Synopsis

The thesis entitled "**Functionalisation of Indoles, Aminoquinolines, Glucal via C-H activation and a Formal synthesis of (+)-Neopeltolide**" is divided into five chapters

Chapter I : This Chapter deals with the $Pd(OAc)_2$ catalysed C-H Activation of Indoles, A Facile Synthesis of 3-Cyano Indoles.

Chapter II : This Chapter deals with metal-free remote C-5 oxytosylation of 8-aminoquinoline amides with koser's reagent.

Chapter III : This Chapter deals with the $Pd(OAc)_2$ catalyzed Direct cross coupling reaction between the Glycals and Benzoic Acids promoted by $PhI(OAc)_2$ as an Oxidant.

Chapter IV : This Chapter deals with the development of synthetic method for the Aza Ferrier rearrangement of Glycals with amides promoted by molecular iodine.

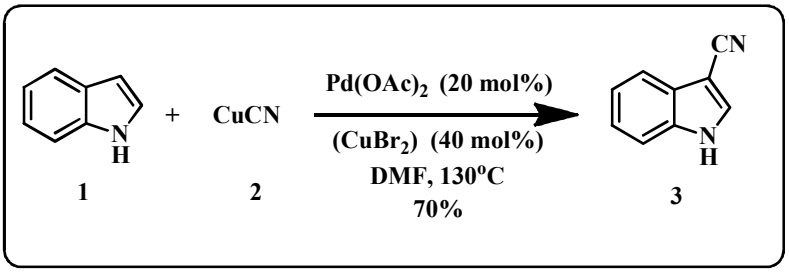
Chapter V : This chapter deals with the introduction, Previous approaches and present work wherein a Formal Synthesis of (+)-Neopeltolide, is described.

Chapter I: $Pd(OAc)_2$ Catalysed C-H Activation of Indoles, A Facile Synthesis of 3- Cyanoindoles.

The indole ring system is the most important heterocycle in nature, owing to the great structural diversity of biologically active indoles. The indole ring is found in many natural products such as the alkaloids, fungal metabolites and marine natural products. Indoles constitute as a diverse array of biologically significant natural compounds which occur in various forms from simple derivatives such as the essential amino acid tryptophan to complex alkaloids like antihypertensive compound. Indole is a nitrogen-containing heterocycle with a central position in organic chemistry and is considered to be a "privileged" structure in medicinal chemistry.

Aryl nitriles are extraordinary important organic compounds in chemistry as well as biology, and they are widely used in the production of pharmaceuticals, agricultural chemicals, and fine chemicals. Aryl nitriles also exhibit an important class of compounds in medicinal science.

In continuation of our interest on the functionalization of indoles **,** we herein report the direct Pd(II)-catalyzed cyanation of indoles through C–H bond activation using CuCN **(2)** as the cyanating agent. We first attempted the cyanation of indole **(1)** with CuCN **(2)** using 0.1 equiv of $Pd(OAc)_2$ and 0.4 equiv of $CuBr_2$ in DMF resulting cyano indoles **(3).**



(Scheme 1)

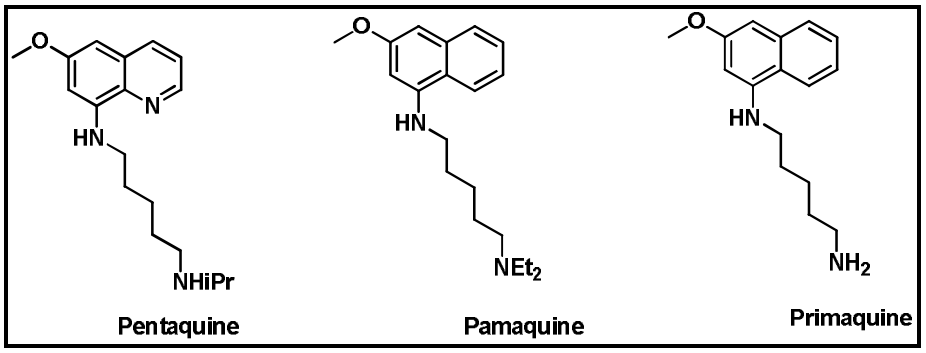
Conclusion:

In summary, we have developed a novel protocol for the cyanation of indoles at C-3 position via C–H activation. This method provides an easy access to a wide range of potentially valuable 3-cyanoindoles **(3)** thereby providing the precursors for the synthesis of natural products.

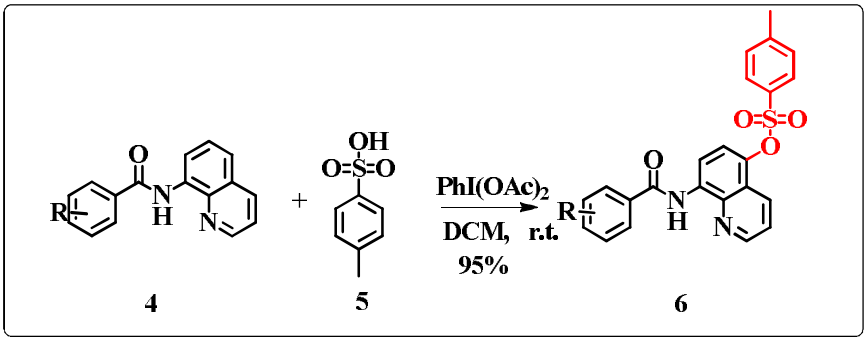
Chapter II: Metal Free Remote C-5 Oxytosylation of 8-Aminoquinoline amides with KOSER's reagent.

The quinoline skeleton is one of the most important aromatic heterocycles present in various natural products and pharmaceuticals. Quinolines can also be employed as ligands and directing groups in organic synthesis, as well as fluorescence probes in analytical chemistry. Thus, considerable efforts have been directed toward the formation and modification of quinoline-based scaffolds.

The first 8-amino quinolines to be extensively clinically investigated were pamaquine and pentaquine. The 8-aminoquinoline primaquine is a key antimalarial drug for both *Plasmodium falciparum* and *P. vivax* . It is postulated that the efficacy and toxicity of 8- aminoquinolines, such as primaquine, are ultimately related to the generation of reactive oxygen intermediates.



In continuation of our interest in developing new C-H activation methodologies under mild conditions and site selective, we attempted a reaction between Aminoquinolinamide (**4**) and Kosers reagent (**5**) . Strangely, oxytosylation reaction did not occur at the phenyl part of the aromatic acid group but at the C5–H position of the quinoline ring in DCM at rt within 15 min resulting the oxytosylated product(**6**).



(Scheme 2)

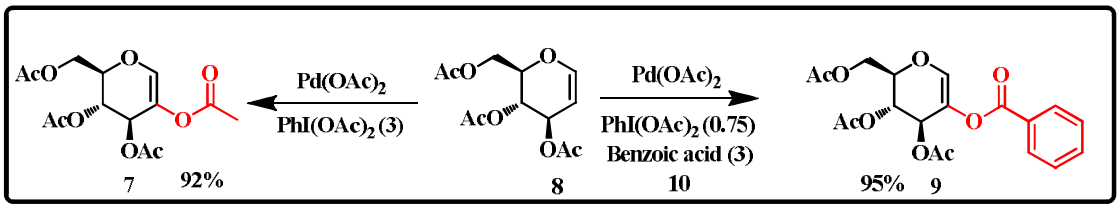
In conclusion, we have established a site-selective C–H oxytosylation approach for the construction of a variety of quinoline derived sulfones. The reaction require commercially available and inexpensive substrates as the Oxytosylation agents**.** More importantly, our work complements the research area concerning the functionalization of remote C–H bonds.

Chapter III: $Pd(OAc)_2$ catalyzed direct cross coupling reaction between the glycals and benzoic acids promoted by $PhI(OAc)_2$ as an oxidant.

Sugar pyranoses are one of the most abundant pyrans that are fully substituted with specific chiral centers. Among the many sugar pyranose derivatives, glycals are preeminent. Glycals are extremely useful carbohydrate derivates, which are not only versatile as glycosyl donors, or as substrates for Ferrier type rearrangements, but find

extensive application for many other synthetic purposes, particularly as chiral building blocks for the synthesis of natural products. Unlike C-1 glycoside derivatives, the synthesis of C-2 substituted carbohydrate derivatives is not very common. To achieve C-2 carbohydrate derivatives some very well-known reactions such as the Suzuki–Miyaura, Wittig and Heck-type reactions have been applied.Although it is uncommon, the formation of the C– C bond at C-2 of glucal derivatives has synthetic importance and it has played a key role in the synthesis of some very interesting and biologically important glycoside derivatives. C2-functionalized glycals could provide access to a large number of natural products and sugar derivatives.

To the best of our knowledge, there are no reports on the Palladium Catalysed cross coupling reaction of glucal with aromatic acids. In continuation of our interest in developing new methods on C-H activation, we herein report a versatile approach for a cross coupling reaction between aromatic acids and glucal. Palladium catalysed Cross Coupling reaction(Scheme **3**) of glucal (**8**) with aromatic acid (**10**) with (**0.75** equiv) of $PhI(OAc)_2$ as oxidant in acetonitrile as solvent furnished the product (**9**) and the product (**7**) with (**3** equiv) of $PhI(OAc)_2$ is shown as below.



(Scheme 3)

Conclusion:

In conclusion, we have reported an efficient and highly regioselective protocol for direct acyloxylation and benzoylation of glucals at the C-2 position via palladium-catalyzed C–H activation. This protocol provided a convenient synthesis of C-2 Functionalised Glucals.

Chapter IV: Aza-Ferrier rearrangement of glycals with amides promoted by molecular iodine

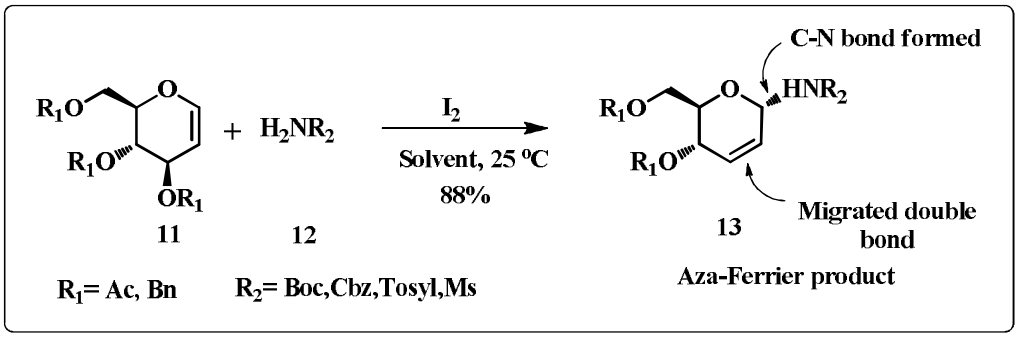
Carbohydrates play a crucial role in many biological processes such as cell development, cell−cell and cell−viral recognition, cell adhesion, inflammation, the immune response, etc., and have become a central theme in glycochemistry and glycobiology. Glycals are amongst the most versatile carbohydrate chiral building blocks that provide oxygen-rich stereochemically pure scaffolds. One of the most

important reactions to produce diversity in glycal chemistry is the Ferrier rearrangement, which plays a very important role in carbohydrate chemistry.

Azaglycosylation is an important reaction in the synthesis of *N*-glycosides, due to the increasing importance of nucleosides having *N*-glycosidic linkages as pharmacological agents such as antibiotics, antineoplastic and antiviral compounds. Among the N-glycosides, glycols having the double bond between C(2) and C(3) (*N*-pseudoglycals), represent a very important class of compounds because the double bond may be easily modified.

In continuation of our interest in developing methodologies with mild conditions, inexpensive and readily available reagents or catalysts, we developed a protocol where in a metal-free approach was utilized for the preparation of *N*-glycosyl amides from glucal using molecular iodine.

We developed a protocol where in sulfonamidoglycosilation was carried out not only on the acetylayed glucals but also on benzylated glucals making this as the first report of ferrier reaction with benzyl substituted glycals. **(Scheme 4)**



Conclusion:

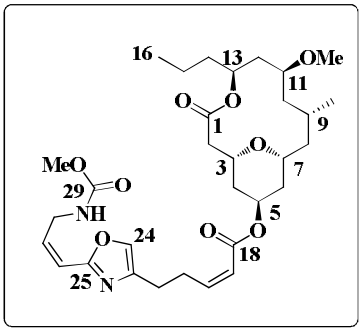
In summary, we have demonstrated molecular iodine promoted aza-Ferrier rearrangement for the synthesis of 2,3-unsaturated *N*-pseudoglycals from glycals and amides under mild and neutral conditions. This method provides good yields of *N*-glycosyl amides/sulfonamides in short reaction time with good α-anomeric selectivity, which makes it an attractive process.

Chapter V: A Formal Synthesis of (+)-Neopeltolide from D-Glucal

Natural products including plants, animals and minerals sometimes exhibit pharmacological or biological property that can be of therapeutic benefit in treating diseases.As such, natural products are the active components not only of most traditional medicines but also of many newer medications. Furthermore, synthetic analogs of natural products with improved potency can be prepared and therefore

natural products are often used as lead compounds for drug discovery. Tetrahydropyrans are structural motifs that are abundantly present in a range of biologically important marine natural products. Neopeltolide, a potent antiproliferative marine natural product, has been an attractive target compound for synthetic chemists because of its complex structure comprised of a 14-membered macrolactone embedded with a tetrahydropyran ring, an oxazole having an unsaturated chain appended through an ester linkage and six stereogenic centers.

Neopeltolide (**14**), a new member of marine macrolide natural products, was identified by Wright and co-workers from a deep-water sponge of the family Neopeltolide, collected off the north coast of Jamaica. The gross structure including the relative configuration was proposed on the basis of extensive 2D-NMR analyses. Later, total syntheses by Panek *et al*. and Scheidt *et al*. partially reassigned the relative configuration and established the absolute configuration.



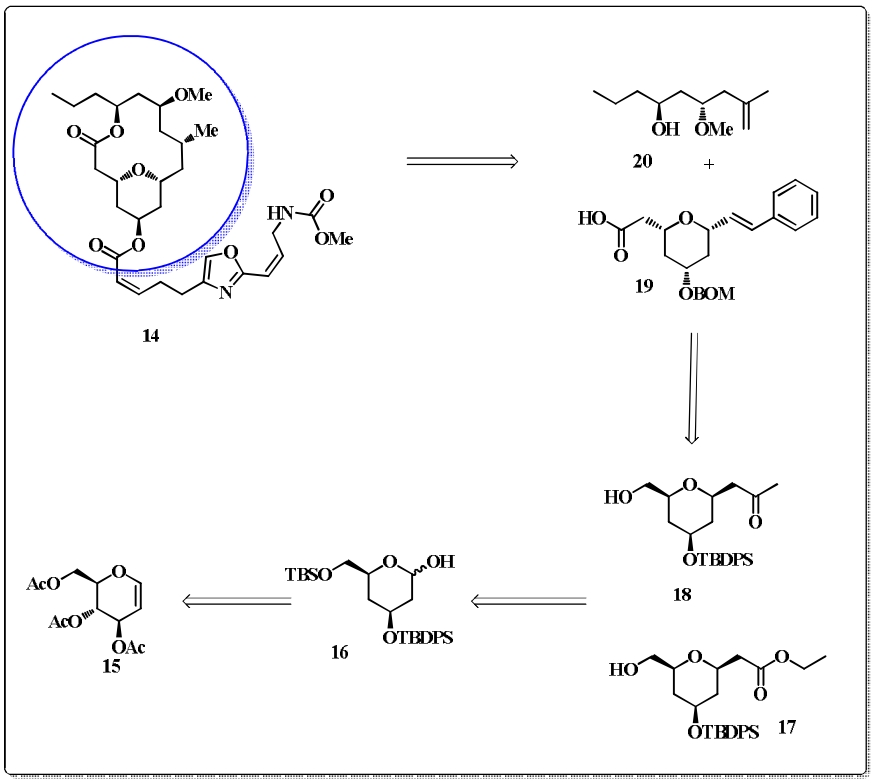
(+) Neopeltolide (14)

The structure of Neopeltolide resembles with that of Leucascandrolide A, another marine macrolide natural product isolated from a calcareous sponge collected along the east coast of New Caledonia. Wright reported that Neopeltolide showed potent antiproliferative activity against several human cancer cell lines at nanomolar concentrations. The Kozmin group has reported that Neopeltolide specifically inhibits the complex III of the mitochondrial electron transport chain. Fuwa et al. have recently described the apoptosis-inducing activity of a synthetic analogue of Neopeltolide in HL-60 human promyelocytic leukemia cells. However, the mode-of-action of this natural product have not been fully elucidated. The intriguing structure and potent biological activities of Neopeltolide have attracted considerable attention from the synthetic community, and twenty total and formal syntheses of this natural product have been reported so far Furthermore, several groups have reported the structure-activity relationships of Neopeltolide by evaluating the antiproliferative

activity of synthetic analogues against cancer cells. These efforts have culminated in the elucidation of the pharmacophoric structural elements for potent antiproliferative activity.

Retro synthetic analysis:

The retrosynthetic analysis of Neopeltolide (**14**) is depicted in (Scheme **5**). The synthesis

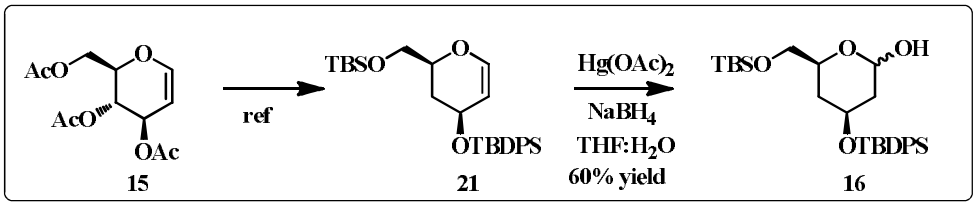


(Scheme 5)

was envisioned from coupling of fragments (**20**) and (**19**), Fragment(**20**) and (**19**) are obtained from the tetrahydropyran ketone (**18**) and tetrahydropyran Ester (**17**) respectively, which in turn are obtained from Lactol (**16**) .The Lactol (**16**) moiety was successively achieved from the Tri-O-Acetyl-D-Glucal (**15**).

Results and Discussion:

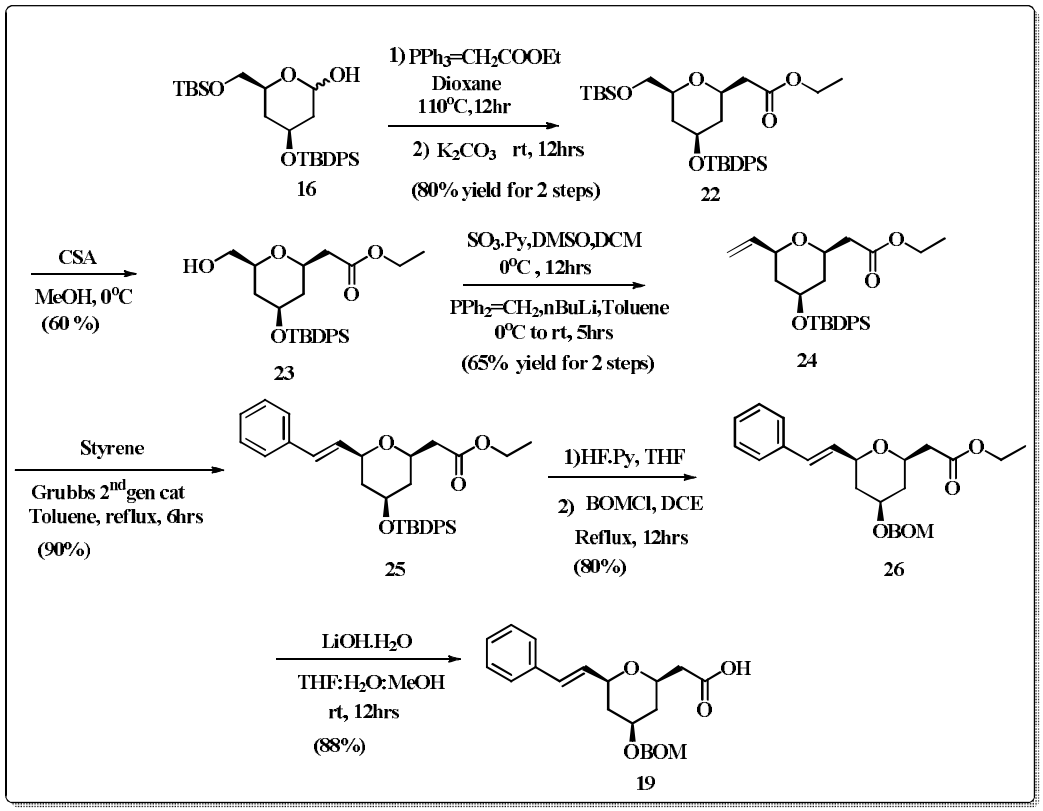
The synthesis commenced from Tri-O-acetyl-D-Glucal (**15**) following the reported procedure resulting the compound(AIBN) (**21**). AIBN(**21**) compound underwent oxymercuration with Mercury acetate and sodiumborohydride in THF:Water in 9:1 ratio from 0°C to rt to achieve compound**(16).**



(Scheme 6)

Synthesis of acid fragment:

The synthesis of acid fragment began with the lactol (**16**) fragment.The lactol fragment underwent one pot Intramolecular two carbon wittig homologation in dioxane under reflux at 110°C for 12 hours and *insitu* OxaMichael addition in the presence of K_2CO_3.



(Scheme 7)

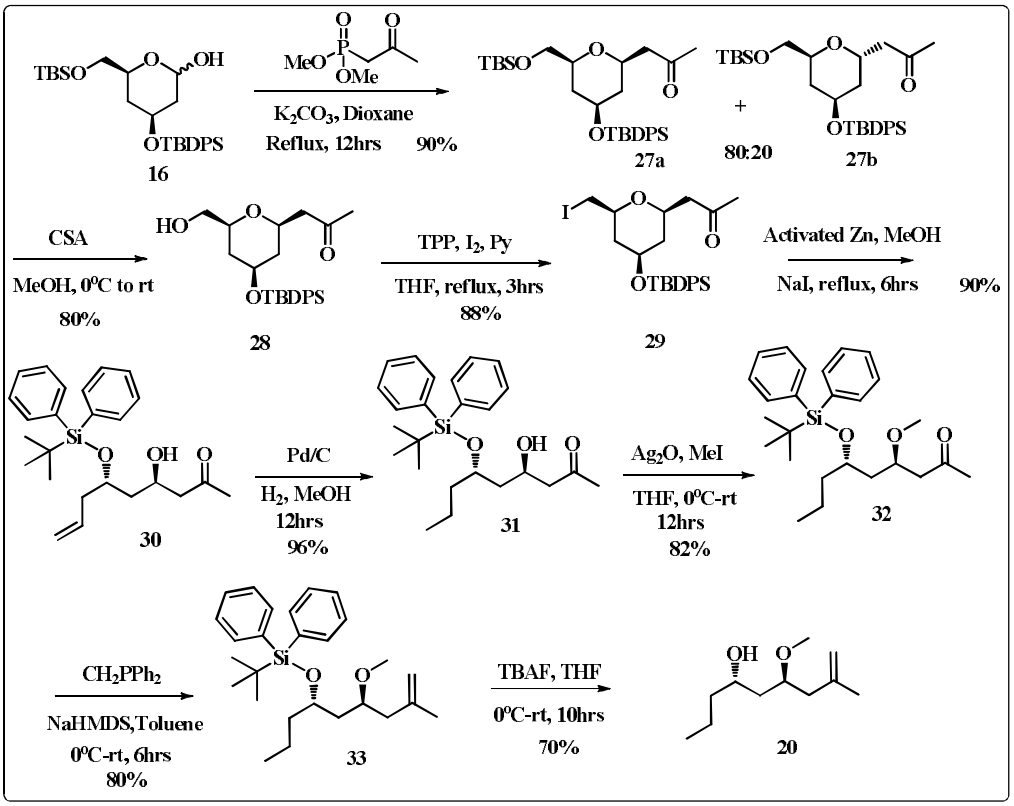
base furnished the ester compound (**22**) with 80% yield..Further the ester compound (**22**) is treated with CSA, MeOH at 0°C for 15min resulting the TBS deprotected alcohol(**23**). Absence of signals corresponding to *tert*-butyl and dimethyl groups in its ^{1}H NMR spectrum confirmed the transformation. The StereoChemistry of the THP compound was confirmed with NOE. Further the alcohol (**23**)was subjected to Parikh-

Doering oxidation at 0°C to the corresponding aldehyde which *insitu* was treated with $PPh_3=CH_2$ and n-BuLi in presence of Toluene to give the C-1Wittig Compound(**24).** This Wittig compound is subjected to olefin Metathesis with Styrene using Grubbs 2nd Generaration Catalyst which furnished the product **(25).** The Olefin compound was subjected to TBDPS deprotection using HF.Py in dry THF which was next subjected to BOMCl and DCE under reflux for 12hours resulting the BOM protected compound(**26**). With this compound in hand we subjected this compound to LiOH.monohydrate in THF:H_2O:MeOH in the ratio of (4:2:2) as solvent for 12hours furnished the ACID Fragment (**19**).

The product was confirmed by ESI-HRMS and it was further supported by comparing the data from the reported literature and all the ^1H, ^{13}C, specific rotation values were in full agreement with the literature.

Synthesis of Alcohol Fragment :

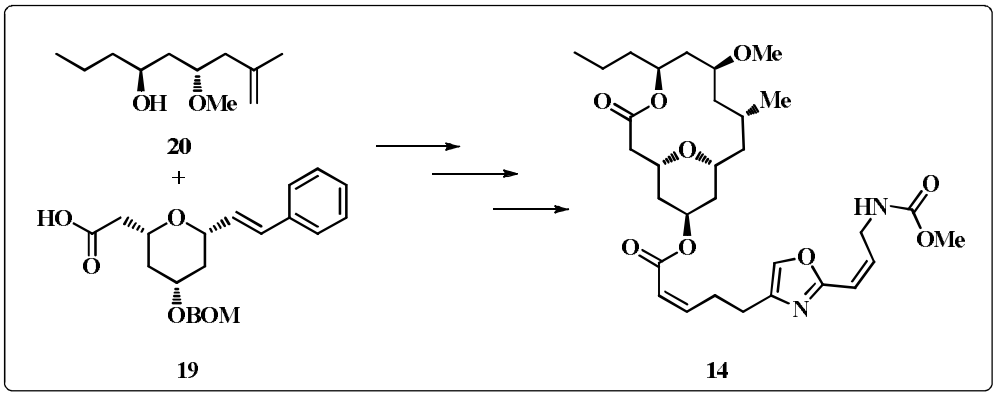
The synthesis of alcohol compound (**20**) was initiated with the conversion of lactol (**16**) compound to ketone (**27**) compound through one pot Two carbon Wittig olefination with dimethyl (2-oxopropyl)phosphonate with K_2CO_3 as base with dioxane as solvent



(Scheme 8)

under reflux conditions for 12hours. The keto compound was subjected to CSA,MeOH at 0°C for 15min resulting the TBS deprotected alcohol(**28**). The stereochemistry of the THP was confirmed with NOE. The Alcohol compound was subjected to iodination with TPP, I_2, Pyridine in THF as reflux for 12hours afforded the iodo compound (**29**) with 80% yield.This Iodo compound was *in situ* subjected to activated Zn, MeOH, NaI under reflux conditions for 12hours resulted the olefin compound(**30**).The olefin(**30**) compound was saturated with Palladium on charcoal with dry MeOH as solvent for 12hours resulted the saturated compound(**31**). The saturated compound(**31**) was O-methylated with Silver Oxide and MeI furnishing the compound **(32).** Next the compound was subjected to one carbon Wittig olefination with $PPh_2=CH_2$ with NaHMDS as base in Toluene as solvent at rt for 5 hours furnished the compound(**33**). The obtained olefin (**33**) compound was treated with TBAF in dry THF to obtain the alcohol.(**20**). The ^1H, ^{13}C, specific rotation values were in full agreement with the Literature.

The fragments **19** and **20** following the reported procedure results the target, the core synthesis of Neopeltolide.



(Scheme 9)

Conclusion

In summary, we described a convergent stereoselective formal synthesis of (+)-Neopeltolide *via* Glycal approach. Our route requires total 16 steps from Glucal. Oxymercuration, one pot Wittig and oxa Michael addition, Parikh-Doering oxidation, and Grubbs Cross metathesis are the key reactions involved.