CHAPTER-III

(Section-A)

Synthesis of O-spiro-C-aryl glycosides using organocatalysis
3.1. INTRODUCTION

Carbohydrates are one of the most abundant natural products. They are presented as free monosaccharides, oligosaccharides, polysaccharides and as essential components of glycoconjugates, including glycolipids, glycoproteins or glycopeptides, and glycosylated natural products. Besides their role in metabolism and as structural building blocks, they are fundamental constituents of every cell surface, where they are involved in vital cellular recognition processes. Carbohydrates are a relatively untapped source of new drugs and therefore offer exciting new therapeutic opportunities. Glycosylated natural products have been commonly used as antimicrobial drugs and are now as emerging anti-cancer drug candidates. The sugar moieties in many bioactive natural products not only increase water solubility thus increasing the bioavailability of the compounds, but also decrease toxicity. Some glycans are also the essential components for the bioactivity of the natural products. Carbohydrate derivatives in which the glycosidic oxygen is replaced by carbon atom are said to be C-glycosides. If the substituted carbon atom is the part of an aromatic ring, the sugars are named as C-aryl glycosides (Fig. 1). C- Aryl glycosides are a subclass of the family of naturally occurring C- glycosides. This moiety is found in nature in a number of natural products which are structurally challenging. The synthesis of naturally occurring C- aryl glycosides has gained considerable attention because of their range of biological activities and resistance to enzymatic hydrolysis. The replacement of C-O linkage with the C-C (Aro) makes the C-aryl glycosides more stable when compared to O- aryl glycosides towards enzymes. O-Glycosides readily undergo acid hydrolysis because of the presence of glycosidic bond as a part of an acetal but in C-aryl glycosides the C-C (Aro) linkage is resistant to hydrolysis. For this reason, over past two decades the design and development of new methods for C-glycoside syntheses has received significant attention.

Fig. 1
It’s worthwhile at this juncture to discuss a few C-aryl glycoside natural products and drugs including C-nucleosides which have been of paramount importance to the mankind and also to the researchers who have been actively involved in the synthesis and isolation of these natural products. A large number of pharmaceutical agents, containing C-aryl glycoside unit have been encountered in a survey of the literature, the important ones are briefed here.

**C-Nucleosides**

C-Nucleosides are sugars where the glycosidic linkage is present between a pentose and a nucleic base or its analogue. This nucleosidic ring may be an unfunctionalized aromatic system, a heterocycle, or a heterocycle functionalized with hydrogen bonding groups, depending on its intended use. Interesting biological activities of C-nucleosides have attracted synthetic chemists in recent times. Now a days oligonucleotides containing nonstandard nucleobases are commercial products made on millimole scale. More than 400,000 people have improved their health using diagnostics tools that incorporate portions of an artificially expanded genetic alphabet.

Pseudouridine 1 is the first reported C-nucleoside which was isolated from transfer RNA in 1957. Other derivatives of this nucleosides that occur naturally are 1-methylpseudouridine 2 and 2’-O-methylpseudouridine 3 (Fig. 2). Many of these naturally occurring C-nucleosides are antibiotics and also exhibit anticancer and antiviral activity. More over C-nucleosides are also used as building blocks of oligonucleotides for the construction of triplex DNA in gene therapy. Ribavirin 4 is an anti viral drug indicated for severe RSV function, hetatitis C infection and other viral infections. Ribavirin is a prodrug which when metabolized resembles purine RNA nucleotides. In this form, it interferes with RNA metabolism required for viral replication. Tiazofurin 5 inhibits IMP dehydrogenase. Recently it is approved as an orphan drug for treatment of chronic myelogenous leukaemia in accelerated phase. Selenazofurin 6 has been reported to have broad-spectrum antiviral activity in vitro and significant antitumor effects activity against a number of RNA viruses and a strong inhibitory effect on influenza A and B viruses in vitro. Its analogues are under investigation for potential use in the treatment of cancer. A characteristic of C-nucleosides is that the C–C bond is resistant to hydrolytic and enzymatic cleavage. 5
40 Years ago the first pluramycin antibiotic was isolated by Umezawa, which was shown to have antimicrobial and anticancer activity. Hurley et al. in 1996 described first characterization of the structure of the pluramycin-DNA adduct and proposed a novel mechanism for the DNA sequence selectivity of the pluramycins. The pluramycins are a group of highly structurally evolved DNA-reactive agents that represent a range of 4H-anthra [1, 2-b]pyran-4,7,12-trione structures with attached carbohydrate and epoxide moieties on the corners of their planar chromophores (Fig. 3). This structurally evolved complexity is predictive of a complex molecular mechanism giving rise to sequence selective interactions with DNA. Pluramycins intercalate through the DNA molecule, interact in both grooves of the DNA helix and those compounds displaying epoxides have the ability to alkylate N7 of guanine in the major groove. Pluramycins have been proven to be a novel group of compounds that combine characteristics of other classes of DNA reactive agents.
Kidamycin

Kidamycin 12 was isolated from secondary metabolites of soil *Streptomyces phaeoveriticillatus* (Fig. 4). Kidamycin is one of the most thoroughly studied pluramycin antibiotics. Its structure and chemistry has been thoroughly reviewed by Séquin. Pluramycins have generally been found to be cardiotoxic and kidamycin is the only member of this family that has been derivatized in an attempt to obtain a less toxic and more therapeutically useful drug. Administration of single dose of kidamycin ranging from just below the LD$_{50}$ to 1/16$^{th}$ of the LD$_{50}$ significantly prolonged lives of mice that were infected with Ehrlich ascites tumors. Kidamycin has been shown to be active against leukemia L-1210, Sarcoma-180 (solid type), NF-sarcoma and Yoshida sarcoma.
Ravidomycin and Gilvocarcin V.

Ravidomycin 13 was isolated from cultures of *Streptomyces ravidus* in an aqueous nutrient medium. Gilvocarcin V 14 was produced by culturing *Streptomyces gilvotanareus*. Ravidomycin and Gilvocarcin V represent a class of aryl C-aryl glycoside antitumor antibiotics, sharing a benzonaphthopyranone tetracycle. They differ in the sugar at the C (4) position (i.e. a fucose for 13, while an amino sugar for 14) (Fig. 5). In view of anticancer properties, the amino congener 14 shows enhanced activity over its non-amino analogues. The presence of an amino function reinforces the biological activity of the molecule in ravidomycin. Gilvocarcin V is thought to act as an inhibitor of catalytic activity of topoisomerase II.

Galtamycinone

Galtamycinone 15 is a typical member of the angucycline family which shows both antibiotic and antitumor characteristics. Galtamycinone is a member of the angucycline family of C-aryl glycosides. It is a synthetic challenge with respect to synthesis of C-aryl glycoside synthesis in addition to an efficient assembly of the linear
tetracyclic framework represented by its aglycone SS-228R 16 (Fig. 6) which is also a natural product.\textsuperscript{14}

![Galtamycinone 15 and SS-228R 16](image)

**Fig. 6**

**Vineomycinone B2**

Vineomycin B2 17 is an antitumor antibiotic isolated from *Streptomyces mafensis veneus* (Fig. 7).\textsuperscript{15} Vineomycines are active against Gram positive bacteria and sarcoma 180 solid tumors in mice. The structure of Vineomycin B2 consists of anthraquinone C-glycoside, which is synthetically attractive since it condenses essential problems in the synthesis of this class of antibiotics.

![Vineomycin B2 17](image)

**Fig. 7**

**Aspalathin and Nothofagin**

Aspalathin 19 is isolated from the leaves of *Aspalathus linearis* and used in the manufacture of rooibos tea in South Africa.\textsuperscript{16} Aspalathin displays a potent antioxidant and radical scavenging activity and has recently been found to inhibit proliferation and infiltration of liver cancer cells.\textsuperscript{17} Nothofagin 18 a structurally related flavonoid is typically coisolated with aspalathin\textsuperscript{16} which also displays antioxidant properties but to a lesser extent than aspalathin. The structures of both natural products consist of a
glucopyranosyl unit carbon-linked to a dihydrochalcone moiety with β-stereochemistry observed at the anomeric carbon atom (Fig. 8).

Medermycin/ Lactoquinomycin A

In 1975, scientists at Kayaku isolated, from chromogenic *Streptomyces tanashinensis*, orange crystals which they found to be significantly active against gram positive organisms including antibiotic-resistant strains of *Staphylococci*. However, in 1985, Tanaka *et al.*\(^\text{18}\) reported the isolation and structure of lactoquinomycin and suggested that medermycin could be an isomer of lactoquinomycin on the basis of their different physicochemical properties and biological activities, although both natural products were not directly compared with each other. Subsequently, to help in securing structural identification of these antibiotics.

Tatsuta *et al.* performed a total synthesis of \(^\text{20}\)\(^\text{19}\) based on the structure proposed for lactoquinomycin A. This enabled a comparison of natural samples of both medermycin (from Omura’s group) and lactoquinomycin A (from Tanaka’s group) with the synthetic material. Quite unexpectedly, all three samples were found to be *identical*; as a
consequence, structure 20 was assigned to both antibiotics. Recently Morin et al.\textsuperscript{20} revised the structure of Medermycin 21 using NMR studies (Fig. 9).

**SGLT2 inhibitors**

Type 2 diabetes is growing worldwide and becoming a threat to human health. This is supported by the increasing number of patients. Type 2 diabetes is responsible for the bulk of glucose reuptake in the kidney which allows control of hyperglycemia in a glucose-dependent, insulin-independent individual. Sodium glucose co-transporter 2 (SGLT2) is a 672-amino acid, high-capacity, low-affinity transporter expressed nearly exclusively in the S1 and S2 segments of the renal proximal tubule and believed to mediate the majority of renal glucose resorption from the glomerular filtrate.\textsuperscript{21} SGLT2 inhibitors have the potential to be useful as add-on agents in patients taking oral hypoglycemic drugs or insulin, with a low risk for hypoglycemia and the potential for weight loss. Selective inhibitors of SGLT2 are expected to be safe because individuals homozygous or compound heterozygous for mutations in SLC5A2, the gene encoding SGLT2, exhibit no significant morbidities. In contrast, penetrant alleles leading to SGLT1 deficiency are the genetic cause of glucose–galactose malabsorption syndrome, which is associated with severe neonatal diarrhea and failure to thrive. In particular, the high selectivity could potentially reduce gastrointestinal side effect.\textsuperscript{22} Hence inhibitors selective for SGLT2 over SGLT1 are attractive candidates for development. Recently SGLT2 inhibition has emerged as a very promising approach for this target. Phlorizin\textsuperscript{22} the O-aryl glucoside natural product, a nonselective inhibitor of SGLT1 and SGLT2, provided an interesting lead for the discovery of antidiabetic agents based on glucose transport inhibition. C-Aryl glucosides also found to be SGLT2 inhibitors after optimization of several glycosides. Out of these several C-aryl glucosides (e.g., dapagliflozin\textsuperscript{25} and canagliflozin\textsuperscript{26} are now in clinical development.\textsuperscript{23} Recently Mascitti et al. at Pfizer disclosed the synthesis and biological activity of spiro C-aryl glycosides of the type 27.\textsuperscript{24} The conformationally constrained glycosides work as chemotypes with improved potency for SGLT2 (Fig. 10).\textsuperscript{25}
Chaetiacandin

Chaetiacandin 28 was isolated from cultures of *Monochaetia dimorphospora*. It is an antiyeast antibiotic structurally related to papulacandins. Chaetiacandin affects glucan biosynthesis in sphereplasts. Three groups namely Parker *et al.*, Beau *et al.* and Friesen *et al.* have independently developed methodologies for chaetiacandin core along with papulacandin nucleus (Fig. 11).
Papulacandins

Isolation

Many metabolites are produced by a wide variety of microbes, insects, plants, fungi and microorganisms which incorporate spiroacetal units. The papulacandins are a group of naturally occurring glycolipids isolated from the fermentation broths of Papularia spherosperma and Dictyochaeta simplex which were first reported by Taxler and co-workers in 1976.\textsuperscript{28}

Structure and Activity

There are various members in this family, which differ in acyl side chain substitution at C-3 and C-6. Papulacandins A-D and the more recently isolated new members Mer-WF3010, L-687-781,\textsuperscript{29} Bu-4794F\textsuperscript{30} and BE-2960210\textsuperscript{31} all share a common spiroketal residue. Saricandin\textsuperscript{32} is isolated from Fusarium sp. AB 2202W-161. Saricandin is a novel antifungal antibiotic of the papulacandin family. The hypothesis is that saricandin may be formed following an analogous biosynthetic pathway to the papulacandins. These congeners vary with respect to the degree of oxidation and saturation of shorter side chains; however, some analogues display more drastic modifications to the overall papulacandin structure. The simplest member, papulacandin D lacks the C-4 galactose with the C-6 acyl group. Classical chemical and spectroscopic investigations led to structures Table 1. The absolute configuration of the spiro center in papulacandins was revealed by an X-ray crystallographic study of a di-p-bromobenzyl derivative. All papulacandins are amphipathic molecules. They are β-C-D-glucosyl derivatives of 1,3-dihydroxy-5-hydroxy-methylbenzene, the oxygen in the benzylic position being attached to the anomeric carbon in the spirocyclic structure. Papulacandins have a common D-galactopyranosyl residue at O-4 and unusual C18 polyunsaturated fatty acid chain at O-3 of the glucosyl moiety.

Papulacandins are naturally occurring antifungal agents. The mechanistic basis for the inhibitory activity of Papulacandin-B towards the growth of Geotrichum lactis was traced to a pencillin-like ability to inhibit glucan synthesis during the manufacture of the cell wall. The papulacandins inhibit 1,3-β-glucan synthase which is essential for cell wall construction in fungal cells but not human cells. The long chain residue at O-3 however is crucial for biological activity. Members of the papulacandin family exhibit potent in vitro
activity against *Candida albicans* and related microorganisms. However little or no efficacy was shown in animal models. The new members Mer-WF3010, L-687-781, Bu-4794F and BE-29602 were found to overcome *Pneumocystis carinii* pneumonia, the common opportunistic infection in AIDS patients. Papulacandin D exhibits significant antifungal activity, hence the synthesis of simpler analogues of papulacandin D may lead to improved biological activity. These substances have low acute toxicities. Papulacandins are inactive against filamentous fungi, bacteria, and protozoa. As an extension of the applications of spiro-C-aryl glycosides, these compounds were found to have inhibitory activity against sodium-dependent glucose cotransporter 2 (SGLT2) involved in glucose reabsorption in the kidney.
### Table 1

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**Chapter III (Section A)**
3.2. PREVIOUS APPROACHES

Barrett’s approach

Barrett’s approach is the first total synthesis of papulacandin-D. This involves the condensation of aryl lithium to sugar lactone and acid-catalyzed spirocyclization. Thus methyl 3,5-dihydroxybenzoate 30 was protected as the bis(triisopropylsilyl) ether. The ester was reduced using LiAlH₄. Benzylic alcohol obtained was brominated using NBS in CCl₄. The benzylic hydroxyl was protected as its TBS ether which afforded 31. Generation of the aryllithium reagent followed by addition of the readily available gluconolactone 31A gave intermediate 32. Direct acidification resulted in desilylation at benzylic position and cyclization to give the desired spiroketal 33 as a single anomer. The selectivity was accounted for the anomeric effect. Tetro 33 was protected selectively to diol 34 (Scheme 1).

Reagents and conditions: (i) \((\text{t-Pr})₃\text{SiCl}, \text{imidazole}, \text{DMAP}, \text{DMF}, 90\%\); (ii) \(\text{LiAlH}_4, \text{Et}_2\text{O}\); (iii) NBS, CCl₄, 84\% (two steps); (iv) \(\text{BuMe}_2\text{SiCl}, \text{imidazole}, \text{DMAP}, \text{CH}_2\text{Cl}_2, 92\%\); (v) \(\text{BuLi}, \text{Et}_2\text{O}, -78\ ^\circ\text{C}\); (vi) \(\text{35}, \text{Et}_2\text{O}, -78\ ^\circ\text{C}\); (vii) Amberlite IR-120 (H⁺ form), MeOH, 29\% (three steps); (viii), \(\text{Bu}_2\text{Si(OTf)}_2, 2,6\)-lutidine, CH₂Cl₂, 85\%.

Scheme 1

Although the total structure of papulacandin D is well established, neither the relative nor absolute stereochemistries of C-7 hydroxy group or the C-14 methyl residue of the acyl side chain are known. For the first time Barrett et al. reported the determination of absolute stereochemistry of the acyl side chain starting from chirally pure L-isoleucine 35. Thus isoleucine 35 was transformed to known pentanol. The alcohol functionality was changed to cyanide by making its corresponding tosylate.
Reduction with DIBAL-H and a two carbon homologation yielded ester 36. Reduction of ester 36 followed by oxidation and chain extension led to diene 37. Diene converted to its corresponding aldehyde 38 using reduction, oxidation sequence (DIBAL-H/ MnO₂). Homologation of the aldehyde 38 with prop-2-ynyl zinc bromide yielded an inseparable alcohol mixture 39. To prepare chirally pure alcohol of 39, Sharpless kinetic resolution was employed to yield alcohol 41 and epoxide 40. By changing conditions all the four possible diastereomeric alcohols were synthesized. The alcohols protected as TES ether, hydrozirconation of alkyne followed by Pd(0) coupling with 3-bromo-(E)-acrylate gave tetraene 44. A comparison with the same fragment derived from natural papulacandin-D eliminated three other isomers which resulted in required tetraene 44 (Scheme 2).

![Scheme 2](image)

**Reagents and conditions:** (i) TsCl, Py, (ii) KCN, 18-crown-6, THF, 80% (both steps); (iii) DIBAL-H, Et₂O, -78 °C; (iv) Ph₃P=CHCO₂Et, CH₂Cl₂, 85% (both steps); (v) DIBAL-H, Et₂O, -78 °C, 95%; (vi) PCC, CH₂Cl₂, 80%; (vii) Ph₃P=CH(Me)CO₂Et, CH₂Cl₂, 85%; (viii) DIBAL-H, Et₂O, -78 °C, 94%; (ix) MnO₂, CH₂Cl₂, 95%; (x) Zn dust, prop-2-ynyl bromide, THF, 95%; (xi) Ti(OiPr)₅, D(-)-DIPT, 'BuOOH, CH₂Cl₂, 4 Å mol. sieves, alcohol 45%, 96% de and epoxide 14% (xii) Et₃SiCl, imidazole, DMAP, CH₂Cl₂, 88%; (xiii) (η⁵-C₅H₅)₂Zr(Cl)H, methyl 3-bromo-(E)-acrylate 43, [(Ph₃P)₂PdCl₂+ DIBAL-H], THF, 82%

**Scheme 2**

Unsaturated ester 44 was cleanly hydrolysed to acid 45 (Scheme 3), using potassium trimethylsilanolate and converted to mixed anhydride 46 with 2,4,6-trichlorobenzoyl chloride. Addition of 46 to a mixture of spiroketal 34 and 4-(dimethylamino)pyridine resulted in selective O-3 esterification to give protected
papulacandin D 48 (57%) and the O-2 ester 47 (14%). Global deprotection of 48 was accomplished by treatment with tris(dimethylamino)sulfonium difluorotrimethylsilicate (TASF) to yield synthetic papulacandin-D 49 (Scheme 3).

Reagents and conditions: (i) Me$_3$SiOK, THF; (ii) Et$_3$N, 2,4,6-trichlorobenzoyl chloride, THF; (iii) 34, DMAP, DMF, 70% (three steps); (iv) TASF, THF, 64%;

Scheme 3

Denmark’s approach

Denmark et al. reported an efficient and enantioselective total synthesis of papulacandin D in which palladium-catalyzed cross-coupling of glucal silanol 54 with aryl iodide 52 and an enantioselective addition of allyltrichlorosilane to conjugated aldehyde 61 are key strategic steps. Thus esterification of commercially available 3,5-dihydroxybenzoic acid 50 to afford methyl ester was followed by protection of the resorcinol hydroxyl groups as benzyl ethers and reduction of the ester with lithium aluminum hydride to afford benzyl alcohol 51. Finally, iodination of 51 with N-iodosuccinimide provided aromatic iodide, which was protected as its pivaloyl ester 52.
Synthesis of spirocyclic C-aryl glycopyranoside starts by saponification of triaceta 53 to give the free hexenopyranose which was protected as its di(tert-butyl)silylene acetal. Protection of the C(3)-hydroxyl group as TES ether provided silyl protected hexenopyranose. Lithiation and silylation gave silane which was subjected to oxidative hydrolysis catalyzed by bis[chloro(p-cymene)ruthenium- (II)] in the presence of water afforded silanol 54. A combination of aryl iodide 52 and silanol 54 proceeded smoothly to afford aryl-hexenopyranose 55.

**Scheme 4**

Removal of the pivaloyl group set the stage to elaborate the aryl-hexenopyranose. The crucial spiro ketalization was effected by treatment with m-CPBA in presence of NaHCO₃ to afford a mixture of chromatographically separable anomers β (77%) and α (15%). The free hydroxyl group was protected with 2-(trimethylsilyl)ethanol to give (TEOC)-protected spiro ketal 56. Debenzylation of 56 and subsequent TEOC protection of the resorcinol portion was achieved using TEOC-Cl in presence of 2,6-lutidine which
gave fully silylated spiro ketal. Selective removal of the $O$-$C(3)$ TES group with PPTS/EtOH afforded 57 (Scheme 4).

Synthesis of the side-chain unsaturated acid was carried out by asymmetric hydrogenation of geraniol 58 with Ru(OAc)$_2$[(S)-BINAP] to give (S)-citronellol (99%, 97:3 $er$) (Scheme 5). The hydroxyl group in geraniol was converted to methyl using tosylation followed by reaction with lithium borohydride to afford 59. Ozonolysis and Horner-Wadsworth-Emmons olefination afforded unsaturated ester 60, an inseparable mixture of isomers.

**Scheme 5**

Reduction with DIBAL-H followed by chromatographic separation of the geometrical isomers and oxidation gave aldehyde 61. At this stage Denmark et al. have employed a enantioselective allylation of 61 using chiral bisphosphoramidate ($R,R$)-65 provided 62. Olefinic metathesis with acrolein using Grubbs’ second generation catalyst
and protection of the C-7 hydroxyl group with TES-Cl gave TES ether. Wittig olefination and saponification using $\text{K}_2\text{CO}_3$ gave 63. A coupling of fragments 63 and 57 was achieved using same protocol as in Barrets approach. Global deprotection with HF/Et$_3$N in DMSO afforded papulacandin D 49 (Scheme 5).

**Doherty’s approach**

Doherty *et al.* used Sharpless catalytic asymmetric dihydroxylation reaction on 5-aryl-2-vinylfurans to give diols of the type 67. Thus the hydroxyl aldehyde 66 was protected as TBS ether, which upon Wittig reaction gave olefin. Under Sharpless dihydroxylation conditions the olefin leads to diol 67. The primary alcohol was protected as pivolate ester to give compound 68, which upon Acmotowich rearrangement gave ketone 69. Ketone 69 was reduced to alcohol 70, which was protected as TBS ether 71. Three isomers of the spirocyclic core *viz.* gluco, manno, and allo were synthesized from this common intermediate 71, dihydroxylation of which using OsO$_4$ gave diols 72 and 73 were obtained. Reduction of pivolate ester using DIBAL-H and TBS ether deprotection gave the two corresponding spiro tetrols 75 and 76. A selective oxidation reduction sequence converted the mannose isomer 72 into the glucose isomer 74. Thus protection of diol 72 as TBS ether and oxidation of the other hydroxyl group and reduction afforded the more feasible gluco isomer 74 which occurs in natural papulacandins (Scheme 6).
Reagents and conditions i) TBSCl, Imidazole; ii) Ph₃P=CH₂; iii) AD mix-α; iv) PivCl; v) NBS, NaHCO₃ then 1M HCl (cat); vi) NaBH₄ (aq); vii) TBSCl, DMF; viii) OsO₄, t-BuOH/H₂O; ix) Dess-Martin; x) DIBAL-H; xi) LiAlH₄; xii) Dibal-H; xiii) TBAF

Scheme 6

Galacto-papulacandin

Doherthy et al. developed a short and highly efficient route to both the pyranose and furanose forms of a galacto-papulacandin ring system. Thus 3,5-dibenzylxylo benzyl alcohol 51 was prepared from corresponding benzoic acid as reported in Denmark synthesis (Scheme 4). Benzylic alcohol 51 was selectively iodinated with NIS and then protected to form TBS ether. Carbonylation with catalytic palladium in methanol gave 77, which upon exposure to a lithiated trimethylphosphate gave β-keto phosphonate gave 78. Exposure of 78 and aldehyde 78a to Cs₂CO₃ gave 79. 2,4-Dienone 79 was exposed to
Sharpless AD-mix conditions to give diol. The obtained diol was exposed to the catalytic dihydroxylation using OsO₄ to afford tetrol product, which was converted to tetra-acetate 80. Finally deprotection of TBS group from tetra-acetate 80 using 3M HCl/MeOH afforded mixed ketal 81 which on exposure to LiOH later 3M HCl gave 82, 83 (Scheme 7).

Reagents and conditions: (i) NIS, DMF; (ii) TBSCI, (91% over two steps) (iii) PdCl₂, PPh₃, CO, MeOH, 82%; (iv) LiCH₂PO(OMe)₂, THF, 75%; (v) BnOCH₂CH=CHCHO 78a, CS₂CO₃, IPA, 70%; (vi) 4% OsO₄, 4.1% (DHQD)₂ PHAL, 3 eq K₃Fe(CN)₆, 3 eq K₂CO₃, MeSO₂NH₂, t-BuOH/H₂O, 60%; (vii) OsO₄/NMO, t-BuOH/acetone; (viii) Ac₂O/Pyridine 42% (for three steps); (ix) 3M HCl, MeOH; (x) LiOH, MeOH; (xi) 3M HCl, 72% (in three steps);

Scheme 7

Parkers approach

Parker et al. have developed a methodology where 1,2-addition of a protected nucleophilic glycol 89 to an electrophilic quinone 90 followed by reductive aromatization of the resulting quinol afford phenols that bear glycals in the para position. Using selectively substituted aromatic and sugar rings they achieved a formal synthesis of papulacandin-D (Scheme 8). Thus, regioselective benzylation of commercially available 2,3-dihydroxybenzaldehyde 84 followed by hydride reduction of monobenzylated aldehyde afforded alcohol 85, which upon second regioselective benzylation gave phenol 86. Salcomine oxidation of 86 furnished appropriately substituted quinone 87. Synthesis
of glycal 89 began with commercially available tri-O-acetyl-D-glucal 88, which on saponification, followed by silylation gave the fully protected glycal 89.

![Chemical structure](image)

**Reagents and conditions:** (i) BnBr, NaH, THF, 73%; (ii) NaBH₄, MeOH, 98%; (iii) BnBr, NaH, DMSO, 68%; (iv) O₂, salcomine, DMF, 72h, 64%; (v) K₂CO₃, MeOH, 98%; (vi) t-Bu₂Si(OTf)₂, 2,6-lutidine, DMF, -50 °C, 91%; (vii) TIPSCI, Imidazole, 45 °C, 24h, 96%; (viii) 2equiv t-BuLi, THF, -78 °C to 0 °C, 2h; (ix) 87, BF₃·Et₂O, THF, -78 °C, 8h, 33%; (x) 5 equiv Na₂S₂O₄, THF/H₂O (5:2); (xi) BnBr, NaH, THF (two steps 85%); (xii) m-CPBA, 10:1 MeOH/THF, 2 days; (xiii) H₂, Pd/C, EtOAc/MeOH; (xiv) TIPSCI, 2.2 equiv NEt₃, CH₂Cl₂, 72% (for three steps); (xv) BH₃·THF, H₂O₂, aq. NaOH, 81%.

**Scheme 8**

Lithiation of silylated glycal 89 and addition to quinone 87 in presence of catalytic BF₃·Et₂O resulted quinol 90. Reductive aromatization with Na₂S₂O₄ afforded phenol which was immediately benzylation to give more stable C-arylglycoside 91. Oxidation of the glycal olefin with m-CPBA, hydrogenolysis of benzyl ethers and selective silyl protection of the phenolic hydroxyl groups gave the papulacandin nucleus 92 which can be further elaborated to natural product. When a hydroboration reaction was employed on the glycal double bond of 91, with an oxidative workup under basic conditions it yielded the chaetiacandin nucleus 93.
Beau’s approach\textsuperscript{37}

Beau et al. used the palladium-catalyzed coupling reaction of sugar stannane with the aromatic bromo compound. Thus, readily available 4,6-\textit{O}-benzylidene-1-thiogluopyranoside 94 was silylated and methylated to afford 95. Oxidation of sulphur gave unsaturated phenylsulfone, which was converted to stannane 96 using tin hydride. The aromatic counterpart 3,5-dibenzylxoy-2-bromo-benzyl alcohol was synthesized, accordingly from 3, 5-dihydroxy benzoic acid (Scheme 4). Finally a palladium mediated coupling of 96 with aryl bromide gave 96a which upon epoxidation gave the papulacandin nucleus 98. The corresponding hexaacetate derivative 100 was prepared by deprotections of silyl and benzyl ethers and standard esterification with acetic anhydride and pyridine (Scheme 9).

Reagents and conditions: (i) TBSCI, Imidazole, DMF, 91%; (ii) MeI, BaO-(BaOH)\textsubscript{2}, DMF, 0 °C, 4h, 94%; (iii) m-CPBA, NaHCO\textsubscript{3}, CH\textsubscript{2}Cl\textsubscript{2}, r.t, 86%; (iv) \textit{n}-BuLi, THF, -78 °C, 0.3 h, 80%; (v) Bu\textsubscript{3}SnH, AIBN, PhCH\textsubscript{3}, reflux, 12h, 72%; (vi) 96a, Pd(PPh\textsubscript{3})\textsubscript{4}, Na\textsubscript{2}CO\textsubscript{3}, PhCH\textsubscript{3}, reflux, 3h, 78%; (vii) m-CPBA, NaHCO\textsubscript{3}, CH\textsubscript{2}Cl\textsubscript{2}, r.t, 70%; (viii) TBAF, THF, r.t, 10h; (ix) H\textsubscript{2}, Pd/C, AcOEt: MeOH (2:1), r.t; (x) Ac\textsubscript{2}O, pyridine 79% (over three steps);

Scheme 9

Schmidt approach\textsuperscript{38}

Schmidt et al. synthesized the papulacandin spiro cyclic core with an attack of aromatic nucleophile on sugar aldehyde or methyl ester. The aryllithium species was generated via a bromo lithium exchange reaction. Bromo compound 97a was synthesized from 3,5 dihydroxy benzoic acid according to Schemes 4 later it was protected as benzyl ether. The aromatic lithium was generated using \textit{n}-BuLi which was added to the per-O-
benzylated D-glucose 101 to give alcohol 102 which on subsequent oxidation furnished the ketone 103. Hydrogenation of the compound 103 underwent debenylation cum spirocyclization which led to tetrol, which was further confirmed by making its acetate derivative 100 (Scheme 10).

Reagents and conditions: (i) 97a, n-BuLi, THF, -15 °C, 15 min, 68%; (ii) DMSO, Ac₂O, 24h, r.t, 95%; (iii) Pd/C, AcOH:EtOAc:EtOH (1:1:1), r.t; (iv) Ac₂O, pyridine 62% (over two steps);

Scheme 10

Danishefsky approach

Danishefsky et al. reported a synthesis of C- aryl glycosides using Diels-Alder strategy for making sugar ring. Commercially available 3,5 dihydroxybenzoic acid was converted to benzyl alcohol as described in Scheme 4. Compound 51 was converted to benzoate which upon Vilsmeier Hack formylations led to aldehyde 104. A cyclocondensation of 104 with diene 105 yielded homogeneous pyrone 106. The pyrone 106 was treated with vinylmagnesium bromide to afford tetrahydropyryrone, which on oxidation with osmium tetroxide-sodium metaperiodate produced a very unstable ketoaldehyde, this was treated with lithium tris(3-ethyl-3-pentyloxyaluminum)hydride to give the expected keto alcohol, which was protected as its benzoyl ester 107. In presence of iodotrimethylsilane the ketone 107 was treated with hexamethyldisilazine to give isomeric silylenol ethers. This mixture upon treatment with 3-chloroperoxybenzoic acid, followed by treatment with methanol, and then with benzoyl chloride in pyridine, afforded the desired benzoyloxyketone. The above sequence of reactions were repeated on the resulting benzoyloxyketone instead Pd(II) acetate was used as oxidant yielded enone 108. Reduction followed by acetylation, afforded the acetate. Oxidation with 3-
chloroperoxybenzoic acid in methanol gave epoxide, which upon saponification afforded pentol 109. Pentol 109 was treated with methanolic HCl which led to spirocyclization. Finally hydrogenolysis and acetylation afforded the racemic hexaacetate( +/-)100 (Scheme 11).

Reagents and conditions: (i) BzCl, NEt3, 1 h, 99%; (ii) POCl3, DMF, 97 °C, 2.5h, 66%; (iii) CDCl3, Diene 105, Yb(fod)3, 14 h, 55 °C, 6 days, 92%; (iv) CuI, Oxalone, DMS, VinylMgBr, 1.5 h, 70%; (v) OsO4, NaIO4, 1,4-dioxane, H2O, 20 h; (vi) Lithium tris(3-ethyl-3-pentyloxy)aluminum hydride, Oxalone, 2 h, 59% (two steps) 70% (two steps); (vii) n-BuLi, Hexamethyldisilazane, iodos(trimethyl)silane, (viii) m-CPBA, NaHCO3, CH2Cl2, r.t, 75% (two steps); (ix) TBAF, THF, r.t, 10h, BzCl, NEt3, 75%; (x) n-BuLi, Hexamethyldisilazane, iodos(trimethyl)silane, (xi) Pd(OAc)2 (xii) NaOH (xiii) m-CPBA, NaHCO3, CH2Cl2, r.t, (xiv) H2, Pd(OH)2/C, AcOEt: MeOH (2:1), r.t; (xv) Ac2O, pyridine 79% (over two steps)

Scheme 11

Kaliappan’s approach40

Kaliappan et al. developep a versatile strategy for the synthesis of C- aryl glycosides involving sequential intermolecular enyne metathesis of C-alkynyl glycosides with ethylene and Diels-Alder reaction. The methodology was explored towards spiro-C- aryl glycosides. Lactone 110 was prepared from D-mannose in two steps. Addition of TMS acetylene on to the lactone 110 gave anomic mixture of alcohols. Desilylation
under standard conditions afforded alkyne 111. O-Glycosidation reaction with allyl alcohol in presence of CSA afforded diol 112 as a single isomer. Diol 112, under standard conditions was converted to its acetate 113. In presence of ethylene an intramolecular enyne metathesis reaction of 113 by using 10 mol% Grubbs first-generation catalyst gave spiro-C-1,3-diene 114. Diene 114 was treated with DMAD in toluene at 80 °C followed by aromatization with basic (Et₃N) silica yielded the spiro-C-aryl glycosides 115 (Scheme 12).

Reagents and conditions: (i) TMS-acetylene, nBuLi, THF, -78 °C, 2 h; (ii) TBAF, THF, 2 h, r.t, 79%; (iii) allylalcohol, CSA, CH₂Cl₂, 12 h, r.t, 61%; (iv) pyridine, Ac₂O, r.t, 12 h, 73%; (v) Grubbs second generation catalyst (10 mol%), toluene, 80 °C, 12 h, 75%. (vi) DMAD, toluene, 80 °C, followed by basic alumina (NEt₃), 20%.

Scheme 12

Yamamoto’s approach

Yamamoto et al. synthesized spirocyclic C-arylglycosides from the appropriately protected D-gluconolactone 116. The route is similar to McDonalds route with a few modifications. In both the routes a [2+2+2] cyclo addition is common, one is Ru catalyzed (Yamamoto) and the other is Rh catalyzed (McDonald). The addition of lithium acetylide to 116 and 119 followed by glycosylation with 3- (trimethylsilyl)propargyl alcohol to lactone resulted in silylated diynes 117 or 120. Desilylation, followed by ruthenium or rhodium catalyzed cycloaddition of the resultant diynes 117 or 120 with alkynes (acetylene or 1-hexyne) gave spirocyclic C-aryl glycosides. The authors extended this strategy to the synthesis of spirocyclic C-aryl ribosides from the known ribonolactone derivative (Scheme 13).
McDonald’s route \(^{42}\)

\[
\begin{align*}
\text{116} & \quad \rightarrow \quad \text{117} \\
\text{117} & \quad \rightarrow \quad \text{118}
\end{align*}
\]

Yamamoto’s route \(^{41}\)

\[
\begin{align*}
\text{119} & \quad \rightarrow \quad \text{120} \\
\text{120} & \quad \rightarrow \quad \text{121}
\end{align*}
\]

Reagents and conditions: (i) \(\text{LiC}≡\text{CMe}, \text{THF}, -78 °C\), 1 h; (ii) \(\text{HOH}_{2}\text{CC}≡\text{CSiMe}_{3}\), montmorillonite K10, MS 4 °A, \(\text{CH}_{2}\text{Cl}_{2}\), r.t, 2 h; (iii) 50% aq. \(\text{NaOH}, \text{BnNEt}_{3}\text{Cl}, \text{CH}_{3}\text{CN/CH}_{2}\text{Cl}_{2}\) (4:1), r.t, 30 min.

Scheme 13

Chen’s approach to SGLT2 inhibitors \(^{25, 43}\)

Chen et al. disclosed metabolically robust agents with high selectivity towards SGLT2. Preliminary studies showed that retention of a chlorine substituent at the 4’-position on the proximal phenyl ring is critical for activity. Information gained from modeling studies and analysis of the crystal structure of dapagliflozin suggested the possibility of creating novel and conformationally constrained chemotypes with improved potency for SGLT2 by cyclizing the 1- and 6’-positions of the glucose moiety and glucose-proximal phenyl ring (Fig. 12).

\[
\begin{align*}
\text{Dapagliflozin} & \quad \rightarrow \quad \text{Putative binding orientation}
\end{align*}
\]

Fig. 12

The synthesis for SGLT2 inhibitors used standard method for the synthesis of \(\text{C-aryl glycosides}\) (Scheme 1). With modifications in the aromatic ring, the aryl sugars have shown good biological activity. Commercially available 3-amino-4-methylbenzoic acid \(122\) was subjected to bromination with \(\text{N-bromosuccinimide (NBS)}\) followed by esterification to yield aniline derivative \(123\). Sandmeyer reaction and subsequent oxidation of \(123\) provided the key electron- deficient tetra-substituted benzene \(124\).
Friedel–Crafts acylation of $R_1$ substituted benzenes followed by selective reduction of the resulting ketone with triethylsilane gave ester 125. Further reduction of the methyl ester gave the corresponding benzyl alcohol and protection of primary hydroxyl group with chloromethyl methyl ether produced bromide 126. Lithium–halogen exchange and subsequent coupling with lactone 31A gave a mixture of lactols, which were converted in situ to the desired spiro[isobenzofuran-1,2'-pyran] derivatives 127 (Scheme 14).

Reagents and conditions: (i) NBS, DMF, 5 °C, 87%; (ii) SOCl$_2$, MeOH, reflux, 99%; (iii) CuCl, NaNO$_2$, conc. HCl, 1,4-dioxane, H$_2$O, 0 °C, 93%; (iv) KMnO$_4$, 18-crown-6, MgSO$_4$, t-BuOH/H$_2$O (1:2), reflux, 32%; (v) oxalyl chloride, DMF, AlCl$_3$, ethylbenzene, CH$_2$Cl$_2$, 87%; (vi) Et$_3$SiH, CF$_3$SO$_3$H, TFA, rt, 100%; (vii) NaBH$_4$, MeOH, THF quantitative; (viii) MOMCl, DIPEA, CH$_2$Cl$_2$, rt, 90%; (ix) n-BuLi, 2,3,4,6-tetra-O-trimethylsilyl-D-gluconolactone 31A, THF/toluene (1:2), -78 °C, then H$_2$O; (x) MeSO$_3$H, THF, -78 °C to rt (40-63% two steps).

Scheme 14
3.3. PRESENT WORK

The spiro-C-glycosides are interesting, as these molecules posed a challenge to synthesize analogues of the sugar configuration and also to allow flexibility in choosing the desired configuration. The previous syntheses\textsuperscript{33, 34, 36-38, 40-43} discussed above use natural sugars (like \(D\)-glucose, \(D\)-galactose, \(L\)-rhamanose) and limitation was that the configuration of the starting material was pre-determined and hence scope for synthesizing analogues was next to nil. To circumvent this, Balachari and O’Doherty\textsuperscript{35} tried to convert both \textit{allo} and \textit{manno} configurations to \textit{gluco} but \textit{allo} derivative did not yield the required stereochemistry and \textit{manno} derivative gave a mixture of both \textit{manno} and \textit{gluco} isomers. In addition, in many cases the product was a mixture of diastereomers at the anomeric centre. As part of our continued interest in the development of simple and elegant strategies for the synthesis of bioactive natural products and drugs especially by combining organocatalytic and organomettalic strategies, herein we disclose the synthesis of spirocyclic core of Papulacandin-D. We chose to form the spiro skeleton by utilizing the enantiopure products obtained from the McMillan’s elegant homo aldol reaction as starting materials.\textsuperscript{44} We have devoleped a methodogy which allows the synthesis of natural \textit{D-gluco} (128) and \textit{D-allo} (129), \textit{D-altro} (130) (Fig. 13) of the spirocyclic cores of papulacandin-D. In addition, our strategy has enabled the synthesis of the elusive \textit{D-altro} isomer of the sugar.

\begin{figure}[h]
\centering
\includegraphics[width=\textwidth]{fig13.png}
\caption{Fig. 13}
\end{figure}

\textit{D-Altrose} is an unnatural sugar and differs from mannose in the configuration at the third carbon. While \textit{D}-glucose, \textit{D}-mannose, and \textit{D}-galactose are the most abundant sugars in nature, \textit{D-altrose} is not found naturally, whereas its \textit{L}-isomer has been isolated from bacteria \textit{Butyrivibrio fibrisolvens}.\textsuperscript{45} It is interesting to see if the synthesis of an \textit{altro} configuration stimulates the existing activity of this class of compounds, especially in control of diabetes.
Retrosynthetic analysis:

The retrosynthetic analysis of the target tetrols (128, 129 and 130) shown in Scheme 15. We envisioned direct aldol reaction and concomitant deprotection and insitu spirocyclization, which revealed key chiral intermediate aldehyde 131 and aromatic precursor 132 enroute the total synthesis. Accordingly, hydroxyl aldehyde 131 could be synthesized from aldehyde 134 using MacMillans homoaldol reaction catalyzed by proline which in turn 134 could be synthesized from the commercially available 1,4 butene diol 135 via a known sequence of reactions. Substituted acetophenone 132 could be prepared from commercially available 3,5-dihydroxybenzoic acid 133 using Friedel-Craft’s acylation as the key reaction.47b

Scheme 15

Asymmetric synthesis of hydroxy aldehyde (131)

Starting aldehyde 13446 for the homo aldol reaction was synthesized from 1,4 butenedioli 135. Initially, diol 135 was protected as its TBDPS ether 136 under classical conditions (TBDPSCl, Imidazole, DCM) in 95% yield, which upon ozonolysis in dichloromethane at -78 °C furnished the known siloxyacetaldehyde 134 in 90% yield (Scheme 16). In the 1H NMR spectrum of 134 the aldehyde proton resonated at 9.2 ppm and phenyl protons in the aromatic region as multiplet.44a

Scheme 16
As we have shown in retro synthesis, proline catalyzed aldol reaction is the key step of our synthesis. McMillan et al. used a simple secondary amino acid proline for the synthesis of erythrose derivatives with high enantiomeric excess.\textsuperscript{44} We utilized the same reaction to introduce chirality in our synthesis. Thus \textit{t}-Butyldiphenylsililxyacetaldehyde 134 was treated with \textit{D}-Proline in 1:1 mixture of DMF and dioxane at room temperature for 48 h which furnished hydroxyl aldehyde 131 in 70\% yield and with 99\% enantiselectivity (Scheme 17). \textsuperscript{1}H NMR analysis revealed, that the resonance peaks at $\delta$ 9.61 corresponds to the aldehyde proton and a single proton at $\delta$ 4.08–4.02 ppm corresponds to CHOH. Chiral purity of the aldehyde was confirmed by comparing the optical rotation of corresponding acetonide 131a with the known compound.\textsuperscript{44a}

\begin{center}
\includegraphics[width=\textwidth]{scheme17.png}
\end{center}

**Scheme 17**

**Synthesis of hydroxy acetophenone (132)**

Synthesis of hydroxyacetophenone 132 started from commercially available 3,5-dihydroxybenzoic acid 133. Acid 133 was converted to dimethoxy benzoate 137 by known protocol\textsuperscript{47a} (dimethyl sulphate and K$_2$CO$_3$) in 95\%. \textsuperscript{1}H NMR of 137 resembles known data. Compound 137 upon treatment with acetyl chloride in carbon disulphide with aluminium trichloride afforded compound 138 in 70\% yield. The ester 138 was confirmed by \textsuperscript{1}H NMR and ESIMS $m/z$ peak at 239. A resonance at $\delta$ 2.45 ppm could be assigned to COCH$_3$ in the \textsuperscript{1}H NMR of 138 which confirms the acetyl derivative (Scheme 18).\textsuperscript{47b}

\begin{center}
\includegraphics[width=\textwidth]{scheme18.png}
\end{center}

**Scheme 18**
For the synthesis of hydroxyacetophenone, ester 138 was transformed to its corresponding diol in dry ether at room temperature for 1 h to yield diol 139 in 90% yield. This was confirmed by $^1$H NMR, $^{13}$C NMR analysis and ESIMS which showed $m/z$ peak at 235. Disappearance of COOCH$_3$ protons at $\delta$ 3.8 ppm in the $^1$H NMR of the diol 139 and absence of carbonyl carbon in the $^{13}$C NMR confirm reaction. Further, diol 139 was converted to its mono TBS ether. The selective protection was done at 0 °C under standard reaction conditions (TBSCl, Imidazole) to yield alcohol 140 in 95% yield. The $^1$H NMR of 140 shows the corresponding silyl protons integrating to 6H and 9H at $\delta$ 0.1 ppm and 0.95 ppm respectively. This supports mono protection. The product was further confirmed by ESIMS analysis, which showed $m/z$ ion peak at 348.9 (Scheme 19).

Oxidation of the alcohol 140 with IBX in THF yielded ketone 141 in 90% yield. $^{13}$C NMR showed carbonyl carbon peak at $\delta$ 203.2 ppm, to confirm the oxidation reaction. Next, our attention was drawn towards the installation of hydroxyl group $\alpha$ to carbonyl carbon. This conversion was achieved by using classical Rubottom oxidation conditions.$^{48}$ Ketone 141 was converted as its TMS enolate using TMSOTf and 2,6 lutidine in dichloromethane, without any purification the crude enolate was treated with $m$-CPBA in dichloromethane which resulted in epoxide, insitu opening of the epoxide gave hydroxyacetophenone 132 in 80% yield. The conversion was confirmed by the appearence of a singlet in $^1$H NMR at $\delta$ 4.61 (s, 2H) which accounted for the CH$_2$OH. Moreover ESIMS showed $m/z$ peak at 363.2 corresponding to structure of 132 (Scheme 20).
Completion of the synthesis of tetrols 128, 129 and 130.

Initially we tried to synthesize the tetrol in a stepwise manner via direct aldol followed by an acid induced spiroketalization. For this the protection of hydroxyl group has to be tert-butylsilylether in the aldehyde 131. Our efforts towards this conversion failed. So the free hydroxyl aldehyde 131 was directly used in the second aldol reaction. Thus hydroxylketone 132 was treated with aldehyde 131 using TiCl₄ and DIPEA at -78 °C and then allowed to warm to room temperature. Gratifyingly during aldol reaction the benzylic TBS was deprotected and concomitant spiroketalization occurred. The yield of the reaction was only 30%. Attempts to improve the yield were unsuccessful even after protecting the hydroxyl group of 132, or by changing the Lewis acids to BF₃·Et₂O or Bu₂BOTf. Therefore, we chose the initial conditions (TiCl₄, DIPEA, -78 °C). This reaction has resulted in three isomers of the spiroketal, allo (142) allo (143) and gluco (144) in the ratio of 75:20:5. Allo isomer was major, allo and gluco were in minor quantities. The three isomers were separated by column chromatography allo and allo were isolated in their pure form but not glucose which is a very minor isomer (Scheme 21).

Conformational studies for 142 and 143

Structures of the spiroketalts 142 and 143 were confirmed by extensive 2D NMR studies and using energy minimized structures. ¹H NMR spectra of both 142 and 143 revealed disappearance of protons corresponding to silyl ether indicating TBS group was
deprotected. In the ESIMS spectrum of 142, appearance mass peak at \( m/z \) 828.2 \([\text{M + Na}]^+\) confirms that spirocyclization has occurred. The stereochemistry of the carbohydrate ring and the stereogenic center at anomic carbon in the spirocycles was confirmed by for 2D NMR studies (COSY and NOESY). The NOESY spectrum of 142 reveals strong nOes of (OCH\(_3\))\text{aro}– Si(CH\(_3\))\(_3\) which fixed the spirocarbon as thermodynamically favorable anomer in both the cases. A nOe in 142 between C\(_2\)H and C\(_4\)H and the absence of other nOe s concludes that the isomer has allo configuration. In the case of 143 no such kind of nOes are present which shows all the protons which are attached to hydroxyl groups are not in proximity and concluded that there are no 1,3diantiarial or diequitorial hydrogens in syn fashion. So the the carbohydrate core with two fixed anti stereogenic centers brought up from elegant proline catalyzed aldol reaction have an alto configuration for the sugar core. The studies were further supported by the energyminimized structures (Fig 14).

Tetrols 128, 129 and 130 were prepared by deprotection of silyl ethers 142, 143 and 144 using TBAF at in THF in 70% yield. The \(^1\)H NMR spectrums of the terols show diappearance of phenyl and silyl protons, moreover the ESIMS shows a peak at \( m/z \) 350.9 \([\text{M + Na}]^+\) confirms tetrols. The spectral data of known tetrols allo and gluco compared with the literature values (Scheme 22).
Synthesis of the altro-papulacandin

Though the above synthesis of spirocycles is short but lacks for sugar configurations selectivity. With an intention to synthesize the unnatural D-altrose configuration of the sugar core as a single isomer, alternate protecting groups were utilized in the proline catalyzed aldol reaction.

Retrosynthetic analysis:

A retro synthetic analysis is shown in Scheme 23. The spirocyclic core 145 could be synthesized from acetonide protected compound 146. In turn it could made from olefin 147. Here our plan is to use TiCl₄ aldol reaction to make the olefin from ketone 141 and aldehyde 148. Ketone 141 could be synthesized from 3,5-dihydroxybenzoic acid 133 (Scheme 18-20). Chiral aldehyde 148 could be prepared from proline aldol reaction of benzyloxy acetaldehyde 149.
The synthesis started in a stepwise manner utilizing ketone 141. Thus the erythro derivative 151 was obtained from the cis-1,4butenediol by a known strategy. 50 Diol 135 was protected as its dibenzyl ether using benzyl chloride and aq. NaOH to furnish dienyl olefin 150 in 90% yield. Olefin 150 was subjected to ozonolysis in dichloromethane at -78 °C to afford aldehyde 149 in 85% yield (Scheme 24).

Proline catalyzed aldol reaction of benzyloxy acetaldehyde 149 in DMF yielded erythro-derivative 151 in 78% yield. The hydroxyaldehyde was not pure enough to characterize, we thought it is better to transform to its corresponding diol 151a. Thus 151 is treated with NaBH₄ in methanol furnished 151a in 90% yield (Scheme 25). ¹H NMR of diol 151a showed peaks at δ 4.63-4.44 (m, 4H), 3.75-3.80 (m, 2H) which could be assigned to (OCH₂Ph)₂ and CH₃OH respectively. The ESI-MS shows m/z at 325. Enatiomeric purity of the diol was checked by comparing optical rotation with the diol.
\([\alpha]^{20}_D = 27\) with value reported in the literature (which was synthesized from natural sugar \([\alpha]^{20}_D = 30\)).

![Scheme 25](image)

We were unsuccessful to protect of the OH in the hydroxyl aldehyde 131, but in the case of aldehyde 151 this reaction is fruitful. Thus aldehyde 151 was treated with TBSOTf and 2,6-lutidine in dichloromethane \(^{51}\) gave TBS protected aldehyde 148 in 80\% yield (Scheme 26). \(^1\)H NMR spectrum of the aldehyde 148 shows \(\delta\) 0.90 (s, 9H), 0.10 (s, 3H), 0.08 (s, 3H); 9.64 (d, \(J = 1.7\), 1H) corresponding to TBS and aldehyde groups confirms the structure.

![Scheme 26](image)

With two aldol partners (148 and 141) in hand, we focused our attention on the TiCl\(_4\) catalyzed aldol reaction. Reaction of ketone with aldehyde using TiCl\(_4\) and DIPEA in dichloromethane gave alcohols 152a and 152b in 75:25 ratio. At this stage we were least worried about the diastereomeric ratio because the two isomers were transformed to enone 147 in the next step \(^{52}\). \(^1\)H NMR of 152a shows OMe peaks as well as OBn peak at \(\delta\) 3.77, 3.64 and 4.78–4.43 (m, 6H) along with HRMS at \(m/z\) 739.4094 which confirms the product. Alcohols 152a and 152b were treated with mesyl chloride and triethylamine in dichloromethane. The crude mesylate was subjected elimination with DBU in dichloromethane to yield the enone 147 in 90\% yield. \(^1\)H NMR shows olefinic protons at \(\delta\) 6.63–6.47 ppm with \(J = 15.8\) Hz, which supports the trans double bond. HRMS showed at \(m/z\) 743.3 [M + Na]\(^+\) confirmed the product (Scheme 27).
Initial attempts for dihydroxylation of 147 with standard OsO$_4$ and NMO in water and acetone at room temperature led to overreaction where the olefin was converted to aldehyde 148 and formyl ketone 153. Then we planned to conduct the reaction at lower temperature 0 °C and changed the solvents systems.\(^{35a}\) Olefin 147 treated with 2 mol% OsO$_4$ and aqueous NMO in 1:1 $t$-BuOH, acetone at 0 °C to give exclusively 154. The selectivity might be due to the steric crowding of olefinic portion of 147. The disappearance of olefinic protons in $^1$H NMR of 154 in $\delta$ 6.63-6.47 region and a mass peak at $m/z$ 755.4026 in HRMS confirmed the product (Scheme 28).
The dihydroxylated product 154 was treated with Lewis acids to hydrolyze the TBS ethers with concomitant cyclization, but trials were unsuccessful. In an instance we used HF.Py which also failed to give required cyclized product. Deprotection of diol with TBAF led to mixture of products. Then we turned to hydrolyze the acetonide protected compound 146. Thus diol 154 was treated with 2-methoxy propene with catalytic pTSA in dichloromethane to give 146 in 90% yield, which upon treatment with TBAF in THF gave the ketal 156 in 80% yield. The absence of silyl protons and the presence of acetonide protons along with a mass ion peak at m/z 549.1 [M-H_2O]^+ revealed the product 156.

![Scheme 29](image)

Compound 156 was subjected to p-TSA catalyzed cyclization reaction in methanol where we ended up with a acetonide deprotected and cyclized diol 157. 1H NMR shows the absence of acetonide protons and presence of spirocarbon at δ 117.8 in 13C NMR spectrum along with HRMS m/z at 509.2176 confirms the cyclized product (Scheme 29). 1H NMR spectrum of 157 was complicated where all the carbohydrate protons appear merged in the region δ 5.10-3.81 ppm. So to study in detail the spirocycle was converted to its diacetate derivative 145 in 95% yield using standard conditions (acetic anhydride and pyridine in CH2Cl2 with catalytic DMAP) (Scheme 30). Compound 145 was fully characterized with 1H and 13C NMR as well as mass peak in HRMS at m/z 593.2381. 1H NMR of 145 showed COCH3 at 1.76, 2.0 ppm. Further the stereo chemistry of 145 was thoroughly studied using 2D NMR studies. Presence of H3-H6a, H4-H6b and absence of the other nOes such as H2-H4, H3-H5 helped in the confirming synthesized
molecule to have *altro* configuration of the sugar moiety. This was also verified by comparing the data of the *allo*, *gluco* and *manno* derivatives reported earlier. Coupling constant of the H2-H3 is 10.6 Hz, so these two hydrogens are axial in orientation which gives the molecule $^4\text{C}^1$ conformation rather than $^4\text{C}_1$ where H2-H3 coupling constant is supposed to be less than 3.0 Hz due to di-equatorial orientation. nOe between OMe protons of the aromatic ring and any proton of the sugar ring could not be observed and consequently the stereochemistry of the glycosidic carbon at the anomeric center could not be established. The configuration is based on literature precedence and coupling constants observed for the ring protons.53 The substitution is $\alpha$, the thermodynamically favored isomer which is supported by the energy minimized structure (Fig. 15)

**Fig. 15**

**Conclusion**
In conclusion we have synthesized the known *allo* and *gluco* isomers of papulacandin aglycone in addition to the *altro* isomer which is new. The use of organo catalysis to build up sugar moiety and flexibility of introducing hydroxyls on the double bond allow one to synthesize any sugar configuration for the spiro-C-glycoside.
3.4. EXPERIMENTAL PROCEDURES AND SPECTRAL DATA

1-(2-(Hydroxymethyl)-4,6-dimethoxyphenyl)ethanol (139).

A solution of ester 138 (1 g, 4.15 mmol) in dry ether (10 mL) was added to LiAlH₄ (0.158 g, 4.15 mmol) in ether (5 mL) at 0 °C. Reaction was stirred for 30 min at same temperature, solution was cooled to 0 °C, and H₂O (0.2 mL), 15% NaOH (0.2 mL), and H₂O (0.6 mL) were added sequentially. Upon warming to room temperature, white suspension was filtered through Celite (2 g) and washed with EtOAc (2 × 10 mL). The filtrate was concentrated under reduced pressure, and crude was purified (30% EtOAc in PE) to result in diol 139 as a white solid (0.79 g, 90%):

Mpt : 85–87 °C.
IR (KBr) : ν_max 3341, 1605, 1458, 1311, 1149, 1053 cm⁻¹;
¹H NMR (300 MHz, CDCl₃) : δ 6.51 (d, J = 2.2 Hz, 1H), 6.43 (d, J = 2.2 Hz, 1H), 5.18 (m, 1H), 4.72 (d, J = 12.8 Hz, 1H), 4.53 (d, J = 12.8 Hz, 1H), 3.83 (s, 3H), 3.79 (s, 3H), 1.51 (d, J = 6.7 Hz, 3H);
¹³C NMR (75 MHz, CDCl₃) : δ 159.2, 158.2, 139.6, 123.4, 105.6, 98.4, 65.5, 63.4, 55.2, 23.7.
ESIMS : m/z 235.2 [M + Na]⁺.
HRMS : calcd for C₁₁H₁₆NaO₄ 235.0941, found 235.0917.
1-(2-((tert-Butyldimethylsilyloxy)methyl)-4,6-dimethoxy phenyl)ethanol (140).

Diol 139 (6.2 g, 29.2 mmol) was dissolved in dry CH$_2$Cl$_2$ (40 mL), to which were added imidazole (2.98 g, 43.8 mmol) and TBS chloride (4.8 g, 32.1 mmol) at 0 °C under nitrogen atmosphere. Reaction was stirred for 30 min at same temperature. Water (20 mL) was added to mixture, organic layer was separated, and aqueous layer was extracted with CH$_2$Cl$_2$ (2 × 30 mL). Combined organic layers were concentrated under a vacuum. The crude was purified (5% EtOAc in PE) to afford the alcohol 140 as a colorless oil (9 g, 95%).

IR (KBr) : $v_{\text{max}}$ 3564, 3444, 2955, 1606, 1463, 1149, 1061, 839, 778 cm$^{-1}$.

$^1$H NMR (300 MHz, CDCl$_3$) : $\delta$ 6.61 (d, $J = 2.2$ Hz, 1H), 6.43 (d, $J = 2.2$ Hz, 1H), 5.05−4.94 (m, 1H), 4.76 (d, $J = 12.8$ Hz, 1H), 4.68 (d, $J = 12.8$ Hz, 1H), 3.76 (d, $J = 10.5$ Hz, 1H), 3.85 (s, 3H), 3.80 (s, 3H), 1.53 (d, $J = 6.7$ Hz, 1H), 0.95 (s, 9H), 0.12 (s, 3H), 0.10 (s, 3H).

$^{13}$C NMR (75 MHz, CDCl$_3$) : $\delta$ 159.1, 158.4, 139.3, 122.8, 104.1, 98.1, 65.8, 63.4, 55.4, 55.1, 25.8, 23.7, 18.2, −5.3, −5.4.

ESIMS : $m/z$ 348.9 [M + Na]$^+$.

HRMS : calcd for C$_{17}$H$_{30}$NaO$_4$Si 349.1806, found 349.1814.
1-(2-((tert-Butyldimethylsilyloxy)methyl)-4,6-dimethoxy phenyl)ethanone (141).

Alcohol 140 (1.5 g, 4.6 mmol) dissolved in 10 mL of THF was added to a stirred solution of IBX (1.93 g, 6.9 mmol) in dry DMSO (2 mL) at 0 °C. Stirring was continued for an hour at room temperature. After completion of reaction, EtOAc (30 mL) was added, and mixture was filtered through a Celite pad (5 g). Filtrate was washed with water (30 mL) and aqueous NaHCO₃ (30 mL) solution. Organic layer was dried over Na₂SO₄ and concentrated in vacuo. Crude was purified (4% EtOAc in PE) to afford 141 as light red colored oil (1.3 g, 90%):

IR (KBr) : νmax 2931, 1680, 1602, 1252, 1156, 1064, 839, 778 cm⁻¹

1H NMR (300 MHz, CDCl₃) : δ 6.74 (d, J = 2.2 Hz, 1H), 6.29 (d, J = 2.2 Hz, 1H), 4.66 (s, 2H), 3.81 (s, 3H), 3.79 (s, 3H), 2.43 (s, 3H), 0.92 (s, 9H), 0.07 (s, 6H).

13C NMR (75 MHz, CDCl₃) : δ 203.2, 161.8, 158.9, 143.2, 121.1, 103.2, 96.8, 62.8, 55.5, 55.2, 32.4, 25.8, 18.3, −5.4.

MS : m/z 347.0 [M + Na]⁺.

HRMS : calcd for C₁₇H₂₈NaO₄Si 347.1649, found 347.1674.

1-(2-((tert-Butyldimethylsilyloxy)methyl)-4,6-dimethoxyphenyl)-2-hydroxyethanone (132).

To a stirred solution of ketone 141 (1 g, 2.73 mmol) in dry CH₂Cl₂ (15 mL) were added 2,6-lutidine (0.95 mL, 8.19 mmol) and TMSOTf (0.75 mL, 4.09 mmol) at 0 °C,
and mixture was stirred for 1 h. Saturated aqueous \( \text{NaHCO}_3 \) (10 mL) was added, and two layers were separated. Aqueous layer was extracted with \( \text{CH}_2\text{Cl}_2 \) (2 \( \times \) 10 mL). Combined organic layers were dried over \( \text{Na}_2\text{SO}_4 \) and concentrated in \textit{vacuo} to give crude enol silane as brown color oil (1.2 g). Crude silane was dissolved in \( \text{CH}_2\text{Cl}_2 \) (10 mL), and \( m\text{CPBA} \) (2.0 g, 8.19 mmol, 70% in \( \text{H}_2\text{O} \)) was added at 0 °C. Mixture was stirred for 1 h at same temperature, and after consumption of enolate, saturated \( \text{Na}_2\text{SO}_3 \) (10 mL) was added, and two layers were separated. Organic layer was washed with saturated \( \text{NaHCO}_3 \) solution (15 mL), dried over \( \text{Na}_2\text{SO}_4 \), and concentrated under a vacuum. Crude was purified (8% EtOAc/PE) to give 132 as a white solid (649 mg, 70%).

\[ \text{Mpt} : 70−72^\circ \text{C}. \]

**IR (KBr)**

\[ \nu_{\text{max}} 3405, 2951, 2934, 1605, 1277, 1161, 1086, 1054, 864, 771 \text{ cm}^{-1}. \]

**\(^1\text{H NMR} (300 \text{ MHz, CDCl}_3)**

\[ \delta 7.00 (d, J = 1.9 \text{ Hz}, 1\text{H}), 6.38 (d, J = 1.9 \text{ Hz}, 1\text{H}), 4.89 (s, 2\text{H}), 4.61 (s, 2\text{H}), 3.86 (s, 3\text{H}), 3.84 (s, 3\text{H}), 0.96 (s, 9\text{H}), 0.11 (s, 6\text{H}). \]

**\(^{13}\text{C NMR} (75 \text{ MHz, CDCl}_3)**

\[ \delta 201.2, 163.5, 161.4, 147.7, 103.6, 96.6, 69.8, 63.7, 55.5, 55.3, 25.8, −5.4. \]

**MS**

\[ m/z 363.2 \text{ [M+ Na]}^+. \]

**HRMS**

\[ \text{calcd for } \text{C}_{17}\text{H}_{28}\text{NaO}_{5}\text{Si} 363.1598, \text{ found 363.1598.} \]

**(2R, 3R)-3-Hydroxy-2,3-bis-(\textit{tert}-butyl-diphenylsilanyloxy)- propionaldehyde (131).**

\[
\text{D-Proline (0.67 mmol, 77 mg) was added to aldehyde 134 (2 g, 6.71 mmol)}
\]

\[
\text{dissolved in a 15 mL mixture of 1,4-dioxane and DMF (1:1), which was stirred for 48 h}
\]

\[
\text{at r.t. Resulting solution was diluted with ethyl acetate (150 mL) and washed successively}
\]

\[
\text{with water (100 mL) and brine (100 mL). Separated organic layer was dried over Na}_2\text{SO}_4
\]

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and concentrated. Purification of resulting residue (4% EtOAc in PE) afforded 131 as clear, colorless oil in 70% yield (1.39 g, 2.33 mmol):

IR(KBr)  : νₓmax 3540, 2933, 1733, 1468, 1428, 1111, 704 cm⁻¹.

¹H NMR (300 MHz, CDCl₃)  : δ 9.61 (s, 1H), 7.75–7.50 (m, 8H), 7.47–7.32 (m, 12H), 4.24 (dd, 1H, J = 3.9, 1.9 Hz), 4.08–4.02 (m, 1H), 3.80 (dd, J = 9.8, 6.9 Hz), 3.64 (dd, 1H, J = 9.8, 5.9 Hz), 2.16 (d, J = 5.9 Hz), 1.12 (s, 9 H), 1.03 (s, 9H).

¹³C NMR (75 MHz, CDCl₃)  : δ 201.2, 135.8, 135.7, 135.4, 132.6, 132.5, 132.4, 130.1, 129.8, 129.6, 127.8, 127.7, 79.5, 73.9, 63.2, 26.9, 26.6, 19.4, 19.08.


[α]₂⁰_D  : -0.5 (c = 1, CHCl₃)

[α]₂⁰_D (For acetonide derivative)  : 30 (c = 1, CHCl₃) [-33 (c = 1, CHCl₃) for acetonide product obtained by using L-proline]

(1S, 5’S)-5’-(tert-Butyldiphenylsilyloxy)-6’-((tert-butyldiphenylsilyloxy)methyl)-5,7-dimethoxy-3’,4’,5’,6’-tetrahydro-3H-spiro-[isobenzofuran-1,2’-pyran]-3’,4’-dial (142, 143, 144).
To a stirred solution of hydroxyacetophenone 132 (340 mg, 1 mmol) in dry CH$_2$Cl$_2$ (5 mL) was added titanium tetrachloride (1 mL, 1 M solution in CH$_2$Cl$_2$) at −78 °C slowly under a nitrogen atmosphere. After 5 min, DIPEA (0.26 mL, 1.5 mmol) was added. Resulting red colored solution was stirred for 15 min at same temperature. Then, a solution of aldehyde 131 (715 mg, 1.2 mmol) dissolved in dry CH$_2$Cl$_2$ (3 mL) was added. Stirring was continued overnight at r.t. After completion of reaction, mixture was cooled to 0 °C, 50% NH$_4$Cl solution (5 mL) was added, and resulting mixture was stirred for 2 h. Organic layer was separated, and aqueous layer was extracted with CH$_2$Cl$_2$ (2 × 5 mL). Combined organic layers were dried over Na$_2$SO$_4$ and concentrated under a vacuum. Crude was purified (15% EtOAc/hexanes) to yield pure diols (30%, 289 mg, 142:143:144 = 75:20:5).

*allo*-isomer 142.

**IR (KBr)**

$\nu_{\text{max}}$ 3442, 2933, 1625, 1426, 1105, 703 cm$^{-1}$.

**$^1$H NMR (500 MHz, CDCl$_3$)**

$\delta$ 7.73 (d, $J = 6.9$ Hz, 2H), 7.69 (d, $J = 7.9$ Hz, 2H), 7.44–7.20 (m, 12H), 7.10 (t, $J = 6.9$ Hz, 2H), 7.00 (t, $J = 7.9$ Hz, 2H), 6.30 (s, 2H), 5.08 (d, $J = 12.8$ Hz, 1H), 4.98 (d, $J = 12.8$ Hz, 1H), 4.18–4.03 (m, 3H), 3.96–3.77 (m, 3H), 3.80 (s, 3H), 3.58 (s, 3H), 2.60 (d, $J = 6.9$ Hz, 1H), 2.43 (d, $J = 10.8$ Hz, 1H), 1.08 (s, 9H), 0.94 (s, 9H);

**$^{13}$C NMR (75 MHz, CDCl$_3$)**

$\delta$ 162.7, 155.7, 143.2, 135.9, 135.7, 135.6, 133.9, 133.6, 133.5, 133.1, 129.9, 129.8, 129.2, 129.1, 127.7, 127.2, 127.0, 118.3, 110.5, 98.8, 96.5, 73.0, 72.0, 69.0, 67.5, 63.1, 55.6, 55.0, 26.9, 26.6, 19.4, 19.1;

**MS**

$m/z$ 828.2 [M + Na]$^+$

**HRMS**

: calcd for C$_{47}$H$_{57}$O$_8$Si$_2$ 805.3586, found 805.3579.

$[\alpha]_D^{20}$

$+14.6$ (c = 0.25, CHCl$_3$).

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**altro-isomer 143.**

**IR (KBr)**

\[ \nu_{\text{max}} 3440, 2951, 1644, 1032, 702 \text{ cm}^{-1}. \]

\(^1\text{H NMR (500 MHz, CDCl}_3\)

\[ \delta 7.83 (d, J = 7.1 \text{ Hz}, 2\text{H}), 7.79 (d, J = 7.1 \text{ Hz}, 2\text{H}), 7.50-7.22 (m, 16\text{H}), 6.39 (s, 1\text{H}), 6.26 (s, 1\text{H}), 4.91 (m, 1\text{H}), 4.85 (d, J = 12.2 \text{ Hz}, 1\text{H}), 4.81 (d, J = 12.2 \text{ Hz}, 1\text{H}), 4.59 (s, 1\text{H}), 4.17-4.10 (m, 1\text{H}), 3.90-3.84 (m, 2\text{H}), 3.82 (s, 3\text{H}), 3.78 (s, 3\text{H}), 3.58 (dd, J = 11.2, 5.0 \text{ Hz}, 1\text{H}), 1.16 (s, 9\text{H}), 0.81 (s, 9\text{H}). \]

\(^{13}\text{C NMR (75 MHz, CDCl}_3\)

\[ \delta 163.0, 143.4, 136.0, 135.4, 132.7, 129.8, 129.7, 129.6, 129.5, 127.8, 127.6, 127.5, 118.0, 114.3, 98.3, 96.6, 79.3, 72.4, 72.0, 69.3, 64.4, 55.6, 55.2, 27.0, 26.6, 19.6. \]

**MS**

\[ m/z 806.1 [M + H]^+ \]

**HRMS**

: calcd for C\(_{47}\)H\(_{57}\)O\(_8\)Si\(_2\) 805.3586, found 805.3611.

[\(\alpha\)]\(_{20}^D\)

: \(-54 (c = 0.5, \text{ CHCl}_3).\)

(1\(S, 5'\)\(S\))-(Hydroxymethyl)-5,7-dimethoxy-3\(, 4'\), 5\(', 6'\)-tetrahydro-3H-spiro[isobenzofuran-1,2\'-pyran]-3\(', 4'\), 5\(', 6'\)-triol (130, 129, 128).

To a stirred solution of \(142, 143, \) and \(144\) (50 mg, 0.06 mmol) in dry THF (1 mL) was added TBAF (0.3 mL, 1 M in THF) at room temperature, and mixture was stirred for 1 h. After consumption of starting material, reaction was diluted with EtOAc (5 mL) and
filtered through Celite (100 mg). Filtrate was concentrated and purified (5% MeOH in CH2Cl2) to afford tetrol 130, 129, and 128 (14.2 mg, 50%). Data for allo 129 and gluco 128 isomers matched with the reported values.

**Altro- isomer (130)**

- **M.pt**: 132–135 °C
- **IR (KBr)**: \( v_{\text{max}} \) 3381, 2925, 2851, 1610, 1151, 1095, 1005 cm\(^{-1}\);
- **\(^1\)H NMR (300 MHz, CD\(_3\)OD)**: \( \delta \) 6.47 (s, 1H), 6.45 (s, 1H), 5.12 (d, \( J = 12.6 \) Hz, 1H), 4.96 (d, \( J = 12.6 \) Hz, 1H), 4.68–4.57 (m, 1H), 4.32 (t, \( J = 7.3 \) Hz, 1H), 3.85 (s, 3H), 3.80 (s, 3H), 3.88–3.69 (m, 3H);
- **\(^{13}\)C NMR (75 MHz, CD\(_3\)OD)**: \( \delta \) 164.9, 157.7, 145.5, 115.7, 99.0, 97.9, 82.4, 79.3, 76.3, 74.5, 73.3, 64.0, 57.1, 55.9, 30.7;
- **ESIMS**: \( m/z \) 350.9 [M + Na]\(^+\);
- **HRMS**: calcd for C\(_{15}\)H\(_{20}\)NaO\(_8\) 351.105, found 351.1078.
- **[\( \alpha \)]\(^{20}\)\(_D\)**: −7.5 (c =0.2, CHCl\(_3\)).

**\((2S,3R)-2,4\)-bis(Benzyloxy)butane-1,3-diol (151a)**

![Chemical Structure](image)

To a stirred solution of aldehyde 151 (500 mg, 1.6 mmol) in MeOH (5 mL) was added NaBH\(_4\) (63 mg, 1.6 mmol) at 0 °C. TLC shows the consumption of aldehyde after 30 min, then MeOH was removed under vacumm. The residue was purified by column chromatography (40% EtOAc/hexanes) to afford the diol 151a (434mg) in 90% yield.
IR (KBr) : \( \nu_{\text{max}} \) 3424, 3030, 2868, 1453, 1092, 739, 698 cm\(^{-1}\);

\( ^1 \)H NMR (300 MHz, CDCl\(_3\)) : \( \delta \) 7.23-7.36 (m, 10H); 4.63-4.44 (m, 4H), 3.92 (m, 1H); 3.75-3.80 (m, 2H); 3.65-3.45 (m, 3H); 3.25 (brs, 1H); 3.15 (brs, 1H).

\( ^{13} \)C NMR (75 MHz, CDCl\(_3\)) : \( \delta \) 137.8, 137.6, 128.2, 127.8, 127.7, 78.7, 73.2, 72.0, 70.9, 70.4, 61.1

ESIMS : \( m/z \) 325.0 [M + Na]\(^+\).

\([\alpha]^{20}_D\) : 27 (c = 1.1, CHCl\(_3\)). [+30 for sugar derived diol]

**\((2R, 3R)-2,4\text{-bis-(Benzyloxy)-3-(tert-butyldimethylsilyloxy)-butanal (148)}.$$**

\[
\begin{align*}
\text{H} & \quad \text{OTBS} \\
\text{O} & \quad \text{OBn} \\
\text{O} & \quad \text{OBn} \\
\text{148} &
\end{align*}
\]

Aldehyde 151 (500 mg, 1.6 mmol) was dissolved in dry CH\(_2\)Cl\(_2\) (10 mL), to which were added 2,6-lutidine (0.3 mL, 2.5 mmol) and TBSOTf (0.42 mL, 1.76 mmol) at 0 °C under nitrogen atmosphere. Reaction was stirred for 1 h at same temperature. Solution was diluted with CH\(_2\)Cl\(_2\) (10 mL) and water (10 mL), and both layers were separated. Organic layer was dried over Na\(_2\)SO\(_4\) and concentrated in vacuo. Crude was purified (4% EtOAc in PE) to afford aldehyde 148 as a colorless liquid (529 mg, 80%):

IR (KBr) : \( \nu_{\text{max}} \) 2929, 1728, 1254, 1110, 836, 779 cm\(^{-1}\)

\( ^1 \)H NMR (300 MHz, CDCl\(_3\)) : \( \delta \) 9.64 (d, \( J = 1.7\), 1H), 7.35–7.22 (m, 10H), 4.69 (s, 2H), 4.50 (s, 2H), 4.22 (m, 1H), 3.86 (dd, \( J = 1.8\), 3.2 Hz, 1H), 3.66–3.60 (dd, \( J = 7.3\), 9.4 Hz, 1H), 3.46 (dd, \( J = 5.4\), 9.4 Hz, 1H), 0.90 (s, 9H), 0.10 (s, 3H), 0.08 (s, 3H).
CH analysis: Anal. calcd for C_{24}H_{34}O_{4}Si (414.61): C, 69.52; H, 8.27. Found: C, 69.41; H, 8.32.

$[\alpha]^{20}_D$: −2.2 (c = 2, CHCl$_3$).

(4S,5R)-4,6-bis-(Benzyloxy)-5-(tert-butyldimethylsilyloxy)-1- (2-((tert-butyldimethylsilyloxy)methyl)-4,6-dimethoxyphenyl)- 3-hydroxyhexan-1-one (152a).

To a stirred solution of ketone 141 (307 mg, 0.84 mmol) in dry CH$_2$Cl$_2$ (10 mL) was added titanium tetrachloride (1 M solution in CH$_2$Cl$_2$, 0.8 mL) at −78 °C slowly under nitrogen atmosphere. After 5 min, DIPEA (0.21 mL, 1.26 mmol) was added, and resulting red colored solution was stirred for 15 min at same temperature. Then, a solution of aldehyde 148 (350 mg, 0.84 mmol) dissolved in dry CH$_2$Cl$_2$ (5 mL) was added. Stirring was continued for 1 h at same temperature. After completion of reaction, mixture was warmed to 0 °C, 50% NH$_4$Cl solution (10 mL) was added, and resulting mixture was stirred for 2 h at room temperature. Organic layer was separated, and aqueous layer was extracted with CH$_2$Cl$_2$ (2 × 10 mL). Combined organic layers were dried over Na$_2$SO$_4$ and concentrated under a vacuum. Crude was purified (20% EtOAc in PE) to yield 152a as a viscous liquid (552 mg, 70%, 20% of syn diastereomer):

IR (KBr): $\nu_{max}$ 3505, 2952, 2930, 1601, 1459, 1254, 1152, 1068, 837, 778 cm$^{-1}$.  

$^1$H NMR (300 MHz, CDCl$_3$): $\delta$ 7.30–7.11 (m, 10H), 6.75 (d, $J = 2.2$ Hz, 1H), 6.23 (d, $J = 2.2$ Hz, 1H), 4.78–4.43 (m, 6H), 4.21–4.11 (m, 1H), 3.77 (s, 3H), 3.64 (s, 3H), 3.65–3.59 (m, 1H), 3.50–3.40 (m, 2H), 3.32–3.22 (m, 1H), 2.84 (d, $J = 9.8$ Hz, 1H), 2.79 (d, $J = 9.8$ Hz, 1H), 2.58 (s, 3H), 1.99 (s, 3H), 1.87 (m, 1H), 1.70 (s, 3H), 1.59 (s, 3H), 1.56–1.62 (m, 1H), 1.25 (s, 3H), 1.23 (s, 3H), 1.19 (s, 3H), 1.15 (s, 3H), 1.10 (s, 3H), 1.08 (s, 3H), 1.06 (s, 3H), 1.04 (s, 3H).
Hz, 1H) 0.90 (s, 9H), 0.83 (s, 9H), 0.04 (s, 6H), 0.02 (s, 6H).

^{13}C NMR (125 MHz, CDCl3) : δ 206.1, 162.0, 158.7, 143.6, 138.6, 138.1, 128.1, 120.8, 127.6, 127.5, 127.3, 120.3, 103.1, 96.7, 83.7, 73.9, 73.2, 72.5, 72.0, 68.7, 62.7, 55.4, 55.2, 47.8, 25.9, 25.8, 18.3, 18.0, −4.4, −4.8, −5.3.

MS : m/z 761.4 [M + Na]⁺.

HRMS : calcd for C₄₁H₆₃O₈Si₂ 739.4056, found 739.4094. 

[α]₂₀° : −10 (c = 0.5, CHCl₃).

(4S,5R,E)-4,6-bis-(Benzyloxy)-5-(tert-butyldimethylsilyloxy)-1-(2-((tert-butyldimethylsilyloxy)methyl)-4,6-dimethoxyphenyl)-hex-2-en-1-one (147).

To an ice-cooled solution of alcohol 152a & 152b (1.3 g, 1.76 mmol) in dry CH₂Cl₂ (5 mL) were added triethylamine (0.5 mL, 3.5 mmol) and mesyl chloride (0.11 mL, 1.43 mmol) under nitrogen atmosphere. Ice bath was removed, and flask was fitted with reflux condenser. Reaction was heated to reflux for 1 h, mixture was cooled to room temperature, and water (5 mL) was added to it. Both layers were separated, and aqueous layer was extracted with CH₂Cl₂ (2 × 10 mL). Combined organic layers were dried over Na₂SO₄ and concentrated under a vacuum. Crude mesylated product was dissolved in dry CH₂Cl₂ (5 mL) and DBU (0.4 mL, 2.64 mmol) was added to it at 0 °C under nitrogen atmosphere, and mixture was stirred for 30 min. Saturated NH₄Cl solution (5 mL) was added to reaction mixture, and two layers were separated. Aqueous layer was extracted with CH₂Cl₂ (2 × 5 mL). Combined organic layers were dried over Na₂SO₄ and concentrated in vacuo. Crude was purified (5% EtOAc in PE) to yield 147 (1.14 g, 90%).

IR (KBr) : ν max 2929, 1661, 1602, 1459, 1255, 1153, 1067, 836, 777 cm⁻¹.
\[ \text{H NMR (300 MHz, CDCl}_3\text{): } \delta 7.28-7.16 (m, 10H), 6.71 (d, J = 2.0 Hz, 1H), 6.63-6.47 (dt, J = 15.8, 5.6, 11.7 Hz, 2H), 6.27 (d, J = 2.0 Hz, 1H), 4.61 (s, 2H), 4.52 (d, J = 11.7 Hz, 1H), 4.41 (s, 2H), 4.34 (d, J = 11.7 Hz, 1H), 4.06 (t, J = 5.0 Hz, 1H), 3.87 (q, J = 4.9 Hz, 1H), 3.76 (s, 3H), 3.62 (s, 3H), 3.47-3.36 (m, 2H), 0.86 (s, 9H), 0.73 (s, 9H), 0.01 (s, 6H), −0.06 (d, J = 1.7 Hz, 3H), −0.09 (s, 3H).

\[ \text{C NMR (75 MHz, CDCl}_3\text{): } \delta 194.9, 161.9, 158.5, 144.2, 143.5, 138.1, 133.7, 128.2, 127.6, 127.5, 119.2, 102.7, 96.8, 79.6, 74.1, 73.3, 71.5, 71.4, 62.2, 55.5, 55.2, 25.9, 25.7, 18.3, 18.0, −4.6, −4.7, −5.3.

ESIMS : m/z 743.3 [M + Na]\text{].

HRMS : calcd for C_{41}H_{60}NaO_7Si_2 743.377, found 743.3802.

[\alpha]^{20}_D : +11.8 (c = 0.5, CHCl_3).

**(2S,3S,4S,5R)-4,6-bis-(Benzyloxy)-5-(tert-butyldimethylsilyloxy)-1-(2-((tert-butyldimethylsilyloxy)methyl)-4,6-dimethoxyphenyl)-2,3-dihydroxyhexan-1-one (154).**

To a solution of enone 147 (1.2 g, 1.66 mmol) in 12 mL of t-butanol/acetone (1:1) were added 50% w/v solution of 4-methylmorpholine-N-oxide in water (1.16 mL, 4.98 mmol) and OsO\textsubscript{4} (8.3 mg, 0.03 mmol, 2 mol %) at 0 °C. Reaction was stirred vigorously at 0 °C for 30 h. Mixture was quenched with solid sodium sulfite (250 mg) at room
temperature. Ethyl acetate (10 mL) was added to reaction, and mixture was filtered through a pad of Celite (2 g). Organic layers were separated and dried over Na2SO4. Solvent was removed under reduced pressure. Crude was purified (8% EtOAc in PE) to yield **154** (980 mg, 80%):  

**IR (KBr)**  
\[ \nu_{\text{max}}\text{ cm}^{-1}: 3462, 2930, 1677, 1601, 1459, 1108, 1067, 837, 777. \]

**\(^1\text{H NMR}\) (300 MHz, CDCl\(_3\))**  
\[ \delta \text{ ppm: } 7.34-7.10 \text{ (m, 10H), 6.90 (d, } J = 2.2 \text{ Hz, 1H), 6.16 (d, } J = 2.2 \text{ Hz, 1H), 5.31 (d, } J = 5.2 \text{ Hz, 1H), 4.88 (d, } J = 15.8 \text{ Hz, 1H), 4.77 (d, } J = 10.5 \text{ Hz, 1H), 4.59 (d, } J = 3.0 \text{ Hz, 1H), 4.55 (s, 1H), 4.41 (d, } J = 12.0 \text{ Hz, 1H), 4.36 (d, } J = 12.0 \text{ Hz, 1H), 4.18 (dt, } J = 1.5 \text{ Hz, 1H), 3.88 (d, } J = 4.5 \text{ Hz, 1H), 3.82-3.75 \text{ (m, 1H), 3.78 (s, 3H), 3.63-3.54 (m, 2H), 3.43 (s, 3H), 3.40 (dd, } J = 6.0, 9.0 \text{ Hz, 1H), 2.39 (d, } J = 8.3 \text{ Hz, 1H), 0.93 (s, 9H), 0.78 (s, 9H), 0.05-0.04 (s, 6H), 0.01 (s, 3H), 0.00 (s, 3H). \]

**\(^{13}\text{C NMR}\) (75 MHz, CDCl\(_3\))**  
\[ \delta \text{ ppm: } 204.5, 163.1, 159.7, 146.4, 138.8, 138.0, 128.3, 128.2, 127.9, 127.5, 127.4, 103.7, 96.7, 80.9, 73.9, 73.2, 73.1, 72.1, 71.8, 62.5, 55.3, 25.9, 25.7, 18.3, 18.0, -4.5, -5.0, -5.2, -5.3. \]

**MS**  
\[ m/z 777.8 [M + Na]^+. \]

**HRMS**  
: calcd for C\(_{41}\)H\(_{63}\)O\(_9\)Si\(_2\) 755.4005, found 755.4026.

**\([\alpha]^{20}_D\)**  
\[ +15.7 \text{ (c = 2, CHCl}_3\). \]
A solution of diol 154 (800 mg, 1.05 mmol), 2-methoxypropene (0.30 mL, 3.17 mmol), and pTSA (10.5 mg, 5 mol %) in dry CH$_2$Cl$_2$ (5 mL) was vigorously stirred at 0 °C for 10 min. The mixture was neutralized with aqueous NaHCO$_3$, and layers were separated. Aqueous phase was extracted with CH$_2$Cl$_2$ (2 × 5 mL). Combined organic layers were washed with brine (10 mL), dried over Na$_2$SO$_4$, and concentrated under a vacuum. Crude was purified (6% EtOAc in PE) to yield 146 (749 mg, 90%):

IR (KBr) : $\nu_{\text{max}}$ 2931, 2856, 1680, 1601, 1459, 1253, 1153, 1069, 836, 776 cm$^{-1}$.

$^1$H NMR (300 MHz, CDCl$_3$) : $\delta$ 7.28−7.15 (m, 10H), 7.01−7.06 (dd, $J = 6.0$, 3.0 Hz, 2H), 6.81 (d, $J = 2.2$ Hz, 1H), 6.23 (d, $J = 2.2$ Hz, 1H), 4.97 (d, $J = 5.2$ Hz, 1H), 4.71−4.28 (m, 2H), 4.54−4.47 (dd, $J = 5.2$, 9.8 Hz, 2H), 4.44 (s, 2H), 4.15 (m, 1H), 3.76 (s, 3H), 3.68 (dd, $J = 9.8$, 4.5 Hz, 1H), 3.67−3.54 (m, 1H), 3.59 (s, 3H), 3.49 (dd, $J = 6.0$, 9.8 Hz, 1H), 1.22 (s, 3H), 1.20 (s, 3H), 0.87 (s, 9H), 0.83 (s, 9H), 0.02 (s, 3H), 0.01 (s, 3H), −0.01 (s, 3H), −0.06 (s, 3H).

$^{13}$C NMR(75 MHz, CDCl$_3$) : $\delta$ 203.1, 161.5, 159.5, 144.7, 138.4, 128.2, 128.0, 127.5, 127.3, 127.2, 118.3, 110.6, 102.9, 96.9, 83.5, 82.3, 77.8, 73.5, 73.2, 72.2, 71.7, 62.4, 55.7, 55.2, 27.5, 26.2, 25.9, 18.3, 18.1, −4.4, −4.7, −5.3.

MS : $m/z$ 816.6 [M + Na]$^+$, 794.6 [M + H]$^+$. 

(4$R$, 5$S$) - 5 - ( (1$S$, 2$R$) - 1 , 3 - bis -(Benzyloxy)-2-(tert-butyldimethylsilyloxy)propyl)-2,2-dimethyl-1,3-dioxolan-4-yl)- (2-((tert-butyldimethylsilyloxy)methyl)-4,6-dimethoxyphenyl)- methanone (146).
Chapter-III (Section A)

HRMS: calcd for $\text{C}_{44}\text{H}_{67}\text{O}_{9}\text{Si}_2$ 795.4318, found 795.4351.

$[\alpha]^\circ_D$: +4.6 ($c = 1, \text{CHCl}_3$).

$((4R,5S)-5-((1R,2R)-1,3-\text{bis}(\text{Benzyloxy})-2-\text{hydroxypropyl})-2,2-\text{dimethyl}-1,3-$
dioxolan-4-yl)(2-(\text{hydroxymethyl})-4,6-\text{dimethoxyphenyl})\text{methanone (156).}$

To a stirred solution of 146 (1 g, 1.25 mmol) in dry THF (10 mL) was added TBAF (3.7 mL, 1 M in THF) at 0 °C, and mixture was stirred for 1 h. After consumption of starting material, saturated NH$_4$Cl (10 mL) and EtOAc (10 mL) were added to reaction. Organic layer was separated, and aqueous layer was extracted with EtOAc (2 × 5 mL). Combined organic layers were concentrated in vacuo to yield diol as colorless oil (566 mg, 80%). The crude diol was taken up to next reaction without further purification. Part of crude product was purified for characterization (35% EtOAc in PE) to yield 156:

IR (KBr): $\nu_{\text{max}}$ 3380, 2930, 2867, 1609, 1455, 1346, 1221, 1153, 1095, 741, 699 cm$^{-1}$.

$^1$H NMR (300 MHz, CD$_3$COCD$_3$): $\delta$ 7.43–7.72 (m, 10H), 6.43 (d, $J = 1.5$ Hz, 1H), 6.41 (d, $J = 1.5$ Hz, 1H), 5.08–4.75 (m, 6H), 4.63–4.53 (m, 2H), 4.17 (m, 1H), 3.91 (dd, $J = 3.7$, 6.0 Hz, 1H), 3.76–3.79 (dd, $J = 3.7$, 8.3 Hz, 1H), 3.83 (s, 3H), 3.80 (s, 3H), 3.75–3.67 (m, 1H), 1.31 (s, 3H), 1.25 (s, 3H).

$^{13}$C NMR (75 MHz, CD$_3$COCD$_3$): $\delta$ 207.2, 164.4, 157.7, 145.0, 140.8, 140.2, 129.9, 129.4, 129.0, 111.0, 109.9, 99.5, 98.4, 82.0, 81.7, 78.7, 75.7, 74.6, 72.4, 56.8, 29.0, 27.8.

MS: $m/z$ 549.1 [M – H$_2$O]$^+$. 

125
CH Analysis

: Anal. calcd for C\textsubscript{32}H\textsubscript{38}O\textsubscript{9} (566.25): C, 67.83; H, 6.76. Found: C, 67.82; H, 6.67.

\[\alpha\]\textsuperscript{20}\textsubscript{D} : +2.6 (c = 1, CHCl\textsubscript{3}).

\((1S,3'R,5'S)-5'-\text{(Benzylloxy)}-6'-(\text{benzyloxymethyl})-5,7\text{-dimethoxy-}3',4',5',6'-\text{tetrahydro-3H-spiro[isobenzofuran-1,2'}-\text{pyran]-3',4'}-\text{dil}

Diol \textbf{156} (100 mg, 0.17 mmol) was dissolved in MeOH (2 mL) and cooled to 0 °C. Dry pTSA (3.4 mg, 10 mol %) was added to it, ice bath was removed, and mixture was stirred for 1 h at room temperature. Reaction was quenched with solid NaHCO\textsubscript{3} solution and filtered through celite (100 mg). MeOH was removed under vacuum, residue was partitioned between EtOAc (3 mL) and water (3 mL), and two layers were separated. Aqueous layer was extracted with EtOAc (2 × 5 mL). Combined organic layers dried over Na\textsubscript{2}SO\textsubscript{4} and concentrated in vacuo. Crude was purified (40% EtOAc in PE) to yield \textbf{157} (43 mg, 50%):  

IR (KBr) : \(\nu_{\text{max}}\) 3443, 2926, 2864, 1610, 1345, 1154, 1093, 1022, 743 cm\textsuperscript{-1};  

\(^1\text{H}\) NMR (300 MHz, CDCl\textsubscript{3}) : \(\delta\) 7.44–7.27 (m, 10H), 6.37 (d, \(J = 1.5\) Hz, 1H), 6.32 (d, \(J = 1.5\) Hz, 1H), 5.10–4.93 (dd, \(J = 12.8, 34.7\) Hz, 2H), 4.85–4.73 (dd, \(J = 10.5, 22.6\) Hz, 2H), 4.53 (s, 2H), 4.51–4.43 (m, 1H), 4.41–4.32 (m, 1H), 4.13– 3.97 (m, 2H) 3.89–3.81 (m, 1H), 3.84 (s, 3H), 3.79 (s, 3H), 3.72– 3.64 (dd, \(J = 4.5, 9.8\) Hz, 1H), 2.52 (d, \(J = 9.0\) Hz, 1H), 1.88 (d, \(J = 7.5\) Hz, 1H);
\(^{13}\)C NMR (75 MHz, CDCl\(_3\)) : \(\delta\) 162.9, 155.7, 143.3, 138.2, 138.0, 128.4, 128.3, 128.2, 128.1, 127.8, 127.6, 127.5, 127.4, 117.8, 111.7, 98.2, 96.7, 73.5, 73.1, 72.5, 71.2, 70.9, 70.1, 68.4, 55.5, 55.4, 55.3;

MS : \(m/z\) 509.2 [M + H]\(^{+}\).

HRMS : calcd for C\(_{29}\)H\(_{33}\)O\(_8\) 509.2170, found 509.2176.

\([\alpha]\)\(^{20}\)\(_D\) : \(-48\) (c = 1, CHCl\(_3\)).

\((1S,3'\, R, 5'\, R)-5'\,-(Benzylxy)-6'- (benzyloxy)methyl)-5,7-dimethoxy-3',4',5',6'- tetrahydro-3H-spiro[isobenzofuran-1,2'-pyran]-3',4' -diyl diacetate (145).

To a stirred solution of diol 157 (96.5 mg, 0.19 mmol) in dry CH\(_2\)Cl\(_2\) (2.0 mL) was added pyridine (63 \(\mu\)L, 0.78 mmol), followed by acetic anhydride (55 \(\mu\)L, 0.59 mmol) and DMAP (2.3 mg, 10 mol %) at 0 °C. Resulting mixture was allowed to stir at room temperature for 4 h. Saturated NaHCO\(_3\) solution (1 mL) was added, and organic layer was separated. Aqueous layer was extracted with CH\(_2\)Cl\(_2\) (2 × 2 mL). Combined organic layers were concentrated in vacuo. Crude was purified (20% EtOAc/hexanes) to yield 145 (107 mg, 95%) as a colorless oil:

IR (KBr) : \(\nu_{\text{max}}\) 2924, 1744, 1609, 1225, 1022, 771 cm\(^{-1}\).

\(^1\)H NMR (300 MHz, CDCl\(_3\)) : \(\delta\) 7.45–7.23 (m, 10H), 6.37–6.23 (m, 3H), 5.51 (dd, \(J = 10.6, 3.3\) Hz, 2H), 5.07 (d, \(J = 12.6\) Hz, 1H), 4.93 (d, \(J = 12.6\) Hz, 1H), 4.73 (d, \(J = 12.4\) Hz, 1H), 4.63 (d, \(J = 12.2\) Hz, 1H), 4.54 (s, 2H), 4.44–4.31 (m, 1H),
4.19 (m, 1H), 3.93 (t, $J = 9.8$ Hz, 1H), 3.85 (s, 3H), 3.78 (s, 3H), 3.74 (dd, $J = 10.3, 4.5$ Hz, 1H), 2.0 (s, 3H), 1.76 (s, 3H).

$^{13}$C NMR (75 MHz, CDCl$_3$) : $\delta$ 170.2, 169.2, 156.2, 143.2, 138.3, 138.1, 128.3, 128.2, 127.7, 116.6, 110.5, 98.0, 75.2, 74.7, 73.3, 73.2, 72.9, 71.7, 70.9, 68.7, 68.6, 55.6, 55.5, 20.9, 20.4.

MS : $m/z$ 592.9 [M + H]$^+$.  
HRMS : calcd for C$_{33}$H$_{37}$O$_{10}$ 593.2381, found 593.2378.  

$[\alpha]_{D}^{20}$ : $-31.4$ (c = 0.5, CHCl$_3$).
3.5. REFERENCES


45. Stack, R. J. *US patent* 4966845.
49. Molecular dynamics for the energy minimized conformation of 142, 143, 145 were carried out using Insight II program on a Silicon Graphics work station.
CHAPTER-III

(Section-B)

Synthesis of amigal, key intermediates for
pipecolic acid and jaspine B using organocatalysis
3.6. INTRODUCTION

Glycobiology is a rapidly growing research area where carbohydrates play a major role. Low molecular-weight polyhydroxylated alkaloidal monosaccharides, with nitrogen atom in the place of the ring oxygen of the corresponding carbohydrates are known as imino sugars. Iminosugars have emerged as important tools for glycobiology research.\(^1\)\(^2\) In recent years, polyhydroxylated iminosugars have attracted a great deal of attention due to their ability to mimic sugars and thereby competitively and selectively inhibit glycosidases and glycosyltransferases. In the case of iminosugars, ring oxygen substituted with nitrogen renders the imino sugars metabolically inert but it does not prevent their recognition by glycoprocessing enzymes. The resemblance of iminosugars to carbohydrates and their polar nature might be responsible for endowing them with several special attributes as potential drug candidates, for example efficient uptake. At the same time, they remain sufficiently distinct from carbohydrates to avoid processing by other carbohydrate-modifying systems and have both chemical and biological stability. This unique combination of properties singles out iminosugars as a special class in the search for new drug molecules.\(^3\)\(^-\)\(^5\) Protonated, imino sugars resemble the transient oxocarbonium ion involved in glycoside hydrolysis and thus can act as transition-state analogues for the competitive inhibition of the glycosidases and glycosyltransferases. Inhibition of these enzymes affects the maturation, transport, secretion, and function of glycoproteins and could alter cell-cell or cell-virus recognition processes.\(^6\)\(^-\)\(^7\) Glycosidase inhibitors have been shown to interact with receptors related to a wide range of prominent diseases including viral infections, cancer, diabetes and other metabolic disorders and are expected to find an increasing number of applications as beneficial drugs. For the above mentioned reasons iminosugars have attracted attention of synthetic community.\(^8\)

Iminosugars can be classified in several ways: according to their carbon structure, functional groups they contain, activities in which they are involved, for their therapeutic applications, or their natural sources, etc. A systematic and intuitive classification is based on their structure (Fig. 16). Iminosugars are broadly classified into six classes based on the core structural skeleton polyhydroxylated pyrrolidines, piperidines, indolizidines, pyrrolizidines, azepanes and nortropanes. The isolation and activity of few important iminosugars were briefed below.
Pyrrolidines

The five-membered pyrrolidine family is one of the important class iminosugars. As a matter of fact, five-membered ring iminosugars have been the object of extensive biological and chemical investigations. 2, 5-Dihydroxymethyl-3, 4-dihydroxypropyrrrolidine (DMDP) 158 was first isolated from leaves of *Derris elliptica* (Fabaceae). 9 DMDP 158 and *homo*-DMDP 159 are selective inhibitors of α- and β-glucosidases. 9a In particular, pyrrolidine imino sugar 2,5-dideoxy-2,5-imino-D-glucitol (DGADP) 161 and its C-4 epimer, 2,5-dideoxy-2,5-imino-D-glucitol (DGDP) 160 recently isolated from Thai medicinal plants, are potent inhibitors of several galactosidases and glucosidases. 10 1,4-Dideoxy-1,4-imino-D-arabinitol (DAB) 163, that was first found in the fruits of *Angylocalyx boutiqueanus*, it is a selective inhibitor of glycosidase. 11 Recently, *cis*-5-benzyl-4-hydroxy-2-pyrrolidinone 162, named as streptopyrrolidine, was isolated from the fermentation of broth of marine *Streptomyces* and shows significant anti-angiogenesis activity. 12 The 1, 4-Dideoxy-1,4- imino-L-arabinitol (LAB) 164, was first isolated from the fruits of *Angylocalyx boutiqueanus*, it is a powerful inhibitor of sucrase and α-glucosidases. 13 (3S, 4S)-3-(Hydroxymethyl) pyrrolidine-3,4-diol reffered as *iso*-LAB 165 shows superior activity to NB-DNJ (N-butyl1-deoxynojirimycin) in assays for restoration of F508 CFTR function. 14 1,4-Dideoxy- 1,4-imino-L-allitol (DIA) 166 is a moderately good inhibitor of human liver α-D-mannosidase and a weak inhibitor of α-L-fucosidase, N-acetyl- β-D-hexosaminidase, and β-D-mannosidase. 15 1, 4-Imino-1, 2, 4-trideoxy-D-arabinitol (167, CYB 3), an analogue of 2-deoxyribose, was found in the leaves and seeds of *Castanospermum austral*. 16 (Fig. 17)
Indolizidines

Indolizidines are bicyclic alkaloids where the azapyranose ring is fused to a pyrrolidine ring via N-bridge. Swainsonine (GD0039) 168 is isolated from Swainsona canescens.\(^1\) It is a potent inhibitor of Golgi alphamannosidase II, an immunomodulator and a potential chemotherapeutic.\(^2\) One of the disadvantage is that it causes neurological disorders in livestock. Castanospermine 169 was isolated from Castanospermum austral.\(^3\) Celgosivir 170, an ester prodrug of natural product castanospermine 169 is the most advanced clinical-stage antiviral iminosugar targeting Hepatitis C virus (HCV) infection.\(^4\) (-)-Lentiginosin 171 was isolated in 1990 from the leaves of Astragalus lentiginosus. It is a competitive inhibitor \(\text{IC}_{50} = 5 \mu\text{g/mL}\) of the amylglucosidase enzyme (Fig. 18).\(^5\)

![Fig. 17](image-url)

![Fig. 18](image-url)
Pyrrolizidines

Pyrrolizidine structure is composed of two fused pyrrolidines with a bridgehead nitrogen atom. The first polyhydroxylated pyrrolizidine alkaloid with a hydroxymethyl group at C-3 was isolated from pods of *Alexa leiopetala* (Leguminosae) in 1988 and designated as alexine 172. Subsequently australine 173 isolated from Australian legume *Castanospermum austral*. Alexine and australine showed strong inhibition on fungal amylglucosidase and on rat intestinal sucrose (IC$_{50}$ = 4.6 μM)$^{15a}$ respectively. Uniflorine 174 was isolated from the leaves of the tree *Eugenia uniflora*. Uniflorines are strong inhibitors of the α-glucosidases, rat intestinal maltase (IC$_{50}$ = 12 μM) and sucrase (IC$_{50}$ = 3.1 μM).$^{24}$

![Chemical structures of pyrrolizidine alkaloids](image)

The highly polyhydroxylated pyrrolizidine casuarine, 175 occurs in related genera in *Casuarinaceae* and *Myrtaceae*. Casuarine is a potent inhibitor of gluosidase I.$^{25}$ Necine bases, the heterocyclic portion of necine alkaloids 176 and 177 have also received interest because of their strong toxicity against insects.$^{26}$ Asano *et al.* isolated hyacinthacine A$_1$ 178, A$_2$ 179, from the bulbs of *Muscari armeniacum* (Hyacinthaceae).$^{26a}$ Hyacinthacine A$_1$ is a good inhibitor of rat intestinal lactase (IC$_{50}$ = 4.4 μM) Hyacinthacine A$_2$ (the 1-
epiphyacinthacine A$_1$) showed enhanced inhibitory activity towards amyloglucosidase (IC$_{50} = 8.6 \, \mu$M) (Fig. 19).$^{26}$

Azepanes

Seven member iminosugars are known as azepanes 180-182 in Fig. 20. This area is not well developed. These class of compounds show promising glycosidase inhibitory activity.$^{27}$ Azepanes are also potentially useful as DNA minor groove binding ligands (MGBL).$^{28}$ The hydroxyl groups in azepanes adopt different conformations due to the flexibility of the seven member ring (compared with five- or six-member rings), thereby increasing the probability of forming hydrogen bonds with the nitrogen bases thus rendering their ability to point into the minor groove of the DNA. The high water solubility, allowing them to circumvent the problem of poor bio-availability, seen with many other MGBL’s, is an additional advantage of these compounds. The designing of azepane molecules therefore is mainly concerned with the different positional and stereochemical orientation of the –OH functionality at C-2/C-3/C-4/C-5 Compound 182 is a better inhibitor of β-N-acetylglucosaminidase than 1-deoxynojirimycin (191), which is often taken as a standard.$^{29}$

![Fig. 20](image)

Fig. 20

Nortropane

The polyhydroxylated nortropane alkaloids (Fig. 21) seem to be restricted to the closely related families Solanaceae and Convolvulaceae, where they co-occur with tropane alkaloids. However, they have also been found in species of *Morus* (Moraceae). Calystegine families of nortropane alkaloids are potent/or good inhibitors of α – and/or β glucosidase, galactosidase and mannosidases.$^{30}$ Calystegine A$_3$ (183) is isolated from the roots of *Lycium chinense*. Other important nortropane alkaloids are N-methylcalystegine B$_2$ 184 and calystegine C$_1$185.
Piperidines

Today, more than 20 natural piperidine aza-sugars are known as a plethora of synthetic derivatives. Nojirimycin 186, which is one of the best known representatives of iminosugars, was shown to be an inhibitor of both α– and β-glycosidases of various origins. 31 Nojirimycin was isolated from bacterial cultures of *Steptomyces roseochromogenes* R-468 and *Streptomyces nojiriensis*. Its is a glucose analogue and naturally occurring iminosugar which was first described as an antibiotic compound produced from the SF-426 by Inouye and coworkers in 1966. 32 Nojirimycin B 187 (mannonojirimycin,) 33 and galactostatin (galactonojirimicyn) 188 34 were isolated soon after. 1-Deoxy-homonojirimycin 190 (adenophorine isolated from *Adenophora* spp) was active on α-glucosidase (IC₅₀ = 34 μ) but not on β-galactosidase. 35 Homonojirimycin 189 (HNJ) is isolated from leaves of *Omphalea diandra* (Euphorbiaceae), which is active against α-glycosidase (Fig. 22). 36
Thereafter hundreds of polyhydroxylated alkaloidal iminosugars have been isolated from plants and microorganisms. Iminosugars are considered to have a high potential therapeutic value as antidiabetic drug candidates, antiviral and anti-infective agents or in lysosomal storage disease treatment.

1-Deoxynojirimycins

DNJ, Glyset and Zavesca

The deoxy analogue 1-Deoxynojirimycin (191, DNJ) is one of the important members of the nojirimycin family and the simplest natural carbohydrate mimic. DNJ is also known as 1, 5-dideoxy-1,5-imino-D-glucitol or Moranoline. Yagi and co-workers isolated Moranoline, from the root bark of various Morus species and microorganisms. Moranoline is a strong α-glucosidase inhibitor. Amicus launched clinical trials for DNJ against Pompe disease. The two marketed iminosugar drugs Glyset 192 and Zavesca 193 are closely related to the naturally occurring iminosugar DNJ 191. Glyset also called Miglitol is a N-propyloxylated form of DNJ. It has been licensed for use in the treatment of type II diabetes since 1996. The proposed mode of action is through inhibition of intestinal α-1,4-glucosidases leading to reduction in glucose absorption from the gut. N-Butyl-deoxynojirimycin (193, Zavesca®) is an N-alkylated iminosugar which is a prescription drug for a mild to moderate type 1 Gaucher disease and Niemann-Pick type C (NPC) disease. It has shown to inhibit human immunodeficiency virus (HIV). Its proposed mechanism of action is through inhibition of glucosylceramide synthase, a glycosyl transferase responsible for the synthesis of many glycosphingolipids (Fig. 23).

Fig. 23
Fagomine, *iso*-fagomine

Three fagomine isomers 194–196 were found from *Xanthocercis zambesiaca* occurring in southern Africa in dry forest.\(^{38}\) Out of these isomers, fagomine 194 and 3-*epi*-fagomine 195 have been shown to have activity against mammalian \(\alpha\)-glucosidase and \(\beta\)-galactosidase.\(^{39}\) Fagomine 194 was also found to have a potent antihyperglycaemic effect in streptozocin-induced diabetic mice and a potentiation of glucose-induced insulin secretion.\(^{39}\) The synthetic analogue of DNJ, where one of the hydroxyl group is replaced by hydroxymethyl, named as isofagomine 197,\(^{40}\) shows activity against Gaucher disease. It is evaluated by Amicus Pharmaceuticals in Phase II trials against Gaucher’s disease\(^{40}\) which is a lysosomal storage disorder caused by \(\beta\)-glucocerebrosidase deficiency. The di tartatrate form (AT2101, Plicera) of 197 is even more active compared to other drugs available such as miglustat (Zavesca, given orally). *iso*-Fagomine is believed to bind to misfolded glucocerebrosidase enzyme, enabling correct processing and trafficking to the lysosome by the endoplasmic reticulum, thereby restoring its intended biological function of degrading glucocerebroside *Fig. 24.*

![Diagram of fagomine isomers](image)

**Fig. 24**

1-Deoxymannonojirimycin (DMJ)

DMJ 198 was isolated from *Lonchocarpus sericeus* and *L. costaricensis* *Fig. 25.* DMJ is a specific inhibitor of Golgi mannosidase I to block conversion of mannose to complex oligosaccharides; DMJ also inhibits \(\alpha\)-L-fucosidase, and \(\alpha\)-D-glucosidase activity.\(^{41}\) Its corresponding lactum *D*-mannolactam 199 inhibits both \(\alpha\)-D-mannosidase and \(\alpha\)-D-glucosidase.\(^{42}\)
Amigal™ (Migalastat)

Migalastat 201 (Amigal, AT1001, 1-deoxygalactonojirimycin, 1-deoxygalactostatin) semi-synthesis was first reported from galactonojirimycin (galactostatin) 200 which is isolated from Streptomyces lydicus PA-572. In May 2006, orphan designation was granted by the European Commission to Amicus Therapeutics for use of 201 against Fabry disease, which was transferred to Shire Pharmaceutical in June 2008. As of now, Amigal is in Phase III trials as monotherapy by Amicus Therapeutics in conjunction with Shire Pharmaceuticals for the treatment of Fabry disease.43b,c

Fleet et al.44 reported DGJNAc [2-acetamido-1, 2-dideoxy-D-galacto-nojirimycin] 203 as the first potent, specific and competitive inhibitor of GalNAcases. DGJNAc 203 is less potent but competitive whereas L-DGJNAc 204 is a very weak non-competitive inhibitor of β-hexosaminidases. Selective inhibition of β-hexosaminidases has potential in the study of osteoarthritis, allergy, Alzheimer’s disease, O-GlcNAcase inhibition, cancer metastasis, type II diabetes, genetic diseases such as Tay-Sachs and Sandhoff diseases, and of plant regulation. Recently the same author’s reported 45 L-DGJ 202 [a noncompetitive inhibitor of human lysosome R-galactosidase A (R-Gal A), Ki 38.5 μM] and DGJ [a competitive inhibitor of R-Gal A, KI 15.1nM] as the first examples of pharmacological chaperones that are enantiomeric iminosugars and have synergistic activity with implications for the treatment of lysosomal storage disorders and other protein deficiency Fig. 26.
Fabry disease and treatments available

It is a rare disease affects only a few thousand people worldwide. Fabry disease causes a wide range of signs and symptoms that can range from mild to severe and life-threatening. Fabry’s disease patients possess inherited mutations in a galactosidase A, A ($\alpha$-Gal A) an enzyme responsible for degradation of the lipid globotriaosylceramide GL-3 in the lysosomes. Over 600 mutations in the gene encoding $\alpha$-Gal A are associated with FD. Without enough of this $\alpha$-Gal A the GL-3 substance builds up in cells. GL-3 build-up in kidney cells may cause severe kidney problems, including kidney failure. People with Fabry disease may experience a wide range of signs and symptoms, including severe conditions such as kidney failure, heart problems, and stroke (Fig. 27).
Enzyme replacement therapy (ERT)

Enzyme replacement therapy provides patients with the enzyme they are lacking. Fabrazyme® (agalsidase beta) is intended to replace the missing enzyme in patients with this progressive disease. This is designed to replace the human enzyme, alpha-galactosidase A, which people with Fabry disease are lacking. The active substances Fabrazyme® (agalsidase beta), is a copy of the human enzyme, produced by a method known as ‘recombinant DNA technology’. It is made by a cell that has received a gene (DNA), which makes it able to produce the enzyme. The replacement enzyme helps to break down the Gb3 and stops building up (accumulating) in the cells.

Unfortunately, due to unforeseen circumstances, misfortune has continued to plague Fabrazyme® production at Genzyme’s Allston manufacturing plant. As a result, world wide Fabrazyme supply continues to remains at low levels. The Food and Drug Administration (FDA) approved treatment IND (investigational new drug), allowing the use of Replagal®, is beginning to provide some relief as treatment sites complete the lengthy application process and are becoming available to start treating patients. In April of 2010, orphan drug law marketing protection ended for Fabrazyme, opening the door for the FDA to provide marketing approval to addition of enzyme replacement drugs such as Replagal. Shire filed a Biologics License Application (BLA) to these ends and is supplying requested data to support this process.

Chaperone mediated therapy (CMT) or pharmacological chaperone therapy (PCT)

Pharmacological or molecular chaperone therapy is among the newest therapeutic ideas for lysosomal storage diseases. Pharmacological chaperones are small molecules that specifically bind and stabilize the functional form or three-dimensional shape of a misfolded protein in the endoplasmic reticulum (ER) of a cell. When misfolded due to a genetic mutation, the protein (Enzyme) is unable to adopt the correct functional shape. This misfolded protein is recognized by the quality control system in the cell, and destroyed, leading to decreased amounts of enzyme that gets transported from the cell’s ER to the cell’s lysosome resulting in reduced enzyme activity. The binding of the chaperone molecule, helps the protein fold into its correct three-dimensional shape. This allows the protein to be properly trafficked from the ER and distributed to the lysosome in the cell, which would increase enzyme activity and cellular function and reduce
substrate and stress on the cells. Amicus therapeutics is in Phase 3 Clinical Trials with their lead product Migalastat (AT1001) for the treatment of Fabry disease. Migalastat seems to stabilize the mutant enzyme by binding to the catalytic site, enabling correct processing and trafficking to the lysosome by the endoplasmic reticulum.

Amicus and GSK are developing migalastat HCl, in collaboration. Under the terms of the collaboration, GSK has an exclusive worldwide license to develop, manufacture and commercialize migalastat HCl. Amicus and GSK are conducting two Phase 3 global registration studies of migalastat HCl monotherapy, along with a Phase 2 study evaluating migalastat co-administered with enzyme replacement therapy (ERT) for the treatment of Fabry disease.
3.7. PREVIOUS APPROACHES

Cheng’ s approach

Cheng et al. deveopled a diastereoselective nucleophilic addition of Grignard reagents to six-membered chiral tri-O-benzyl cyclic nitrones. Wittig olefination of 2, 3, 4-tri-O-benzyl-L-lyxopyranoside 205 gave olefin 206. Oxidation of hydroxyl group of alkene 206 followed by oxime formation with NH₂OTBDPS afforded compound 207. Ozonolysis of 207 followed by reduction and mesylation gave mesylated product 208. Deprotection of TBDPS ether underwent cyclization to give cyclic nitrone 209. Treatment of nitrone with vinylmagnisiumbromide in THF gave 90% diastereomeric excess. The aminoxo bond in the product was cleaved by using excess of zinc in AcOH and the free amine was protected with (Boc)₂O to give 210. Olefin 210 upon ozonolysis and reduction gave alcohol which on deprotection with Pd/C in 10%HCl afforded DGJ 201 (Scheme 31).

Reagents and conditions: (i) MePPh₃Br, n-BuLi, THF, −78 °C to r.t; (ii) DMSO, (COCl)₂, CH₂Cl₂, (iPr)₂EtN, −78 °C to r.t; (iii) H₂NOTBDPS, PPTS, MgSO₄, toluene, reflux; (iv) O₃, MeOH, −78 °C, then Me₂S; (v) NaBH₄, MeOH, 0 °C, r.t; (vi) MsCl, Et₂N, CH₂Cl₂; (vii) TBAF, THF, reflux. (35% from 205) (viii) vinylMgBr, THF, −78 °C, 83%, dr (95:5); (ix) excess Zn, AcOH, r. t.; (x) (Boc)₂O, Et₂N, DCM; (xi) O₃, MeOH/ CH₂Cl₂, −78 °C, then Me₂S; (xii) NaBH₄, MeOH, 10% HCl(aq.), MeOH, 70 °C; (xiii) H₂ (g), Pd(OH)₂/C, 10% HCl/MeOH, r. t. (38% from 209)

Scheme 31

Timmer’s approach

Recently Timmer et al. reported an efficient synthesis of the 1-deoxygalactonojirimycin (DGJ) 201. The key to this strategy is the development of a novel carbamate annulation reaction that favors formation of a six-membered carbamate-
containing piperidine skeleton 216 over its five-membered counterpart 214. Thus, synthesis of key intermediate 213 involved the installation and subsequent removal of acetonides at the 1, 2 and 3,4 positions of galactose while converting the primary hydroxyl to an iodide 212. Modified Vasella-reductive amination protocol was employed for the formation of linear alkenylamine 213. Amine 213 was treated with aqueous NH₄HCO₃ and iodine, which provided the isomers 214:215:216 in 1:1:3 with required isomer in major quantities. The required carbamate 216 was hydrolysed using NaOH to afford DGJ 201 (Scheme 32).

![Chemical structure diagram]

**Scheme 32**

**Ojea’s approach**

Ojea et al. have developed a general strategy for the synthesis of 1-deoxy-azasugars from a chiral glycine equivalent and 4-carbon chiral building blocks. A diastereoselective aldol addition of metalated bislactim ethers to matched and mismatched erythrose or threose acetonides is the key step. The Schöllkopf’s bislactim ethers cyclo-[Gly-L-Val] 217 derived from glycine and L-valine using standard method.⁴⁸b Compound 217 was treated with corresponding aldehyde using n-BuLi in presence of tin chloride to give the alcohol, which was protected as benzyl ether to afford 218. The TBDPS ether was deprotected with TBAF to furnish the alcohol, which was mesylated later and the auxiliary was removed using triethylamine in DMSO to yield the
mesyl ester **219.** A nucleophilic displacement by the amino group which was appropriate for the cyclization gave the cyclized product **220.** Reduction of ester **220** gave alcohol **221.** Finally a hydrogenolysis of the benzyl ether and deprotection of the acetonide of **221** furnished DGJ **201** (Scheme 33).

Reagents and conditions:  
(i) $n$-BuLi, SnCl$_2$, THF, -78 °C, 1 h; 79%; ($dr$ 95:5)  
(ii) NaH, BnBr, THF, r.t, 24 h; 75%;  
(iii) TBAF, THF, r.t, 95%;  
(iv) MsCl, Et$_3$N, CH$_2$Cl$_2$, r.t, 99%;  
(v) 0.25M HCl, EtOH, r.t, 9 h; 65%;  
(vi) Et$_3$N, DMSO, 70 °C, 2 h; 85%;  
(vii) LiBEt$_3$H, 0 °C, 3 h, 84%;  
(viii) H$_2$, Pd/C EtOH, 9 h (ix) Dowex-H$^+$, 90% (two steps).

Scheme 33

**Koskinen’s approach**

Koskinen et al. reported a highly diastereoselective synthesis of DGJ in eight steps from commercial starting materials. The key step in the synthesis is an addition of vinylzinc species to chiral aldehyde **223.** Thus TBS ether **222** was treated with Schwartz’s reagent furnished the vinylzirconium intermediate which was then transmetalated to the corresponding zinc species by treating it with diethylzinc. The addition of Garner’s aldehyde **223** to the above vinyl zinc species gave desired allylic alcohol, which was protected as its benzyl ether to afford compound **224.** Dihydroxylation under Upjohn conditions lead to diol which upon desilylation gave the triol **225.** Selective mesylation of the primary alcohol with mesyl chloride and 2, 4, 6-collidine afforded diol **226.** $N$, $O$-Acetonide and Boc protections of diol **226** were deprotected using 6N HCl to give the triolamine **227.** Cyclization in presence of Huinig’s
base provided the cyclized product, which upon deprotection of benzyl group with palladium on charcoal under hydrogen atmosphere in acidic methanol delivered DGJ 201 as its hydrochloride salt (Scheme 34).

![Scheme 34](image)

**Reagents and conditions:** (i) Schwartz’s reagent, 0 °C, Et₂Zn, -40 to 0 °C, CH₂Cl₂, 78%; (dr 20:1) (ii) NaH, BnBr, TBAI, THF, reflux, 85%; (iii) OsO₄, NMO, H₂O, Acetone/H₂O (8:1), 70%; (iv) TBAF, THF, 95%; (v) MsCl, Et₃N, CH₂Cl₂, 0-2 °C, 89%; (vi) 6M HCl, MeOH (vii) DIPEA, MeOH, 60 °C; (viii) Pd/C, H₂, HCl, MeOH, 78% (three steps).

**Takahata’s approach**

Starting from the Garner’s aldehyde Takahata et al. synthesized dioxanylpireridene which is a precursor for deoxyazasugars. The key step involved is a catalytic ring-closing metathesis (RCM) for the construction of the piperidine ring. Diastereoselective addition of vinyl zinc to aldehyde 223 furnished syn vinyl alcohol 5:1 diastereoselectivity (syn:anti). 67% de of the syn-preferred product was improved to 92% de (72%) by single recrystallization. Recrystallized alcohol was treated with HCl gas in chloroform, then it was converted to the 1, 3-acetonide 228. N-Allylation of 228 with allyl iodide using NaH gave the diolefin product 229. Finally, diolefin 229 was subjected to RCM in presence of Grubbs’ catalyst to provide desired piperidene 230. The syn epoxide was obtained by hydroxy-directed epoxidation of the diol, prepared by hydrolysis of the acetonide of 230 with p-TsOH in methanol. Epoxidation of diol with m-CPBA followed by acetonization afforded the syn epoxide 231. Finally acid hydrolysis of epoxy ring of the syn epoxide 231 was accomplished by using a mixture of H₂SO₄/1.4-
dioxane/H₂O in a ratio of 0.2/3/2, and further treatment with an ion exchange resin (DOWEX 1x2, OH- form) to get DGJ 201 (Scheme 35).

**Reagents and conditions:** (i) vinylzinc bromide, ether, -78 °C to rt; (ii) recrystallization from n-hexanes-ethyl acetate (5:1); (iii) HCl (g), CHCl₃, rt; (iv) allyl iodide, NaH, THF, 0 °C; (v) Grubb’s catalyst, CH₂Cl₂, rt; p-TsOH.H₂O, MeOH, rt; (vi) m-CPBA, NaH₂PO₄, CH₂Cl₂, 0 °C to r.t; (vii) 2,2-dimethoxypropane, cat. PPTS, acetone, rt; (ix) H₂SO₄, 1,4-dioxane, H₂O, reflux, (x) Amberlite IRA-410 (OH- form), (xi) DOWEX 1x2 (OH form);

Scheme 35

**Overkleeft’s approach** 51

Overkleeft et al. reported a chemoenzymatic synthesis of three 1-deoxyribojirimycin-type iminosugars. The key steps in the synthetic scheme includes a *Dibal reduction-transimination-sodium borohydride reduction* cascade of reactions on enantiomERICALLY pure cyanohydrins 233. Cyanohydrin itself was prepared using almond hydroxynitrile lyase (*pa*HNL) catalyzed hydrocyanation reaction. Application of Ellman reaction conditions to the addition of vinylmagnesium bromide to imine 232 afforded adduct 234 in a diastereomeric ratio of 96:4. Using the *Dibal reduction-transimination-NaBH₄ reduction* sequence of reactions, cyanohydrin 233 was converted to amine 236. Amine 236 was protected as Boc amide, followed by RCM with first-generation Grubbs catalyst afforded cyclic iminosugar precursor 237. Under Upjohn dihydroxylation conditions alkene 237 gave a 1:1 mixture of compounds 238a and 238b. Finally deprotection of TBDPS, benzyl ethers and Boc in compound 238b using TBAF followed by catalytic hydrogenation under acidic conditions afforded DGJ 201 (Scheme 36).
**Reagents and conditions:**

(i) vinylmagnesium bromide, AlMe$_3$, toluene, -78 °C, 80%; (ii) Dibal-H, -78°C - 10°C; (iii) -90°C, MeOH; (iv) r.t, 18h; (v) NaBH$_4$, 0°C - r.t, 3h (80% three steps); (vi) Boc$_2$O, Et$_3$N, THF; (vii) Grubbs' catalyst, CH$_2$Cl$_2$, rt, (91% two steps); (viii) K$_2$OsO$_4$ (4.4 mol%), NMO, THF, H$_2$O, 24-48h, rt; (ix) TBAF, THF, r.t, 3-18h; (x) H$_2$, Pd/C, 6M HCl. MeOH, 18h, rt 83%;

**Scheme 36**

**Fleets’s approach**$^{45}$

Fleet *et al.* reported concise syntheses of *L*-DGJ 202 and DGJ 201 from enantiomers of tagatose in an overall yield of 66%. The reaction of *D*-tagatose 239$^{52}$ with acetone in presence of copper (II) sulfate and catalytic sulfuric acid gave the diacetonide 240. The primary hydroxyl group in 240 was converted to azide 241 through its triflate,. Acetonide groups in 241 were deprotected with Dowex in water to give 6-azidotagatose as a 3:1 mixture of anomers. Hydrogenation of the azide gave corresponding amine which underwent a highly stereoselective intramolecular reductive amination to afford DGJ 201. Similarly enantiomer of DGJ 202 was synthesized by an identical route from *L*-tagatose 242 (Scheme 37).
Reagents and conditions: (i) Acetone, CuSO$_4$, H$_2$SO$_4$, r.t, 18h (82%, L-79%); (ii) Tf$_2$O, Py, CH$_2$Cl$_2$, -30 to -10°C, 3h (iii) NaN$_3$, DMF, r.t, 18h (96%, L-93% over two steps); (iv) Dowex (50W x 8 H$^+$), 1,4 dioxane, H$_2$O, r.t, 3days (86%, L-99%); (v) H$_2$, Pd/C, EtOH, H$_2$O, r.t, 18h (86%, L-97%).

Scheme 37
3.8. PRESENT WORK

During the course of our ongoing program on the synthesis of various natural and unnatural sugars, using organocatalysis, we initiated a program on the synthesis of imino sugar 1-deoxygalactonojirimycin (DGJ) 201 (Fig. 28). DGJ also known as amigal is recently undergoing a phase II clinical trial for the treatment of Fabry’s disease. With an interest in developing novel methodology for the synthesis of iminosugars, we devised a strategy that enables six-membered nitrogen-containing rings, to be synthesized from readily available chiral starting materials in excellent yields and diastereoselectivity. The key steps involved are McMillan proline catalyzed homo aldol reaction with TBDPS protected hydroxyl acetaldehyde 134 and Upjohn dihydroxylation of the unstaturated ester 249. The key intermediate azide 249 was utilized in the synthesis of pipridinol 243 which is a reduced anleoge of hydroxyl pipecolic acid. Hydroxypipeolic acids 245 are an important family of nonproteinogenic cyclic α-amino acids with a chiral substituted piperidine skeleton. The cis-isomer of 3-hydroxy pipecolic acid structural unit is found in diverse natural products and biologically significant molecules such as tetrazomine 246 also found in the structure of the antimalarial isofebrifugine (Figure 28).

More over the key azide 249 is utilized in the synthesis of a precursor for jaspine B. Jaspine B 248 is one of the naturally occurring anhydro phytosphingosine derivatives isolated from marine sponges, Pachastrissa sp. and Jaspis sp.. It exhibited a significant cytotoxicity against P388, A549, HT29, and MEL28 carcinoma cell lines in vitro. The two TBDPS ethers in azide 249 were deprotected and insitu cyclized to 3-epi-Jaspine B
core. All the above said targets were synthesized as both L- and D- isomers by tuning the catalyst from L- to D- proline.

**Retrosynthesis:**

A retro synthetic analysis is shown in Scheme 38. Accordingly, DGJ could be synthesized from the key azide 249 via Upjohn dihydroxylation, hydrogenation cum lactumization and finally deprotection of TBDPS ethers. The key intermediate for Jaspine B 244 could be constructed by a TBAF hydrolysis of TBDPS ether functionality and concomitant oxa-Michael addition. 3-Hydroxypipeolic acid 245 can also be derived from the azide by a catalytic hydrogenation and TBDPS group deprotection. Finally the key azide can be made from the aldehyde 131 by a two carbon wittig reaction and azide displacement. Hydroxyaldehyde 131 could be obtained from TBDPS protected acetaldehyde 134 using McMillan homo aldol reaction, with L-Proline as the catalyst. The other antipodes of three targets ent-201, ent-244 and ent-243 could be synthesized using the above sequence of reactions, where D-Proline can be used as the catalyst.

**Scheme 38**
Synthesis of key azide 249.

TBDPS protected hydroxyacetaldehyde 134 was prepared from 1,4 butenediol by a well documented procedure which is also described in the previous section (Scheme 16). Aldehyde was utilized in McMillan homo-aldol reaction. Thus the aldehyde 134 treated with 10 mol% of L-proline in DMF and dioxane (1:1) to afford the hydroxyaldehyde ent-131 in 70% yield. The product was confirmed by comparing $^1$H and $^{13}$C analysis with the previously synthesized aldehyde (Scheme 17). Aldehyde ent-131 was treated with C2 Wittig reagent in benzene to give unsaturated ester 250 in 90% yield. $^1$H NMR of 250 shows olefinic protons at $\delta$ 6.83-6.74 and 5.71, the coupling constant is 15.8 Hz reveals that the double bond has trans stereochemistry. The ESIMS showed m/z peak at 690 [M+Na] $^+$ which confirms the product formation. Conversion of the β-hydroxy group to azide was accomplished by preparing its triflate. Thus, ester 250 was subjected to triflic anhydride and pyridine conditions in dichloromethane which gave the crude triflate which was further treated with sodium azide in dimethyl formamide to furnish azidoester 249 in 80% yield. The IR spectrum of azide 249 clearly showed absorption at 2105 cm$^{-1}$ confirming presence of azide group. More over the ESIMS spectrum of 249 showed m/z peak at 691 [M+H]$^+$ which supports the formation of azide (Scheme 39).

Conversion of azide 249 to DGJ 201

Azido ester 249 was subjected to catalytic dihydroxylation using Upjohn condition (OsO$_4$/NMO) in acetone and water which gave a mixture of diol 252 in 85%
yield. The two isomers were not separable by column chromatography. Formation of diols confirmed by $^1$H and ESIMS. $^1$H NMR of 252 comprises a mixture of diol in a 8:2 ratio, the absence of olefinic protons at $\delta$ 6.83-6.74 and 5.71 and the protons attached to the hydroxyl group CHOH at $\delta$ 3.77 and 3.36 confirmed the product formation. ESIMS spectrum of the diols 252 showed m/z at 749 [M+Na]$^+$ which supports the product formation. The mixture obtained above was subjected to catalytic hydrogenation underwent the reduction of azide and lactumization to get the lactums 253a and 253b, which were separable by column chromatography. In the IR spectrum of 253a, the absence azide absorption in 2100 cm$^{-1}$ region confirmed reduction of azido group. $^1$H NMR spectrums showed the absence of ethyl group protons at $\delta$ 4.10, 1.26 and presence of amide NH at $\delta$ 6.22 which supports cyclization. The m/z 654.3084 in HRMS spectrum of 253a further confirmed the product (Scheme 40).

![Scheme 40]

Lactum 253a was reduced with borane dimethylsulphide complex in THF to give amine. Under basic condition the TBDPS groups also got deprotected in the reaction mixture and the amine was not isolated in pure form, it was treated with 6N HCl under reflux and chromatographic purification with NH$_4$OH solution gave the target DGJ 201 (Scheme 41). $^1$H NMR and $^{13}$C NMRs were identical with the reported values. $^1$H NMR shows the absence of silyl attached protons at $\delta$ 0.99, 0.095 and amide proton at $\delta$ 6.22 ppm confirmed the formation of the product. Further the product was confirmed by CHN analysis.
Synthesis of hydroxy piperidinol

Synthesis of the reduced form hydroxyl-pipolic acid commenced from the key azidoester 249, which was subjected to catalytic hydrogenation using Pd/C which underwent reduction of the olefin and azide along with concomitant cyclization to give lactum 254 in 90% yield. The conversion was confirmed by $^1$H NMR and ESIMS. The $^1$H NMR shows the absence of olefinic protons at $\delta$ 6.83-6.74 and 5.71 ppm, ethyl protons $\delta$ 4.10, 1.26 ppm, and presence of lactum proton at $\delta$ 6.17 ppm. IR spectrum shows the absence of azide functionality in 2100 cm$^{-1}$ range, which supports the product formation. Lactum 254 was converted to diolamine 243 by a known sequence employed in the synthesis of DGJ 201 (Scheme 40). Thus 254 was treated with borane dimethyl sulphide complex, followed by acid hydrolysis of TBDPS ethers using 6N HCl to give diol amine 243 in 95% yield (Scheme 42). The analytical data is in accordance with the reported values. Compound 243 can be further converted to 3-hydroxy pipolic acid by a known route.

Synthesis of key precursor for Jaspine B 244.

To explore further application of the key azidoester 249 it is converted to cyclic product 244. Azide 249 was treated with TBAF in THF which underwent a silyl deprotection as well as an oxo-Michael reaction to afford cyclized product 244 (Scheme 43). $^1$H NMR of 244 reveals the absence of olefinic protons at $\delta$ 6.83-6.74 and 5.71 ppm.
IR spectrum of 244 shows a peak corresponding to azide functionality at 2102 cm\(^{-1}\) which supports the product formation.

\[
\text{TBDPSO} \quad \text{COEt} \quad \text{249} \quad \text{TBAF, THF} \quad \text{rt, 12h, 50\%} \quad \text{N}_3 \quad \text{OH} \quad \text{244}
\]

**Scheme 43**

**Synthesis of enantiomers of target compounds**

Enantiomers of the target compounds *ent-201*, *ent-244* and *ent-243* were synthesized from the key azide *ent-249* which in turn was prepared from TBDPS protected hydroxyacetaldehyde 134 using *D*-proline as the catalyst. *ent-201*, *ent-244* and *ent-243* were obtained from the ester *ent-249* in 34, 43, 25\%-yields respectively (Scheme 44) by performing the same sequence of reactions as described in the Schemes 39-43.

**Scheme 44**

**Conclusion**

The development of this methodology for the synthesis of six-membered iminosugars would provide a useful route for the preparation of important iminosugars, and, would represent a major synthetic achievement, particularly if using precursor azidoester 249 that has the capacity to undergo both five- and six-membered intramolecular cyclization. Explorations of other applications of the azide 249 are in progress. In conclusion we have achieved a short and flexible synthesis of biologically important iminosugar DGJ along with the intermediates 243 and 244 which are useful in the synthesis of 3-pipecolic acid and jaspine B.
3.9. EXPERIMENTAL PROCEDURES AND SPECTRAL DATA

(4R, 5S, Z)- Ethyl 4, 6-bis (tert-butyldiphenylsilyloxy)-5-hydroxyhex-2-enoate (250)

![Chemical Structure](image)

Aldehyde *ent-131* (2 g, 3.35 mmol) was taken up in benzene (10 mL) and carboethoxymethylene triphenylphosphorane (1.4 g, 4.02 mmol) was added to it. The reaction was stirred overnight at room temperature, and concentrated *in vacuo*. The residue was purified by flash chromatography (hexane/ EtOAc 9:1) to give 250 (2.12 g 95%).

**IR (KBr)**: $\nu_{\text{max}}$ 3475, 3071, 2932, 1714, 1110, 702 cm$^{-1}$.

**$^1$H NMR (300 MHz, CDCl$_3$)**: $\delta$ 7.65- 7.47 (m, 8H), 7.41-7.24 (m, 12H), 6.83-6.74 (dd, $J = 6.6, 15.8$ Hz, 1H), 5.71 (dd, $J = 1.1, 15.8$ Hz, 1H), 4.42 (t, $J = 5.8$ Hz, 1H), 4.12 (q, $J = 7.1$Hz, 2H), 3.76-3.68 (m, 1H), 3.59-3.47 (m, 2H), 2.24 (d, $J = 3.2$ Hz, 1H), 1.27 (t, $J = 7.1$ Hz, 3H), 1.04 (s, 9H), 0.97(s, 9H).

**$^{13}$C NMR (75 MHz, CDCl$_3$)**: $\delta$ 165.8, 145.2, 135.8, 135.7, 135.4, 133.0, 132.9, 129.9, 129.8, 129.7, 127.7, 127.5, 123.1, 74.5, 73.9, 64.1, 60.3, 27.0, 26.7, 19.3, 19.0, 14.2.

**ESIMS**: $m/z$ 690 [M+Na]$^+$.  

**HRMS**: calcd for C$_{40}$H$_{54}$O$_5$NSi$_2$ 684.3535 found 684.3557

$\lbrack\alpha\rbrack_D^{20}$: -23.1 ($c = 5$, CHCl$_3$).

$\lbrack\alpha\rbrack_D^{20}$ for *ent-250*: 23.5 ($c = 2$, CHCl$_3$).
Chapter III (Section B)

(4R, 5R, Z)- Ethyl 5-azido-4, 6-bis (tert-butyldiphenylsilyloxy) hex-2-enoate (249):

In a dry 100 mL round bottom flask, under nitrogen ester 250 (1 g, 1.49 mmol) was dissolved in dry dichloromethane (10 mL) and cooled to -20 °C. To this solution pyridine (0.17 mL, 2.23 mmol) followed by triflic anhydride (0.27 mL, 1.64 mmol) were added. This red turbid solution was stirred at -10 °C for 1 h. TLC showed that all of the starting material had been consumed and product had been formed. The mixture was poured into ice cold water (20 mL) and extracted with dichloromethane (2 X 5 mL). The organic layer was washed with water, brine, dried over Na₂SO₄, and concentrated to yield crude triflate. This was then dissolved in DMF (5 mL). To this solution NaN₃ (290 mg, 4.47 mmol) was added. This solution was stirred at room temperature for 1 h. After consumption of the starting material, ice cold water (5 mL) and diethyl ether (10 mL) were added to it and layers separated. Organic layer was washed with cold water and brine, dried over Na₂SO₄, concentrated in vacuo. This crude material was then loaded onto a SiO₂ column and chromatographed (2% EtOAc in petroleum ether) to yield azide 249 (926 mg, 90%).

IR (KBr) : ν max 2956, 2105, 1722, 1110, 703 cm⁻¹.

¹H NMR (300 MHz, CDCl₃) : δ 7.65-7.50 (m, 8H), 7.45-7.28 (m, 12H), 6.79-6.72 (dd, J = 6.3, 15.9 Hz, 1H), 5.69 (d, J = 15.9 Hz, 1H), 4.40 (t, J = 5.3 Hz, 1H), 4.11 (q, J = 7.4 Hz, 2H), 3.83 (dd, J = 3.1, 10.6 Hz, 1H), 3.67 (dd, J = 7.4, 10.6 Hz, 1H), 3.31 (m, 1H), 1.23 (t, J = 7.4 Hz, 3H), 1.03 (s, 9H), 1.02 (s, 9H).

¹³C NMR (75 MHz, CDCl₃) : δ 165.5, 145.0, 135.8, 135.7, 135.5, 132.7, 132.5, 130.0, 129.9, 129.7, 128.2, 127.8, 127.7, 127.6, 122.6, 72.4, 67.2, 63.3, 60.3, 26.9, 26.6, 19.0, 14.1.

ESIMS : m/z 691[M+H]⁺.
HRMS: calcd for C\textsubscript{40}H\textsubscript{49}O\textsubscript{4}N\textsubscript{3}NaSi\textsubscript{2} 714.3153 found 714.3179

\([\alpha]_D^{20}\): -16.3 (c = 3, CHCl\textsubscript{3}).

\([\alpha]_D^{20}\) for \textit{ent}-249: 16.7 (c = 1, CHCl\textsubscript{3}).

\((2R, 3R, 4S, 5R)\)-Ethyl 5-azido-4, 6-
\textit{bis} (tert-butyldiphenylsilyloxy)-2, 3-
\textit{dihydroxyhexanoate} (252)

To a solution of \textbf{249} (1.5 g, 2.17 mmol) in 15 mL of acetone/ water (1:2) were added 4-methylmorpholine-\textit{N}-oxide in water (762 mg, 6.51 mmol) and OsO\textsubscript{4} (27.5 mg, 0.10 mmol, 5 mol %) at room temperatur. Reaction was stirred vigorously at the same for 20 h. Then it was quenched with solid sodium sulfite (500 mg) at room temperature. Acetone was removed in vacum. Ethyl acetate (30 mL) was added to the residue, organic layer was separated and dried over Na\textsubscript{2}SO\textsubscript{4}. Solvent was removed under reduced pressure. The crude was purified (10% EtOAc in PE) to yield \textbf{252} (1.3g, 85%).

IR (KBr): \(\nu_{\text{max}}\) 3475, 2933, 2110, 1727, 1110, 703 cm\textsuperscript{-1}.

\(^1\text{H} \text{NMR} \) (500 MHz, CDCl\textsubscript{3}): \(\delta\) 7.76-7.17 (m, 20H), 4.26-4.17 (m, 2H), 3.89 (t, \(J = 8.39\) Hz, 1H), 3.77 (d, \(J = 7.9\) Hz, 1H), 3.36 (dd, \(J = 2.9, 9.8\) Hz, 1H), 4.10 (q, \(J = 6.9\) Hz, 2H), 1.26(t, \(J = 6.9\) Hz, 3H), 0.99 (s, 9H), 0.97 (s, 9H).

ESIMS: \(m/z\) 749 [M+Na]\textsuperscript{+}

HRMS: calcd for C\textsubscript{40}H\textsubscript{49}O\textsubscript{4}N\textsubscript{3}NaSi\textsubscript{2} 748.3208 found 748.3233.
(3R, 4R, 5S, 6R)-5-(tert-Butyldiphenylsilyloxy)-6-((tert-butyldiphenylsilyloxy)methyl)-3, 4-dihydroxypiperidin-2-one (253a):

Diol 252 (1 g, 1.37 mmol) dissolved in EtOH (5 mL) and added Pd/C (291 mg 20 mol%) was added to it. The mixture was stirred for 12 h at room temperature under hydrogen atmosphere. Consumption of the starting material confirmed by TLC. The reaction mixture was filtered through celite (2 g). The filtrate was concentrated under vacuum and crude was purified by silicagel columnn (20% EA in pet ether) to yield lactums in 765mg (85% yield, 75:25 ratio).

IR (KBr) : $v_{\text{max}}$ 3390, 2932, 1668, 1110, 770 cm$^{-1}$.

$^1$H NMR (300 MHz, CDCl$_3$) : $\delta$ 7.56-7.10 (m, 20H), 6.22 (s, 1H), 4.54 (d, $J$ = 9.8 Hz, 1H), 4.00 (s, 1H), 3.79 (d, $J$ = 8.9 Hz, 1H), 3.69 (t, $J$ = 9.8 Hz, 1H), 3.30 (d, $J$ = 9.8 Hz, 1H), 2.91 (dd, $J$ = 2.9, 10.8 Hz, 1H), 2.66 (bs, 1H), 0.99 (s, 9H), 0.90 (s, 9H);

$^{13}$C NMR (75 MHz, CDCl$_3$) : $\delta$ 172.2, 136.2, 135.9, 135.3, 132.6, 132.4, 131.6, 129.9, 129.7, 129.6, 128.2, 127.7, 127.6, 127.5, 73.5, 70.3, 70.1, 64.8, 57.0, 27.0, 26.7, 19.9, 18.9.

ESIMS : $m/z$ 654[M]$^+$.  
HRMS : calcd for C$_{38}$H$_{48}$O$_2$NSi$_2$ 654.3065 found 654.3084

$[\alpha]_D^{20}$ : 47.9 ($c$ = 1, CHCl$_3$);  
$[\alpha]_D^{20}$ for ent–253a : -46.8 ($c$ = 2, CHCl$_3$).

For minor isomer (253b)  
IR (KBr) : $v_{\text{max}}$ 3346, 2929, 1672, 1109, 769 cm$^{-1}$.  

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\(^1\)H NMR (300 MHz, CDCl\(_3\)) : \(\delta 7.63-7.55\) (m, 8H), \(7.46-7.27\) (m, 12H), 5.87 (s, 1H), 4.04-4.00 (m, 1H), 3.85 (dd, \(J = 4.9\), 5.9 Hz, 1H), 3.81 (d, \(J = 7.9\) Hz, 1H), 3.59 (dd, \(J = 3.9\), 9.8 Hz, 1H), 3.51 (bs, 1H), 3.36 (m, 1H), 2.19 (bs, 1H), 1.03 (s, 9H), 0.97 (s, 9H);

\(^{13}\)C NMR (75 MHz, CDCl\(_3\)) : \(\delta 172.1, 135.9, 135.7, 135.5, 135.4, 132.9, 132.5, 132.4, 132.3, 130.1, 130.0, 129.9, 128.3, 127.8, 74.7, 72.0, 71.8, 63.1, 55.1, 26.8, 26.7, 19.3, 19.0;

ESIMS : \(m/z\) 654 [M\(^+\)].

HRMS : calcd for C\(_{38}\)H\(_{48}\)O\(_5\)NSi\(_2\) 654.3065 found 654.3088

\([\alpha]_D^{20}\) : 18.5 (c = 0.35, CHCl\(_3\)).

\([\alpha]_D^{20}\) for \textit{ent–253b} : -19.0 (c = 1, CHCl\(_3\)).

\((2R, 3S, 4R, 5S)-2\)-(Hydroxymethyl) piperidine-3, 4, 5-triol (201)

To a stirred, cooled (0 °C, ice bath) solution of 252b (500 mg, 0.76 mmol) in THF (5 mL) was added borane dimethylsulfide complex (2.0 M in THF, 2.29 mL, 4.59 mmol). After 30 min, the cold bath was removed, and reaction was allowed to warm to room temperature and then refluxed for 2 h. The reaction was then quenched with saturated aqueous Na\(_2\)SO\(_4\) (1 mL), stirred for 30 min and then extracted with EtOAc (3 \(\times\) 5 mL). The combined organic extracts were dried (Na\(_2\)SO\(_4\)) and concentrated under reduced pressure to yield the crude amine. The crude amine was taken in 6N HCl (6mL) and refluxed for 12h. Then water was removed under reduced pressure and residue was purified on dowex resin (eluted with NH\(_4\)OH) to yield the pure tetrol amine 201 (86.3g, 70%)
IR (KBr) : $\nu_{\text{max}}$ 2923, 2853, 1739, 1219, 772 cm$^{-1}$.

$^1$H NMR (500 MHz, D$_2$O) : $\delta$ 3.91 (dd, $J = 1.2, 2.9$ Hz, 1H), 3.77-3.66 (m, 1H), 3.60 (d, $J = 6.4$ Hz, 2H), 3.32-3.21 (m, 2H), 3.08 (dd, $J = 5.2, 12.6$ Hz, 1H), 2.64 (dt, $J = 1.3, 6.4$ Hz, 1H), 2.35 (dd, $J = 10.8, 12.6$ Hz, 1H);

$^{13}$C NMR (75 MHz, D$_2$O) : $\delta$ 74.8, 69.0, 67.9, 61.1, 58.7, 48.7;

CHN Analysis : Anal. calcd for C$_6$H$_{14}$ClNO$_4$ (199.06): C, 36.10; H, 7.07; Cl, 17.76; N, 7.02; O, 32.06 Found: C, 36.14; H, 7.02; N, 7.03.

$[\alpha]_D^{20}$ : 9.5 (c 0.5, H$_2$O).

$[\alpha]_D^{20}$ for ent–201 : -9.8 (c 0.2, H$_2$O).

(5$R$, 6$R$)-5-((tert-Butyldiphenylsilyloxy)-6-((tert-butyldiphenylsilyloxy)methyl)piperidin-2-one (254)

Followed the same procedure as described for the compound 253 starting with 249 (2 g, 2.89 mmol) using Pd/C (61 mg, 20 mol%) to yield 254 (1.61 g, 90%).

IR (KBr) : $\nu_{\text{max}}$ 2931, 1668, 1109, 704 cm$^{-1}$.

$^1$H NMR (300 MHz, CDCl$_3$) : $\delta$ 7.61-7.15 (m, 20H), 6.17 (bs,1 H), 3.95 (m, 1H), 3.79 (t, $J = 10.5$ Hz, 1 H), 3.42-3.32 (m, 2H), 2.71-2.58 (m, 1H), 2.32-2.21 (m, 1H), 1.89-1.77 (m, 1H), 1.67-1.54 (m, 1H), 1.02 (s, 9H), 0.95 (s, 9H);

$^{13}$C NMR (75 MHz, CDCl$_3$) : $\delta$ 171.1, 135.7, 135.6, 135.4, 135.3, 133.0, 132.7, 132.6, 132.5, 129.8, 129.7, 129.6, 128.2, 127.7,

ESIMS
\[ m/z \ 621 \ [M]^+ \]

HRMS
\[ \text{calcd for C}_{38}\text{H}_{48}\text{O}_3\text{NSi}_2 \ 622.3167 \text{ found 622.3179} \]

\[ [\alpha]_D^{20} \]
: 15.2 (c = 1, CHCl_3);

\[ [\alpha]_D^{20} \text{ for ent-254} \]
: -15.7 (c = 2, CHCl_3).

(2R, 3R)-2-(Hydroxymethyl)piperidin-3-ol (243)

Followed the same procedure as described for 201 starting with 254 (300 mg, 0.48 mmol) using borane dimethylsulfide complex (2.0 M in THF, 1.4 mL, 2.8 mmol) and 6 mL of aq. 6N HCl to yield 243 (47.1 mg, 75%). Column chromatography:
(Dowex, NH_4OH)

IR (KBr)
\[ v_{\text{max}} \ 2923, 2853, 1732, 772 \ \text{cm}^{-1}. \]

\(^1\)H NMR (500 MHz, D_2O)
\[ \delta \ 4.24 \ (s, 1H), \ 3.91 \ (dd, J = 4.0, \ 12.0 \ Hz, 1H), \]
\[ 3.83 \ (dd, J = 12.0, \ 9.4 \ Hz, 1H), \ 3.52-3.47 \ (m, 1H), \]
\[ 3.58-3.35 \ (m, 1H), \ 3.14-3.07 \ (dt, 3.3, \ 10.0 \ Hz, 1H), \]
\[ 2.13-1.99 \ (m, 2H), \ 1.87-1.78 \ (m, 2H). \]

\(^{13}\)C NMR (75 MHz, C D_2O)
\[ \delta \ 63.4, \ 61.2, \ 60.6, \ 45.0, \ 29.2, \ 17.1. \]

ESIMS
\[ m/z \ 132 \ [M+H]^+ \]

HRMS
\[ \text{calcd for C}_6\text{H}_{14}\text{O}_2\text{N} \ 132.1019 \text{ found 132.1021} \]

\[ [\alpha]_D^{20} \]
: -12.6 (c 3.0, H_2O).

\[ [\alpha]_D^{20} \text{ for ent-243} \]
: -12.9 (c = 2, H_2O).
Ethyl 2-((2S,3R,4S)-4-azido-3-hydroxytetrahydrofuran-2-yl)acetate (244)

Azide 249 (1 g, 1.4 mmol) dissolved in dry THF (5 mL) to which was added TBAF (4.34 mL, 4.34 mmol, 1M in THF) at 0 °C. The reaction was stirred till the starting material consumed. Then EtOAc (10 mL), saturated NH₄Cl (5 mL) were added and two layers separated. Organic layer was washed with brine and dried over Na₂SO₄ and concentrated. The crude was chromatographed (30% EA in pet ether) to yield azido alcohol as a light yellow oil 244 (210 mg) in 70% yield.

IR (KBr) : $\nu_{\text{max}}$ 3431, 2923, 2102, 1725, 772 cm$^{-1}$.

$^1$H NMR (300 MHz, CDCl$_3$) : $\delta$ 4.18 (q, $J = 7.1$ Hz, 2H), 4.07-3.96 (m, 3H), 3.91-3.85 (dd, $J = 8.8$, 1.8 Hz, 1H), 2.89-2.79 (dd, $J = 16.6$, 5.4 Hz, 1H), 2.71-2.62 (dd, $J = 16.5$, 8.0 Hz, 1H), 2.12 (bs, 1H), 1.29 (t, $J = 7.1$ Hz, 3H).

$^{13}$C NMR (75 MHz, CDCl$_3$) : $\delta$ 171.5, 81.5, 81.4, 70.4, 67.6, 61.2, 37.9, 14.0

ESIMS : $m/z$ 238 [M+Na]$^+$

HRMS : calcd for C$_8$H$_{13}$O$_4$N$_3$Na 238.0798 found 238.0804

$[\alpha]_D^{20}$ : 46.1 ($c = 1$, CHCl$_3$).

$[\alpha]_D^{20}$ for ent-244 : -45.5 ($c = 0.5$, CHCl$_3$).
3.10. REFERENCES


4. Iminosugars: From Synthesis to Therapeutic Applications; Compain, P.; Martin, O.R. 2007, John Wiley and Sons Ltd.


**LIST OF PUBLICATIONS**


