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Total Synthesis of Macrolides

Chebolu Naga Sesha Sai Pavan Kumar

Abstract

Structurally complex macrolide natural products, isolated from a variety of marine and other sources, continue to provide a valuable source of targets for the synthetic chemist to embark. In this account, we provide the recent progress and pathways in the total synthesis of macrolides and discussed the synthesis of (+)-neopeltolide, aspergillide D, miyakolide and acutiphycin natural products.

Keywords: macrolide, aldolization, macrolactonization, ring closing metathesis, coupling reactions, total synthesis

1. Introduction

Macrolides are a class of antibiotics that consist of a large macrocyclic lactone ring attached to deoxy sugars. These antibiotics are bacteriostatic in nature and act by inhibiting protein synthesis of bacteria. These are obtained mainly from certain actinomycetes genus, such as *Streptomyces* and related species. The original macrolide complex, erythromycin A, was isolated in 1952 as a natural product of *Saccharopolyspora erythraea* (formerly *Streptomyces erythreus*). Other examples include clarithromycin, azithromycin, telithromycin, cethromycin, modithromycin, etc. Macrolides structurally contain three characteristic parts in every molecule, that is, a macrocyclic lactone ring, multiple ketone & hydroxyl group, and two deoxy sugars attached by glycosidic bond. According to the carbon number of lactone ring, macrolides are classified into several types. That is, 12-membered ring, 13-membered ring, 14-membered ring, 15-membered ring, 16-membered rings, etc. (**Figure 1**). Out of these, most of the antibiotic drugs comprised of 14-membered and 16-membered lactone rings.

The construction of macrocyclic structures is a recurrent and challenging problem in synthetic organic chemistry. Theoretically, macrocyclic systems can be generated by cyclization of open, long chain precursors or by cleavage of internal bonds in polycyclic systems. In the course of synthesis, numerous problems are encountered to achieve target molecules. Despite the several problems, however, recent interest in the chemistry of macrolide antibiotics and other biologically active macrolactones and macrolactams resulted in the discovery and development of several new synthetic methods for macrolide formation. In this chapter, total synthesis of some of the macrolides is discussed with scrupulous emphasis on the key macrolide ring forming reactions.
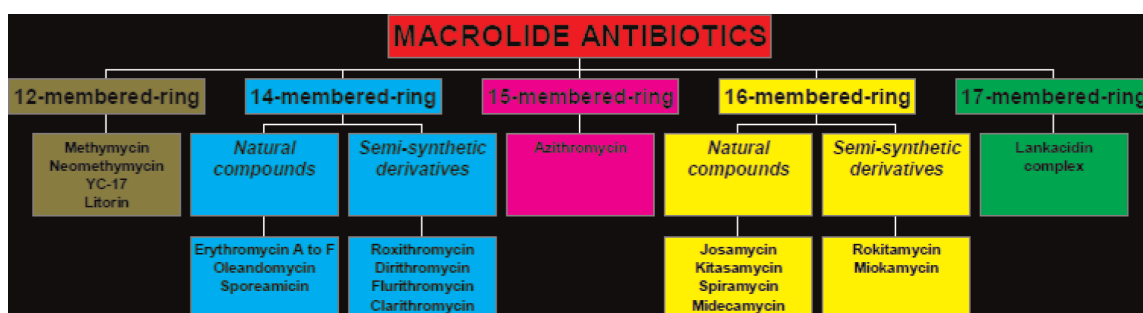
Figure 1.
Classification of macrolide antibiotics.

2. Synthetic strategy for macrolide synthesis

In the polyoxomacrolide ring, generally we will observe the 1,3-diol systems as a core. There are two synthetic approaches for the edifice of 1,3-diols which are illustrated here. They are asymmetric aldol reaction and the other one is asymmetric epoxide and epoxide ring-opening.

2.1 Aldolization

Asymmetric synthesis of β-hydroxy ketones by aldol reactions of ketones with aldehydes is the general and efficient method for the synthesis of 1,3-diol systems and is of great interest in the field of total synthesis. By using the range of chiral ketones, highly diastereoselective *syn* and *anti* aldol products are produced using various boron enolates [1–3]. Some of the reagents shown below (**Figure 2**) direct the relative and absolute stereochemistry of C━C bond formation between various achiral and chiral ketones, thus providing a ubiquitous synthetic tool for macrolide synthesis (**Figure 3**).

A highly efficient and extensively used method for diastereoselective aldol reactions is the Evans aldol reaction using boron enolate derived from a chiral imide [4, 5]. Upon treatment of imide **1** with n-Bu$_2$BOTf and i-Pr$_2$NEt in CH$_2$Cl$_2$ followed by addition of aldehyde, aldol reaction proceeds smoothly in stereoselective manner through the chelation transition state to attain 1,2-*syn*-aldol adduct **2** in high yield and with excellent diastereoselectivity. After the reaction, the chiral auxiliary is cleaved by hydrolysis to acid, then reduction to aldehyde or alcohol, conversion to
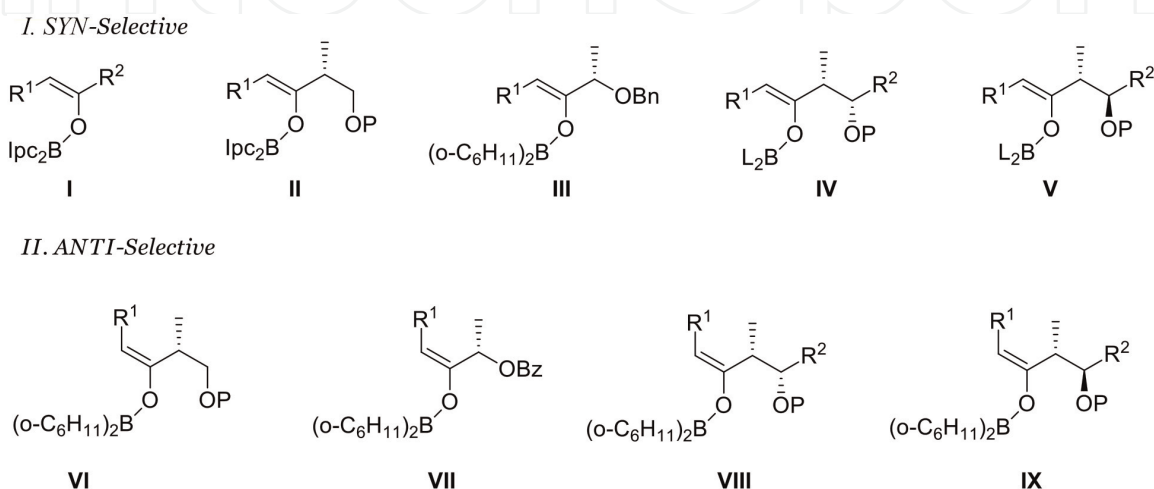

Figure 2.
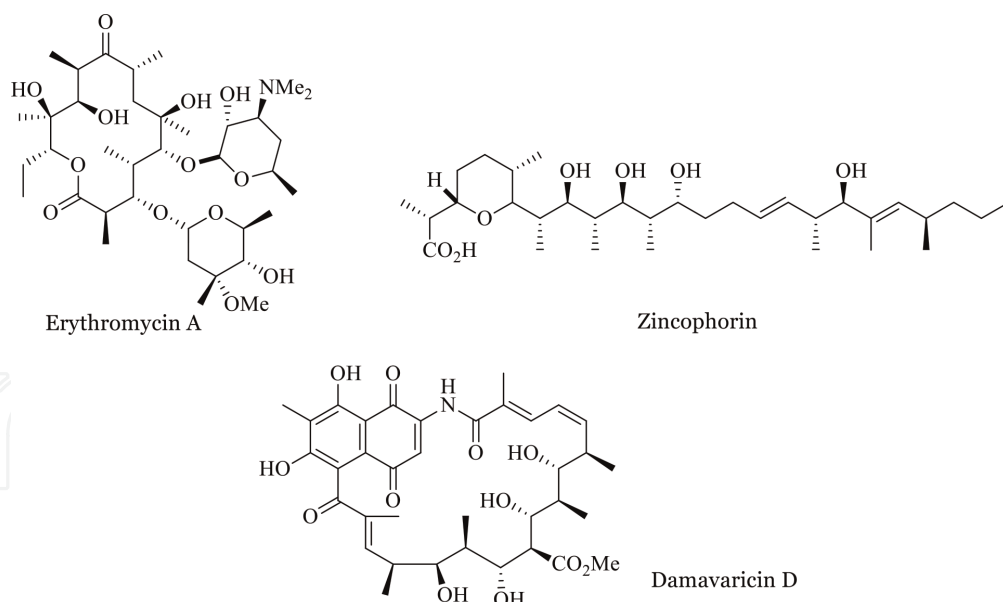*Reagents for asymmetric Aldol reactions.*

Figure 3.
Macrolide antibiotics: evidence for the chemists interested in the stereochemistry of the Aldol reaction.

Weinreb amide, etc. In contrast, addition of a Lewis acid to the boron enolate provides either *anti*-diol **3** or non-Evans 1,2-*syn*-aldol **4** with excellent diastereoselectivity [6] (**Figure 4**).

2.2 Asymmetric epoxidation and dihydroxylation

The asymmetric epoxidation of allylic alcohols introduced by Katsuki and Sharpless in 1980 has tremendous applications in the synthesis of various
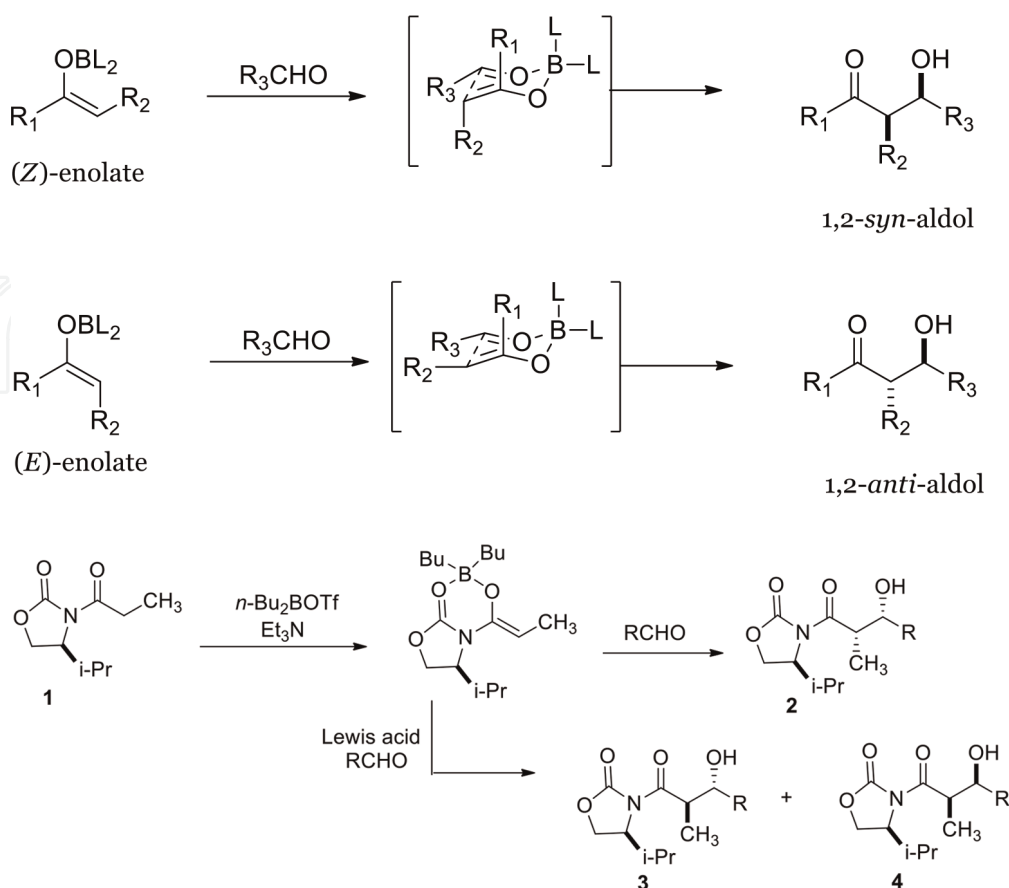

Figure 4.
Evan's Aldol strategy.

3

compounds [7]. The Sharpless asymmetric epoxidation (AE) is the efficacious reagent in the synthetic organic chemistry particularly in the synthesis of variety of natural products. Epoxidation is carried out from allylic alcohols **5** with *tert*-butyl hydroperoxide in the presence of Ti(O*i*Pr)$_4$. The resulting epoxide stereochemistry is determined by the enantiomer of the chiral tartrate ester (usually diethyl tartrate or diisopropyl tartrate) employed in reaction. When (−)-diester is used, β-epoxide **6** is obtained, while (+)-diester produces α-epoxide **7** (**Figure 5**).

The Sharpless dihydroxylation [8] is another tool used in the enantioselective preparation of 1,2-diols (**9a/9b**) from olefins (**8**). This reaction is performed with osmium catalyst and a stoichiometric oxidant (e.g., K$_3$Fe(CN)$_6$ or NMO). Enantioselectivity is produced by the addition of enantiomerically-enriched chiral ligands [(DHQD)$_2$PHAL also called AD-mix-β, (DHQ)$_2$PHAL also called AD-mix-α or their derivatives] (**Figure 6**). These reagents are also commercially available as stable and not so expensive.

Stereoselective ring-opening of 2,3-epoxy alcohols **10** is extremely valuable for the synthesis of different functionalized compounds [9]. A wide range of nucleophiles such as secondary amine, alcohol, thiol, azide and carboxylic acid predominantly at C-3 position to give 1,2-diol **11** (**Figure 7**).
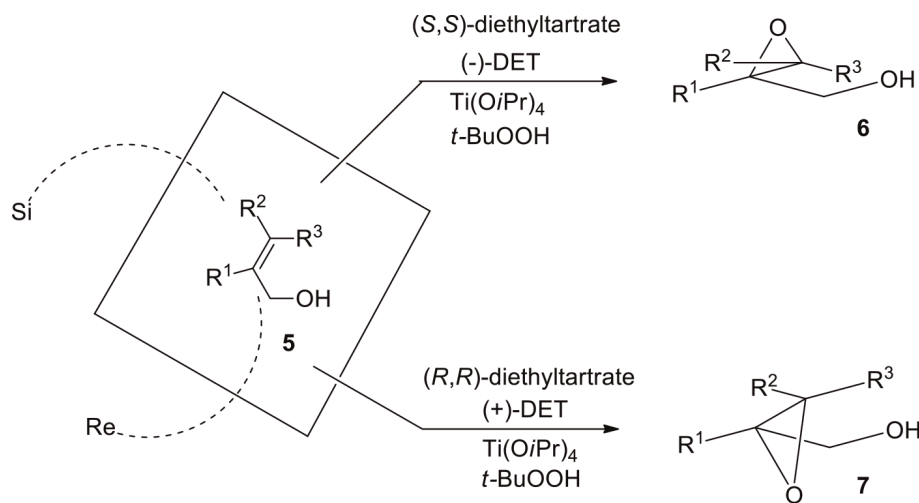

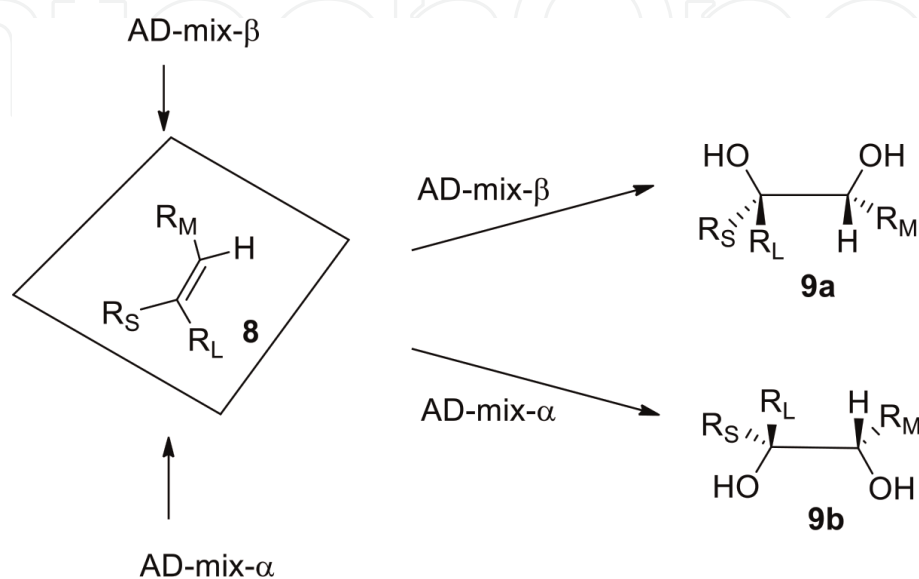**Figure 5.**
Sharpless asymmetric epoxidation strategy.

Figure 6.
Sharpless asymmetric dihydroxylation.

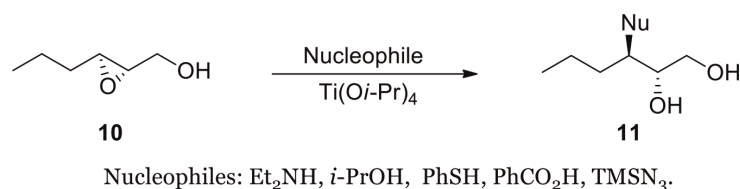Nucleophiles: Et_2NH, *i*-PrOH, PhSH, $PhCO_2H$, $TMSN_3$.

Figure 7.
Stereoselective ring-opening of epoxy alcohols.

The logic of macrocyclization in natural product synthesis can be investigated by different strategies; some of them are Prins reaction [10], lactonization [11, 12], ring closing metathesis [13], Wittig reaction [14], Horner Wadsworth Emmons (HWE) reaction [15], Julia-Kocienski reaction [16], metal-mediated cross coupling reaction [17], etc. However, it is true that there is no universal macrocyclization method is reliable in the total synthesis of natural products.

2.3 Macrolactonization

Macrolactonization is the one of the effective and popular methods in the synthesis of macrolactones. The method is based on the lactonization of the corresponding seco-acid. Thus various methods are reported in the literature for the macrolactone synthesis, some of the most commonly used methods are Corey-Nicolaou [18], Shiina [19], Yamaguchi [20], Mitsunobu [21], Keck-Boden [22], and Mukaiyama [23] macrolactonizations (**Figure 8**).
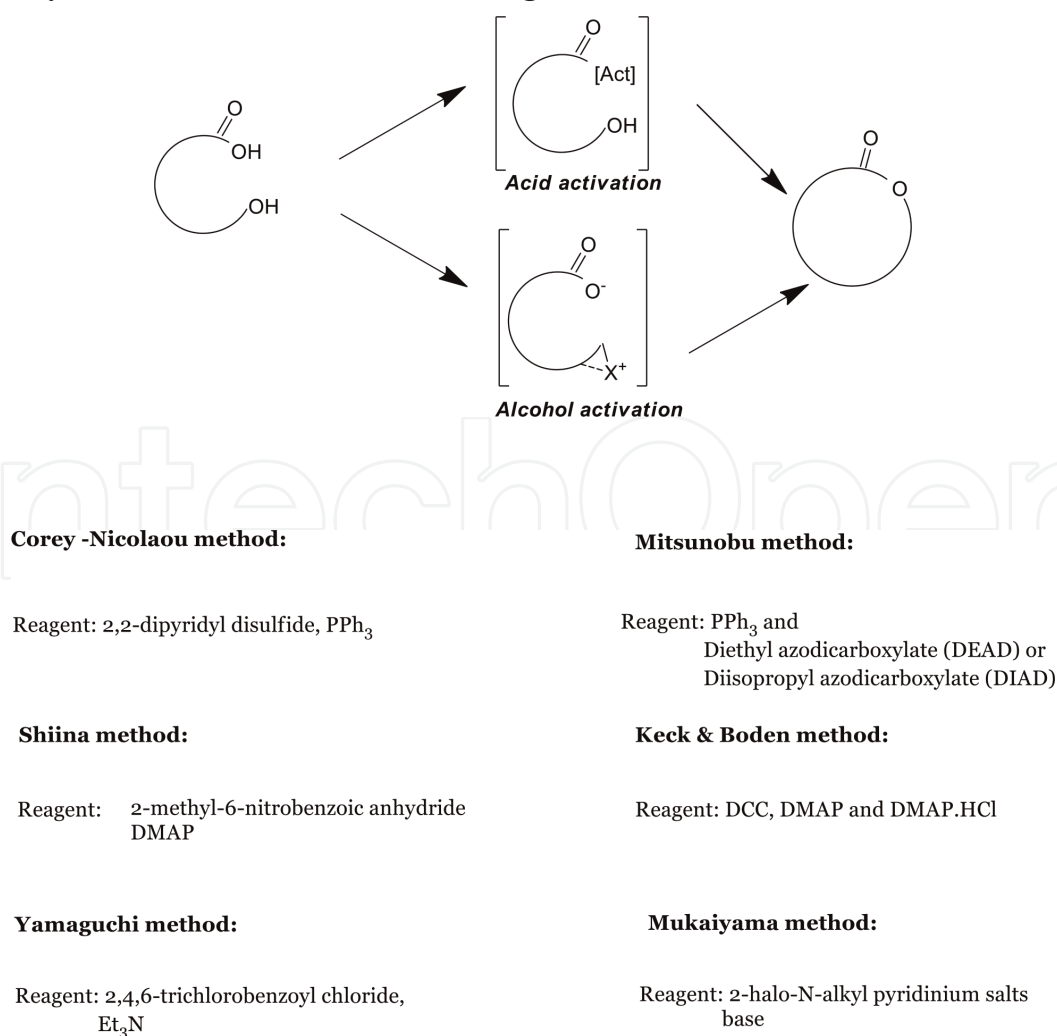

Corey -Nicolaou method:

Reagent: 2,2-dipyridyl disulfide, PPh_3

Mitsunobu method:

Reagent: PPh_3 and
Diethyl azodicarboxylate (DEAD) or
Diisopropyl azodicarboxylate (DIAD)

Shiina method:

Reagent: 2-methyl-6-nitrobenzoic anhydride
DMAP

Keck & Boden method:

Reagent: DCC, DMAP and DMAP.HCl

Yamaguchi method:

Reagent: 2,4,6-trichlorobenzoyl chloride,
Et_3N

Mukaiyama method:

Reagent: 2-halo-N-alkyl pyridinium salts
base

Figure 8.
Some of the popular methods used for macrolactonization.

Hansen et al. [24] reported the synthesis of (−)-aplyolide A from **12** in which they adopted the Corey-Nicolaou macrolactonisation as the key step with 78% yield (**Figure 9**).

Narasaka et al. [25] used the Mukaiyama method for the effective construction of macrocycle ring from corresponding seco-acid **13** in the synthesis of Prostaglandin F-lactone (**Figure 10**).

Enev et al. [26] in his studies towards the total synthesis of laulimalide, crucial Yamaguchi macrolactonization was employed on the ynoic seco-acid **14** and then reducing the triple bond obtained the desired macrolactone **15** (**Figure 11**).

In the synthetic studies towards the synthesis of colletodial, Keck et al. [27] effectively used DCC-DMAP protocol for the macrolactonization of **16** to precursor of colletodial **17** (**Figure 12**).
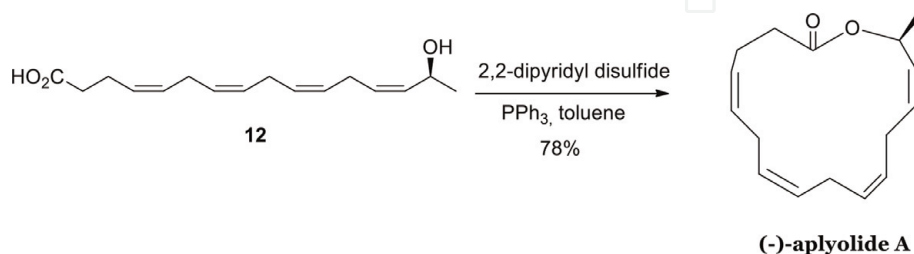

Figure 9.
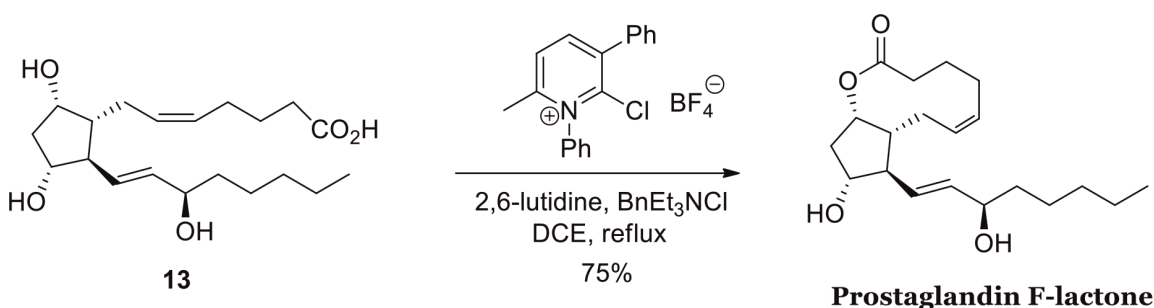*Application of Corey-Nicolaou macrolactonisation.*

Figure 10.
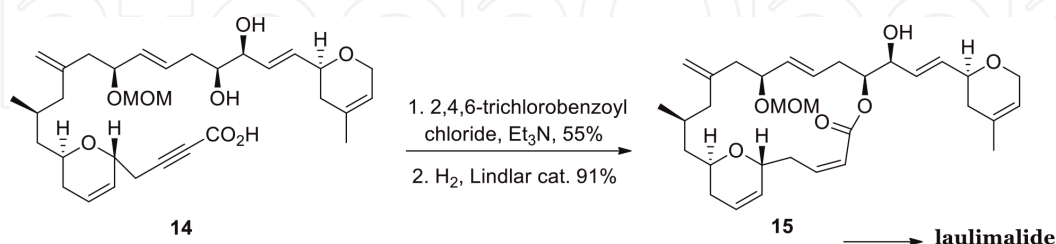*Mukaiyama method in the synthesis of prostaglandin F-lactone.*

Figure 11.
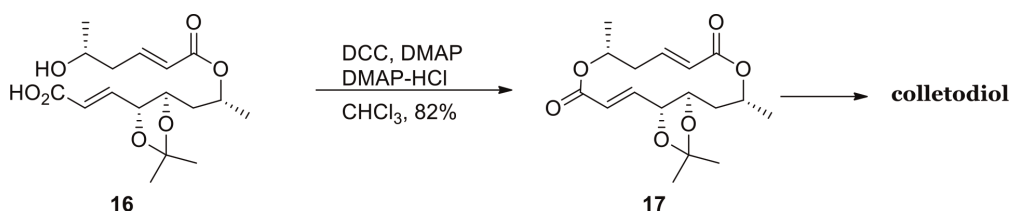*Yamaguchi protocol in the synthesis of laulimalide.*

Figure 12.
Keck et al. lactonisation for the synthesis of colletodial.

Mitsunobu macrolactonization protocol based on the activation of the seco-acid alcohol **18** to **19** using diisopropyl azodicarboxylate (DIAD) and triphenylphosphine is used in the total synthesis of natural product (+)-amphidinolide K by Williams and Meyer [28] (**Figure 13**).

In the total synthesis of iejimalide by Schweitzer et al. [29], Shiina macrolactonization (2-methyl-6-nitro benzoic anhydride/DMAP) is used as the key step for the construction of macrolactone **21** in moderate yield. Even the yield is somewhat low, other methods failed to construct the lactone while Shiina protocol worked successfully from **20** (**Figure 14**).
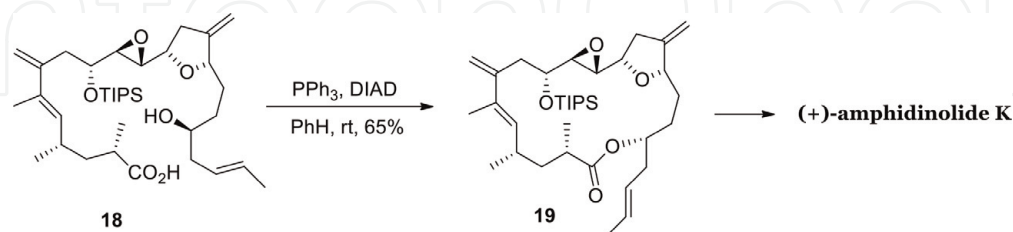

Figure 13.
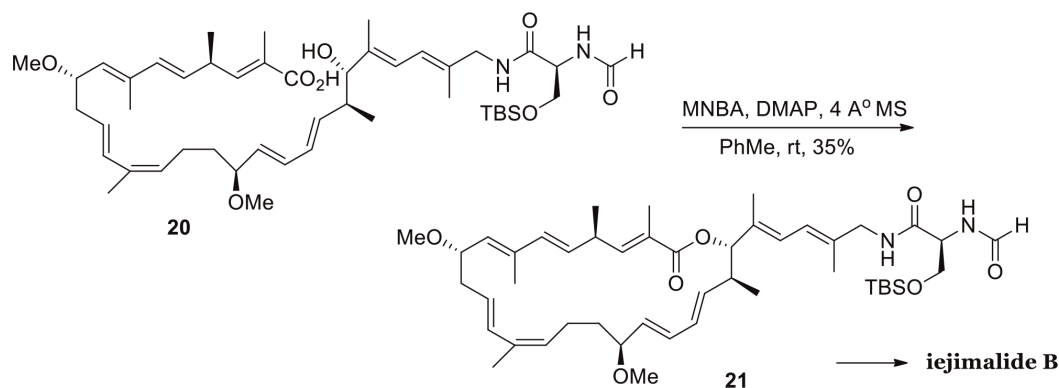*Mitsunobu esterification in the total synthesis of (+)-amphidinolide K.*

Figure 14.
Shiina macrolactonization towards the synthesis of iejimalide B.

2.4 Ring-closing olefin metathesis

In recent years, ring closing metathesis (RCM) has become one of the most paramount tools in synthetic organic chemistry especially in the field of total synthesis of macrolide natural products [13, 30, 31]. Furthermore, RCM is becoming the most popular way to construct large rings and has the advantage of being compatible with a wide range of functional groups such as ketones, ethers, esters, amides, amines, epoxides, silyl ethers, alcohols, thioesters, etc. In view of this, among the several reagents developed by Grubbs, Shrock, and Chauvin, the catalysts **A**–**D** represents two generations of ruthenium complexes, while **E** is the molybdenum Shrock catalyst (**Figure 15**). **A** is popularly known as Grubbs first generation catalysts, **B** and **C** are Grubbs second generation catalysts and **D** is
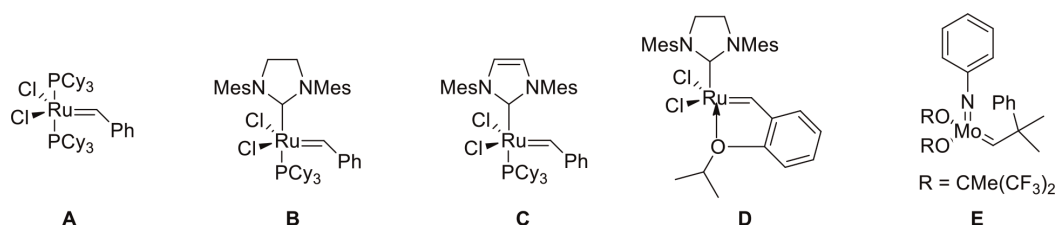

Figure 15.
Various catalysts for ring closing metathesis.

Hoveyda-Grubbs catalyst. The choice of the catalysts can be used in the synthetic organic transformations based on the reactivity of the substrate, and other reaction condition parameters. Substitution in the aromatic ring of **D** has given rise to a new family of third generation catalyst.

Here, some of the applications of ring closing metathesis in the total synthesis of macrolides salicylihalamide A [32], *trans*-resorcylide [33], (+)-lasiodiplodin [34], oximidine III [35], and Sch 38516 [36] by various metathesis catalysts have been illustrated (**Figure 16**).
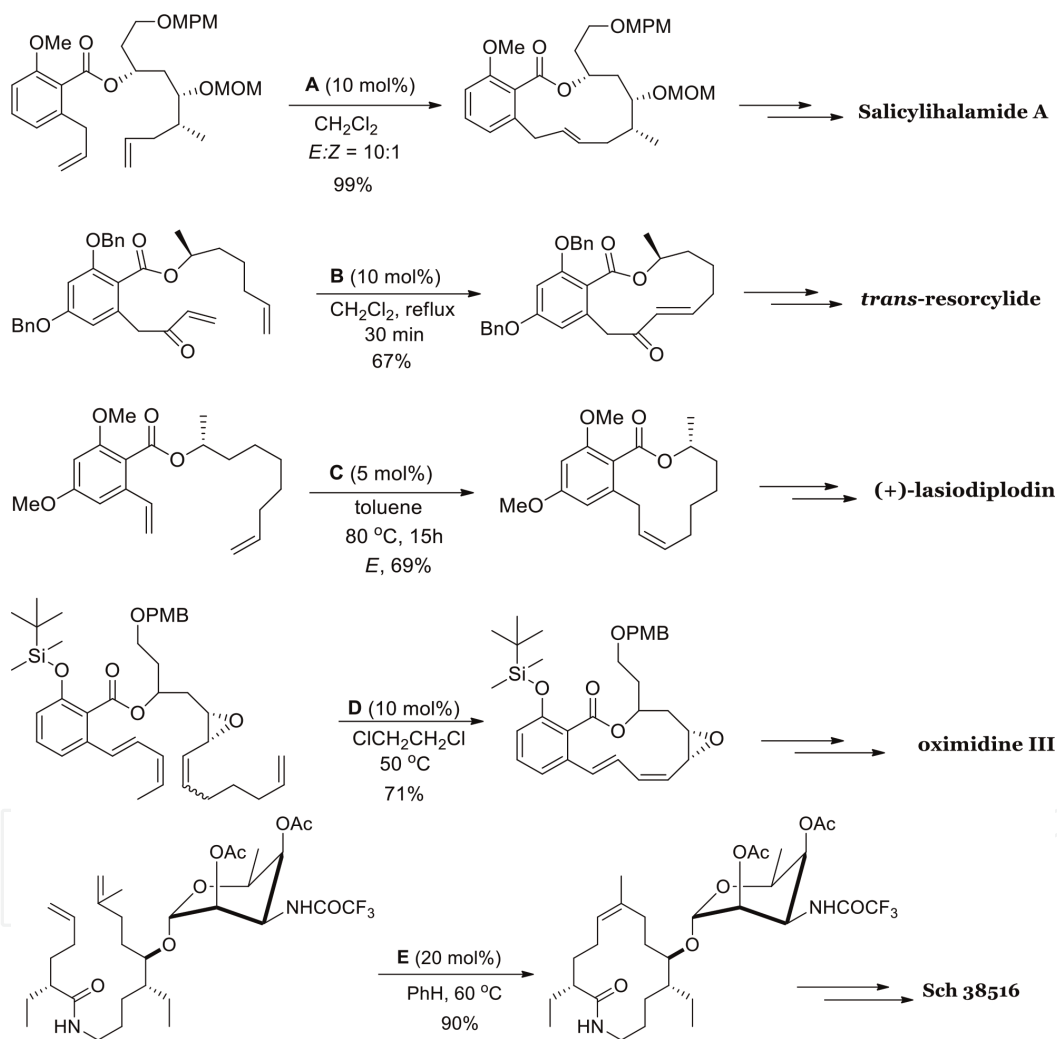

Figure 16.
Some of the applications of ring closing metathesis in total synthesis of macrolides.

2.5 Palladium catalyzed coupling reactions

Palladium-catalyzed coupling reactions have gained more attention in recent years in the field of organic chemistry. In this course, Suzuki reaction using organoboron compounds [37], Heck reaction using alkenes [38], Stille reaction with organostannate [39, 40], Sonogashira reaction with terminal alkyne [41] and Tsuji-Trost reaction with π-allylpalladium intermediate [42, 43], etc. are the most frequently employed reactions in the total synthesis of macrolide natural products. Some of them are depicted here.

Tortosa and co-workers [44] in the synthesis of (+)-superstolide A, Suzuki macrocyclisation approach is used for the construction of 24-membered macrocyclic octane **23** (**Figure 17**).

The first application of the Heck cyclisation to a macrocyclic substrate was reported by Ziegler and co-workers [45] in 1981 during the synthesis of aglycone of the macrocyclic antibiotic carbomycin B. They achieved the cyclisation to the model substrate **25** in 55% yield, by slow addition to a solution of $PdCl_2(MeCN)_2$, Et_3N and formic acid in MeCN at ambient temperature (**Figure 18**).

Stille macrocyclisation as illustrated below used as the key step in the total synthesis of the biselyngbyolide A by Tanabe et al. [46] using $Pd_2(dba)_3$ and lithium chloride in DMF (**Figure 19**).

The utility of Sonogashira macrocyclisation in the first total synthesis of penarolide sulfate A1, an α-glucosidase inhibitor is demonstrated by Mohapatra and co-workers [47]. The macrocyclisation was successfully achieved from compound **28** with catalytic $Pd(PPh_3)_4$ and CuI in Et_2NH at room temperature (**Figure 20**).

Towards the total synthesis of antibiotic natural product A26771B, Trost and co-workers [48] effectively constructed the macrolactone **31** (**Figure 21**) by the use of bidentate phosphine ligand (1,4-bis(diphenylphosphino)butane (DPPB)).
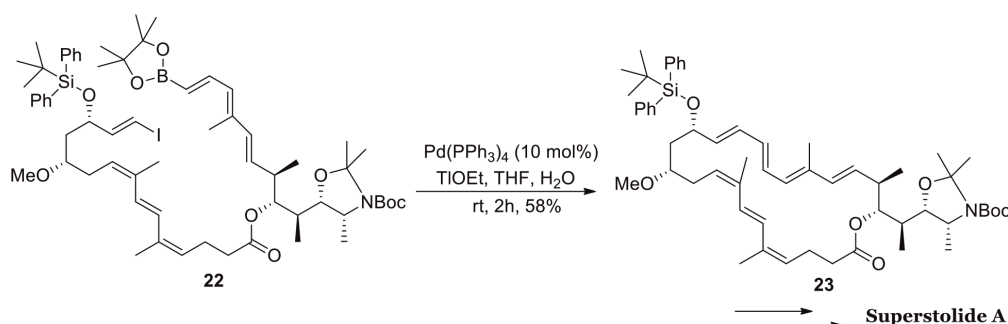

Figure 17.
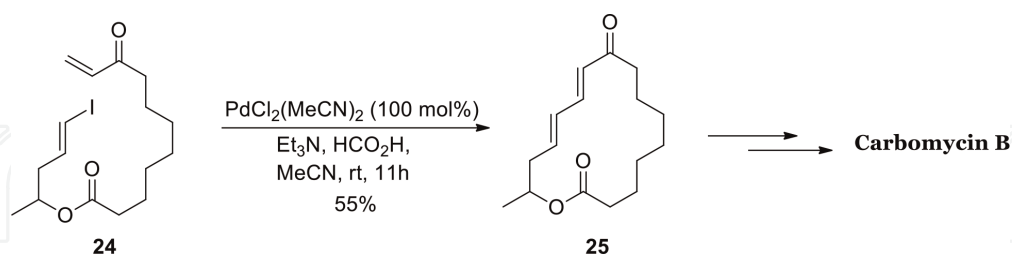*Suzuki macrocyclisation in the synthesis of superstolide A.*

Figure 18.
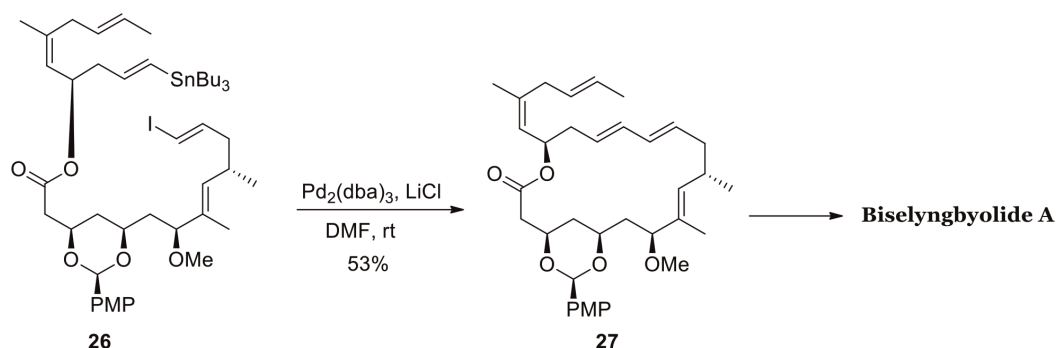*Heck cyclisation in the synthesis of carbomycin B.*

Figure 19.
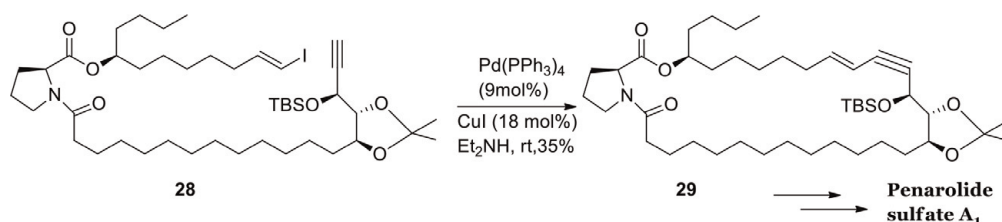*Stille macrocyclisation in the total synthesis of biselyngbyolide A.*

Figure 20.
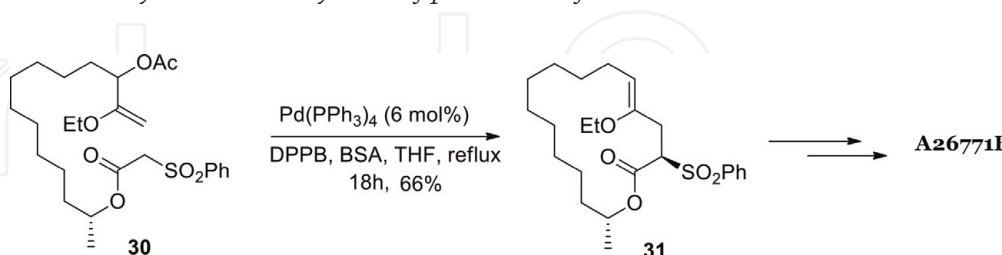*Sonogashira macrocyclisation in the synthesis of penarolide sulfate A1.*

Figure 21.
*Tsuji-Trost lactonization for the synthesis of A26771B.*

In the end game of total synthesis of macrolides, glycosidation to the aglycon also have more significance. Thus, a wide variety of methods are reported for glycosidation in the literature [49, 50].

3. Total synthesis of selected macrolides

In this section, the total synthesis of selected macrolides is discussed: (+)-neopeltolide (**32**), aspergillide D (**33**) and briefly about miyakolide (**34**) and acutiphycin (**35**).

3.1 (+)-Neopeltolide

(+)-Neopeltolide is a 14-membered macrolide isolated from north coast of Jamaica by Wright and coworkers from a deep water sponge [51]. It was tested for *in vitro* antiproliferative activity against several cancer cell lines comprising A549 human lung adenocarcinoma, NCI/ADR-RES ovarian sarcoma and P388 murine leukemia and shows IC$_{50}$ values 1.2, 5.1 and 0.56 nM. Besides this, neopeltolide also exhibits anti-fungal activity against *Candida albicans* [52]. The complexity of the structure with six chiral centres, tetrahydropyran ring, and an oxazole-bearing unsaturated side chain and its efficacious biological activity led to several total syntheses, few of them are discussed below.
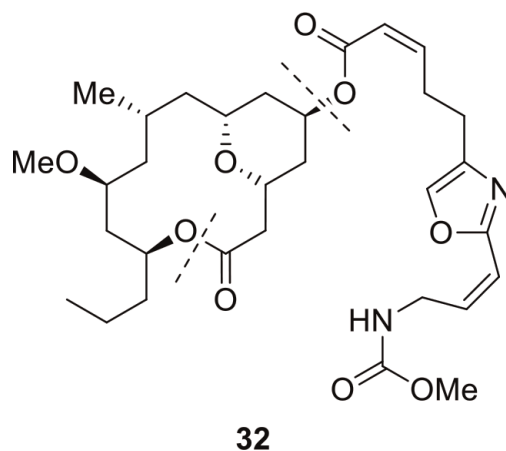
32

In 2013, Ghosh et al. [53] in their total synthesis adopted the retrosynthetic pathway as follows. Disconnection of O—C bond of the oxazole side chain would give acid which can undergo Mitsunobu esterification. Yamaguchi macrolacto-nization of acid would in turn give the desired macrolactone. The tetrahydropyran ring in acid could be constructed via a hetero Diels-Alder reaction between alde-hyde and silyloxy diene ether using Jacobsen's chromium catalyst.

The synthesis of the macrolactone ring of (+)-neopeltolide began with commer-cially available 3-methyl glutaric anhydride as shown in the scheme. 3-methyl glutaric anhydride, **36** was desymmetrized using PS-30 'Amano' lipase to obtain acid. The resulting acid was treated with borane-dimethyl sulfide complex to afford alcohol, **37**. Alcohol **37** was oxidized to corresponding aldehyde by Swern oxidation and then protected to its acetal, **38**. Ester of **38** was then reduced to alcohol and on Swern oxidation obtained aldehyde and the resulting aldehyde was subjected to Brown's allylation protocol using (+)-Ipc$_2$BOMe and allyl magnesium bromide to attain alcohol, **39**. Alcohol **39** was methylated with MeI, and on Lemieux-Johnson oxidation gave aldehyde and on Brown's allylation protocol afforded alcohol, **40**. Acetal protection was deprotected and the aldehyde was converted to α,β-unsatu-rated ketone, **41** using standard Horner-Wadsworth-Emmons olefination condi-tions. Secondary alcohol in **41** was then protected with TESOTf to obtain the silyloxy diene, **42** in excellent yield (**Figure 22**).

After the completion of requisite silyloxy diene, hetero-Diels Alder reaction of tosyl oxyacetaldehyde, **43** with **42** using chiral chromium catalyst (**44**) gave tetrahydropyranone, **45** in 83% yield (**Figure 23**). After protection of ketone group in **45** as ketal and displaced the tosylate to nitrile **46** using NaCN in DMF. Nitrile **46** was hydrolysed to acid and on deprotection of ketone to afford ketone **47**. Intra-molecular Yamaguchi macrolactonization attained the key macrolactone **48** in 40% yield. Olefin **48** was subjected to hydrogenation with 10% Pd/C to give saturated compound and on reduction with NaBH$_4$/EtOH to attain alcohol **49**. Next, the synthesis of unsaturated oxazole side chain **50** is started with known alkyne with LDA and Bu$_3$SnCl to obtain the alkynyl stannate, which on hydrozirconation gave the carbamate in 38% yield. Crucial Stille cross coupling of carbamate with iodooxazole using Pd(MeCN)$_2$Cl$_2$ in DMF gave oxazole which can be easily
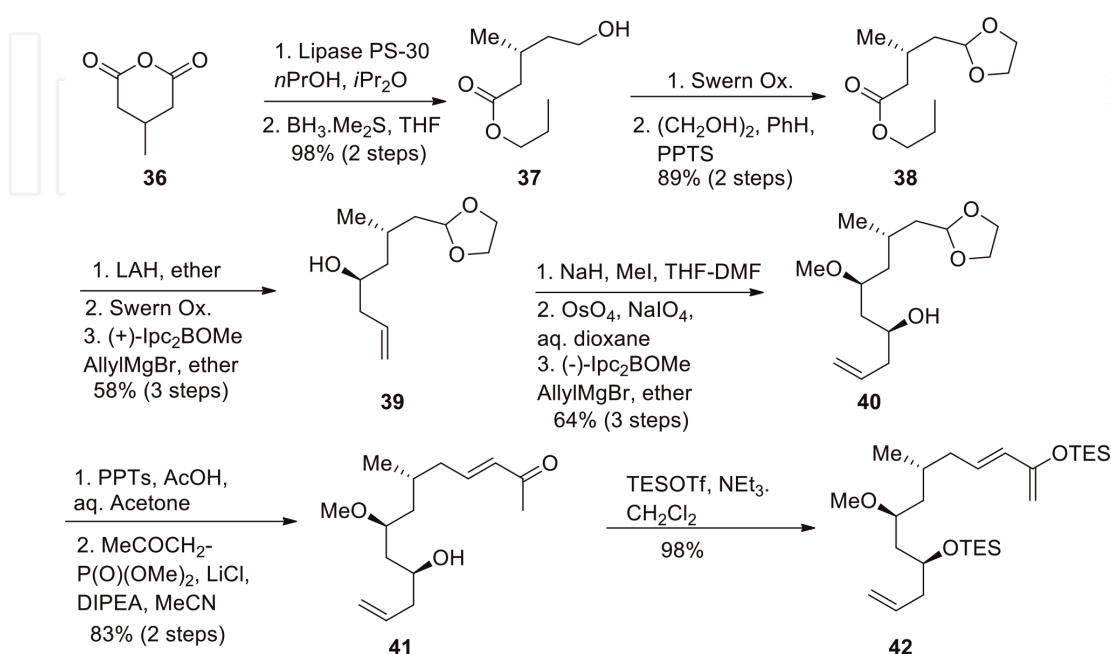

Figure 22.
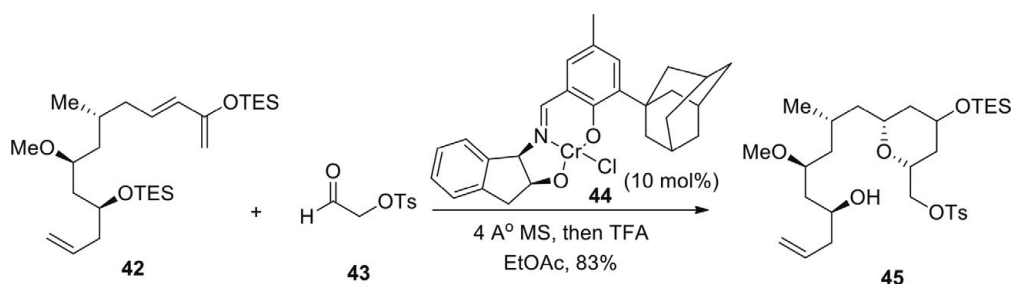*Synthesis of silyloxy diene 42 fragment.*

Figure 23.
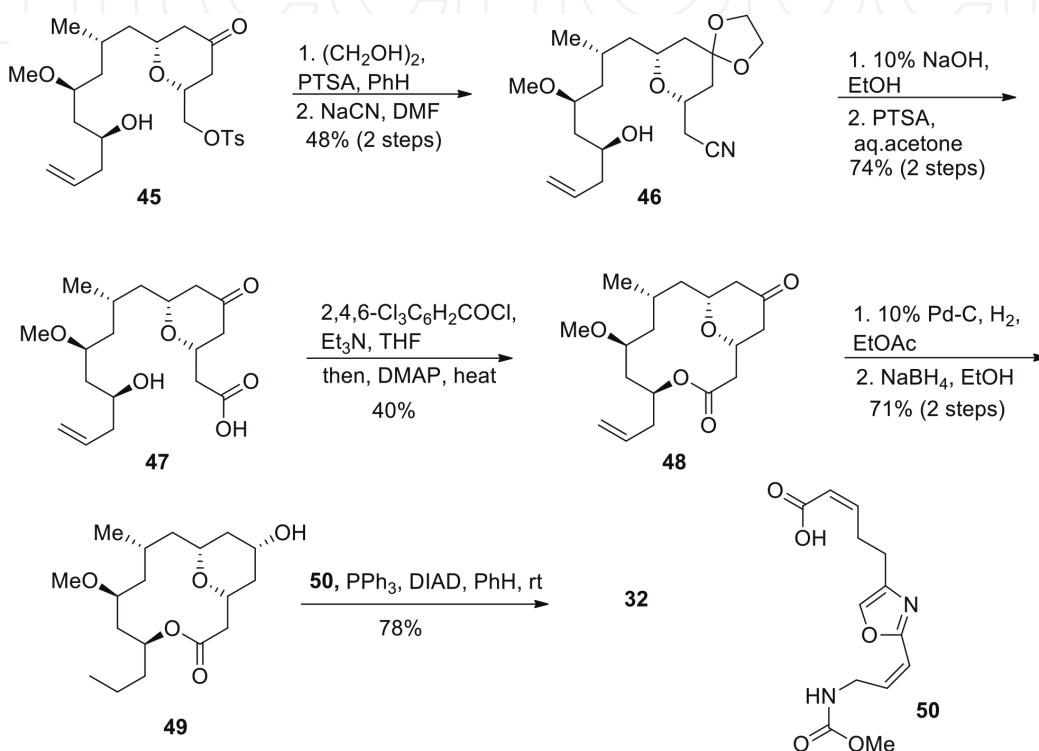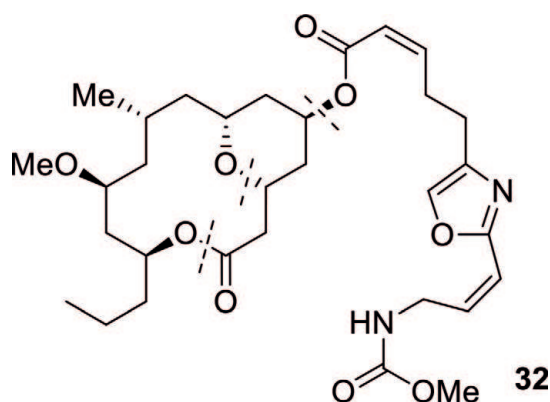*Hetero-Diels-Alder reaction for the synthesis of tetrahydropyrarone moiety.*

Figure 24.
Completion of synthesis of (+)-neopeltolide.

converted to desired side chain **50**. The target neopeltolide compound was furnished by standard Mitsunobu esterification of **49** with acid **50** (**Figure 24**).

3.2 Paterson strategy

Paterson and coworkers [54] reported the synthesis of neopeltolide as follows. Aldehyde was synthesized starting from known β-keto ester, **51**, which on treatment with (*S*)-BINAP-Ru (II) catalyst under Noyori asymmetric hydrogenation to afford (13*S*)-alcohol. The alcohol on TBS protection and DIBAL reduction of the ester produced the enantiopure aldehyde **52**. Aldehyde **52** was subjected to Brown's methallylation using 2-methyl propene and (−)-Ipc₂BOMe furnished the desired C11 alcohol with 94:6 dr, and the alcohol was methylated into the methyl ether **53** by NaH, MeI. Methyl ether **53** was subjected to ozonolysis to obtain methyl ketone and on Horner Wadsworth Emmons reaction with trimethyl phosphonoacetate to attain ester **54** in E/Z isomers (75,25). Esters **54** were reduced to its alcohol by DIBAL-H and on subsequent oxidation with Dess-Martin periodinane produced aldehyde **55**. Next, organo catalytic hydride reduction of enal **55** using MacMillan strategy with imidzolidinone catalyst **56**. TFA (20 mol%) and Hantzch ester furnished as 1,4-reduction product **57** with 76:24 of epimers at C9 stereocentre (**Figure 25**). Further, Jacobsen asymmetric hetero Diels-Alder reaction between **57** and known 2-silyloxy diene **58** produced *cis*-tetrahydropyranone **60** in 60% yield using chiral tridentate chromium (III) catalyst **59**. On PMB deprotection and further oxidation of alcohol to corresponding acid followed by TBS deprotection furnished seco-acid **61**. Macrolactonization of **61** under standard Yamaguchi conditions afforded macrolactone **62** in 80% yield. Reduction of macrolactone **62** to the alcohol with NaBH₄ in MeOH followed by Mitsunobu esterification with the oxazole side chain **50** achieved (+)-neopeltolide (**32**) in 52% yield (**Figure 26**).
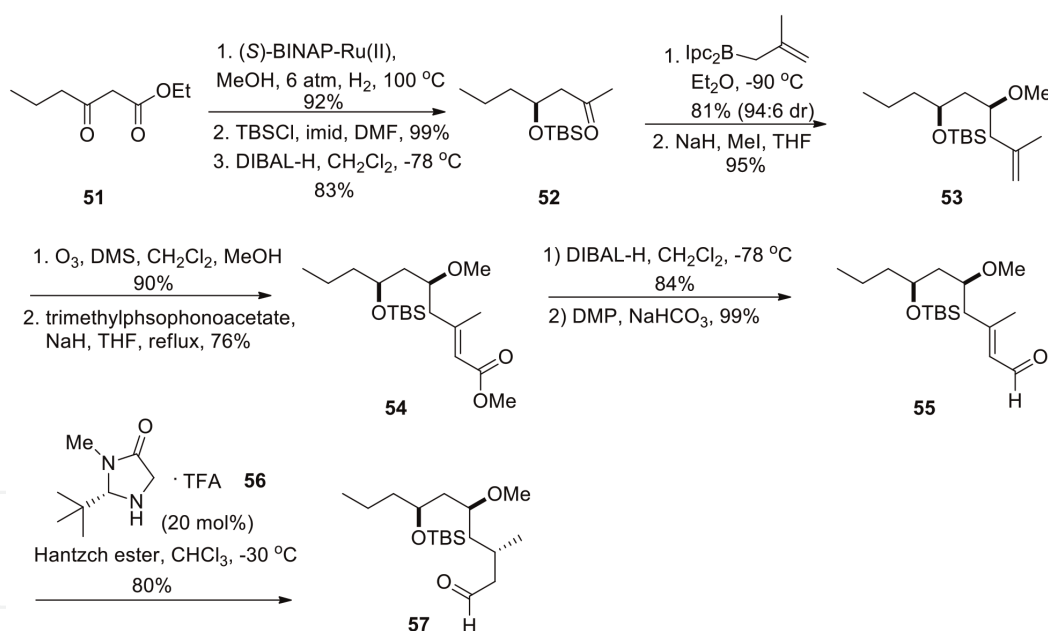

Figure 25.
Synthesis of aldehyde 57.

3.3 Ulanovskaya strategy

The synthesis of neopeltolide by Ulanovskaya et al. [55] is depicted as follows, Prins desymmetrization of diene **63** followed by benzyl protection and Wacker oxidation of alkene afforded ketone **64**. Formation of boron enolate from ketone and on addition of aldehyde **65** gave the anticipated aldol product with >98:2 diastereoselectivity, which was treated with Ph₃P=CH₂ (Wittig methylenation) followed by cleavage of dioxolone by acidic work-up afforded ketone **66** in 75%

yield. Ketone **66** was selectively reduced to *syn*-alcohol using Et_2BOMe and $NaBH_4$ followed by ester hydrolysis gave acid which was subjected to Yamaguchi macrolactonization to furnish desired macrolactone **67**. Alkene in **67** was hydrogenated using Pd/C to afford desired alcohol **68** as a major product. Alcohol **68** was subjected to Mitsunobu conditions, followed by hydrolysis with K_2CO_3 in MeOH to get the inversion product. Subsequent methylation with MeO_3BF_4 & hydrogenolysis of benzyl ether achieved desired macrolide **49**. The final coupling of fragment **49** with oxazole side chain **50** with standard Mitsunobu conditions furnished target (+)-neopeltolide **32** (**Figure 27**).
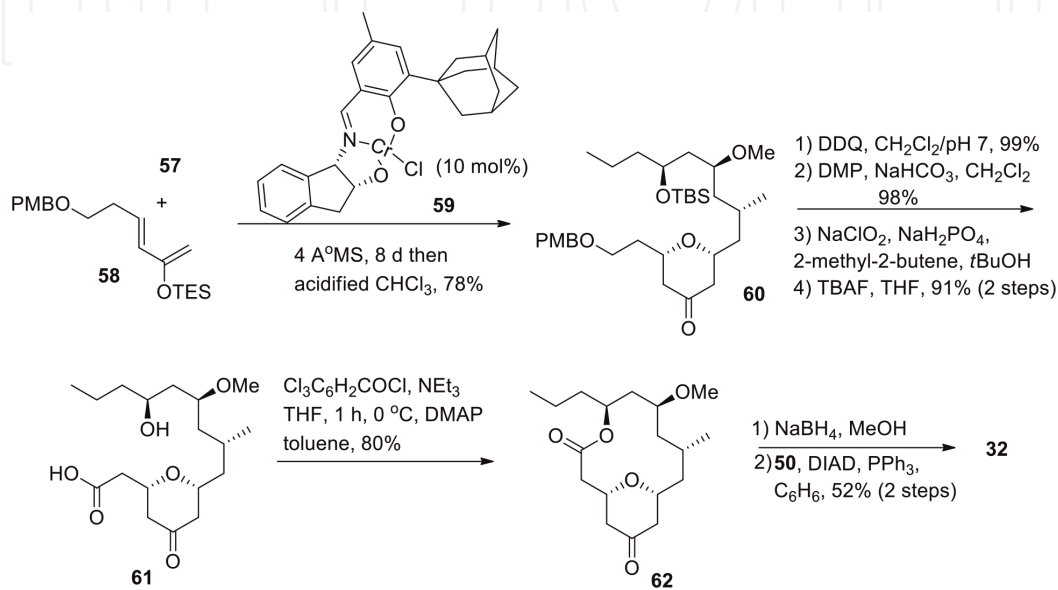

Figure 26.
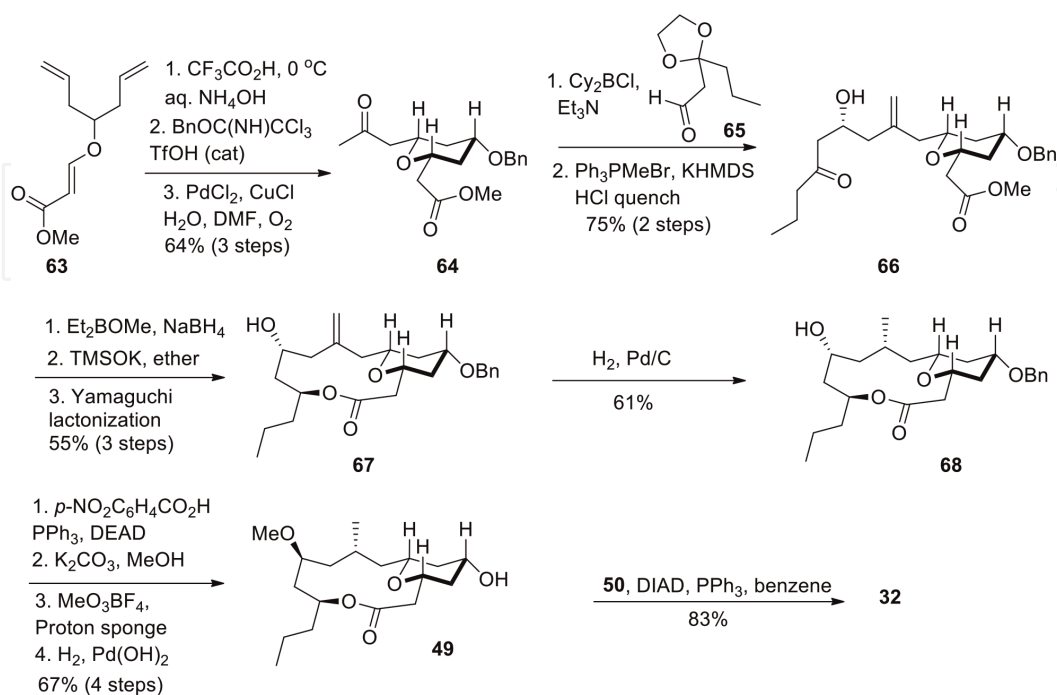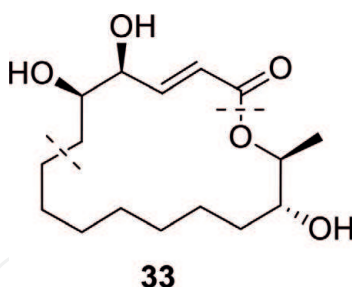*Total synthesis of (+)-neopeltolide.*

Figure 27.
Alternate synthesis of (+)-neopeltolide.

3.4 Aspergillide-D

Bao and coworkers in 2013 isolated 16-membered macrolide, aspergillide D, from the extract of *Aspergillus* sp. SCSGAF 0076 [56]. Aspergillide D macrolactone contains four chiral centres, α,β-unsaturation, three hydroxyl groups and the first total synthesis was reported by Jena et al. in 2017 as follows [57].

The retrosynthetic analysis of aspergillide D was depicted as shown above, macrolactone could be synthesized from seco acid via intramolecular Shiina esterification. For the total synthesis of Aspergillide D, the acid fragment was synthesized from commercially available D-ribose which was transformed to lactol **69** by using three step sequence, that is, catalytic amount of H_2SO_4 & acetone to form acetonide which on reduction with $NaBH_4$ and on oxidative cleavage of the diol with $NaIO_4$. The lactol was subjected to Wittig type olefination using $PPh_3=CH_2$ and the obtained primary alcohol **70** was oxidized to carboxylic acid **71** by using TEMPO/ BAIB conditions (**Figure 28**). The synthesis of alcohol fragment was started with mono-PMB protection **73** of commercially available 1,8-octane diol **72** and the other alcohol was converted to racemic allyl alcohol **74** by Swern oxidation and subsequent treatment of aldehyde with vinyl magnesium bromide in the presence of CuI. The allylic alcohol **74** was subjected to standard Sharpless kinetic resolution conditions by using (−)-DIPT & Ti(OiPr)₄ to obtain enantiomeric epoxy alcohol **75**. Upon MOM protection **76** to the secondary alcohol **75** and PMB deprotection produced **77**, which on oxidation with Dess-Martin periodinane to afford aldehyde. Aldehyde was converted to olefin **78** by treating $PPh_3=CH_2$ in THF. **78** was cleaved to alcohol **79** by reduction with LAH in THF (**Figure 29**).

Acid **71** and alcohol **79** fragments were coupled together under Yamaguchi esterification conditions afforded diene ester **80** in 65% yield. Intramolecular RCM was employed on diene ester by using Grubbs' second generation catalyst in refluxing CH_2Cl_2 to produce the requisite macrolactone **81**. Double bond in **81** was hydrogenated by using PtO_2 in MeOH to attain saturated lactone **82**. Lactone **82** was reduced with DIBAL-H to afford lactol which on further treatment with $Ph_3P=CHCO_2Et$ in C_6H_6 afforded α,β-unsaturated ester **83**. The ester was converted to carboxylic acid **84** by LiOH in THF/H_2O which on adopting key Shiina's
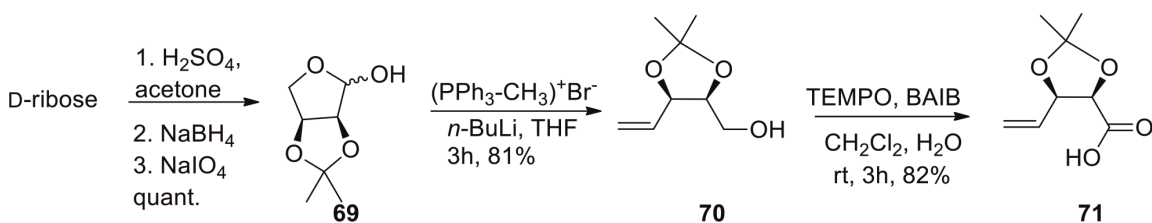

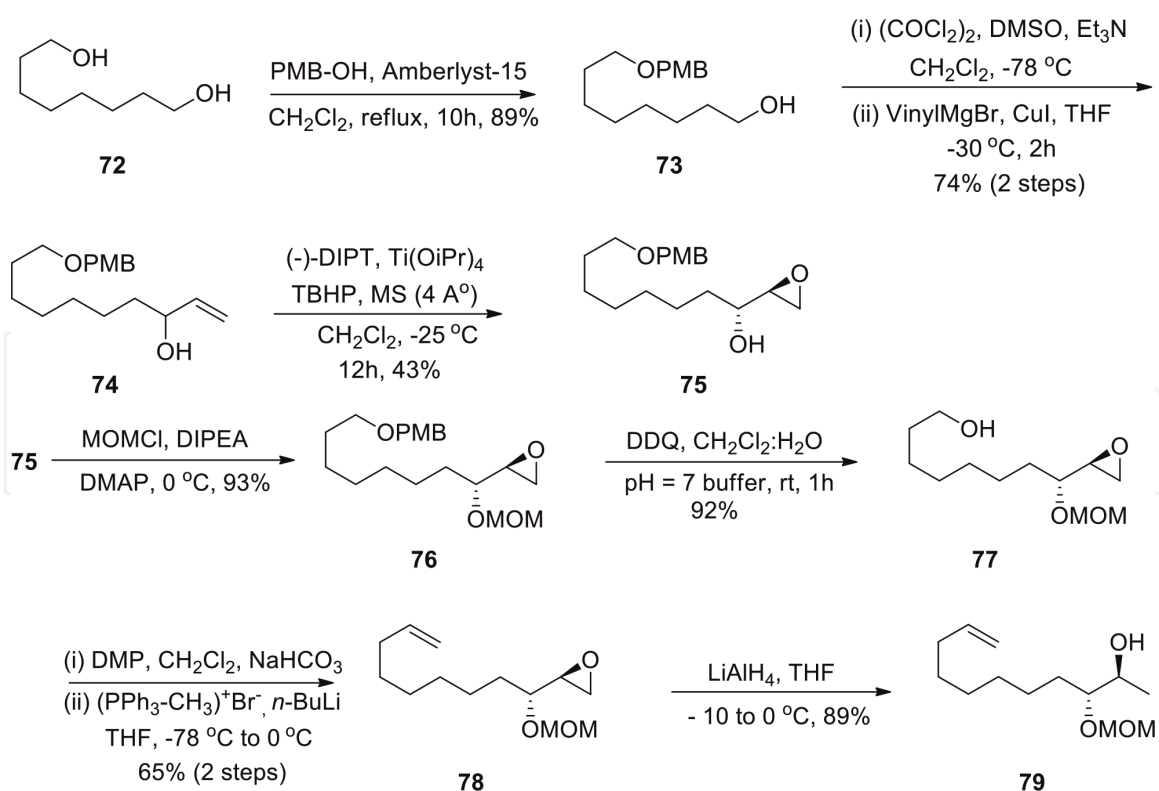**Figure 28.**
Synthesis of acid fragment 71.

Figure 29.
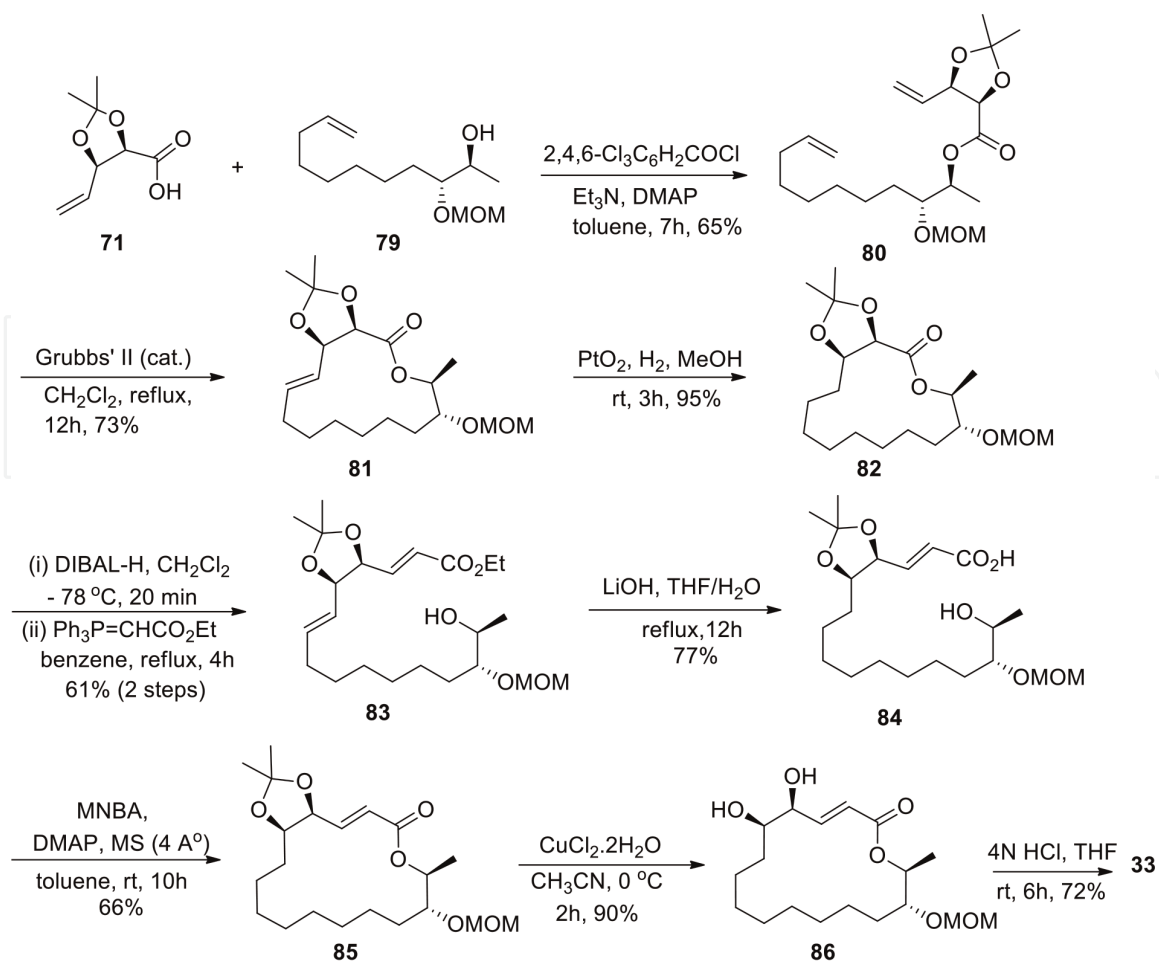*Synthesis of alcohol fragment 79.*

Figure 30.
Completion of synthesis of aspergillide D.

macrolactonization protocol to provide the desired mactrolactone **85** in 51% yield. On deprotection of acetonide with $CuCl_2.2H_2O$ gave diol **86** and removal of MOM group, the synthesis of aspergillide D **33** was achieved (**Figure 30**).

3.5 Miyakolide

Evan's strategy of bond connections & key reactions in the synthesis of **34** is illustrated [58].
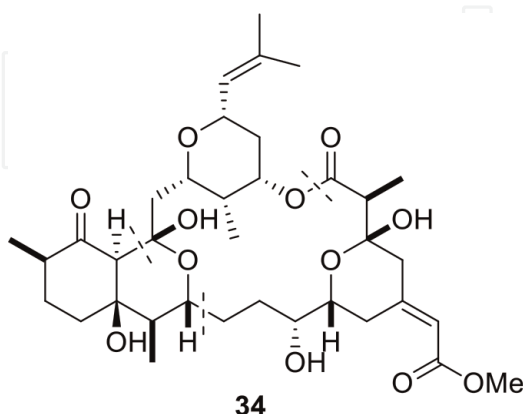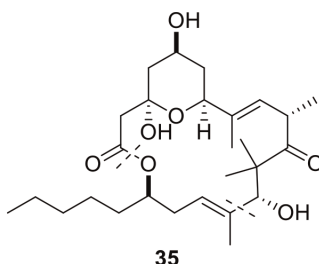
Evan's strategy

1. aldol reaction
2. [3+2] dipolar cycloaddition
3. Yamaguchi macrolactonization

34

3.6 Acutiphycin

Smith's strategy [59] & Moslin's strategy of acutiphycin [60] is shown below (**Figure 31**).

Smith's strategy

1. vinyl Grignard addition
2. Yamaguchi macrolactonization

Moslin's strategy

1. Hydrozirconation-transmetallation -carbonyl addition method
2. SmI_2-mediated Reformatsky reaction
3. Retro-ene reaction

35

Figure 31.
Key reactions and strategies in the synthesis of miyakolide and acutiphycin.

4. Conclusions

A number of new macrolide antibiotics with fascinating biological activities have been isolated everyday with the unique and complex structures have been determined with extensive spectroscopic studies. Toward the total synthesis of such macrolide antibiotics, very efficient synthetic strategies and various new methodologies are also developed. Recent advances in macrolide synthesis based on newly developed strategies and methodologies are noteworthy. Further synthetic studies on macrolide antibiotics will make an immense contribution to progress in both organic and medicinal chemistry.

Acknowledgements

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