SYNOPSIS

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The thesis entitled "**Towards the Total Syntheses of Biologically Active Natural Products: FR252921, Amaminol B, (−)-Lardolure and (2*R*,4*R*,6*R*,8*R*)-2,4,6,8-Tetramethylundecanoic Acid"** has been divided into three chapters.

- **Chapter I:** This chapter is further subdivided into two sections.
  - **Section A:** This section deals with introduction of immunosuppressant and important previous approaches to immunosuppressant FR252921.
  - **Section B:** This section describes the formal total synthesis of immunosuppressant FR252921.
- **Chapter II:** This chapter is further subdivided into two sections.
  - **Section A**: This section brings flavor of some introduction of IMDA cycloaddition and its application for earlier synthetic approaches of different bicyclo[4.3.0]nonane derivatives.
  - **Section B**: This section projects the studies towards the synthesis of Amaminol B.
- **Chapter III:** This chapter is further subdivided into two sections.
  - **Section A**: This section deals with the iterative strategies for the synthesis of different deoxypropionates.
  - **Section B**: This section describes the total synthesis of (−)-Lardolure and (2*R*,4*R*,6*R*,8*R*)-2,4,6,8-Tetramethylundecanoic Acid using enzymatic desymmetrization technique.

CHAPTER-I

Section A: Introduction

The immune system is a marvel of nature. It functions through an exotic information network which is constantly engaged in imperceptible war against foreign invaders like bacteria, viruses, fungi and parasites and is not controlled by any central organ. Immunosuppressants, used to prevent rejection of transplanted organs in surgery, have played an important role in our understanding of the immune system.

The success of organ transplantation surgery is based on the miracle drugs, such as Cyclosporine A, FK-506, Rapamycin, 506BD etc. which triggered important developments in transplantation, autoimmunity, and basic immunology. Outstanding progress of experimental immunology in gaining more insight into the mechanisms controlling an immune response, but learning how to by pass an undesirable immune reaction, it still appears that clinical immunosuppression will continue to rely for quite some years on a chemotherapeutic strategy using a subtle combination of more selective as well as better tolerated immunopharmachologically effective drugs.

Section B: Formal total synthesis of immunosuppressant FR252921:

A novel immunosuppressive agent, FR252921 was isolated from the cultured broth of a species of *Pseudomonas fluorescens* No. 408813. It has been seen that FR252921 inhibited splenic proliferation stimulated with LPS, insensitive to calcinuerin inhibitor. Analysis of transcription activity revealed that FR252921 inhibited activating protein-1 (AP-1). Exposures of antigen presenting cells (APC) to FR252921 attenuated proliferation supplemented by naïve T cells. Furthermore, FR252921 strongly suppressed splenic dendritic cell proliferation stimulated with LPS and anti-CD40 mAb, while it did not inhibit purified T cell activation, including CD154 expression and IL-2 production. These results suggest that APC is dominant target cell population. The pronounced biological activities and challenging structural features of FR252921 attracted the attention of organic chemists. As part of our studies on synthesis of natural products with biologically interesting activities, we undertook the synthesis of FR252921 (Figure 1).

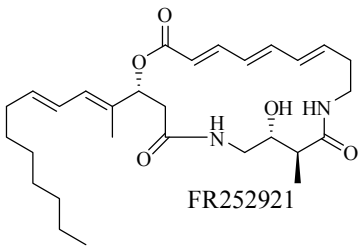
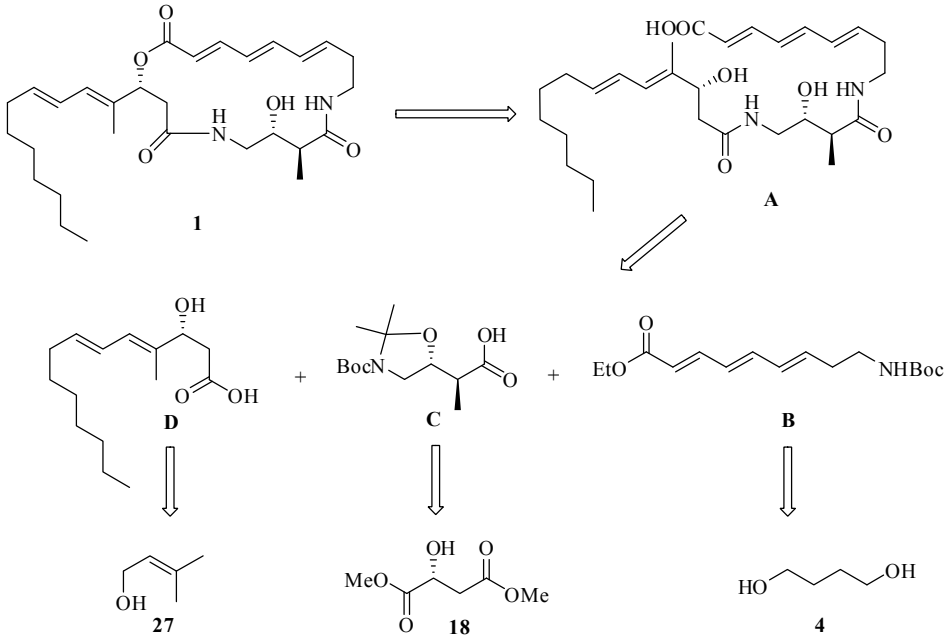


Figure 1.

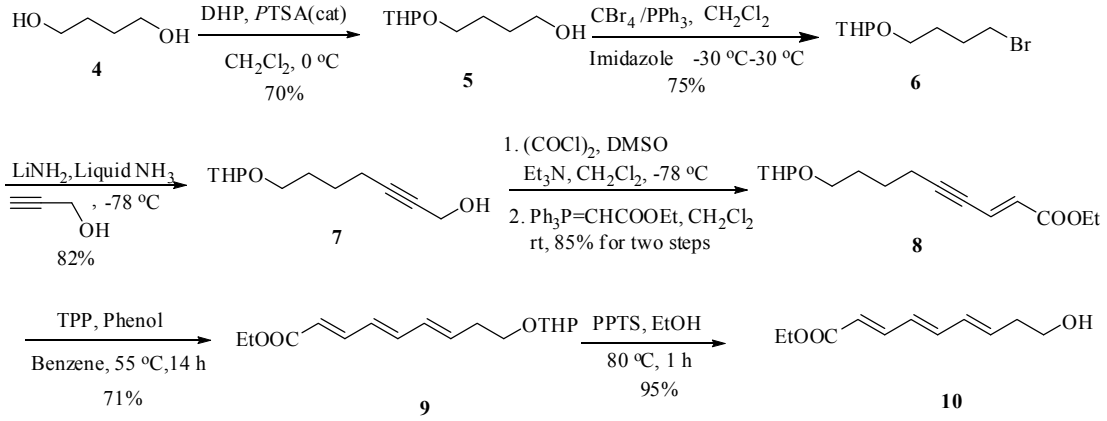
Retrosynthetic analysis of FR252921:

Our retrosynthetic analysis suggests that FR252921 **1**, possessing a 19- membered ring structure, would be obtained by macrolactonization of the seco-acid **A**, which is divided into three key fragments **B-D**. The first amide bond would be formed by the combination of trienic ester fragment **B** and carboxylic acid fragment **C**, and another peptide coupling between amine part of resulting peptide and another acid fragment **D** would install the second amide bond. The first key fragment **B** of our synthetic strategy was prepared from 1,4-butane diol, while the other fragment **C** was obtained from (*R*)-malic acid and the last fragment **D** was synthesized from commercially available prenol, depicted in (Scheme 1).



Scheme 1.

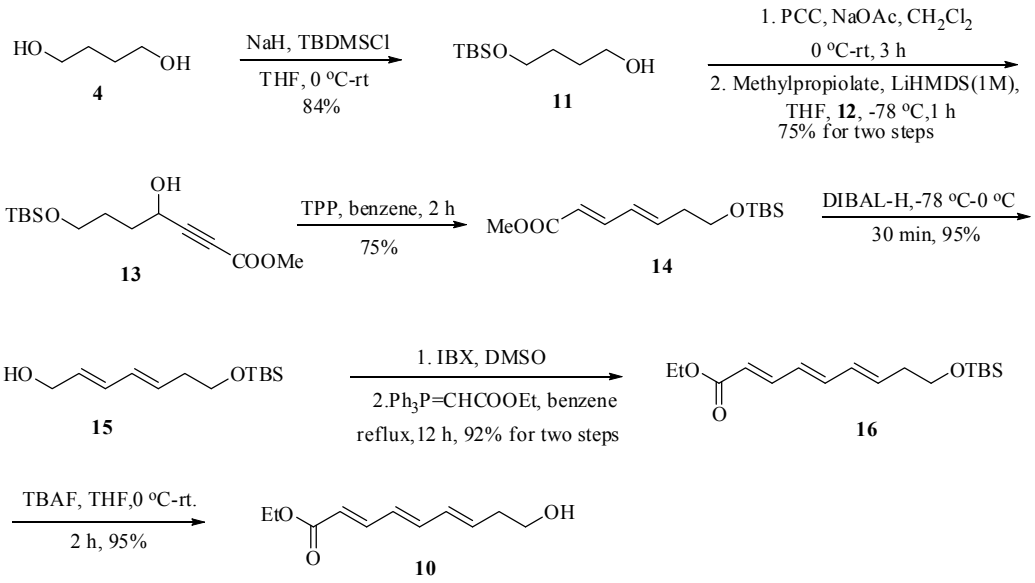
As described for the synthesis of trienic ester fragment **B**, we started from commercially available 1,4-butane diol **4**. Accordingly 1,4-butane diol was mono protected as its THP-ether using 3,4-dihydropyran with a catalytic amount of *p*-TSA in anhydrous CH_2Cl_2 to get **5** with 70% yield. The free hydroxyl functionality of **5** was brominated with CBr_4-TPP in anhydrous CH_2Cl_2 to afford **6** in 75% yield . Compound **6** was coupled with propargyl alcohol using $LiNH_2$ in liquid ammonia to yield the acetylenic alcohol **7** (82% yield), which was consecutively subjected to Swern oxidation and C-2 Wittig reaction to yield enyne-ester **8** (85% yield over two steps) with (*E*:*Z* >95:5) selectivity (judged by ^1H and ^{13}C NMR of crude mixture) which was easily separated by column chromatography. Isomerisation of enyne ester **8** to (*E*,*E*,*E*) triene ester **9** (exclusively by ^1H and ^{13}CNMR spectroscopy) was achieved in presence of TPP and phenol as an effective co-catalyst at 55 ^oC. After complete deprotection of the THP-ether of triene ester **9** by PPTS in ethanol, we got **10** with 95% yield depicted in (scheme 2).



Scheme 2.

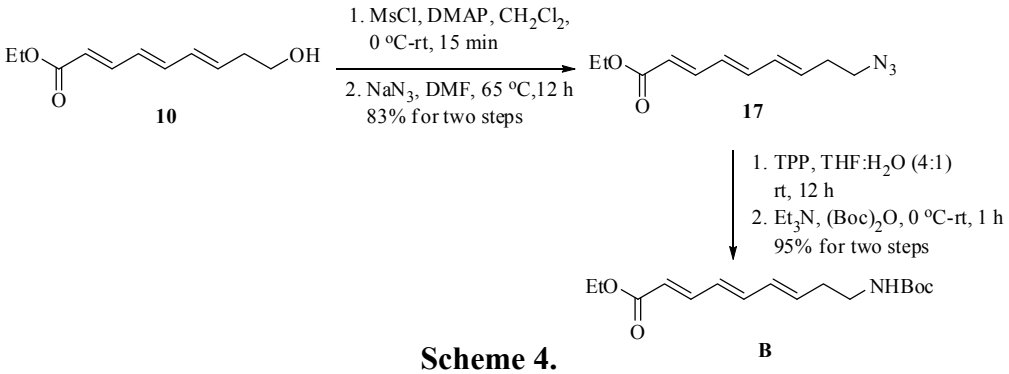
But the overall yield was not satisfactory enough to get good yield of the macrocycle product so we decided to go for another route from which we got satisfactory yield. We started from same starting material 1,4-butane diol, monoprotected as *tert*-butyl di-methyl silyl ether **11** (84% yield). Subsequent oxidation of the alcohol to the corresponding aldehyde **12** and methyl propiolate addition afforded the alkynoate **13** (75% over two steps). The "allene-type" rearrangement of **13** with TPP gave the diene **14** in 75% yield. Diene ester **14** was then underwent DIBAL-H reduction to get alcohol **15** in 95% yield. Consecutive IBX oxidation and C-2 Wittig reaction of alcohol **15** gave us

triene ester **16** with excellent (*E*:*E*:*E*) selectivity (as judged by ^{1}H and ^{13}C NMR spectroscopy) and excellent yield (92% over two steps). After deprotection of silyl group by TBAF we got **10** with better overall yield for same number of steps, as depicted in (scheme 3).



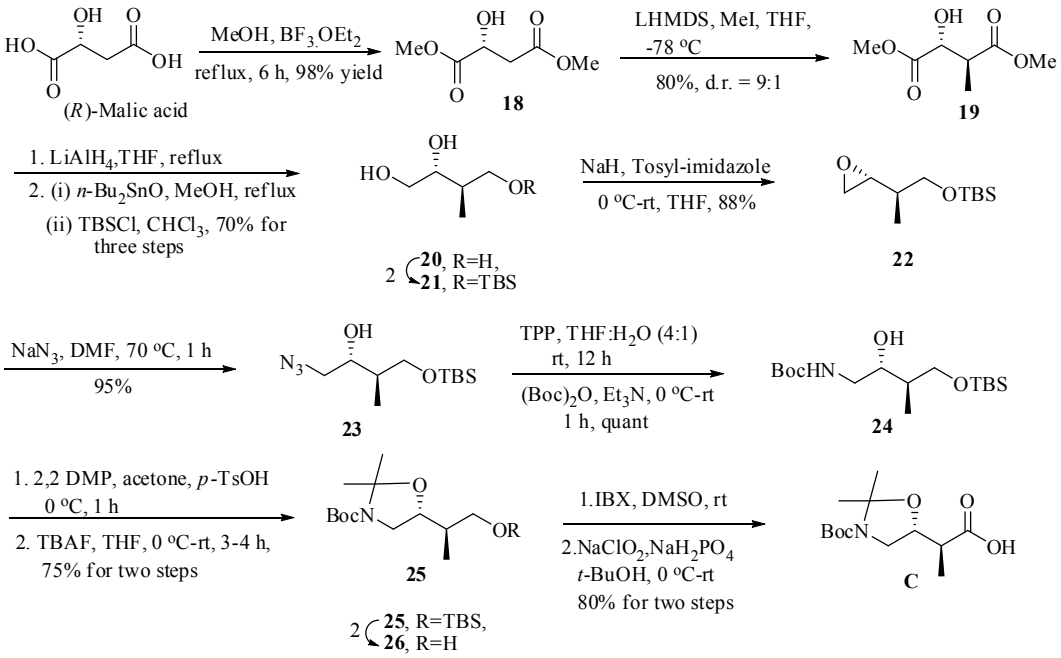
Scheme 3.

Now we proceeded for the synthesis of the fragment **B** with trienic ester **10**. Firstly, ester **10** was mesylated with triethylamine, mesyl chloride and catalytic amount of DMAP in CH_2Cl_2 and used without any further purification for azide formation by sodim azide in DMF at 55 ^{o}C to get azide **17** (83% yield for two steps). Staudinger reaction of azide delivered crude amine which was Boc protected to furnish the title fragment **B** in 95% yield for two steps and 30% overall yield (Scheme 4).



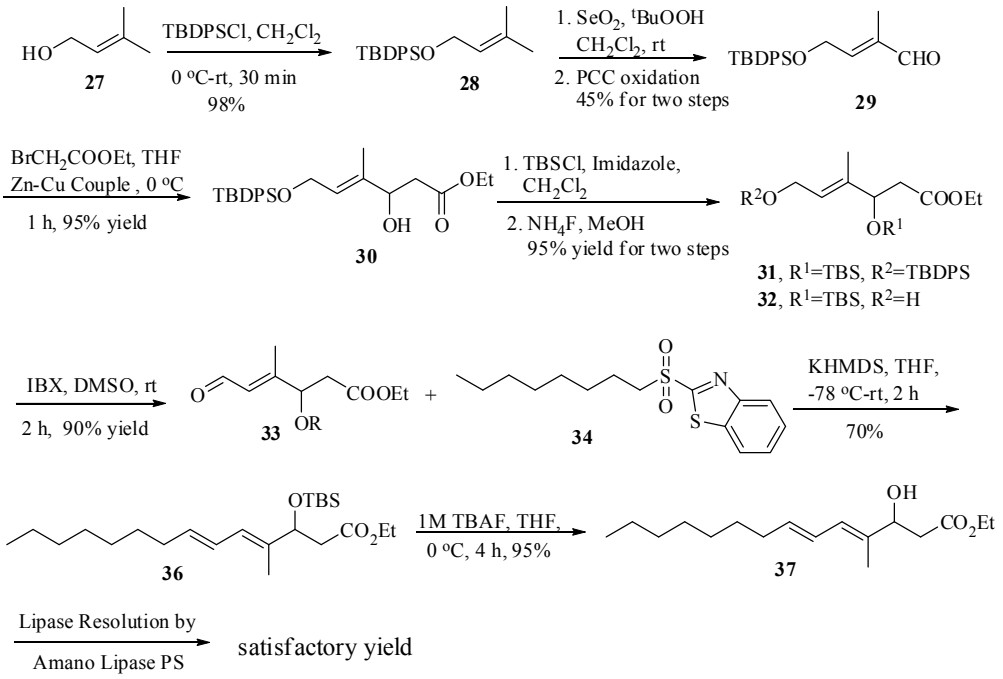
Scheme 4.

The carboxylic acid fragment **C** was derived from commercially available (*R*)-malic Acid. Following the procedure reported by Seebach, dimethyl malonate **18** (prepared from malic acid in MeOH and using catalytic amount of $BF_3.OEt_2$, under refluxing) was alkylated with MeI and LHMDS in THF to give alcohol **19** (80% yield) along with its *syn* diastereomer (diastereoselectivity = 9:1). Reduction of **19** using $LiAlH_4$ under reflux, provided the triol **20** in excellent yield. The triol **20** was selectively protected to give TBS-ether **21** via a dibutyltin ketal intermediate in 70% yield for three steps .The resulting diol **21** was converted to epoxide **22** with NaH and tosyl-imidazole, in 88% yield. Regioselective opening of epoxide **22** with NaN_3 in DMF at 70 ^oC for 1 h gave azido alcohol **23** in 95% yield. Azido alcohol **23** was sunjected to Staudinger reaction and Boc protection consecutively to yield Boc protected amine **24** quantitatively, which was completely separable from its minor *syn* diastereomer. Subsequent *N-O*, acetonide protection and TBS deprotection of **24** gave **25** and primary alcohol **26** respectively in 75% yield over two steps. Our targeted acid fragment **C** was obtained from alcohol **26** by consecutively IBX oxidation of alcohol to corresponding aldehyde and transformation of aldehyde to acid by $NaClO_2$, NaH_2PO_4, in 80% for two steps. (Scheme 5).



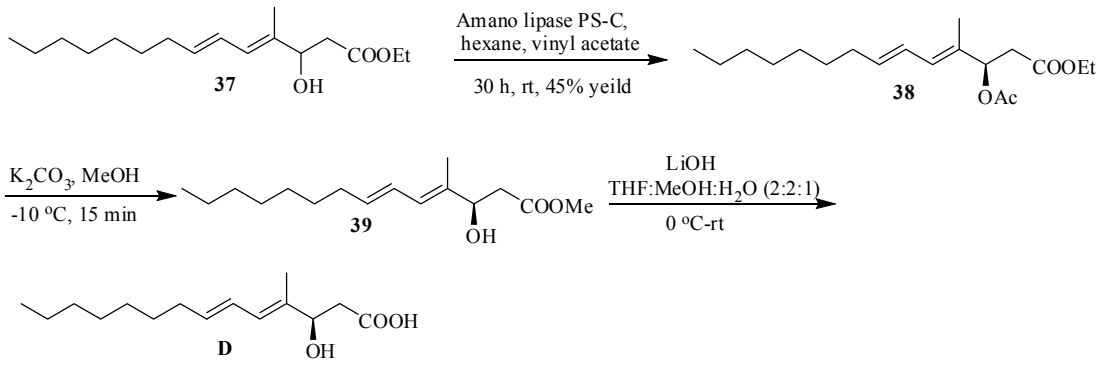
Scheme 5.

With fragment **B** and **C** in our hand we tried to obtain *β*-hydroxy acid fragment **D** which was synthesized from a cheap starting material prenol **27**. Firstly, The hydroxyl group of prenol **27** was protected as its *tert*-butyldiphenylsilyl ether **28**. Allylic oxidation of **28** was done with SeO_2 and *tert*-BuOOH to deliver allylic aldehyde and alcohol (3:2) mixture which was completely converted to aldehyde **29** by PCC oxidation in 45% yield for two steps. Aldehyde **29** was converted to *β*-hydroxy ester **30** by Zn-Cu Couple with $BrCH_2CO_2Et$ in THF with 95% yield. Protection of secondary hydroxyl group of **30** with TBS ether gave **31** and selective deprotection of primary TBDPS group with NH_4F yielded primary alcohol **32** in 95% yield for two steps. Compound **33** was obtained from IBX oxidation of primary alcohol **32** which was directly used for Julia olefination with C-8 sulfone **34** to construct conjugated trisubstituted diene **36** with 70% yield. Deprotection of secondary silyl ether **36** by TBAF furnished racemic **37** in 95% yield. The resolution of racemic **37** was attempted in three different ways. Carrot reduction of the keto (which was obtained from IBX oxidation of **37**) gave negative result .Then Sharpless asymmetric resolution of secondary alcohol also gave very poor yield, later lipase resolution of secondary alcohol resulted into good yield (Scheme 6).



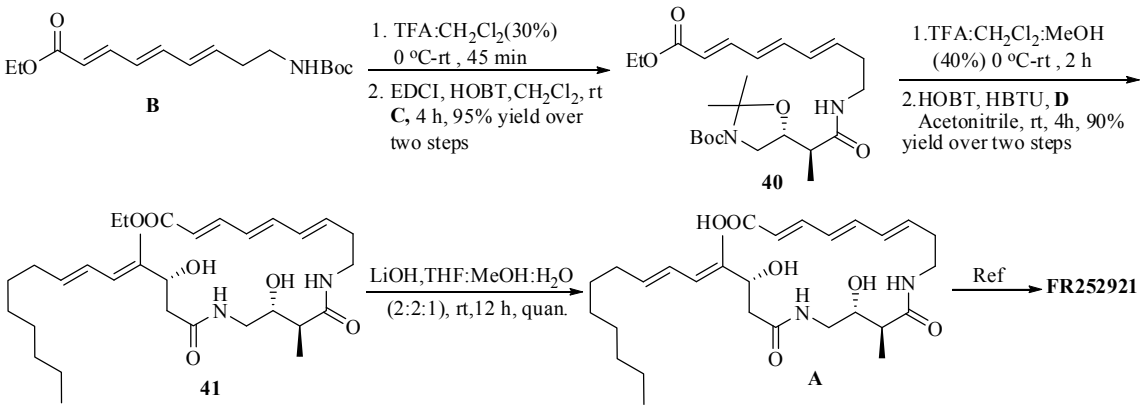
Scheme 6.

Among several lipases and solvent system screened for this resolution, Amano lipase PS-C and hexane solvent in presence of vinyl acetate gave satisfactory yield (45%) and enantiomeric excess (92%, determined by chiral HPLC). The enantio-enriched acetate **38** was the desired (*R*)-configured confirmed after careful acetyl deprotection and transesterification of **38** in K_2CO_3/MeOH at −10 ^oC, to get *β*-hydroxy methylester (*R*)-**39** whose optical rotation and spectral data were in full agreement with those previously reported by Jannine Cossy *et al*. The final *β*- hydroxyl acid fragment **D** was derived from ester hydrolysis with LiOH in THF:MeOH:H_2O (2:2:1) and used for next step without any further purification which is depicted in (Scheme 7).



Scheme 7.

Now the stage is well set for the coupling of three fragments **B**, **C**, **D**, and we start with trienic ester fragment **B** and carboxylic acid fragment **C**. After complete deprotection of Boc group in presence of TFA in CH_2Cl_2 (30%) the free amine of trienic ester fragment **B** was coupled with carboxylic acid fragment **C** using EDCI, HOBt in CH_2Cl_2 to give peptide **40** in 95% yield over two steps. Boc and acetonide group of compound **40** was then deprotected by TFA in MeOH:CH_2Cl_2 (40%) at room temperature produces free hydroxy amine. Without any further purifiacation it was coupled with *β*-hydroxy acid fragment **D** in presence of HBTU, HOBt in acetonitrile to obtain bis-amide **41** in 90% yield over two steps. Hydrolysis of bis-amide **41** produces seco acid **A** in quantitative yield. Among the several methods, only MNBA proved to be little effective to produce title compound **1**, but we were unable to purify it .We are looking for alternate routes (eg. macrolactamisation) to sort out the problem in our lab (Scheme 8).



Scheme 8.

In conclusion we have designed a macrocyclisation path to construct the natural product FR252921. The methodology described here is applicable for the synthesis of other series of molecules of this family, as well as other cyclic depsipeptides. Although, we got very poor result for the crucial macrolactonisation reaction, after trying several methods, as mentioned earlier, attributed to an inherent structural feature of the cyclisation intermediate, which possibly could not attain the required conformation for ester bond formation due to the presence of consecutive double bonds.

CHAPTER-II

Section A: Introduction of IMDA Cycloaddition and its application for earlier synthetic approaches of different bicyclo[4.3.0]nonane derivatives.

IMDA cycloaddition is undoubtedly the most universal approach to prepare bicyclo[4.3.0]nonane containing natural compounds. The preparation methods of bicyclo[4.3.0]nonane structures can be divided roughly into thermal IMDA, Lewis acid promoted IMDA, chiral auxiliary induced IMDA and other cycloadditions. Diels-Alder reaction is assumed to follow a concerted mechanism. IMDA reactions may be divided into two categories based on the point of connection of the diene to the dienophile. In the type I reactions, the connecting chain is in the terminus of the diene. The IMDA of *E*-dienes may produce *trans*- and *cis*-fused cycloadducts. If the chain connecting the diene

and dienophile is short (less than four carbons), a bridged product is not possible. *Z*-Dienes with three or four atoms in the connecting chain produce only *cis*-fused products. Type II IMDA includes a tethered dienophile connected to one of the internal diene positions. Type II reaction may produce both *syn*- or *anti*-products. It is not surprising that several methods for preparing bicyclo[4.3.0]nonane derivatives have been developed. This is thanks to the wide variety of interesting compounds, which include the bicyclo[4.3.0]nonane substructure or can be derived from a bicyclo[4.3.0]nonane derivative.

Section B: **Studies towards the synthesis of Amaminol B.**

Amaminols are cytotoxic against P388 murine leukemia cells isolated in 1999 from an unidentified tunicate of the family *Polyclinidae*, with an IC_{50} value of 2.1 μg/mL. Their mode of action is unknown, but they are structurally closely related to aliphatic cytotoxic aminoalcohols such as sphingosines, xestoaminols, halaminols, leucettamols, crucigasterins, and obscuraminols. Amaminol A (**44**) and B (**45**) contains an interesting *trans*-fused hexahydroindene substructure (Figure 2), which has most likely been formed by an intramolecular Diels-Alder reaction from a triene in nature.

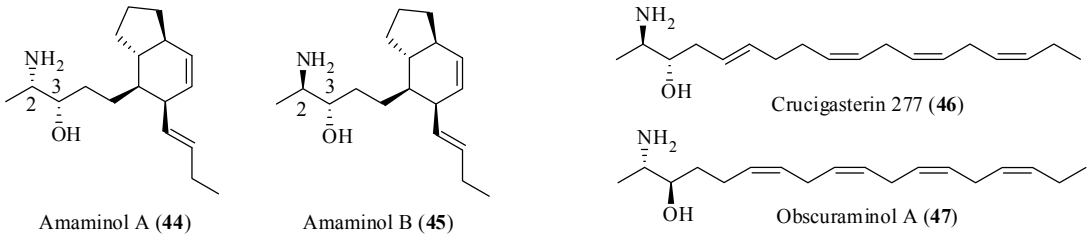
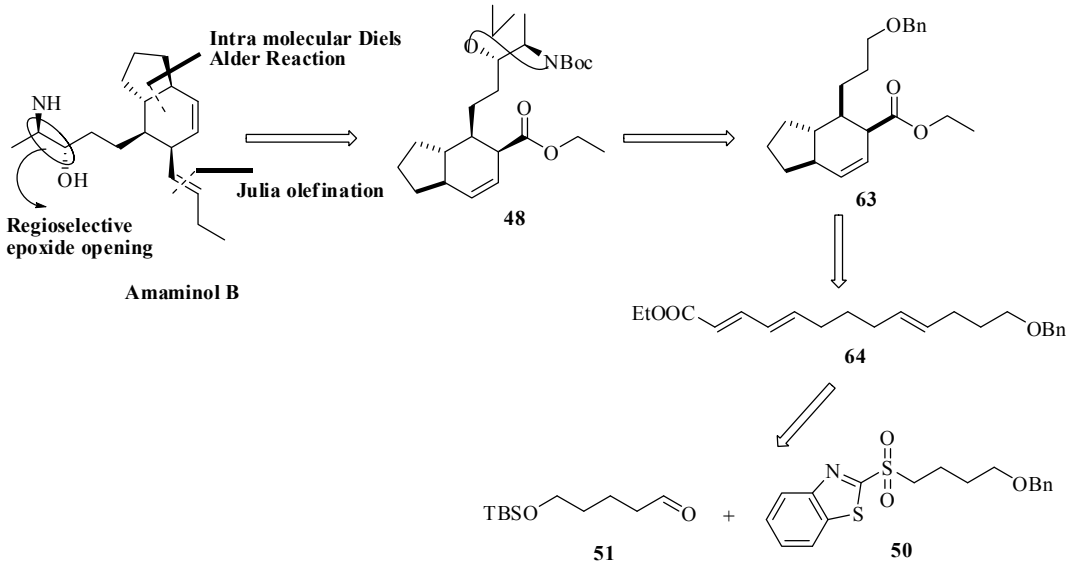


Figure 2.

Retrosynthetic analysis of Amaminol B

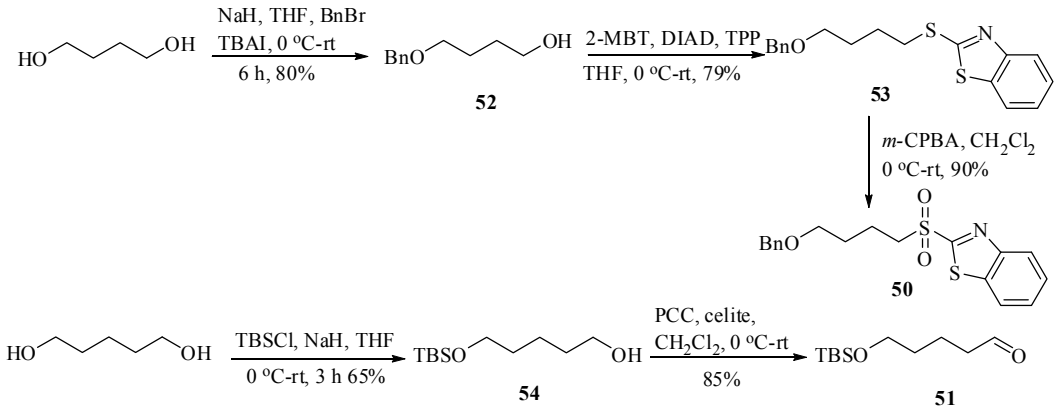
Retrosynthetic analysis reveals a route based on three consecutive olefinations by Julia-Kocienski olefination and Horner-Wadsworth-Emmons olefination. The stereogenic center at C2 and C3 were envisaged to be formed through Sharpless asymmetric epoxidation and controlled regioselecitve opening of epoxide to form desired amino alcohol. The rest of the stereocenters of **48** were to be formed in an intramolecular Diels-Alder reaction of inverse electron demand of the intermediate ester **64** through **63**.

Obvious disconnections of **64** leads to benzyl protected sulfone **50,** and TBS protected aldehyde **51** (Scheme 9).



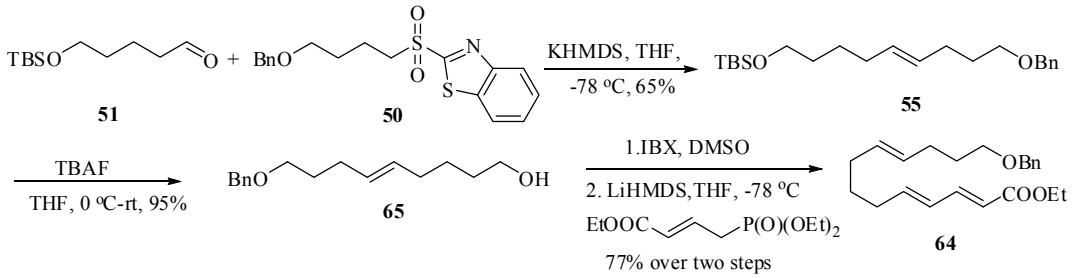
Scheme 9.

Sulfone **50** and aldehyde **51**, which were the main key materials for construction of intermediate ester **64**, synthesized from 1,4-butane diol and 1,5-pentane diol respectively. Monobezyl protection of 1,4-butane diol was done to obtain **52** and conversion of another hydroxyl of **52** to sulfide **53** was achieved in the next step under Mitsunobu conditions (marcaptobenzothoizole, TPP, DEAD, in dry THF). Sulfide **53** was oxidized by *m*CPBA in CH_2Cl_2 to afford sulfone **50** in 57% yield for three steps. 1,5-Pentane diol was first monoprotected as its *tert*-butyl dimethylsilyl (TBS) ether **54** and then another hydroxyl group was oxidized by PCC to obtain aldehyde **51** in 56% yield over two steps (Scheme 10).



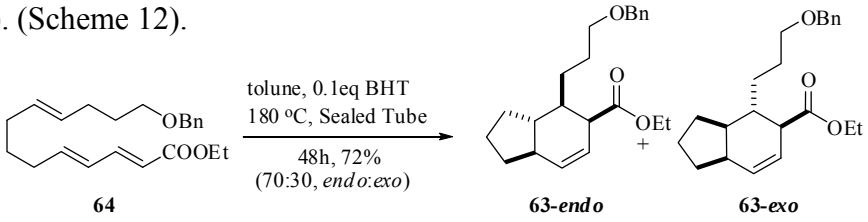
Scheme 10.

Now with sulfone **50** and aldehyde **51** in our hand, we went for Julia-Kocienski olefination. The sulfone **50** and aldehyde **51** were mixed and cooled at –78 ^{o}C in THF, and 0.5 M KHMDS was added to get the Julia-Kocienski olefination product **55** in 65% yield. Deprotection of TBS-ether of **55** was done by TBAF to obtain primary alcohol **65** in 95% yield. Oxidation of alcohol **65** with IBX yielded the corresponding aldehyde which in turn subsequently went through Horner-Wadsworth-Emmons olefination reaction with the known phosphonate in presence of 1 M LiHMDS to produce our desired trienic ester **64** in 77% yield over two steps (Scheme 11).



Scheme 11.

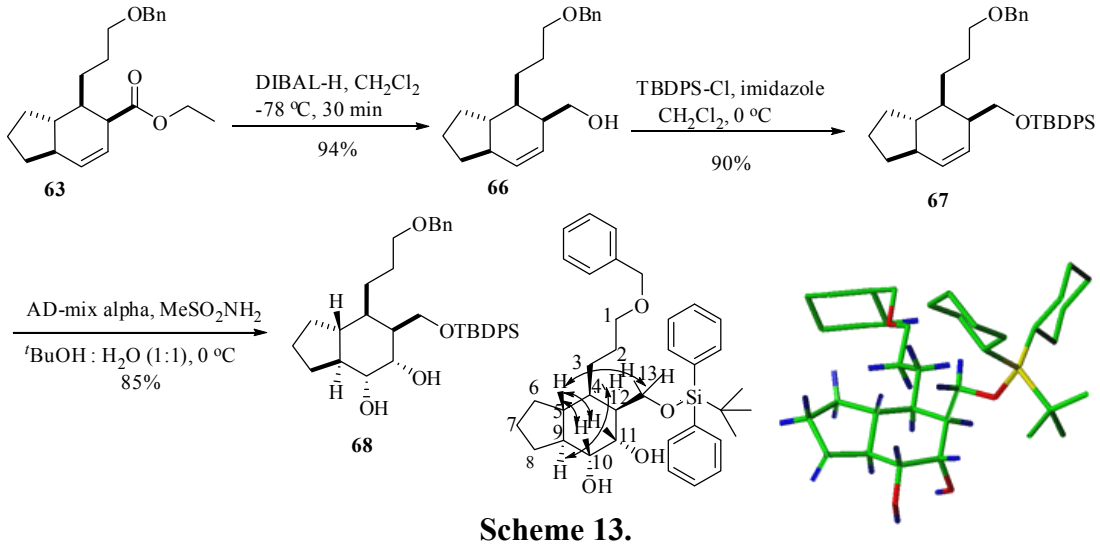
The trienic ester **64** on heating at 180 ^{o}C in toluene with catalytic amount of BHT for 2 days in a sealed tube underwent intramolecular Diels-Alder cyclization to afford **63,** the fused five and six membered ring of Amaminol skeleton in 72% yield with an *endo*/*exo* diastereomeric ratio of 70:30 (determined by wt.% and chromatographic separation). (Scheme 12).



Scheme 12.

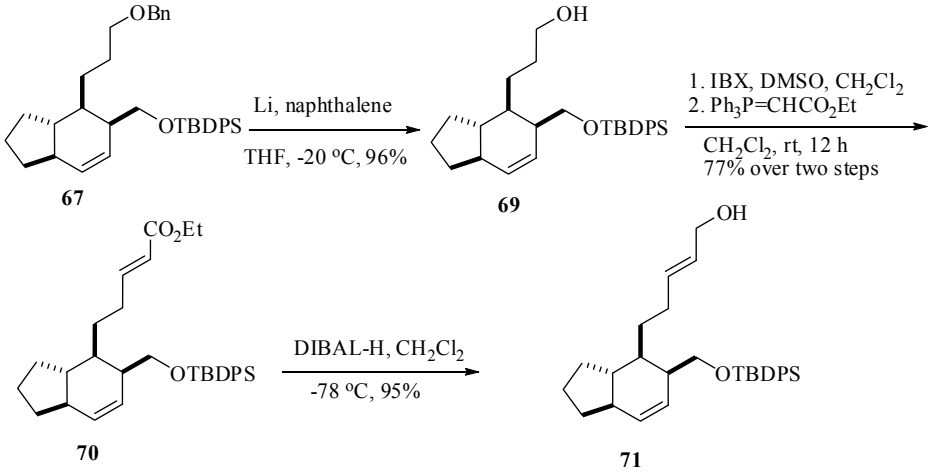
The required *endo*-Diels-Alder Compound **63** was in our hand and we decided first to construct the amino alcohol part. For this reason, ester **63** was reduced to alcohol **66** by DIBAL-H in 94% yield and then protected as *tert*-butyl diphenylsilyl (TBDPS) ether **67** in 90% yield. Compound **67** was treated with AD-mix alpha and methane sulphonamide in *tert*-butanol:H_2O (1:1) at 0 ^{o}C to afford the desired diol **68** in 85% yield and was used for NMR study to confirm the stereochemistry. The strong NOE

correlations between $C_5H/C_{11}H$, $C_5H/C_{10}H$, $C_5H/C_{13}H$, $C_5H/C_{13}H$, C_4H/C_9H, $C_2H/C_{12}H$ provides the clear cut evidence for the structure and the energy minimized structure as shown in (Scheme 13) was also agreement with assigned structure from the NMR data.



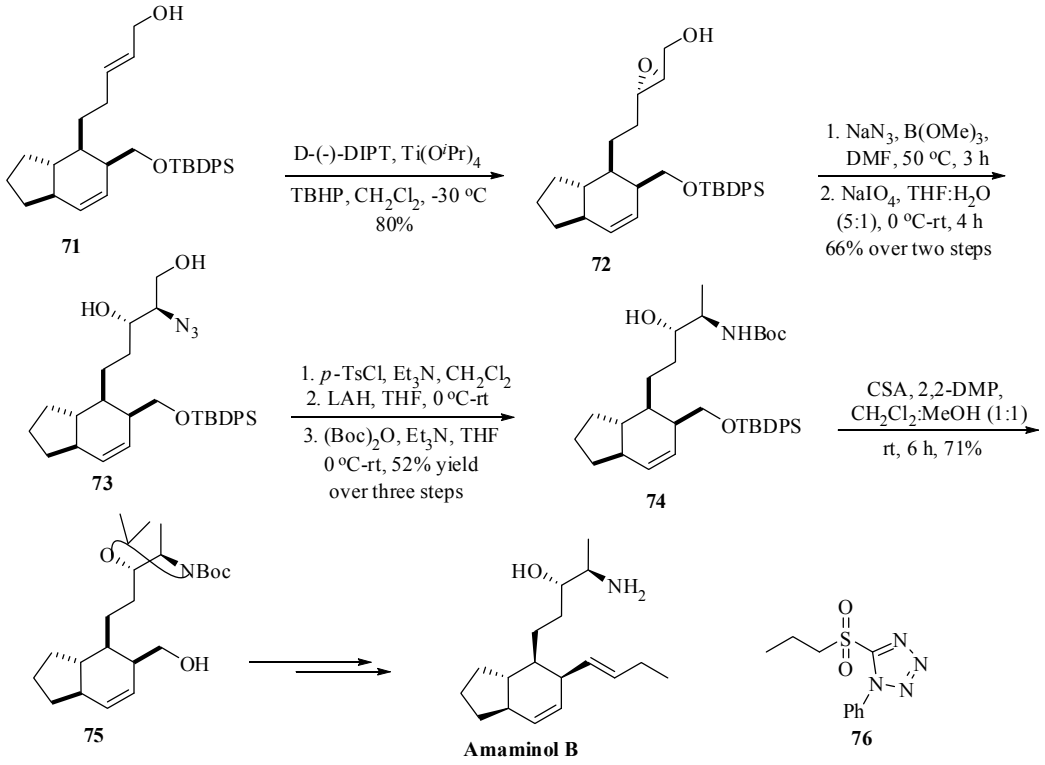
Scheme 13.

Benzyl deprotection of **67** by lithium/naphthalene at −20 °C in THF, yielded alcohol **69** in 96% yield, which was oxidized to aldehyde with IBX/DMSO and subsequently underwent C-2 Wittig reaction in CH_2Cl_2 to provide the *α,β*-unsaturated ester compound **70** in 77% yield over two steps. The chemoselective reduction of *α,β*-unsaturated ester **70** with DIBAL-H was achieved at −78 °C to afford the allyl alcohol **71** in 95% yield (Scheme 14).



Scheme 14.

Allylic alcohol **71** on Sharpless asymmetric epoxidation using D-(−)-DIPT, $Ti(O^iPr)_4$ and TBHP in CH_2Cl_2 yielded epoxy alcohol **72** in 80% yield. Regioselective epoxide opening of **72** with sodium azide and trimethyl borate at 50 ^oC afforded 1,3-diol **73** (minor 1,2-diol was separated by periodate oxidation) in 66% yield over two steps. Primary alcohol **73** was tosyl protected by *p*TsCl and Et_3N, in CH_2Cl_2 and without any further purification it was reduced by $LiAlH_4$ in THF to get amino alcohol, which was protected as its Boc derivative by $(Boc)_2O$, Et_3N, in THF to obtain desired Boc-amino alcohol **74** in 52% yield over three steps. *N*,*O*-acetonide protection and primary silyl group deprotection of compound **74** was achieved simultaneously by 2,2-DMP and catalytic amount of CSA (camphorsulfonic acid) in MeOH:CH_2Cl_2 (1:1) solvent system to afford primary alcohol **75** in 71% yield (Scheme 15).



Scheme15.

Finally, DMP (Dess Martin Periodinane) oxidation of alcohol **75** in CH_2Cl_2 at 0 ^oC afforded corresponding aldehyde which was found to be very unstable and immediately used for Julia olefination reaction with C-3 sulfone **76**. Unfortunately no product was isolated due to immediate decomposition of aldehyde. Different purification techniques

were used to solve this problem and it is an ongoing process in our lab to come with a fruitful result.

In conclusion, we have designed a new approach towards the total synthesis of Amaminol B by using Diels-Alder reaction with inverse electron demand as the key step. Other reactions involved are Julia olefination, HWE olefination, and regioselective ring opening reactions.

CHAPTER-III

Section A: Iterative strategies for the synthesis of different deoxypropionates.

Polypropionates (polyketides) are synthesized in nature by the polymerization of propionyl subunits via Claisen condensation reactions followed by reduction of the resulting keto-function. This results in a continuous methyl-hydroxy-methyl iteration with all possible stereoconfigurations, coming in cyclic as well as acyclic structures. However, nature sometimes deviates from the polypropionate pattern by formal removal of the hydroxyl group resulting in syn or anti 1,3,5,… *n*-polymethyl alkyl chains (Figure 3), the deoxypropionates. Deoxypropionates are the enzymatically dehydrated and reduced products of polypropionates and are widely distributed as individual and combined structures in natural products.

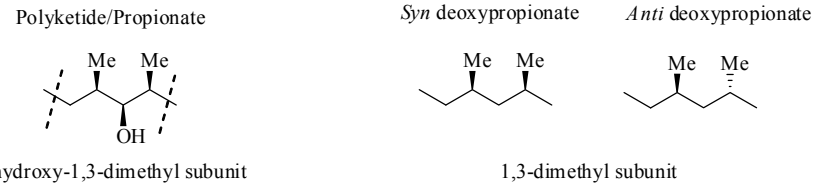


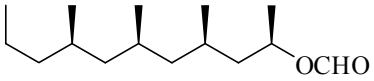
Figure 3: The polyketide/propionate structure compared to the related deoxypropionate structure.

Deoxypropionates are synthesized by bacteria, fungi, and plants. Because of the abundant presence of deoxypropionate units in natural products, many synthetic strategies have been developed over the last three decades. These strategies are often

based on the selective introduction of methyl substituents in an consecutive (iterative) fashion, either *syn* or *anti*, and can be divided in non-catalytic and catalytic strategies.

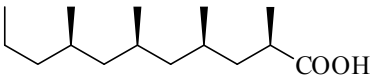
Section B: Total synthesis of (−)-Lardolure and (2*R*,4*R*,6*R*,8*R*)-2,4,6,8-Tetramethylundecanoic Acid using enzymatic desymmetrization technique.

Lardolure (**80**) is the aggregation pheromone of the acarid mite (*Lardoglyphis konoi*), while (2*R*,4*R*,6*R*,8*R*)-2,4,6,8-tetramethylundecanoic acid (**81**) is the acid component of the preen-gland wax of the graylag goose (*Anser anser*) (Figure 4).



(-)-Lardolure

80

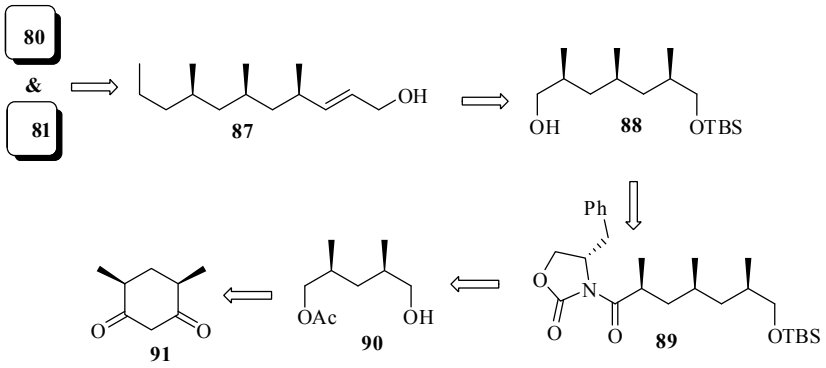


(2*R*,4*R*,6*R*,8*R*)-2,4,6,8-Tetramethylundecanoic Acid

81

Figure 4.

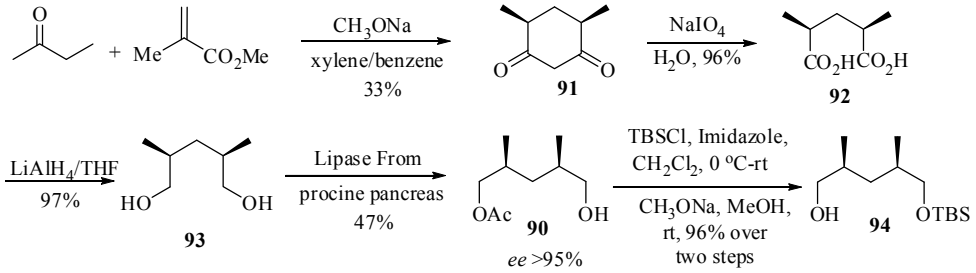
The retrosynthetic approach for the targeted molecules **80** and **81** can easily be envisioned from the common allylic alcohol intermediate **87** which has three chiral methyl groups. Furthermore, **87** could be obtained from primary alcohol **88**, which was synthesized from **90** via **89** by using Wittig reaction and Evan's alkylation reaction. Compound **90** on the other hand was prepared from *cis*-4,6-dimethyl cyclohexan-1,3-dione **91** in four steps (Scheme 16).



Scheme 16.

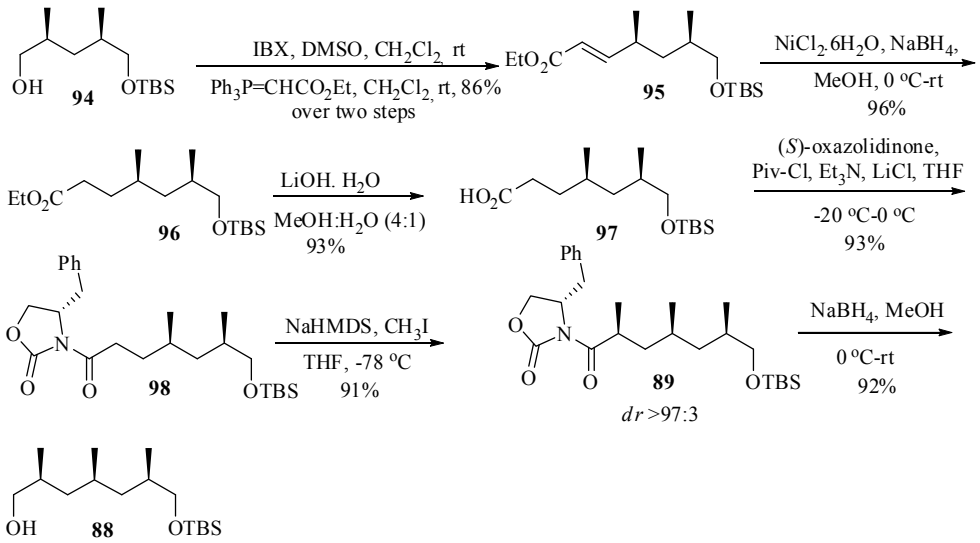
Our synthesis began with the known precursor **90** that has two chiral centres already in place. Compound **90** was synthesized in four steps starting from *cis*-4,6-dimethylcyclohexan-1,3-dione **91** following a well-reported protocol. Accordingly, *cis*-diketone was converted into the diacid **92** by periodate oxidation in 96% yield. $LiAlH_4$

reduction of the diacid **92** in THF at room temperature gave the *meso*-diol **93** in 97% yield. Desymmetrization of *meso*-diol by using porcine pancreatic lipase (PPL) and vinyl acetate in THF at ambient conditions furnished the mono acetate **90** in 47% yield and at least 95% *ee* along with the *meso*-diacetate. It is noteworthy to mention that the *meso*-diacetate obtained was again converted back to the *meso*-diol by treatment with CH_3ONa in methanol in quantitative yield for further utilizations. Mono acetate **90** in hand was protected as its silyl ether using TBSCl and imidazole in dichloromethane and then treated with CH_3ONa in methanol to furnish the desired terminal alcohol **94** with 96% for two steps (Scheme 17).



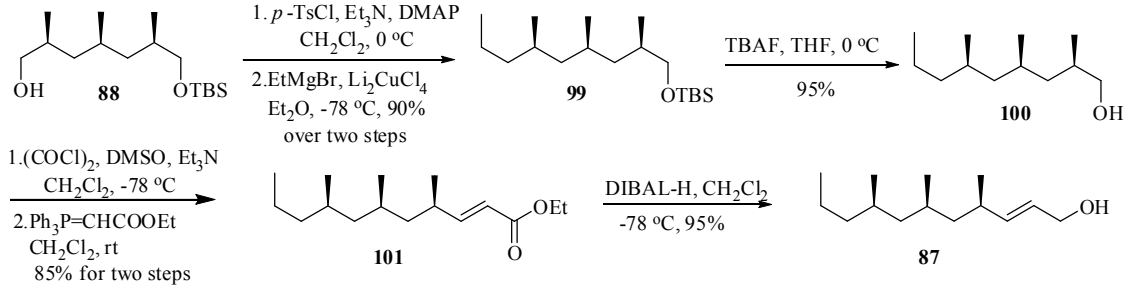
Scheme 17.

Subsequently, oxidation of alcohol **94** followed by two-carbon atoms extension by means of Wittig reaction gave the α,β-unsaturated ester **95** in 86% yield in overall two steps. Reduction of the double bond with $NaBH_4$ in the presence of $NiCl_2 \cdot 6H_2O$ in MeOH afforded the saturated ester **96** in 96% yield which was then hydrolyzed under basic conditions to furnish the corresponding carboxylic acid **97** in 93% yield. Coupling of acid **97** with the Evan's chiral oxazolidinone using pivaloyl chloride in presence of triethylamine and LiCl furnished the required compound **98** in 93% yield. Diastereoselective methylation of the Na-enolate of compound **98** with MeI furnished the desired compound **89** in 91% yield and in >97:3 diastereomeric exess, which was confirmed by ^1H NMR spectroscopy, and then subjected to reduction by $NaBH_4$ in MeOH to obtain the desired primary alcohol **88** having a new additional chiral centre in 92% yield. (Scheme 18).



Scheme 18.

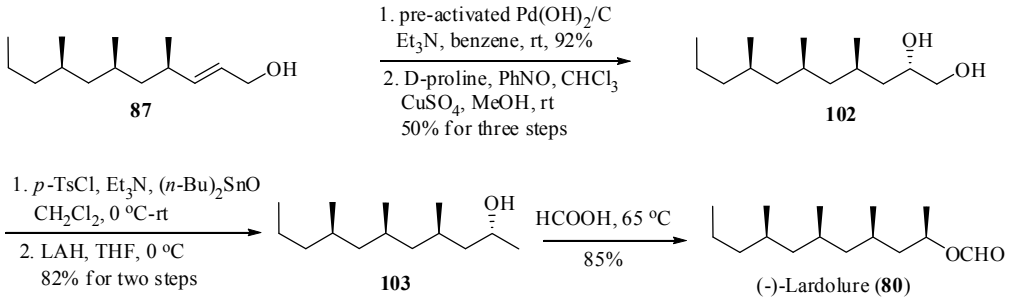
Alcohol **88** was then tosylated with Et_3N, *p*TsCl, DMAP at 0 °C and subsequently reacted with freshly prepared ethyl grignard to furnish compound **99**, in 90% yield for two steps. Deprotection of *tert*-butyl dimethylsilyl (TBS) ether of **99** was done by 1 M TBAF in THF at 0 °C to obtain long chain alcohol **100** in 95% yield, which was then oxidized by Swern condition and subsequently underwent Wittig reaction to yield α,β-unsaturated ester **101** in 85% yield for two steps. The α,β-unsaturated ester **101** was reduced by DIBAL-H at −78 °C to the corresponding common allylic alcohol intermediate **87** in 95% yield (Scheme 19).



Scheme 19.

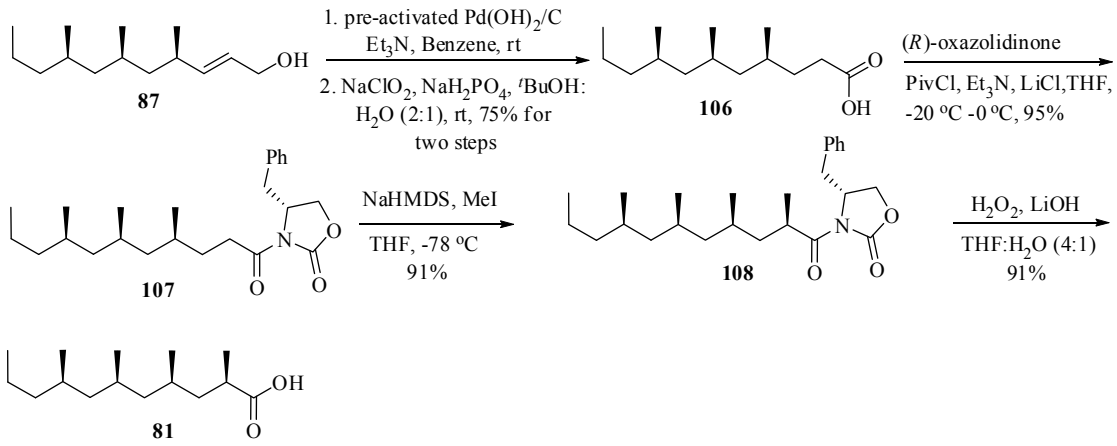
Common allylic alcohol **87** was converted to saturated aldehyde (which was not isolated due to volatile) by using $Pd(OH)_2/C$ in benzene, the methodology developed by our group recently. α-hydroxylation of the aldehyde by D-proline and PhNO in $CHCl_3$ at

room temperature and then subsequent breaking of O-N linkage by $CuSO_4$/MeOH produces terminal diol **102** in 50% yield for three steps and >99% diastereoselectivity (determined by HPLC analysis). Under selective monotosylation of primary alcohol by *p*-TsCl, Et_3N, and subsequent treatment with $LiAlH_4$ yielded secondary alcohol **103**, in 82% yield for two steps. Finally, alcohol **103** was formylated at 65 ^oC with formaldehyde to produce the desired product (−)-lardolure **80** (Scheme 20).



Scheme 20.

After successfull completion of synthesis of (−)-lardolure **80**, we targeted for (2*R*,4*R*,6*R*,8*R*)-2,4,6,8-tetramethylundecanoic acid **81**, which we synthesized from common allylic alcohol intermediate **87**. Accordingly, the allylic alcohol **8**7 was subjected to Pd-mediated oxidation to saturated aldehyde as mentioned earlier, followed by transformation of aldehyde to the corresponding acid **106** under Pinnick conditions using $NaClO_2$, NaH_2PO_4, in ^tBuOH:H_2O (2:1) with 75% yield in two steps. Coupling of acid **106** with the Evan's chiral oxazolidinone using pivaloyl chloride in presence of triethylamine and LiCl furnished the required compound **107** in 95% yield. Diastereoselective methylation of the Na-enolate of compound **107** with MeI furnished the desired compound **108** in 91% yield. Finally, hydrolysis of **108** with LiOH, H_2O_2 yielded (2*R*,4*R*,6*R*,8*R*)-2,4,6,8-tetramethylundecanoic acid **81** in 91% yield and with >99 % diastereoselectivity (determined by HPLC analysis) (Scheme 21).



Scheme 21.

In conclusion, we have accomplished a convergent synthetic protocol for the synthesis of two biologically active molecules (−)-lardolure and (2*R*,4*R*,6*R*,8*R*)-2,4,6,8-tetramethylundecanoic acid from a common intermediate using enzymatic desymmetrization of *meso*-diol, diastereselective methylation, chiral α-hydroxilation as the key steps and the synthesis was achieved in a stereoselective manner.

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