Synopsis

Chapter-I: Total synthesis of (-) cephalosporolide E and (+) cephalosporolide F

Introduction: Cephalosporolide E (1) and F (2) Figure 1, isolated from the fungus *Cephalosporium aphidicola* ACC 3490[1] in 1985 and subsequently from *Cordyceps militaris* BCC 2816[2] in 2004 belong to a small group of natural products possessing [5,5]-spiroketal moiety that is fused to the lactone ring. Their novel structure added to the fact that several members of the family possess anti-inflammatory activity and ability to treat Alzheimer's disease has attracted the attention of synthetic chemists.

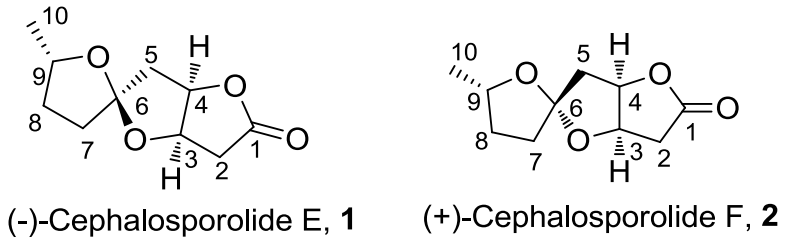
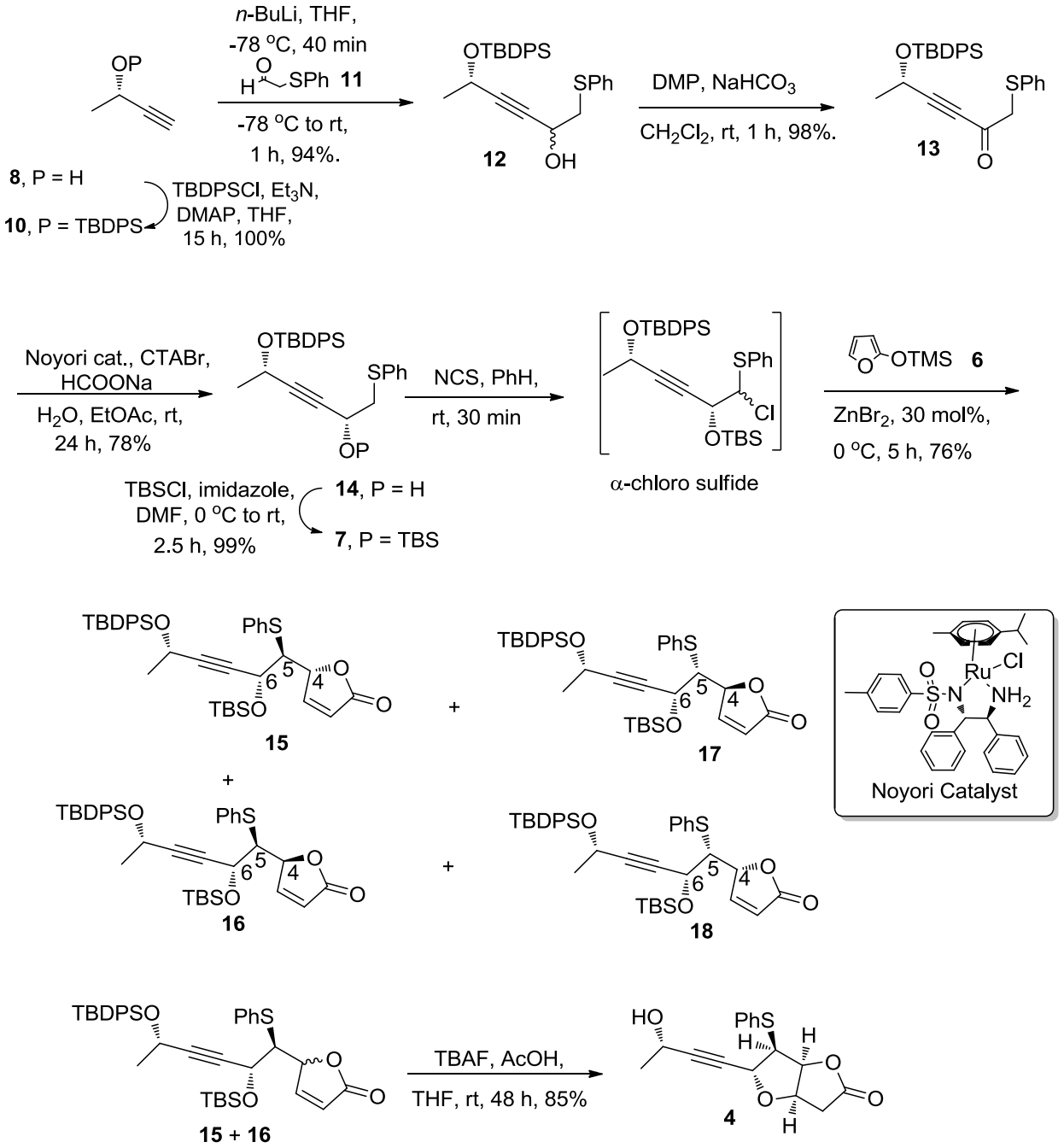


Fig 1. Structures of (-) Cephalosporolide E and (+) Cephalosporolide F.

Statement of problem: Even though the synthesis of cephalosporolide E and cephalosporolide F have been reported by a few groups, there still remains a need for a general, efficient and short approach to the its synthesis. Herein, is described the synthesis of cephalosporolides E and F by taking advantage of a vinylogous silylketene acetal addition to an α-chloro sulfide to introduce the butenolide ring eventually the C3 and C4 stereocenters and Noyori reduction of a propargylic ketone to create the stereocenter at C6.

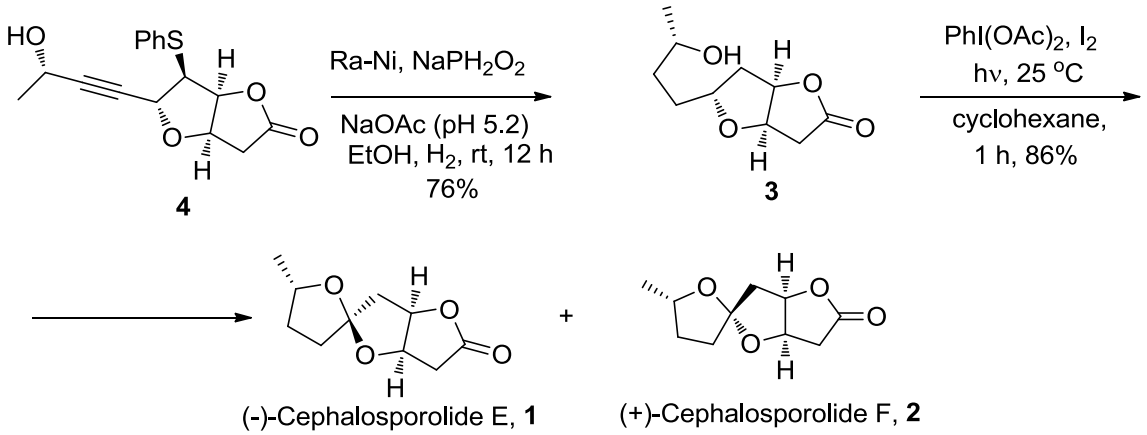
Results & discussion: The synthesis of the targets began with the protection of commercially available alcohol **8** to yield the silyl ether **10**. Reaction of the lithium acetylide of **10** with phenylthio acetaldehyde **11**, obtained by oxidation of phenylthio ethanol **9** with IBX, furnished an inseparable equimolar mixture of alcohols **12**. Oxidation of **12** afforded ketone **13** which on reduction using (*S*,*S*)-Noyori catalyst furnished alcohol **14** (dr 98:2). Protection of the carbinol **14** as its TBS ether afforded compound **7**.Treatment of sulfide **7** with *N*-chlorosuccinimide in

benzene afforded an epimeric mixture of α-chloro sulfides which without isolation was reacted with siloxyfuran **6** in the presence of zinc bromide to furnish a mixture of all possible diastereomers **15-18** in a 10:2:1:1 ratio respectively. Further deprotection using buffred TBAF led to concomitant epimerization followed by oxy-Michael reaction to afford compound **4** as the sole product as shown below in Scheme 1.



Scheme 1. Synthesis of Bicyclic Lactone **4.**

The synthesis of the targets was accomplished in two steps. Thus, the sulfanyl group and triple bond in lactone **4** was reduced by treatment with Ra-Ni under a hydrogen atmosphere using buffered conditions to furnish alcohol **3**. The key oxidative radical cyclization of alcohol **3** using iodobenzene diacetate and iodine afforded a 1:1 mixture of cephalosporolide E and F, Scheme 2.



Scheme 2: Completion of Total Synthesis of Target Compounds **1** and **2**.

Conclusion: In conclusion, a short, highly flexible synthesis of cephalosporolides E and F is disclosed. The configuration at C9 and the length of the side chain (*n*-heptyl for cephalosporolide H) can be varied by an appropriate choice of propargylic alcohol (obtained by reduction of the corresponding propargylic ketone using the Noyori's catalyst). The configuration at C6 that translates into C3 and C4 stereogenic centers can be varied by the appropriate choice of enantiomeric Noyori catalyst. The vinylogous Mukaiyama type reaction with the chloro sulfide, reported for the first time and oxidative cyclization are other key steps in the disclosed route. It is noteworthy that related members of the family will be readily accessible by modification of the disclosed strategy.

Chapter-II: Experimental procedure for the total synthesis of (-) cephalosporolide E and (+) cephalosporolide F

This chapter deals with detailed experimental procedure for the synthesis of each compound and its characterisation data.

Chapter-III: **Studies towards the synthesis of phoslactomycin-B**

Introduction: Phoslactomycins A-F were isolated in 1989 from the culture broth of a soil bacteria species *Steptomyces nigrescens*. Phoslatomycin B, **20** (**Figure-2**) was also isolated from fermentation broth of a strain of *Streptomyces hygroscopicus*. Phoslatomycin B exhibits potent activity against L1210, P388 and EL4 murine cancer cell lines. Its antitumor activity is a consequence of it being a highly potent and selective inhibitor of protein serine/threonine phosphatase 2A (PP2A), an enzyme involved in the regulation of many crucial biological events.

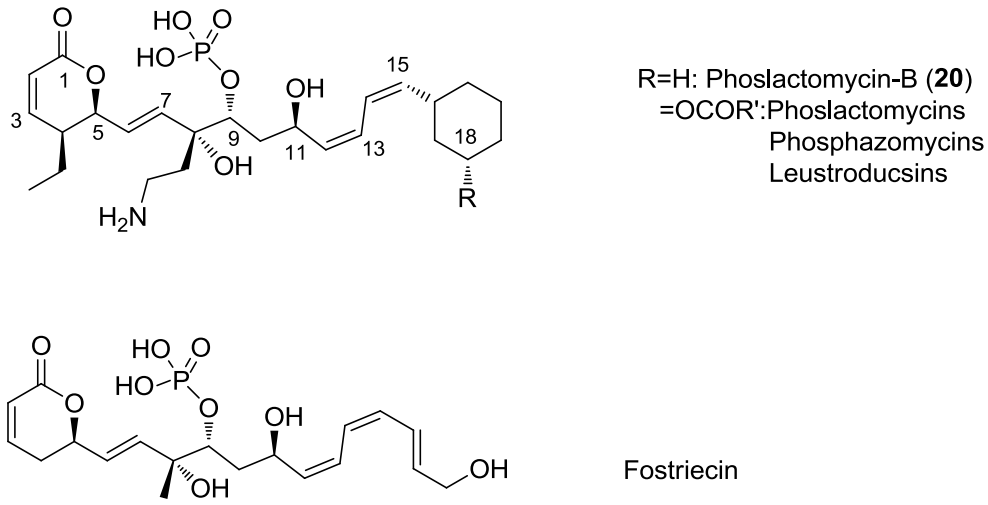
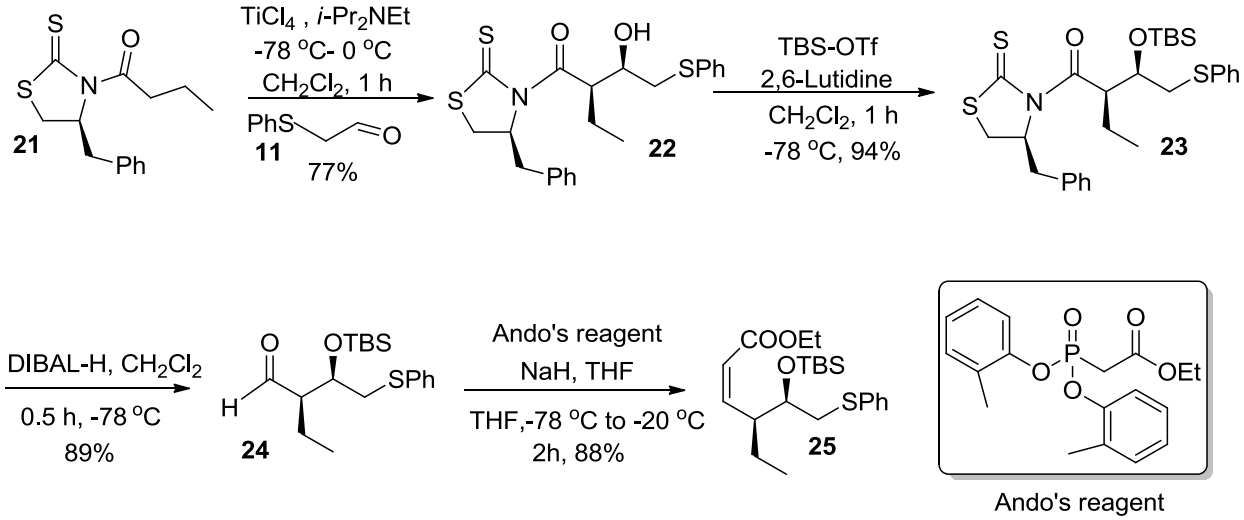


Figure-2. Phoslatomycins, phosphazomycins, leustroduscin and fostriecin.

Statement of problem: Phoslactomycin B **20** has attracted a great deal of attention in the chemical and biological communities due to its intriguing molecular architecture and its potential as a lead compound for anticancer drugs as well as its importance as a biological tool. The structural features include an α,β-unsaturated δ-lactone, a disubstituted alkene of (*E*)-configuration (C6-C7), a tertiary alcohol at C8 substituted by a 2-aminoethyl chain, a phosphate at C9, a secondary alcohol at C11, a conjugated (*Z*,*Z*)-diene (C12-C15) and a cyclohexane ring.

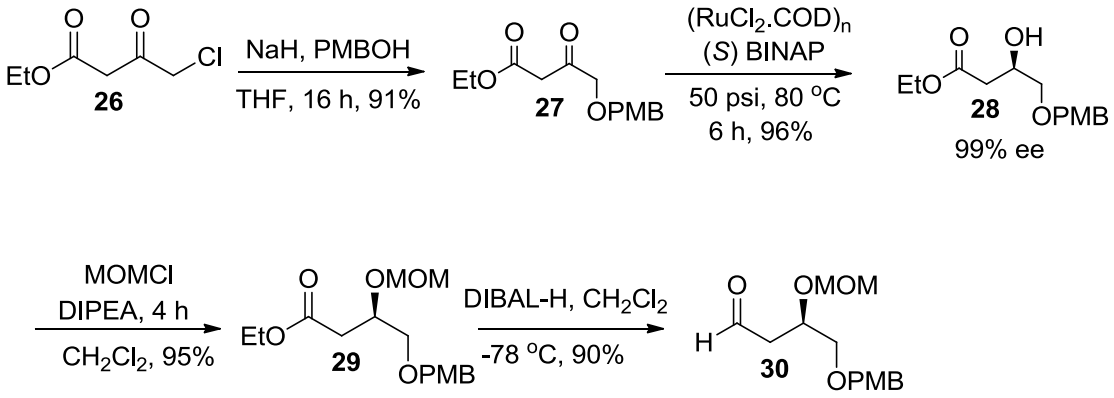
Results & discussion: The synthesis of sulphide **25** constituting the C1-C6 fragment commenced with the Crimmins aldol reaction of thiozolidinethione **21** with 2-phenyl

thioacetaldehyde **11** to give aldol **22.** Protection of the hydroxyl group as its TBS ether using TBS-triflate afforded compound **23**. DIBAL-H reduction resulted in the formation of aldehyde **24** with the recovery of the chiral auxiliary. Treatment of aldehyde **24** with the anion generated from Ando's reagent gave the *cis* ester **25** selectively as shown in the Scheme 3.



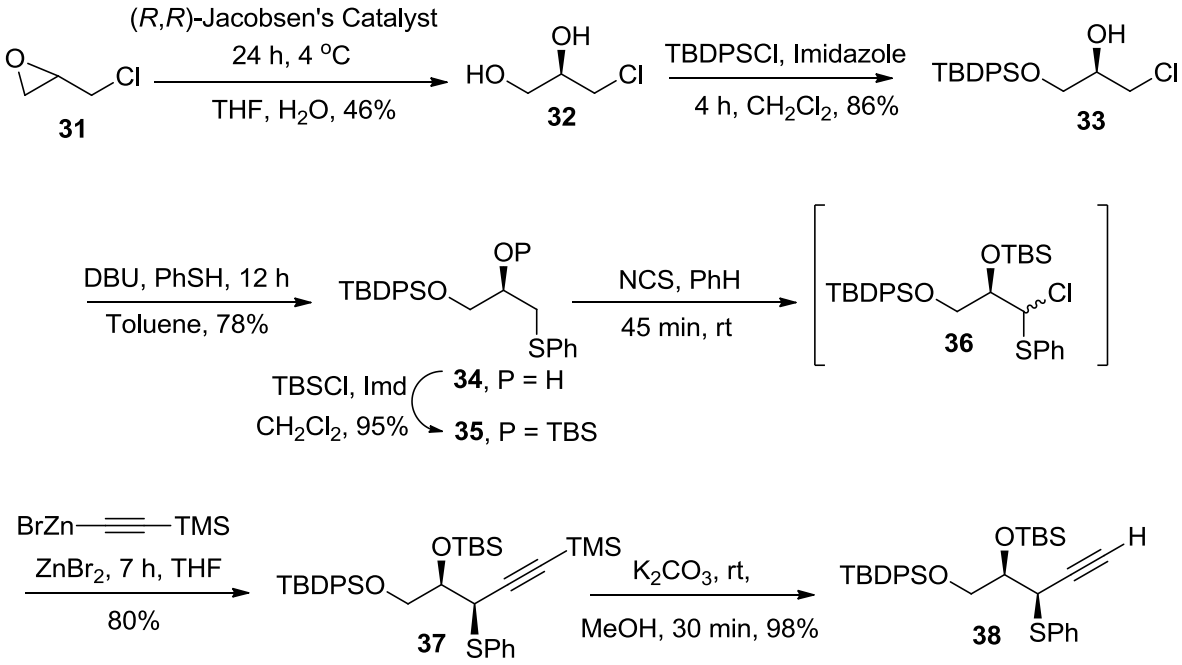
Scheme 3. Synthesis of Sulphide **25**.

The aldehyde **30** constituting the C9-C12 subunit was synthesized from commercially available chloro keto ester **26** as depicted in Scheme 4. The chlorine in compound **26** was displaced by *p*-methoxybenzyl alkoxide to afford the β-keto ester compound **27.** The keto group of **27** was selectively reduced using Ru-Binap catalysed hydrogenation at 80 ^{o}C and 50 psi hydrogen pressure in pressure reactor to afford β-hydroxyester **28** with excellent selectivity. The free hydroxy group was protected as its methoxy methyl ether **29** under standard conditions. Finally ester group was subjected to controlled reduction with DIBAL-H to afford aldehyde **30**, Scheme 4.



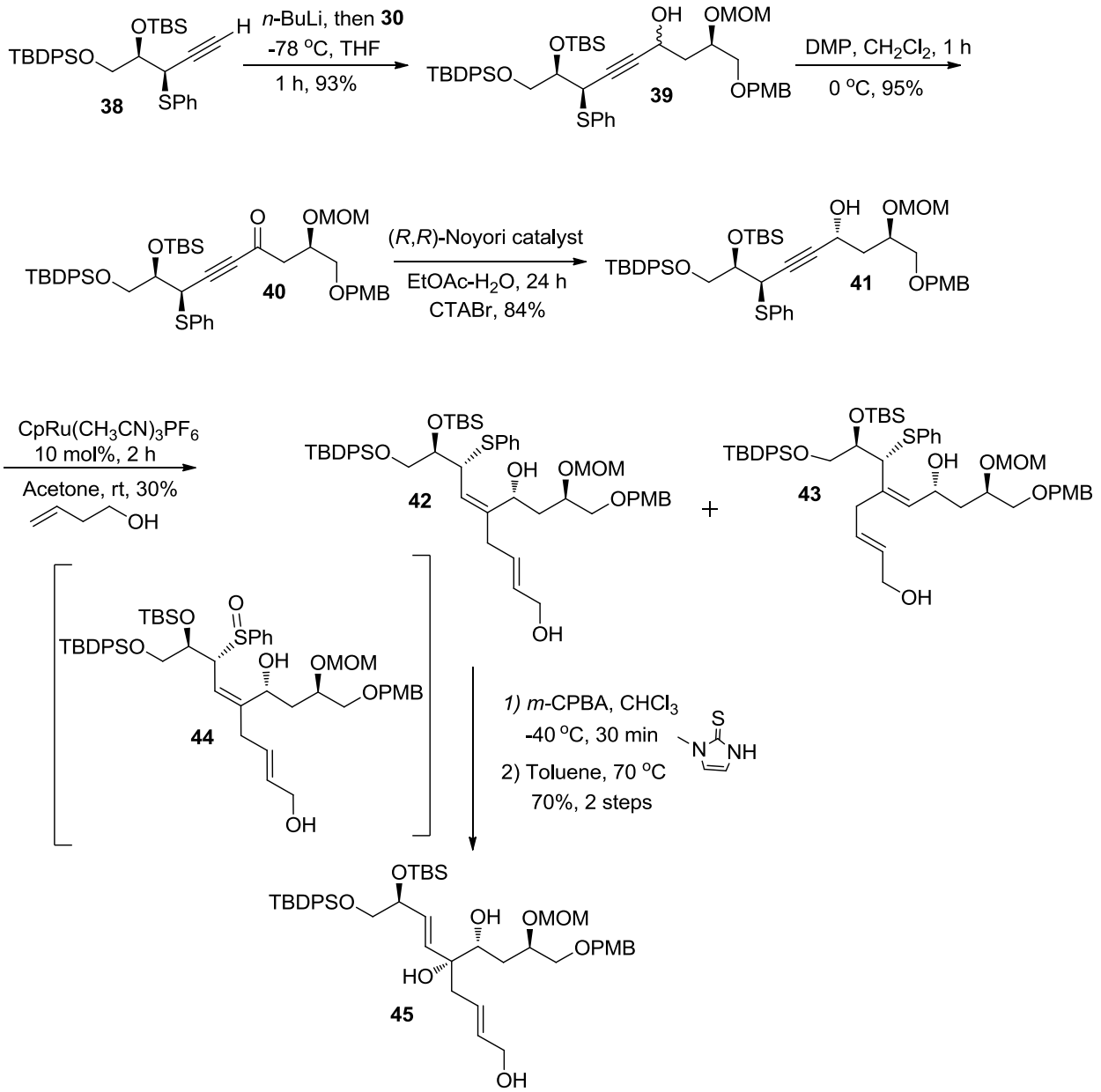
Scheme 4. Synthesis of Aldehyde **30**.

The C8 tetrasubstituted stereocenter was envisioned to be introduced by a regioselective enyne coupling following Trost's protocol followed by Mislow-Evans rearrangement of an allylic sulfoxide. The requisite alkyne was imagined to be obtained by coupling the chloro sulfide **25** with an alkyne derived from aldehyde **30**. However, it was thought that to test the feasibility of the proposal on a simpler substrate which was prepared as depicted in Scheme 5. The synthesis of the model fragment started from the resolution of epichlorohydin **31** using (*R,R*) Jacobsen's catalyst to afford enantiomerically pure diol **32**.



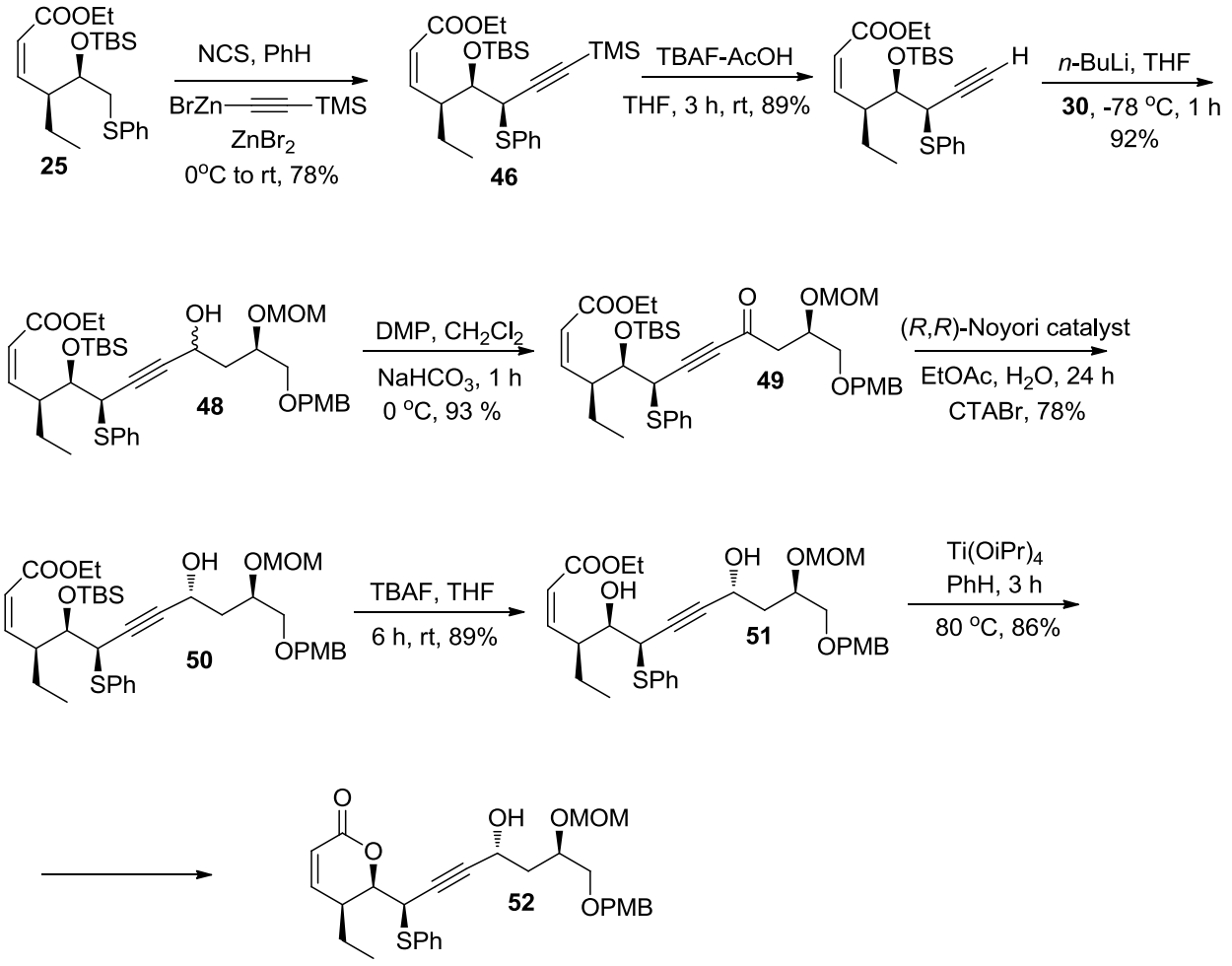
Scheme 5. Synthesis of Terminal Alkyne **38**.

Selective monoprotection of the primary hydroxyl group using TBDPSCL furnished siliyl ether **33** in excellent yield. Nucleophilic substitution of chlorine by using thiophenol and DBU yielded hydroxy sulphide **34**. The free secondary hydroxyl was protected as its TBS ether under standard conditions to give sulphide **35.** Reaction of sulfide **35** with N-chlorosuccinimide afforded the chlorosulfide **36** which on reaction with zinc acetylide prepared from TMS-acetylene furnished propargylic sulfide **37** with excellent selectivity. Base catalyzed deprotection of the TMS group yielded terminal alkyne **38** Scheme 5.



Scheme 6. Synthesis of Tertiary Alcohol **45.**

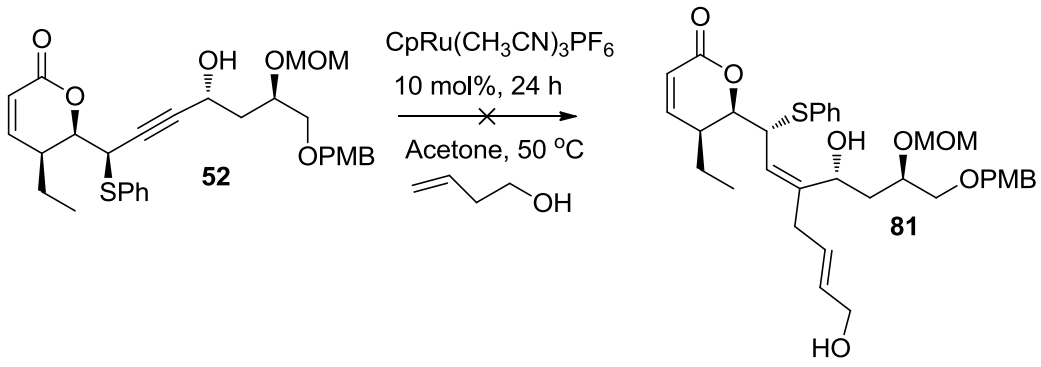
The lithium acetylide generated from alkyne **38** using *n*-BuLi was reacted with aldehyde **30** to afford an epimeric mixture of propargylic alcohol **39** which was subsequently oxidized using DMP to furnish the corresponding ketone **40**. Stereoselective reduction using Noyori's asymmetric transfer hydrogenation conditions delivered alcohol **41**. Alcohol **41** was subjected to enyne coupling with homoallyl alcohol using Trost's catalyst to afford readily separable regioisomers **42** and **43** in (2:1 ratio) a combined yield of 30%. The predominant isomer **42** was assumed to be the desired regioisomer and taken ahead to the next step. Thus oxidation of sulfide to sulfoxide **44** followed by Mislow-Evans rearrangement yielded diol **45**, Scheme 6. The selective functionalization of the disubstituted alkene in substrate **42** or **45** would provide a suitable handle for the introduction of the amino ethyl side chain, Scheme 6.



Scheme 7. Synthesis of Lactone **52**.

Though the regioselectivity of enyne coupling had to be addressed, attempts were made on a more complex substrate. Thus the chlorosulfide intermediate obtained from sulfide **25** was treated with the zinc acetylide prepared from TMS-acetylene furnished propargylic sulfide **46**. C-TMS group of **46** was selectively deprotected in presence of TBS group using TBAF-AcOH to afford the terminal alkyne **47.** Lithium acetylide generated from alkyne **47** was reacted with aldehyde **30** to give an epimeric mixture of propargylic alcohol **48** which on oxidation using Dess-Martin periodinate provided propargylic ketone **49.**Stereoselective reduction following Noyori's protocol afforded alcohol **50** in good yield. The secondary TBS ether was deprotected under standard TBAF conditions to give diol **51** which on treatment with titanium tetraisopropoxide in benzene delivered the α β-unsaturated lactone **52**, Scheme 7.

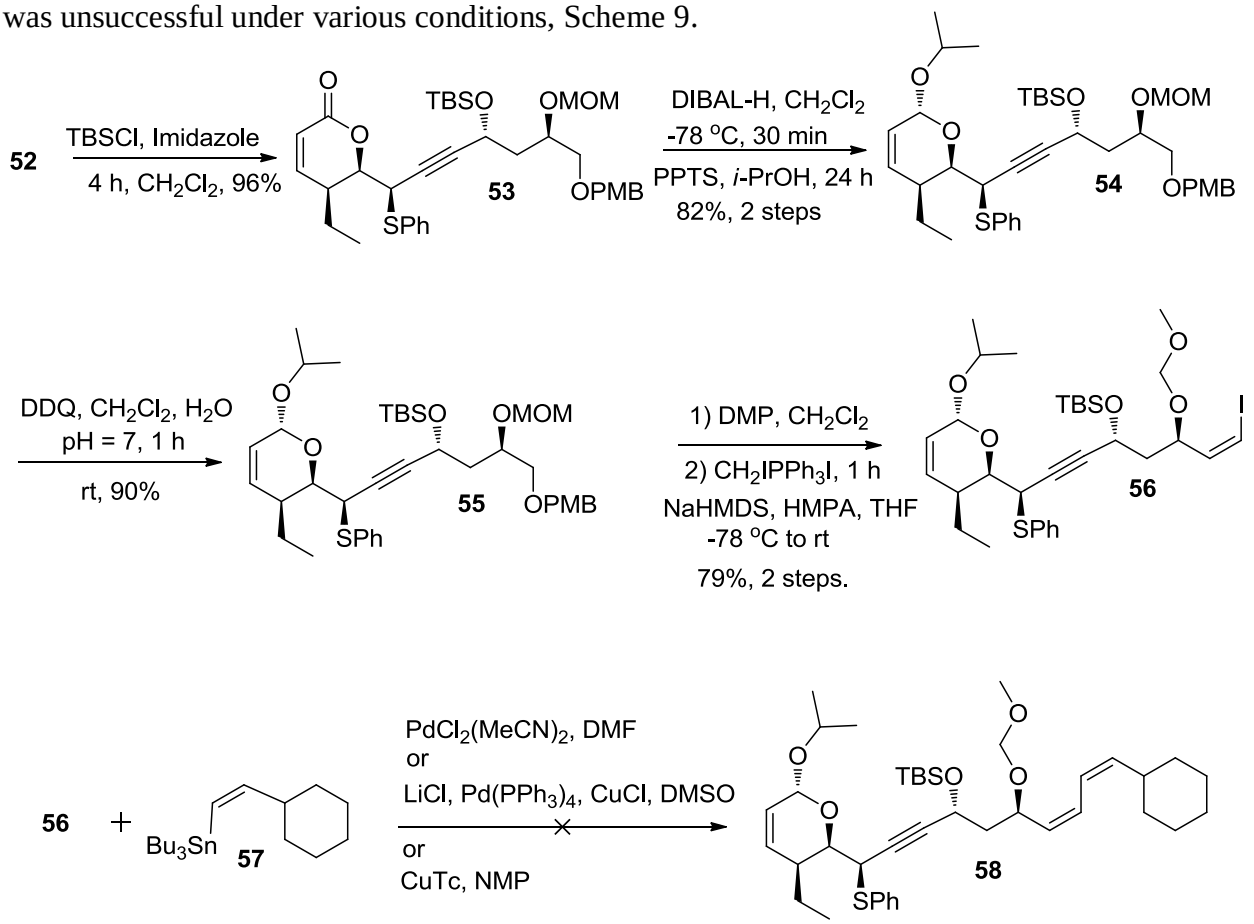
After having experience of enyne coupling on simpler substrate, enyne coupling was attempted on propargylic alcohol **52** was not forwarded after many trials in different solvents, Scheme 8.



Scheme 8. Attempt of Enyne Coupling.

Thus the enyne coupling failed on substrate **52**. With compound **52** in hand, it was decided to check the feasibility of the Stille coupling for the introduction of the (*Z,Z*) moiety. Thus the free secondary hydroxyl group of **52** was protected as its TBS ether under standard conditions to afford the TBS ether **53.** The lactone **53** was reduced to an epimeric mixture of lactols using DIBAL-H and further reacted with *i*-prOH and PPTS to yield hemiacetal **54**. The

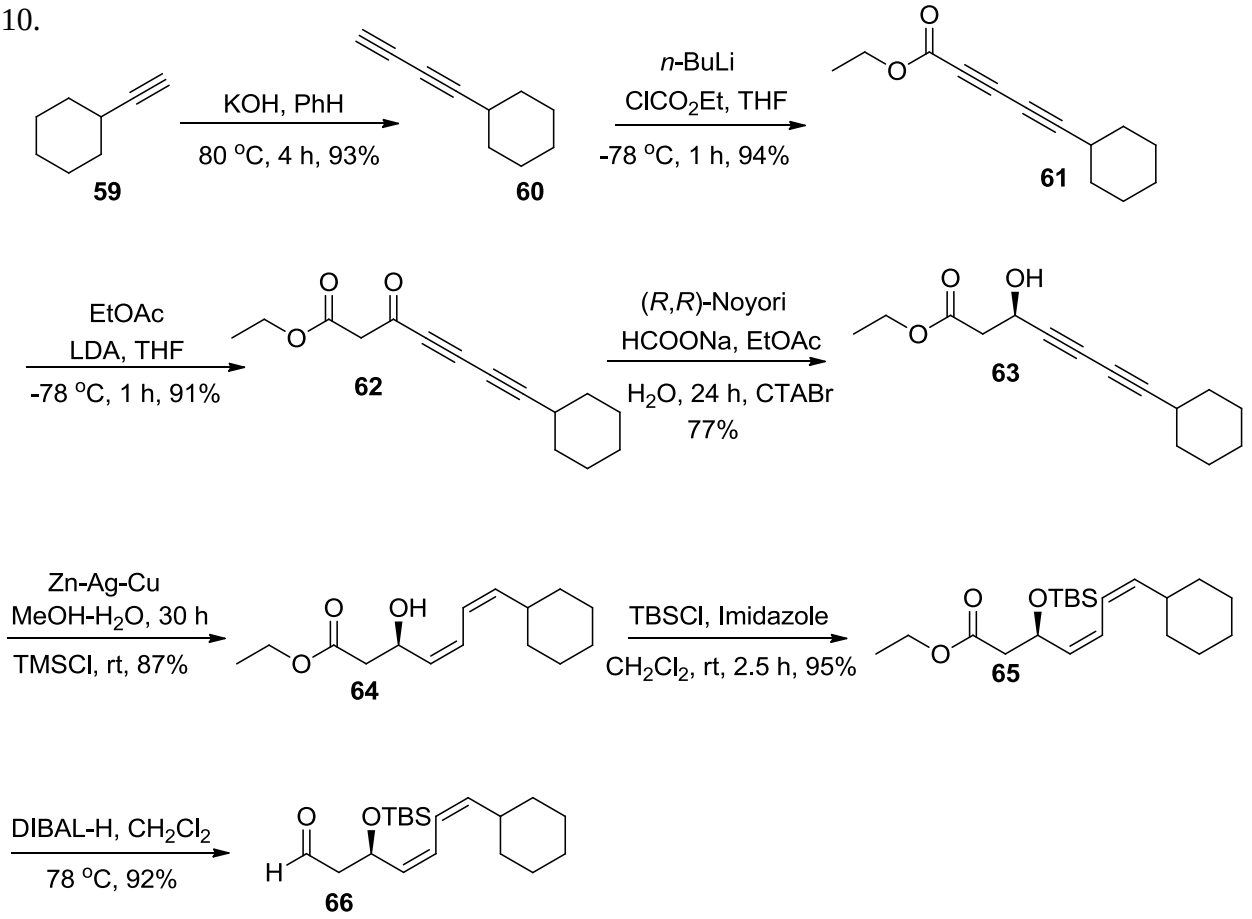
PMB ether in **54** was deprotected using DDQ to furnish the primary alcohol **55** in excellent yield. Dess-Martin periodinate promoted oxidation of **55** alcohol to aldehyde and further wittig reaction afforded vinyl iodide **56**. With vinyl iodide **56** in hand the Stille coupling with vinyl tin **57** was attempted. Unfortunately, the reaction failed after several trials using different catalysts in many solvents and reaction conditions. Due to the curiosity about enyne coupling reaction we had attemped Trost's protocol on hemiacetal internal alkyne **54** with 3-butenol but the reaction was unsuccessful under various conditions, Scheme 9.



Scheme 9. Synthesis of Vinyl Iodide and Attempted Stille Coupling.

Having been unsuccessful in the Stille coupling in the previous attempt, it was decided to introduce the conjugated *Z,Z*-diene even at an earlier stage in the synthesis. The synthesis commenced from compound **60** which was obtained from ethynylcyclohexane **59** following procedures reported in the literature. The lithium anion of **60** was quenched with ethyl choroformate at low temperature to afford compound **61**. To the lithium enolate of ethyl acetate,

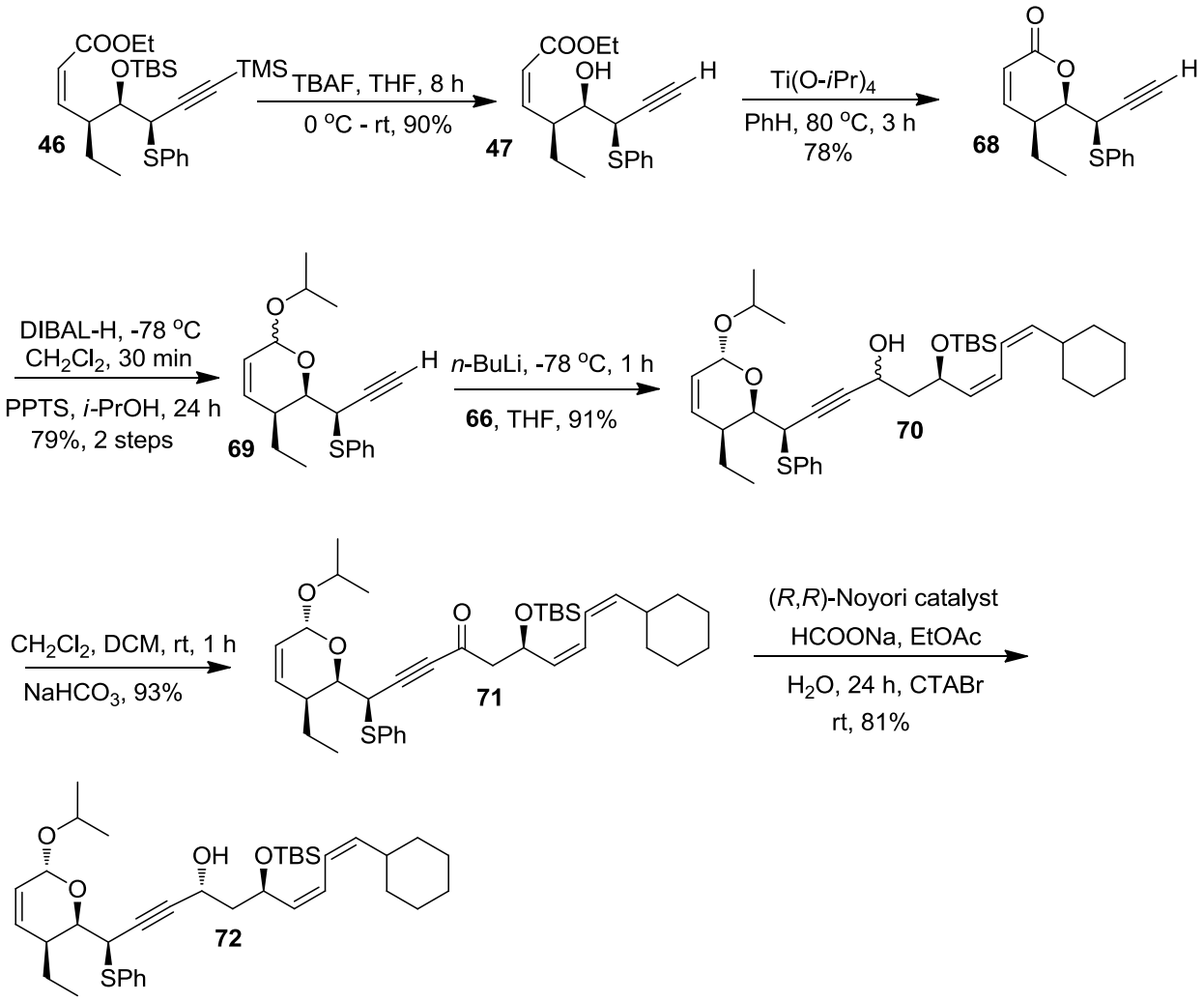
compound **61** was added to afford β-keto ester **62.** Enatioselective reduction of the keto carbonyl in **62** using (*R,R*)-Noyori catalyst yielded β-hydoxy ester **63**. The conjugated alkyne of **63** was chemoselectively reduced by applying Hansen's modification to the Boland protocol for *Z* stereoselective semi reduction of alkynes to afford diene **64**. The free hydroxyl group in **64** was protected as its TBS ether under standard conditions to furnish compound **65**. Contolled reduction of ester to aldehyde **66** was carried out using DIBAL-H at low temperature, Scheme 10.



Scheme 10. Synthesis of Aldehyde **66**.

The propargylic sulfide **46** was subjected to treatment with TBAF which resulted in the deptotection of TBS and TMS in one step to afford terminal alkyne **67,** Compound **67** underwent intramolecular lactonisation in the presence of titanium tetraisopropoxide to afford lactone **68**. The lactone **68** was reduced to the corresponding lactol using DIBAL-H and subsequently converted to hemiacetal **69**. The lithium anion of terminal alkyne **69** was reacted

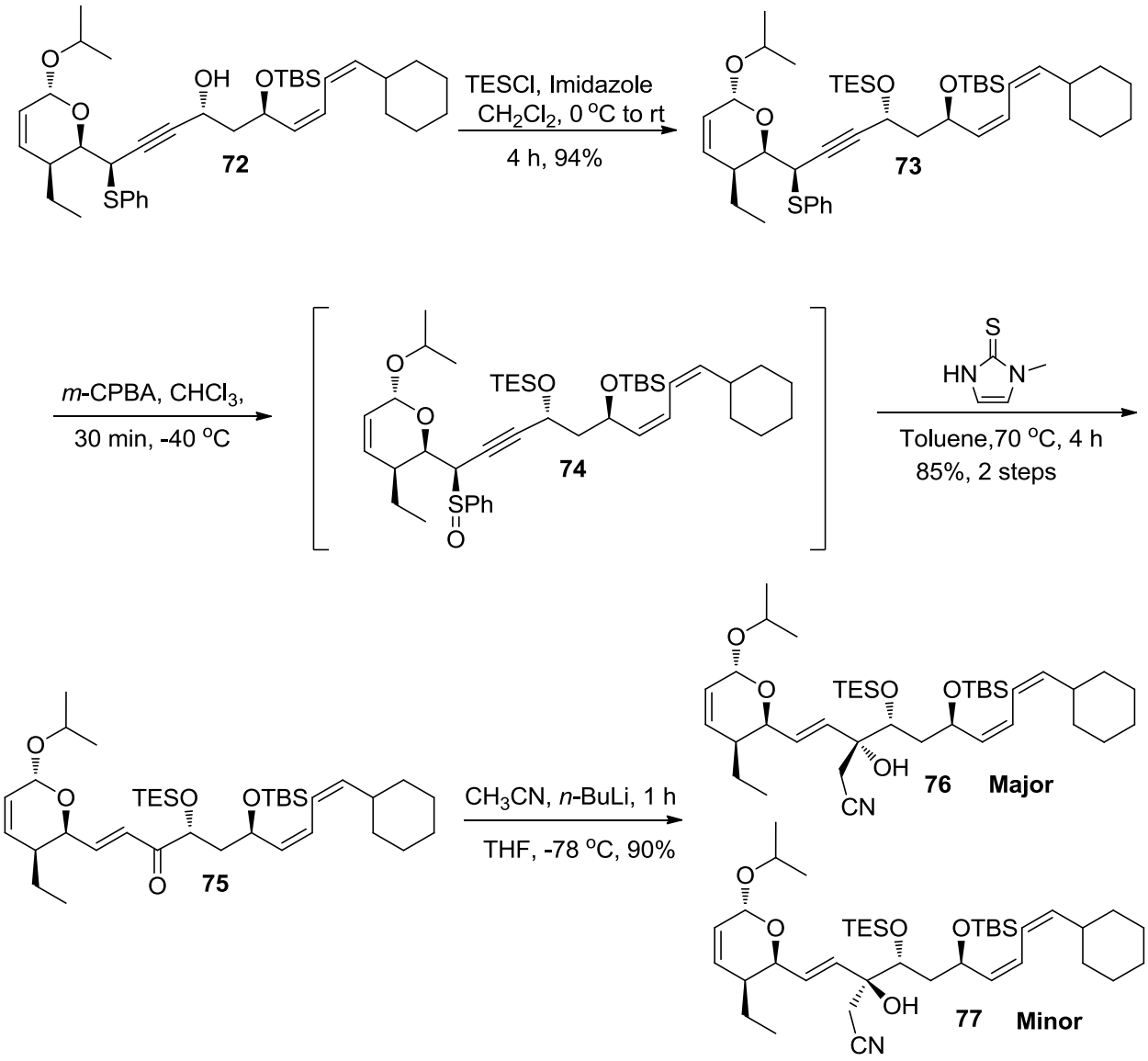
with aldehyde **66** to furnish compound **70**. Dess-Martin periodinane oxidation of alcohol **70** afforded propargylic ketone **71**, which on Noyori's asymmetric transfer hydrogenation afforded alcohol **72** as shown in Scheme 11.



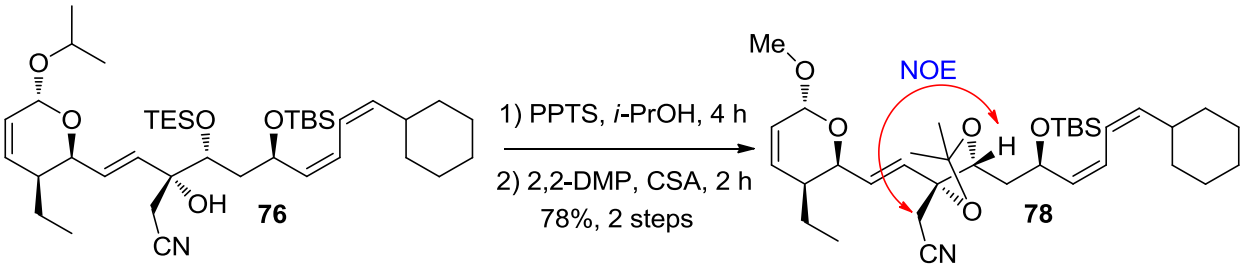
Scheme 11. Synthesis of Propargylic Alcohol **72.**

Propargylic alcohol **72** on treatment with triethylsilyl chloride and imidazole in anhydrous DCM afforded TES ether **73** Scheme 11. The sulfide in compound **73** was oxidized to sulfoxide **74** using *m*CPBA in chloroform. The sulfoxide **74** was subjected to Milsolw-Evans rearrangement in the same pot to afford α,β-unsaturated ketone **75**. The amino ethy side chain was introduced by the reaction of anion of acetonitrile with ketone **75** to furnish a mixture of

tertiary alcohols **76** & **77** in a **4:1** ratio which can be easily separated by column chromatography, Scheme 12.

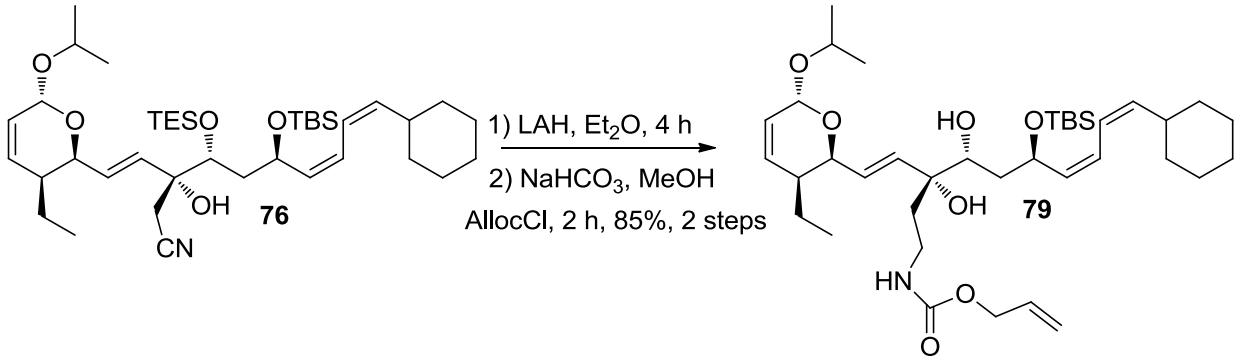


Scheme 12. Synthesis of Tertiary Alcohol **76**.



Scheme 13: Confirmation of Stereochemistry of Tertiary Alcohol.

Moving ahead towards target our next attention was to confirm the stereochemistry at newly generated tertiary alcohol for that reason TES group of major compound **76** was selectively deprotected by using PPTS in *iso*-propanol to afford diol in good yield which was subsequently protected as its acetonide under 2,2-DMP condition to furnish protected diol **78**. As expected in compound **78** NOE was observed between –CH_2CN and methine proton at C9 thus confirmed stereochemistry at tertiary alcohol center as required in the target compound phoslactomycin B Scheme 13.



Scheme 14. Towards Synthesis of Phoslactomycin-B.

In the next step compound **76** was subjected to LAH reduction in which cyanide group was reduced to primary amine and also nearby TES group was deprotected in same pot. Obtained amino diol was used without further purification and amino group was protected as a allyloxy carbonyl to give protected amino diol **79**. Scheme 14.

Conclusion: The hydroxyl ester was prepared by Noyori's asymmetric hydrogenation of β-keto ester, other key reactions include C-C bond formation using α-chloro sulfide, asymmetric transfer hydrogenation, witting olefination to prepare iodo alkene, Ando's cis olefination, Evans-Mislow rearrangement and Hansen's modification of Boland protocol for *Z* selective semi reduction of alkynes.

Chapter-IV: **Experimental procedure for the studies towards the synthesis of phoslactomycin-B.**

This chapter deals with detailed experimental procedure for the synthesis of each compound and its characterisation data.