponding tosylate 32. The reduction of tosylate 32 with Lithium aluminium hydride provided the protected aminal 33. Finally, the removal of the aminal in 33 by para-toluene sulphonic acid furnished aldehyde, which without isolation was subjected to olefination with one carbon Wittig reagent allowed the formation of the desired β-C-furanoside 20. The carbohydrate fragment 20 was characterized from its ¹H NMR by the appearance of peaks at 5.18 (d, 1H, $J = 10.9 \text{ Hz}$), 5.34 (d, 1H, $J = 17.4 \text{ Hz}$).
Scheme 6: Reagents and conditions: (i) TMSCN, SnCl₄, CH₂Cl₂, rt, 3 min; (ii) NH₃, MeOH, 0 °C, 4.5 h; (iii) DMP, HClO₄, acetone, rt, 2 h; (iv) Raney nickel, NaH₂PO₄, N,N’-DPED, HOAc-pyridine–H₂O (1:2:1), rt, 1 h; (v) NaOMe, MeOH, rt; (vi) TsCl, pyridine, 0 °C to rt, 24 h; (vii) LiAlH₄, THF, 0 °C-rt, 3 h; (viii) PTSA, acetone, CH₂Cl₂, at 0 °C then rt, 1 h; (ix) tBuOK, methyltriphenylphosphonium iodide, ether, 12 h.

The final cross metathesis of aromatic and carbohydrate fragments (18 and 20) in presence of Grubbs’ second-generation carbene catalyst provided the protected natural product 34, which on deprotection with 1M hydrochloric acid afforded (-)-varitriol 17 (Scheme 7). The formation of 17 is evident from its ¹H NMR spectrum by appearance of characteristic olefin peaks at δ 6.20 (dd, 1H, J = 15.8, 6.6), 6.89 (d, 1H, J = 8.0).

Scheme 7: Reagents and conditions: (i) Grubbs 2nd generation catalyst (5 mol%), CH₂Cl₂, reflux, 18 h; (ii) 1 M HCl, THF, rt, 2 h.
Synthesis of aromatic metabolite RKB 3564S:

The aromatic metabolite RKB 3564S (37) with varied biological activity has structural similarity to varitriol. The common intermediate 25 in the synthesis of aromatic fragment of varitriol was used as a starting material, which was obtained from sequential etherification, radical bromination and acetolysis starting with 2, 3-dimethyl phenol 19 (Scheme 8). The benzaldehyde derivative 25 was subjected to two- carbon Wittig olefination, followed by deacetylation using sodium methoxide to provid the benzylic alcohol 36. Finally, the benzylic alcohol derivative 36 was subjected to demethylation using boron tribromide to afford the target compound RKB 3564S. It was characterized from the 1H NMR by the disappearance of corresponding methoxy peak at δ 3.86 and the other values were in agreement with that reported in literature.

Scheme 8: Reagents and conditions: i) CH₃I, AqKOH, TBAH, CH₂Cl₂; ii) NBS, CCl₄, reflux; iii) NaOAc, CH₃COOH; iv) CH₃CH₂=PPh₃I, THF, rt; v) NaOMe/MeOH, rt; vi) BBr₃, CH₂Cl₂, rt.

In conclusion, we have completed a convergent total synthesis of (-)-varitriol from D-ribose and 2, 3-dimethyl phenol as well as the synthesis of aromatic metabolite RKB 3564S.
Chapter III: Development of novel synthetic processes for biologically active compounds.

Section A: Synthesis and process for the preparation of 4,1′,6′-trichloro-4,1′,6′-trideoxy galactosucrose. (Sucralose)

Sucralose (42) is a chlorinated disaccharide and a zero-calorie artificial sweetener sold under the brand names Splenda and SucraPlus. It is about 600 times as sweet as sugar and used in various food and beverage products. Most of the earlier approaches to sucralose synthesis require five steps of organic transformation and therefore a limitation in the development of efficient process. In view of this, we have developed and improved the process for sucralose preparation by carrying out it in four steps.

The feasible synthesis was successfully attempted using sucrose as a raw material (Scheme 9). The primary and secondary hydroxyl groups of sucrose 38 were selectively protected to give tri-O-trityl penta-O-acetyl sucrose in quantitative yield. The detritylation of the protected sucrose 39 was carried out with 5% trifluoro acetic anhydride in dichloromethane at room temperature in order to obtain 2,3,4,3′,4′-penta-O-acetyl sucrose. However, we found that the use of TFA for the deprotection of trityl group also effected the migration of acetyl group from secondary to primary position. This improved one-pot deprotection-rearrangement reaction provided the intermediate 2,3,6,3′,4′-penta-O-acetyl sucrose 40. Moreover, this one-pot reaction avoids the use of acetic acid in boiling conditions and tedious workup of purification as mentioned in literature.

The intermediate 40 was transformed to tri chlorinated compound 4,1′,6′-trichloro-4,1′,6′-trideoxygalactosucrose penta-acetate 41 by reaction with carbon tetrachloride as chlorinating agent in the presence of triphenylphosphine in good yield. Finally, the derivative 41 was subjected to deacetylation with sodium methoxide in methanol to give a target compound 4,1′,6′-trichloro-4,1′,6′-trideoxygalactosucrose 42 (sucralose) in 80% yield. The formation of target
compound 42 was characterized from $^1$HNMR by disappearance of acetate peaks at $\delta$ 2.00-1.09 and the other peaks were in complete agreement with literature values.

Scheme 9: Reagents and conditions: i) Trityl chloride, pyridine, 40 °C; $\text{Ac}_2\text{O}$, rt; ii) Trifluoroacetic acid, CH$_2$Cl$_2$, rt; iii) CCl$_4$, pyridine, imidazole; iv) NaOAc, MeOH.

In conclusion in this section an efficient process for the preparation of sucralose is described. The key step is the one pot reaction in which deprotection and rearrangement by acyl migration takes place. In the other synthetic steps, the overall yields were improved and the reactions carried out under milder conditions.

Section B: Synthesis of $\beta$-D-Galactopyranosyl (1→6)-D-glucose (allolactose).

Allolactose, the isomer of lactose, plays an important role in bacterial metabolism by acting as inducer of the lac operon. It is not available commercially and most of the approaches are based on the use of enzymes. In
continuation to our research on disaccharides we are interested to synthesize allolactose in an economical route.

In the present section, allolactose was synthesized from galactose bromide and glucose tetraacetate employing Koenigs Knorr reaction for galactosylation. The bromo galactose 43 was prepared from D-galactose, whereas glucose 1, 2, 3, 4 tetra acetate 44 was obtained from from D-glucose. The galactosylation of 43 and 44 using silver carbonate provided acetyl derivative of allolactose 45, which on deacetylation with ion-exchange basic resin (IR 400 OH− Amberlite) provided the target compound 46 (Scheme 10).

![Scheme 10. Reagents and conditions: i) (MeCO)₂O/HClO₄, P/Br₂/H₂O; ii) Trityl chloride, pyridine, acetic anhydride, 60 °C. iii) HBr in CH₃COOH; iv) Ag₂CO₃, CHCl₃, rt; v) IRA-400 resin (OH) form.](image)

In the present section, a facile and economical synthetic route for the synthesis of allolactose is described. The key step of glycosidation was carried out by celite supported silver carbonate in improved yields. The reusable ion-exchange basic resin was used for the deprotection of acetyl groups in quantitative yield. The synthesized allolactose is under investigation for DNA binding studies and preliminary results are encouraging.

**Section C: A facile synthetic route to myristicinaldehyde.**

Myristicinaldehyde is the key component in the synthesis of some alkaloids such as nascopine, which is helpful in suppression of cough and used
as intermediate for synthesis of other natural products. Further, it is used in the
design and structural activity relationship studies of new anti-cancer agents
especially combrestatins analogues and arylethylamine psychotropic recreational
drugs. The methods used in the preparation of these key compound 50 reported
in literature, make use of hazardous chemical reagents, tedious workup and
purification procedures. So, we have planned a new synthetic route to
myristicinaldehyde which devoid of use of hazardous reagents, particularly
bromine and tedious purification procedures.

In the present synthetic route, the cheap starting material vanillin 47 on
Vilsmaier formylation provided the dialdehyde 48, which upon treatment with
3% hydrogen peroxide in 1N NaOH solution provided the substituted catechol,
3,4-dihydroxy-5-methoxy benzaldehyde 49 in good yield. Finally, the
methylenation of substituted catechol using methylene chloride provided
myristicinaldehyde 50 in good yields. The formation of target compound was
characterized from its melting point (131 °C) and 1HNMR spectrum by
appearance of peaks as methylene protons at δ 6.12 (s, 2H) and aromatic protons
at δ 7.00 and 7.10 (2s, 2H).

\[
\begin{align*}
\text{CHO} & \quad \text{CHO} & \quad \text{CHO} \\
\text{H}_3\text{C} & \quad \text{H}_3\text{C} & \quad \text{H}_3\text{C} \\
\text{O} & \quad \text{O} & \quad \text{O} \\
\text{OH} & \quad \text{OH} & \quad \text{OH} \\
47 & \quad 48 & \quad 49 \\
\text{CHO} & \quad \text{CHO} & \quad \text{CHO} \\
\text{H}_3\text{C} & \quad \text{H}_3\text{C} & \quad \text{H}_3\text{C} \\
\text{O} & \quad \text{O} & \quad \text{O} \\
\text{O} & \quad \text{O} & \quad \text{O} \\
\text{CH}_3 & \quad \text{CH}_3 & \quad \text{CH}_3 \\
\text{N}^+ & \quad \text{N}^+ & \quad \text{N}^+ \\
50 & \quad 51 & \quad 51 \\
\end{align*}
\]

**Scheme 11** Reagents and conditions: i) Hexamine, acetic acid, 60 °C; (ii) H$_2$O$_2$, rt; iii) 50% aq. NaOH, DMSO, CH$_2$Cl$_2$.

In literature the myristicinaldehyde has been used in the synthesis of
cotarnine 51. In addition to this, alternative route to myristicinaldehyde starting
from trimethoxy benzaldehyde was also attempted. In conclusion, in the present synthetic route, the use of hazardous bromine is avoided with improved yields.

**Chapter IV: Synthesis of benzoxanthenes and substituted amido naphthols by recyclable solid acid catalysts**

Section A: Efficient synthesis of aryl-14H-dibenzo[a,j]xanthenes employing tungstated zirconia as heterogeneous catalysts in solvent free media.

Benzoxanthenes has emerged as a attractive scaffold in organic synthesis due to their biological and therapeutic properties such as antibacterial, antiviral, and anti-inflammatory activities. Furthermore due to their useful spectroscopic properties, they are used as dyes, in laser technologies, and in fluorescent materials for visualization of biomolecules. Even though various procedures are reported, disadvantages including low yields, prolonged reaction times, use of an excess of reagents /catalysts and use of toxic organic solvents necessitate the development of an alternative route for the synthesis of xanthenes derivatives. In this pursuit a simpler and greener protocol has been developed for the preparation of aryl-14H-dibenzo[a,j]xanthenes by a one-pot condensation of β-naphthol and aryl aldehydes, in the presence of tungstated zirconia (5%WO₃/ZrO₂) as heterogeneous catalysts. The reactions were investigated in solvent-free conditions under conventional heating (125 °C) as well as microwave conditions.

![Scheme 12](image)

**Scheme 12** Reagents and conditions: 5% WO₃/ZrO₂, Neat 125 °C or microwave.
The present methodology for the synthesis of benzoxanthenes offers several advantages such as excellent yields (80-96 %), simple procedure, short reaction times (2-8 h) and milder conditions. Further, the recyclability of the catalyst was investigated and good conversions were observed after successive operations.

Section B: Potassium dodecatungstocobaltate trihydrate: A mild and efficient reusable catalyst for the synthesis of amidoalkyl naphthols in solution and under solvent-free conditions.

An efficient and direct procedure has been developed for the preparation of amidoalkyl naphthols by a one-pot condensation of aryl aldehydes, β-naphthol and urea or amides, in the presence of potassium dodecatungstocobaltate trihydrate [K₅CoW₁₂O₄₀·3H₂O,(1 mol%)] as a heterogeneous catalyst. The reactions were carried out in 1,2-dichloroethane at room temperature or under solvent-free media at elevated temperature. The present methodology offers several advantages such as excellent yields ranging from 90-96%, simple procedure and the catalyst exhibited remarkable reusability.

\[
\begin{align*}
53 \quad & + \quad \text{CHO} \quad \text{R}_1 \quad + \quad \text{RCONH}_2 \\
& \xrightarrow{\text{K}_5\text{CoW}_{12}\text{O}_{40}\cdot3\text{H}_2\text{O}} \quad (1 \text{ mol%}) \\
& \quad \text{57}
\end{align*}
\]

\[\text{R} = \text{CH}_3, \text{NH}_2\]
\[\text{R}_1 = \text{H}, 4-\text{Br}, 4-\text{Cl}, 3-\text{Cl}, 2,2-\text{Cl}, 3-\text{NO}_2, 3-\text{OCH}_3, 4-\text{CH}_3\]

Scheme 13 Reagents and conditions: K₅CoW₁₂O₄₀·3H₂O, EDC, rt (or) neat (or) microwave

The recyclability of the catalyst was investigated and good conversions were observed after successive operations.